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Preliminary survey of 3D image-guided brachytherapy for cervical cancer at representative hospitals in Asian countries

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ABSTRACT

3D image-guided brachytherapy (3D-IGBT) has become a standard therapy for cervical cancer. However, the use of 3D-IGBT is limited in East and Southeast Asia. This study aimed to clarify the current usage patterns of 3D-IGBT for cervical cancer in East and Southeast Asia. A questionnaire-based survey was performed in 11 countries within the framework of the Forum for Nuclear Cooperation in Asia. The questionnaire collected the treatment information of patients with cervical cancer who underwent 3D-IGBT. The cumulative external beam radiotherapy and 3D-IGBT doses were summarized and normalized to a biological equivalent dose of 2 Gy per fraction (EQD_2) using a linear-quadratic model. Of the 11 institutions representing the participating countries, six (55%) responded to the questionnaire. Overall, data of 36 patients were collected from the six institutions. Twenty-one patients underwent whole-pelvic irradiation and 15 underwent whole-pelvic irradiation with central shielding. Patients received a median of four treatment sessions of 3D-IGBT (range, 2–6). All 3D-IGBT sessions were computed tomography (CT)-based and not magnetic resonance image-based. The median doses to the high-risk clinical target volume D_{90}, bladder D_{2cc},

rectum D_{2cc} and sigmoid colon D_{2cc} were 80.9 Gy EQD_2 (range, 58.9–105.9), 77.7 Gy EQD_2 (range, 56.9–99.1), 68.0 Gy EQD_2 (range, 48.6–90.7) and 62.0 Gy EQD_2 (range, 39.6–83.7), respectively. This study elucidated the current patterns of 3D-IGBT for the treatment of cervical cancer in East and Southeast Asia. The results indicate the feasibility of observational studies of CT-based 3D-IGBT for cervical cancer in these countries.

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

INTRODUCTION

Cervical cancer is among the most common types of cancers affecting women worldwide [1]. Worldwide, the number of new cases of uterine cervical cancer in 2018 was 569 000 [2]. Previous meta-analyses showed that concurrent chemoradiotherapy for cervical cancer improved local control and overall survival, compared to radiotherapy alone [3–5]. However, the associated mortality rate remains high in Asian countries, because many patients are diagnosed at a relatively advanced stage. In fact, more than 315 000 new cases of cervical cancer were diagnosed in Asia in 2018, and 168 000 deaths have been reported [2]. The cervical cancer mortality rate exceeds 50% in Asia, compared to the rates of 1.9–8.3% in North America and Europe [2].

The Forum for Nuclear Cooperation in Asia (FNCA) is a Japanese government-led framework of regional cooperation between Asian countries [6]. The FNCA aims to promote the peaceful and safe application of nuclear science and technology. The FNCA Radiation Oncology Project was launched in 1993. This project aims to standardize radiotherapy and improve the clinical outcomes of predominant cancers, including cervical cancer, in Asia. At present, 11 countries are participating in the project: the People's Republic of Bangladesh, the People's Republic of China, the Republic of Indonesia, Japan, the Republic of Kazakhstan, the Republic of Korea, Malaysia, Mongolia, the Republic of the Philippines, the Kingdom of Thailand and the Socialist Republic of Vietnam. The institutions belonging to FNCA are recognized as leading institutions in terms of cancer treatment in each country. Thus far, we have successfully conducted several multi-institutional clinical studies of radiotherapy or concurrent chemoradiotherapy for advanced cervical cancer [7–11].

Currently, 3D image-guided brachytherapy (3D-IGBT) plays an essential role in radiotherapy for cervical cancer. Since the publication of the concept and terms of 3D-IGBT for cervical cancer, clear guidelines have been developed regarding the imaging protocol, contouring, applicator reconstruction and planning with 3D volumes [12, 13]. This type of individually optimized brachytherapy has been reported to improve clinical outcomes [14–16]. To date, the results of several surveys on the practice of 3D-IGBT have been published by various groups worldwide [17–21]. However, reports of 3D-IGBT use in East and Southeast Asia remain limited, mainly due to a shortage of medical resources. The induction of clinical trials of 3D-IGBT in East and Southeast Asia will require an understanding of the current patterns of practice of 3D-IGBT for cervical cancer in these countries. Thus, the purpose of the present study was to evaluate the current patterns of 3D-IGBT for the treatment of cervical cancer in East and Southeast Asian countries within the framework of the FNCA.

MATERIALS AND METHODS

Data collection

In August 2016, a questionnaire was sent to FNCA-cooperative institutions in each of the 11 participating countries. We collected treatment information about cervical cancer patients who underwent 3D-IGBT. Images of the dose distributions and delineated target volumes or organs at risk (OARs) were also collected to assess the quality of treatment. We requested that each facility provide the data of at least five cases. The questionnaire included items about disease information, external beam radiotherapy (EBRT) method, 3D-IGBT imaging modality and other 3D-IGBT details (e.g. doses to the high-risk clinical target volume [HR-CTV], bladder, rectum and sigmoid colon). Non-responders received reminders in October 2016. Details of the questionnaire are shown in Supplementary Table 1, see online supplementary material. This study was approved by our Institutional Review Board (Study number: 17–007). Participants provided informed consent or had the opportunity to opt-out of the study. The study was performed in accordance with the principles of the Declaration of Helsinki.

Data analyses

The cumulative EBRT and 3D-IGBT doses were summarized and normalized to a biological equivalent dose of 2 Gy per fraction (EQD_2) using a linear-quadratic model with an α/β of 3 Gy for the OARs and 10 Gy for the tumors. The doses of whole-pelvic irradiation with central shielding (CS) were not added to the EQD_2, in accordance with previous studies [15, 22–24]. EQD_2 was calculated as follows:

$$EQD_2 = D \times [\{d + (\alpha/\beta)\}/\{2 + (\alpha/\beta)\}].$$

D = total dose in Gy.
d = dose per fraction in Gy.
α/β = dose at which the linear and quadratic components of cell killing are equal.

RESULTS

Respondents

Of the 11 institutions invited to participate, six (55%) institutions representing China, Indonesia, Malaysia, The Philippines, Thailand and Japan responded to the questionnaire. The six institutions reported the following 3D-IGBT planning.

China: A 6-Gy isodose line is modified to achieve a HR-CTV D_{90} (minimum dose delivered to 90% of the HR-CTV) of 6–7 Gy while minimizing the D_{2cc} (minimum dose delivered to the highest irradiated 2-cc area) in the OARs.

Table 1. Patients' characteristics

Items (n = 36)	
Age at diagnosis (years)	53 (34–72)
ECOG performance status	
0–1	35
2	1
Imaging modality for staging	
Including MRI	27
Without MRI	9
Stage	
T stage	
2b	26
3a	2
3b	8
N stage	
0	26
1	10
Maximal tumor size (mm)	54 (40–89)
Parametrium invasions	
Left	
None	1
2B	30
3B	5
Right	
None	4
2B	25
3B	7
Vaginal invasion (lower 1/3 or not)	
None	14
Within upper 2/3 of vagina	20
Lower 1/3 of vagina	2

ECOG = Eastern Cooperative Oncology Group.

Table 2. Data of external beam radiotherapy and brachytherapy

Items (n = 36)	
EBRT	
WP alone (without CS)	21
WP and CS	15
WP doses (Gy), median (range)	45 (30–50)
WP fractions, median (range)	25 (15–25)
CS doses (Gy), median (range)	6 (5.4–20)
CS fractions, median (range)	3 (3–10)
Use of concurrent chemotherapy	
Yes	36
No	0
Regimen of chemotherapy	
Cisplatin based	26
Others (taxol, carboplatin, etc.)	10
Brachytherapy	
Imaging modality for brachytherapy	
CT	36
MRI	0
Slice thickness (mm), median (range)	3 (1.25–3.0)
Applicator type	
Tandem and ovoid	29
Tandem and ring	6
Vaginal cylinder	1
Use of interstitial method	
Yes	7
No	29
Times of brachytherapy for each patient	4 (2–6)
Mean point A dose (Gy), median (range)	5.9 (3.4–7.9)
HR-CTV $D_{90\%}$ per fraction (Gy), median (range)	6.5 (2.5–11.7)
Bladder D_{2cc} per fractions (Gy), median (range)	5.1 (2.5–9.5)
Rectum D_{2cc} per fractions (Gy), median (range)	4.1 (1.0–7.8)
Sigmoid colon D_{2cc} per fraction (Gy), median (range)	3.4 (0.6–7.4)
HR-CTV $D_{90\%}$ (EQD_2 Gy), median (range)	80.9 (58.9–105.9)
Bladder D_{2cc} (EQD_2 Gy), median (range)	77.7 (56.9–99.1)
Rectum D_{2cc} (EQD_2 Gy), median (range)	68.0 (48.6–90.7)
Sigmoid colon D_{2cc} (EQD_2 Gy), median (range)	62.0 (39.6–83.7)

ICRU = International Commission on Radiation Units and Measurements.

Indonesia: The prescribed dose is delivered to the HR-CTV D_{90} (6–7 Gy) while minimizing the D_{2cc} in the OARs. A low D_{2cc} in the OARs dose would lead to an increase in the HR-CTV D_{90}.

Malaysia: The HR-CTV D_{90} should achieve a minimum of 6.5 Gy while minimizing the D_{2cc} in the OARs. The OAR tolerance is always respected; accordingly, the HR-CTV D_{90} dose may be compromised to maintain the OAR doses within the tolerance limit.

The Philippines: The D_{98} and D_{90} for the HR-CTV and D_{2cc} and D_{1cc} for the OARs are evaluated. The dose to the HR-CTV may be increased, with respect to the dose limit of the OARs.

Thailand: A 7-Gy isodose line is modified to achieve an HR-CTV D_{90} of $\geq$7 Gy while minimizing the D_{2cc} in the OARs.

Japan: A 6-Gy isodose line is modified to achieve an HR-CTV D_{90} of >6.5 Gy while minimizing the D_{2cc} in the OARs.

Four institutions had not yet implemented 3D-IGBT, and one institution that had already installed a 3D IGBT system did not respond to the questionnaire.

Collected data

The data of 36 patients were collected from the six institutions. The median patient age was 53 (range, 34–72) years, and the median tumor size was 54 (range, 40–89) mm at diagnosis. All but one enrolled patient had a performance status of 0 or 1. A total of 27 patients underwent magnetic resonance imaging (MRI) for staging. The patients' characteristics are summarized in Table 1.

Regarding the EBRT method, 21 patients underwent whole-pelvic (WP) irradiation and 15 patients underwent WP irradiation CS. Regarding the applicator type, 29 patients used tandem and ovoid applicators, six used tandem and ring applicators, and one with T3a

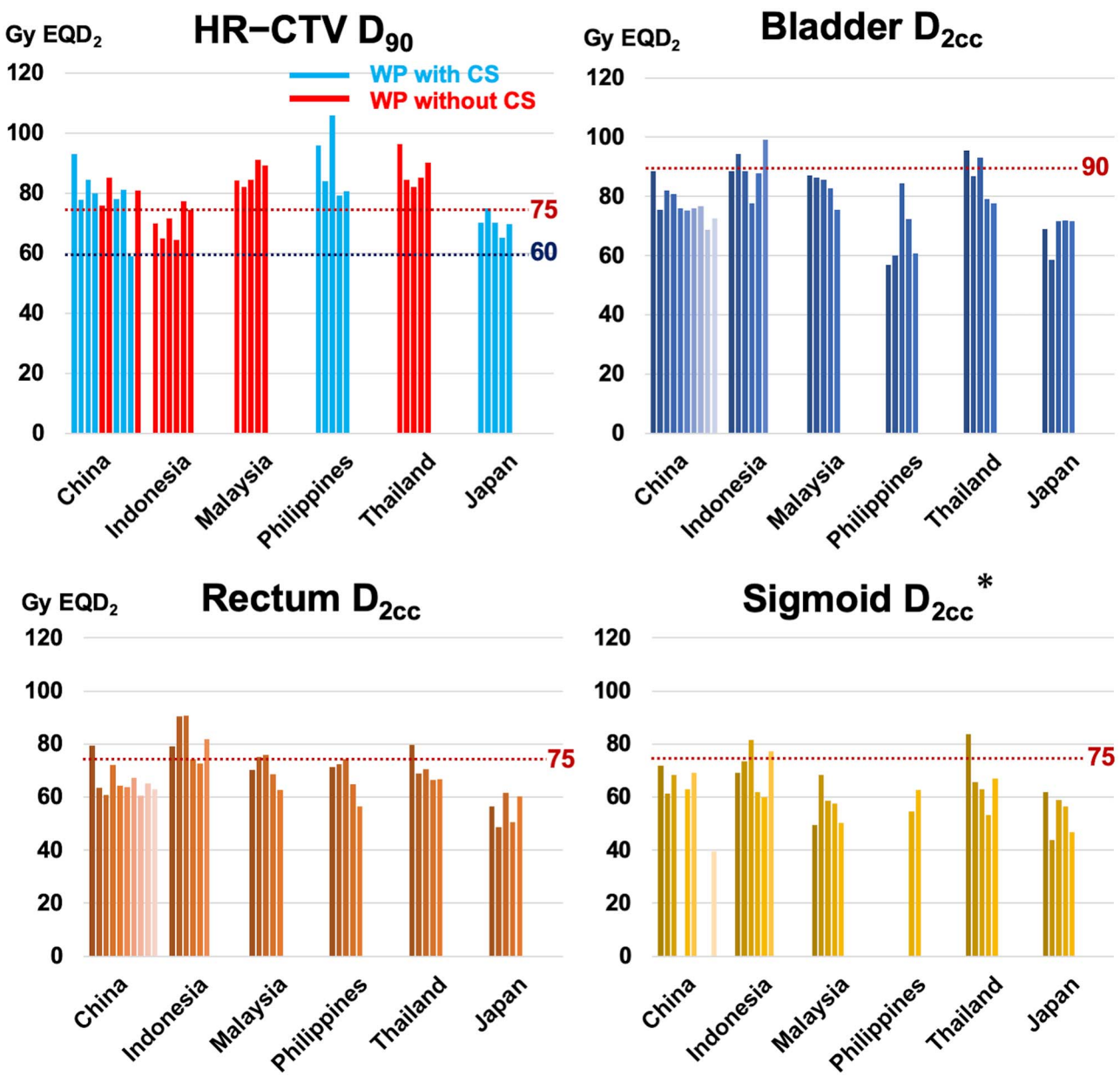


Fig. 1. Comparison of cumulative doses of external beam radiation and 3D image-guided brachytherapy in each patient. Four bar graphs show the cumulative doses to the HR-CTV D_{90}, bladder D_{2cc}, rectum D_{2cc} and sigmoid colon D_{2cc}. Each bar indicates the cumulative dose of external beam radiation and 3D image-guided brachytherapy in each patient. The dotted line corresponding to '60 Gy EQD_2' represents the reference dose of HR-CTV D_{90} for patients who were treated by whole-pelvic irradiation with central shielding according to the study by Murakami [23]. Other doted lines represent the reference doses for patients who were treated by whole-pelvic irradiation alone according to the EMBRACE study [25]. *Sigmoid D_{2cc} was not reported in seven patients. D_{90} = the minimum dose delivered to 90% of the volume, D_{2cc} = the minimum dose delivered to the highest irradiated 2-cc area, EQD_2 = equivalent dose of 2 Gy per fraction.

disease used a vaginal cylinder. At one institution, WP irradiation was performed without CS, and brachytherapy was administered in two or three sessions. At another institution, up to six session of brachytherapy were performed. The details of all cases are shown in Supplementary Table 2, see online supplementary material. The median number of brachytherapy sessions per patient was four (range, 2–6). The median doses to the HR-CTV D_{90}, bladder D_{2cc}, rectum D_{2cc} and sigmoid colon D_{2cc} were 80.9 Gy EQD_2 (range, 58.9–105.9), 77.7 Gy EQD_2 (range, 56.9–99.1), 68.0 Gy EQD_2 (range, 48.6–90.7) and 62.0 Gy EQD_2 (range, 39.6–83.7), respectively. All collected images

Table 3. Comparison of country difference in 3D-IGBT

Region	Sessions of BT	HR-CTV D_{90}	Bladder D_{2cc}	Rectum D_{2cc}	Sigmoid D_{2cc}
(A) Comparison of country difference in 3D-IGBT per fractions					
China (WP alone)	4	6.0 (4.6–7.6)	5.0 (3.1–5.6)	4.1 (2.2–4.4)	3.9 (3.3–5.0)
(WP with CS)	6	6.1 (2.7–7.1)	4.9 (4.0–5.5)	4.0 (1.0–5.4)	3.2 (1.4–4.9)
Indonesia (WP alone)	2 or 3	5.8 (2.5–8.3)	7.1 (5.5–9.5)	6.4 (3.5–7.8)	5.0 (1.8–7.4)
Malaysia (WP alone)	4	7.3 (6.2–8.6)	6.0 (4.6–7.0)	4.8 (3.3–5.1)	2.4 (0.9–5.0)
The Philippines (WP with CS)	4	7.3 (5.8–11.7)	3.9 (2.5–7.2)	4.7 (1.9–6.0)	3.4 (1.2–4.0)
Thailand (WP alone)	4	6.4 (3.3–7.2)	4.9 (4.1–7.6)	3.3 (2.7–4.7)	2.2 (0.6–5.2)
Japan (WP with CS)	4	7.0 (6.1–8.0)	5.8 (3.4–6.6)	4.1 (2.7–6.0)	4.2 (2.2–5.9)
(B) Comparison of country difference in cumulative dose of external beam RT and 3D-IGBT					
China (WP alone)	4	81.0 (75.9–85.2)	75.2 (72.6–75.9)	63.9 (62.9–64.3)	66.0 (62.9–69.1)
(WP with CS)	6	79.9 (58.9–93.0)	76.6 (68.8–88.4)	65.1 (60.6–79.4)	65.0 (39.6–72.0)
Indonesia (WP alone)	2 or 3	70.6 (64.6–77.4)	88.5 (77.7–99.1)	80.5 (72.6–90.7)	71.4 (59.9–81.6)
Malaysia (WP alone)	4	84.5 (82.1–91.1)	85.7 (75.5–87.0)	70.3 (62.6–76.0)	57.6 (49.4–68.3)
The Philippines (WP with CS)	4	84.1 (79.3–105.9)	60.8 (56.9–84.4)	71.2 (56.5–74.4)	58.6 (54.6–62.6)
Thailand (WP alone)	4	85.3 (82.2–96.4)	86.9 (77.7–95.6)	69.0 (66.6–79.6)	65.6 (53.3–83.7)
Japan (WP with CS)	4	70.2 (65.2–70.2)	71.6 (58.5–71.8)	56.6 (48.6–61.7)	56.5 (43.8–62.0)

RT = radiotherapy, BT = brachytherapy.

of dose distributions and the delineated target volumes or OARs were reviewed by all members of the FNCA Radiation Oncology Project. The details of EBRT and 3D-IGBT are listed in Table 2.

Figure 1 shows the cumulative doses of EBRT and 3D-IGBT administered to each patient. Dotted lines indicate reference doses from the literature: '60 Gy EQD_2 for HR-CTV D_{90}' in WP irradiation with CS refers to Murakami *et al.* [23], whereas '75 Gy EQD_2 for HR-CTV D_{90}', '90 Gy EQD_2 for bladder D_{2cc}' and '75 Gy EQD_2 for rectum D_{2cc} or sigmoid D_{2cc}' refer to the EMBRACE study [25]. Compared with the reference doses, 30 (83%) of 36 patients achieved adequate doses to the HR-CTV D_{90}. Moreover, 32 (89%) of 36 patients achieved the dose constraint for the bladder D_{2cc}, and 29 (81%) achieved the dose constraint for the rectum D_{2cc}. Regarding the dose to the sigmoid colon, the corresponding D_{2cc} was not reported in seven patients; 26 (90%) of the remaining 29 patients achieved the dose constraint for the sigmoid colon D_{2cc}.

Table 3 shows a comparison of the differences in 3D-IGBT and cumulative doses of EBRT and 3D-IGBT among the participating countries. Representative two cases are shown in Figure 2. As shown in Table 3, the median doses of the HR-CTV D_{90} or the D_{2cc} of the OARs per fraction varied across those six countries. The values of the HR-CTV D_{90}, bladder D_{2cc}, rectum D_{2cc} and sigmoid D_{2cc} per fraction were 5.8–7.3, 3.9–7.1, 3.3–6.4 and 2.2–5.0 Gy, respectively. The cumulative total treatment doses of the HR-CTV D_{90}, bladder D_{2cc}, rectum D_{2cc} and sigmoid D_{2cc} ranged from 70.2–85.3, 60.8–88.5, 56.6–80.5 and 56.5–71.4 Gy EQD_2, respectively.

DISCUSSION

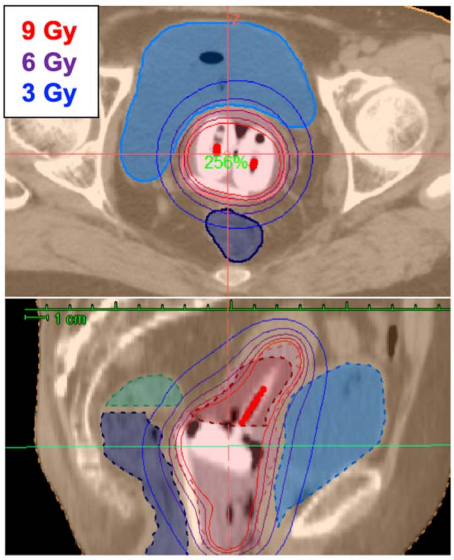
This is the first preliminary survey of current patterns of practice of 3D-IGBT in East and Southeast Asia. Our study revealed that some countries in this region have not yet implemented 3D-IGBT. As previous studies have clearly indicated that 3D-IGBT improves the clinical outcomes of cervical cancer patients [14–16], our results suggest that action is needed to introduce 3D-IGBT in institutions/countries without this technology.

Our survey showed that the participating institutions held a certain level of 3D-IGBT skill. However, we also found that EBRT was conducted in a heterogeneous manner. Of the six responding institutions, three used WP alone, two used WP irradiation with CS, and one used both strategies. Increasingly, evidence supports the use of both strategies of EBRT for cervical cancer [14–16, 23–25]. Thus, both strategies of EBRT should be available for the treatment of cervical cancer. However, this heterogeneity with respect to EBRT may be a barrier to the interpretation of clinical results when we plan the next step in the FNCA Radiation Oncology Project in Asian countries. Notably, a recent report suggested that the dose contributions of CS were variable but not negligible when analysing the total doses delivered to the HR-CTV [26]. Therefore, an observational study to evaluate the clinical outcomes based on current patterns of 3D-IGBT in each institution, rather than a clinical trial based on 3D-IGBT requiring uniform dose constraints, would be warranted as the next step.

All 3D-IGBT sessions in the present study were computed tomography (CT)-based, not MRI-based. Studies have demonstrated that CT is inferior to MRI when visualizing cervical tumors. Hegazy *et al.* reported that CT-based contouring overestimates the contour width compared to MRI-based CTV delineation in 3D-IGBT for cervical cancer [27]. However, the introduction of MRI-based brachytherapy in developing countries would be challenging, given the national economic statuses, the burdens on the patients and medical staff, and the time delays for irradiation. In fact, >80% of cervical cancer cases occur in developing countries. Therefore, CT-based brachytherapy is a practical method of 3D-IGBT in developing countries.

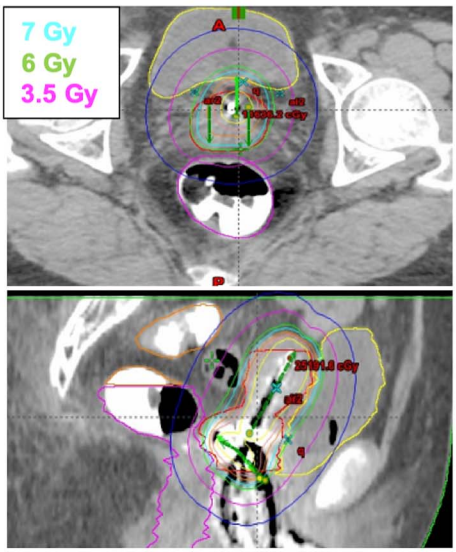
The doses to the HR-CTV and OARs appeared to be acceptable. The doses in >80% of the cases were comparable to the reference doses described previously [23, 25]. However, some regional differences in doses to the HR-CTV and OARs were found (Supplementary

Case 1



	HR CTV D_{90}	Bladder D_{2cc}	Rectum D_{2cc}	Sigmoid D_{2cc}
WP	30 Gy/15 fr.			
CS	20 Gy/10 fr.			
1st BT	6.29 Gy	5.39 Gy	3.93 Gy	2.92 Gy
2nd BT	6.08 Gy	5.19 Gy	4.20 Gy	3.01 Gy
3rd BT	6.12 Gy	5.24 Gy	4.57 Gy	3.19 Gy
4th BT	5.84 Gy	5.24 Gy	4.57 Gy	3.19 Gy
5th BT	6.52 Gy	4.63 Gy	4.67 Gy	N/R
6th BT	6.46 Gy	5.42 Gy	4.84 Gy	N/R
Total EQD_2	80.5 Gy	81.0 Gy	72.1 Gy	N/A

Case 2



	HR CTV D_{90}	Bladder D_{2cc}	Rectum D_{2cc}	Sigmoid D_{2cc}
WP	50 Gy/25 fr.			
CS	-			
1st BT	5.60 Gy	7.28 Gy	6.51 Gy	2.98 Gy
2nd BT	8.34 Gy	9.45 Gy	7.78 Gy	7.43 Gy
Total EQD_2	70.0 Gy	88.5 Gy	79.2 Gy	69.1 Gy

Fig. 2. Representative cases that were treated with different sessions of brachytherapy. Left: dose distribution images of the first brachytherapy are shown for each patient. Right: the doses to the HR-CTV D_{90}, bladder D_{2cc}, rectum D_{2cc} and sigmoid colon D_{2cc} are summarized in tables. Case 1 includes the data of a patient who underwent six sessions of brachytherapy. Case 2 includes the data of a patient who underwent two sessions of brachytherapy.
D_{90} = the minimum dose delivered to 90% of the volume, D_{2cc} = the minimum dose delivered to the highest irradiated 2-cc area, fr. = fraction, BT = brachytherapy, EQD_2 = equivalent dose of 2 Gy per fraction.

Table 2, Table 3). These differences may be the result of variations in the number of brachytherapy sessions, with the median for each patient being 4 (range, 2–6) sessions. This variation was attributable not only to the patients' disease statuses but also to the geographical characteristics. Many countries in East and Southeast Asia comprise several islands. This geographical characteristic, when combined with economic issues, makes it difficult for patients to undergo routine radiotherapy. In addition, there is a pronounced shortage of institutions that provide radiotherapy in East and Southeast Asia. These regional characteristics should be taken into consideration when aiming to establish 3D-IGBT throughout East and Southeast Asia.

Regarding the limitations of the present study, this survey did not include all the countries in East and Southeast Asia. In addition, the HR-CTV D_{90} values may not be accurate because all brachytherapy sessions were CT-based, not MRI-based. Moreover, this survey did not collect data on the clinical outcome of each patient. However, this

survey indicated the feasibility of observational studies of CT-based 3D-IGBT for cervical cancer in East and Southeast Asian countries. Regarding quality assurance/quality control in radiation therapy, the FNCA-cooperative institutions have successfully conducted domestic dose audits. This fact encourages the initiation of observational studies in these institutions.

In conclusion, we have reported the current patterns of practice of 3D-IGBT for the treatment of cervical cancer in East and Southeast Asian countries. The results of this study suggest that observational studies of CT-based 3D-IGBT for cervical cancer in East and Southeast Asian countries are feasible. Further studies to determine the efficacy of 3D-IGBT for cervical cancer in Asian populations, and especially in developing countries, are warranted.

SUPPLEMENTARY DATA

Supplementary data are available at the *Journal of Radiation Research* online.

AUTHOR CONTRIBUTIONS

N.O.: study conceptualization, data collection and analysis, and manuscript writing. M.W.: study conceptualization and manuscript writing. J.C., H.K., L.F.N., M.J.C., R.H.d.l.R., Y.C.: data collection and study conceptualization. H.M., S.F., A.F.M.K.U., T.A., C.-K.C., U.T., N.C.H.: study conceptualization. T.O., T.N., S.K.: study conceptualization and oversight of study. All authors read and approved the final manuscript.

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CONFLICT OF INTEREST

None declared.

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