JJCO Japanese Journal of Clinical Oncology

Jpn J Clin Oncol 2013;43(5)547–552
doi:10.1093/jjco/hyt029
Advance Access Publication 8 March 2013

High-dose-rate Intra-cavitary Brachytherapy Combined with External Beam Radiation Therapy for Under 40-Year-old Patients with Invasive Uterine Cervical Carcinoma: Clinical Outcomes in 118 Patients in a Japanese Multi-institutional Study, JASTRO

Hideomi Yamashita[1,*], Yuzuru Niibe[2], Takafumi Toita[3], Tomoko Kazumoto[4], Tetsuo Nishimura[5], Takeshi Kodaira[6], Hidehiro Eto[7], Rumiko Kinoshita[8], Kayoko Tsujino[9], Hiroshi Onishi[10], Mitsuhiro Takemoto[11] and Kazushige Hayakawa[2]

[1]Department of Radiology, University of Tokyo Hospital, Hongo, Tokyo, [2]Department of Radiology and Radiation Oncology, School of Medicine, Kitasato University, Minami-ku, Kanagawa Sagamihara, [3]Department of Radiology, The University of Ryukyus Hospital, Okinawa, [4]Department of Radiology, Saitama Cancer Center, Saitama, [5]Department of Radiation Oncology, Shizuoka Cancer Center, Nagaizumi-cho, Shizuoka, [6]Department of Radiation Oncology, Aichi Cancer Center, Chikusa-ku, Nagoya, [7]Department of Radiology, Kurume University School of Medicine, Asahi-cho, Kurume-city, [8]Department of Radiology, School of Medicine, Hokkaido University Graduate, Kita-ku, Sapporo, [9]Department of Radiation Oncology, Hyogo Cancer Center, Kitaojicho, Akashi, [10]Department of Radiation Oncology, Yamanashi University, Yamanashi and [11]Department of Radiology, Okayama University Hospital, Okayama, Japan

*For reprints and all correspondence: Hideomi Yamashita, Department of Radiology, University of Tokyo Hospital, 7-3-1, Hongo, Bunkyo-ku, Tokyo, 113-8655 Japan. E-mail: yamachan07291973@yahoo.co.jp

Received August 15, 2012; accepted February 11, 2013

Background: The current study was designed to evaluate the clinical outcomes of curative intent radiation therapy for young patients with invasive uterine cervical carcinoma in Japan.
Methods: One hundred and eighteen patients aged ≤40 were registered in the multi-institutional study of the Japanese Society of Therapeutic Radiology and Oncology (JASTRO) from 26 major institutions in Japan. The age range was 24–39 years and the maximum tumor diameter was 2.0–9.2 cm. The International Federation of Gynecology and Obstetrics clinical stages were Ib, IIa, IIb, IIIa, IIIb and IVa in 17, 6, 40, 2, 50 and 3, respectively. Curative intent radiation therapy consisted of the combination of external beam radiation therapy and high-dose rate intra-cavitary brachytherapy. The total dose of external beam radiation therapy ranged between 44 and 68 Gy. Both the median and mode of total high-dose-rate intra-cavitary brachytherapy dose to point A were 24 Gy in four fractions. Ninety-six patients (58%) received chemotherapy.
Results: The 5-year overall survival rate and local control rate of all patients were 61 and 65%, respectively. The 5-year overall survival rates of International Federation of Gynecology and Obstetrics Stage Ib, IIa, IIb, IIIa, IIIb and IVa were 88, 100, 75, 100, 37 and 0%, respectively. The 5-year local control rates of International Federation of Gynecology and Obstetrics Stage Ib, IIa, IIb, IIIa, IIIb and IVa were 82, 75, 75, 100, 51 and 0%, respectively. Sixteen patients experienced grade 3 or greater late radiation morbidity.
Conclusions: The 5-year overall survival rate of young patients with Stage IIIb was comparatively low at 37%.

Key words: young age – radiation therapy – uterine cervical cancer

INTRODUCTION

The incidence of cervical carcinoma has tended to increase since the late 1990s, especially among young women (1). Many earlier reports demonstrated a poorer prognosis in young women (2), while some studies indicated no difference or a better prognosis for young patients (3). Therefore, it remains controversial whether young patients with invasive cervical carcinoma have a poorer prognosis than older women. Research has suggested that the prognosis of the younger age group is worse than that of the older age group (4).

It is reported that convalescence is bad for the young fellow uterine cancer, but a radiation therapy method and a dose of radioactivity to use and the combination therapy are the same as other age groups.

It has been reported that prognosis is bad for the young patients with uterine cervical cancer, but a radiation therapy method and a total irradiated dose to use and the combination therapy are the same as other age groups. Therefore, the possibility that biological properties were different was suggested. Each past report is around dozens of cases, and this study is the largest. As for the report in the well-organized case of young patients with cervical cancer, the trial of this national investigation may discover a new fact as never before in Japan.

The aim of this study was to examine the outcomes in young (age <40 years) woman with invasive cervical cancer treated in Japan.

Table 1. Patient characteristics

	Number	
Age (years)	24–39 (median: 34.5)	
Histopathological type		
Squamous cell carcinoma	105	89%
Adenocarcinoma	7	6%
Adenosquamous	3	3%
Others	3	3%
FIGO stage		
Ib	17	14%
IIa	6	5%
IIb	40	34%
IIIa	2	2%
IIIb	50	42%
Iva	3	3%
Pelvic lymph node metastasis		
Without	73	62%
With	45	38%
Para-aortic lymph node metastasis		
Without	109	92%
With	9	8%
Maximum tumor diameter (mm)	20–92 (median: 55)	
Treatment method		
CRT	96	81%
CCRT	69	58%
Radiotherapy alone	22	19%

CRT, chemoradiotherapy; CCRT, concurrent chemoradiotherapy; FIGO, International Federation of Gynecology and Obstetrics.

PATIENTS AND METHOD

Patient Information

Patients <40 years of age with cervical carcinomas treated from 2000 to 2005 in the multi-institutional study of Japanese Society of Therapeutic Radiology and Oncology (JASTRO) chaired by Niibe Y. MD, from 26 major institutions in Japan were retrospectively reviewed (Table 1). Carcinoma *in situ* of the cervix was not registered, and only cases of invasive cervical cancer were included in the study. The clinical staging was based on the International Federation of Gynecology and Obstetrics (FIGO) classification.

Radiotherapy

Curative intent radiation therapy was given with a combination of external beam radiation therapy (EBRT) and high-dose rate intra-cavitary brachytherapy (HDR-ICBT). HDR-ICBT was performed with iridium-192 applications. The median total dose of EBRT was 50.4 Gy (range: 44–68 Gy). EBRT was directed at whole pelvis before inserting a midline block using AP/PA parallel opposed or a 4-field box with $\geq$10 MV. The para-aortic node region was included in EBRT fields for para-aortic node positive patients. The median dose per fraction was 2.0 Gy (range: 1.8–2.0 Gy). The median dose to the whole pelvis without a midline block was 30.6 Gy (range: 0–51.3 Gy). The median remaining dose of EBRT with a midline block as a boost was 19.8 Gy (range: 10.8–51.3 Gy). The median total dose of HDR-ICBT to point A was 24 Gy (range: 12–48 Gy). The median dose per fraction to point A was 5.7 Gy (range: 4.0–7.5 Gy). The median biological effective dose (BED) was 76.8 Gy_{10} (range: 45.82–96.0 Gy_{10}) (α/β is 10) in the central area. In T3b, the median BED was 80.2 Gy_{10} (range: 64.5–96.0 Gy_{10}).

The tandem length was 5–6 cm from the external uterine orifice. No interstitial implantation was used in this multi-center study. It does not mean that young patients were excluded from this report because of an interstitial implantation technique.

Chemotherapy

Chemotherapy was administered to 96 patients. Out of them, 69 patients received concurrently. Other 27 patients received chemotherapy before RT. It decided on different policies at

each institution. In all case, platinum-based chemotherapy was carried out. The number of patients who underwent chemotherapy was 11 in stage Ib, 5 in stage IIa, 35 in stage IIb, 1 in stage IIIa, 41 in stage IIIb and 3 in stage IVa.

Statistical Analysis

The Kaplan–Meier method was used for the estimation of overall survival and local control rate. The times for survival were calculated from the start of any therapy for cervical cancer. Statistical analyses were performed using SAS version 9.0 software (SAS Institute, Inc., Cary, NC). A P value of <0.05 was considered significant. All tests were two-sided.

Both acute and late complications were graded in accordance with the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0.

RESULTS

Patients

We registered 118 patients <40 years of age treated between 2000 and 2005 in this multi-institutional study. The median age was 34.5 years old (range: 24–39 years old). The median maximum tumor diameter was 5.5 cm (range: 2.0–9.2 cm). In most patients (104 cases), the histopathological type was a squamous cell carcinoma. The number of FIGO clinical Stages Ib, IIa, IIb, IIIa, IIIb and IVa was 17, 6, 40, 2, 50 and 3. Forty-five patients had pelvic lymph node metastasis and 9 patients had para-aortic lymph node metastasis. Computed tomography and MRI and/or PET were used for nordal evaluation.

The proportion of pelvic lymph node metastasis of patients with Stages IIb, IIIb and IVa was 48% (19 of 40 cases), 46% (23 of 50 cases) and 67% (2 of 3 cases), respectively. The median maximal tumor size of patients with Stages IIb, IIIb and IVa was 5.2 cm (range: 3.7–8.2 cm), 5.8 cm (range: 2.0–9.2 cm) and 7.5 cm (range: 6.0–7.5 cm).

Survival

The median follow-up of 76 survivors was 48 months, with a range of 2–100 months until the last follow-up date of 10 December 2008. Of the living patients, six have recurrent disease. Sixty-six patients have no evidence of disease relapse and are still alive. Thirty-seven patients died of cervical cancer and five patients died of other diseases. As for the cause of death of the five patients, unidentified sudden death, acute asthma, cerebral hemorrhage and chronic heart failure were by for each one person.

The 5-year overall survival rate and local control rate of all patients was 61.1 ± 4.8 and 64.7 ± 4.6%, respectively. The 5-year overall survival rates of FIGO Stages Ib, IIa, IIb, IIIa, IIIb and IVa were 88.2 ± 7.8, 100, 75.3 ± 7.2, 100, 36.7 ± 7.5 and 0%, respectively (Fig. 1). The 5-year local control rates of FIGO Stages Ib, IIa, IIb, IIIa, IIIb and IVa were 81.6 ± 9.6, 75.0 ± 21.7, 75.2 ± 7.3, 100, 51.3 ± 7.4 and 0%, respectively (Fig. 2).

Out of 36 patients with local recurrence, 25 (69%) received chemotherapy, and the median total treatment time of RT was 48 days (range: 37–75 days). On the other hand, out of 82 patients without local recurrence, 70 patients (85%) received chemotherapy and median total treatment time of RT was 48 days (range: 11–82 days).

Patterns of Failure

Loco-regional disease within the radiation field persisted in six patients (five patients were Stage IIIb and one patient was Stage IIb). Half of them had adenocarcinoma. With the exception of those 6 patients, the first site of recurrence was uterine cervix in 13 patients, pelvic lymph nodes in 7 patients, both uterine and pelvic lymph nodes in 7, parametrium in 1 patient, per-rectal in 1 patient, lung in 3 patients, and liver in 1 patient. No isolated para-aortic lymph node recurrences were seen.

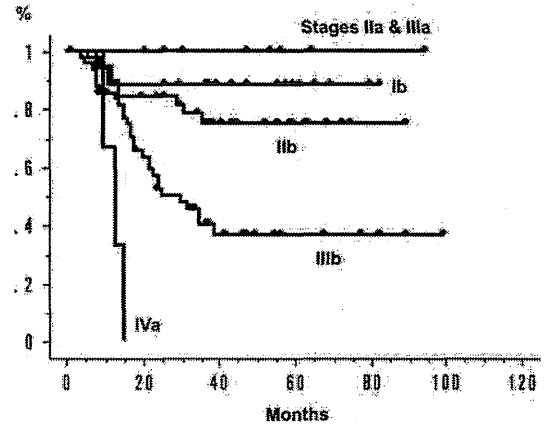


Figure 1. Overall survival curves by FIGO stages.

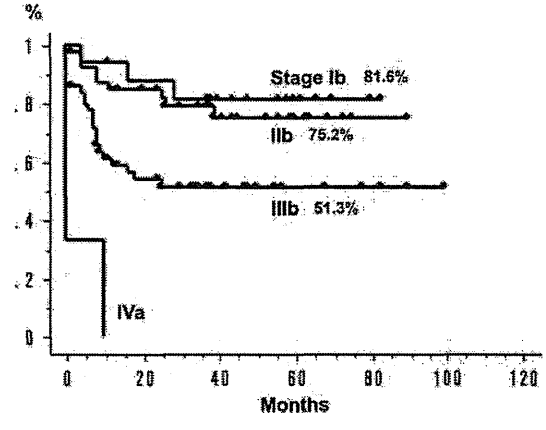


Figure 2. Local disease-free survival curves by FIGO stages.

Toxicity

Number of cases with toxicity was shown in Table 2. Late urinary, rectal and small-intestinal morbidities grade ≥3 occurred in 3 patients, 5 patients and 9 patients, respectively. Late lower-limb edema grade ≥3 was one patient.

DISCUSSION

In Japan, uterine cervical cancer increases rapidly in their 20s. This retrospective study was designed to evaluate the prognosis of young women with cervical carcinoma in Japan. This retrospective study was certified by the Japanese Society of Therapeutic Radiology and Oncology (5). The 5-year overall survival rates of FIGO Stages Ib, IIa, IIb, IIIa, IIIb and IVa in our study were 88, 100, 75, 100, 37 and 0%, respectively. We think that it is valuable to examine younger patients with cervical cancer, even though this is a retrospective study by a single arm without the control arm (appropriate comparative object). Although there are several previous studies examining the clinical outcome in young patients with invasive cervical cancer from abroad, this is naive in the country of Japan as for the report of RT results of the young fellow. There is more number of cases in our study than other studies including the foreign countries. Earlier reports (2, 6) demonstrated that young patients with cervical cancer have a poorer prognosis than older patients. However, some reports (7–10) indicate that the prognosis by FIGO stage at diagnosis is worse in older aged women than young women. In this way, the effect of age on survival is variable. In our population, patients with stage IIIb and IVa had a worse outcome than those with stage I to II disease that is trivial.

Table 2. Number of cases with toxicity

	Grade 1	Grade 2	Grade 3	Grade 4
Acute				
Hematological toxicity	2	2	22	3
Fever	0	0	3	0
Proctitis	6	5	3	2
Dermatitis	6	0	0	0
Urinary tract	4	0	3	0
Late				
Pelvic fracture	0	0	0	0
Rectal and sigmoid	0	0	0	0
Vagina	0	0	0	0
Small intestine	4	2	9	0
Cystitis	2	1	4	0
Infection	0	0	1	0
Lower-limb edema	3	1	1	0

In 2010, Kokawa et al. (7) in the Kinki District in Japan reported that the prognosis trends were better in younger women than in older patients, especially in Stage III disease. The 5-year survival rate of 441 young women aged <35 years in their study (7) was 95% for Stage I disease, 73% for Stage II, 68% for Stage III and 19% for Stage IV. Although our outcome in stages I and II was nearly equal to this, stages III and IV were inferior to this. However, 418 among 441 young patients (95%) were treated with surgery and only 4 patients with CRT and 9 patients with RT-alone were included in the study (7).

In Japan, the 5-year OS of all ages was FIGO Stage Ib = 88%, II = 69%, IIIb = 56% and IVa = 21% in 1148 patients treated with a combination of EBRT and HDR-ICBT from 1968 to 1986 (11). According to some retrospective studies in Japan, 5-year OS of FIGO Stages III and IVa was 77 and 43% (12) and 52 and 34% (13). In a French Cooperative Group study of 1875 patients who received RT according to Fletcher's guidelines, Barillot et al. (14) reported a 5-year survival rate of 45% in patients having stage IIIb tumors. The FIGO annual report (15) showed that 5-year survival rates for Stages IB, IIB, IIIB and IVA patients treated from 1993 to 1996 were 90.3, 73.4, 64.3 and 20.0%, respectively. Clinical outcomes of FIGO Stages I–II (5-year OS: 88% in Stage Ib, 100% in Stage IIa and 75% in Stage IIb) were equivalent to the Japanese standard treatment results of all ages. However, clinical outcomes of FIGO Stages IIIb and IVa (5-year OS: 37% in Stage IIIb and 0% in Stage IVa) were lower than those of all ages.

In Japan, 30 years' experience with the use of HDR-ICBT with EBRT for locally advanced uterine cervical carcinoma suggests that the BED of 67 to 86 Gy_{10} is an acceptable dose as stated in the Patients and Methods section, and this is recognized as the community standard dose (11). The American Brachytherapy Society recommends HDR-ICBT dose of 100–108 Gy_{10} for locally advanced uterine cervical carcinoma (16), much higher dose than that generally used in Japan. We also used a lower dose than generally recommended/used for tandem and ovoid brachytherapy in Europe and the USA (i.e. 6 Gy × 5 fractions or 7 Gy × 4 fractions). The EBRT and the brachytherapy in this study do not reflect the modern method of European practice (17). In phase II JCOG 1066 study of concurrent chemoradiation with HDR-ICBT in patients with locally advanced (FIGO stages III–IVA) uterine cervical cancer, Toita et al. (21) reported efficacy and toxicity of a low cumulative radiation dose schedule. They demonstrated that CCRT using HDR-ICBT with a low cumulative RT dose schedule, in which the cumulative linear quadratic equivalent dose (EQD2) was 62–65 Gy prescribed at point A, achieved comparable outcome as those achieved with global dose schedules (EQD2 = 85 Gy) with a lower incidence of late toxicity for locally advanced uterine cervical cancer in a Japanese population of 72 patients. However, the lower radiation doses in this study may contribute to the poor results of FIGO Stages IIIb or IVa.

In Japan, young patients tended to be more willing to undergo surgery. In Japan, a report in 2005 demonstrated that the population of primary treatment including surgery was 79 of 719 (11%) for Stage III. In Kokawa's cases aged <35, primary treatment including surgery was 6 of 11 (54.5%) women for Stage III (7). Therefore, it is possible that the distribution of treatment methods affects the poorer prognosis observed in our young patients with FIGO Stages IIIb and IVa. In other words, in Japan, definitive radiotherapy might be performed for Stages IIIb and IVa cases with relative poor prognosis since radical surgery is selected for better prognosis. Japanese patients may have a higher rate of surgery for advanced stage disease than elsewhere, although surgery in not recommended for stage III or IV patients by the treatment guideline for the cervical cancer in 2011 edition by Japan Society of Gynecologic Oncology. As such the advanced stage cases treated with definitive RT may represent a population with a worse outcome than elsewhere. The experts of each institution talk about the treatment methods (RT or surgery) and decide it.

In our study, no isolated para-aortic lymph node recurrence was seen. According to Niibe et al. (18), of the 3137 patients with uterine cervical carcinoma in staged IA–IVA in 12 Japanese hospitals between 1994 and 2003, 2.1% experienced recurrence in isolated para-aortic lymph nodes and isolated para-aortic lymph node recurrence was better prognosis than the other site (19–20). The first recurrent site was within the pelvis in 35 patients including local residual case and distant metastasis in four patients in our study.

However, this study has also some limitations. First, the power of this study may be poor because it involved only 118 patients in a retrospective setting. Especially, FIGO Stages IIIa and IVa were only two and three patients, respectively. Secondly, we collected eligible cases from 26 institutions in Japan. Therefore, radiation dose, with or without combined chemotherapy, chemotherapy regimen, follow-up method or salvage therapy after recurrence were not uniform. Although the patients with stages III and IV disease have a BED of 80.2 Gy to Point A, it is recommended in patients with bulkier disease such as IIIB and IV that, perhaps, dose be increased beyond that which was achieved in the multicenter study. The increase in dose may have improved the results of the stage III or IV patients independent of their age.

CONCLUSIONS

Although clinical outcomes of young patients with FIGO Stages I–II were equivalent, Stages IIIb and IVa were lower than the Japanese standard treatment results of all ages.

Acknowledgements

We thank Hidehiro Eto MD (Department of Radiology, Kurume University School of Medicine), Rumiko Kinoshita MD (Department of Radiology, Hokkaido University Graduate School of Medicine) and Kayoko Tsujino MD (Department of Radiation Oncology, Hyogo Cancer Center), for taking care of by the registration of cases.

Funding

We received a research grant from JASTRO.

Conflict of interest statement

None declared.

References

1. Marugame T, Matsuda T, Kamo K, et al. Japan Cancer Surveillance Research Group. Cancer incidence and incidence rates in Japan in 2001 based on the data from 10 population-based cancer registries. *Jpn J Clin Oncol* 2007;37:884–91.
2. Serur E, Fruchter RG, Maiman M, et al. Age, substance abuse, and survival of patients with cervical carcinoma. *Cancer* 1995;75:2530–38.
3. Mariani L, Iacovelli A, Vincenzoni C, et al. Cervical carcinoma in young patients: clinical and pathological variables. *Int J Gynecol Obstet* 1993;41:61–6.
4. Hall SW, Monaghan JM. Invasive carcinoma of the cervix in younger women. *Lancet* 1983;2:731.
5. Niibe Y, Kenjo M, Onish H, et al. High-dose-rate intracavitary brachytherapy combined with external beam radiotherapy for stage IIIb adenocarcinoma of the uterine cervix in Japan: a multi-institutional study of Japanese Society of Therapeutic Radiology and Oncology 2006–2007 (study of JASTRO 2006–2007). *Jpn J Clin Oncol* 2010;40:795–9.
6. Rutledge FN, Mitchell MF, Munsell M, et al. Youth as a prognostic factor in carcinoma of the cervix: a matched analysis. *Gynecol Oncol* 1992;44:123–30.
7. Kokawa K, Takekida S, Kamiura S, et al. The incidence, treatment and prognosis of cervical carcinoma in young women: a retrospective analysis of 4,975 cases in Japan. *Eur J Gynaecol Oncol* 2010;31:37–43.
8. Ward BG, Shepherd JH, Monaghan JM. Occult advanced cervical cancer. *Br Med J* 1985;290:1301–2.
9. Kosary CL. FIGO stage, histology, histologic grade, age and race as prognostic factors in determining survival for cancers of the female gynecological system: an analysis of 1973–87 SEER cases of cancers of the endometrium, cervix, ovary, vulva, and vagina. *Semin Surg Oncol* 1994;10:31–46.
10. Chen RJ, Lin YH, Chen CA, et al. Influence of histologic type and age on survival rates for invasive cervical carcinoma in Taiwan. *Gynecol Oncol* 1999;73:184–90.
11. Nakano T, Kato S, Ohno T, et al. Long-term results of high-dose rate intracavitary brachytherapy for squamous cell carcinoma of the uterine cervix. *Cancer* 2005;103:92–101.
12. Yamashita H, Nakagawa K, Tago M, et al. Treatment results and prognostic analysis of radical radiotherapy for locally advanced cancer of the uterine cervix. *Br J Radiol* 2005;78:821–6.
13. Sakurai H, Mitsuhashi N, Takahashi M, et al. Analysis of recurrence of squamous cell carcinoma of the uterine cervix after definitive radiation therapy alone: patterns of recurrence, latent periods, and prognosis. *Int J Radiat Oncol Biol Phys* 2001;50:1136–44.
14. Barillot I, Horiot JC, Pigneux J, et al. Carcinoma of the intact uterine cervix treated with radiotherapy alone: a French cooperative study: update and multivariate analysis of prognostics factors. *Int J Radiat Oncol Biol Phys* 1997;38:969–78.
15. Benedet JL, Odicino F, Maisonneuve P, et al. Carcinoma of the cervix uteri. *J Epidemiol Biostat* 2001;6:7–43.
16. Cengiz M, Gürdalli S, Selek U, et al. Effect of bladder distension on dose distribution of intracavitary brachytherapy for cervical cancer:

Three-dimensional computed tomography plan evaluation. *Int J Radiat Oncol Biol Phys* 2008;70:464–8.
17. Pötter R, Haie-Meder C, Van Limbergen E, et al. Recommendations from gynaecological (GYN) GEC ESTRO working group (II): concepts and terms in 3D image-based treatment planning in cervix cancer brachytherapy-3D dose volume parameters and aspects of 3D image-based anatomy, radiation physics, radiobiology. *Radiother Oncol* 2006;78:67–77.
18. Niibe Y, Kazumoto T, Toita T, et al. Frequency and characteristics of isolated para-aortic lymph node recurrence in patients with uterine cervical carcinoma in Japan: a multi-institutional study. *Gynecol Oncol* 2006;103:435–8.
19. Niibe Y, Kenjo M, Kazumoto T, et al. Japanease Isolated Para-Aortic Lymph Node Recurrence of Uterine Cervical Carcinoma Study Group. Multi-institutional study of radiation therapy for isolated para-aortic lymph node recurrence in uterine cervical carcinoma: 84 subjects of a population of more than 5,000. *Int J Radiat Oncol Biol Phys* 2006;66:1366–9.
20. Eng-Yen H, Yu-Jie H, Chan-Chao C, et al. Pretreatment carcinoembryonic antigen level is a risk factor for para-aortic lymph node recurrence in squamous cell carcinoma of the uterine cervix. *Radiat Oncol* 2012;7:13.
21. Toita T, Kitagawa R, Hamano T, et al. Phase II study of concurrent chemoradiotherapy with high-dose-rate intracavitary brachytherapy in patients with locally advanced uterine cervical cancer: efficacy and toxicity of a low cumulative radiation dose schedule. *Gynecol Oncol* 2012;126:211–6.

Kasuya et al. Radiation Oncology 2013, 8:139
http://www.ro-journal.com/content/8/1/139

RADIATION ONCOLOGY

RESEARCH Open Access

Distribution patterns of metastatic pelvic lymph nodes assessed by CT/MRI in patients with uterine cervical cancer

Goro Kasuya[1*], Takafumi Toita[1], Kazuhisa Furutani[2], Takeshi Kodaira[2], Tatsuya Ohno[3], Yuko Kaneyasu[4], Ryouichi Yoshimura[5], Takashi Uno[6], Akira Yogi[1], Satoshi Ishikura[7] and Masahiro Hiraoka[8]

Abstract

Background: To investigate the three-dimensional (3D) distribution patterns of clinically metastatic (positive) lymph nodes on pretreatment computed tomography (CT)/magnetic resonance imaging (MRI) images of patients with locally advanced cervical cancer.

Methods: We enrolled 114 patients with uterine cervical cancer with positive nodes by CT/MRI (≥10 mm in the shortest diameter). Pretreatment CT/MRI data were collected at 6 institutions. The FIGO stage was IB1 in 2 patients (2%), IB2 in 6 (5%), IIA in 3 (3%), IIB in 49 (43%), IIIB in 50 (44%), and IVA in 4 (4%) patients. The median cervical tumor diameter assessed by T2-weighted MRI was 55 mm (range, 10–87 mm). The anatomical distribution of the positive nodes was evaluated on CT/MRI images by two radiation oncologists and one diagnostic radiologist.

Results: In these patients, 273 enlarged nodes were assessed as positive. The incidence of positive nodes was 104/114 (91%) for the obturator region, 31/114 (27%) for the external iliac region, 16/114 (14%) for the internal iliac region, 22/114 (19%) for the common iliac region, and 6/114 (5%) for the presacral region. The external iliac region was subdivided into four sub-regions: lateral, intermediate, medial, and caudal. The obturator region was subdivided into two sub-regions: cranial and caudal. The majority of patients had positive nodes in the cranial obturator and/or the medial external iliac region (111/114). In contrast, few had positive nodes in the lateral external iliac, caudal external iliac, caudal obturator, internal iliac and presacral regions. All cases with positive nodes in those low-risk regions also had positive nodes in other pelvic nodal regions concomitantly. The incidence of positive nodes in the low-risk regions/sub-regions was significantly related to FIGO stage ($p=0.017$) and number of positive nodes ($p<0.001$).

Conclusions: We demonstrated the 3D distribution patterns of clinical metastatic pelvic lymph nodes on pretreatment CT/MRI images of patients with locally advanced cervical cancer. These findings might contribute to future individualization of the clinical target volume of the pelvic nodes in patients with cervical cancer.

Keywords: Radiotherapy, Lymph node, Clinical target volume, Uterine cervical cancer

* Correspondence: k108711@eve.u-ryukyu.ac.jp
[1]Department of Radiology, Graduate School of Medical Science, University of the Ryukyus, Okinawa, Japan
Full list of author information is available at the end of the article

Background

Radiotherapy plays very important roles in the treatment of uterine cervical cancer. Definitive radiotherapy for cervical cancer consists of external beam radiotherapy and intracavitary brachytherapy. Recently, external beam radiotherapy techniques have advanced considerably, as have those for intracavitary brachytherapy. Treatment planning for uterine cervical cancer has transitioned from a two-dimensional (2D) approach based on bony landmarks to a three-dimensional (3D) technique based on computed tomography (CT)/magnetic resonance imaging (MRI). Intensity-modulated radiotherapy (IMRT) has been proven to have a significant dosimetric advantage and less toxicity compared with conventional 2D/3D treatment planning for various malignancies, including gynecologic cancers [1]. It is essential to define the proper clinical target volume (CTV) for appropriate delivery of IMRT. Guidelines that provide a standard definition of CTV nodes are now published by the Radiation Therapy Oncology Group (RTOG) [2], UK investigators [3] and the Japan Clinical Oncology Group (JCOG) [4]. However, these guidelines were developed mainly from information on the normal anatomical pelvic lymph node distribution. The actual distribution of clinically metastatic (positive) nodes in the pelvis has not been studied in definitive radiotherapy series. If areas with a low risk of node metastases could be deleted from the CTV, toxicity could be reduced without sacrificing regional control.

The purpose of this study was to investigate the 3D distribution patterns of clinically metastatic nodes assessed by CT/MRI in patients with uterine cervical cancer.

Methods

We enrolled 114 patients with uterine cervical cancer who were diagnosed as having clinically metastatic (positive) pelvic nodes by CT/MRI (≥10 mm in the shortest diameter) and treated by definitive radiotherapy/chemoradiotherapy at 6 institutions between January 2001 and December 2007. This study conformed to the ethical principles contained in the Declaration of Helsinki [5], and was approved by the institutional review board of the principal investigator (T.T.). Lymph nodes greater than or equal to 10 mm in the shortest diameter, as assessed by CT/MRI, were defined as positive in this study. Patient characteristics are summarized in Table 1. Digitized CT/MRI images burned to CD-ROMs were collected from each institution. The images were reviewed by two radiation oncologists (G.K., T.T.) and one diagnostic radiologist (A.Y.).

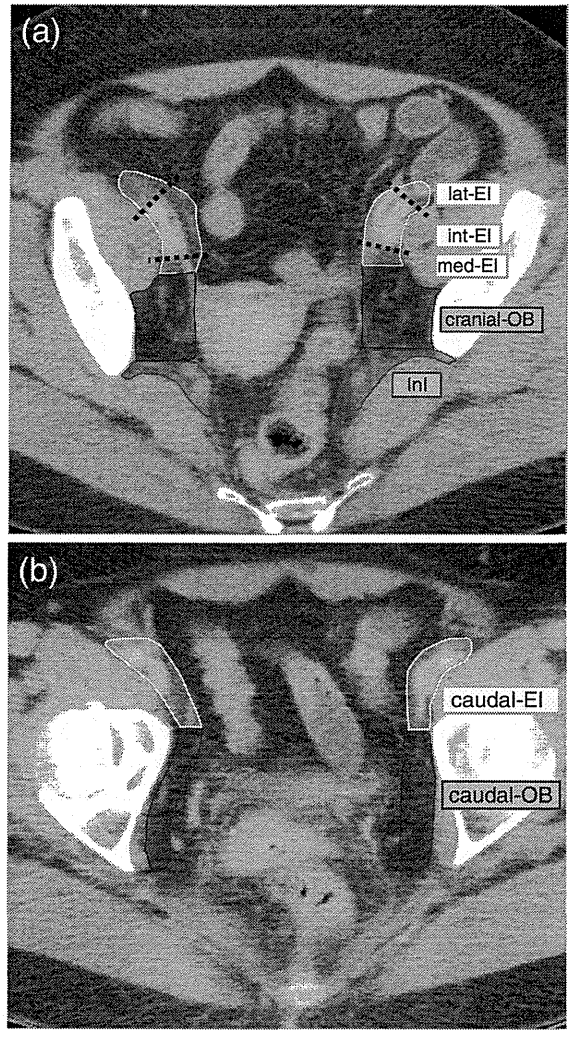
Pelvic lymph node area was divided into five anatomical regions: the obturator region, the external iliac region, the internal iliac region, the common iliac region, and the presacral region. The external iliac was further divided into four sub-regions: the medial external iliac, the intermediate external iliac, the lateral external iliac, and the caudal external iliac. The subcategories of medial external iliac, intermediate external iliac, and lateral external iliac refer to the definitions proposed by Taylor et al. [6] and Lengelé et al. [7]: medial external iliac=the dorsal area of attachment and along the external iliac vein, intermediate external iliac=the anterior area between the external iliac artery and vein, and lateral external iliac=the lateral area of the external iliac artery. These three sub-regions are all located cranial to the aspect of the femoral head. On the other hand, the caudal external iliac is located caudal to the aspect of the femoral head. The obturator was also divided into two sub-regions, with the border of the aspect of the femoral head as the external iliac: cranial obturator and caudal obturator. An atlas of these sub-regions (except for common iliac region) is presented in Figure 1 (a)-(b).

First, the number of positive nodes in each region and in the sub-regions was counted. Next, the distribution

Table 1 Patient characteristics (n=114)

Characteristic		(n)
FIGO stage		
	IB1	2
	IB2	6
	IIA	3
	IIB	49
	IIIB	50
	IVA	4
Age		
	median 52	range 26-88
Histology		
	SCC	109
	Adeno	5
Tumor size*		
	<20 mm	0
	21-40 mm	18
	41-60 mm	58
	61 mm<	38
Number of metastatic LN in the pelvis		
	1	32
	2	36
	3	23
	4	14
	≥5	9

*assessed by MRI.
FIGO=Federation Internationale de Gynecologie et de Obstetrique.
SCC=Squamous cell carcinoma.
LN=Lymph node.



OB=obturatorregion, EI = external iliac region, lat-EI = lateral external iliac region, int-EI = intermediate external iliac region, med-EI = medial external iliac region, InI= internal iliac region, PS = presacralregion

Figure 1 Atlas of the CTV nodes: regions and sub-regions. Middle-level of pelvis' for (**a**), and 'low-level of pelvis' for (**b**).

patterns of the positive nodes were analyzed in each area.

Statistical analyses were performed with the chi-square test. A probability level of 0.05 was chosen for statistical significance.

Results

There were 273 positive nodes as assessed by CT/MRI. The median number of positive nodes per patient was 2 (range, 1–7). Figure 2 shows the incidence of positive nodes in each nodal region. The area that most frequently contained positive nodes was the obturator region. In contrast, positive nodes were rarely observed in the presacral region. Table 2 shows the anatomical distribution of positive nodes in the pelvis. A solitary positive node was observed only in the obturator and the external iliac regions. In contrast, no solitary positive node was observed in the internal iliac, common iliac, and presacral regions. Within the obturator and external iliac regions, positive nodes were rarely observed in the caudal and lateral external iliac sub-regions. Ninety-seven percent of the patients (111/114) had one or more positive nodes in the cranial obturator and/or the medial external iliac regions. A solitary positive node was observed only in the cranial obturator, and medial/intermediate external iliac regions. For other regions or sub-regions, patients with positive nodes also had positive nodes concomitantly in other pelvic nodal

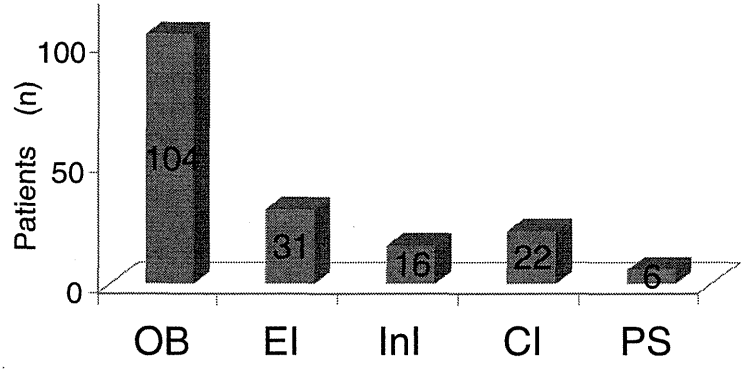


Figure 2 Incidence of clinically metastatic pelvic lymph nodes in each region. *Including duplication.

regions or sub-regions. We defined each of these regions as a NSR (non-solitary region). Patients with NSR metastases had high FIGO stages or a large number of positive nodes. Patients with high FIGO-stage disease (III, IVA) had a significantly higher frequency of positive nodes in the NSR (23/54, 43%) compared with patients who had low FIGO-stage disease (15/60, 25%) (P=0.047). The average number of metastatic lymph nodes was 3.7 for patients with NSR and 1.9 for patients with non-NSR. There was no significant relationship between tumor diameter and the incidence of NSR metastases: 6/18 (30%) for tumors≤40 mm, 20/58 (34%) for tumors 41–60 mm, and 15/38 (38%) for tumors≥61 mm. All 16 patients with nodal metastases in less common (≤ 6/114, 5%) areas (presacral, caudal obturator, and caudal/lateral external iliac regions) had large tumors (> 4 cm), of which all 9 cases who had NSR metastases in the lateral external iliac and presacral regions were stage IIB or more. In addition, all 9 cases with NSR metastases in the caudal obturator or caudal external iliac regions also had positive lymph nodes in the ipsilateral cranial obturator or medial external iliac region, and all 3 cases with NSR metastases in the lateral external iliac region had positive nodes in the ipsilateral intermediate external iliac region.

Discussion

To minimize the risk of inter-planner variability on pelvic node CTV contouring, consensus-based CTV guidelines have been developed for patients with cervical cancer [2-4]. Modification of the standard CTV guidelines based on the probability of subclinical disease, in other words, risk of recurrence is the next challenge for individualized treatment planning.

The CTV could be divided into subgroups, e.g., high-risk CTV and low-risk CTV, according to the probability of recurrence. The high-risk CTV would be defined as the volume that involves frequent metastases, and should be treated for every patient. In contrast, the low-risk CTV would be defined as a region with rare disease involvement, and might be able to be excluded from the CTV in certain situations. The arrangement of CTV nodes could reduce the dose/volume of organs at risk (OAR) and lead to lower side effects. In the previously published guidelines, the CTV nodes cover the entire anatomical pelvic node distribution [2-4,6]. The guidelines did not emphasize the actual probability of nodal involvement, in other words, the risk of recurrence. In head and neck cancers, individualization of CTV nodes for 3D planning was proposed according to the primary

Table 2 Number of patients* with clinically pelvic nodal metastases # by region/subdivided region

	Total	OB		EI				InI	CI	PS
		Cranial	Caudal	Med	Int	Lat	Caudal			
Positive nodes in other regions	82	76	5	10	13	3	6	16	22	6
No positive nodes in other regions	32	28	0	2	2	0	0	0	0	0
Total	114	104	5	12	15	3	6	16	22	6

*including duplication, # assesed by CT/MRI (>= 10 mm in shortest diameter).
OB = obturator region, EI = external iliac region, InI = internal iliac region, CI = common iliac region, PS = presacral region, Med = medial, Int = intermediate, Lat = lateral.

site or T/N stage [8]. For uterine cervical cancer, in an attempt at dose reduction for OAR, small pelvic field irradiation has been investigated [9,10]. The treatment fields were designed to exclude the common iliac region. In this study, we tried to analyze the 3D distribution patterns of positive nodes in the pelvis assessed by pretreatment CT/MRI to quantify the nodal metastasis probability in patients with uterine cervical cancer.

Some surgical series have indicated that the obturator and external iliac regions have the highest frequency of metastatic lymph nodes [11,12]. This is consistent with the findings demonstrated in the present study. We subdivided the obturator and external iliac regions according to craniocaudal distribution at the border of the femoral head. Analyses with this subdivision revealed that positive lymph nodes were rarely seen on the caudal side, and most were observed on the cranial side. Benedetti and colleagues also subdivided the obturator region into deep and superficial regions. They demonstrated that there were few metastatic lymph nodes in the deep region [12]. Our results are consistent with that report. No previous study supports our finding that the caudal external iliac sub-region rarely had positive nodes. However, the present results suggest the appropriateness of the definition of the external iliac region in the RTOG and JCOG guidelines, which set the lower end of the external iliac region at the top of the femoral head [2,4].

For the external iliac region above the aspect of the femoral head, 3 anatomically subdivided regions have been proposed [6,7]. According to the definition, positive nodes in the medial external iliac and intermediate external iliac regions were frequent in contrast to the lateral external iliac regions in our study. This observation was also made by Graham et al. [13]. Taylor et al. demonstrated that the normal node distribution extended more than 10 mm laterally to the external iliac artery and veins in their USPIO MRI study. Based on this finding, they recommended that the CTV should expand 17 mm laterally from the vessels to cover the region sufficiently [6]. However, our present study demonstrated that positive nodes were rare in the lateral external iliac region, and suggested that the expansion that Taylor proposed could be omitted in some cases.

Based on the findings from our present analyses, high-risk regions such as the cranial obturator and the medial and intermediate external regions must be irradiated sufficiently in all cases. In contrast, the caudal external iliac, caudal obturator, lateral external iliac and presacral regions, which demonstrated a very low incidence (≤ 5%) of positive nodes, might be allowed to be excluded in patients who satisfy all of the following criteria: small tumor size (≤ 4 cm) and no positive nodes on CT/MRI. The CTV shrinkage might help to reduce complications in the surrounding organs. Further investigation is needed to justify such modification in clinical practice. In the other remaining regions (i.e., common iliac, internal iliac), although no patient in this study had a solitary positive lymph node, the positive rate was not low. Therefore, we suggest that the common iliac and internal iliac regions should continue to be included in all cases for radical radiotherapy for patients with uterine cervical cancer.

This study has some limitations. First, the insufficient sensitivity of CT/MRI is critical. Bellomi and colleagues reported that the sensitivity and specificity of CT were 64% and 93%, respectively, and those of MRI were 72% and 93%, respectively [14]. The results of this study should be interpreted carefully due to the inadequate sensitivity and specificity of these methods. Meanwhile, Choi and coworkers compared the sensitivity and specificity of MRI and positron emission tomography/computed tomography (PET/CT) [15]. With MRI, the sensitivity and specificity were 30% and 92%, respectively, and with PET/CT, the sensitivity and specificity were 57% and 92%, respectively. Further study using PET/CT is encouraged. Second, the absence of histopathological confirmation is a serious weakness of the present study. Although some surgical series presented detailed data on the pathological positive node distribution [11,12], data for inoperable advanced-stage patients were sparse. In addition, it is difficult to apply the distribution of metastatic nodes from surgical findings directly to the 3D distribution on CT/MRI images for accurate CTV contouring. For these reasons, despite its insufficient sensitivity and specificity, some surrogate information could be obtained from the study using CT/MRI. Third, this study consists of a relatively small number of patients and a heterogenous population (i.e. stage, tumor size). Various systematic and random errors due to multicenter assessment over a long time period might negatively affect the validity of the study.

Conclusions

The present study demonstrated distribution patterns of positive pelvic nodes in patients with cervical cancer treated with definitive radiotherapy/chemoradiotherapy. The findings might contribute to future investigations for the individualization of CTV node contouring.

Abbreviations

3D: Three-dimensional; CT: Computed tomography; MRI: Magnetic resonance imaging; FIGO: Federation Internationale de Gynecologie et de Obstetrique; RTOG: Radiation Therapy Oncology Group; UK: United Kingdom; JCOG: Japan Clinical Oncology Group; CTV: Clinical target volume; NSR: Non-solitary region; OAR: Organs at risk; PET: Positron emission tomography.

Competing interests

The authors declare that they have no competing interests regarding this manuscript.

Authors' contributions
GK and TT designed this study, assembled the data, performed the statistical analysis and interpretation, and wrote the manuscript. KF, TK, TO, YK, RY, and TU provided study materials from each institution and proofed the manuscript. AY participated as a diagnostic radiologist and confirmed the distribution of positive lymph nodes. SI and MH helped to revise the manuscript. All authors read and approved the final manuscript.

Acknowledgment
This study was supported in part by the Grant-in-Aid for Cancer Research (20S-5) from the Ministry of Health, Labor and Welfare, Japan and National Center Research and Development Fund (23-A-21).

Author details
[1]Department of Radiology, Graduate School of Medical Science, University of the Ryukyus, Okinawa, Japan. [2]Department of Radiation Oncology, Aichi Cancer Center, Nagoya, Japan. [3]Heavy Ion Medical Center, Gunma University, Maebashi, Japan. [4]Department of Radiation Oncology, Graduate School of Biomedical Sciences, Hiroshima University, Hiroshima, Japan. [5]Department of Radiology, Tokyo Medical and Dental University, Tokyo, Japan. [6]Department of Radiology, Graduate School of Medicine, Chiba University, Chiba, Japan. [7]Department of Radiation Oncology, Juntendo University, Tokyo, Japan. [8]Department of Radiation Oncology and Image-applied Therapy, Kyoto University Graduate School of Medicine, Kyoto, Japan.

Received: 22 January 2013 Accepted: 1 June 2013
Published: 8 June 2013

References

1. Roeske JC, Lujan A, Mundt AJ, *et al*: **Intensity-modulated whole pelvic radiation therapy in patients with gynecologic malignancies.** *Int J Radiat Oncol Biol Phys* 2000, **48**:1613–1621.
2. Small W Jr, Mell LK, Anderson P, *et al*: **Consensus guidelines for delineation of clinical target volume for intensity-modulated pelvic radiotherapy in postoperative treatment of endometrial and cervical cancer.** *Int J Radiat Oncol Biol Phys* 2008, **71**:428–434.
3. Vilarino-Varela MJ, Taylor A, Rockall AG, *et al*: **A verification study of proposed pelvic lymph node localisation guidelines using nanoparticle-enhanced magnetic resonance imaging.** *Radiother Oncol* 2008, **89**:192–196.
4. Toita T, Ohno T, Kaneyasu Y, *et al*: **A consensus-base guideline defining the clinical target volume for pelvic lymph nodes in external beam radiotherapy for uterine cervical cancer.** *Jpn J Clin Oncol* 2010, **40**:456–463.
5. World Medical Association Declaration of Helsinki: **Ethical principles for medical research involving human subjects.** *JAMA* 2000, **284**:3043–3045.
6. Taylor A, Rockall AG, Reznek RH, *et al*: **Mapping pelvic lymph nodes: guidelines for delineation in intensity-modulated radiotherapy.** *Int J Radiat Oncol Biol Phys* 2005, **63**:1604–1612.
7. Lengelé B, Scalliet P: **Anatomical bases for the radiological delineation of lymph node areas. Part III: Pelvis and lower limbs.** *Radiother Oncol* 2009, **92**:22–33.
8. Grégoire V, Eisbruch A, Hamoir M, *et al*: **Proposal for the delineation of the nodal CTV in the node-positive and the post-operative neck.** *Radiother Oncol* 2006, **79**:15–20.
9. Ohara K, Tsunoda H, Satoh T, *et al*: **Use of the small pelvic field instead of the classic whole pelvic field in postoperative radiotherapy for cervical cancer: reduction of adverse events.** *Int J Radiat Oncol Biol Phys* 2004, **60**:258–264.
10. Oike T, Ohno T, Wakatsuki M, *et al*: **The benefit of small bowel and pelvic bone sparing in excluding common iliac lymph node region from conventional radiation fields in patients with uterine cervical cancer: a dosimetric study.** *J Radiat Res* 2010, **51**:715–721.
11. Sakuragi N, Satoh C, Takeda N, *et al*: **Incidence and distribution pattern of pelvic and paraaortic lymph node metastasis in patients with Stages IB, IIA, and IIB cervical carcinoma treated with radical hysterectomy.** *Cancer* 1999, **85**:1547–1554.
12. Benedetti-Panici P, Maneschi F, Scambia G, *et al*: **Lymphatic spread of cervical cancer: an anatomical and pathological study based on 225 radical hysterectomies with systematic pelvic and aortic lymphadenectomy.** *Gynecol Oncol* 1996, **62**:19–24.
13. Perez CA: *Uterine Cervix: principles and Practice of Radiation Oncology.* 3rd edition. Philadelphia: Lippincott-Raven; 1998:1736.
14. Bellomi M, Bonomo G, Landoni F, *et al*: **Accuracy of computed tomography and magnetic resonance imaging in the detection of lymph node involvement in cervix carcinoma.** *Eur Radiol* 2005, **15**:2469–2474.
15. Choi HJ, Roh JW, Seo SS, *et al*: **Comparison of the accuracy of magnetic resonance imaging and positron emission tomography/computed tomography in the presurgical detection of lymph node metastases in patients with uterine cervical carcinoma: a prospective study.** *Cancer* 2006, **106**:914–922.

doi:10.1186/1748-717X-8-139
Cite this article as: Kasuya *et al.*: Distribution patterns of metastatic pelvic lymph nodes assessed by CT/MRI in patients with uterine cervical cancer. *Radiation Oncology* 2013 **8**:139.

Journal of Radiation Research, 2013, 54, 919–924
doi: 10.1093/jrr/rrt025 Advance Access Publication 22 March 2013

Preliminary analysis of risk factors for late rectal toxicity after helical tomotherapy for prostate cancer

Natsuo TOMITA[1,*], Norihito SOGA[2], Yuji OGURA[2], Norio HAYASHI[2], Hidetoshi SHIMIZU[1], Takashi KUBOTA[1], Junji ITO[1], Kimiko HIRATA[1], Yukihiko OHSHIMA[1], Hiroyuki TACHIBANA[1] and Takeshi KODAIRA[1]

[1]Department of Radiation Oncology, Aichi Cancer Center Hospital, 1-1 Kanokoden, Chikusaku, Nagoya 464-8681, Japan
[2]Department of Urology, Aichi Cancer Center Hospital, 1-1 Kanokoden, Chikusaku, Nagoya 464-8681, Japan
*Corresponding author. Department of Radiation Oncology, Aichi Cancer Center Hospital, 1-1 Kanokoden, Chikusaku, Nagoya 464-8681, Japan. Tel: +81-52-762-6111; Fax: +81-52-752-8390; Email: ntomita@aichi-cc.jp

(Received 26 November 2012; revised 28 February 2013; accepted 28 February 2013)

The purpose of this study is to examine risk factors for late rectal toxicity for localized prostate cancer patients treated with helical tomotherapy (HT). The patient cohort of this retrospective study was composed of 241 patients treated with HT and followed up regularly. Toxicity levels were scored according to the Radiation Therapy Oncology Group grading scale. The clinical and dosimetric potential factors increasing the risk of late rectal toxicity, such as age, diabetes, anticoagulants, prior abdominal surgery, prescribed dose, maximum dose of the rectum, and the percentage of the rectum covered by 70 Gy (V70), 60 Gy (V60), 40 Gy (V40) and 20 Gy (V20) were compared between ≤ Grade 1 and ≥ Grade 2 toxicity groups using the Student's t-test. Multivariable logistic regression analysis of the factors that appeared to be associated with the risk of late rectal toxicity (as determined by the Student's t-test) was performed. The median follow-up time was 35 months. Late Grade 2–3 rectal toxicity was observed in 18 patients (7.4%). Age, the maximum dose of the rectum, V70 and V60 of the ≥ Grade 2 toxicity group were significantly higher than in those of the ≤ Grade 1 toxicity group ($P = 0.00093$, 0.048, 0.0030 and 0.0021, respectively). No factor was significant in the multivariable analysis. The result of this study indicates that the risk of late rectal toxicity correlates with the rectal volume exposed to high doses of HT for localized prostate cancer. Further follow-up and data accumulation may establish dose–volume modeling to predict rectal complications after HT.

Keywords: prostate cancer; helical tomotherapy; late toxicity; intensity-modulated radiation therapy; image-guided radiation therapy

INTRODUCTION

Intensity-modulated radiation therapy (IMRT) has been shown to reduce late rectal toxicity in high-dose external beam radiation therapy (EBRT) for prostate cancer [1], but essential issues remain to be solved. Factors increasing the risk of late rectal toxicity include not only the prescribed dose and radiation technique delivering the dose, but also some clinical characteristics. Major factors reportedly associated with rectal complication risks include diabetes mellitus [1, 2], advanced age [3], androgen deprivation therapy (ADT) [4], rectum size [5], and prior abdominal surgery [6]. In addition, acute rectal toxicity is now recognized to be associated with an increased risk of developing late rectal complications [7]. Rectum volumes at especially high-dose areas on the dose–volume histogram (DVH) also have an impact on late rectal toxicity. The following dose–volume constraints are provided as a conservative starting point for 3-dimensional conformal radiotherapy (3DCRT): V50 < 50%, V60 < 35%, V65 < 25%, V70 < 20%, and V75 < 15% [8], which have been derived from some 3DCRT experiences. However, such conventional dose–volume constraints may not be valuable in current clinical practices because the significance of IMRT has already been established in EBRT for localized prostate cancer [9]. IMRT planning yields DVH curves in distinctly different

shapes from those of forward-planned 3DCRT. In fact, the ratio of IMRT vs 3DCRT increased from 0.15% in the year 2000 to 95.9% in the year 2008 in the United States [10]. The significance of image-guided radiation therapy (IGRT) has also been established in this category [9]. Thus, dose–volume modeling derived from non-image guided 3DCRT may inevitably be modified to predict complications derived from image-guided IMRT (IG-IMRT). Data are, however, still too poor or insufficient to address dose–volume constraints in this modern combination technique.

Helical tomotherapy (HT, TomoTherapy, Madison, WI) is a form of IMRT, and detectors within the tomotherapy system provide megavolt–age computed tomographic (MVCT) images of patients, which can be obtained immediately before processes for setup, registration, and repositioning (i.e. IGRT). Next, we examined the impact of patient clinical characteristics and DVH parameters on late rectal toxicity after HT treatment for non-metastatic prostate cancer. We report the results of the examinations. It is of particular interest to describe dose–volume modeling to predict rectal complications after HT.

MATERIALS AND METHODS

Patients and treatment methods

A total of 241 consecutive patients clinically diagnosed with non-metastatic prostate cancer, who were treated with HT between June 2006 and December 2010 and followed up regularly at our institution, were enrolled in this study. Written informed consent for the treatment and an anonymous data application were obtained from each of the patients before the treatment. Pretreatment evaluations, androgen deprivation therapy (ADT), and HT treatment were described circumstantially in our previous study [11]. In brief, the clinical target volume (CTV) was defined as the entire prostate and the proximal seminal vesicle. The planning target volume 1 (PTV1) included the CTV with a 6–8 mm margin except for the prostatorectal interface, where a 4–6 mm margin was used. Outside PTV1, PTV2 was defined as the seminal vesicle with a similar margin to that of PTV1. By our definition, only the rectum around the PTV1 area with a cranio-caudal 10-mm margin is delineated as an organ at risk. Prescribed doses were PTV1 D95 (i.e. dose delivered to 95% of PTV1): 74 Gy in the low-risk group, 78 Gy in the intermediate- and high-risk groups, and PTV2 D95: 64 Gy in all of the risk groups. Patients had a tube inserted or were encouraged to defecate when their rectums were dilated on daily MVCT, and were checked on MVCT again.

Follow-up evaluations and data collection

Follow-up evaluations after the treatment were performed at 3-month intervals. Toxicity levels were scored according to the Radiation Therapy Oncology Group (RTOG) morbidity grading scale [12]. In brief, Grade 1 toxicity represents minimal side effects not requiring medication for symptom control; Grade 2 toxicity indicates symptoms requiring medication; Grade 3 indicates complications requiring minor surgical intervention (i.e. laser coagulation); and Grade 4 requires hospitalization and major intervention. The time until the occurrence of late toxicity was represented as the period from the start date of HT.

Patient characteristics (e.g. age, T-stage, diabetes mellitus, anticoagulants, and history of abdominal surgery) and DVH parameters (prescribed dose, PTV volume, rectal volume, mean dose of the rectum, maximum dose of the rectum, the percentage of the rectum at least covered by 70 Gy [V70], 60 Gy [V60], 40 Gy [V40], or 20 Gy [V20]) were collected from the patients on their initial visits to our departments. Total ADT time and acute and late rectal toxicities were reviewed on the patients' charts in the analysis. The prescribed dose on the DVH and the practically delivered dose varied from one another in seven of the patients, because of HT cessation for a range of reasons such as acute rectal symptoms. Practically delivered doses were 74 Gy in six of the patients and 70 Gy in one patient, despite the prescribed dose of 78 Gy on the DVH. In these patients, the prescribed dose, the mean dose of the rectum, the maximum dose of the rectum, V70, V60, V40, and V20 were approximately shown by these values on the DVH × practically delivered dose (70 or 74 Gy)/prescribed dose on the DVH (78 Gy) in this analysis. Table 1 shows patient characteristics and DVH parameters for this patient cohort.

Statistical analyses

The impact of clinical and dosimetric factors on Grade 2 or higher late rectal toxicity was analyzed. The clinical and dosimetric potential factors increasing the risk of late rectal toxicity were compared between the ≤ Grade 1 and the ≥ Grade 2 toxicity groups and were then analyzed by the Student's t-test. The following factors were examined: the patient characteristics described above, total ADT time, the presence of Grade 2 or higher acute rectal toxicity, and the DVH parameters described above. Multivariable logistic regression analysis was carried out for the factors that previously appeared to be associated with the risk of late rectal toxicity by the Student's t-test ($P < 0.10$). Significance was determined at a P value of <0.05.

RESULTS

Late rectal toxicity

The median follow-up time from the start of HT was 35 months (range, 13–66 months). Rectal toxicity has been described in detail in our previous study [11]. Briefly, 18 (7.4%) of the patients developed late Grade 2 or 3 rectal toxicity. Of the 16 patients (6.6%) who developed late

Table 1. Patient characteristics and DVH parameters

Characteristic	Total	($n = 241$)
Age (years)	69	(49–81)
PSA level (ng/ml)	15.17	(1.40–502.00)
Gleason score	7	(5–10)
Tumor stage		
T1–T2	109	(45.2%)
T3–T4	132	(54.8%)
Risk group		
Low	17	(7.0%)
Intermediate	53	(22.0%)
High	171	(71.0%)
Diabetes (%)	23	(9.5%)
Anticoagulants (%)	41	(17.0%)
Abdominal surgery (%)	21	(9.4%)
ADT (month)	27	(4–92)
≥ Grade 2 acute toxicity (%)	27	(11.2%)
PTV volume (cc)	59.0	(20.7–190.9)
Rectum volume (cc)	41.9	(21.8–113.7)
Prescribed dose (Gy)	78.0	(70.0–78.0)
Rectum mean dose (Gy)	38.8	(27.0–46.4)
Rectum max dose (Gy)	80.2	(70.1–83.8)
V70 (%)	7.2	(0.1–13.6)
V60 (%)	15.5	(1.9–25.6)
V40 (%)	38.1	(20.0–77.8)
V20 (%)	90.0	(45.0–100.0)

DVH = dose-volume histogram, ADT = androgen deprivation therapy, V dose = the percentage of the rectum at least covered by each dose; PTV = planning target volume. Age, PSA, ADT and DVH parameters are represented as mean and ranges.

Grade 2 rectal toxicity, 13 developed Grade 2 rectal bleeding. Other Grade 2 symptoms were pain on defecation in two of the patients and subtle fecal incontinence in one of the patients. Two patients (0.8%) developed Grade 3 rectal bleeding requiring laser coagulation. No Grade 4 late rectal complications were observed. Figure 1 shows the rate of developing late Grade 2 or higher rectal toxicity in the time course after HT.

Analysis of risk factors associated with late rectal toxicity

Table 2 shows the effects of patient characteristics and DVH parameters on Grade 2 or higher late rectal toxicity as analyzed by the Student's t-test. Age, maximum dose of the rectum, V70, and V60 were significantly variable between the ≤ Grade 1 and the ≥ Grade 2 toxicity groups as analyzed by the Student's t-test ($P = 0.00093$, 0.048, 0.0030 and 0.0021, respectively). To further evaluate the independent effects of the factors that displayed a P-value <0.10 by the Student's t-test, such as age, anticoagulants, the maximum dose of the rectum, V70 and V60 on ≥ Grade 2 late rectal toxicity, a multivariable logistic regression analysis was performed. None of the factors were found to be significantly correlated by this analysis, as shown in Table 3.

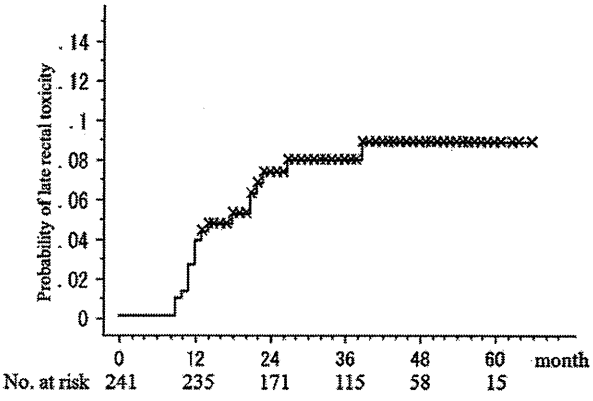


Fig. 1. The rate of developing late ≥ Grade 2 rectal toxicity after helical tomotherapy.

Figure 2 shows the mean DVH and standard deviations (SD) of patients with or without Grade 2 or higher late rectal toxicity after HT. The maximum dose of the rectum, V70, V60, V40 and V20 for patients with ≥ Grade 2 late rectal toxicity vs those with ≤ Grade 1 late rectal toxicity were 80.1 ± 2.0 Gy vs 79.2 ± 3.3 Gy, 9.0 ± 2.9% vs 6.8 ± 3.5%, 17.6 ± 3.5% vs 14.8 ± 5.0%, 39.6 ± 8.4% vs 39.9 ± 8.7%, and 84.7 ± 10.3% vs 87.1 ± 10.1%, respectively.

DISCUSSION

The DVH curves of IMRT are distinctly different from those of forward-planned 3DCRT. The combined use of IGRT may also have a possible impact on the DVH difference between IGRT and non-IGRT treatments because significant margin reduction between the prostate and PTV could be implemented clinically with the combined use of IGRT [13]. The results of the present study indicate that the risk of late rectal toxicity correlates with the rectal volume exposed to high doses in the HT treatment (i.e. IG-IMRT) for localized prostate cancer, although there were no significant factors in the multivariable logistic regression analysis. This suggestion is consistent with other reports derived from the 3DCRT data. Kuban *et al.* assessed the impact of 70 Gy vs 78 Gy doses on gastro-intestinal (GI) toxicity in 301 patients treated with 3DCRT. After a median follow-up

Table 2. The effects of patient characteristics and DVH parameters on ≥ Grade 2 late rectal toxicity after helical tomotherapy, as analyzed by the Student's t-test

Characteristic	≤ Grade 1 ($n = 223$)	≥ Grade 2 ($n = 18$)	*P*-value
Age (years)	68.5 ± 6.1	71.2 ± 4.2	0.0093*
Tumor stage (≥T3)	55.2%	50.0%	0.34
Diabetes (%)	9.4%	11.1%	0.42
Anticoagulants (%)	15.7%	33.3%	0.074
Abdominal surgery (%)	9.0%	5.6%	0.28
ADT (≥27 months)	48.4%	27.8%	0.26
Acute toxicity (%)	11.7%	5.6%	0.11
PTV volume (cc)	62.1 ± 22.9	66.6 ± 18.3	0.17
Rectum volume (cc)	44.5 ± 13.9	42.1 ± 16.4	0.28
Prescribed dose (Gy)	77.5 ± 1.4	77.3 ± 1.5	0.28
Rectum mean dose (Gy)	39.2 ± 5.0	38.6 ± 3.5	0.27
Rectum max dose (Gy)	79.2 ± 3.3	80.1 ± 2.0	0.048*
V70 (%)	6.8 ± 3.5	9.0 ± 2.9	0.0030*
V60 (%)	14.8 ± 5.0	17.6 ± 3.5	0.0021*
V40 (%)	39.9 ± 8.7	39.5 ± 8.4	0.43
V20 (%)	87.1 ± 10.1	84.7 ± 10.3	0.18

DVH = dose-volume histogram, ADT = androgen deprivation therapy, V dose = the percentage of the rectum at least covered by each dose. Age and DVH parameters are represented as mean ± SD. *Statistically significant.

Table 3. The effects of patient characteristics and DVH parameters on ≥ Grade 2 late rectal toxicity after helical tomotherapy, as analyzed by multivariable logistic regression analysis

Characteristic	*P*-value	Hazard ratio (CI)
Age (years)	0.10	1.08 (0.99–1.19)
Anticoagulants (%)	0.12	2.18 (0.81–5.88)
Rectum max dose (Gy)	0.87	0.99 (0.82–1.19)
V70 (%)	0.16	1.30 (0.91–1.85)
V60 (%)	0.85	0.98 (0.78–1.23)

DVH = dose–volume histogram, ADT = androgen deprivation therapy, V dose = the percentage of the rectum at least covered by each dose, CI = 95% confidence interval, NA = not applicable.

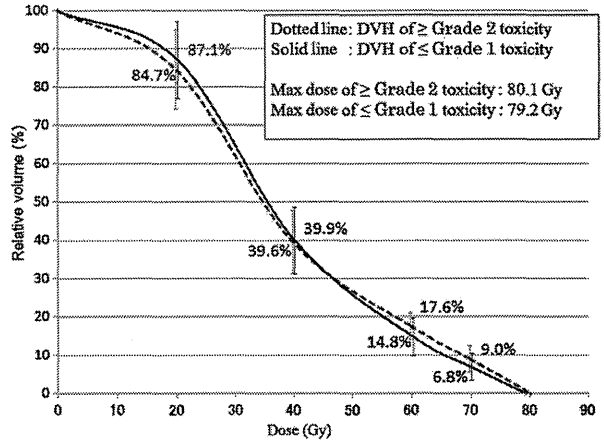


Fig. 2. The mean dose–volume histograms and standard deviations (SD) of patients with or without ≥ Grade 2 late rectal toxicity after helical tomotherapy.

period of 8.7 years, GI toxicity more severe than RTOG Grade 2 was often observed in high-dose patients (28% vs 15%; $P = 0.013$). DVH analysis showed that the incidence of complications could be significantly decreased by reducing the volume of the treated rectum. When <25% of the rectum was treated with >70 Gy, the Grade 2-or-greater complication incidence at 6 years post-treatment was much reduced, 16% as compared with 46% when this dose–volume cutoff point was exceeded [14]. Tucker *et al.* also analyzed DVH data from 1009 patients treated with 3DCRT on RTOG protocol 94-06. In these data, no evidence was found of any influence of the intermediate doses on the risk of ≥ Grade 2 late rectal toxicities. The critical dose for this endpoint seemed to be ≥75 Gy [15]. The results of our present study suggests that patients with advanced age are at risk of rectal complication. The routine

medication of anticoagulants may be also associated with rectal bleeding, as shown in Table 2 and 3. These results are in line with the reports of Skwarchuk *et al.* [3] and Pederson *et al.* [16]. Even when optimal dose–volume constraints are applied, rectal complications can still occur due to clinical factors such as anticoagulant medications or advanced age.

Most of the mature published clinical data on dose-related rectal toxicity originate from 3DCRT. Some data derived from 3DCRT experiences recommended V60 < 35% and V70 < 20% as a conservative starting point for the dose–volume constraints for 3DCRT [8]. As shown in Table 1, the mean values of V70 and V60 were 7.2 (range, 0.1–13.6) and 15.5 (range, 1.9–25.6), respectively, in this patient cohort treated with HT. Although these values fulfill the terms of the conventional dose–volume constraints described above, we observed late Grade 2 or 3 rectal toxicities in 7.4% of the patients. This result indicates that tighter dose–volume constraints of the rectum would be necessary for IG-IMRT than the conventional constraints derived from the clinical data of 3DCRT. On the other hand, caution should be taken in interpreting this result, because Fig. 2 simply shows the mean DVH with or without Grade 2 or higher late rectal toxicity. In fact, the SDs of patients with or without late rectal toxicity overlapped considerably at each of the doses, as shown in Fig. 2. Further follow-up and data accumulation are needed to evaluate the clinical significance of the small absolute difference in the high-dose areas. To our knowledge, only one study has investigated dosimetric risk factors for late rectal toxicity after IMRT. Pederson *et al.* have reported that the incidence of ≥ Grade 2 rectal toxicity was 5% in 296 consecutive patients treated with IMRT with a median follow-up period of 41 months [16]. They found that 100% of men with rectal V70 ≤ 10%, V65 ≤ 20%, and V40 ≤ 40% were free from ≥ Grade 2 rectal toxicity; 92% of men with rectal V70 ≤ 20%, V65 ≤ 40%, and V40 ≤ 80% as well as 85% of men exceeding these criteria were also free from the toxicity. The results of their study together with those of our study also suggest that more stringent dose–volume constraints are necessary for IMRT compared with 3DCRT.

The reliability of this study resides in the use of IGRT involving MVCT. The position of the rectum at the time of the treatment planning CT scan is likely not fully representative of the position during RT because of intrafraction variations in rectal filling, intestinal gas, and bladder filling. We think that these uncertainties have little influence on the present study because we checked these situations carefully in both the CT simulation and the pretreatment MVCT, and because patients had a tube inserted or were encouraged to defecate as necessary. On the other hand, two essential points need to be considered when interpreting the results of this study. Firstly, we need to define the rectum. This study has specified rectal lengths only around the PTV1 area with a cranio-caudal 10-mm margin. However, DVH studies so far have used variable definitions for the rectum [8, 16]. The rectosigmoid flexure is an uncertainty as the superior limit in determining where the rectum starts. The inferior limit has been variably defined as being at the level of the anal verge, the ischial tuberosities, or above the anus. Our definition of the rectum has been reasonably accepted so far among physicians. It is frequently contoured as a solid, and we have adopted this definition in our study. Secondly, we need to consider the problem of the diversity of the toxicity. We brought together all late rectal symptoms in the analyses of factors associated with late rectal toxicity, including some types of sequelae such as rectal bleeding, pain on defecation, and fecal incontinence. Refined knowledge of the location of dose maximums in combination with separate scoring and modeling of the different aspects of rectal toxicity clarifies specific anatomic regions of dose sensitivity [8]. However, the symptoms were mostly rectal bleeding in this study (15 of 18 patients who developed late Grade 2 or 3 rectal toxicity). We considered that lumping all rectal symptoms had little influence on the results of this study.

The treatment of rectal bleeding is also a critical issue in high-dose EBRT for prostate cancer. Takemoto *et al.* evaluated the results of the treatment for hemorrhagic proctitis after IMRT for prostate cancer [17]. Among 403 patients treated with IMRT, 64 developed late rectal bleeding with a median follow-up time of 35 months. Most patients were ameliorated with the steroid suppositories as medication, or even without any treatment, but one patient treated with steroid enemas for 12 months developed septic shock and died of multiple organ failure. All of the 12 patients treated with Argon plasma coagulation (APC) were ameliorated in that study. They concluded that steroid suppositories/enemas and APC were effective, although a short duration of the administration with an appropriate steroid dosage is recommended. We also treated patients developing rectal bleeding with steroid suppositories. Two of these patients showed no response to steroid suppositories so they then received APC. All patients with Grade 2 or 3 rectal bleeding got an improvement with steroid suppositories or APC in our present study, as in the report by Takemoto *et al.*

In conclusion, we have demonstrated the impact of patient clinical characteristics and DVH parameters on late rectal toxicity in a large number of non-metastatic prostate cancer patients after HT treatment. Late Grade 2–3 rectal toxicities were observed in 7.4% of the patients. The result of this study indicates that the risk of late rectal toxicity correlates with increase in age and the rectal volume exposed to high doses in HT treatment for localized prostate cancer. Further follow-up and data accumulation may establish dose–volume modeling to predict rectal complications after HT.

ACKNOWLEDGEMENTS

This study was presented at the 25th Annual Meeting of the Japanese Society for Therapeutic Radiology and Oncology.

REFERENCES

1. Peeters ST, Lebesque JV, Heemsbergen WD *et al.* Localized volume effects for late rectal and anal toxicity after radiotherapy for prostate cancer. *Int J Radiat Oncol Biol Phys* 2006;**64**:1151–61.
2. Vavassori V, Fiorino C, Rancati T *et al.* Predictors for rectal and intestinal acute toxicities during prostate cancer high-dose 3D-CRT: results of a prospective multicenter study. *Int J Radiat Oncol Biol Phys* 2007;**67**:1401–10.
3. Skwarchuk MW, Jackson A, Zelefsky MJ *et al.* Late rectal toxicity after conformal radiotherapy of prostate cancer (I): multivariate analysis and dose-response. *Int J Radiat Oncol Biol Phys* 2000;**47**:103–13.
4. Liu M, Pickles T, Agranovich A *et al.* Impact of neoadjuvant androgen ablation and other factors on late toxicity after external beam prostate radiotherapy. *Int J Radiat Oncol Biol Phys* 2004;**58**:59–67.
5. Wachter S, Gerstner N, Goldner G *et al.* Rectal sequelae after conformal radiotherapy of prostate cancer: dose-volume histograms as predictive factors. *Radiother Oncol* 2001;**59**:65–70.
6. Valdagni R, Vavassori V, Rancati T *et al.* Increasing the risk of late rectal bleeding after high-dose radiotherapy for prostate cancer: the case of previous abdominal surgery. Results from a prospective trial. *Radiother Oncol* 2012;**103**:252–5.
7. Zelefsky MJ, Levin EJ, Hunt M *et al.* Incidence of late rectal and urinary toxicities after three-dimensional conformal radiotherapy and intensity-modulated radiotherapy for localized prostate cancer. *Int J Radiat Oncol Biol Phys* 2008;**70**:1124–9.
8. Michalski JM, Gay H, Jackson A *et al.* Radiation dose-volume effects in radiation-induced rectal injury. *Int J Radiat Oncol Biol Phys* 2010;**76**:S123–9.
9. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: prostate cancer V1 2011. http://www.nccn.org/ (10 April 2012, data last accessed).
10. Sheets NC, Goldin GH, Meyer AM *et al.* Intensity-modulated radiation therapy, proton therapy, or conformal radiation therapy and morbidity and disease control in localized prostate cancer. *JAMA* 2012;**307**:1611–20.
11. Tomita N, Soga N, Ogura Y *et al.* Preliminary results of intensity-modulated radiation therapy with helical tomotherapy for prostate cancer. *J Cancer Res Clin Oncol* 2012;**138**: 1931–6.
12. Cox JD, Stetz J, Pajak TF. Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). *Int J Radiat Oncol Biol Phys* 1995;**31**:1341–6.
13. Crehange G, Mirjolet C, Gauthier M *et al.* Clinical impact of margin reduction on late toxicity and short-term biochemical control for patients treated with daily on-line image guided IMRT for prostate cancer. *Radiother Oncol* 2012;**103**:244–6.
14. Kuban DA, Tucker SL, Dong L *et al.* Long-term results of the M. D. Anderson randomized dose-escalation trial for prostate cancer. *Int J Radiat Oncol Biol Phys* 2008;**70**:67–74.
15. Tucker SL, Dong L, Michalski JM *et al.* Do intermediate radiation doses contribute to late rectal toxicity? An analysis of data from radiation therapy oncology group protocol 94-06. *Int J Radiat Oncol Biol Phys* 2012;**84**:390–5.
16. Pederson AW, Fricano J, Correa D *et al.* Late toxicity after intensity-modulated radiation therapy for localized prostate cancer: an exploration of dose-volume histogram parameters to limit genitourinary and gastrointestinal toxicity. *Int J Radiat Oncol Biol Phys* 2012;**82**:235–41.
17. Takemoto S, Shibamoto Y, Ayakawa S *et al.* Treatment and prognosis of patients with late rectal bleeding after intensity-modulated radiation therapy for prostate cancer. *Radiat Oncol* 2012;**7**:87.

Japanese Journal of Clinical Oncology Advance Access published March 17, 2013

JJCO Japanese Journal of Clinical Oncology

Jpn J Clin Oncol 2013
doi:10.1093/jjco/hyt030

Original Article

Phase II Study of Cetuximab Plus Concomitant Boost Radiotherapy in Japanese Patients with Locally Advanced Squamous Cell Carcinoma of the Head and Neck

Susumu Okano[1,2], Takayuki Yoshino[1,*], Masato Fujii[3], Yusuke Onozawa[4], Takeshi Kodaira[5], Hirofumi Fujii[6], Tetsuo Akimoto[7], Satoshi Ishikura[8], Masahiko Oguchi[9], Sadamoto Zenda[7,10], Barbara de Blas[11] and Makoto Tahara[1]

[1]Department of Gastroenterology and Gastrointestinal Oncology, National Cancer Center Hospital East, Chiba, [2]Department of Otorhinolaryngology, Jikei University School of Medicine, Tokyo, [3]Department of Otolaryngology, National Tokyo Medical Center, Tokyo, [4]Division of Clinical Oncology, Shizuoka Cancer Center, Shizuoka, [5]Department of Radiation Oncology, Aichi Cancer Center Hospital, Aichi, [6]Department of Clinical Oncology, Jichi Medical University Hospital, Tochigi, [7]Department of Radiation Oncology and Particle Therapy, National Cancer Center Hospital East, Chiba, [8]Department of Radiology, Juntendo University, Tokyo, [9]Radiation Oncology Department, Cancer Institute Hospital, Tokyo, [10]Department of Head and Neck Surgery, Tokyo Medical and Dental University, Tokyo, Japan and [11]Merck KGaA, Darmstadt, Germany

*For reprints and all correspondence: T. Yoshino, National Cancer Center Hospital East, 6-5-1 Kashiwanoha, Kashiwa, Chiba 277-8577, Japan. E-mail: tyoshino@east.ncc.go.jp

Received November 6, 2012; accepted February 11, 2013

Background: We investigated the tolerability of cetuximab plus radiotherapy in Japanese patients with untreated locally advanced squamous cell carcinoma of the head and neck.
Methods: Patients with epidermal growth factor receptor-expressing locally advanced squamous cell carcinoma of the head and neck received cetuximab (400 mg/m^2 initial dose then 250 mg/m^2 weekly) for 7 weeks plus concomitant boost radiotherapy (weeks 2–7: once daily [1.8 Gy] for 3.6 weeks, then twice daily [1.8 Gy morning and 1.5 Gy afternoon] for 2.4 weeks). The primary endpoint was treatment completion rate (the rate of treated patients completing $\geq$70% of the planned cetuximab dose and the full dose of radiotherapy within 2 weeks over the planned schedule).
Results: Twenty-two patients were evaluable. The treatment completion rate was 100% (95% confidence interval 85–100). The response rate 8 weeks post-radiotherapy was 82% (95% confidence interval 60–95). The most common grade 3/4 treatment-emergent adverse events were mucosal inflammation (73%); dermatitis (27%); and infection, radiation skin injury and stomatitis (23% each).
Conclusions: Cetuximab plus concomitant boost radiotherapy can be safely administered to Japanese patients with locally advanced squamous cell carcinoma of the head and neck. Tolerability and efficacy were in line with those reported in the Phase III Bonner trial in a Western population of patients with locally advanced squamous cell carcinoma of the head and neck.

Key words: cetuximab – concomitant boost – Japanese – locally advanced – radiotherapy – squamous cell carcinoma of the head and neck

INTRODUCTION

Globally, cancers of the lip, oral cavity, pharynx (other than nasopharynx) and larynx account for over 4% of all malignancies, with more than 500 000 new cases worldwide and 300 000 attributed deaths reported in 2008 (1). In Japan alone, in 2007, 7879 people died of head and neck cancer, representing 2.3% of all cancer deaths that year (2).

Patients with locally advanced squamous cell carcinoma (SCC) of the head and neck (LASCCHN) have a number of treatment options available, depending on regulatory authority approvals. These options include concurrently administered chemoradiotherapy with or without surgery and the combination of the EGFR-targeting IgG1 monoclonal antibody cetuximab and radiotherapy (3,4). The use of cetuximab in combination with radiotherapy grew out of the finding that epidermal growth factor receptor (EGFR) is expressed by almost all SCCs of the head and neck (SCCHN) (5,6) and the observation from *in vivo* models that this combination enhanced tumor regression compared with radiation or cetuximab alone (7). Regulatory approval of the combination of cetuximab and radiotherapy in the USA and the EU was based on the results of the large Phase III trial conducted by Bonner et al. in centers in the USA and 14 other countries (8). This trial reported that the addition of cetuximab to once-daily, twice-daily or concomitant boost radiotherapy significantly improved overall survival, progression-free survival and locoregional control compared with radiotherapy alone in patients with LASCCHN. Survival benefits were maintained long term, with 5-year overall survival rates of 46% in the cetuximab plus radiotherapy arm and 36% in the radiotherapy alone arm (9).

It was notable that the addition of cetuximab to radiotherapy in the Bonner trial did not exacerbate the adverse events commonly associated with radiotherapy of the head and neck, including mucositis, xerostomia and dysphagia (8). Among grade ≥ 3 reactions, only acneiform rash and infusion reactions, both with a known association to cetuximab, occurred with a higher incidence in the cetuximab plus radiotherapy arm compared with the radiotherapy arm of the trial.

The Phase II study reported here was initiated to assess the tolerability and feasibility of administering cetuximab together with the concomitant boost radiotherapy regimen used in the Bonner trial to Japanese patients with newly diagnosed LASCCHN. The concomitant boost radiotherapy regimen was chosen because it was the most frequently used in the Bonner trial and the results from our trial would therefore be appropriate for comparison with those from the Bonner trial. Tumor response to treatment was also evaluated in this study.

PATIENTS AND METHODS

Patient Selection

The inclusion criteria used in this study closely followed those used in the Bonner trial to ensure that the patient, disease and treatment characteristics were similar in the two studies. Japanese patients with Stage III or IV (Union for International Cancer Control TNM classification) pathologically proven SCC of the oropharynx, hypopharynx or larynx confirmed by magnetic resonance imaging (MRI) and computed tomography (CT) and with tumor EGFR expression and an expected survival of at least 12 months were eligible for inclusion in the study. Tumor EGFR expression was determined at a single reference laboratory (SRL Medisearch, Inc., Tokyo, Japan) by immunohistochemistry on formalin-fixed or paraffin-embedded tumor tissue using the DAKO pharmDx kit (Glostrup, Denmark). The minimum criterion required to confirm EGFR expression was any intensity of membrane staining above-background level by at least one cell. Other main criteria were: at least bi-dimensionally measurable disease; age ≥ 20 years; Karnofsky performance status (KPS) ≥ 60; adequate bone marrow, kidney and liver function; no distant metastases; no prior chemotherapy within the last 3 years; no prior radiotherapy to the head and neck; and no prior treatment with cetuximab.

The study protocol was approved by institutional review boards and the trial was conducted in accordance with the protocol and with the ethical principles of the Declaration of Helsinki, as well as with the International Conference on Harmonization (ICH) Note for Guidance on Good Clinical Practice (GCP) (ICH Topic E6, 1996), the Japanese ministerial ordinance on GCP, the standard stipulated in Articles 14-3 and 80-2 of the Japanese Pharmaceutical Affairs Law, and applicable regulatory requirements. A quality assurance review of the data was conducted and an independent Radiation Therapy Quality Assurance Committee was set up to ensure compatibility of the type of radiotherapy used at each center with that defined in the protocol. All patients provided written informed consent and were also asked to provide informed consent for investigation of biomarkers other than EGFR in their tumor tissue.

Study Design and Treatment

This was an open-label, Phase II study conducted in patients with newly diagnosed LASCCHN across four centers in Japan. The primary endpoint of the study was tolerability, the main variable of which was treatment completion rate: the rate of patients who completed $\geq 70\%$ of the cetuximab planned dose administration (in terms of relative dose intensity [RDI] of cetuximab) and the full dose of radiotherapy within 2 weeks over the planned schedule of ≤ 8 weeks. The RDI of cetuximab of $\geq 70\%$ was estimated to be equivalent to no more than one missed dose of cetuximab, which, based on calculations on dose intensity data from the Bonner trial, was considered to be the minimum dose level required for cetuximab clinical activity. The selection of an RDI of $\geq 70\%$ as a component of the treatment completion rate was therefore considered to represent tolerability at clinically effective doses. A secondary efficacy endpoint was the best