GYNECOLOGIC ONCOLOGY

Radiotherapy for Japanese elderly patients with cervical cancer: preliminary survival outcomes and evaluation of treatment-related toxicity

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Abstract

Purpose To examine the preliminary survival outcomes and treatment-related toxicity for elderly patients with cervical cancer treated with radiotherapy (RT).

Methods Forty patients ≥75 years old with cervical cancer who were treated with RT were evaluated. Of these 40 patients, 25 were classified as FIGO stage I or II and 15 as stage III or IVA. Thirty-five patients were treated with radical RT (RRT), and five were treated with surgery plus adjuvant RT (S + ART). External beam radiotherapy combined with high-dose-rate intracavitary brachytherapy was performed on 31 patients who were treated with RRT and on 2 patients who were treated with S + ART because of positive vaginal surgical margins. The patients' median age was 78 years (range 75–89 years). Concurrent chemotherapy (CCT) was performed on five patients (RRT: 3, S + ART: 2).

Results The median follow-up period was 20 months (range 1–85 months). Only one patient could not complete RT. The 3-year overall and disease-specific survival (OS and DSS) rates for all patients were 58 and 80%, respectively. Five patients experienced Grade 3 acute toxicity; two were treated with RRT (2/35), and three were treated with S + ART (3/5, 2 of them with CCT). Two patients experienced Grade 3 late toxicity; one was treated with RRT (1/35, with CCT) and the other was treated with S + ART (1/5). No Grade 4 or higher toxicity was experienced.

Conclusions RRT for elderly patients with cervical cancer is generally effective and safe, but severe toxicity may occur with more aggressive treatment modalities.

Keywords Cervical cancer · Radiotherapy · Elderly patients · Treatment-related toxicity

This study was selected for presentation at the 52nd Annual Meeting of the American Society for Therapeutic Radiology and Oncology (ASTRO 52), October 31–November 4, 2010, in San Diego, CA, USA.

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Introduction

The population of elderly people has been rapidly increasing in Japan. According to statements by the Ministry of Health, Labor and Welfare, the average life expectancy for men and women in 2008 was 79 and 86 years old, respectively [1]. In particular, the life expectancy of a Japanese woman is the longest in the world. With an increasingly aged society, the number of elderly patients with various malignancies continues to

increase. In addition, the number of younger cancer patients has also been increasing due to changes in lifestyle and viral infections. In Japan, malignant neoplasms have the highest mortality rate, surpassing cerebrovascular and heart diseases in 1981.

For cervical cancer, the most commonly afflicted age group is women in their late 30s to early 40s; the affliction of young women is usually emphasized [2–4]. However, the incidence of cervical cancer increases again after age 70, and the mortality rate increases with age. Therefore, the increase in the ratio of elderly patients with cervical cancer must be evaluated, and an appropriate treatment modality should be identified. Surgery and/or radiotherapy (RT) are the radical treatment modalities for cervical cancer. For advanced-stage disease, RT with or without concurrent chemotherapy (CCT) is usually the radical treatment of choice. For early-stage disease, the survival outcomes of surgery and RT are known to be similar [5–8]. Although RT seems to be a less invasive treatment, its long-term complications and negative impact on sexual function when compared with surgery are important considerations for younger patients [9–11]. Therefore, there is a trend emerging in which surgery is usually used for younger patients and RT is used for elderly patients. However, although it is obvious that RT plays an important role in the treatment of most stages (I–IVA) of cervical cancer, the recent increase in the elderly population may further increase RT's importance [12, 13].

In this study, we retrospectively analyzed the preliminary survival outcomes and evaluated treatment-related toxicity for Japanese elderly patients (≥75 years old) with cervical cancer treated with RT.

Materials and methods

Patients

At Kobe University Hospital between 2000 and 2009, 40 patients aged 75 or older who had cervical cancer and were treated with RT as the radical or postoperative adjuvant modality were retrospectively evaluated. Patients who received only palliative RT were excluded. Those patients who were followed for <6 months, except when this was due to recurrence or death, were also excluded. Between 2000 and 2005, 9 patients were treated, whereas 31 were treated between 2006 and 2009. Clinical staging was performed according to the International Federation of Gynecology and Obstetrics (FIGO) stages [14]. Among the 40 patients, 35 were treated with radical RT (RRT), and 5 were treated with surgery and adjuvant RT (S + ART). Six patients had pelvic nodal metastases (4 were clinical, 2 were pathological). Thirty-eight tumors were histologically

confirmed as squamous cell carcinoma (SCC), and two were confirmed as adenocarcinoma. On the Karnofsky Performance Scale (KPS), 20 patients had scores >70, 17 had scores between 50 and 70, and 3 had scores <50. Twenty-five patients had stage I or II disease (IA: 1, IB: 4, IIA: 7, IIB: 13), and 15 had stage III or IVA disease (IIIA: 2, IIIB: 11, IVA: 2). The median age was 78 years (range 75–89 years). In addition, 29 of the 40 patients had concurrent medical complications. Three patients had a previous history of malignancy (breast cancer, colon cancer, and malignant lymphoma), and one had early-stage lung cancer concurrent with the advanced cervical cancer. Patient information according to clinical factors is shown in Table 1.

Table 1 Patient information according to clinical factors

Factors	Number of patients (total = 40)	%
Treatment period		
2000–2005	9	22.5
2006–2009	31	77.5
Age (years old)		
≤80	27	67.5
>81	13	32.5
Median age (range)	78 (75–89)	
Karnofsky performance scale score		
>70	20	50
50–70	17	42.5
<50	3	7.5
Stage (FIGO)		
IA	1	2.5
IB	4	10
IIA	7	17.5
IIB	13	32.5
IIIA	2	5
IIIB	11	27.5
IVA	2	5
Histology		
SCC	38	95
Adenocarcinoma	2	5
Nodal metastasis		
Yes	6	15
No	34	85
Medical complications		
Yes	29	72.5
No	11	27.5
History of other cancers		
Yes	4	10
No	36	90

SCC squamous cell carcinoma

Treatment

In our institution, RRT is recommended as the definitive treatment for patients with cervical cancer ≥75 years old. Surgery is considered if the following criteria are met: young age, high KPS score (>70), and FIGO I or II. Medical complications and histology (adenocarcinoma) are also important considerations. In addition, the patient's desired treatment choice (RT or surgery) is also considered. Indications for the use of ART are based on pathological findings (nodal metastasis, parametrium invasion, surgical margin, vascular invasion, and/or lymphatic invasion). Based on this institutional guideline, 35 patients were treated with RRT, and the remaining 5 were treated with S + ART. Among the 35 patients treated with RRT, 31 were treated with external beam radiotherapy (EBRT) combined with high-dose-rate intracavitary brachytherapy (HDR-ICBT), 3 were treated with EBRT alone, and 1 was treated with HDR-ICBT alone. The four patients treated with EBRT or HDR-BT alone had KPS scores = 50 or less. Of the 31 patients treated with EBRT combined with HDR-ICBT, 2 received boost irradiation for pelvic lymph node metastases. Two of the three patients treated with EBRT alone received boost irradiation for the primary tumor instead of HDR-BT. Among the five patients treated with S + ART, three received EBRT alone, and two received EBRT combined with HDR-ICBT because of positive vaginal surgical margins. CCT using a platinum-based regimen was performed on five patients. Three were treated with RRT with CCT, and two were treated with S + ART with CCT. At our institution, RRT with CCT is performed on younger patients (<80) with high KPS scores (>70) and FIGO IIB or higher. The presence of medical complications is also an important consideration. Based on these criteria, three patients were treated with RRT with CCT. Adjuvant CCT has been performed on patients with multiple pathological risk factors (at least 3) since 2008. Postoperative KPS score (>70) is also considered to be important because S + ART with CCT is a very aggressive treatment for elderly patients; two were ultimately treated with this modality. The patient distribution per treatment modality is shown in Table 2.

The patients who received EBRT combined with HDR-ICBT were initially treated with whole pelvic irradiation using a box field and high-energy 10 MV X-ray photons from a linear accelerator with a daily fraction size of 1.8–2.0 Gy delivered five times per week. A centrally shielded field using anterior/posterior opposed portals was applied just before starting HDR-ICBT. The patients who received EBRT alone were also initially treated with whole pelvic irradiation. A boost to the primary tumor was delivered using a three-dimensional conformal technique, and a pelvic lymph node boost was delivered using the

Table 2 Patient distribution per treatment modality

	Number of patients	Use of CCT
RRT		
EBRT + HDR-ICBT (with nodal boost)	31 (2)	3
EBRT (with local boost)	3 (2)	0
HDR-ICBT	1	0
S + ART		
EBRT	3	1
EBRT + ICBT	2	1

RRT radical radiotherapy, *EBRT* external beam radiotherapy, *HDR-ICBT* high-dose-rate intracavitary brachytherapy, *S* surgery, *ART* adjuvant radiotherapy, *CCT* concurrent chemotherapy

anterior/posterior opposed portals. The median total dose of EBRT was 50.4 Gy (range 16.2–61.2 Gy). The HDR-ICBT was done with a Microselectron HDR (Nucletron, The Netherlands) using a 192-Iridium remote afterloading system at 1-week intervals during the period of EBRT. The median total dose to point A was 20.0 Gy (range 4.5–31.0 Gy) with a single fraction size of 4.0–6.5 Gy. Treatment planning for HDR-ICBT was performed at each irradiation using PLATO Brachytherapy Planning System version 3.2 (Nucletron, The Netherlands). Evaluation of the rectal and bladder dose was performed according to ICRU Report 38 [15].

Follow-up, evaluation of treatment-related toxicity, and statistical analysis

After completion of their treatment, most patients were followed up by gynecological and radiation oncologists every month during the first year, primarily because elderly patients tolerate RT less well and unexpected toxicity might be experienced. However, patients who lived far from our institution were followed up every 2–3 months. Afterward, follow-up was conducted every 3–6 months to detect recurrence and late toxicity. A gynecological examination was performed, and the tumor marker was checked at every visit. SCC Antigen was used for patients who had SCC, and Carcinoembryonic Antigen (CEA) was usually used for patients who had adenocarcinoma. Radiographic examinations (CT scan or MRI) were performed as necessary.

Both acute and late treatment-related toxicity were evaluated using medical records and CTC-AE version 4.0 [16]. Acute toxicity was defined as those events that occurred within 90 days from the start of the treatment, and late toxicity was defined as those events that either occurred >90 days from the start of the treatment or persisted beyond 90 days.

Statistical analyses were performed using Sigma Plot 9.0 software (Systat Corporation, CA, USA). Survival rates were calculated with the Kaplan–Meier method and compared with the use of log-rank test. The follow-up period was calculated from the start of the treatment. P values <0.05 were considered statistically significant.

Results

Patient status and patterns of failure

The median follow-up period for all patients was 20 months (range 1–85 months). The median follow-up period for survivors was also 20 months (range 6–85 months). Of the initial 40 patients, 38 completed the treatment as planned, 1 completed with a delay due to concomitant heart disease, and 1 could not complete the treatment because of acute toxicity. These two patients who experienced delay or cancellation had lower KPS scores (<50). Seven patients experienced recurrence: four locally, one in the para-aortic lymph nodes, one distantly, and one with only tumor marker (SCC Antigen) elevation. Even though a thoracic-abdominal contrast enhanced CT scan, a pelvic MRI, a gynecologic examination and cytology were performed, a recurrent tumor could not be detected at any site. However, this patient was presumed to have microscopic recurrence because SCC Antigen increased continuously. Regarding the clinical stages, one patient was classified as IIA, one as IIIA, and five as IIIB. Six of the seven patients with recurrence were treated with RRT, and one was treated with S + ART. During the period of this study, nine patients died. Among them, five died because of the primary disease, and four died from other causes. The patient who could not complete the treatment had persistent disease and died of the primary disease. Of the remaining two patients who experienced recurrence, one with the para-aortic lymph nodes

metastases is alive with the disease and one with tumor marker elevation apparently died from a different cause. The patient who had early-stage lung cancer concurrently with the cervical cancer received the left lower lobe resection after completion of RT. The pathological diagnosis was adenocarcinoma, pT2N0M0. This patient experienced multiple bone metastases (bilateral sacroiliac joints and lumber spine) about 22 months after surgery. Bisphosphonate has been continuously administered, and the patient is doing well without pain.

Preliminary survival outcomes

The 3-year overall and disease-specific survival (OS and DSS) rates for all the patients were 58 and 80%, respectively (Fig. 1a, b). The 3-year OS rate for patients in FIGO stage I or II was 69%, and the rate for stage III or IVA patients was 40% ($P = 0.04$). The 3-year DSS rate for patients in FIGO stage I or II was 89% and that for stage III or IVA patients was 66% ($P = 0.04$). The patients were also divided into two groups according to age; there were 27 patients aged ≤80 years with a median follow-up of 26 months (range 1–85 months) and 13 patients aged >80 years with a median follow up of 14 months (range 7–61 months). The 3-year OS rates for patients aged ≤80 and >80 years were 62 and 42%, respectively ($P = 0.89$). The 3-year DSS rates for patients aged ≤80 and >80 years were 75 and 100%, respectively ($P = 0.21$). Survival was also analyzed according to KPS score. The 3-year OS rates for patients with KPS scores >70 and ≤70 were 61 and 55%, respectively ($P = 0.15$). The 3-year DSS rates for patients with KPS scores >70 and ≤70 were 92 and 65%, respectively ($P = 0.11$).

Treatment-related toxicity

The details regarding acute toxicity are shown in Table 3. The most common acute toxicity was diarrhea (18/40

Fig. 1 Preliminary overall and disease-specific survival (OS and DSS) rates for all patients ($n = 40$) using the Kaplan–Meier method with a median follow-up of 20 months (range 1–85 months). The 3-year OS and DSS rates were 58% (**a**) and 80% (**b**), respectively
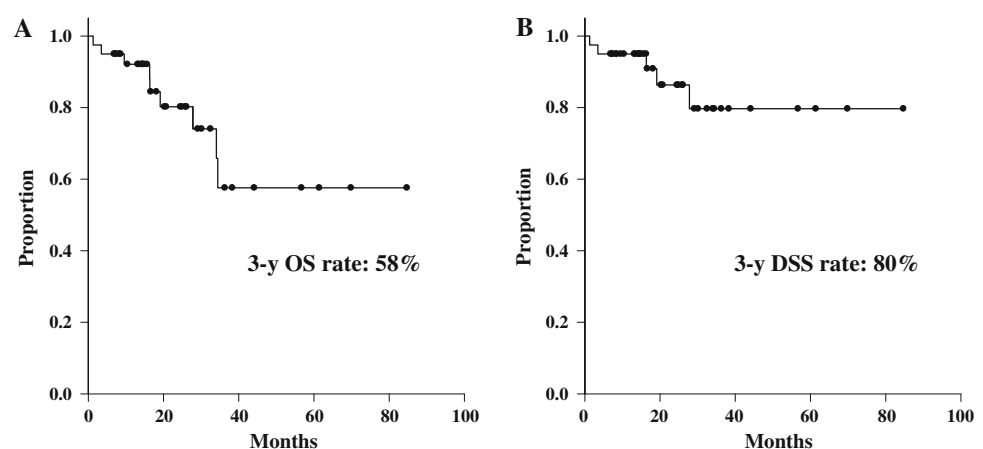
Table 3 Acute treatment-related toxicity according to treatment modality (CTC-AE version 4.0)

	RRT (use of CCT), total: 35	S + ART (use of CCT), total: 5
Gastrointestinal		
Grade 1–2	Diarrhea: 16 (2), gastrointestinal pain: 2	Diarrhea: 1(1)
Grade 3	Diarrhea: 1	Intestinal infection: 1(1)[a], intestinal obstruction: 1
Grade 4	0	0
Genitourinary		
Grade 1–2	Urinary frequency: 3, cystitis: 1	Urinary tract obstruction: 1
Grade 3	Cystitis: 1	Cystitis: 1, urinary tract obstruction: 1(1)[a]
Grade 4	0	0

RRT radical radiotherapy, *S* surgery, *ART* adjuvant radiotherapy, *CCT* concurrent chemotherapy

[a] Same patient

patients, 45%). Grade 3 acute toxicity occurred in five patients, but no Grade 4 or greater acute toxicity was experienced. Among the five patients with Grade 3 acute toxicity, two were treated with RRT (2/35 patients, 5%) and three were treated with S + ART (3/5 patients, 60%). As for the patients treated with RRT, one experienced Grade 3 diarrhea and selectively cancelled her treatment at 16.2 Gy after nine fractions, and the other experienced Grade 3 cystitis. As for the patients treated with S + ART, one receiving CCT experienced a Grade 3 small intestine infection during RT and a urinary tract obstruction soon after the completion of RT, the different one receiving CCT experienced Grade 3 cystitis during RT, and the remaining one experienced a small intestine obstruction soon after RT. The patient who could not complete RT was managed by the administration of anti-diarrheal agents and continuous intravenous transfusion. RT was postponed, but after recovery from the diarrhea, the patient refused to restart RT. The patients who experienced cystitis or small intestine infections were managed by the administration of antibiotics and intravenous transfusions without delaying the RT. The urinary tract obstruction was resolved by urological intervention. The small intestine obstruction was managed by conservative treatment, such as fasting, antibiotic administration, and continuous intravenous transfusion. In both the urinary tract and small intestine obstructions, abdominal CT scans were performed immediately after the symptoms occurred, and progressive disease was excluded.

Currently, Grade 3 late toxicity has occurred in two patients (2/40 patients, 5%). One of these two patients (treated with RRT with CCT) experienced Grade 3 hemorrhagic cystitis. The other patient (treated with S + ART) experienced a Grade 3 acute small intestine obstruction and a Grade 3 late small intestine obstruction. No Grade 4 or greater late toxicity was experienced. The hemorrhagic cystitis was managed by endoscopic hemostasis. The small intestine obstruction was also managed by conservative treatment. Abdominal CT scans were performed in both

Table 4 Late treatment-related toxicity according to treatment modality (CTC-AE version 4.0)

	RRT (use of CCT), total: 35	S + ART (use of CCT), total: 5
Gastrointestinal		
Grade 1–2	Rectal bleeding: 2	0
Grade 3	0	Intestinal obstruction
Grade 4	0	0
Genitourinary		
Grade 1–2	Cystitis: 2	0
Grade 3	Cystitis: 1(1)	0
Grade 4	0	0
Other		
Grade 1–2	Lymphedema: 2	Lymphedema: 1
Grade 3	0	0
Grade 4	0	0

RRT radical radiotherapy, *S* surgery, *ART* adjuvant radiotherapy, *CCT* concurrent chemotherapy

cases and progressive disease was excluded before starting the toxicity management. The details regarding late toxicity are shown in Table 4.

Discussion

Choosing a treatment for elderly patients with various malignancies is usually difficult. Careful evaluation of their general condition and concomitant medical problems must be performed before the treatment begins. Compared with young patients, safer and more effective modalities should be chosen because severe toxicity may lead to cancellation or delay of the treatment and subsequent loss of quality of life [17–21]. Generally, RT is thought to be less invasive than surgery or chemotherapy. Moreover, with recent technical developments, a reduction of radiation-related toxicity has been achieved, and the safety of RT is

increasing markedly. Therefore, RT is usually chosen for elderly patients as a single modality, although sometimes RT is combined with surgery and/or chemotherapy. Certainly, RT has taken on a greater role in aging societies such as Japan. For example, in this study, just 9 patients were treated from 2000 to 2005, but 31 were treated from 2006 to 2009.

Although there are several large retrospective studies that have analyzed treatment results and prognostic factors, whether age is a negative prognostic factor remains controversial [12, 13, 22–27]. However, most reports have demonstrated that RT is effective for elderly patients. For example, Ikushima et al. analyzed 727 patients with cervical cancer and reported that the 5- and 10-year disease-specific survival rates of 132 patients aged ≥75 years were 66 and 57%, respectively. Thus, age was not a significant prognostic factor in that study [13]. Chen et al. analyzed a total of 295 patients. They reported that the 5-year cause-specific survival rates of 79 patients aged ≥70 years with respect to FIGO stage were 100% for IB, 85% for IIA, 78% for IIB, and 42% for III. Thus, again age was not a significant prognostic factor in this case [26]. On the other hand, Brun et al. analyzed a total of 308 patients and reported that the 5-year survival rate of 31 patients aged ≥75 years was 42% and that age was a significant prognostic factor. However, they also reported that the survival of those over 75 years was not different from that of the rest of the population [23]. Although the median follow-up of our study was shorter and the number of cases is currently smaller, our observed survival rates are reasonable compared with previous reports. Our results also indicate that the clinical stage might have prognostic value in determining survival outcomes, but age did not have prognostic value in such an elderly population. Interestingly, the DSS rate of patients aged >80 years was 100%. Whether "slow oncological progression" was associated with this result is unclear because of the small number of patients and the short follow-up period. Therefore, this result cannot be used as evidence for a more limited treatment choice at present. However, RRT alone should be the first choice for patients >80 years old. The survival rates of the patients with high KPS scores (>70) were better than those with low KPS scores (≤70), but the difference was not significant. KPS was not a significant prognostic factor in this preliminary result, but it may have a large impact on long-term survival. To evaluate survival outcomes accurately and verify prognostic factors such as clinical stage, age, and KPS, more cases need to be analyzed, a longer follow-up period is needed, and the results need to be compared with those of a younger population. Finally, the most appropriate treatment choice for elderly patients should be established.

Both acute and late toxicity should be evaluated carefully to establish a safe modality that achieves better survival outcomes and preserves the quality of life of elderly patients with cervical cancer. Lindegaard et al. reported that treatment was completed as planned in 68% of cases, delayed in 29% of cases, and stopped prematurely in 3% of cases. They concluded that elderly patients with cervical cancer in otherwise good health may tolerate radical radiotherapy with acceptable toxicity and reasonable survival rates [28]. In our study, 38 of 40 (95%) patients completed the treatment as planned; 1 (2.5%) completed after a delay and 1 (2.5%) could not complete the treatment. The two patients who experienced delay or cancellation of the treatment had KPS scores <50 and had RRT performed, but they could not receive HDR-BT. This result also indicates that elderly patients in good health can tolerate RRT (EBRT combined with HDR-ICBT). However, those with a poor performance status should be treated carefully; in some instances, a less invasive RRT (EBRT alone) must be chosen. For elderly patients in good health, tolerance for more aggressive treatment modalities such as RRT with CCT or S + ART with or without CCT should be discussed carefully. In our study, 8 patients with KPS scores >70 were treated with these more aggressive modalities (RRT with CCT: 3, S + ART: 3, S + ART with CCT: 2). As described above, the indications for the use of these aggressive modalities involved age, KPS, FIGO stage, and pathological risk factors. Regarding the patients treated with RRT with CCT, all of them were <80 years old and had KPS scores >70. Two of them were FIGO IIB and the remaining one was IIIB. Regarding the patients treated with S + ART with or without CCT, 4 were 75, and 1 was 76 years old. All of them had KPS scores >70 and had stage II disease (IIA: 2, IIB: 3). Adjuvant CCT has been performed on patients with postoperative KPS scores >70 and multiple pathological risk factors (at least 3) since 2008. As a result, two were treated with S + ART with CCT. One had wide parametrium invasion and both vascular and lymphatic invasion. The other had a large tumor (>4 cm), parametrium invasion, vascular invasion, and a positive vaginal surgical margin. Although nodal metastasis was the most important prognostic factor, two patients who had pathological nodal metastasis did not receive adjuvant CCT. This was because one had postoperative KPS score = 50, whereas the other was one of the oldest patient treated in 2000 and adjuvant CCT was not performed for elderly patients at that time. Therefore, they were treated with S + ART without CCT. All of the patients treated with these aggressive modalities completed the treatment without delay, but three of them (37.5%) experienced Grade 3 acute toxicity during and soon after the completion of RT. These results indicate that these aggressive modalities are not always safe in terms of

acute toxicity. As for late toxicity, although the median follow-up was shorter, Grade 3 late toxicity was experienced by 2 of 40 (5%) patients, and no Grade 4 or higher late toxicity was experienced in our study. Several authors reported that the occurrence rates of Grade 3 or greater late morbidities were less than approximately 10%, and our results are compatible with those of previous reports [12, 13, 28, 29]. However, we should emphasize that Grade 3 late toxicity was only experienced in patients treated with the more aggressive modalities (RRT with CCT: 1, S + ART: 1). Aggressive modalities may be tolerable for patients with a good performance status, but they can easily cause severe acute or late toxicity compared with RRT alone. Considering these results, when aggressive treatment modalities are performed in elderly patients, management of both acute and late toxicity is very important to avoid delay or cancellation and to maintain quality of life. The finding that patients with KPS scores >70 can tolerate aggressive modalities with appropriate management, whereas those with KPS scores <50 may not tolerate even RRT alone, is also very important. KPS should be considered as one of the determinants in selecting a treatment modality for elderly patients.

In conclusion, the number of elderly patients with cervical cancer is increasing, and RRT provides good survival outcomes with acceptable toxicity. However, indications for the use of more aggressive modalities should be assessed carefully, even for patients who are in quite good health. Therefore, to establish appropriate treatment strategies, including combinations of RT with less invasive surgery and/or chemotherapy, larger studies and prospective studies should be performed. Finally, better survival outcomes and preservation of the quality of life may be achievable for the growing elderly population.

Conflict of interest We declare that we have no conflict of interest.

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