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Cancer Science
Japanese Cancer Association JCA
Open Access

Impact of *KRAS* mutation on response and outcome of patients with stage III non-squamous non-small cell lung cancer

Shigehiro Yagishita,[1,2] Hidehito Horinouchi,[1,3] Kuniko S. Sunami,[1,3,5] Shintaro Kanda,[1] Yutaka Fujiwara,[1] Hiroshi Nokihara,[1] Noboru Yamamoto,[1] Minako Sumi,[4] Kouya Shiraishi,[5] Takashi Kohno,[5] Koh Furuta,[6] Koji Tsuta,[7] Tomohide Tamura[1] and Yuichiro Ohe[1,3]

[1]Department of Thoracic Oncology, National Cancer Center Hospital, Tokyo; [2]Department of Respiratory Medicine, Juntendo University Graduate School of Medicine, Tokyo; [3]Advanced Clinical Research of Cancer, Juntendo University Graduate School of Medicine, Tokyo; [4]Department of Radiation Oncology, National Cancer Center Hospital, Tokyo; [5]Division of Genome Biology, National Cancer Center Research Institute, Tokyo; Departments of [6] Clinical Laboratories, Tokyo; [7]Pathology, National Cancer Center Hospital, Tokyo, Japan

Key words

Biomarkers, chemoradiotherapy, *KRAS*, non-small cell lung cancer, relapse

Correspondence

Hidehito Horinouchi, Department of Thoracic Oncology, National Cancer Center Hospital, Tsukiji 5-1-1, Chuo-ku, Tokyo 104-0045, Japan.
Tel: +81-3-3542-2511; Fax:+81-3-3542-3815;
E-mail: hhorinou@ncc.go.jp

Funding Information

This work was supported in part by the National Cancer Center Research and Development Fund (23-A-30, 24-A-1), by Grants-in-Aid from the Ministry of Education, Culture, Sports, Science, and Technology of Japan for Scientific Research on Innovative Areas (22131006), and by a Grant-in-Aid for the Third-Term Comprehensive 10-Year Strategy for Cancer Control of Japan including Awardee of Research Resident Fellowship from the Foundation for Promotion of Cancer Research (Japan).

Received April 28, 2015; Revised July 8, 2015; Accepted July 9, 2015

Cancer Sci **106** (2015) 1402–1407

doi: 10.1111/cas.12740

The frequency and clinical profile of patients with stage III non-small cell lung cancer harboring *KRAS* mutations have not yet been well documented. Here, we analyzed hotspot *KRAS* mutations using high-resolution melting analyses in tumor specimens from patients who received chemoradiotherapy between January 2001 and December 2010 at the National Cancer Center Hospital. The associations between the presence of *KRAS* mutations and the response rate, relapse-free survival, first relapse sites, survival post-progression and overall survival were investigated. A total of 274 non-squamous non-small cell lung cancer patients received chemoradiotherapy at our hospital. After excluding 121 patients for whom tumor specimens were not available and 34 patients with *EGFR* mutations, the remaining 119 patients were included in the analysis. *KRAS* mutations were found at a frequency of 13%. Patients with *KRAS* mutations had a shorter median relapse-free survival (6.1 *vs* 10.9 months) and a lower response rate (63% *vs* 81%). As for the first relapse site, patients with KRAS mutations had fewer local relapses (8% *vs* 23%) and more brain metastases (46% *vs* 12%). After disease progression, patients with *KRAS* mutations had a significantly shorter median survival post-progression (2.5 *vs* 7.3 months, $P = 0.028$) and median overall survival (15.1 *vs* 29.1 months, $P = 0.022$). Our results suggested that *KRAS* mutation could be associated with a reduced efficacy of chemoradiotherapy and a shortened survival time.

Lung cancer remains the leading cause of cancer-related deaths worldwide.[1] Non-small cell lung cancer (NSCLC) accounts for 80% of all lung cancer cases, and approximately 30% of patients with NSCLC present with stage III disease.[2,3] For patients with a good performance status and adequate organ function, combined chemotherapy plus radiotherapy (RT) is the standard of care.[4,5] Combined platinum-containing chemotherapy with concurrent radiotherapy (CRT) has been reported to offer a median survival time of approximately 20 months.[6–10]

The Kirstein rat sarcoma viral oncogene homolog (*KRAS*) mutation is one of the most frequently observed somatic mutations in NSCLC, particularly non-squamous NSCLC. Hotspot *KRAS* mutations induce the irreversible and continuous activation of RAS-dependent downstream signals.[11] The impact of *KRAS* mutations in NSCLC was reported over 20 years ago as being associated with a poor prognosis.[12] Since then, the clinical significance of the *KRAS* mutation has been widely studied[13–16]zx; however, the results of studies have not been consistent, probably because of the heterogeneity of patients included in the analyses. Thus, association studies for *KRAS* mutations should be performed in a cohort of patients with a defined progressive status who are receiving a standard therapy.

In the present study, the prevalence of *KRAS* mutations and their impact on the therapeutic responses and outcomes were examined in a patient cohort with stage III non-squamous NSCLC. All the patients received definitive CRT at a single hospital. The impact of *KRAS* mutation on the therapeutic responses and outcomes was examined.

Materials and Methods

Patients. Between January 2001 and December 2010, a total of 528 NSCLC patients received CRT at the National Cancer Center Hospital, Japan. Under an institutional review board-approved protocol, we reviewed the medical records of these

patients (approval number: 2012-187). During the review, we identified 274 patients with unresectable stage III non-squamous NSCLC. We excluded patients with epidermal growth factor receptor (EGFR)-activating mutations because we had observed a characteristic effect of EGFR mutation on the pattern of recurrence and patient outcome among patients with stage III non-squamous NSCLC.[17]

The following data regarding the pretreatment patient characteristics were collected: patient age, sex, Eastern Cooperative Oncology Group (ECOG) performance status (PS) and smoking history. The tumor characteristics were noted, including the histology and TNM stage, according to the sixth edition of the Union for International Cancer Control. T and N staging was based on computed tomography (CT) findings, [18F] fluorodeoxyglucose PET findings, and a pathological diagnosis of N2 based on the results of invasive procedures, if applicable. Data on the treatment characteristics, including the radiation dose, the timing of RT (concurrent or sequential), the chemotherapy regimens, the number of chemotherapy cycles and the treatment after disease relapse were also collected.

***KRAS* mutational analysis.** Screening for *KRAS* mutations in exon 2 (codon 12 and 13) was performed using cytological specimens or paraffin-embedded tumor specimens and a high-resolution melting analysis, as previously described.[18] All the *KRAS* mutational statuses were determined using tumor specimens obtained at the time of first diagnosis. For tumors with an unknown *KRAS* mutational status, we analyzed specimens obtained before the initial treatment for the purpose of this study. All tumor specimens were checked by HE stain for tumor content before analyses.

Efficacy analysis. Tumor responses were classified according to the Response Evaluation Criteria for Solid Tumors (RECIST), version 1.1. In compliance with the protocols of clinical trials or clinical practice, all the patients were regularly followed up every 1 to 2 months in the outpatient department. Regular work-ups were performed every 3 to 6 months within the first year after the completion of CRT and were subsequently performed every 6 months. Regular systemic work-ups included chest X-ray, chest and abdominal CT, brain CT or MRI and PET examinations, as needed. Relapse-free survival (RFS) was defined as the time from the first day of chemotherapy to the detection of the earliest signs of disease progression using CT or MRI, or death from any cause. The time to local relapse (TTLR) and the time to distant relapse (TTDR) were defined as the time from the first day of chemotherapy until the detection of the earliest signs of disease progression within and outside of the field of radiotherapy, respectively. Overall survival was defined as the time from the first day of chemotherapy until the last day on which the patient was confirmed to be alive or dead from any cause, and survival post-progression (SPP) was calculated by subtracting the RFS from the OS, as previously described.[19]

Statistical analysis. Differences between covariates among NSCLC patients with *KRAS* mutations and those with wild-type *KRAS* were analyzed using the Fisher exact test and the χ^2-test. Clinical outcomes were analyzed using the Kaplan–Meier method, and the log-rank test was used to compare survival according to the mutational status. To investigate the association between TTLR and factors related to the patient characteristics, the Cox proportional hazards model was used. The following potential factors were investigated: *KRAS* mutational status, age, clinical stage (IIIA *vs* IIIB), and timing of RT (concurrent *vs* sequential). Differences with probability values of <0.05 were considered to be statistically significant. All the analyses were performed using STATA, ver. 12.0 (Stata, College Station, TX, USA).

Results

***KRAS* mutation in the study cohort.** Among the 274 patients for whom a *KRAS* mutational analysis was planned, 134 patients including 16 patients with EGFR-activating mutations

Table 1. Patient characteristics

	Mutated *KRAS*	Wild-type *KRAS*	*P*-value†	Total
Number of patients (%)	16 (13)	103 (87)		119
Age				
Median (range)	60 (41–74)	61 (33–76)	0.521	61 (33–76)
Sex				
Male/female (%)	12/4 (75/25)	85/18 (83/17)	0.337	97/22 (82/18)
ECOG performance status				
0/1 (%)	1/15 (6/94)	25/78 (24/76)	0.090	26/93 (22/78)
Smoking status (pack-year)				
Median (range)	28 (0–84)	42 (0–150)	0.064	40 (0–150)
Never/former–current (%)	3/13 (19/81)	14/89 (14/86)	0.409	17/102 (14/86)
Clinical stage				
IIIA/IIIB (%)	10/6 (63/37)	55/48 (53/47)	0.343	65/54 (55/45)
Histology				
Adenocarcinoma/NOS (%)	11/5 (69/31)	86/17 (84/17)	0.143	97/22 (82/18)
Type of radiotherapy				
Concurrent/sequential (%)	13/3 (81/19)	91/12 (88/12)	0.325	104/15 (87/13)
Radiotherapy dose (Gy)				
Median (range)	60 (60–60)	60 (52–78)	0.979	60 (52–78)

†For differences between mutated *KRAS* and wild-type *KRAS*. ECOG, Eastern Clinical Oncology Group; NOS, not otherwise specified.

were excluded from the present study either because a tumor specimen was not available (47 cases) or the specimen was insufficient for the analysis (87 cases; Suppl. Fig. S1). In addition, 21 patients with EGFR-activating mutations were excluded because of the distinct response patterns and patient outcomes that have been observed among this population.[17] The remaining 119 patients were subjected to the KRAS mutation screening: 16 patients (13%) had *KRAS* mutations, while 103 patients (87%) had wild-type *KRAS*.

***KRAS* mutation and patient baseline characteristics.** The baseline patient characteristics are shown in Table 1. Among the 119 patients for whom a *KRAS* mutational analysis was performed, the median age was 61 years (range: 33–76 years), 97 patients (82%) were male, and 65 patients (55%) had clinical stage IIIA disease. No significant differences in age, sex, ECOG-PS, smoking status, clinical stage, histology, type of radiotherapy or radiotherapy dose were observed between the patients with *KRAS* mutations and those with wild-type *KRAS*. Patients with *KRAS* mutations had a marginally lighter smoking habit than those with wild-type *KRAS*, but the difference was not statistically significant (median smoking status of patients with *KRAS* mutations versus patients with wild-type *KRAS*: 28 *vs* 42 pack-year, $P = 0.064$).

***KRAS* mutation and therapeutic response.** Of the 119 patients who were analyzed, 104 (87%) had received concurrent CRT and 15 (13%) had received sequential CRT (Table S1). All the patients received platinum-containing chemotherapy regimens. The most frequently used chemotherapy regimens were cisplatin plus vinorelbine in the concurrent CRT group (86%) and carboplatin plus paclitaxel in the sequential CRT group (60%). In a phase I trial, 7 patients received nedaplatin plus paclitaxel, and, in line with a phase II trial, 5 patients received gefitinib.[6,20] These patients were included in the analysis because their survival results compared favorably to that of standard chemoradiotherapy for stage III NSCLC. The median radiation dose was 60 Gy (range, 52–78 Gy). There were 28 patients who received radiation doses of 60 Gy (66 Gy: 13 patients, 72 Gy: 13 patients, 78 Gy: 2 patients) and all these patients were included in a phase I dose-escalation trial reported previously.[9]

Patients with *KRAS* mutations had a lower ORR and a higher progressive disease (PD) rate than those with wild-type *KRAS* (Table 2, patients with *KRAS* mutations versus those with wild-type *KRAS*: 63% *vs* 81% for ORR, 19% *vs* 4% for PD).

***KRAS* mutation and local/distant relapses.** A total of 96 patients (81%, 96/119) relapsed; the relapsed cases consisted of 13 patients with *KRAS* mutations and 83 patients with wild-type *KRAS* (Table 3). The frequency of local relapse was lower among the patients with *KRAS* mutations than among those with wild-type *KRAS* (8% *vs* 23%).

Patients with *KRAS* mutations tended to have a shorter median TTDR than those with wild-type *KRAS* (Suppl. Fig. S2a,

Table 2. Response

	Mutated *KRAS*	Wild-type *KRAS*
Number of patients	16	103
Objective response rate	10 (63%)	83 (81%)
Complete response	0 (0%)	6 (6%)
Partial response	10 (63%)	77 (75%)
Stable disease	3 (19%)	15 (15%)
Progressive disease	3 (19%)	4 (4%)
Not evaluable	0 (0%)	1 (1%)

Table 3. Type of first relapse

	Mutated *KRAS*	Wild-type *KRAS*
Number of relapses	13	83
Local relapses	1 (8%)	19 (23%)
Mixed relapse	3 (23%)	16 (19%)
Distant relapses	9 (69%)	48 (58%)
Brain only	6 (46%)	10 (12%)
With brain	0 (0%)	9 (11%)
Without brain	3 (23%)	29 (35%)

Local relapses are defined as radiologic recurrences within the range of radiation field. Distant relapses are defined as recurrences outside of the radiation field.

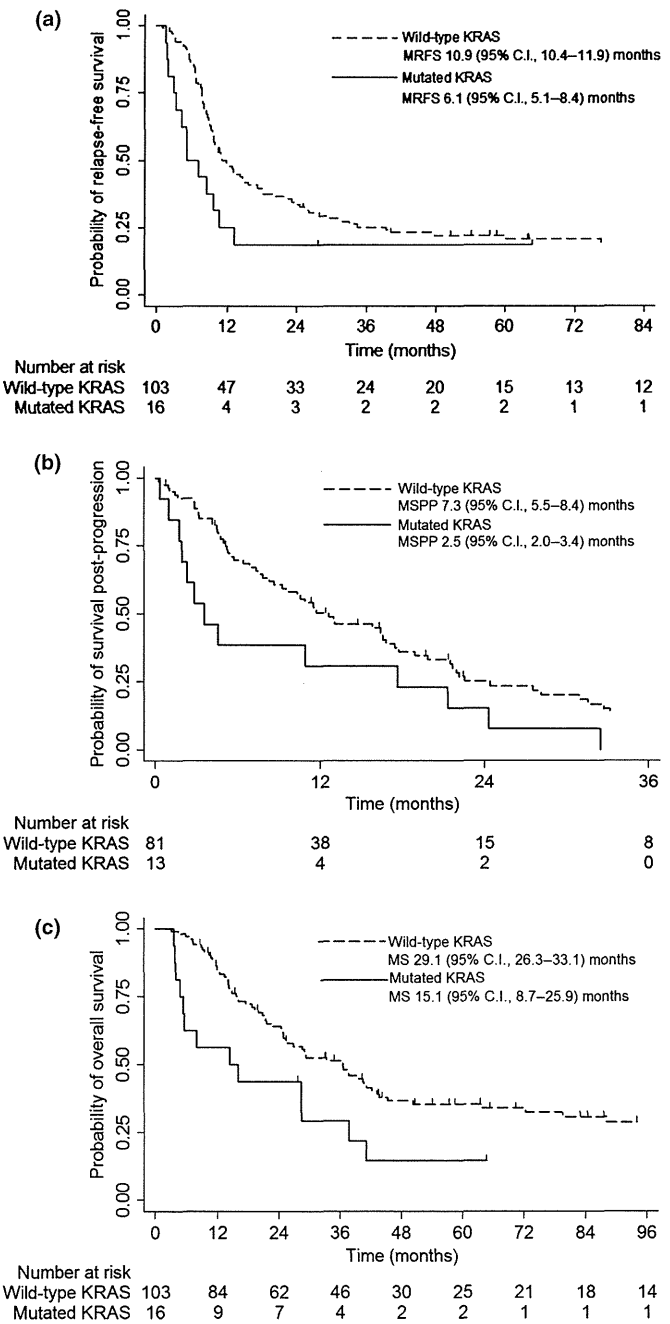

Fig. 1. Kaplan–Meier survival analyses for relapse-free survival (RFS) (a), overall survival (OS) (b), and survival post-progression (SPP) (c).

patients with *KRAS* mutations *vs* those with wild-type *KRAS*: 6.3 *vs* 13.0 months for median TTDR, $P = 0.0865$), while the TTLR was similar for both groups (Suppl. Fig. S2b).

As a post-relapse treatment, 23% of the patients with *KRAS* mutations and 36% of the patients with wild-type *KRAS* received cytotoxic chemotherapy; this difference was not statistically significant ($P = 0.278$). Some of the patients (those treated before 2004) received EGFR-TKI as a second-line therapy (Table 4).

***KRAS* mutation and survival.** Of the 119 patients who were analyzed, 82 (69%) had died by the end of the median follow-up period of 29 months (range, 3–140 months). No statistically significant differences in the 2-year relapse-free rate (patients with *KRAS* mutations *vs* those with wild-type *KRAS*: 18.8% *vs* 33.6%, $P = 0.204$) and the 5-year survival rate (14.6% *vs* 35.3%, $P = 0.149$) were seen according to the *KRAS* mutational status (Suppl. Table S2). We observed a tendency toward a shorter median RFS (Fig. 1a, 6.1 *vs* 10.9 months, $P = 0.083$) and a statistically significant shorter median SPP (Fig. 1b, 2.5 *vs* 7.3 months, $P = 0.028$) and OS (Fig. 1c, 15.1 *vs* 29.1 months, $P = 0.022$).

In a univariate analysis, the *KRAS* mutational status exhibited statistically significant associations with OS ($P = 0.025$) and SPP ($P = 0.031$), but not with RFS ($P = 0.087$; Table 5). In a multivariate analysis, the *KRAS* mutation was more strongly associated with OS ($P = 0.042$) and SPP ($P = 0.035$) than with age, clinical stage or timing of radiotherapy (Table 5).

Table 4. Second-line treatment

	Mutated *KRAS*	Wild-type *KRAS*
Number of relapses	13	83
Cytotoxic chemotherapy	3 (23%)	30 (36%)
Docetaxel	2 (67%)	25 (83%)
Pemetrexed	0 (0%)	2 (7%)
TS-1	0 (0%)	2 (7%)
CBDCA + PTx	1 (33%)	0 (0%)
Investigational drug	0 (0%)	1 (3%)
EGFR-TKI	2 (15%)	11 (13%)
Supportive care	8 (62%)	42 (51%)

Discussion

In this study, we demonstrated that *KRAS* mutation acts as a negative prognostic factor in patients with stage III non-squamous NSCLC receiving definitive CRT. A marginally weaker clinical effect in terms of RR and RFS was also observed in patients with *KRAS* mutation, compared with those with wild-type *KRAS*. These results suggest a therapeutically resistant phenotype of *KRAS*-mutated tumors. Patients with *KRAS* mutations had fewer local relapses and more brain metastases after CRT. In addition, these patients experienced a shorter TTDR than those with wild-type *KRAS*.

Reports describing the association between the *KRAS* mutation and the clinical effect of radiotherapy have been limited. In particular, its association with chemoradiotherapeutic effects in stage III NSCLC has been unclear. Broermann *et al.* analyzed *KRAS* exon 2, codon 12 mutations in 28 patients who underwent tumor resection after neoadjuvant treatment with two cycles of chemotherapy (ifosfamide, carboplatin and etoposide) and subsequent twice-daily radiotherapy (45 Gy) with concurrent carboplatin and vindesine.[21] In their study, *KRAS* mutation was found to be a negative predictive and prognostic factor. Hallaqvist *et al.*[22] analyzed 66 cases from two phase II studies of chemoradiotherapy for *KRAS* exon 2 mutation and showed that the *KRAS* mutation was a negative prognostic factor. In contrast, Ready *et al.* report an analysis of the *KRAS* exon 2 mutation in a clinical trial evaluating the effect of the

Table 5. Univariate/multivariate analysis, Cox proportional hazard model

	RFS			OS			SPP		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Univariate *KRAS*									
Mt *vs* W/T	1.67	0.93–3.00	0.087	1.98	1.09–3.59	0.025	1.94	1.06–3.53	0.031
Age (years)									
65 *vs* <65	0.89	0.59–1.35	0.581	0.67	0.43–1.05	0.080	0.63	0.40–1.00	0.051
Clinical stage									
Stage IIIA *vs* IIIB	1.04	0.69–1.55	0.867	0.94	0.61–1.47	0.798	0.89	0.57–1.39	0.606
Radiotherapy									
Seq *vs* Conc	0.77	0.43–1.35	0.358	0.64	0.35–1.19	0.158	0.75	0.39–1.42	0.369
Multivariate *KRAS*									
Mt *vs* W/T	1.69	0.93–3.06	0.083	1.87	1.02–3.42	0.042	1.98	1.05–3.73	0.035
Age (years)									
65 *vs* <65	0.86	0.57–1.31	0.488	0.69	0.44–1.08	0.103	0.63	0.39–1.01	0.055
Clinical stage									
Stage III A *vs* IIIB	1.09	0.72–1.65	0.695	0.98	0.62–1.54	0.929	0.88	0.56–1.39	0.589
Radiotherapy									
Seq *vs* Conc	0.78	0.44–1.39	0.403	0.71	0.37–1.33	0.283	1.01	0.49–2.05	0.989

Conc, concurrent; Mt, mutation; OS, overall survival; W/T, wild-type; RFS, relapse-free survival; Seq, sequential; SPP, survival post-progression.

addition of gefitinib, an EGFR-TKI, to sequential or concurrent CRT in stage III NSCLC. In their study, no obvious correlation was seen between the *KRAS* mutation and the RFS or OS of the 45 patients who were analyzed.[23] All three of these studies had limitations, such as the inclusion of a relatively small number of subjects, the uniformity of the therapeutic strategy, or the inclusion of squamous cell carcinoma. In the present study, we analyzed stage III non-squamous NSCLC cases that were consecutively collected over a 10-year period, and all the patients were treated according to defined CRT protocols at a single hospital. Thus, the present results should help to understand the impact of *KRAS* mutation on the prediction of CRT response and on the prognosis of patients.

We also analyzed the relapse patterns after CRT and found that patients with *KRAS* mutations experience early distant relapses, especially in the brain, more frequently than patients with wild-type *KRAS*. Johung *et al.* (2013) report differences in the intracranial relapse pattern after gamma-knife surgery for brain metastases depending on the *EGFR* mutation, *ALK* translocation or *KRAS* mutation status.[24] In patients with *KRAS* mutation, the time to distant-brain recurrence tended to be shorter than that of patients with *EGFR* mutation or *ALK* translocation. Because the findings of the present study showed that patients with *KRAS* mutations had a shorter RFS, SPP and OS, *KRAS*-mutated tumors may possess a radio-resistant phenotype and might not be responsive to chemotherapy for distant metastasis control. As for the fewer local relapses in patients with *KRAS* mutations that we observed in the present study, we could not find reasonable molecular mechanisms which elucidate this phenomenon. Because the present study included only 16 patients with *KRAS* mutations, these results should be evaluated in future studies.

The present study has several limitations. First, our report is based on a retrospective study. Although we tried to collect tumor samples for diagnosis from all the patients in this study cohort, we could not analyze the *KRAS* mutational status in 121 patients. Furthermore, the patients did not necessarily have the same follow-up periods, although all the patients were regularly followed up every 1 to 2 months in the outpatient department and underwent work-ups every 3 to 6 months within the first year after the end of CRT, and were subsequently examined every 6 months using X-ray, CT, MRI and/or PET-CT. Second, we conducted the *KRAS* mutational analysis focusing on exon 2, which contains approximately 90% of all *KRAS* mutations in non-squamous NSCLC (data from the Catalogue of Somatic Mutations in Cancer database [COSMIC]). The impact of other minor *KRAS* mutations remains unknown.

In summary, our results suggest that *KRAS* mutations could be associated with the reduced efficacy of definitive CRT and a shortened survival time in patients with stage III non-squamous NSCLC.

Acknowledgments

This work was supported in part by the National Cancer Center Research and Development Fund (23-A-30, 24-A-1), by Grants-in-Aid from the Ministry of Education, Culture, Sports, Science, and Technology of Japan for Scientific Research on Innovative Areas (22131006), and by a Grant-in-Aid for the Third-Term Comprehensive 10-Year Strategy for Cancer Control of Japan including Awardee of Research Resident Fellowship from the Foundation for Promotion of Cancer Research (Japan).

Disclosure Statement

The authors have no conflict of interest to declare.

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Supporting Information

Additional supporting information may be found in the online version of this article:

Fig. S1. Consort diagram.

Fig. S2. (a) Time to distant relapse. (b) Time to local relapse.

Table S1. Treatment.

Table S2. Survival analysis.

Journal of Radiation Research, Vol. 56, No. 6, 2015, pp. 897–903
doi: 10.1093/jrr/rrv047
Advance Access Publication: 11 August 2015

A questionnaire-based survey on 3D image-guided brachytherapy for cervical cancer in Japan: advances and obstacles

Tatsuya Ohno[1], Takafumi Toita[2]*, Kayoko Tsujino[3], Nobue Uchida[4], Kazuo Hatano[5], Tetsuo Nishimura[6] and Satoshi Ishikura[7]

[1]Gunma University Heavy Ion Medical Center, Gunma University, 3-39-22 Showa-machi, Maebashi, Gunma, 371–8511, Japan
[2]Department of Radiology, Graduate School of Medical Science, University of the Ryukyus, 207 Uehara, Nishihara-cho, Okinawa, 903–0215, Japan
[3]Department of Radiation Oncology, Hyogo Cancer Center, 13–70 Kitaoji-cho, Akashi, Hyogo, 673–8558, Japan
[4]Department of Radiation Oncology, Tottori University Hospital, Nishi-cho, Yonago, Tottori, 683–8504, Japan
[5]Tokyo Bay Advanced Imaging and Radiation Oncology Clinic MAKUHARI, 1–17 Toyosuna, Mihama-ku, Chiba, 261–0024, Japan
[6]Division of Radiation Oncology, Shizuoka Cancer Center, 1007 Shimonagakubo, Nagaizumi-cho, Shizuoka, 411–8777, Japan
[7]Department of Radiology, Koshigaya Municipal Hospital, 10-47-1 Higashikoshigaya, Koshigaya, Saitama 343–8577, Japan
*Corresponding author: Department of Radiology, Graduate School of Medical Science, University of the Ryukyus, 207 Uehara, Nishihara-cho, Okinawa, 903–0215, Japan. Tel: +81-98-895-3331; Fax: +81-98-895-1420; Email: b983255@med.u-ryukyu.ac.jp
Received May 20, 2015; Revised July 5, 2015; Accepted July 13, 2015

ABSTRACT

The purpose of this study is to survey the current patterns of practice, and barriers to implementation, of 3D image-guided brachytherapy (3D-IGBT) for cervical cancer in Japan. A 30-item questionnaire was sent to 171 Japanese facilities where high-dose-rate brachytherapy devices were available in 2012. In total, 135 responses were returned for analysis. Fifty-one facilities had acquired some sort of 3D imaging modality with applicator insertion, and computed tomography (CT) and magnetic resonance imaging (MRI) were used in 51 and 3 of the facilities, respectively. For actual treatment planning, X-ray films, CT and MRI were used in 113, 20 and 2 facilities, respectively. Among 43 facilities where X-ray films and CT or MRI were acquired with an applicator, 29 still used X-ray films for actual treatment planning, mainly because of limited time and/or staffing. In a follow-up survey 2.5 years later, respondents included 38 facilities that originally used X-ray films alone but had indicated plans to adopt 3D-IGBT. Of these, 21 had indeed adopted CT imaging with applicator insertion. In conclusion, 3D-IGBT (mainly CT) was implemented in 22 facilities (16%) and will be installed in 72 (53%) facilities in the future. Limited time and staffing were major impediments.

KEYWORDS: image-guided brachytherapy, cervical cancer, 3D planning, questionnaire-based survey, high-dose-rate brachytherapy

INTRODUCTION

Recent patterns of care for brachytherapy have demonstrated that gynecological brachytherapy remains the most common application of this technology, although with regional and community-specific variations [1, 2]. Since publication of the concept and terms of 3D image-guided brachytherapy (3D-IGBT) for cervical cancer in 2005, a common approach for ensuring target coverage and avoiding excessive exposure to organs at risk has been developed [3, 4]. Regarding dose–volume histogram (DVH) parameters in particular, a dose–response relationship has been reported between cervical tumor control and D90 for the high-risk clinical target volume (HR-CTV), as well as between late complications and $D2cm^3$ for the rectum and bladder [5, 6]. Recent clinical data using MRI-guided adaptive brachytherapy have shown excellent 3-year local control rates of 95–100% for limited/favorable disease (Stages IB/IIB) and 85–90% for large/poor response disease (Stages IIB/III/IV), with acceptable treatment-related morbidities [7].

Advances in image guidance for applicator insertion and treatment planning seem to have influenced clinical practice in brachytherapy for cervical cancer. However, reports regarding practice patterns

have been scarce worldwide. Although the results of several surveys on the practice of 3D-IGBT have been published by various study groups worldwide [8–11], practices in Asian countries, including Japan, have been generally undocumented. The purpose of this survey was to determine the current patterns of practice of and obstacles to implementation of 3D-IGBT use for cervical cancer in Japan.

MATERIALS AND METHODS

In July 2012, a 30-item questionnaire (see Appendix) was sent to 171 Japanese facilities possessing high-dose-rate brachytherapy machines. Questions focused on the practice of brachytherapy for cervical cancer, plans for transitioning to 3D-IGBT, and the obstacles faced in implementation. Only one set of answers was allowed per facility to prevent redundancy. Non-responders received reminders in August 2012. A follow-up survey was sent in January 2015 to 38 facilities that had indicated plans to transition to 3D-IGBT in the first survey to query whether they had in fact followed through and, if so, which type of imaging modality was routinely used for treatment planning.

RESULTS

Respondents

Of 171 facilities, 144 (84%) responded to the questionnaire. Nine respondents did not use brachytherapy for gynecological malignancies; thus, 135 (78%) surveys were analyzed. Of these facilities, 34% treated 20–49 patients; 31% treated 10–19 patients; 19% treated <10 patients; 9% treated no patients; and 6% treated ≥50 patients, in 2011.

Imaging modality

Ultrasound guidance for applicator insertion was used by 2% (3 of 135) of respondents routinely and 25% (34 of 135) occasionally when necessary; 73% (98 of 135) did not use it. With brachytherapy applicator insertion, X-ray films alone were acquired in 62% (84 of 135, Group 1) of the facilities. Various types of 3D images were acquired with applicator insertion in the remaining 51 facilities, 8 of which used 3D imaging exclusively. Table 1 lists the types of images acquired with applicator insertion as well as the imaging used for actual treatment planning. CT inside the brachytherapy room was available at 9 facilities. Of 43 facilities where X-ray films and CT or MRI were acquired with an inserted applicator, 29 facilities used X-ray films for actual treatment planning (Group 2) and 14 facilities used CT or MRI for treatment planning. Thus, 22 facilities in total used CT or MRI for treatment planning (Group 3). The most common answer regarding patient number in 2011 was 10–19 for Group 1, 20–49 for Group 2 and 20–49 for Group 3, respectively.

Table 1. Imaging used for image-guided brachytherapy (n = 135)

	Number	%
Imaging acquired with inserted applicator		
X-ray films alone	84	62
X-ray films + CT	41	30
X-ray films + CT + MRI	2	1
CT	7	5
CT + MRI	1	1
Imaging used for actual treatment planning		
X-ray films	113	84
CT	20	15
MRI	2	1

2D planning group not acquiring 3D imaging (Group 1)

On whether Group 1 (n = 84) was considering introducing a 3D treatment planning system within the next three years, 45% (38 of 84) of the facilities replied affirmatively. Among the positive respondents, 89% (34 of 38) intended to use CT for treatment planning, while the other 11% (4 of 38) intended to use both CT and MRI. In the follow-up survey, to which 31 of the original 38 facilities that had stated intentions to introduce a 3D planning system responded, 68% (21 of 31) indicated that they had begun acquiring CT images with applicator insertion, and 55% (17 of 31) used CT for treatment planning. Table 2 lists the reasons why 46 respondents indicated they were not considering a 3D treatment planning system.

2D planning group acquiring 3D imaging (Group 2)

In Group 2 (n = 29), 31% of the facilities acquired 3D images via CT in every session, while 31% obtained images only for the first session. The remaining facilities used 3D imaging only when necessary. CT/MRI-compatible applicators and metal applicators were used in 17% and 83% of the facilities, respectively. The most common reason for acquiring 3D images in addition to X-ray films was visualizing the anatomical relationship between applicator and the organs at risk or

Table 2. Reasons for using X-ray films in lieu of 3D imaging for treatment planning

	Number	%
Group 1 (n = 46)[a]		
geographically limited access to CT/MRI	17	37
applicators used were not CT/MRI-compatible	17	37
limited time for treatment planning	15	33
lack of knowledge for the planning	11	24
Group 2 (n = 29)[b]		
limited time for planning with CT/MRI	21	72
inadequate manpower	14	48
inadequate planning software	9	31
lack of knowledge for the planning	7	24
applicators used were not CT/MRI-compatible	6	21

[a]In Group 1, 46 of 84 facilities did not consider the introduction of a 3D-IGBT treatment planning system. [b]In Group 2, all 29 facilities acquired CT but used X-ray films for treatment planning.

the tumor (97%), followed by confirming perforation (52%), calculating DVH parameters after treatment (52%), and setting a secondary reference point alternative to Point A (24%). Table 2 lists the reasons for using X-ray films only for actual treatment planning. All 29 facilities chose CT and not MRI for acquiring 3D images. The reasons for using CT in lieu of MRI in Groups 1 and 2 are shown in Table 3.

3D planning group (Group 3)

In Group 3 ($n = 22$), 20 facilities used CT and not MRI for treatment planning, the reasons for which are shown in Table 3. Fifteen facilities (68%) acquired imaging by CT or MRI in every session, while 5 (23%) obtained images only for the first session. CT/MRI-compatible applicators and metal applicators were used in 6 (27%) and 16 (73%) of the facilities, respectively. For target dose specification, 21 facilities (95%) used Point A, while none of the facilities used HR-CTV alone. Table 4 lists the responses regarding detailed information on 3D treatment planning for cervical cancer.

Table 3. Reasons for using CT in lieu of MRI

	Number	%
Group 1 ($n = 34$)[a]		
geographically limited access to MRI	22	65
difficulty in ensuring reservations for MRI	14	41
applicators used were not MRI-compatible	13	38
inadequate manpower	11	32
long examination times	9	26
CT image is regarded as sufficient	9	26
Group 2 ($n = 29$)[b]		
difficulty in ensuring reservations for MRI	22	76
geographically limited access to MRI	20	69
applicators used were not MRI-compatible	12	41
inadequate manpower	11	38
long examination time	9	31
CT image was regarded as sufficient	7	24
Group 3 ($n = 20$)[c]		
difficulty in ensuring reservations for MRI	12	60
geographically limited access to MRI	8	40
applicators used were not MRI-compatible	6	30
CT image was regarded as sufficient	5	25
inadequate manpower	3	15
long examination time	3	15

[a]In Group 1, 34 of 84 facilities intended to use CT but not MRI for treatment planning in the future. [b]In Group 2, all 29 facilities chose CT for acquiring 3D images. [c]In Group 3, 20 of 22 facilities used CT for treatment planning.

DISCUSSION

According to our survey results, 3D imaging with brachytherapy applicator insertion was adopted in 38% (51 of 135) of the facilities in 2012, and was used for treatment planning in 16% (22 of 135). Two and a half years later, an additional 16% (21 of 135) and 13% (17 of 135) of the facilities had begun acquiring 3D images and adopting 3D image-based planning, respectively. Conversely, a separately published national survey in Japan reported that, of 816 linear accelerators in use in 2009, 81% and 41% were used for 3D conformal radiotherapy and intensity-modulated radiotherapy (IMRT), respectively, indicating a significant delay in the dissemination of 3D-IGBT [12]. Several study groups have reported the incidence of 3D planning using CT or MRI for gynecological brachytherapy, with a range of 50–74% (Table 5) [8–11]. Similarly, 3D planning for gynecological brachytherapy has lagged compared with external beam radiotherapy (EBRT) [13–14].

A recent study suggests that gynecological brachytherapy is underutilized in New South Wales, Western Europe and the USA [15]. In a Japanese study, 22% of cervical cancer patients were still not given brachytherapy during 2003–2005 [16]. Gill *et al.* also showed an increasing trend of EBRT boost utilization with IMRT and stereotactic body radiotherapy for cervical cancer [17]. Importantly, studies by Han *et al.* and Gill *et al.* demonstrated that combined use of EBRT and brachytherapy produced significantly better survival compared with EBRT alone, indicating that local brachytherapy offers a marked survival benefit in cervical cancer patients [17, 18]. Additionally, recent clinical reports on 3D-IGBT from single institutions have shown excellent local control (89–97%) as well as minimal late toxicities (2–8% of Grade 3 or worse) [7, 19, 20]. Thus, while EBRT boost ought not to be replaced, 3D-IGBT should be implemented alongside it in order to achieve maximum patient benefit.

In terms of obstacles to the implementation of 3D planning, both Group 1 and Group 2 reported similar deterrents (Table 3). MRI has been considered the gold standard for 3D-IGBT for cervical cancer because it provides more precise anatomical information; however, the transition to 3D planning with MRI has been slow (Table 5) [8–11]. Our survey showed that difficulty in ensuring reservations and geographically limited access were common reasons for using CT rather than MRI for treatment planning in Groups 1, 2 and 3 (Table 2).

At present, CT is most commonly used for IGBT treatment planning for cervical cancer (Table 5). Although a guideline for CT-based CTV in brachytherapy for cervical cancer was proposed independently of MRI-based HR-CTV, further evaluation of its feasibility and reliability will be necessary in the clinical setting [21]. Viswanathan *et al.* reported that CT-based tumor contours could significantly overestimate tumor width, resulting in significant differences in DVH parameters compared with MRI [22]. On the other hand, the accuracy of CT-based HR-CTV contouring was improved by adding information from 3D documentation of physical examinations [23]. In addition, a combination of MRI for the first fraction and subsequent CT-based planning is feasible when automatic applicator-based image registration and target transfer are technically available [24]. Therefore, the advantages and disadvantages of CT-based brachytherapy should be recognized, and efforts to minimize the uncertainty of contouring should be made at centers where the full use of MRI for treatment planning is limited.

Table 4. Summary of answers regarding 3D treatment planning for cervical cancer ($n = 22$)

Question	Answers (%)							
Which normal tissues do you routinely contour?	Not determined (18%)	Bladder (68%)	Rectum (73%)	Sigmoid colon (45%)	Small intestine (41%)	Vagina (5%)	Other (5%)	
Which targets do you routinely contour?	Not determined (27%)	GTV-BT (23%)	HR-CTV (45%)	IR-CTV (14%)	Other (5%)			
Which DVH parameter(s) do you routinely use?	HR-CTV D90 (36%)	HR-CTV D100 (36%)	HR-CTV D150 (0%)	HR-CTV D200 (5%)	V100 (9%)	V150 (0%)	V200 (0%)	Other (27%)
Which method do you use for dose specification to the target?	Point A (55%)	HR-CTV (0%)	Both (41%)	NR (5%)				
Is the treatment plan optimized whenever the CTV or GTV could not be fully covered by the prescribed dose?	Yes (77%)	No (14%)	NR (9%)					
If yes, what reference is used for the optimization?	Point A (23%)	HR-CTV D90 (45%)	Other DVH parameter (9%)	Other (14%)				
Which DVH parameters do you routinely use for the organs at risk?	D0.1cm^3 (36%)	D1cm^3 (32%)	D2cm^3 (50%)	D5cm^3 (9%)	Other (14%)			
Which method do you use for dose specification to the rectum?	ICRU points (27%)	DVH parameters (41%)	Both (27%)	NR (5%)				
Is optimization carried out using the rectal/sigmoid colon dose?	Yes (91%)	No (9%)						
If yes, what reference is used for the optimization?	ICRU points (23%)	D2cm^3 (32%)	Other DVH parameter (5%)	Other (32%)	NR (9%)			
Which method do you use for dose specification to the bladder?	ICRU points (5%)	DVH parameters (36%)	Both (23%)	NR (36%)				
Is optimization carried out using the bladder dose?	Yes (55%)	No (45%)						
If yes, what reference was used for the optimization?	ICRU points (36%)	D2cm^3 (32%)	Other DVH parameter (0%)	Other (9%)	NR (23%)			

GTV-BT = gross tumor volume at brachytherapy; CTV-BT = clinical target volume at brachytherapy; HR-CTV = high-risk clinical target volume; IR-CTV = intermediate-risk clinical target volume; Dn = dose receiving n cm^3 of HR-CTV from 90 to 200; Vn = volume receiving n% of prescribed dose in the target; ICRU = International Commission on Radiation Units.

Despite the small number of respondents, the present survey highlighted several insufficiencies concerning 3D-IGBT in Japan. First, the routine use of ultrasound for applicator insertion was only 2%, and occasional use was 24% in our survey. Second, we found that 23% of respondents obtained CT or MRI images only for the first session, while 68% acquired the images with each insertion. Finally, the relatively higher incidence of use of the D90 of HR-CTV was noted for plan optimization in a setting where CT was the main imaging modality. Originally, HR-CTV is a concept defined on MRI with no guidelines yet for contouring on CT. Using HR-CTV in facilities of limited MRI usage must be addressed.

In Group 3, Point A alone (55%) was most frequently used in our survey as a dose specification to the target, while 41% used both Point A and HR-CTV. In the ABS survey, Point A (76%) remained the most frequent prescription method [8]. The Canadian survey reported that 53% of respondents utilizing CT-based planning used Point A alone for dose prescription and 20% used both Point A and the HR-CTV [9]. The UK survey demonstrated that 93% of centers

Table 5. Imaging modality for treatment planning in IGBT for cervical cancer

Study group	Year	Number	Responder	Response rate	X-ray films	CT	MRI
ABS [8]	2007	256	Physician	55%	43%	55%	2%
CANADA [9]	2009	58	Physician	62%	50%	45%	5%
UK [10]	2008→2011	45	Facility	96%	73%→26%	22%→53%	4%→21%
Australia & New Zealand [11]	2009	20	Facility	100%	30%	65%[a]	5%
The present study	2012	171	Facility	84%	84%	15%	1%

[a]One facility (5%) used CT in a 2D fashion to assess implant geometry. ABS = American Brachytherapy Society; IGBT = image-guided brachytherapy.

in both 2008 and 2011 provided their standard prescription for EBRT and brachytherapy dose to Point A [10]. Thus, even in the era of 3D-IGBT, together with the concept of CTV, Point A still has an important role for dose specification to the target. In conclusion, limited time and inadequate manpower were major barriers to the implementation of 3D-IGBT. Based on the promising clinical outcomes reported in the literature, removing these barriers and expanding the adoption of 3D-IGBT should be prioritized.

FUNDING

Funding to pay the Open Access publication charges for this article was provided by a Grant-in-Aid for Clinical Cancer Research, Health and Labour Sciences Research Grants from the Japanese Ministry of Health, Labour, and Welfare [10103757] and for KAKENHI from the Japan Society for the Promotion of Science [26461879].

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APPENDIX

1. Please state which of the following hospitals are you associated with?

1) Prefectural or Metropolitan Designated Cancer Center or Hospital; 2) Regional Designated Cancer Center or Hospital; 3) Other ( )

2. How many new cases of intracavitary irradiation for cervical cancer did your institution have in the year 2011?

1) N/A; 2) Less than 10; 3) 10–19; 4) 20–49; 5) 50 or more

This question relates to analysis of the circumstances surrounding image-guided three-dimensional treatment planning for cervical cancer.

The question deals with both applicator insertion and image acquisition.

3. Is ultrasonography used for applicator insertion?

1) Always; 2) If necessary; 3) No

4. What imaging modality is acquired with insertion of the applicator? (Please mark all applicable answers)

1) X-ray films; 2) CT in the treatment room; 3) CT outside the treatment room; 4) MRI; 5) Ultrasound

5. What imaging modality is used for the actual treatment planning?

1) X-ray films; 2) CT; 3) MRI; 4) Ultrasound

The following questions are categorized into three groups.

Group 1: If only response 1) was selected for questions 4 and 5

⇒ The survey ends after questions 6 through 9 below are answered.

Group 2: If response numbers 2), 3), 4), or 5) are selected for question 4 above and response 1) is selected for question 5 above

⇒ The survey ends after questions 10 through 14 below are answered.

Group 3: If responses 2), 3), 4), or 5) are selected for question 4 and responses 2), 3), or 4) are selected for question 5

⇒ The survey ends after questions 15 through 31 are answered.

Questions for Group 1

The 2012 Health and Labor Sciences Research Grant Cancer Clinical Research Projects "Research relating to promotion and quality control of radiotherapy contributing to eliminating cancer care disparities" Team

6. Are you considering introducing a three-dimensional treatment planning system within the next three years?

1) Yes; 2) No

7. This question is to be answered only by those hospitals that selected response 1) in question 6: What imaging modality do you intend to use for treatment planning? (Please mark all applicable answers)

1) CT; 2) MRI; 3) Other ( )

8. This question is to be answered only by those hospitals that selected response 1) in question 7: What is the reason for using CT and not MRI for treatment planning? (Please mark all applicable answers)

1) Difficulty in ensuring reservations for MRI; 2) Geographically limited access to MRI; 3) Long examination times; 4) Inadequate manpower; 5) Applicators used were not MRI-compatible; 6) CT examination is regarded as sufficient; 7) Other ( )

9. This question is to be answered only by those hospitals that selected response 2) in question 6: Please state the reason for not considering the introduction of a three-dimensional treatment planning system? (Please mark all applicable answers)

1) Did not consider it to be necessary; 2) Lack of evidence; 3) Limited time for treatment planning; 4) Inadequate manpower; 5) Lack of knowledge for the planning (target/OAR definitions, calculations, etc.); 6) Applicators used were not CT/MRI-compatible; 7) Insufficient planning software; 8) Geographically limited access to the CT/MRI; 9) Not covered by national insurance system; 10) Other ( )

This concludes the questionnaire for Group 1. Thank you for your participation.

Questions for Group 2

10. How often is CT or MRI imaging performed with insertion of the applicator?

1) Every session; 2) Only the first session; 3) Other ( )

11. What applicator do you use?

1) CT/MRI-compatible applicator; 2) Metal applicator

12. What is the reason for acquiring images other than X-ray films? (Please mark all applicable answers)

1) To confirm the perforation; 2) To see the anatomical relationship between the applicator and the organ at risk or tumor; 3) To set a reference point other than Point A; 4) To calculate DVH parameters after treatment; 5) Other ( )

13. State the reason for using X-ray films for the actual treatment planning? (Please mark all applicable answers)

1) Lack of evidence for planning other than the X-ray films; 2) Limited time for planning with CT/MRI; 3) Inadequate manpower;

4) Lack of knowledge for the planning (target/OAR delineation, calculations, etc.); 5) Applicators used were not CT/MRI-compatible; 6) Inadequate planning software; 7) Other ( )

14. This question is to be answered only by those hospitals that selected CT in question 4: What is the reason for using CT and not MRI? (Please mark all applicable answers)

1) Difficulty in ensuring reservations for MRI; 2) Geographically limited access to MRI; 3) Long examination time; 4) Inadequate manpower; 5) Applicators used were not MRI-compatible; 6) CT is regarded as sufficient; 7) Other ( )

This concludes the questionnaire for Group 2. Thank you for your participation.

Questions for Group 3

15. This question is to be answered only by those hospitals that selected CT in question 4: What is the reason for using CT and not MRI in treatment planning? (Please tick all applicable answers)

1) Difficulty in ensuring reservations for MRI; 2) Geographically limited access to MRI; 3) Long examination time; 4) Inadequate manpower; 5) Applicators used were not MRI-compatible; 6) CT is regarded as sufficient; 7) Other ( )

16. How often is CT or MRI imaging performed with insertion of the applicator?

1) Every session; 2) Only the first time; 3) Other ( )

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17. Which applicator do you use?

1) CT/MRI-compatible applicator; 2) Metal applicator

18. Which normal tissues do you routinely contour? (Please tick all applicable answers)

1) Not determined; 2) Bladder; 3) Rectum; 4) Sigmoid colon; 5) Small intestine; 6) Vagina; 7) Other ( )

19. Which targets do you routinely contour? (Please tick all applicable answers)

1) Not determined; 2) GTV-BT; 3) HR-CTV; 4) IR-CTV; 5) Other ( )

20. Which DVH parameter(s) do you routinely use? (Please tick all applicable answers)

1) D90; 2) D100; 3) D150; 4) D200; 5) V100; 6) V150; 7) V200; 8) Other

21. Which method do you use for dose specification to the target?

1) Point A; 2) HR-CTV; 3) Both

22. Is the treatment plan optimized whenever the CTV or GTV could not be fully covered by the prescribed dose?

1) Yes; 2) No

23. If yes, what reference is used for the optimization?

1) Point A; 2) HR-CTV D90; 3) Other DVH parameter; 4) Other

24. Which DVH parameters do you routinely use for the organs at risk? (Please tick all applicable answers)

1) D0.1cc; 2) D1cc; 3) D2cc; 4) D5cc; 5) Other (----------)

25. Which method do you use for dose specification to the rectum?

1) ICRU points; 2) DVH parameters; 3) Both

26. Is optimization carried out using the rectum/sigmoid colon dose?

1) Yes; 2) No

27. If yes, what reference is used for the optimization?

1) ICRU points; 2) D2cc; 3) Other DVH parameter; 4) Other

28. Which method do you use for dose specification to the bladder?

1) ICRU points; 2) DVH parameters; 3) Both

29. Is optimization carried out using the bladder dose?

1) Yes; 2) No

30. If yes, what reference was used for the optimization?

1) ICRU points; 2) D2cc; 3) Other DVH parameter; 4) Other

This concludes the questionnaire for Group 3. Thank you for your participation.

Journal of Radiation Research, Vol. 56, No. 4, 2015, pp. 735–741
doi: 10.1093/jrr/rrv020
Advance Access Publication: 9 April 2015

A surveillance study of intensity-modulated radiation therapy for postoperative cervical cancer in Japan

Naoya Murakami[1]*, Hiroyuki Okamoto[1], Fumiaki Isohashi[2], Keiko Murofushi[3], Tatsuya Ohno[4], Daisaku Yoshida[5], Makoto Saito[6], Koji Inaba[1], Yoshinori Ito[1], Takafumi Toita[7] and Jun Itami[1]

[1]Department of Radiation Oncology, National Cancer Center Hospital, T5-1-1 Tsukiji, Chuo-ku, Tokyo 104–0045, Japan
[2]Department of Radiation Oncology, Osaka University Hospital, Suita, Osaka
[3]Department of Radiation Oncology, University of Tsukuba, Tsukuba, Ibaraki
[4]Department of Radiation Oncology, Gunma University Graduate School of Medicine, Gunma
[5]Department of Radiology, Gunma Prefecture Cancer Center, Gunma
[6]Department of Radiation Oncology, Chiba Cancer Center, Chiba
[7]Department of Radiology, Graduate School of Medicine, University of Ryukyus, Okinawa
*Corresponding author. Department of Radiation Oncology, National Cancer Center Hospital, T5-1-1 Tsukiji, Chuo-ku, Tokyo 104–0045, Japan.
Tel: +81-3-3542-2511; Fax: +81-3-3545-3567. Email: namuraka@ncc.go.jp
Received July 25, 2014; Revised February 8, 2015; Accepted March 10, 2015

ABSTRACT

Intensity-modulated radiation therapy (IMRT) was recently introduced to the field of gynecologic malignancies; however, its value is not yet validated. A clinical trial is in preparation to investigate the efficacy and feasibility of IMRT for postoperative cervical cancer. The object of this study was to perform a surveillance study of IMRT for post-operative cervical cancer. A questionnaire regarding the precise methods of conducting IMRT was sent to six institutions that had already introduced IMRT for post-operative cervical cancer, and the data were analyzed. Half of the institutions used static IMRT and the others used volumetric-modulated arc therapy (VMAT). Most institutions used body-immobilizing devices for patient fixation. Most institutions instructed patients to fill their bladder before undergoing planning CT or daily treatment. While one institution inserted metallic markers and another one used radio-contrast–soaked gauze to visualize the vaginal cuff, the other institutions used nothing for vaginal cuff visualization. Most institutions defined the clinical target volumes according to the Japan Clinical Oncology Group or the Radiation Therapy Oncology Group guidelines. Only one institution used a prescribed dose based on 95% of the PTV (D_{95}), while the rest used the mean dose (D_{mean}). This valuable information from six leading institutions will be utilized in a future prospective clinical trial.

KEYWORDS: intensity-modulated radiation therapy, postoperative adjuvant radiation therapy, cervical cancer, surveillance, Japan

INTRODUCTION

Post-operative radiotherapy is an established adjuvant treatment after radical hysterectomy with intermediate- and high-risk early-stage cervical cancer patients [1, 2]. A conventional radiation technique for post-operative cervical cancer patients is whole-pelvic radiation therapy (WPRT) requiring four static photon fields. This technique exposes most of the contents of the true pelvis, including the small bowel as well as the target volume. The highly conformal technique of intensity-modulated radiation therapy (IMRT) has the potential for delivering the required radiation dose to the target volume, while avoiding surrounding normal tissues, and its effectiveness has been validated in several anatomical sites such as head-and-neck [3, 4] or prostate cancer treatment [5, 6]. However, the advantage of using the complex IMRT technique in the field of gynecologic cancer has not

yet been determined [7–9] and demands a prospective clinical trial for its validation. The Radiation Therapy Oncology Group (RTOG) launched a multi-institutional prospective Phase II trial (RTOG 0418) using IMRT for post-operative endometrial and cervical patients in order to determine whether IMRT could reduce short-term bowel toxicity. Recently, a positive preliminary result was presented [10]. In Japan, because of the concern about possible severe late bowel complications related to the combination of surgery and radiotherapy, and because of a positive result from adjuvant chemotherapy alone for intermediate- and high-risk post-operative cervical cancer patients [11], several institutions dare not use adjuvant radiation therapy for early-stage intermediate- or high-risk post-operative cervical cancer patients. Since the RTOG 0418 trial included not only cervical cancer but also endometrial cancer patients, it was decided that the effectiveness and safety of IMRT should be validated including only post-operative cervical cancer patients in a Japanese multicenter prospective clinical trial. As a preparation for this clinical trial, it was regarded as important to ascertain the current status of IMRT for post-operative cervical cancer in Japan. The object of this study was to perform a surveillance study of IMRT for post-operative cervical cancer in a Working Group within the Radiation Therapy Study Group (RTSG) of the Japan Clinical Oncology Group (JCOG).

MATERIALS AND METHODS

In 2013, the Working Group conducted a surveillance using a questionnaire asking about the precise methods of conducting IMRT. Six leading academic institutions in the field of gynecologic oncology, who have already commenced applying IMRT for post-operative cervical cancer patients in clinical practice, were selected for the current survey. The academic institutions included cancer center hospitals and university hospitals. Data collection included: (i) the technical environment for IMRT; (ii) patient preparation before taking planning computed tomography (CT); (iii) the technique for determining the target volume and the normal structure; (iv) the prescription dose, the dose constraint for organs at risk (OARs), how to define the prescription dose; and (v) how patients were set up in daily treatment.

RESULTS

Figure 1 describes the technical environment for IMRT. Half of the institutions used conventional static IMRT, while the others used volumetric-modulated arc therapy (VMAT). One institution used a 15-MV photon beam, which could deliver radiation to deep-seated organs.

Figure 2 summarizes the preparation of patients before taking planning CT. All except one institution used either a vacuum cushion or a shell for patient body fixation, which was important for highly precise radiation therapy as IMRT. One institution used a Baseplate® (Orfit Industries n.v., Vosveld 9A, 2110 Wijnegem, Belgium), which was capable of fixing a patient's hips, legs and feet. According to the RTOG 0418 protocol, all except one institution used full bladder CT for treatment planning. In contrast to the RTOG protocol, most of the institutions did not visualize the vaginal cuff before taking planning CT.

Figure 3 shows how physicians define the clinical target volume (CTV). For the elective lymph node region, all institutions used the guideline for pelvic nodal CTV created by the Japan Clinical Oncology Group Gynecologic Cancer Study Group (JCOG–GCSG) [12]. For contouring the vaginal cuff, the paracolpium and the parametrium, which may contain microscopic cancer cells after radical hysterectomy, four institutions used the RTOG guideline [13] for reference, while two institutions used the JCOG–GCSG guideline for the intact uterus [14] with modification, because the uterus no longer existed after surgery. Two institutions used the fusion CT images taken with the bladder full and empty according to the RTOG protocol to account for the internal motion of the CTV vaginal cuff, while others contoured the CTV vaginal cuff based on one CT series, adding a 5–10 mm internal margin.

Figure 4 described the normal structures selected as the OARs in treatment planning. The organs which were commonly selected as OARs were the rectum, the bladder, the femoral head, and the small bowel/peritoneal cavity. One institution contoured the bowel loop, four the peritoneal cavity, and one did not contour either the bowel loop or the peritoneal cavity.

Figure 5 summarizes the total prescription dose and the prescription point. The total prescription dose was either 50 Gy/25 fr in

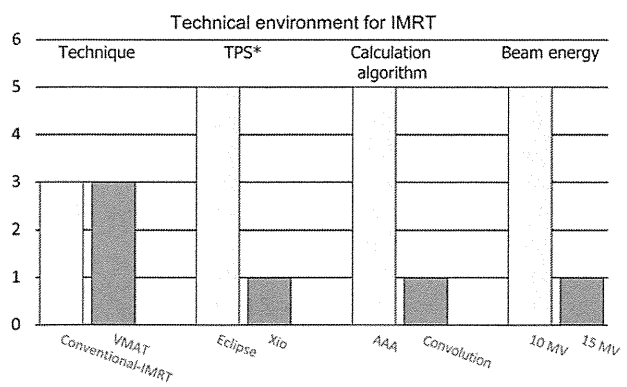

Fig. 1. A bar graph summarizes the technical environment for IMRT between institutions.

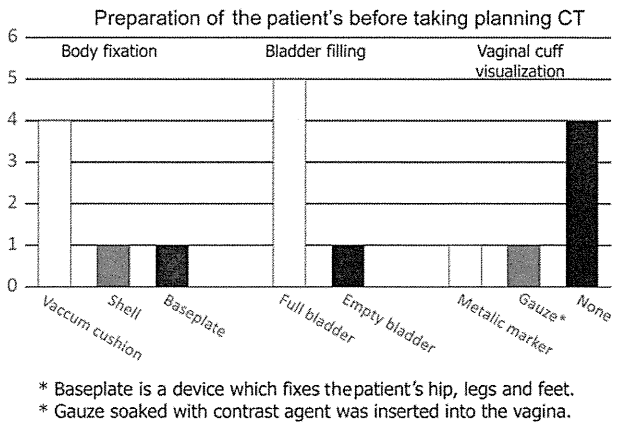

Fig. 2. A bar graph showing the way of patient preparation before taking planning CT.

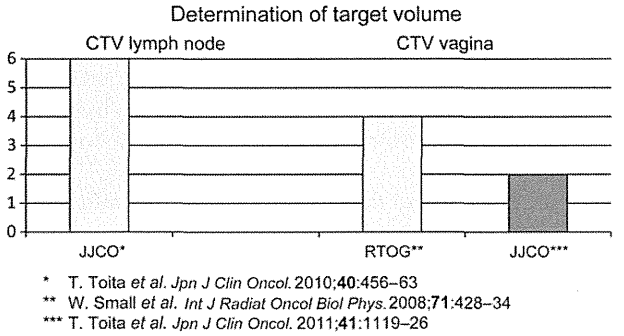

Fig. 3. A bar graph showing which guidelines physicians used as a reference when contouring the target volumes.

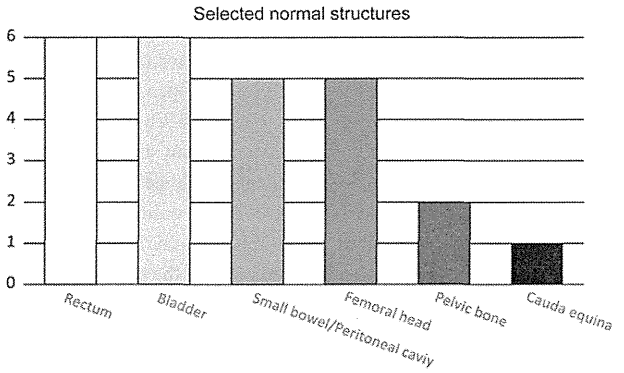

Fig. 4. A bar graph showing which normal structures were selected as organs as risk (OARs).

2 Gy per fraction or 50.4 Gy/28 fr in 1.8 Gy per fraction. Five institutions used the planning target volume (PTV) D_{mean} (mean dose of the PTV) as a prescription point, while one institution used PTV D_{95} (lowest dose encompassing 95% of the PTV). As for the dose constraint for OARs, one institution did not set any specific dose constraint. In this institution the attending physician checked the dose distribution and paid careful attention to hot spots in OAR. The other five institutions used the individual dose constraint definition, and this is summarized in Table 1. Preliminary compliance rates of dose constraints for OARs for five to eleven patients treated during the study period are also summarized in Table 1.

With regard to the daily set-up of image-guided radiation therapy (IGRT), three institutions took Cone-Beam CT (CBCT) every day, one three times a week and two once a week. As for the rectum preparation, no institution gave patients an enema before treatment. Three institutions encouraged patients to empty the rectum every day before treatment, whereas no instruction concerning rectum emptying was given to patients in the other three institutions; however, in two out of these three institutions, CBCT was taken every day and if large amounts of gas or stools were found, patients were asked to empty the rectum before irradiation.

Figure 6 shows a typical dose distribution of IMRT for post-operative cervical cancer patients from the six institutions participating in this study.

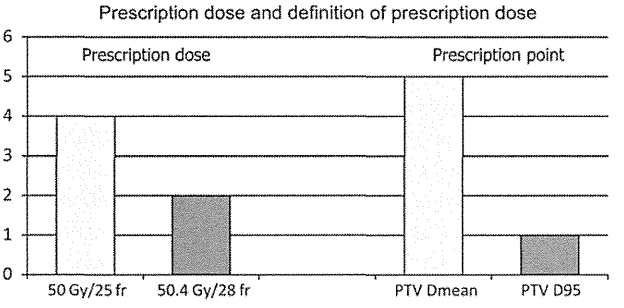

Fig. 5. A bar graph showing the prescription dose and the definition of prescription dose.

DISCUSSION

Planning and delivery of radiation therapy have changed dramatically over the past several decades [15], and IMRT is one of the most complicated and error-prone techniques, and thus requires thorough quality assurance programs, not only for multicenter clinical trials but for daily practical use. As a preparation for a future clinical trial using adjuvant IMRT for post-operative cervical cancer patients, it was considered to be important to know the current status of IMRT in terms of post-operative radiotherapy for cervical cancer in Japan; therefore, the current surveillance study was performed.

Half of the institutions used VMAT, for which it was shown that the treatment time will be shortened compared with conventional static IMRT for pelvic irradiation, but a dosimetric benefit would not be expected [16]. One institution used a 15-MV photon beam. The high-energy photon beam has an advantage of delivering photons to deep-seated organs with less attenuation; however, it brings with it a concern about creating neutrons along with photons. In the latest patterns of care study (PCS) for cervical cancer in Japan, the majority of institutions used photon beams of between 10 and 14 MV [17]. The most appropriate machine energy should be discussed for developing the protocol of a future clinical trial.

Although visualization of the vaginal cuff was recommended in the RTOG protocol, most institutions did not visualize them. It was supposed that inserting markers into the vaginal cuff would require manpower, time and patients endurance of pain. One institution inserted a small piece of gauze soaked with a contrast agent into the vaginal cuff, whereas it was not permitted to insert gauze into the vagina in the RTOG protocol because it would potentially cause anatomical changes relative to the surrounding structures. It was considered to be feasible if only a small piece of gauze was manipulated; however, the impact from volume changes of the bladder and the rectum is considered to be more significant. Therefore, inserting a small piece of gauze with a contrast agent will be included in the protocol of a future clinical trial.

All except one institution used full bladder CT for treatment planning. It was supposed that when the bladder was filled with urine, the bowel would be pushed away from the small pelvis and it would protect the small bowel from radiation exposure. However, reproducibility of bladder filling is problematic because the pelvic nerve plexus has already been damaged to varying degrees by radical hysterectomy; therefore, monitoring daily bladder filling by some means needs to be considered to ensure the accuracy of the treatment.

Table 1. Dose constraint for OAR

	Institution A (adherence rate, $n = 10$)	Institution B (adherence rate, $n = 10$)	Institution C (adherence rate, $n = 11$)	Institution D (adherence rate, $n = 5$)	Institution E (adherence rate, $n = 5$)
Rectum	$V_{50\ Gy} < 40\%$, $D_{max} < 55$ Gy (100%)	$V_{50\ Gy} < 35\%$ (80%)	$V_{40\ Gy} < 60\%$ (18.2%)	$V_{50\ Gy} < 35\%$ (100%)	$V_{40\ Gy} < 80\%$ (40%)
Bladder	$V_{45\ Gy} < 50\%$, $D_{max} < 55$ Gy (80%)	$V_{45\ Gy} < 70\%$, $V_{50\ Gy} < 35\%$ (80%)	$V_{45\ Gy} < 35\%$ (36.4%)	$V_{50\ Gy} < 35\%$ (100%)	$V_{45\ Gy} < 35\%$ (60%)
Small bowel/ peritoneum	$V_{40\ Gy} < 40\%$, $V_{55\ Gy} < 1$ cc (80%)	$V_{40\ Gy} < 40\%$ (40%)	$V_{40\ Gy} < 30\%$ (45.5%)	$V_{40\ Gy} < 30\%$ (80%)	$V_{40\ Gy} < 30\%$ (80%)
Femoral head	$V_{30\ Gy} < 20\%$ (80%)	$V_{30\ Gy} < 15\%$ (20%)	$V_{30\ Gy} < 15\%$ (36.4%)	$D_{mean} < 30$ Gy (80%)	
Pelvic bone		$V_{20\ Gy} < 80\%$ (80%)			$V_{10\ Gy} < 90\%$, $V_{40\ Gy} < 37\%$ (20%)
Cauda equina		$D_{max} < 50$ Gy (40%)			

OAR = organ at risk.

All institutions used the JCOG–GCSG guideline [12] as a reference in order to contour the CTV lymph node. The reason why the RTOG guideline [13] was not used as a reference to contour the CTV lymph node was that the definition of the CTV lymph node according to the JCOG–GCSG guideline differed slightly from the RTOG guideline. First, in the JCOG–GCSG guideline, the cranial margin was set at the bifurcation of the aorta, not based on the bony structure as in the RTOG guideline. It would be difficult to categorize the recurrence as a regional (pelvic recurrence) or a distant (para-aortic nodal) failure when the previous pelvic field was constructed based on the bony anatomy. Second, the Japanese guideline involved the adipose connective tissue between the iliopsoas muscles and the lateral surface of the vertebral body, which was not included in the RTOG guideline. This area was also included in the atlas of Taylor *et al.* [18, 19]. Therefore, the current RTOG definition may be insufficient in terms of lateral expansion of the CTV for the internal iliac node. As for the CTV vaginal cuff, while four institutions used the RTOG guideline [13], two institutions used the JCOG–GCSG guideline for the intact uterus [14]. Not all institutions used the RTOG guideline, because the RTOG guideline did not describe the paracolpium and the parametrium in detail. Although, theoretically, the JCOG–GCSG guideline for the intact uterus was not appropriate for contouring the post-operative female pelvis, the JCOG–GCSG description of the parametrium was more specific than the RTOG guideline. Therefore, this guideline can be used as a reference in contouring the paracolpium and the parametrium after making some modification. We are now creating a consensus-based guideline for CTV vaginal cuff as well as the paracolpium and the parametrium (which may contain microscopic cancer cells, even after R0 radical hysterectomy), because there exists no such consensus guideline other than the RTOG guideline. With regard to the internal organ motion of the CTV vaginal cuff, two institutions used the fusion CT with the bladder full and empty according to the RTOG protocol, while others contoured the CTV vaginal cuff based on one CT series, adding 5–10 mm internal margin to CTV vaginal cuff. The vagina is sandwiched by the rectum and the bladder, whose volume will potentially vary from time to time; therefore, it was considered to be important to make a consensus on the internal margin for the CTV vaginal cuff.

Whereas all but one institution selected the small bowel or the peritoneal cavity as an OAR, with four institutions contouring the peritoneal cavity and one the bowel loop, it was not standardized as to whether to contour only the bowel loop itself or the peritoneal cavity as well. In the current study, four institutions contoured the peritoneal cavity and one the bowel loop. The dose–volume relationship will not be reliable if it is not consistent whether the bowel loop or the peritoneal cavity is contoured. For example, Isohashi *et al.* demonstrated that a dose–volume relationship was found between chronic gastrointestinal (GI) complications and dose to the small bowel loops, whereas no parameter for the peritoneal cavity was significantly associated with GI complications [20]. On the other hand, some modification of the definition will be required if the peritoneal cavity is to be used as an OAR, because part of the bowels are embedded in the retroperitoneal space, such as the ascending or the descending colon. Therefore, we will also develop a consensus-based definition of what constitutes normal structures for the post-operative cervical cancer patient.

Most institutions did not employ PTV D_{95} as the prescription point for concern about possible dose escalation compared with the conventional dose prescription according to *ICRU Report 50* [21]. Consequently, the RTOG 0418 protocol [10], in which PTV D_{97} was used as a prescription dose, was considered to be a more aggressive prescription dose in our Working Group. The dose constraint for OARs and preliminary compliance rates of dose constraints for OARs are summarized in Table 1. Because every institution used individual dose constraints, and contouring of the small bowel/peritoneum was not uniform, a large variation in the actual compliance rate was found. RTOG 0418 [10] reported that 66–76% of patients did not meet the dose criteria for the bladder and the rectum, and the dose constraint was loosened in the next RTOG 1203 protocol because it was considered to be too strict. It is, therefore, important to set achievable and clinically relevant dose constraints as well as to develop a consensus of contours for OARs, especially the small bowel/peritoneum, for a future clinical trial using IMRT for post-operative cervical cancer patients.

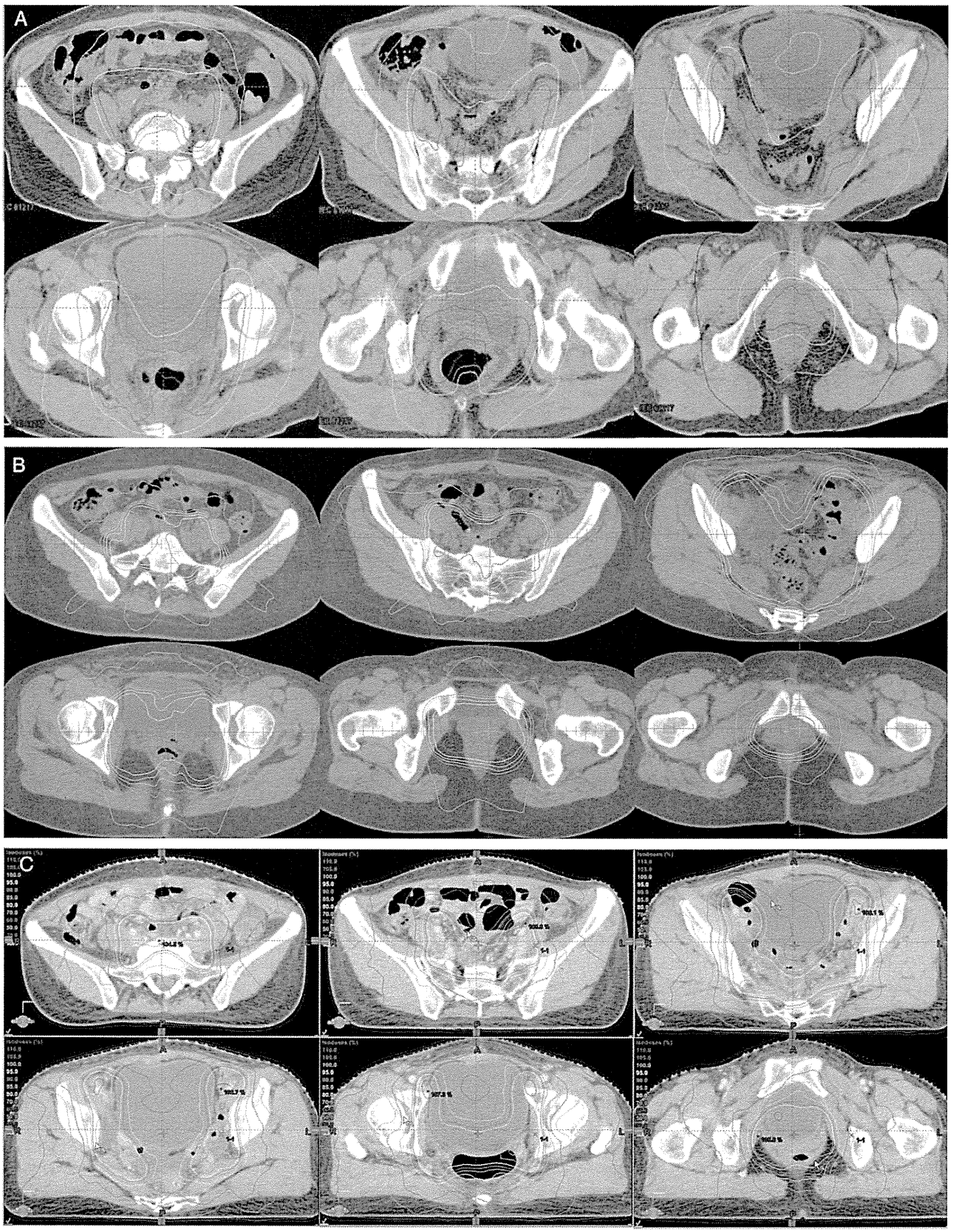

Fig. 6. A typical dose distribution of IMRT for postoperative cervical cancer patients from six institutions participating in this study: Institutions A–F (A–F).

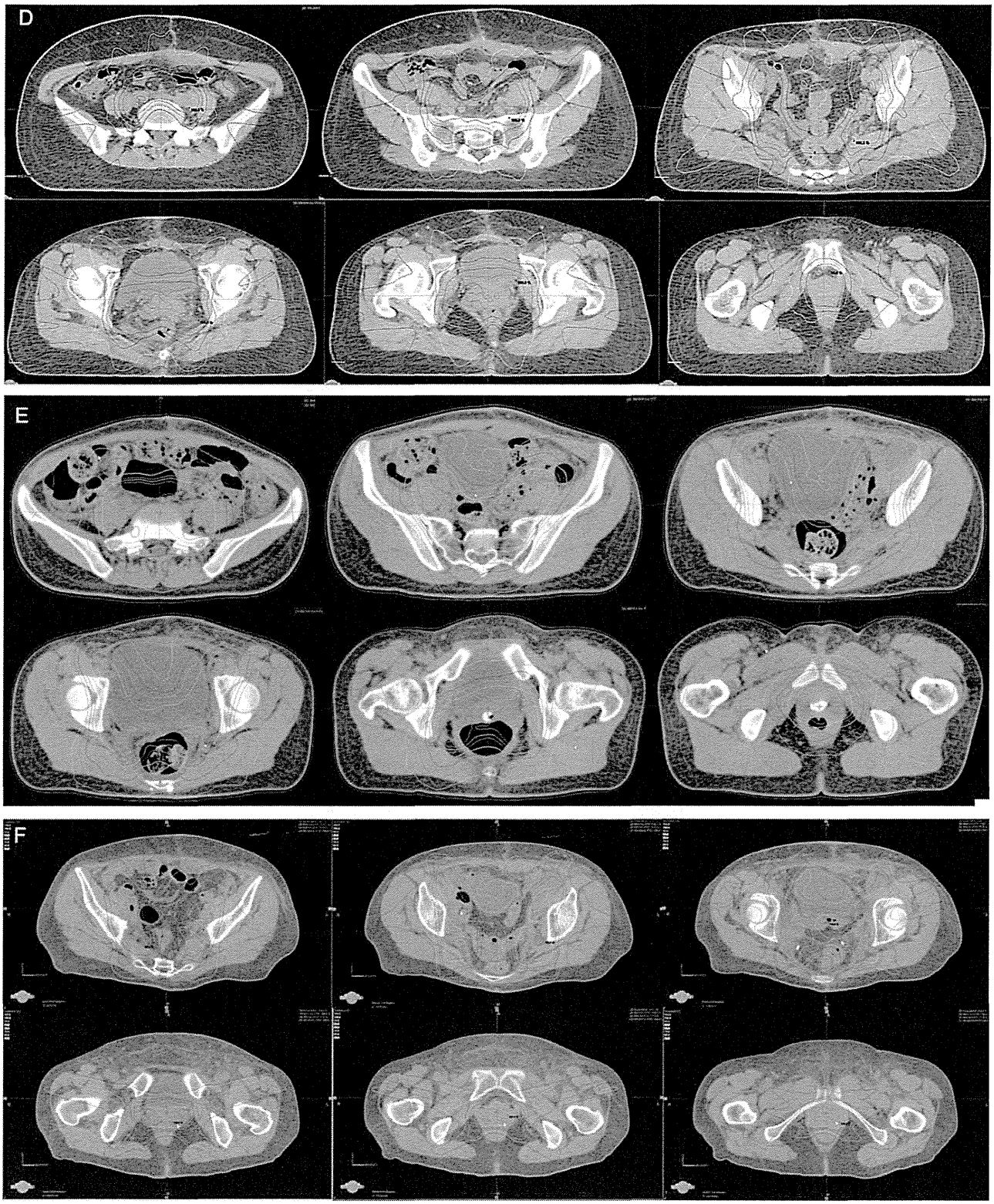

Fig. 6 Continued

The six institutions that contributed to this study were equipped with modern linear accelerators capable of doing CBCT for daily set-up. It is very important to ensure accurate daily patient set-up when using IMRT, which can generate a very steep and complicated dose distribution, especially when applied in such a large field as the pelvic region. If IMRT is to become a standard therapy for post-operative