Arch Gynecol Obstet (2011) 284:1007–1014
DOI 10.1007/s00404-010-1777-6

GYNECOLOGIC ONCOLOGY

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

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Received: 5 August 2010 / Accepted: 11 November 2010 / Published online: 30 November 2010

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 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].

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

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

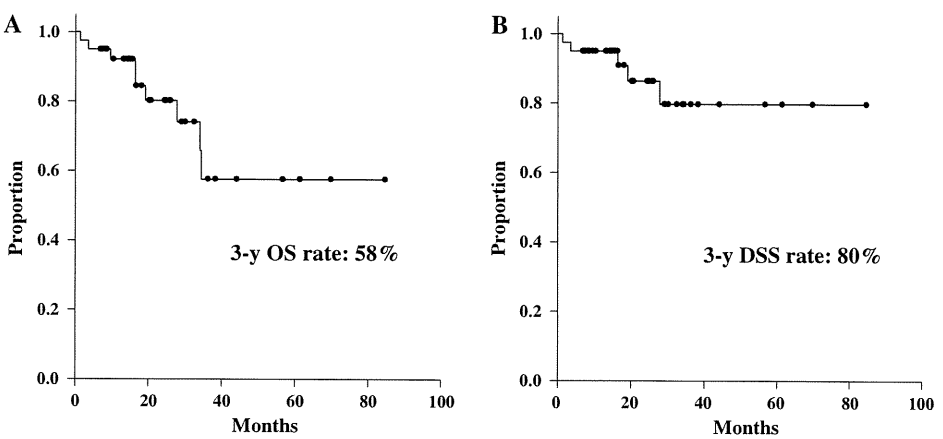

Fig. 1 Preliminary overall and disease-specific survival (OS and DSS) rates for all patients ($n = 40$) using the Kaplan–Meier method with a median follow-up of 20 months (range 1–85 months). The 3-year OS and DSS rates were 58% (**a**) and 80% (**b**), respectively

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

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

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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Breast Cancer
DOI 10.1007/s12282-012-0345-2

ORIGINAL ARTICLE

Long-term outcome of hypofractionated radiotherapy to the whole breast of Japanese women after breast-conserving surgery

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Received: 29 November 2011 / Accepted: 30 January 2012

Abstract
Background In Japan, there are still no reports of long-term outcome for hypofractionated radiotherapy to the whole breast after breast-conserving surgery (BCS). We report our institution's results from evaluation of the efficacy and safety of hypofractionated radiotherapy for Japanese women.
Methods Data in the medical records of 327 patients were retrospectively reviewed. The patients were treated with hypofractionated radiotherapy between January 2003 and December 2006 at the Kawasaki Medical School Hospital and were followed for more than 3 years. The median age was 54 years old (the age range was 28–80 years). The whole breast was irradiated with a total dose of 42.56 Gy/16 fx with boost irradiation to positive margins. Adjuvant therapy consisted of chemotherapy and/or hormone therapy and was administered to 300 patients, based on their stage or pathological findings.
Results Follow-up periods ranged from 21 to 92 months; the median follow-up period was 60 months. At 5-year follow-up, overall survival, cause-specific survival, relapse-free survival, and local control were 96.0, 97.5, 95.3, and 99.7% respectively. Grade 2 radiation pneumonitis occurred in five patients. Grade 2 radiation dermatitis occurred in 17 patients. Severe late complications were not observed.
Conclusions In our study, hypofractionated radiotherapy led to good results without severe toxicity. We believe hypofractionated radiotherapy after BCS is safe and efficient treatment for Japanese women.

Keywords Breast cancer · Breast-conserving surgery · Hypofractionated radiotherapy

Introduction

Breast-conserving therapy, consisting of breast-conserving surgery (BCS) followed by whole breast irradiation, is an established standard treatment for patients with early breast cancer [1–10]. In Japan, a fraction dose of 1.8–2 Gy and a total dose of 45–50 Gy are usually applied in the postoperative setting with or without additional boost irradiation of the excision site. In late years, alternative hypofractionated radiotherapy (e.g., 42.56 Gy/16 fx, 41.6 Gy/13 fx, 40 Gy/15 fx) has been reported to be feasible and acceptable [11–17] and is becoming popular as a convenient regimen. There are few reports of long-term results of hypofractionated radiotherapy for Japanese women. Morbidity of breast cancer is lower in Japan than in Europe and the United States. In addition, large breasts are more common in Europe and the United States than in Japan. Therefore, an original survey is needed to investigate the

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Published online: 22 February 2012

efficacy and safety of hypofractionated radiotherapy for Japanese women. We introduced hypofractionated radiotherapy after BCS as practical clinical treatment in 2003. We retrospectively investigate and describe the long-term results in this article.

Patients and methods

Patient selection

In our institution, since January 2003, all patients planned to receive postoperative radiotherapy after BCS were informed about the merits and demerits of two regimens, 50 Gy/25 fx (conventional regimen) and 42.56 Gy/16 fx (hypofractionated regimen), on the basis of published data [14]. The choice was entrusted to each patient, and more than 95% of patients selected the hypofractionated regimen, and gave written informed consent. Therefore, 910 patients were treated with the hypofractionated regimen from January 2003 to September 2010. Patient data in the medical records were retrospectively reviewed. Eligibility criteria for this analysis were:

1 treated with BCS followed by whole-breast hypofractionated radiotherapy consisting of 42.56 Gy in 16 fractions with or without boost irradiation to the tumor bed;
2 patients with early-stage breast cancer of pStage0-IIB; and
3 follow-up period of more than 3 years after the completion of radiotherapy.

To avoid statistical complexity, exclusion criteria were:

1 lost to follow-up within 3 years ($n = 16$);
2 died of other disease within 3 years without recurrence of breast cancer ($n = 3$);
3 simultaneous bilateral breast cancer ($n = 7$);
4 history of breast cancer ($n = 13$);
5 induction chemotherapy ($n = 5$); and
6 incomplete radiotherapy ($n = 2$).

As a result, 327 patients were included in this retrospective analysis. Patient characteristics are summarized in Table 1.

Table 1 Clinical, tumor, and treatment characteristics

Clinicopathologic characteristic	*n*
Age	28–80 (median 54)
<50/≥50	115/212
PS	
0-1/2/3≥	325/2/0
Surgery	
Bp or Bq only/SNB/Ax	29/117/181
Bp/Bq/Tm	185/142/0
Chemotherapy	
Yes/no	109/218
Hormone therapy	
Yes/no	261/66
pT stage	
is/1/2/3	29/206/91/1
pN stage	
0/1	261/66
pStage	
Stage 0	29
Stage I	164
Stage II A	107
Stage II B	27
Histology	
DCIS	28
IDC	268
Special types	29
Unclassified or NA	2
Margins	
Positive/negative	66/261
ER and/or PgR*	
Positive/negative/NA	253/38/36
HER2	
Positive/negative/NA	30/252/45

Ax axillary dissection; *Bp* wide excision; *Bq* quadrantectomy; *CR* complete response; *DCIS* ductal carcinoma in situ; *ER* estrogen receptor; *IDC* invasive ductal carcinoma; *NA* not available; *PgR* progesterone receptor; *SNB* sentinel node biopsy; *Tm* tumorectomy

* The definition of hormone-receptor positive is that one or both of ER or PgR receptor is positive

Surgery

All patients received BCS: wide excision (Bp) in 185 patients and quadrantectomy (Bq) in the other 142. No patient received tumorectomy (Tm). If cancer cells remained within 5 mm from the surgical margin, the specimen was defined as "stump-positive." In this study, 66 patients had positive margins at final pathological examination. 181 patients underwent level I/II axillary lymph nodes dissection. 117 patients underwent sentinel node biopsy (SNB) alone. Twenty-nine patients received no axillary surgery.

Radiotherapy

Techniques of radiotherapy, except for dose fractionation, were as same as for traditional methods. Patients were treated with external beam radiotherapy to the whole breast, using tangential fields with 4–6 MV photons. The field border was determined in the following way: the inferior border was located 1–2 cm below the

inframammary fold; the superior border, at the height of the suprasternal notch; the medial border, at the midsternal line; and the lateral border, at the mid-posterior axillary line. The anterior margin was located at least 2 cm from the surface of the breast and the posterior margin was maintained with a gantry-tilting technique to limit the maximum lung depth included in the field to 3 cm or less. A total dose of 42.56 Gy/16 fr was prescribed generally at the isocenter and, when necessary, wedge filters and/or the field-in-field technique were used to optimize dose homogeneity. The objective of optimization was to keep the minimum dose in the deep part of the breast no less than 95% and to limit the maximum dose within the breast to no more than 107% of the prescribed dose. For positive margins, additional boost irradiation of 10–13.3 Gy/4–5 fractions (using 4–11 MeV electrons) was administered to the excision site.

Adjuvant therapy

Any limitation of adjuvant therapy was not made in association with the hypofractionated radiotherapy. Adoption of adjuvant therapy depended on attending surgeon, and chemotherapy and/or hormone therapy were selected according to commonly-accepted criteria based on pathological stage or histological findings. 300 patients received adjuvant systemic therapy. Chemotherapy involved various combinations of the following drugs: cyclophosphamide, adriamycin, 5-fluorouracil, methotrexate, epirubicin, paclitaxel, docetaxel, tegaful-uracil, and doxifluridine. Chemotherapy was administered sequentially (not concurrently) with radiotherapy. Hormone therapy involved the following drugs: anastrozole, exemestane, tamoxifen, toremifene citrate, leuprorelin, goserelin, and letrozole. Hormone therapy was generally maintained from 2 to 5 years after the completion of radiotherapy.

Follow-up and patient evaluation

Patients were seen at least once a week during radiotherapy and at 1 month after completing radiotherapy. They were then seen every 3 months for 3 years. After 3 years, they were seen annually. At each visit, physicians recorded a history and performed a physical examination (mainly skin reaction and respiratory symptoms related to radiotherapy). A chest X-ray was taken before a radiotherapy session, and then at each follow-up visit during the first year. From the second year they had a routine chest X-ray semi-annually. When X-ray films or physical symptoms suggested radiation pneumonitis, more frequent X-ray tests or computed tomography (CT) were considered. Bilateral mammography, bone scan, and abdominal ultrasonography were performed annually. Radiation dermatitis and radiation pneumonitis were evaluated by use of the Radiation Therapy Oncology Group (RTOG)-acute radiation morbidity scale scoring criteria and the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer (RTOG/EORTC) late radiation morbidity scoring scheme [18].

Statistical analysis

The survival time was calculated from the date of surgery. Survival curves and actuarial rates of recurrence were calculated using Kaplan–Meier method, and the significance of prognostic factors was assessed by log rank test [19]. Multivariate analysis was performed using stepwise Cox proportional hazard regression models [20]. A $P < 0.05$ between groups was considered significant. Stat View (version 5.0) software was used for all statistical analysis.

Results

Median follow-up period was 60 months. Of 327 patients, 14 patients died; 9 died of breast cancer and 5 died of other causes. Recurrence was observed in 15 patients. Of these patients, 14 developed distant metastases (bone, brain, lung, liver). Local recurrence in the ipsilateral breast was observed in one patient only, who was salvaged by mastectomy. Metachronous contralateral breast cancer occurred in four patients (one patient also had distant metastases).

Figure 1 shows overall survival (OS), cause-specific survival (CSS), relapse-free survival (RFS), and the local control (LC). Actuarial 5-year OS, CSS, RFS and LC were 96.0, 97.5, 95.3 and 99.7%, respectively. Figure 2 shows

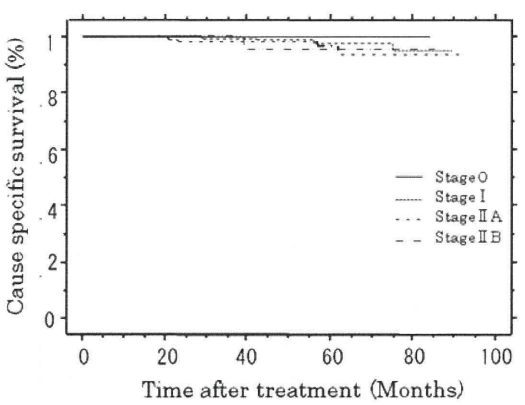

Fig. 1 Survival graphs showing overall survival, cause-specific survival, relapse-free survival, and local control ($n = 327$)

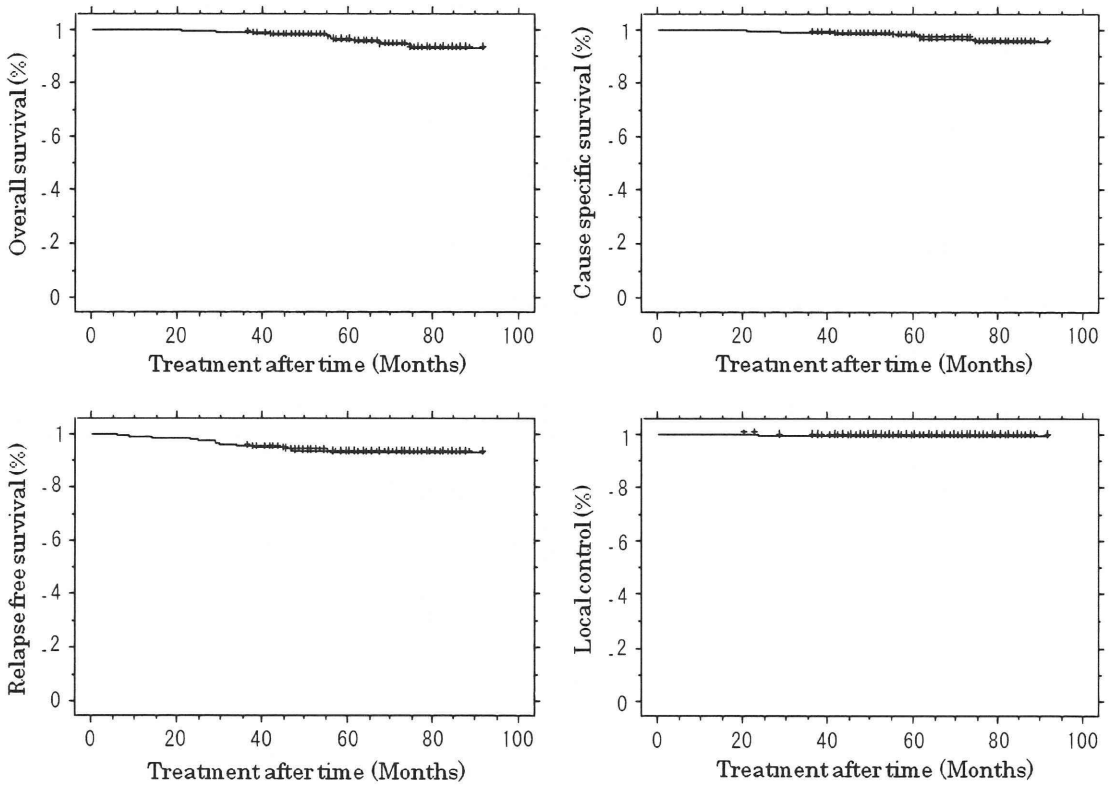

Fig. 2 Cause-specific survival of 327 patients at each pStage. The patients were divided by stage, as follows: stage 0, 29 patients; stage I, 164 patients; stage IIA, 107 patients; and stage IIB, 27 patients

5-year CSS for each stage. Actuarial 5-year CSS for each stage were: stage 0, 100%; stage I, 97.7%; stage IIA, 96.7%; and stage IIB, 96.3%.

Table 2 summarizes the relationship between RFS and other variables. Univariate analysis indicated that hormone therapy ($P = 0.0009$; HR 4.75; CI 1.72–13.10) was a significant prognostic factor for RFS. Multivariate analysis, using stepwise selection, similarly showed that hormone therapy ($P = 0.0027$; HR 4.71; CI 1.71–13.01) was a significant prognostic factor for RFS in this study.

Radiotherapy-induced dermatitis was observed for 268 patients (251 patients with grade 1, 17 with grade 2). Most patients did not need treatment for their dermatitis, but some were given appropriate drugs (e.g., an ointment or a steroid-containing cream). Two to six months after the completion of radiotherapy, 16 patients developed radiation pneumonitis (11 patients with grade 1, five with grade 2). No patients had radiation pneumonitis of grade 3 or higher. In addition, two patients were diagnosed with bronchiolitis obliterans organizing pneumonia (BOOP). They received treatment with prednisolone and the symptoms improved. Concerning late toxicity, we observed no patients with grade 2 or higher toxicity.

Discussion

Hypofractionated radiotherapy to the whole breast after BCS is an alternative to radiotherapy with conventional fractionation. In Japan, however, there are no studies that report the long-term outcome of hypofractionated radiotherapy, and in fact, it is still less common. We previously reported preliminary results of the hypofractionated regimen [21]. At a median follow-up of 26 months, we obtained good results for OS, CSS, DFS, and LC. The objective of this study was to update our previous findings, after long-term observation.

Our current study shows acceptable results (with regard to OS, CSS, RFS, and LC); in Table 3 these are compared with those from other studies that used a hypofractionated or conventional regimen [14, 17, 22, 23]. The high LC is particularly notable. We believe there are two main reasons for this. First, all patients in this study received either Bp or Bq. Veronesi et al. [4, 24] reported that annual local recurrence was low for patients treated with Bq + radiotherapy (RT) whereas it was significantly higher for patients treated with Tm + RT. Another reason may be the definitions of "margin-free." In Japan, the definition of "stump-positive" is that cancer cells remain within 5 mm

Table 2 Characteristics of 327 breast cancer patients listed by the number of patients at risk, number of relapses, relapse-free survival, log rank test, Cox-regression, and specific hazard risk (HR)

Factor	No. of patients	No. of relapses	Relapse-free survival (5 years) (%)	*P*-value (log rank)	HR (CI 95%)†	*P* value (Cox-regression)	HR (CI 95%)††
Age							
<50	115	2	98.3		0.28 (0.06–1.24)		0.28 (0.06–1.25)
≥50	212	13	93.7	0.07	1.0 (reference)	0.09	1.0 (reference)
Bp or Bq	29	1	96.6		0.68 (0.08–5.67)		
+SNB	117	6	94.6		1.0 (reference)		
+Ax	181	8	95.5	0.92	0.85 (0.30–2.48)		
Chemotherapy							
Yes	109	7	93.5		1.0 (reference)		
No	218	8	96.2	0.26	0.56 (0.21–1.57)		
Hormone therapy							
Yes	261	7	97.3		1.0 (reference)		1.0 (reference)
No	66	8	87.4	0.0009	4.75 (1.72–13.10)	0.0027	4.71 (1.71–13.01)
PN stage							
0	261	11	95.7		0.69 (0.22–2.17)		
1	66	4	93.8	0.52	1.0 (reference)		
Margins							
Positive	66	5	92.3		1.0 (reference)		
Negative	261	10	96.0	0.18	0.49 (0.17–1.43)		
ER and/or PgR*							
Positive	253	11	95.5		1.0 (reference)		
Negative	38	4	89.5	0.09	2.59 (0.83–8.14)		
HER2*							
Positive	30	3	90.0		1.0 (reference)		
Negative	252	11	95.5	0.17	0.42 (0.11–1.51)		

For other abbreviations, see Table 1

* Some data are missing

† Univariate analysis

†† Multivariate analysis using Cox proportional hazard regression

Table 3 Comparison of our data with published data

Ref.	Patients	Operation type	RT dose/fraction	Overall survival	Local recurrence
Lyon [22]	1,024	Bp	50 Gy/25 fr	99% (4 years)	4.5% (4 years)
			50 Gy/25 fr + boost	99% (4 years)	3.5% (4 years)
EORTC [23]	5,318	Tm	50 Gy/25 fr	87% (5 years)	7.3% (5 years)
			50 Gy/25 fr + boost	91% (5 years)	4.3% (5 years)
OCOG trial [14]	622	Tm	42.56 Gy/16 fr	97.2% (5 years DFS)	3.4% (5 years)
START B trial [17]	1,110	BCS or Bt	40 Gy/15 fr ± boost	92% (5 years)	2.2% (5 years)
Our data	327	Bp or Bq	42.56 Gy/16 fr ± boost	96.0% (5 years)	0.3% (5 years)

Bt mastectomy; *fr* fraction; for other abbreviations, see Table 1

of the surgical margin; this is a more rigid criterion than that widely used in other countries. In our study, 66 patients had positive stumps and received additional boost irradiation. Several studies report that additional boost irradiation of the tumor bed after BCS reduced local recurrence irrespective of the stump status [4, 5, 7, 22, 23]. Therefore, the fact that many patients in our series received additional boost irradiation based on the rigid criterion may have resulted in good LC. Furthermore, our boosted dose of 13.3 Gy/5 fx seems relatively high, although the

appropriate dose of boost irradiation has not been established. These factors may be responsible for low local recurrence.

Radiation dermatitis and pneumonitis after breast-conserving therapy in our institution has been surveyed previously. Yoden et al. [25] reported the incidence of this toxicity for patients treated with conventional regimen and Fujii et al. [21] reported it for patients treated with hypofractionated regimen. They reported similar results, and the results from this study are compatible with these two reports. Irradiation of the breast using a hypofractionated schedule may cause more severe skin telangiectasia, fibrosis, or indurations, which worsens the final cosmetic outcome. Two randomized trials proved, by long-term observation, there was no difference in cosmetic outcomes between conventional and hypofractionated regimens [14, 15, 17]; our study also obtained satisfactory results for late toxicity. The follow-up period of this study may not be long enough to clarify late toxicity, because it is known that occurrence and grade of late toxicity increase in proportion to the time from completion of radiotherapy. Longer follow up is needed.

The purpose of this study was to prove the efficacy and safety of hypofractionated radiotherapy after BCS in Japanese women. In conclusion, we observed acceptable local control and survival without severe late toxicity after 5 years in our retrospective study. Although cosmetic outcomes must be clarified with longer follow up, we believe that this hypofractionated regimen can be used as practical clinical treatment. We believe that widespread of hypofractionated radiotherapy after BCS will help to reduce financial and temporal burdens on patients, and also help to accommodate the exponentially increasing number of cancer patients needing radiotherapy.

Conflict of interest None.

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Radiotherapy and Oncology 103 (2012) 25–31

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Proton RT in pancreatic cancer

A phase I/II study of gemcitabine-concurrent proton radiotherapy for locally advanced pancreatic cancer without distant metastasis ☆

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ARTICLE INFO

Article history:
Received 20 August 2011
Received in revised form 15 December 2011
Accepted 20 December 2011
Available online 31 January 2012

Keywords:
Proton radiotherapy
Gemcitabine
Pancreatic cancer
Locally advanced
Chemoradiotherapy

ABSTRACT

Purpose: We conducted the study to assess the feasibility and efficacy of gemcitabine-concurrent proton radiotherapy (GPT) for locally advanced pancreatic cancer (LAPC).
Materials and methods: Of all 50 patients who participated in the study, 5 patients with gastrointestinal (GI)-adjacent LAPC were enrolled in P-1 (50 Gy equivalent [GyE] in 25 fractions) and 5 patients with non-GI-adjacent LAPC in P-2 (70.2 GyE in 26 fractions), and 40 patients with LAPC regardless of GI-adjacency in P-3 (67.5 GyE in 25 fractions using the field-within-a-field technique). In every protocol, gemcitabine (800 mg/m^2/week for 3 weeks) was administered concurrently. Every patient received adjuvant chemotherapy including gemcitabine after GPT within the tolerable limit.
Results: The median follow-up period was 12.5 months. The scheduled GPT was feasible for all except 6 patients (12%) due to acute hematologic or GI toxicities. Grade 3 or greater late gastric ulcer and hemorrhage were seen in 5 patients (10%) in P-2 and P-3. The one-year freedom from local-progression, progression-free, and overall survival rates were 81.7%, 64.3%, and 76.8%, respectively.
Conclusion: GPT was feasible and showed high efficacy. Although the number of patients and the follow-up periods are insufficient, the clinical results seem very encouraging.
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The prognosis of pancreatic cancer is poor, with a five-year survival rate of about 5% in total [2]. Only radical surgical resection has been shown to cure the condition, although the five-year survival rate remains low at about 10–20%. And only 15–20% of all patients with pancreatic cancer can be treated by resection, while the other patients cannot undergo resection because of local invasion or distant metastasis at diagnosis [4,9].

For the treatment of non-resectable pancreatic cancers, chemoradiotherapy (CRT) with concurrent 5-fluorouracil (5-FU) is historically considered the standard therapy for locally advanced pancreatic cancer (LAPC) [6,18,26]. Recently, based on a background of favorable results of gemcitabine-based chemotherapy [1,9], and the fact that gemcitabine is a potent radio-sensitizer [16], many studies on gemcitabine-concurrent CRT have been performed for LAPC [7,17,20,24], and indicate the possibility of an improvement in survival. These studies have shown that reduction of the irradiation doses and target fields was necessary when gemcitabine was administered at or near the full dose (1000 mg/m^2). In contrast, a reduction of the gemcitabine dose was needed when irradiation was administered at doses over 50 Gy, which is necessary for the local control of malignant tumors. The reason for these restrictions of the chemoradiotherapy was speculation that the region of gastrointestinal (GI) tract located near the pancreas was irradiated beyond tolerable doses. Consequently, we thought that proton beam radiotherapy could deliver higher dose above 50 Gy concurrently with a higher dose of gemcitabine to a larger field containing the draining and paraaortic lymph nodes and peripheral regions surrounding the celiac artery and superior mesenteric artery.

Radiotherapy using protons or carbon-ions is currently attracting worldwide interest because of its physical properties including superior dose distribution to a target, which allows selective irradiation to the tumor, while minimizing irradiation of the surrounding normal tissues [10,15,25]. In our pilot study, proton beam radiotherapy alone was performed at doses of 40 and 50 GyE for patients with LAPC between November 2004 and October 2006 [12]. Although local control and survival did not reach significance in

☆ This study has not been presented previously.

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doi:10.1016/j.radonc.2011.12.029

comparison with other treatments, such as chemotherapy alone or CRT, we confirmed the feasibility and safety of proton radiotherapy. Based on this pilot study, we started gemcitabine-concurrent proton radiotherapy (GPT) for LAPC to assess the feasibility and efficacy of this regimen. To our knowledge, this is the first report on the clinical use of concurrent gemcitabine and proton radiotherapy for the treatment of pancreatic cancer.

Patients and methods

Patient eligibility

Patients with LAPC which was defined as borderline resectable cancer and unresectable cancer without distant metastases [28], that was cytologically or histologically confirmed to be adenocarcinoma, with an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, and were in adequate physical condition to tolerate chemotherapy were eligible for this study. Patients with a history of abdominal radiotherapy or previous treatment of pancreatic tumor were excluded.

All patients provided written informed consent prior to enrollment. The study was approved by the institutional review board and registered on the University Hospital Medical Information Network Clinical Trials Registry (UMIN-CTR, http://www.umin.ac.jp/ctr, UMIN ID: UMIN000002173).

Pretreatment workup

At baseline, all patients underwent an abdominal contrast-enhanced computed tomography (CT) scan, chest CT scan, positron emission tomography with ^{18}F-fluorodeoxy glucose (FDG-PET), and gastrointestinal fiberscopy (GIF) and were assessed for tumor markers (CA19-9, CEA, DUPAN-2, and SPAN-1). The disease was staged according to the International Union Against Cancer (UICC) TNM staging system, 6th edition.

Treatment regimen

Concurrent and adjuvant chemotherapy

In all protocols, all patients were scheduled to receive intra-venous infusion of gemcitabine (800 mg/m^2) for 30 min for the initial 3 weeks (days 1, 8, and 15) during 5 weeks of proton radiotherapy. We determined the dose of gemcitabine according to the studies by Casper et al. [3] and Burris et al. [1], and the schedule according to the study by Murphy et al. [20]. Gemcitabine was administered if the absolute granulocyte count was >2000/mm^3 and the platelet count was >70000/m^3 on the scheduled day.

Following GPT, all patients received systemic gemcitabine-based chemotherapy for as long as possible.

Proton radiotherapy

Hyogo Ion Beam Medical Center (HIBMC) treats patients with both proton and carbon-ion beams. We decided to use proton therapy for this study, because proton beams can be delivered to the target from any direction by using a rotating gantry so that irradiation of the GI tract is minimized. However, a rotating gantry is not available for carbon ion therapy. Furthermore, we anticipated that the administration of gemcitabine would have a sensitizing effect on proton therapy, as previously shown in human pancreatic cancer cells [5].

The patients were treated with 150–210 MeV proton beams. A respiratory gating system was used for all patients to irradiate the beam during the exhalation phase. Patient set-up was performed daily by subtraction of the 2 sets of orthogonal digital radiographs before irradiation. The translation and rotation of the patient detected by the positioning system were compensated for by adjustment of the treatment couch. The setup was continued until the bony landmarks on the digitally reconstructed radiographs agreed within 1 mm. The biologic effects of proton therapy at our institution were evaluated in vitro and in vivo. The relative biologic effectiveness (RBE) values were determined to be 1.1 by biologic experiments [11]. Because all tissues are assumed to have almost the same RBE, doses expressed in GyE are directly comparable to photon doses.

Treatment planning

Proton beam treatment plans were developed using a CT-based 3-dimensional treatment planning system. The gross tumor volume (GTV) was defined as the primary tumor plus the apparent lymph nodes as determined by a fusion contrast-enhanced CT subsidiary using FDG-PET. The clinical target volume (CTV) comprised the addition of a 5-mm margin to the GTV and prophylactic irradiation regions containing the draining lymph nodes and paraaortic lymph nodes as well as peripheral regions surrounding the celiac artery and superior mesenteric artery. We defined the CTV to contain the prophylactic region because metastases to regional lymph nodes have been recognized as prognostic factors in some studies of CRT [8] and resection [23,27] for LAPC. The planning target volume (PTV) was defined as the CTV plus a setup margin (5 mm) and a respiratory gating margin (1–5 mm), which was measured on CT images between inspiratory and expiratory phases. In general, the stomach, small bowel including the duodenum, kidneys, and spinal cord were defined as organs-at-risk (OAR). The dose restrictions for stomach, duodenum, and spinal cord were approximately 50 GyE, 50 GyE, and 45 GyE, respectively [13,14]. Additionally, we planned the irradiated volumes of the stomach, duodenum, and kidneys to be as small as possible.

Dose-fractionation

A total of 3 protocols were used in this study. In the early phase of the study, 2 protocols were used contemporaneously; protocol P-1 (50 GyE in 25 fractions) was used for patients with GI-adjacent LAPC, and P-2 (70.2 GyE in 26 fractions) was used for those with non-GI-adjacent LAPC. The non-GI-adjacent LAPC were defined as tumors that could be treated with irradiation plans that covered the GTV: over 95% of the prescribed dose in P-2 (70.2 GyE), which kept the dose administered to the GI-tract under 50 GyE. The others were defined as GI-adjacent LAPC who were treated with P-1. After the early phase, all patients were treated with protocol P-3 (67.5 GyE in 25 fractions) using the field-within-a-field technique.

In P-1, a total dose of 50 GyE was delivered in 25 fractions over 5 weeks to the PTV, based on our pilot study [12] and the report of 5-FU-concurrent CRT [19], in which irradiation doses of 39.6–50.4 Gy did not result in any late GI toxicity. In P-2, 70.2 GyE in 26 fractions over 6 weeks was delivered to the PTV. This approach was designed based on our experiences in treating head and neck cancers and lung cancer as well as other tumors, in which 70.2 GyE in 26 fractions was employed after dose escalation from 65 GyE in 26 fractions [21].

In P-3, 67.5 GyE in 25 fractions over 5 weeks was delivered using the field-within-a-field technique. With this technique, we used three types of split doses: 2 + 0.7 GyE, 1.8 + 0.9 GyE, and 1.6 + 1.1 GyE. For example, we delivered 1.8 GyE to the whole PTV (Fig. 1a) and 0.9 GyE to the PTV excluding the GI tract including stomach, small bowel, and large bowel, in one fraction (Fig. 1b). Consequently, a maximum dose of 2.7 GyE was administered as a single fraction (total 67.5 GyE) to the majority of the PTV (Fig. 1c), in parallel with limiting the dose to the GI tract to approximately

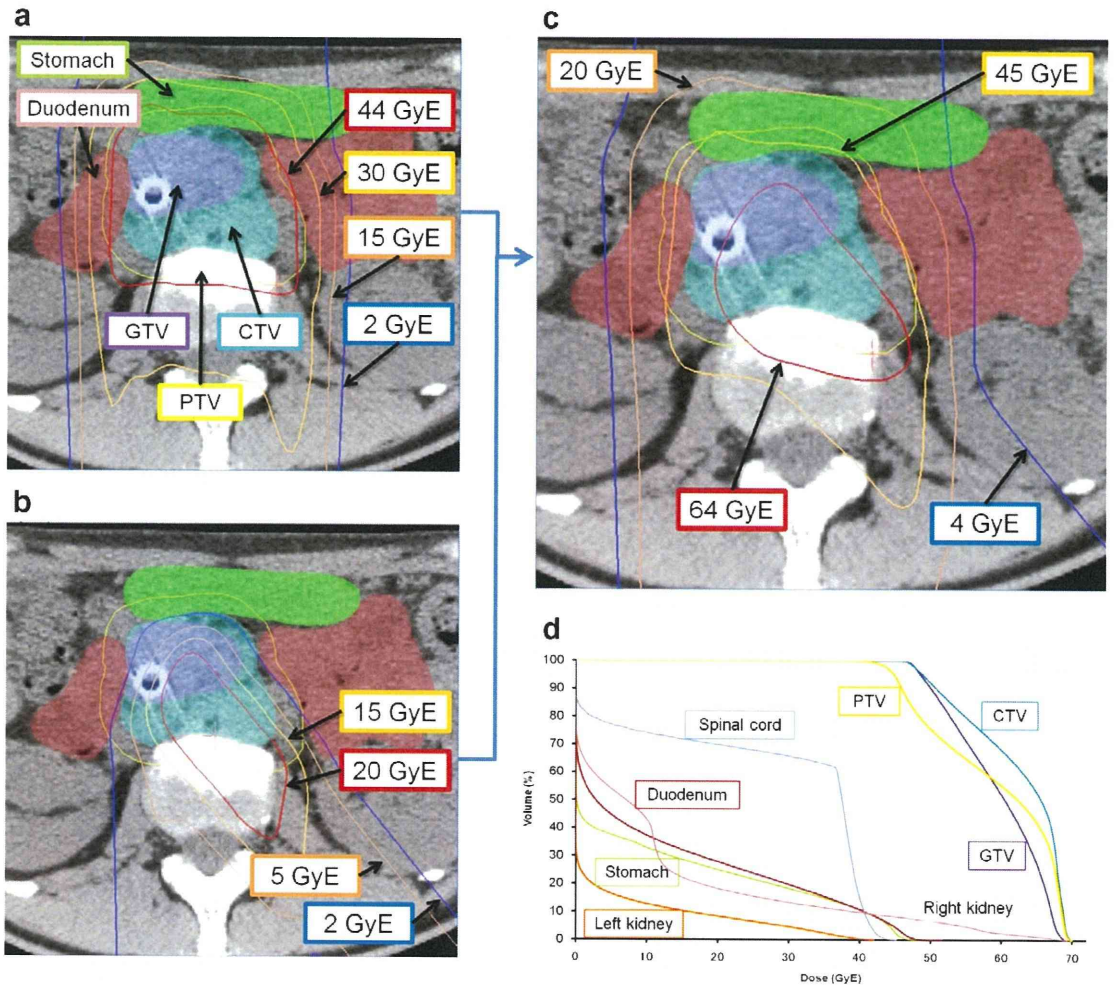

Fig. 1. A representative patient with locally advanced pancreatic cancer that was adjacent to the GI tract, treated with the gemcitabine-concurrent proton therapy (GPT) under protocol-3 (using the field-within a-field technique). (a) Dose distribution of the proton beam only at 1.8 GyE per fraction. A total dose of 45 GyE, which was the minimal dose administered to the PTV, was administered to the entire PTV. (b) Dose distribution at 0.9 GyE per fraction. A total dose of 22.5 GyE was irradiated to the PTV except for the GI tract (stomach and duodenum). (c) Summation of 1.8 GyE and 0.9 GyE in daily fractions. A total dose of 67.5 GyE was administered as the maximum dose, while the stomach and duodenum were only irradiated with approximately 45 GyE. (d) The dose–volume histogram of this plan for gross tumor volume (GTV), clinical target volume (CTV), planning target volume (PTV), and the organs-at-risk (stomach, duodenum, bilateral kidneys, and spinal cord).

1.8 GyE (total 45 GyE). With this technique, it became possible to treat all patients with the P-3 protocol alone, independent of GI-adjacency.

Follow-up

All patients received abdominal contrast-enhanced CT every three months and tumor marker monitoring every month after GPT. GIF was performed at the end of the GPT and every three-months thereafter to evaluate GI toxicity. Toxicity was assessed using the Common Terminology Criteria for Adverse Events (CTCAE) v3.0.

Comparison of the protocols

To clarify the characteristics and effectiveness of the field-within-a-field technique, we analyzed the treatment plans for proton therapy using a dose-volume histogram (DVH) and compared P-3 with P-1 and P-2 in terms of $D_{80\%}$, $D_{50\%}$, and $D_{20\%}$ ($D_{x\%}$ indicates the dose delivered to $x\%$ of the target volume) of the GTV, CTV, and PTV, as well as D_{max} (a maximum dose to the target) of the stomach and duodenum.

Evaluation of local control

As the radiographic changes caused by the GPT were not significant, local control was judged comprehensively by changes in the maximum tumor diameter, the inner density on contrast-enhanced CT, the levels of tumor markers including CA19-9 and CEA, which are particularly useful for pancreatic cancer [29], and the accumulation on FDG-PET. We conclusively defined local progression as radiographic enlargement of the primary tumor or locoregional recurrence or tendency to increase in tumor markers for at least three months without any distant metastases.

End points and statistical analysis

The primary end points were feasibility and toxicity, and the secondary end points were freedom from local progression (FFLP), progression-free survival (PFS), and overall survival (OS). These were estimated from the date of the GPT initiation to the date of the event or the last follow-up.

The FFLP, PFS, and OS rates were calculated using the Kaplan–Meier method. Unpaired Student's *t*-test was used to compare parameters of dose–volume histograms between the protocols.

Statistical analyses were carried out with SPSS Version 17.0 software (SPSS, Chicago, Illinois, USA).

Role of funding source

The sponsors of the study did not play any role in the study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Patient and tumor characteristics

A total of 50 eligible patients with LAPC were enrolled in this study between February 2009 and August 2010. Five patients were enrolled in P-1, 5 in P-2, and 40 in P-3. The patient characteristics are summarized in Table 1.

The analyses of proton therapy performed using the dose–volume histogram (DVH) are shown in Table 2. When compared between P-1 (for non-GI-adjacent LAPC) and P-3 using Student's *t*-test, all of the parameters, except $D_{80\%}$ of the PTV, were significantly higher in P-3 than in P-1, even though P-3 included many patients with GI-adjacent LAPC. The comparison between P-2 and P-3 did not detect any significant difference. We could not find a significant difference for D_{max} of the stomach among P-1, P-2, and P-3. While there was a possibility that bias of tumor location (all 5 patients in P-2 had tumors in the body/tail of the pancreas) and tumor size (apparently smaller in P-2 than P-3) affected to the statistical result, the mean dose of D_{max} to the duodenum in P-3 was significantly lower than in P-2. These findings support the superiority of the field-within-a-field technique.

Adjuvant chemotherapy

Among 50 patients, 45 patients (90%) were able to continue adjuvant systemic gemcitabine-based chemotherapy after GPT. Five patients (10%) failed because of unacceptable toxicity of the adjuvant chemotherapy or rapid disease progression.

Feasibility and toxicity

P-1 and P-2 protocols

All 5 patients completed the scheduled GPT in P-1. Four patients completed treatment in P-2; 1 patient (20%) could not complete proton therapy at 62.1 GyE in 23 fractions due to gastric bleeding caused by acute radiation mucositis and was cured by medication only. There was no late toxicity in that case. In P-1 and P-2, hematologic toxicities were tolerable. The acute and late toxicities in all protocols are summarized in Table 3.

P-3 protocol

Of the 40 patients in P-3, 5 patients (13%) could not receive the third gemcitabine administration because of acute hematologic and GI toxicities. The most common toxicities were neutropenia, anorexia, and weight loss (Table 3).

The major late toxicities were gastric hemorrhage and ulcer. Late gastric ulcer with hemorrhage of grade 3 or greater was observed in 4 (10%) of 40 patients. All of them had pancreatic cancer arising in the body/tail of pancreatic region. Among these 4 patients, 3 patients (8%) were cured with medication (grade 3), but 1 patient (3%) died of gastric hemorrhage six months after GPT (grade 5). This death might have been related to the GPT because gastric ulcer and erosion were confirmed by GIF on the posterior wall of the lower gastric body 2 weeks prior to death. This patient had received the maximum dose of 52 GyE to the stomach.

Local control, distant metastases and survival

The one-year FFLP, PFS, and OS rates for all patients were 81.7% (95% CI: 65–99%), 64.3% (95% CI: 48–81%), and 76.8% (95% CI: 64–89%), respectively (Figs. 2 and 3), and 79.9% (95% CI: 58–100%), 60.8% (95% CI: 41–80%), and 78.8% (95% CI: 65–93%), respectively for patients treated with P-3. Of all 50 patients, local progression developed in only 4 patients (8%), while distant metastasis developed in 15 patients (30%), within one year. Frequent sites of distant metastasis were the liver in 9 patients (18%), lung in 1 patient (2%), and the peritoneum in 3 patients (6%). Five patients (10%) were already diagnosed with liver metastases at the end of GPT. None of

Table 1
Patient characteristics.

Characteristic	Protocol P-1 ($n = 5$)	Protocol P-2 ($n = 5$)	Protocol P-3 ($n = 40$)
Follow-up time, months			
Median (range)	12.3 (8.2–18.6)	19.6 (17.7–21.5)	12.1 (3.2–22.3)
Age, years			
Median (range)	57 (55–75)	56 (45–72)	64 (49–83)
Gender			
Male	3	2	18
Female	2	3	22
ECOG-PS			
0	2	3	27
1	3	2	10
2	0	0	3
UICC-TNM			
T3N1M0	0	1	4
T4N0M0	1	2	6
T4N1M0	4	2	30
Tumor location			
Head	1	0	18
Body/tail	4	5	22
Tumor size, cm			
Median (range)	4.6 (3.1–5.6)	3.2 (4.5–7.2)	3.7 (2.5–7)
CEA, ng/mL			
Median (range)	3.8 (1–12)	1.6 (1–6)	3 (0.9–16.4)
CA19–9, U/mL			
Median (range)	999 (0–6010)	73.2 (15–731)	185 (0–27600)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; PS, performance status; UICC-TNM, the International Union Against Cancer (UICC) TNM staging system.

sitive to therapeutic megavoltage irradiation. There is no "safe" radiation threshold for megavoltage radiation. Even when the device is not in a radiation field, scatter radiation has the potential to cause malfunction.[13] However, radiation therapy is not absolutely contraindicated in cancer patients with ICPs or ICDs. Radiation therapy can be delivered safely if direct irradiation to the device is avoided, adequate monitoring is done during irradiation. Also essential is close collaboration with the cardiologist and the pacemaker clinic; thorough monitoring of the patient throughout treatment and for a several weeks afterward; and reevaluation of pacing and sensing function after completion of radiotherapy.

In Japan, no national guidelines exist, and most radiotherapy departments have no formal clinical risk-management strategy in place. Therefore, we conducted a prospective national survey of patients with these devices who received radiation therapy. We found that, for 38 (61%) of the 62 study participants, the device dose had not been estimated before radiation therapy. Our previous study on policies concerning the management of patients with ICPs or ICDs treated with radiation therapy showed that only 18 (17%) of 108 institutions had policies for estimating device exposure before radiation therapy.[2] For 35 cases (56%) in the present study, a cardiologist was consulted. However, our previous study showed that only 17% of institutions had policies involving consultation with a cardiologist. Although the study design differed between our current and previous research (i.e., the present study involved prospective registration and a survey of policies used by radiation oncology departments), the risk of ICP/ICD malfunction had been recognized in Japanese radiation oncology departments.

In the present study, one patient who was treated by intensity-modulated radiation therapy to the prostate experienced ICP malfunction, which obviously was distant from the device site. The reason of this malfunction was probably due to neutron contamination. The whole body effects of neutron contamination from high energy beams were well known, so some papers recommended not to treat with an energy > 6 MV to prevent stray neutron emission, a suspected cause of electrical interference.[11] Therefore, it should be recognized that malfunction of an ICP or ICD can occur even when the device is not within the field of radiation therapy. This suggests that malfunctioning of the device is not related to the dose of radiation. In the present study, many institutes estimated absorbed dose of device by DVH. However, estimated dose by DVH was inaccurate in low-dose region.[14] So commissioning of out-of field region is needed if absorbed dose is estimated by DVH. For patients with an ICP or ICD, effective collaboration with a cardiologist is essential, as is thorough patient monitoring during the course of the treatment and for several weeks thereafter, as well as reevaluation of pacing and sensing function after radiotherapy. Recently, image guided radiation therapy (IGRT) became widespread. However, absorbed doses received by ICP or ICD are thought to be higher in IGRT, especially in the use of megavolt cone beam CT. So, enough attention is necessary when patients are treated by IGRT.

For these reasons, appropriate guidelines are proposed herein, which have been authorized by the Japanese Society of Therapeutic Radiation Oncology. Below is a summary of these recommendations.

Patient management before initiation of radiation therapy

1. Inform patients about the possibility of malfunction of an ICD or ICP caused by radiation therapy.
2. Consult a cardiologist to determine whether the patient is pacemaker dependent or non-pacemaker dependent and to assess potential complication that might occur.
3. Inform the radiation oncology department that the patient has and ICP or ICP.
4. Determine whether the generator is located outside the direct, unshielded radiation therapy field.
5. Estimate the cumulative ionizing radiation dose to generator.

Patient management during radiation therapy

1. Check the function of ICPs and ICDs after the first radiation treatment.
2. Keep the device outside the collimated radiation beam during portal imaging.
3. Observe and monitor the patient. All patients should have their pulse and blood pressure measured before and after each treatment. Pacemaker-dependent patients should have continuous ECG monitoring during their first treatment.

Patient management after completion of radiation therapy

1. Full assessment of ICP or ICD function by the cardiologist.

CONCLUSION

A prospective survey of patients with ICPs or ICDs treated with radiation therapy was conducted. As results, only in 50% of patients, the radiation doses absorbed by the ICP/ICD were estimated before radiation therapy. And there was a patient with malfunction of the device outside of the field of radiation. To minimize the risk to patients, precautions must be taken during the planning and administration of radiation therapy. Practical management guidelines have been proposed.

ACKNOWLEDGMENT

This study was supported by a grant from the Japanese