した研修会も必要である．本研究班では，主に首都圏で開催される研修会には参加困難な施設も多いことから，島根・鳥取県，沖縄県，兵庫県等の都道府県がん診療連携拠点病院において研修会を開催し，各施設におけるIMRTの臨床導入に向けた支援を行ってきたが，今後も継続的な研修会の実施が必要である．

小線源治療については，地域間，施設間格差が著明である子宮頸がん腔内照射技術の標準化・均てん化が急務である．本研究班では手技の標準化に資するツールとして手技のデモンストレーションを含む研修用DVDを作成し，日本放射線腫瘍学会の研究会で上映するとともに腔内照射装置保有全173施設に送付した．送付した施設を対象とした評価アンケートでは，医師，診療放射線技師，看護師の計302名より回答が寄せられ，高い評価が得られた．また研修用DVDに合わせたテキストとして子宮頸癌腔内照射マニュアルも作成し標準化を図ってきた．今後は海外で普及が進む画像誘導小線源治療（IGBT）を我が国でも普及するための課題の抽出と対応が必要であり，さらには適切な診療報酬についての検討も重要である．

4．放射線治療の品質管理・第三者評価

放射線治療の実施過程は複雑かつ多岐にわたる．治療に先立つ放射線治療計画では，治療計画用画像の取得や放射線を照射する部位（標的体積），照射方法，線量の決定，さらにモニターユニット値という放射線照射量の算出等々，種々の過程が存在する．また標的体積の決定一つを取っても，病巣進展範囲の認識には治療計画者間でばらつきが生じるところである．そのため放射線治療の実施にあたっては，その一連の過程に対して品質管理（Quality Control：QC）および品質保証（Quality Assurance：QA）を行い治療の質を保つことが必須となる [4]．もちろん誤って使用すれば死亡にもつながる障害を引き起こす危険もあり，放射線の照射装置そのもののQC/QAも欠くことができない．また，一般診療，臨床試験を問わず，施設間差を解消し均てん化を図る観点からも品質管理，品質保証は重要な役割を担っている．不適切な治療により治療成績が低下することは想像に難くないが，臨床試験においてもプロトコール規定の逸脱により治療成績が低下することが報告されている [5, 6]．一方で近年のInformation Technology（IT）技術の進歩により，放射線治療も一般的な三次元放射線治療からSRT/SBRT，IMRTなどへと急速に高度化が進んでいる．これらの先端的技術を安全に使用するためにも各技術に応じた適切なQC/QAプログラムの実施が求められている [7]．

わが国では放射線の照射装置のQC/QAの第三者評価として，2007年11月から全国の放射線治療施設を対象とした「治療用照射装置（X線）の出力線量測定（郵送測定）」事業が開始されているが，2011年までの実施施設数は137施設であり，都道府県がん診療連携拠点病院であっても実施は27施設（53%）にとどまっている．今後は質の担保を図るためにもがん診療連携拠点病院指定要件の必須条件となることが必要である．

また，医療安全の観点から放射線治療に関するヒヤリ・ハット/インシデント報告システムも重要である．現在，医療安全対策ネットワーク整備事業として公益財団法人日本医療機能評価機構において医療行為全般を対象としたヒヤリ・ハット事例の収集およびフィードバックが図られているが，放射線治療に関する報告事例はごく一部を占めるのみであり，放射線治療の専門スタッフ間の情報共有の場として十分生かされているとは言い難い状況である．放射線治療の急速な高度化が進む現在，海外の先行事例も参考に放射線治療を対象とした効率的・効果的なヒヤリ・ハット/インシデント報告システムの立ち上げが必要である．

5．その他の重要課題

上記以外にも重要な課題として「啓発活動」があげられる．患者，一般のがん医療に関わる医師を始めとする医療従事者，がん専門相談員等における放射線治療に関する知識および理解が未だ十分とは言えない状況であり，放射線治療の普及が進まない一因となっている．大学医学部においては放射線腫瘍学講座の設置を推進し，放射線治療に関する卒前・卒後の教育の充実を図ること，モデルコアカリキュラムに放射線治療の適応を取り入れ，教育の均てん化を図ること，また放射線治療に携わる医療従事者にも専門的知識が求められており，放射線技師，看護師に対する放射線腫瘍学の卒前・卒後教育の充実を図ることも必要である．今後さらに啓発・教育活動を進め放射線治療の認知度を高めていくことが重要である．

Ⅳ．まとめ

近年の技術革新による先端的放射線治療が普及しつつあり，これまで以上に放射線治療の発展が期待される一方で，今後は量のみならず質の充実が求められている．ここで述べたのは重要な課題の一部に過ぎないが，今後これらの課題が解決され，安全かつ質の高い放射線治療の均てん化と先端的放射線治療の普及が進み，がんの治療成績が向上することを切に願うものである．

参考文献

[1] 石倉聡，研究代表者．厚生労働科学研究費補助金がん臨床研究事業「がん医療の均てん化に資する放射線治療の推進及び品質管理に係る研究」（課題番号：H22-がん臨床-一般-001）平成23年度研究報告書．2012.

[2] Inter-Society Council for Radiation Oncology. Radiation oncology in integrated cancer management: report of the Inter-Society Council for Radiation Oncology. Philadelphia: ISCRO, PA. 1991.

[3] Slotman BJ, Cottier B, Bentzen SM, Herren G, Lievens Y, van den Bogaert W. Overview of national guidelines for infrastructure and staffing of radiotherapy. ESTRO-QUARTS: Work package 1. Radiother Oncol.

2005;75:349-54.
[4] 加藤洋一. ISO9000による品質保証の基本的な考え方. 臨床評価. 2000;28:33-50.
[5] Abrams RA, Winter KA, Regine WF, Safran H, Hoffman JP, Lustig R, et al. Failure to adhere to protocol specified radiation therapy guidelines was associated with decreased survival in RTOG 9704 - a phase III trial of adjuvant chemotherapy and chemoradiotherapy for patients with resected adenocarcinoma of the pancreas. Int J Radiat Oncol Biol Phys. 2012;82:809-16.
[6] Peters LJ, O'Sullivan B, Giralt J, Fitzgerald TJ, Trotti A, Bernier J, et al. Critical impact of radiotherapy protocol compliance and quality in the treatment of advanced head and neck cancer: results from TROG 02.02. J Clin Oncol. 2010;28:2996-3001.
[7] Bekelman JE, Deye JA, Vikram B, Bentzen SM, Bruner D, Curran WJ Jr, et al. Redesigning radiotherapy quality assurance: opportunities to develop an efficient, evidence-based system to support clinical trials–report of the National Cancer Institute Work Group on Radiotherapy Quality Assurance. Int J Radiat Oncol Biol Phys. 2012;83:782-90.

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ORIGINAL ARTICLE

Radiotherapy quality assurance review for a multi-center randomized trial of locally advanced esophageal cancer: the Japan Clinical Oncology Group (JCOG) trial 0303

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Abstract
Background and purpose The purpose of this study was to evaluate the radiotherapy (RT) quality assurance (QA) for JCOG 0303.
Methods and materials JCOG 0303 was a multi-center phase II/III trial that compared two types of chemotherapy administered concomitantly with RT for locally advanced esophageal cancer. RT requirements included a total dose of 60 Gy in 30 fractions and CTV with a 2-cm margin cranio-caudally to the primary tumor. The QA assessment was given as per protocol (PP), deviation acceptable (DA), violation unacceptable (VU), and incomplete/not evaluable following predefined criteria for quality parameters.
Results A total of 142 cases were accrued. After excluding 36 incomplete/not evaluable, 106 (75%) were fully evaluable for RT quality review. Of these 106, there were 4 VU (4%) and overall RT compliance (PP + DA) was 96%. Comparing the incidence of VU based on the numbers enrolled by institution, the highest quarter of enrollment ($\geq$7 cases) had no VU, while all VU (4; 11%) were from institutions enrolling <7 patients.
Conclusions The results of the RTQA assessment for JCOG 0303 were sufficient to provide reliable results. Additional improvements will be needed for institutions with low accrual rates.

Keywords Clinical trial · Esophageal cancer · Quality assurance · Quality control · Radiotherapy

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Introduction

The validity of clinical trials among multiple institutions is predicated on the premise that the selection of patients and their treatments will be uniform at all of the participating institutions. This assumption requires a concise definition of the population to be studied, the treatment regimens to be followed, and the methods used for evaluating the results [1]. Quality assurance (QA) programs attempt to document the validity of the assumptions and to quantify the extent of any variations. High-standard QA programmes result in improvement of practice quality, which is known as a flow-on effect. It is important to apply the study results and to introduce the trial outcomes into practice. A QA evaluation therefore requires consideration of clinical validity and flexibility with regard to reasonable standards of care.

With the development of multi-modality studies, particularly for radiation therapy (RT), RT planning and delivery procedures have changed dramatically. As a result, assessments of the appropriateness of therapies delivered in each institution have become more complex. After the introduction of 3-dimensional (3-D) treatment planning in the 1980s, the improved technology for RT procedures has gradually spread to general practice from

the mid-1990s up to today. During the transition period from conventional 2-dimensional (2-D) to 3-D RT planning, the first proactive QA programs for the Japan Clinical Oncology Group (JCOG) started in 2002.

JCOG 0202, a multi-center phase III trial, compared two types of consolidation chemotherapy after concurrent chemoradiotherapy for limited-disease, small cell lung cancer. As a result, JCOG 0202 demonstrated excellent compliance, as high as 92% [2]. The next trial for esophageal cancer, JCOG 0303, also implemented an on-going RTQA program. This study is an evaluation of the protocol compliance for JCOG 0303. In addition, by being involved in the JCOG RTQA process, we discuss the current conditions and problems of QA for multi-institution trials, as well as the perspectives for future clinical trials.

Materials and methods

Study design and RT requirements

JCOG 0303 was a multi-center phase II/III trial that compared two types of chemotherapy which were administered concomitantly with radiotherapy for locally advanced (T4 and/or unresectable metastatic lymph nodes) thoracic esophageal cancer (Fig. 1). The primary endpoint of this study was overall survival and the secondary endpoints included the proportion of complete responses and the toxicity profile of each treatment. JCOG 0303 was carried out according to the principles set out in the Declaration of Helsinki 1964 and all subsequent revisions, informed consent was obtained, and the relevant institutional review board had approved the study.

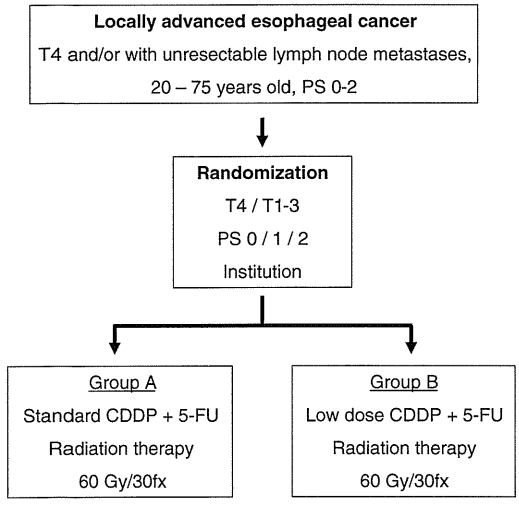

Fig. 1 Outline for JCOG 0303. *PS* performance status, *CDDP* cisplatin, *5-FU* 5-fluorouracil

Patients were randomized to receive either low-dose cisplatin/5-fluorouracil (5-FU) (6 weeks of cisplatin 4 mg/m^2 plus 5-FU 200 mg/m^2 on days 1–5) or standard-dose cisplatin/5-FU (cisplatin 70 mg/m^2 on days 1 and 29 plus 5-FU 700 mg/m^2 for days 1–4, and 29–32). Both regimens included concurrent RT.

Regarding the current practice for advanced esophageal cancer, RT requirements included a total dose of 60 Gy in 30 fractions and an overall treatment period of 40–63 days [3–5]. For treatment planning, both conventional 2-D X-ray simulation and 3-D computed tomography (CT) simulation were allowed. Gross tumor volume (GTV) was defined as the volume of a primary tumor demonstrated by a CT scan and/or an endoscope, as well as metastatic lymph nodes that measured $\geq$1 cm in the long axis. For this trial, a clinical target volume (CTV) for the primary tumor was created to add a 2-cm margin cranio-caudally by considering subclinical extension. A CTV margin for metastatic lymph nodes was not added and CTV did not include elective regional lymph nodes. A planning target volume (PTV) was defined by adding margins at the discretion of radiation oncologists (typically 0.5–1 cm for lateral margins and 1–2 cm for cranio-caudal margins, depending on respiratory motion and patient fixation). A dose of 60 Gy was prescribed at the center of the PTV. Tissue heterogeneity correction was not used for monitor unit calculation, because if heterogeneity correction was required and different calculation algorithms were allowed, the inter-institutional variation of the delivered dose would have been significant, and the convolution–superposition algorithm was not available in some participating institutions at the beginning of this trial.

Dose constraints were defined with regard to maximum point doses to the spinal cord and the digestive organs. The dose to the spinal cord was kept at $\leq$44 Gy. The doses to the gastric antrum, small intestine, and colon were kept at <50, <40, and <45 Gy, respectively.

If a tumor was located in the middle or lower thoracic esophagus, treatment using 3–4 ports was recommended to reduce the possible risk of heart toxicity. For the treatment of tumors in the upper thoracic esophagus and supraclavicular lymph node metastases, the number of ports used was at the discretion of each institution.

Quality assurance review

For the initial QA review, copies of pre-treatment diagnostic X-rays and CTs, simulation and verification films, worksheets for monitor unit calculations for the prescribed doses, and RT charts were sent to the QA review center within 7 days after beginning RT. Information on the total RT course was required to be sent within 30 days after completing RT. These documents were to be submitted for

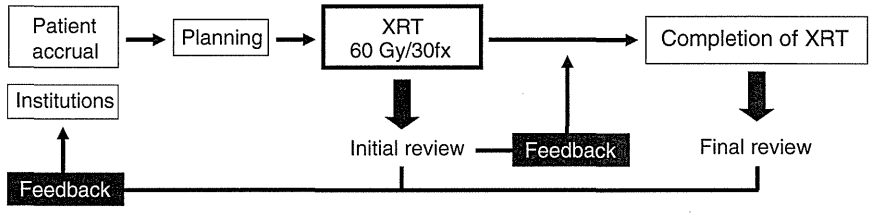

Fig. 2 Flow chart for QA review After the QA review, feedback was given to the institutions. Treatment planning was modified when possible

Table 1 Criteria for QA scores

	PP	DA	VU
GTV			
Distance to field borders	Lateral: 1–2.5 cm	Neither PP nor VU	Lateral: <1 cm or >2.5 cm
	Cranio-caudal: 3.5–6 cm		Cranio-caudal: <2 cm or >6 cm
Overall treatment time	40–63 days	NA	<40 or >63 days
Organs at risk			
Spinal cord	≤44 Gy	Neither PP nor VU	>50 Gy
Gastrointestinal	Within constraints (gastric antrum: 50 Gy, small intestine: 40 Gy, Colon: 45 Gy)	NA	Above constraints
Total dose at reference point	57–63 Gy	Neither PP nor VU	<54 Gy or >66 Gy
Heterogeneity correction	No	Yes (≤10% total dose difference)	Yes (>10% total dose difference)

GTV gross tumor volume, *PP* per protocol, *DA* deviation acceptable, *VU* violation unacceptable, *NA* not applicable

all accrued patients. They were collected during patient accrual and after the completion of accrual to provide for a final compliance assessment. The criteria for QA assessment were defined before the start of this trial, but they were not described in the protocol. Immediately after the initial records were available, the radiation oncology principal investigator (S.I.) sent each institution a letter reporting whether they had complied with the treatment protocol and an inquiry regarding QA documentation, when necessary (Fig. 2). Progress remarks and problems were reported at periodic meetings for investigators.

To assess RT protocol compliance, the following parameters were reviewed: dose and field border placement (adequacy of margins for GTV), doses to organs at risk, overall treatment time, and dose calculations without heterogeneity corrections. The QA assessment was given as per protocol (PP), deviation acceptable (DA), violation unacceptable (VU), and incomplete/not evaluable. "Protocol compliance" included both PP and DA.

Individual cases were reviewed both by an independent radiation oncologist (N.S.) and the radiation oncology principal investigator (S.I.) using the same criteria. For GTV coverage, VU was defined as the distance from the field edge of the blocks or multi-leaf collimators to the periphery of GTV <1 cm or >2.5 cm laterally and <2 cm or >6 cm cranio-caudally. For the dose at the reference point, a dose <54 or >66 Gy was judged as VU. If the margins for GTV were insufficient in order to avoid an overdose to the organs at risk, this was regarded as DA. However, if GTV was shielded for any reason, it was regarded as VU. If heterogeneity correction was considered for dose calculation and the dose difference exceeded 10%, it was judged as VU. Other criteria for the QA assessment are listed in Table 1.

Details of each assessment were analyzed. The incidence of VU was compared based on the numbers enrolled by institution among 106 fully evaluable cases.

Results

A total of 142 cases were accrued from April 2004 to September 2009. After excluding 36 cases, 106 (75%) were fully evaluable (Table 2). Partially evaluable cases were included for the evaluation of each item.

Among 132 patients who were evaluable for the treatment planning methods, conventional 2-D X-ray simulations were performed for 9 (7%) patients and 123 (93%) had 3-D CT simulations. Of 31 participating institutions, 22 institutions had introduced 3-D CT simulations, 3 used only 2-D X-ray simulations, and 6 used both. Two opposing ports were used for 61 (46%) patients. Three

ports, 4 ports, and 5 or more ports were used for 27 (21%), 40 (30%), and 4 (3%) patients, respectively.

Overall RT compliance (PP + DA) was 96% (102 of 106 fully evaluable). Details for the QA scores are listed in Table 3. There were 4 VU cases: 3 in GTV coverage with insufficient margins for GTV (although 1 VU case resulted from avoiding an excessive dose to the spinal cord); 1 in organs at risk due to an excessive dose to the gastric antrum. No VU case was found for the overall treatment period, dose to the spinal cord, or total dose and dose calculations.

A miscellaneous variation, other than the pre-defined criteria for the QA assessment, was found for 4 cases; although CTV was not intended to include regional lymph nodes in the protocol, elective nodal irradiation was performed for these 4 cases (3 cases to the supraclavicular region and 1 case to the paraesophageal region).

Institutions with the highest quarter of enrollment recruited more than 7 patients (mean = 11, range = 7–18), which accounted for 68 patients. In those centers that enrolled fewer than 7 patients (mean = 2, range = 1–5) and that recruited a total of 38 patients, 4 cases (11%) were judged as VU, while all of the cases from centers that enrolled 7 patients or more were compliant (Table 4).

Table 2 Numbers of evaluable cases and QA scores

	Number	%
Total	142	
Data insufficient/partially evaluable	25	
Off-protocol	8	
Ineligible	3	
Fully evaluable	106	100
PP	80	75
DA	22	21
VU	4	4
Compliance (PP + DA)	102	96

QA quality assurance, *PP* per protocol, *DA* deviation acceptable, *VU* violation unacceptable

Discussion

An overall compliance of 96% was sufficient to provide reliable results for the current study. There was a substantial number of feedbacks in QA assessment reports after initial case reviews between the radiation oncology principal investigator and investigators at participating institutions, and these were effective in better understanding of the protocol specification and in preventing unacceptable violations. In this trial, the number of unacceptable violations was too few to see the feedback effects, but such were observed in JCOG 0202 [2] in which protocol violations and deviations were seen more frequently in the earlier period of the trial. In the previous esophageal trial JCOG 9708, RT quality was not optimal [6]. JCOG 9708 was conducted to evaluate the efficacy and toxicity of chemoradiotherapy with 5-FU plus cisplatin for patients with Stage I esophageal squamous cell carcinoma. According to a retrospective RTQA review after the closure of this trial, the overall protocol compliance was 70%. After this review, the QA assessment reports were sent to participating institutions, most of which overlapped with those in JCOG 0303. As the influence of clinical trial experience over the years was recognized in RTOG studies [7], the good RTQA compliance in JCOG 0303 also appeared to be attributable to JCOG 9708 experience. Furthermore, as the importance of the pre-trial QA program has been well recognized [8–13], JCOG will also implement a dry-run as a pre-trial credentialing program.

Impact of RT quality on treatment outcome

The Trans-Tasman Radiation Oncology Group (TROG) conducted a large international phase III trial to evaluate any additional benefit of tirapazamine (TPZ), an hypoxic cytotoxin agent, to standard cisplatin-based chemoradiotherapy for locally advanced head and neck cancer [14]. Although this trial failed to demonstrate any benefits for TPZ, they reported the outcomes of a planned secondary analysis that was used to assess the impact of RT quality planning and delivery on outcomes, which might have

Table 3 Breakdown of QA scores

	Evaluable cases	PP	%	DA	%	VU	%
GTV	122	99	81	20	16	3	3
Overall treatment time	108	108	100	NA		0	0
Organs at risk							
Spinal cord	117	117	100	0	0	0	0
Gastrointestinal	125	124	99	NA		1	1
Total dose	108	106	98	2	2	0	0
Heterogeneity correction	126	120	95	6	5	0	0

QA quality assurance, *GTV* gross tumor volume, *NA* not applicable

Table 4 Numbers of VU cases based on the numbers enrolled among 106 fully evaluable cases

	Number of cases evaluable/NE	VU	%	*p* value
High-volume institutions ($n = 8$)[a]	68/20	0	0	0.015
Low-volume institutions ($n = 23$)[b]	38/16	4	11	

NE not evaluable

[a] High-volume institutions, with the highest quarter of enrollment, accrued 7 cases or more

[b] Low-volume institutions accrued less than 7 cases

provided some explanation for the negative overall trial results [15]. As a result, they found a 20% absolute difference in 2-year overall survivals between those who had protocol-compliant plans and those with plans that had a predicted major adverse impact on tumor control (70 vs. 50%, respectively). This was twice the hypothesized survival benefit of TPZ used in the trial design.

They also showed that centers that treated only a few patients were the major source of RT quality problems. While many reports have shown that failure to adhere to the treatment protocol degraded the outcomes of clinical trials [7, 16–22], for the first time they quantified the penalty associated with poor RT and demonstrated a more substantial impact of RT quality on outcomes than any additional effects for new agents. In our study, the numbers enrolled by each institution also adversely affected the number of VU cases. The overall outcomes may also have been influenced by poor quality RT, even though the absolute number of VU cases was small. As pointed out by the TROG trial, it is desirable to limit a trial's participation to those sites that can contribute a significant number of patients.

Relationships between deviation, eligibility criteria, and protocol

Although the first step in minimizing the variations in clinical trials is the use of a detailed trial protocol, it is sometimes impossible to define a uniform acceptable technique for the treatment of advanced esophageal cancers; however, a certain margin is usually included to cover individual variations in order to identify those variations that are due to clinically valid judgments.

The significance of elective nodal irradiation for locally advanced esophageal cancer, especially for those with T4 and/or unresectable metastatic lymph nodes, has not yet been clarified [3, 23, 24]. In the current JCOG 0303 trial, the protocol specified that such subclinical areas were not to be included as CTV. However, there were 4 cases that received elective nodal irradiations, all of which did not appear to have predicted impacts on tumor control or toxicity. They were still acceptable when assessed by the criterion of reasonable standards of care and, therefore, were judged as DA cases.

We found that most of the DA cases were due to insufficient margins for GTV caused by avoiding overdoses to organs at risk. Such conditions are often experienced due to the anatomy of esophageal cancer. The esophagus is located in contact with vertebrae that embrace the spinal cord. Esophageal cancer often grows to be a bulky mass lying across the anterior walls of the vertebrae, or it frequently metastasizes to the lymph nodes along the right recurrent nerve. Therefore, an off-cord boost is often difficult to create for delivering an adequate dose to the PTV while avoiding an overdose to the spinal cord. In fact, in the current trial, there was one VU case for GTV that was due to avoiding an excessive dose to the spinal cord. This may be more a matter of the eligibility criteria for this trial than of protocol compliance. As a result, during a QA assessment, it can sometimes be difficult to distinguish a VU case from a DA case. Effects of these variations on outcomes are to be assessed with the final results.

Suboptimal proportion of evaluable cases

In the current study, there was a substantial number of cases that were excluded ($n = 36$; 25% of all cases), while the overall compliance was excellent when the subjects were limited to fully evaluable cases. Among the 36 excluded cases, the data were insufficient or only partially evaluable for 25 cases, 8 cases went off protocol, and 3 cases were ineligible. Improvements of evaluability are another challenge for RTQA, not only for trial outcomes, but also for trial cost effectiveness. Although the support of cooperative group trials is costly due to the involvement of various professionals, improvement of evaluability would make up for the cost by decreasing the exclusion loss from the analysis [1].

Frequency of 3-D CT simulation and credentialing

In early clinical trials, data acquisition was non-uniform and inconsistent, and radiation dose calculations varied significantly. Improvements in the QA procedures have increased treatment uniformity of the study, which has helped to validate the study conclusions. Recently, protocols have been developed with increasing complexity. Especially for RT, current studies have introduced CT-based treatment planning, enabling precise target definitions and dose deliveries. The use of advanced treatment modalities in clinical trials requiring volumetric digital

data submission is one of the great challenges in RTQA [25].

Previously, the Radiation Therapy Oncology Group (RTOG) 9415, a randomized phase III trial that compared high-dose radiotherapy with standard doses for esophageal cancer, recommended the use of CT simulation, although it was not mandatory. Dose prescription was conventionally specified at an isocenter. As from the next esophageal trial, E0113, a randomized phase II study of two paclitaxel-based chemoradiotherapy regimens, all participating institutions had to utilize 3-D CT planning. Furthermore, RTOG 0436, a phase III trial evaluating the addition of cetuximab to paclitaxel, cisplatin, and radiation for patients with esophageal cancer, required a facility questionnaire for each institution, as well as a dry-run QA test, in order to prove that the institution was eligible to enter patients into the study.

In the current JCOG 0303 trial, a majority of the participating institutions had introduced 3-D CT simulations; however, in patients with 2-D X-ray simulation, precise 3-D volumetric dose evaluation was not available. Today, CT-based 3-D planning is standard and it will be mandatory in coming JCOG trials. In 2004, the JCOG RT group implemented a pre-trial credentialing program for a phase II trial of stereotactic body RT for early stage non-small cell lung cancer (JCOG 0403). The next trial for intensity-modulated RT for nasopharyngeal cancer will require a dry-run test for all participating centers. As we move to multimodal image-based definitions of target volumes for protocols, timely interactions between study investigators and QA centers through protocol development will become more and more important in future trials.

In conclusion, the results of the RTQA assessment for JCOG 0303 were sufficient to provide scientifically reliable results. Further improvements will be needed for institutions with low accrual rates. A dry-run and credentialing program are being implemented in JCOG trials to further improve RT quality.

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Conflict of interest No author has any conflict of interest.

References

1. Glicksman AS, Reinstein LE, McShan D et al (1981) Radiotherapy Quality Assurance Program in a cooperative group. Int J Radiat Oncol Biol Phys 7:1561–1568
2. Sanuki-Fujimoto N, Ishikura S, Hayakawa K et al (2009) Radiotherapy quality assurance review in a multi-center randomized trial of limited-disease small cell lung cancer: the Japan Clinical Oncology Group (JCOG) trial 0202. Radiat Oncol 4:16
3. Ohtsu A, Boku N, Muro K et al (1999) Definitive chemoradiotherapy for T4 and/or M1 lymph node squamous cell carcinoma of the esophagus. J Clin Oncol 17:2915–2921
4. Gomi K, Oguchi M, Hirokawa Y et al (2003) Process and preliminary outcome of a patterns-of-care study of esophageal cancer in Japan: patients treated with surgery and radiotherapy. Int J Radiat Oncol Biol Phys 56:813–822
5. Kenjo M, Uno T, Murakami Y et al (2009) Radiation therapy for esophageal cancer in Japan: results of the Patterns of Care Study 1999–2001. Int J Radiat Oncol Biol Phys 75:357–363
6. Kato H, Sato A, Fukuda H et al (2009) A phase II trial of chemoradiotherapy for stage I esophageal squamous cell carcinoma: Japan Clinical Oncology Group Study (JCOG9708). Jpn J Clin Oncol 39:638–643
7. Wallner PE, Lustig RA, Pajak TF et al (1989) Impact of initial quality control review on study outcome in lung and head/neck cancer studies—review of the Radiation Therapy Oncology Group experience. Int J Radiat Oncol Biol Phys 17:893–900
8. Poortmans PM, Davis JB, Ataman F et al (2005) The quality assurance programme of the Radiotherapy Group of the European Organisation for Research and Treatment of Cancer: past, present and future. Eur J Surg Oncol 31:667–674
9. Hurkmans CW, Borger JH, Rutgers EJ et al (2003) Quality assurance of axillary radiotherapy in the EORTC AMAROS trial 10981/22023: the dummy run. Radiother Oncol 68:233–240
10. Dixon P, O'Sullivan B (2003) Radiotherapy quality assurance: time for everyone to take it seriously. Eur J Cancer 39:423–429
11. Haworth A, Kearvell R, Greer PB et al (2009) Assuring high quality treatment delivery in clinical trials—results from the Trans-Tasman Radiation Oncology Group (TROG) study 03.04 "RADAR" set-up accuracy study. Radiother Oncol 90:299–306
12. Matzinger O, Poortmans P, Giraud JY et al (2009) Quality assurance in the 22991 EORTC ROG trial in localized prostate cancer: dummy run and individual case review. Radiother Oncol 90:285–290
13. Poortmans P, Kouloulias V, van Tienhoven G et al (2006) Quality assurance in the EORTC randomized trial 22922/10925 investigating the role of irradiation of the internal mammary and medial supraclavicular lymph node chain works. Strahlenther Onkol 182:576–582
14. Rischin D, Peters LJ, O'Sullivan B et al (2010) Tirapazamine, cisplatin, and radiation versus cisplatin and radiation for advanced squamous cell carcinoma of the head and neck (TROG 02.02, HeadSTART): a phase III trial of the Trans-Tasman Radiation Oncology Group. J Clin Oncol 28:2989–2995
15. Peters LJ, O'Sullivan B, Giralt J et al (2010) Critical impact of radiotherapy protocol compliance and quality in the treatment of advanced head and neck cancer: results from TROG 02.02. J Clin Oncol 28:2996–3001
16. White JE, Chen T, McCracken J et al (1982) The influence of radiation therapy quality control on survival, response and sites of relapse in oat cell carcinoma of the lung: preliminary report of a Southwest Oncology Group study. Cancer 50:1084–1090
17. Abrams R, Winter K, Regine W (2006) RTOG 9704—Radiotherapy Quality Assurance (QA) Review and Survival. Int J Radiat Oncol Biol Phys 66:S22
18. Fabian CJ, Mansfield CM, Dahlberg S et al (1994) Low-dose involved field radiation after chemotherapy in advanced Hodgkin disease. A Southwest Oncology Group randomized study. Ann Int Med 120:903–912
19. Perez CA, Stanley K, Grundy G et al (1982) Impact of irradiation technique and tumor extent in tumor control and survival of patients with unresectable non-oat cell carcinoma of the lung:

report by the Radiation Therapy Oncology Group. Cancer 50:1091–1099
20. Duhmke E, Franklin J, Pfreundschuh M et al (2001) Low-dose radiation is sufficient for the noninvolved extended-field treatment in favorable early-stage Hodgkin's disease: long-term results of a randomized trial of radiotherapy alone. J Clin Oncol 19:2905–2914
21. Poortmans PM, Venselaar JL, Struikmans H et al (2001) The potential impact of treatment variations on the results of radiotherapy of the internal mammary lymph node chain: a quality-assurance report on the dummy run of EORTC Phase III randomized trial 22922/10925 in Stage I–III breast cancer. Int J Radiat Oncol Biol Phys 49:1399–1408
22. Bentzen SM, Bernier J, Davis JB et al (2000) Clinical impact of dosimetry quality assurance programmes assessed by radiobiological modelling of data from the thermoluminescent dosimetry study of the European Organization for Research and Treatment of Cancer. Eur J Cancer 36:615–620
23. Ishikura S, Nihei K, Ohtsu A et al (2003) Long-term toxicity after definitive chemoradiotherapy for squamous cell carcinoma of the thoracic esophagus. J Clin Oncol 21:2697–2702
24. Hironaka S, Ohtsu A, Boku N et al (2003) Nonrandomized comparison between definitive chemoradiotherapy and radical surgery in patients with T(2–3)N(any) M(0) squamous cell carcinoma of the esophagus. Int J Radiat Oncol Biol Phys 57:425–433
25. Purdy JA (2008) Quality assurance issues in conducting multi-institutional advanced technology clinical trials. Int J Radiat Oncol Biol Phys 71:S66–S70

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Patterns of Practice in Intensity-modulated Radiation Therapy and Image-guided Radiation Therapy for Prostate Cancer in Japan

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Background: The purpose of this study was to compare the prevalence of treatment techniques including intensity-modulated radiation therapy and image-guided radiation therapy in external-beam radiation therapy for prostate cancer in Japan.
Methods: A national survey on the current status of external-beam radiation therapy for prostate cancer was performed in 2010. We sent questionnaires to 139 major radiotherapy facilities in Japan, of which 115 (82.7%) were returned.
Results: Intensity-modulated radiation therapy was conducted at 67 facilities (58.3%), while image-guided radiation therapy was conducted at 70 facilities (60.9%). Simulations and treatments were performed in the supine position at most facilities. In two-thirds of the facilities, a filling bladder was requested. Approximately 80% of the facilities inserted a tube or encouraged defecation when the rectum was dilated. Some kind of fixation method was used at 102 facilities (88.7%). Magnetic resonance imaging was routinely performed for treatment planning at 32 facilities (27.8%). The median total dose was 76 Gy with intensity-modulated radiation therapy and 70 Gy with three-dimensional radiation therapy. The doses were prescribed at the isocenter at the facilities that conducted three-dimensional radiation therapy. In contrast, the dose prescription varied at the facilities that conducted intensity-modulated radiation therapy. Of the 70 facilities that could perform image-guided radiation therapy, 33 (47.1%) conducted bone matching, 28 (40.0%) conducted prostate matching and 9 (12.9%) used metal markers. Prostate or metal marker matching tended to produce a smaller margin than bone matching.
Conclusions: The results of the survey identified current patterns in the treatment planning and delivery processes of external-beam radiation therapy for prostate cancer in Japan.

Key words: radiation therapy – urologic-radoncol – radiation oncology

INTRODUCTION

External beam radiation therapy (EBRT) has developed rapidly in recent years (1,2) and treatment equipment with which intensity-modulated radiation therapy (IMRT) and/or image-guided radiation therapy (IGRT) can be conducted are being introduced into Japan (3). IMRT and IGRT are particularly useful in EBRT for prostate cancer and are routinely used in the USA (4) and recommended in worldwide guidelines (5,6).

In Japan, IMRT and IGRT were listed as eligible for insurance reimbursement in 2008 and 2010, respectively. However, the present situation regarding the use of these techniques in EBRT for prostate cancer remains unclear (7,8). Therefore, we conducted a survey that would clarify the operational situation, treatment planning and treatment processes of IMRT and/or IGRT when used in EBRT for prostate cancer.

PATIENTS AND METHODS

In February 2010, we sent a questionnaire on EBRT for prostate cancer to 139 major facilities including university hospitals, cancer centers and designated prefectural cancer centers and hospitals. The questionnaire was also sent to the hospitals which had treatment machines with IGRT functions, including Novalis (BrainLAB, Heimstetten, Germany), Tomotherapy (Accuray Inc., Sunnyvale, USA) and MHI-TM2000 (Mitsubishi Heavy Industries, Ltd., Nagoya, Japan).

The survey was composed of categories regarding treatment planning, dose fractionation and methods of implementation of EBRT for prostate cancer. If methods differed according to the type of radiation techniques used such as three-dimensional radiation therapy (3DCRT) or IMRT, we required responses regarding the most precise radiation method presently used. Among the 139 facilities to which we sent the survey, 115 (82.7%) gave responses, which were then analyzed. The high response rate allowed an extensive and representative data analysis.

RESULTS

General Information

Figure 1 shows the distribution of the number of patients with prostate cancer treated with EBRT at facilities in 2009 over the course of 1 year. There were 30 facilities (26.1%) at which over 50 patients were treated in 1 year. Of the 115 total facilities, 67 (58.3%) conducted IMRT, 70 (60.9%) conducted IGRT and 58 (50.4%) conducted both.

Treatment Planning

Figure 2 shows the condition of the bladder at the treatment planning stage and during the treatment. In approximately

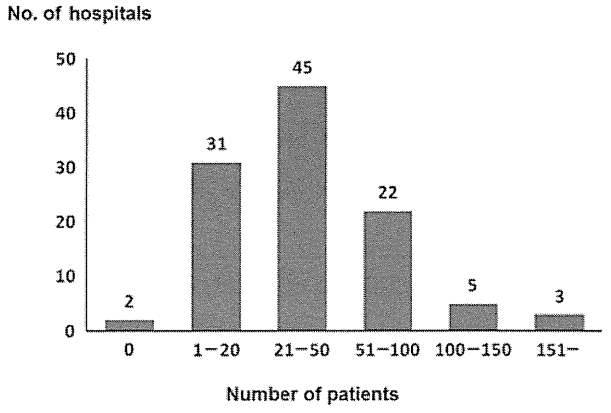

Figure 1. Total number of patients with prostate cancer treated with external-beam radiation therapy at facilities in 2009. Because some data were missing, the total numbers of patients were less than the actual number.

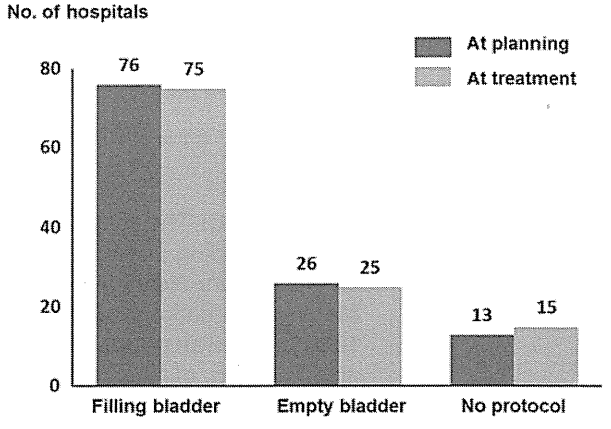

Figure 2. Condition of the bladder at the treatment planning stage and during treatment.

two-thirds of the facilities, a filling bladder was requested. The time spent pooling urine was 1 h at 56 facilities (48.7%), 1–2 h at 8 facilities (7.0%) and 30 min at 7 facilities (6.1%). Seven facilities (6.1%) also asked patients to drink water prior to treatment.

Figure 3 shows the condition of the rectum. Approximately 80% of the facilities inserted a tube or encouraged defecation when the rectum was dilated. Laxative medication was used at one-quarter of the facilities.

Simulations and treatments were performed in the supine position at 105 facilities (91.3%) and the prone position at 10 facilities (8.7%). Figure 4 shows methods of patient fixation. Some kind of fixation method was used at 102 facilities (88.7%). Although various methods were reported, a vacuum cushion, thermoplastic shell and foot support were used most frequently.

Magnetic resonance imaging (MRI) was routinely performed for treatment planning at 32 facilities (27.8%). Of these, 15 facilities (13.0%) performed computed tomography

(CT)-MRI image fusion with treatment planning software. MRI taken at the time of diagnosis was used as a reference at 66 facilities (57.4%), while 17 facilities (14.8%) did not use MRI for treatment planning.

Treatment

Radiation therapy was carried out with 2 Gy per fraction at 100 facilities (86.9%), 2.1–3 Gy at 14 facilities (12.2%) and 1.8 Gy at 1 facility (0.9%). Most facilities conducted treatment five times a week. Treatment was conducted three times a week at five facilities (4.3%) and four times a week at three facilities (2.6%).

Figure 5 shows the distributions of radiation doses delivered to the prostate at facilities using a fraction dose of 2 Gy. The median total dose was 76 Gy with IMRT and 70 Gy with 3DCRT. The doses were prescribed at the isocenter at the facilities that conducted 3DCRT. In contrast, the dose prescription varied greatly at the facilities that conducted IMRT. Of the 67 facilities that conducted IMRT, D95, which is the minimum absorbed dose that covers 95% of the planning target volume (PTV), was used as a dose prescription at 24 facilities (35.8%). A dose prescription requiring that 95% of the prescribed isodose line cover 95% of the PTV was used at 4 facilities (6.0%), the mean PTV dose was used at 13 facilities (19.4%) and other methods at 26 facilities (38.8%).

The most popular IGRT methods (54 facilities) involved 2D matching with X-ray fluoroscopy or 3D matching with a flat-panel cone-beam CT. Eight facilities used CT on rail and 4 facilities used ultrasonic devices. Of the 70 facilities that could perform IGRT, 33 (47.1%) conducted bone matching, 28 (40.0%) conducted prostate matching and 9 (12.9%) used metal markers. At the treatment of prostate cancer, 60 facilities (85.7%) always conducted IGRT, while 9 (12.9%) conducted IGRT at regular intervals.

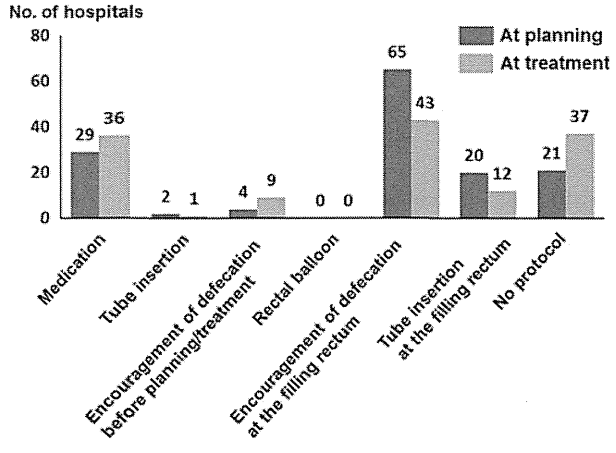

Figure 3. Condition of the rectum at the treatment planning stage and during treatment. Multiple answers allowed.

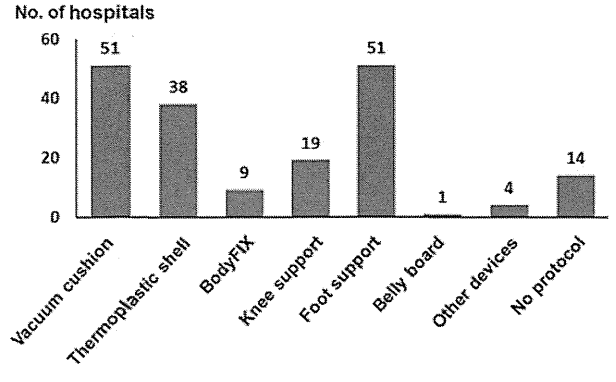

Figure 4. Fixation of the patients at the treatment planning stage and during treatment. Multiple answers allowed.

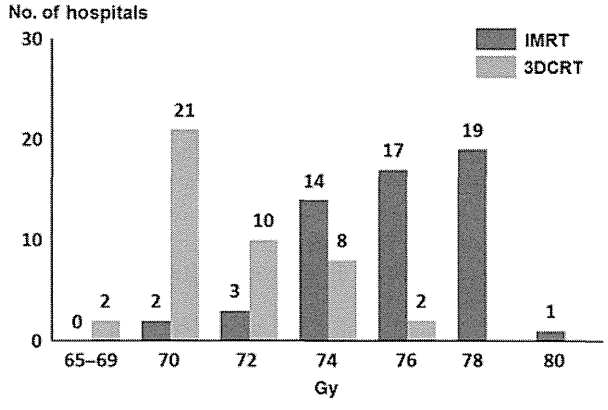

Figure 5. Total dose to the prostate.

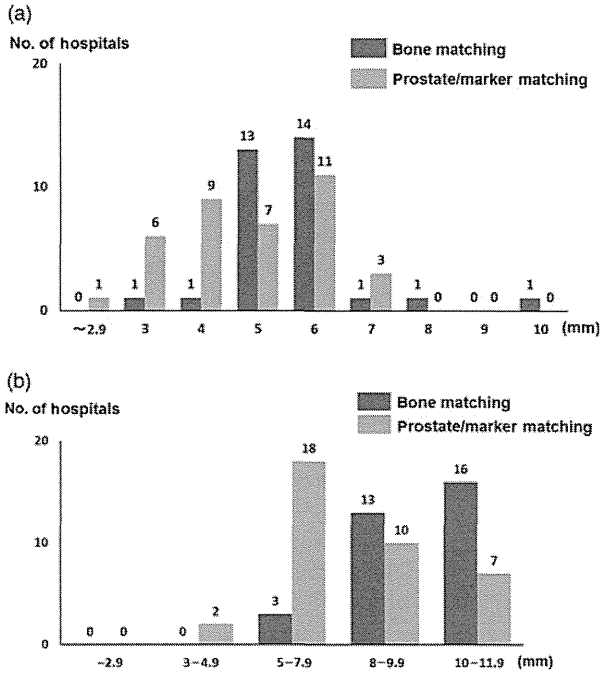

Figure 6. Margins from the prostate to planning target volume for patients with T1–2 tumors treated with IGRT: (a) rectal side and (b) other sides.

Figure 6 show the distribution of the prostate-PTV margins for patients with typical T1–2 tumors treated with IGRT. Prostate or metal marker matching tended to produce slightly smaller margins than bone matching.

DISCUSSION

This study provides a clear picture of present practices of IMRT and/or IGRT for prostate cancer in Japan.

Simulations and treatments were performed in the supine position at most facilities. However, facilities employed various fixation methods. In most facilities, some kind of fixation method was used, although immobilization devices for body malignancies are not covered by health insurance in Japan. In the patterns of care study on prostate cancer patients who were treated with EBRT from 2003 to 2005, immobilization devices were used on only 15% of patients (7). One reason for the high frequency of the usage of patient immobilization devices in this study could be the gradual popularization of fixation methods over time. An additional reason is probably the fact that some sort of fixation method tends to be used in more precise radiation treatment, because patient immobilization can be an important contributor to the reproducibility and accuracy of radiotherapy (9).

The pretreatment condition of the bladder and rectum also varied greatly among facilities. Although fixation of the prostate is frequently conducted with a rectal balloon in Western countries (10), this method has not been used at all in Japan.

In this study, we did not investigate PTV margins when IGRT was not used. Therefore, we were unable to clarify whether IGRT causes decreased margins. However, PTV margins tended to be slightly smaller with prostate or fiducial marker matching than that with bone matching. PTV margins should be determined at each facility taking into account position errors caused not only by the IGRT method, but also by the patient position, fixation method and pretreatment condition of the bladder and rectum. Enmark et al. (11) demonstrated that a margin of 4 mm in all directions was adequate to account for uncertainties including the inter- and intrafraction motions, if IGRT with fiducial markers is performed on a daily basis. Some facilities have chosen prostate-PTV margins of <4 mm. Because of uncertainties such as intrafraction motion or uncertainty of the target delineation, decreases in the PTV margin should be carefully performed even when IGRT is applied.

The radiation dose administered at most facilities was 2 Gy per fraction. The median value of the total radiation dose was 76 Gy with IMRT and 70 Gy with 3DCRT. It is well known that the radiation dose is a strong independent predictor of failure (12), and IMRT can reduce the unwanted doses to nearby organs at risk. Therefore, as IMRT becomes more widespread in Japan, more appropriate higher dosages of radiation should be utilized. However, a significant problem is the fact that the IMRT dose prescription varies. It is necessary to define and develop recommended guidelines for dose prescription and a dose reporting system for IMRT in Japan (13).

IMRT and IGRT were being conducted at approximately half of the facilities in this study. However, our survey targeted large-scale facilities. If all radiation therapy facilities in Japan were to be surveyed, this proportion would probably be smaller (3). At present, high-precision radiation therapy devices such as IMRT and IGRT are being rapidly introduced (3,14), and an increasing number of facilities will surely come to adopt IMRT and IGRT. The results of the survey in this study will provide beneficial information to those facilities as they begin treatment.

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Conflict of interest statement

None declared.

References

1. Harmenberg U, Hamdy FC, Widmark A, Lennernas B, Nilsson S. Curative radiation therapy in prostate cancer. *Acta Oncol* 2011;50(Suppl 1):98–103.
2. Ghilezan M, Yan D, Martinez A. Adaptive radiation therapy for prostate cancer. *Semin Radiat Oncol* 2010;20:130–7.
3. Teshima T, Numasaki H, Shibuya H, Nishio M, Ikeda H, Sekiguchi K, et al. Japanese structure survey of radiation oncology in 2007 based on institutional stratification of patterns of care study. *Int J Radiat Oncol Biol Phys* 2010;78:1483–93.
4. Kupelian P, Meyer JL. Image-guided, adaptive radiotherapy of prostate cancer: toward new standards of radiotherapy practice. *Front Radiat Ther Oncol* 2011;43:344–68.
5. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: prostate cancer V1 2011. http://www.nccn.org/.
6. Horwich A, Parker C, Kataja V. Prostate cancer: ESMO clinical recommendations for diagnosis, treatment and follow-up. *Ann Oncol* 2009;20(Suppl 4):76–8.
7. Nakamura K, Ogawa K, Sasaki T, Onishi H, Koizumi M, Araya M, et al. Patterns of radiation treatment planning for localized prostate cancer in Japan: 2003–05 patterns of care study report. *Jpn J Clin Oncol* 2009;39:820–4.
8. Ogawa K, Nakamura K, Sasaki T, Onishi H, Koizumi M, Araya M, et al. Radical external beam radiotherapy for clinically localized prostate cancer in japan: changing trends in the patterns of care process survey. *Int J Radiat Oncol Biol Phys* 2011, in press.
9. Fiorino C, Reni M, Bolognesi A, Bonini A, Cattaneo GM, Calandrino R. Set-up error in supine-positioned patients immobilized

with two different modalities during conformal radiotherapy of prostate cancer. *Radiother Oncol* 1998;49:133–41.
10. Smeenk RJ, Teh BS, Butler EB, van Lin EN, Kaanders JH. Is there a role for endorectal balloons in prostate radiotherapy? A systematic review. *Radiother Oncol* 2010;95:277–82.
11. Enmark M, Korreman S, Nystrom H. IGRT of prostate cancer; is the margin reduction gained from daily IG time-dependent? *Acta Oncol* 2006;45:907–14.
12. Viani GA, Stefano EJ, Afonso SL. Higher-than-conventional radiation doses in localized prostate cancer treatment: a meta-analysis of randomized, controlled trials. *Int J Radiat Oncol Biol Phys* 2009;74:1405–18.
13. ICRU. International Commission on Radiation Units and Measurements. Prescribing, Recording, and Reporting Photon-Beam Intensity-Modulated Radiation Therapy (IMRT). Report 83. Oxford: Oxford University Press 2010.
14. Teshima T, Numasaki H, Shibuya H, Nishio M, Ikeda H, Ito H, et al. Japanese structure survey of radiation oncology in 2005 based on institutional stratification of patterns of care study. *Int J Radiat Oncol Biol Phys* 2008;72:144–52.

国内のラルス稼働状況と子宮頸癌の治療

●静岡県立静岡がんセンター　放射線治療科　西村哲夫

1. 国内のラルスの設置と稼働の状況

国内のラルス設置状況に関する最近の日本アイソトープ協会の調べによると、2007年より2年おきに見た設置施設数は196→182→176、稼働施設数は182→169→160と減少傾向にあった（図1）。この中で旧型コバルトラルスに限ってみると設置施設数は49→31→14、稼働施設数は40→24→4と激減していた（図2）。このように全国のラルス稼働施設の減少の主な理由は旧型ラルスの廃棄に際して、新たな装置への更新が行われなかったものである。しかし2011年非稼働の16施設のうち旧型ラルスは10施設であったが、残りの6施設はイリジウムラルス使用施設であり、装置を備えていても十分な患者数が確保できずに使用しない施設もあることが推測された。

厚労省石倉班では2009年以来、子宮頸癌のラルス治療の均てん化の検討を行ってきた。2011年の都道府県別ごとの稼働施設数の中央値は2（1～19）であり、1施設のみの県は8であった。また全国のがん診療連携拠点病院388のうちラルスが稼働しているものは146（37.6％）であり、拠点病院が稼働施設数に占める割合は146/162（90.1％）であった（検討の段階では上記全稼働ラルス施設数は162とみなした）。すなわちラルス治療はがん診療連携拠点病院がその大きな役割を担っていることが分かった。

以上のデータをまとめると、全国のラルスを持つ施設は、大都市を除くとがん診療連携拠点病院に集約されつつあり、二次医療圏を超えた患者の移動が行われていると考えられる。また場合によっては都道府県の枠（三次医療圏）を超えた患者の移動もあると思われる。なおこれらのデータは2010年の診療報酬の改定の影響は反映していないものと考えられるが、最近新たにラルス治療を始めた2施設もあり今後の動向が注目される。

2. 子宮頸癌ラルス治療潜在適応患者数の推定

国内では子宮頸癌のほぼすべての腔内照射はラルスによって行われている。ラルス治療潜在適応の患者数を推定することにより、ラルス施設数の適正配置について検討した。

日本産科婦人科学会子宮頸癌患者年報に登録され、放射線治療主体で治療が行われた症例と手術主体で治療が行われた症例の半数を合わせてラルス治療の潜在的適応とみなし，子宮頸癌全体の中で占める割合を求めた。一方全国がん罹患モニタリング集計にある全国推定患者数を求めて、潜在適応患者数を算出した。

2007年の子宮頸癌患者年報には5024人が登録された。放射線治療主体で治療が行われた1397人と

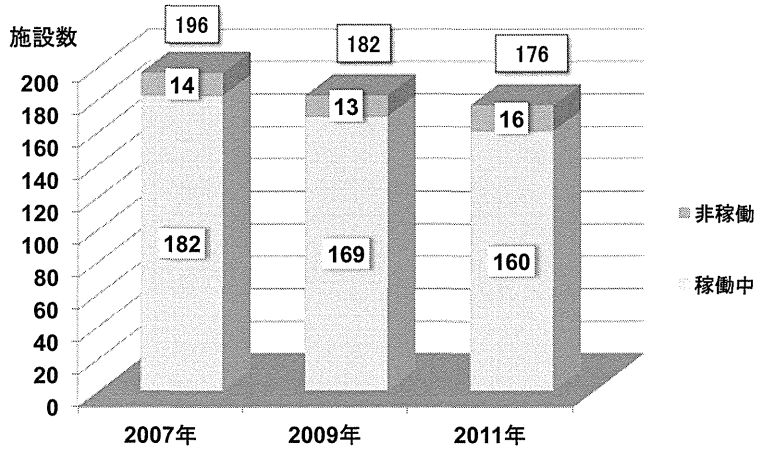

図1. RALSの設置と稼働状況の推移

手術主体で治療が行われた2273人の半数1186人の合わせた2583人(51.4%)をラルス治療の潜在的適応とみなした。一方2005年罹患数推定値は8474人であり、ラルス治療潜在適応患者数は8474×0.516＝4357人と算出された。これを人口1億2702万人で割ると人口100万人当たり3.4人がラルス治療の潜在患者になると推定された。この推定値を稼働している各都道府県の1施設当りの患者数に換算すると中央値25(11-81)であったが20人未満が11県、一方40人以上が10県と大きな差があった。これらの現状は患者数の過剰な負荷が掛かる施設がある一方で、少ない患者数のままで非効率的な運用を行わざるを得ない施設のあることが分かった。

3.子宮頸癌の腔内照射患者の居住医療圏の調査

2010年に腔内照射を行った子宮頸癌患者について特定の県(静岡、沖縄)の施設に協力を得て、居住する二次医療圏別の患者数を調査した。二次医療圏別の子宮頸癌の腔内照射の患者数は沖縄県では1施設で51例の治療が行われ、人口100万人あたりの患者数は平均3.7人で患者が居住する5つの二次医療圏別には1.9～5.6(中央値3.8)だった。一方主として3施設で治療が行われた静岡県では85人の治療が行われ、県外の2例をのぞいた人口100万人あたり患者数平均は2.5人で8つの二次医療圏別では0.8～5.4(中央値2.5)だった。前記の潜在患者数3.4人と比べる特に沖縄県では離島などの問題があるにも関わらず、適切に治療が行われていることが分かる。このような調査は均てん化を考える上で有用と思われる。

4.患者の選択による子宮頸癌の治療

静岡がんセンターは2002年4月開設され今年で丁度10年が経過した。子宮頸癌については開院当初よりⅠb期とⅡ期の切除可能な扁平上皮癌については、手術と放射線治療の両方を提示して患者が選択できるようにした。

2002年9月から2008年12月の期間の152名の患者については、手術を選択したものが117名(76%)、放治を選択したものが35例(24%)であった。その全生存割合は手術選択89.2%、放治選択91.3%(p=0.8020)、無再発生存割合は手術選択79.2%、放治選択85.1%(p= 0.4341)で両群に有意差はなかった。

2011年改定となった子宮頸癌の診療ガイドラインでは、手術と放射線治療は同等の治療としてみなされるようになった。この点に関しては私どもの経験でも全く問題がないと考えている。しかし診療ガイドラインに手術と同等と記載されていても、放射線治療が適切に実施される体制が整っていることが前提である。設備がないから、信頼できる放射線腫瘍医がいないからという理由で、患者に放射線治療の説明が行われないことは避けるべきである。このために各医療機関の内部の診療体制の確立とコンセンサス作りが必要である。また場合によっては医療機関を超えた地域の事情に応じた診療体制を整えることが大切である。

5.まとめ

ラルス治療は子宮頸癌の治療に必須である。都道府県や医療圏別にみると、尚整備の不十分な地域がある。今後はがん診療連携拠点病院を中心とした各地域のネットワーク作りと人材育成が課題と考えられる。

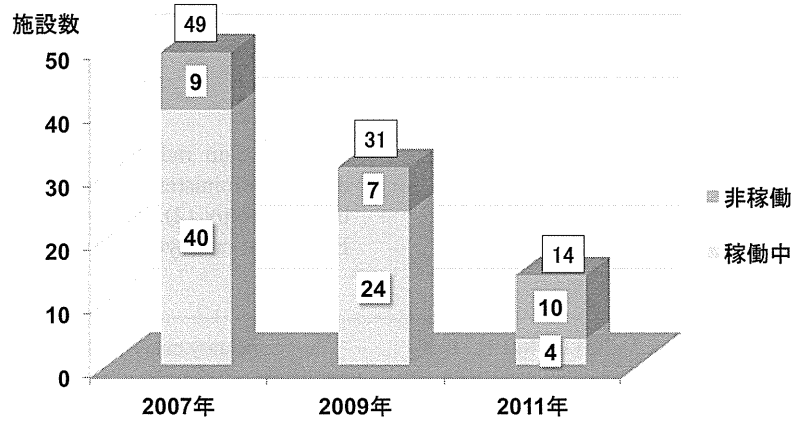

図2. 旧型国産RALSの設置と稼働状況の推移

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CLINICAL INVESTIGATION **Gynecologic Cancer**

INTERNATIONAL BRACHYTHERAPY PRACTICE PATTERNS: A SURVEY OF THE GYNECOLOGIC CANCER INTERGROUP (GCIG)

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Purpose: To determine current practice patterns with regard to gynecologic high-dose-rate (HDR) brachytherapy among international members of the Gynecologic Cancer Intergroup (GCIG) in Japan/Korea (Asia), Australia/New Zealand (ANZ), Europe (E), and North America (NAm).

Methods and Materials: A 32-item survey was developed requesting information on brachytherapy practice patterns and standard management for Stage IB–IVA cervical cancer. The chair of each GCIG member cooperative group selected radiation oncology members to receive the survey.

Results: A total of 72 responses were analyzed; 61 respondents (85%) used HDR. The three most common HDR brachytherapy fractionation regimens for Stage IB–IIA patients were 6 Gy for five fractions (18%), 6 Gy for four fractions (15%), and 7 Gy for three fractions (11%); for Stage IIB–IVA patients they were 6 Gy for five fractions (19%), 7 Gy for four fractions (8%), and 7 Gy for three fractions (8%). Overall, the mean combined external-beam and brachytherapy equivalent dose (EQD2) was 81.1 (standard deviation [SD] 10.16). The mean EQD2 recommended for Stage IB–IIA patients was 78.9 Gy (SD 10.7) and for Stage IIB–IVA was 83.3 Gy (SD 11.2) ($p = 0.02$). By region, the mean combined EQD2 was as follows: Asia, 71.2 Gy (SD 12.65); ANZ, 81.18 (SD 4.96); E, 83.24 (SD 10.75); and NAm, 81.66 (SD, 6.05; $p = 0.02$ for Asia vs. other regions).The ratio of brachytherapy to total prescribed dose was significantly higher for Japan ($p = 0.0002$).

Conclusion: Although fractionation patterns may vary, the overall mean doses administered for cervical cancer are similar in Australia/New Zealand, Europe, and North America, with practitioners in Japan administering a significantly lower external-beam dose but higher brachytherapy dose to the cervix. Given common goals, standardization should be possible in future clinical trials. © **2012 Elsevier Inc.**

Brachytherapy, Cervical cancer, Radiation dose.

INTRODUCTION

Globally, cervical cancer represents the most common gynecologic malignancy (1). Patients with locally advanced cervical cancer (Stage IB2–IVA) require treatment with external-beam radiation (EBRT) with concurrent chemotherapy administered as a radiation sensitizer followed by brachytherapy (2). The recommended cumulative dose of EBRT and brachytherapy to cure locally advanced disease

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ranges from 80 to 90 Gy recorded at point A using low-dose-rate (LDR) brachytherapy (2).

Over the past 20 years, high-dose-rate (HDR) brachytherapy has increased and replaced LDR in many practices (3). The Patterns of Care for cervical cancer radiation practice in the United States reported a 16% HDR utilization rate in 1999 (4), whereas 85% of surveyed physician members of the American Brachytherapy Society (ABS) reported having HDR at their institution in 2007 (3). Overall, randomized studies indicate that outcomes with HDR resemble those with LDR, though many issues exist regarding the methodology of randomization and the follow-up duration across the studies (5). However, caution regarding large fractions given to normal tissues and adequate tumor coverage have increased awareness and recommendations for the use of computed tomography (CT) or magnetic resonance imaging (MRI) to determine doses to the tumor and the organs at risk (6).

The biologic equivalent dose formulas allow calculation of the brachytherapy dose (7, 8). However, these formulas require an assumption that the α/β ratio for tumor is 10, which may be an underestimation for squamous cell carcinoma. Furthermore, concerns regarding the validity of the linear quadratic model exist for very low or very high doses per fraction (9). Publication of standard fractionation regimens for HDR cervical cancer brachytherapy with point A–based standard loading (10, 11) led to widespread adoption in the United States of the regimen 6 Gy for five fractions over approximately 2.5 weeks. Preliminary results demonstrate a 2-year Grades 3 and 4 bowel toxicity rate of 11% with this HDR regimen (12). By contrast, with 2-year follow-up, only three (5%) Grade 3 or greater gastrointestinal complications occurred in a group of 65 patients treated with 6 Gy for five fractions in one report (13). It remains unknown whether 6 Gy for five fractions has a higher toxicity rate than 5.5 Gy per fraction or than LDR brachytherapy.

The Gynecologic Cancer Intergroup (GCIG) strives to forge collaborations between cooperative groups to move the development of oncologic clinical trials forward in a highly constructive and cost-effective manner. Randomized trials with international participation will accrue cervical cancer patients rapidly and result in advances on a global stage. To determine brachytherapy practice patterns and the HDR brachytherapy regimens most frequently prescribed by GCIG members, a survey of GCIG members was conducted. The goal is to clarify which regimen would be acceptable for future international collaborative clinical trials.

METHODS AND MATERIALS

The GCIG represents an international association of member cooperative groups conducting large clinical trials for gynecologic malignancies. Since its inception in 1997, 18 cooperative groups have joined, including the AGO-Austria (Austria), AGO-OVAR (Germany), ACRIN (USA), ANZOG (Australia, New Zealand), DGOG (the Netherlands), EORTC (Europe), GEICO (Spain), GINECO (France), GOG (USA), JGOG (Japan), MANGO (Italy), MITO (Italy), MRC/NCRI (Great Britain), NCIC (Canada), NSGO (Scandinavia), RTOG (USA), SGCTC (Scotland), and SWOG (USA).

A 32-question survey was designed to address questions regarding standard practice patterns for locally advanced cervical cancer management, such as routine doses of external beam and the use of concurrent chemotherapy, and also to determine baseline brachytherapy practice patterns, including both HDR and LDR utilization, at the time of the survey (Appendix EI available online at at www.redjournal.org). An e-mail providing background information, the purpose of the survey, and a link to a web page for easy retrieval of the survey was sent electronically to the chair of each GCIG member cooperative group in December 2008. Each cooperative group chair could choose to forward the email to six radiation oncology members from separate representative centers that had a large volume of cervical cancer cases. Respondents could complete only one survey on a computer, and entered their names and e-mail addresses to avoid duplicate submissions. The survey website closed in May 2009. Appendix E1 (available online at at www.redjournal.org) lists the specific items queried.

The biologically equivalent doses were calculated in 2-Gy equivalents using the EQD2 equation. For respondents that used a midline block, the total dose to the nodes and the dose to the cervix were summed separately. The EBRT and brachytherapy EQD2 doses were calculated at point A for patients with Stage IB–IIA and those with Stage IIB-IVA disease; then the average was taken for a cumulative sum for all stages. Analysis of reported HDR fractionation regimens was divided by country and by region, including Asia (Japan/Korea); Australia/New Zealand; Europe (Austria, Denmark, England, Finland, Germany, Italy, Ireland, the Netherlands, Scotland, Spain); and North America (USA, Canada). Quartiles of dose were evaluated to determine whether any particular region or country grouped into the highest or lowest dose ranges. The *t*-test statistic was performed to determine whether any significant differences in dose existed by region.

RESULTS

Respondent characteristics

A total of 16 cooperative groups gave member responses to this survey. Of 74 respondents, two were excluded: one non-GCIG member and one GCIG member who did not answer questions regarding brachytherapy, yielding a final study population of 72 respondents. Cooperation was received from the AGO-Austria (n = 3), ABO-Germany (n = 2), ACRIN (n = 1), ANZGOG (n = 6), DGOG (n = 6), EORTC (n = 5), GEICO (n = 1), GOG (n = 5), JGOG (n = 6), KGOG (n = 4), MANGO (n = 3), MITO (n = 2), MRC/NCRI (n = 9), NCIC (n = 10), NSGO (n = 3), and the RTOG (n = 6). Regions of the world represented were Japan/Korea (n = 10), Australia/New Zealand (n = 6), Europe (n = 34), and North America (n = 22).

Of the 72 respondents, 63 (88%) practice radiation oncology; 8 (11%), both medical and radiation oncology; and one (1%), gynecologic oncology. Regarding the average number of cervical cancer patients treated per year, 7 (10%) treat 1 to 9, 18 (25%) treat 10 to 19, 11 (15%) treat 20 to 29, 9 (13%) treat 30 to 39, 6 (8%) treat 40 to 49, 10 (14%) treat 50 to 59, 6 (8%) treat 60 to 69, 4 (6%) treat 70 to 79, and 1 (1%) treats more than 140.

External-beam radiation to the cervix

Physicians were queried regarding the standard EBRT dose prescribed for treating cervical cancer. For those who reported administering a parametrial boost dose, the parametrial doses were excluded from the EBRT cumulative cervical dose calculation, since the goal of a midline block is to avoid significant radiation to the cervix during these fractions. After averaging all respondents' reported dose to the cervix, the mean EBRT dose was 44.2 Gy (range, 19.8–50.4) for Stage IB–IIA patients and 47.2 Gy (range, 30.6–54) for Stage IIB–IVA patients. The average cervical dose for the Japanese respondents (not including the parametrial boost dose) was 23.3 Gy (range, 19.8–30) for Stage IB-IIA patients and 36.7 Gy (range, 30.9–40) for Stage IIB–IVA patients. All Japanese respondents commented that after insertion of a midline block, the total dose to the parametria and pelvic nodes equals 50 Gy (30 Gy to the cervix plus 20 Gy after insertion of the midline block). By contrast, all other countries reported a mean EBRT dose of 46.11 Gy (range, 40–50.4) for Stage IB–IIA patients and 48.2 Gy (range, 40–54) for Stage IIB–IVA patients. The most commonly added parametrial boost dose is 5.4 Gy after 45 Gy to the entire pelvis. For Stage IB–IIA patients, the most common EBRT doses are 45 Gy (n = 41, 57%) and 50.4 Gy (n = 15, 21%). For Stage IIB–IVA, the most common EBRT doses are 45 Gy (n = 26, 36%), 50.4 Gy (n = 27, 38%), and 54 Gy (n = 5, 7%).

All respondents prescribe concurrent chemotherapy with EBRT. In addition, 4% (three respondents) consider giving neoadjuvant chemotherapy before concurrent chemoradiation. The chemotherapy agents marked on the survey included cisplatin (97%), 5-flourouracil (4%), carboplatin (5%), paclitaxel (5%), and nedaplatin (2%).

Brachytherapy

With regard to dose rate, 61 respondents (85%) have HDR available, 13 (18%) had LDR, and 8 (11%) have pulse-dose-rate. Chemotherapy is given on the same day as an HDR fraction by four respondents (6%). An HDR fraction is given on the same day as an EBRT fraction by three respondents (4%). A total of 38% of respondents might hospitalize patients overnight for HDR treatment. For those using LDR, an equal number of respondents use on average one or two fractions, with a per-fraction dose ranging from 10 to 40 Gy. Three respondents administer chemotherapy during an inpatient LDR hospitalization.

The tandem and ovoid is the most frequently used applicator for HDR, pulse-dose-rate, and LDR, with 54% using this applicator for more than 75% of their cases annually. The tandem and ring applicator is used in 24% of cases, tandem and cylinder in 4%, tandem and interstitial in 3%, and interstitial only in 1%. For applicator insertion, 97% of respondents' patients receive anesthesia, consisting of general (46%), spinal (27%), intravenous conscious sedation (28%), and/or oral pain medication (14%). Ultrasound is used for assistance with applicator insertion by 62% of respondents; 24% use ultrasound less than 10% of the time, 12% use it for 10–25% of cases, 7% use it for 26–50% of cases, 1% use it for 51–75% of cases, and 18% use it for more than 75% of their cases.

With regard to imaging the brachytherapy applicator after insertion, 17 centers (24%) reported that they use plain x-ray films, either alone or in combination with MRI and/or CT. By contrast, CT is the most commonly used imaging modality (n = 41, 57%); 27 respondents use CT for every fraction, and 14 use CT for the first fraction only. MRI is used by 18 centers (25%), of which eight use MRI for every fraction and 10 for the first fraction only; of these 10, eight acquire a CT scan for every fraction. In terms of prescribing to the cervix, 56 (78%) prescribe to point A, 8 (11%) follow the GEC-ESTRO guidelines (14, 15) alone, 15 (21%) follow the GEC-ESTRO and report dose to point A, 4 (6%) follow the ABS guidelines alone, and 8 (11%) use both the ABS and point A.

The major HDR fractionation patterns are depicted in Fig. 1 and listed in the table. For Stage IB–IIA patients, the most common HDR fractionation pattern is 6 Gy for five fractions (n = 11, 15%), as it is for Stage IIB–IVA patients (n = 14, 19%). A total of 28 fractionation regimens are reported, of which 18 are used by only one institution. The most common fractionation regimen, 6 Gy for five fractions, is prescribed by centers in the United States, Canada, Australia, New Zealand, the United Kingdom, Spain, Italy, and Germany. The second most common regimen, 7 Gy for four fractions, is prescribed by centers in the United States, Australia, Austria, and the Netherlands. For HDR dose reporting, of the 68 respondents to this question, 32 (47%) calculate equivalent dose using the 2-Gy (EQD2) formula, whereas 31 (46%) use only the biologic equivalent dose formula, and five (7%) multiply the raw cumulative dose by 1.33.

The recommended mean combined EBRT plus brachytherapy EQD2 was 78.9 Gy (standard deviation [SD] 10.7) for Stage IB–IIA patients and 83.3 Gy (SD 11.2) for Stage IIB–IVA patients for all countries (p = 0.02 Stage IB–IIA vs. IIB–IVA). For all stages and all countries, the mean EBRT plus brachytherapy dose was 80.9 (SD 10.14). By region, the mean combined EQD2 for Australia/New Zealand was 81.18 (SD 4.96); for Europe, 83.35 (SD 10.75); for North America, 81.66 (SD 6.05); and for Asia, 71.2 Gy (SD 12.65; p = 0.02 for Asia vs. other regions). The mean EBRT plus brachytherapy dose for Japan was 62.73 (SD 6.7), and for Korea it was 83.9 (SD 6.86). Therefore, the only significant difference was between Japan and the other countries in the survey. Overall, 17 centers (7 Europe, 3 North America, 6 Japan, and 1 New Zealand) had EQD2 cumulative values ranging from 56.8 to 75 Gy; 6 centers (all in Europe) reported EQD2 values over 95 Gy, ranging from 97.6 to 115.4 Gy. The highest reported dose was from a center that uses a fractionation regimen of 7 Gy for seven fractions after full-dose radiation to the pelvis. Figure 2 depicts the EQD2 by region.

The average ratio of brachytherapy dose to total sum (EBRT plus brachytherapy) dose was 0.45 (SD 0.08) for Stage IB–IIA and 0.44 (SD 0.08) for Stage IIB–IVA (p = NS). However, for Japanese respondents, the all-stages ratio

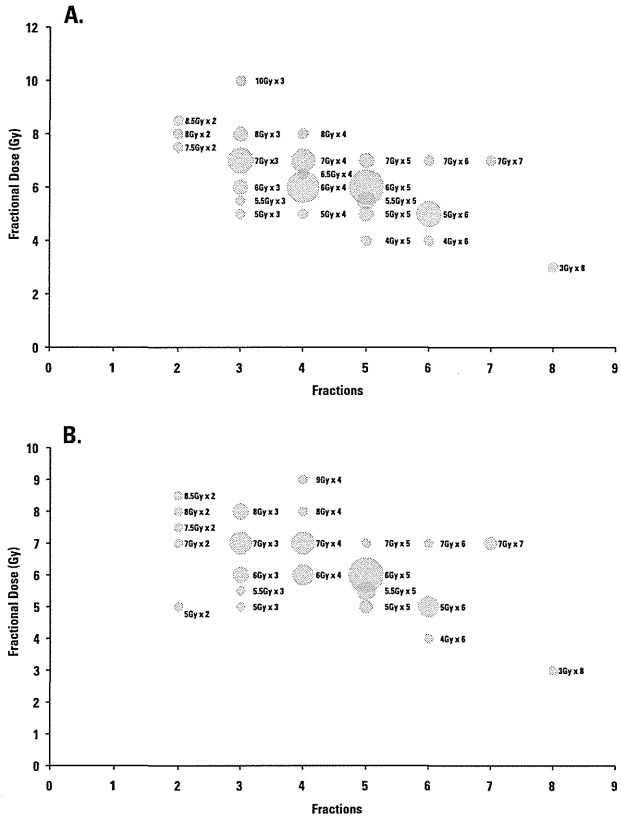

Fig. 1. Cervical cancer high-dose-rate brachytherapy fractionation patterns by dose in Gray (Gy) and number of brachytherapy fractions prescribed. (A) Respondents' answers regarding the fractionation pattern prescribed for Stages IB–IIA cervical cancer. (B) Fractionation pattern recommended for Stages IIB–IVA cervical cancer. The size of the circle is proportional to the number of respondents, with the largest number reporting 6 Gy for five fractions.

was 0.51 (SD 0.03), which was significantly different from the average ratio for all other countries (p = 0.0002). When stratified by stage, this difference in brachytherapy ratio was seen only for the Stage IB–IIA subgroup. For Japanese respondents, the ratio of brachytherapy to EB plus brachytherapy was 0.58 (SD 0.05) for Stage IB–IIA and 0.45 (SD 0.06) for Stage IIB–IVA (p = 0.002). In other words, to accommodate their reduced EBRT dose, the Japanese use a higher brachytherapy dose for patients with Stage I–IIA tumors than that typically used elsewhere.

Complications

When queried about the number of patients treated for cervical cancer who were hospitalized annually for a complication, most respondents indicated 0 (n = 12, 17%), 1 (n = 37, 60%), or 2 (n = 9, 13%).

DISCUSSION

The primary goal of this survey was to gauge variation in HDR fractionation for cervical cancer and to determine brachytherapy practice patterns internationally, in order to assist with the development of the brachytherapy portion of international randomized clinical trials. Inasmuch as cervical cancer remains a leading cause of mortality in developing countries, international collaborative randomized trials that can advance treatment approaches on a global level are needed. In particular, before undertaking this study, we questioned whether the heterogeneity of brachytherapy practice might hinder standardization. As part of this survey, other items of interest were queried, including the utilization of three-dimensional (3D) imaging during brachytherapy. Other questions were designed to provide a 3-year update to selected general management information queried on the 2007 survey (16).

With regard to the general management of cervical cancer, this survey showed that the use of concurrent chemoradiation is similar to that reported in the 2007 survey, as are EBRT doses. In terms of brachytherapy, a greater proportion of respondents in this survey reported the use of HDR than in a United States–based survey from 1999 (4). However, the use of HDR in the United States also seem to be increasing, with 85% of ABS members having HDR brachytherapy available in their practices in 2007, indicating a growing acceptance of HDR brachytherapy in the United States that matches international implementation (3). The transition from LDR to HDR has been based on an increased acceptance of the feasibility, safety, and efficacy of HDR when carefully administered, with a concomitant increase in the use of 3D imaging. Three-dimensional imaging allows dose optimization away from the normal tissues in an attempt to spare them the large fractional dose used in HDR brachytherapy.

Overall, a significant proportion of GCIG members have access to 3D imaging for gynecologic brachytherapy. The most frequently used method for brachytherapy imaging is CT. In a recent ABS survey, 70% of respondents used CT after brachytherapy applicator insertion, and 57% used CT imaging in this survey (3). Before the 1990s, plain x-ray film simulation was the standard of care. After the integration of CT into radiation oncology departments, 3D imaging use increased and now represents the standard for external beam. The integration of 3D imaging into brachytherapy has also expanded, albeit later than for EBRT. This study found a significant proportion using the best available 3D imaging modality available at their institution, either CT or MRI, for cervical cancer brachytherapy planning.

In this survey, HDR brachytherapy dose fractionation recommendations varied considerably. The most common fractionation internationally was 6 Gy for five fractions, although this regimen is used by fewer than 20% of reporting institutions. Despite the high degree of individuality in brachytherapy prescribing, the biologic equivalence was remarkably similar for all countries and regions except Japan. All six Japanese respondents follow a regimen of treating to 20 to 30 Gy for early stage disease, then place a midline block, which significantly reduce the cumulative EQD2 cervical dose compared to that used in other countries. Nevertheless, the EQD2 dose to the cervix was equivalent, on average 80 Gy for all regions of the world surveyed. The Japanese cervix dose reduction to approximately 70 Gy, instead of the