Table 4. Structure and personnel by Patterns of Care Study institutional stratification

	Structure and personnel					
	A1 (n = 71)	A2 (n = 71)	B1 (n = 288)	B2 (n = 291)	Total (n = 721)	Comparison with data of 2005* (%)
Institutions/total institutions (%)	9.8	9.8	39.9	40.4	100	—
Institutions with RT bed (n)	59 (83.1)	35 (49.3)	120 (41.2)	67 (23.3)	281 (39.0)	−2.1 (−1.3†)
Average RT beds/ institution (n)	12.9	3.2	2.8	1.0	3.1	−13.9
No. of ROs (full time + part time)	350 + 47	142 + 35	336 + 188	179 + 264	1007 + 534	6.1
JASTRO*-certified ROs* (full time)	198	64	169	46	477	12.0
Average JASTRO-certified ROs/institution	2.8	0.9	0.6	0.2	0.7	16.7
Total (full time and part time) RO FTE*	301.9	100.2	287.8	136.4	826.3	6.7
Average FTE ROs/ institution	4.3	1.4	1.0	0.5	1.1	0.9
Patient load/FTE RO	200.1	218.2	327.3	209.9	248.2	0.6
No. of RT technologists (full time + part time)	471 + 24	267 + 7	1046 + 31	833 + 3	2617 + 65	—
Total (full time and part time) RT* technologists FTE	375.8	178.7	648.9	430.7	1634.1	—
Average FTE RT technologists/institution	5.3	2.5	2.3	1.5	2.3	—
Patient load/FTE RT technologist	160.7	122.4	145.2	66.5	125.5	—
No. of nurses (full time + part time)	162 + 16	129 + 11	454 + 72	319 + 38	1064 + 137	68.9
Total (full time and part time) nurses FTE	118.5	57.7	220.9	97.3	494.4	—
No. of medical physicists (full time + part time)	80 + 2	37 + 2	104 + 6	47 + 1	268 + 11	129.1
Total (full time and part time) medical physicists FTE	26.2	6.3	27.4	8.5	68.4	—
No. of RT QA staff (full time + part time)	132 + 1	70 + 2	222 + 5	104 + 0	528 + 8	105.6
Total (full time and part time) RT QA staff FTE	31.5	12.1	46.4	16.6	106.6	—

Abbreviations: A1 = university hospitals/cancer centers treating 440 patients or more per year; A2 = university hospitals/cancer centers treating 439 patients or fewer per year; B1 = other national/public hospitals treating 140 patients or more per year; B2 = other national hospital/public hospitals treating 139 patients or fewer per year; RT = radiotherapy; RO = radiation oncologist; JASTRO = Japanese Society of Therapeutic Radiology and Oncology; FTE = full-time equivalent (40 hours/week only for RT practice); QA = quality assurance.

Data in parentheses are percentages. "Full time or part time" means only the style of employment at each institution. However, FTE data were surveyed depending on clinical working hours for RT of each person. This is a measure to represent actual personnel at each institution.

* Rate of increase compared with data of 2005. The calculating formula was as follows: $\frac{data\ of\ 2007\ (n) - data\ of\ 2005\ (n)}{data\ of\ 2005\ (n)} \times 100\ (\%)$.

† Comparison with data of 2005. The calculating formula was as follows: Data of 2007 (%) − Data of 2005 (%).

United States. However, the numbers of patients in Japan increased significantly during the next 17 years by a factor of 2.8 compared with the number in 1990 (3). However, the utilization rate of radiation for new cancer patients remained at 26.1%, less than half that recorded in the United States and European countries, although the rate increased slightly, by 0.8% per year between 2005 (5) and 2007. For the implementation of the anticancer law, comparative data of the structure of radiation oncology in Japan and in the United States, as well as relevant PCS data, proved to be very helpful.

Compared with 1990, the number of linac systems increased significantly by a factor of 2.45 and grew by 5.5% over 2005 (5) whereas the percentage of systems using telecobalt decreased to only 15. Furthermore, the various functions of linac, such as dual energy, 3D CRT (multileaf collimator width <1 cm), and IMRT, improved significantly. The number of high dose rate (HDR) RALSs in use has increased by 1.4 times, and ^{60}Co RALSs have been largely replaced by ^{192}Ir RALSs. In 2007 CT simulators were installed in 65.6% of institutions throughout the country for

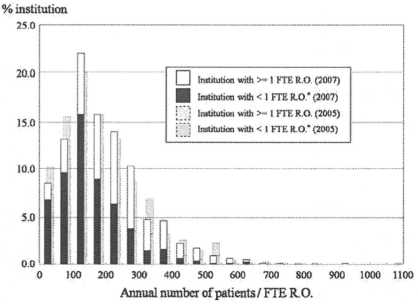

Fig. 1. Percentage of institutions by patient load per full-time equivalent (FTE) staff of radiation oncologists (RO) in Japan. White bars or gray bars represent institutions with 1 or more FTE staff, and blue bars or aqua bars represent institutions with fewer than 1 FTE RO*. Spacing of the bars represents intervals of 50 patients per FTE RO. Asterisk, The number of FTEs for institutions with FTE fewer than 1 was calculated as FTE equal to 1 to avoid overestimating patient load per FTE RO.

a 10.3% increase over 2005 (5) and exceeded the percentage of X-ray simulators (60.9%). Radiotherapy planning systems were used in 95.3% of institutions, for an increase in the number of radiotherapy planning systems of 5.54 times compared with 1990 (3). Maturity of the functions of linac and possession rates of CT simulators and systems using ^{192} Ir RALS also improved further compared with 2005 (5) but still closely correlated with the PCS institutional stratification, which could therefore aid in the accurate discrimination of structural maturity and immaturity and the identification of structural targets for improvement.

The staffing patterns in Japan also improved in terms of numbers. However, institutions with fewer than 1 FTE RO

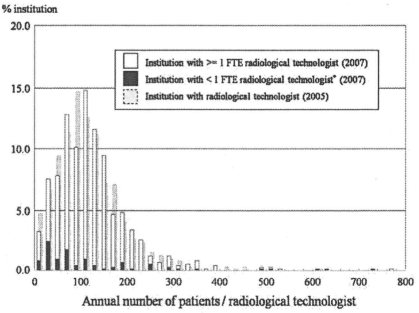

Fig. 2. Percentage of institutions by patient load per full-time equivalent (FTE) radiotherapy technologist in Japan. Spacing of the bars represents intervals of 20 patients per FTE staff. Asterisk, The number of FTEs for institutions with FTE fewer than 1 was calculated as FTE equal to 1 to avoid overestimating patient load per FTE radiotherapy technologist.

on their staff still account for 56% nationwide, representing a 4% decrease compared with 2005 data (5). Therefore more than half the institutions in Japan still rely on part-time ROs. There are two reasons for this. First, the number of cancer patients who require radiation is increasing more rapidly, by 7.3% in the last 2 years, than the number of FTE ROs, which grew by 6.7% during the same period. Second, specialist fees for ROs in academic institutions are not recognized by the Japanese medical care insurance system, which is strictly controlled by the government. Therefore most ROs or other oncologists at academic institutions must work part time at affiliated hospitals in the B1 and B2 groups to earn a living. To reduce the number of institutions that rely on part-time ROs and thus may encounter problems with their quality of care, a reform of Japan's current medical care system, especially as it applies to staff at academic institutions, is required based on treatment outcome. However, great care is needed to ensure that the long-term success of radiation oncology in Japan and patient benefits are well balanced with costs. Therefore personal identification of ROs in all four types of institutions (A1, A2, B1, and B2) was recorded in this survey for further detailed analysis of patient load and real cost. Even under current conditions, however, the number of FTE ROs increased by 2.26 times compared with 1990 (3), with a 6.7% increase over 2005 (5). On the other hand, patient load per FTE RO also increased by 1.44 times to 248.2 during the same period, that is, a 0.6% increase over 2005 (5). This may reflect the growing popularity of RT because of an increase in the elderly population and recent advances in technology and improvement in clinical results. The caseload ratio in Japan has already exceeded the limit of the Blue Book guidelines of 200 patients per RO and has been getting worse (19, 20). The percentage distribution of institutions by patient load per RO showed a smaller distribution than that in the United States in 1989 (3) but also showed a major shift to a larger size in 2007 compared with 1990 (3). Therefore Japanese radiation oncology seems to be catching up quickly with the Western system despite limited resources. Furthermore, additional recruiting and education of ROs are still top priorities for JASTRO.

The distribution of patient load per RT technologist shows that only 14.7% of institutions met the narrow guideline range (100–120 per RT technologist) and the rest were densely distributed around the peak level. Compared with the distribution in the United States in 1989, nearly 18% of institutions in Japan had a relatively low caseload of 10 to 60, because there are still a large number of smaller B2-type institutions, which account for nearly 40% of institutions that do not attain the range specified by the guidelines. As for medical physicists, a similar analysis for patient load per FTE staff remains difficult, because their number was very small and they were working mainly in metropolitan areas. In Japan, however, RT technologists have been acting partly as medical physicists. Their education has been changed from 3 to 4 years during the last decade, and graduate and postgraduate courses have been introduced. Currently, those who have obtained a master's degree or RT

Table 5. Primary sites of cancer treatment with radiotherapy in 2005 by Patterns of Care Study institutional stratification for new patients

Primary site	A1 (n = 71)		Comparison with data of 2005* (%)	A2 (n = 70)		Comparison with data of 2005* (%)	B1 (n = 282)		Comparison with data of 2005* (%)	B2 (n = 283)		Comparison with data of 2005* (%)	Total (n = 706)		Comparison with data of 2005* (%)
	n	%		n	%		n	%		n	%		n	%	
Cerebrospinal	2,021	4.1	−22.4	720	4.1	−6.5	5,569	7.2	25.7	1,396	5.9	75.6	9,706	5.8	12.9
Head and neck (including thyroid)	6,522	13.1	3.2	2,124	12.0	−10.5	6,262	8.1	3.8	1,655	6.9	0.3	16,563	9.8	1.2
Esophagus	3,448	6.9	9.0	1,179	6.7	0.7	4,068	5.3	−8.1	1,474	6.2	1.5	10,169	6.0	−0.4
Lung, trachea, and mediastinum	7,460	15.0	5.5	2,852	16.1	8.1	16,811	21.7	12.5	5,844	24.5	8.5	32,967	19.5	9.7
Lung	6,794	13.6	24.2	2,452	13.9	7.9	14,546	18.8	12.6	5,393	22.6	13.9	29,185	17.3	14.9
Breast	10,336	20.8	15.6	3,663	20.7	20.1	17,334	22.4	22.5	5,011	21.0	21.7	36,344	21.5	20.1
Liver, biliary tract, and pancreas	1,929	3.9	−0.4	674	3.8	−5.5	2,806	3.6	2.3	1,023	4.3	6.1	6,432	3.8	1.2
Gastric, small intestine, and colorectal	2,075	4.2	9.4	1,015	5.7	25.9	4,034	5.2	7.8	1,498	6.3	7.1	8,622	5.1	9.9
Gynecologic	3,315	6.7	1.9	1,058	6.0	−8.5	3,059	4.0	−10.2	781	3.3	−8.7	8,213	4.9	−5.3
Urogenital	6,772	13.6	22.2	2,498	14.1	22.3	9,750	12.6	20.8	2,993	12.6	3.0	22,013	13.0	18.6
Prostate	5,394	10.8	25.7	1,748	9.9	26.2	7,015	9.1	24.7	2,068	8.7	7.9	16,225	9.6	22.7
Hematopoietic and lymphatic	2,591	5.2	5.3	900	5.1	−14.4	3,631	4.7	0.2	935	3.9	3.4	8,057	4.8	0.2
Skin, bone, and soft tissue	1,456	2.9	−9.4	484	2.7	−35.4	1,879	2.4	2.7	751	3.2	−26.2	4,570	2.7	−12.2
Other (malignant)	894	1.8	26.8	237	1.3	0.9	897	1.2	9.1	292	1.2	−6.7	2,320	1.4	11.8
Benign tumors	988	2.0	48.8	266	1.5	−0.7	1,288	1.7	−0.1	186	0.8	37.8	2,728	1.6	15.8
Pediatric <15 y (included in totals kiabove)	440	0.9	1.1	116	0.7	−5.7	374	0.5	100.0	126	0.5	−58.3	1,056	0.6	0.9
Total	49,807	100	7.9	17,670	100	3.8	77,388	100	11.3	23,839	100	8.9	168.704†	100	9.1

Abbreviations: A1 = university hospitals/cancer centers treating 440 patients or more per year; A2 = university hospitals/cancer centers treating 439 patients or fewer per year; B1 = other national/public hospitals treating 140 patients or more per year; B2 = other national hospital/public hospitals treating 139 patients or fewer per year.

* Rate of increase compared with data of 2005. The calculating formula was as follows: $\frac{\text{data of 2007 } (n) - \text{data of 2005 } (n)}{\text{data of 2005 } (n)} \times 100\ (\%)$.

† The total number of new patients was different with these data because no data on primary sites were reported by some institutions.

Table 6. Distribution of specific treatments and numbers of patients treated with these modalities by Patterns of Care Study stratification of institutions

Specific therapy	A1 (n = 71)		A2 (n = 71)		B1 (n = 288)		B2 (n = 291)		Total (n = 721)		Comparison with data of 2005* (%)
	n	%	n	%	n	%	n	%	n	%	
Intracavitary RT											
Treatment facilities	65	91.5	32	45.1	70	24.3	5	1.7	172	23.9	
Cases	1,795		497		925		18		3,235		−0.3
Interstitial RT											
Treatment facilities	51	71.8	19	26.8	22	7.6	5	1.7	97	13.5	
Cases	1,968		392		895		46		3,301		19.0
Radioactive iodine therapy for prostate											
Treatment facilities	43	60.6	12	16.9	22	7.6	1	0.3	78	10.8	
Cases	1,613		311		759		7		2,690		52.4
Total body RT											
Treatment facilities	64	90.1	34	47.9	68	23.6	19	6.5	185	25.7	
Cases	701		185		688		133		1,707		−1.8
Intraoperative RT											
Treatment facilities	15	21.1	9	12.7	10	3.5	7	2.4	41	5.7	
Cases	92		39		105		15		251		−35.1
Stereotactic brain RT											
Treatment facilities	40	56.3	24	33.8	92	31.9	30	10.3	186	25.8	
Cases	1,920		433		8,805		1,396		12,554		12.9
Stereotactic body RT											
Treatment facilities	43	60.6	14	19.7	54	18.8	12	4.1	123	17.1	
Cases	878		204		1,189		219		2,490		50.2
IMRT											
Treatment facilities	25	35.2	4	5.6	25	8.7	4	1.4	58	8.0	
Cases	1,142		38		1,534		85		2,799		270.7
Thermoradiotherapy											
Treatment facilities	8	11.3	5	7.0	8	2.8	2	0.7	23	3.2	
Cases	233		34		69		4		340		−41.5

Abbreviations: A1 = university hospitals/cancer centers treating 440 patients or more per year; A2 = university hospitals/cancer centers treating 439 patients or fewer per year; B1 = other national/public hospitals treating 140 patients or more per year; B2 = other national hospital/public hospitals treating 139 patients or fewer per year; RT = radiotherapy; IMRT = intensity-modulated radiotherapy.

* Rate of increase compared with data of 2005. The calculating formula was as follows: $\frac{data\ of\ 2007\ (n) - data\ of\ 2005\ (n)}{data\ of\ 2005\ (n)} \times 100\ (\%)$.

technologists with enough clinical experience can take the examination for qualification as a medical physicist, as can those with a master's degree in science or engineering, like those in the United States or Europe. In Japan a unique, hybrid-like education system for medical physicists has been developed since the anticancer law actively started to support improvement in QA/quality control specialization for RT. However, the validity of this education and training system remains to be proven, not only for QA/quality control but also for unique research and developmental activities. The discrepancy between FTE medical physicists and the number of registered medical physicists in Japan reflects the fact that their role in the clinic is not recognized as a full-time position only for medical physics service.

The distribution of the primary site for RT showed that more lung cancer patients were treated in B1- or B2-type non-academic institutions whereas more head-and-neck cancer patients were treated in A1- or A2-type academic institutions.

Table 7. Brain metastasis or bone metastasis patients treated with radiotherapy in 2005 by Patterns of Care Study institutional stratification

Metastasis	No. of patients										
	A1 (n = 71)		A2 (n = 71)		B1 (n = 288)		B2 (n = 291)		Total (n = 721)		Comparison with data of 2005* (%)
	n	%	n	%	n	%	n	%	n	%	
Brain	3,761	6.2	1,402	6.4	13,097	13.9	2,977	10.4	21,237	10.4	38.6
Bone	6,893	11.4	2,761	12.6	13,332	14.2	4,984	17.4	27,970	13.6	1.8

Abbreviations: A1 = university hospitals/cancer centers treating 440 patients or more per year; A2 = university hospitals/cancer centers treating 439 patients or fewer per year; B1 = other national/public hospitals treating 140 patients or more per year; B2 = other national hospital/public hospitals treating 139 patients or fewer per year.

* Rate of increase compared with data of 2005. The calculating formula was as follows: $\frac{data\ of\ 2007\ (n) - data\ of\ 2005\ (n)}{data\ of\ 2005\ (n)} \times 100\ (\%)$.

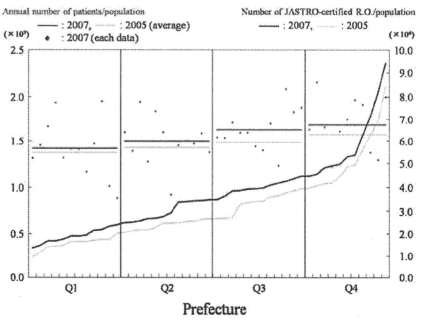

Fig. 3. Geographic distribution for 47 prefectures of annual numbers of patients (new plus repeat) per 1,000 population arranged in order of increasing number of Japanese Society of Therapeutic Radiology and Oncology (JASTRO)–certified radiation oncologists (ROs)/1,000,000 population by prefecture: Q1, 0–25%; Q2, 26–50%; Q3, 51–75%; and Q4, 76–100%. Horizontal lines show average annual number of patients (new plus repeat) per 1,000 prefectural population per quarter.

These findings may reflect the fact that more curative patients are referred to academic institutions and more palliative patients with lung cancer are treated at nonacademic institutions in Japan. However, the increase in the number of lung cancer patients in A1 institutions and that in prostate cancer patients in A1-, A2-, and B1-type institutions in 2007 were noteworthy. This suggests that the use of stereotactic body RT for lung cancer in A1 and of 3D CRT for prostate cancer in A1, A2, and B1 increased in 2007. The number of patients with brain metastasis increased significantly by 38.6% over 2005. This may also reflect dissemination of stereotactic RT for brain metastasis. The use of specific treatments and the number of patients treated with these modalities were significantly affected by institutional stratification, with more specific treatments being performed at academic institutions. These findings indicate that significant differences in patterns of care, as reflected in structure, process, and possibly outcome for cancer patients, continued to be prevalent in Japan in 2007. These differences point to opportunities for improvement. The Japanese PCS group published structural guidelines based on PCS data (20), and we are using the structural data obtained in 2007 to revise the Japanese structural guidelines for radiation oncology. The use of intraoperative RT and thermoradiotherapy decreased significantly, so these two modalities may not be considered as mainstay treatments anymore in Japan.

Geographic patterns showed that there were significant differences among prefectures in the use of RT, and the number of JASTRO-certified physicians per population was associated with the utilization of RT in both 2005 (5) and 2007, so a shortage of ROs or medical physicists on a regional basis will remain a major concern in Japan. However, the overall utilization rate of radiation in 2007 improved further compared with 2005 (5). The Japanese Society of Therapeutic Radiology and Oncology has been making every effort to recruit and educate ROs and medical physicists through public relations, to establish and conduct training courses at academic institutions, to become involved in the national examination for physicians, and to seek an increase in the reimbursement by the government-controlled insurance scheme and other actions.

In conclusion, the Japanese structure of radiation oncology has clearly and steadily improved over the past 17 years in terms of installation and use of equipment and its functions, although a shortage of personnel and differences in maturity by type of institution and by caseload still remain. Structural immaturity is an immediate target for improvement, whereas for improvements in process and outcome, the PCS and National Cancer Database, which are currently operational and the subject of close examination, can be expected to play an important role in the near future in Japan.

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産科と婦人科　別刷

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特集 婦人科がん臨床試験参加に必要な知識

9. がん臨床試験と放射線療法：放射線治療の品質保証(QA)・品質管理(QC)の重要性

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要旨

放射線治療を含む臨床試験において，放射線治療規定の遵守は科学的妥当性の高い結果を得るために必須の条件である．放射線治療の品質保証(quality assurance：QA)，品質管理(quality control：QC)は極めて重要である．米国に引き続き，わが国でも婦人科領域多施設共同臨床試験における放射線治療QAシステムの構築と運用が開始された．

Key Words 臨床試験，放射線治療，QA/QC

約10年前に同時化学放射線療法（CCRT）の有用性を明らかにした無作為比較試験（RCT）結果が発表された後，次々とCCRTの新規臨床試験が行われている．わが国でも婦人科悪性腫瘍化学療法研究機構（JGOG）等でCCRTをはじめとした放射線治療を含む多施設共同臨床試験が行われつつある．

臨床試験における放射線治療の品質保証の重要性

放射線治療が関連する臨床試験への参加にあたり，実施計画書に記載された放射線治療規定の臨床的意義を理解しておく必要がある．線量の計算アルゴリズム等が守られ，放射線が投与されるべき範囲（target volume），あるいは投与が可及的回避されるべき臓器（organ at risk）が臨床的に正しく定義されなければならない．総治療期間は，子宮頸癌を含め多くの癌において治療成績を左右する重要な因子である．また子宮頸癌の腔内照射では，手技とともに線量の処方と計算が適切である必要がある．

臨床試験において，放射線治療の規定が遵守されることは極めて重要である．早期Hodgkinリンパ腫の最適線量を確認する試験において，放射線治療規定（線量以外）が遵守された症例の5年生存率が82%であったのに対し，違反（protocol violation）があった症例では70%と有意に不良であったことが報告されている[1]．すなわち，実施計画書に規定された放射線治療内容の逸脱は，治療成績や有害事象発生率等のエンドポイントに大きく影響し，本来明らかにしたいクリニカルクエスチョンに対し科学的に妥当な回答が得られないことはもちろん，参加した患者に不利益を及ぼす危険さえ生じる．した

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がって，放射線治療の品質保証（quality assurance：QA），品質管理（quality control：QC）は極めて重要である．米国の臨床試験グループ Radiation Therapy Oncology Group（RTOG）では，1970年代初頭には放射線治療の品質に問題があったものの，その後のQA活動により劇的に向上したことが示されている[2]．わが国においても日本臨床腫瘍研究グループJCOGでの肺癌に対するCCRTのRCTで40%という不良な放射線治療規定コンプライアンスが明らかになった後，2002年に放射線治療QAプログラムが策定され，その結果遵守率が改善されたことが報告され[3]，その後も急速にQAシステムが整備されつつある[4]．

臨床試験における放射線治療QA/QCの実際：婦人科腫瘍領域

現在，婦人科腫瘍領域において最も精力的に放射線治療QAを行っているのは米国の臨床試験グループである．Gynecologic Oncology Group（GOG）内にはRadiation Committeeが組織され，CCRTの臨床試験における放射線治療QAが行われている．また，米国NCIのFundingにてMDアンダーソンがんセンター内に設置されたRadiological Physics Center（RPC）では，臨床試験における体系的な放射線治療QA/QCシステムを構築しGOG，RTOG等の大規模臨床試験グループのQA支援が行われている（http://rpc.mdanderson.org/rpc）．

1．治療装置QA（おもに出力について）

処方され計画された線量が正しく治療装置（ライナック）から出力されているかどうかの確認と検証は，外部照射におけるQAの基本である．日本放射線腫瘍学会（JASTRO）の施設認定においては，月1回以上のリファレンス線量計による装置の精度管理および医療用線量標準センターによる2年に1回以上のリファレンス線量計の校正が義務づけられている．多施設臨床試験においても装置出力の管理は重要な要件であり，GOG試験では線量投与が±5%以内の精度に保たれていることを参加の要件としている．局所進行子宮頸癌に対するCCRT試験JGOG1066では放射線治療に関する3つの施設基準が設定された（**表1**）．そのなかの「認定施設である」という条件は，装置出力の精度を担保することを目的としたものであった．International Atomic Energy Agency（IAEA）や米国RPCにおいてはthermoluminescent dosimetry（TLD）郵送による装置出力の外部評価が行われており，わが国でも同様の郵送測定による評価が利用可能となった．今後は臨床試験においてこのような外部評価を参加の条件とすることが検討されるべきである．

表1 JGOG1066：放射線治療の施設基準（実施計画書より抜粋）

子宮頸癌の放射線治療においては外部照射とともに，腔内照射の手技の適否が治療成績を大きく左右し，CCRTにおいても放射線治療の品質確保は重要と考えられる．この観点より，施設は放射線治療に関する以下の規準を満たすことを参加の原則とする．

1）日本放射線腫瘍学会（JASTRO）の認定放射線治療施設であり，JASTRO認定医が常勤すること．
2）高線量率腔内照射の手技はJASTRO認定医あるいは，その指導のもとで，放射線腫瘍医が行うこと．
3）過去1年間に10例以上の子宮頸癌患者に対し，高線量率腔内照射を行っていること．

2．放射線治療パラメータのレビュー

前述した各種放射線治療パラメータが計画書の規定通りに実行されたかどうかのチェック，individual case review（ICR）は極めて重要かつ有効なQAプロセスである．通常，治療記録（放射線治療照射録，モニターユニット値算出のための各種パラメータが記録された原資料），治療計画画像（シミュレーション写真，DRR画像），線量分布図，照合画像（ライナックグラフィ，EPID画像）等の放射線治療に関係する資料を収集し，QA委員会によりそれらの評価が行わ

表2 JAROG0401/JROSG04-2：I，II期子宮頸癌に対する高線量率腔内照射を用いた根治的放射線治療に関する多施設共同前向き臨床試験*

対象：
FIGO臨床病期IB1，II期子宮頸癌（扁平上皮癌）
断端癌でない
最大腫瘍径40 mm未満（MRI T2強調像）
短径10 mm以上の骨盤内/傍大動脈リンパ節腫大なし（CT/MRI）
20～85歳，PS 0-2
Primary endpoint：2年骨盤内無増悪割合
Secondary endpoints：急性有害事象発生割合，治療完遂割合，晩期有害事象割合，2年原病生存割合，2年無再発生存割合，2年全生存割合，再発部位
目標症例数：60例，登録期間：3年（2004年9月～2007年9月）
試験治療：放射線治療単独
全骨盤照射50 Gy/25回（20 Gy時より中央遮蔽）．
高線量率腔内照射A点6 Gy×4回
....合計BED（A点）=62 Gy_{10}

BED：biologically effective dose
*早期子宮頸癌に対するわが国の標準線量の安全性と有効性を確認するために行われた．本試験により，米国よりも著しく線量の低いわが国の治療スケジュールの妥当性に関するエビデンスが得られることが期待されている．

れる．厚生労働省がん研究助成金加賀美班/小口班において，早期子宮頸癌に対する放射線治療の多施設共同臨床試験：JAROG0401/JROSG04-2）が行われた（**表2**），2004～2007年に予定60例の登録が達成され，現在最終結果の解析中である．この試験では全登録例について放射線治療内容のICRが行われた．**表3**にその項目と結果を示す．実施計画書へのコンプライアンスは良好であり，本試験により得られる各エンドポイントの結果が科学的に信頼できることの証左となっている[5]．ICRは約20例ずつ計3回行われ，結果は随時参加施設にフィードバックされた．その結果，逸脱を有した症例割合は，初回：40%，第2回：35%，第3回：14%と経時的に減少していた[5]．これはEORTC試験におけるICRでも示唆されており[6]，QAのQC効果を示すものであると考えられる．2009年に予定症例数の登録を終了したJGOG1066試験においても同様のICRがJGOG放射線治療委員会にて進められている．

腔内照射を併用される子宮頸癌の放射線治

表3 放射線治療に関するindividual case review項目と結果（JAROG0401/JROSG04-2）

項目	評価	
	逸脱	遵守
1）登録から治療開始まで日数	1	59
2）外部照射X線エネルギー	0	60
3）外部照射処方線量（1回）	0	60
4）外部照射処方線量（合計）	0	60
5）照射野	1	59
6）線量分布均一性（外部照射）	1	59
7）中央遮蔽設置時期	0	60
8）中央遮蔽形状	1	59
9）1日全門照射	0	60
10）照射野照合	6	54
11）腔内照射開始日	1	59
12）腔内照射処方線量（1回）	1	59
13）腔内照射処方線量（合計）	1	59
14）A点設定法	10	50
15）リスク臓器（直腸，膀胱，腟）線量計算	3	57
16）総治療期間	0	60

療QAにおいては，毎回の腔内照射アプリケータ設置状態評価とA点設定の妥当性の検証が不可欠である．前述のJAROG0401/JROSG04-2

の放射線治療QAでは，A点設定のICRが行われ，60例中10例に逸脱を認めた．一方，米国GOGのCCRT試験（GOG165）においては，ICRに加えて全症例の腔内照射線量の再計算（independent calculation of patient dose）が行われている．その結果，A点設定の妥当性の問題から大幅な線量逸脱（15%以上）が6.6%に認められたと報告している[7]．わが国でのJAROG/JROSG試験およびJGOG試験では残念ながらindependent calculationは行えなかったが，今後導入に向けたシステム構築が検討されている．

3．credentialing

多施設臨床試験の参加要件として，放射線治療に関する各施設の担当医のプロトコル治療理解度，施設の装置/設備/スタッフの対応/充足度，治療内容の確認を行うcredentialing（参加資格証明）が，米国のGOGやRTOG試験で行われている．credentialingにより臨床試験における放射線治療の逸脱が減ったことが報告され，有用性が示唆されている[8]．特に腔内照射は，放射線物理/生物学的に専門的な知識と，それに裏付けられた手技の熟練を併せもつことが治療の品質を確保するために必須である．そのためJGOG1066試験では施設参加基準として，腔内照射の手技がJASTRO認定医あるいはその指導のもとで放射線腫瘍医が行うこと，年間10例以上の子宮頸部癌患者に対しHDR-ICBTを施行していることを条件とするcredentialingを行った（**表1**）．今後の臨床試験においては，施設で治療された実患者（実臨床）の腔内照射施行例のデータ（フィルム，線量計算原資料，線量分布図等）の提出を義務づけ評価を行うBenchmark case reviewの導入も検討すべきかもしれない[9]．さらにテストケースについて計画を行い，ファントムにて線量評価を行うcredentialingがIMRTを用いる臨床試験への参加要件としてRPCでは採用されている．放射線治療内容が高度で複雑化になるとともに，各施設が実施計画書の治療内容を正しく理解し遂行しうるかどうかを事前に確認することは，臨床試験を円滑に進め，科学的に正しい結果を得るために重要なQAプロセスであると考えられる．

おわりに

今後婦人科腫瘍においては，ますますCCRT等，放射線治療が関与する多施設共同臨床試験が広く行われ，それによりわが国独自のエビデンスが創出されていくことが期待される．科学的に妥当性の高い結果を得るには，正しい試験のデザインとともに試験治療のコンプライアンスの確保は重要である．化学療法と同様に，今後さらに高度化・複雑化していく放射線治療のQA/QCは重要である．

プログラムの構築とともに，各参加施設における婦人科腫瘍医と放射線腫瘍医のコミュニケーション強化は最も重要なQAプロセスである．JCOGでは2009年に婦人科腫瘍グループを含む各グループにおいて，施設の放射線治療責任者を登録し，婦人科腫瘍医と合同のメーリングリストが作成された．これにより臨床試験に関わる情報や放射線治療に関する問題点の共有が促進され，試験における放射線治療規定の遵守につながることが期待される．今後，他の臨床試験グループにおいても同様のシステムが構築されることが期待される．

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CLINICAL INVESTIGATION

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. © **2011 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.

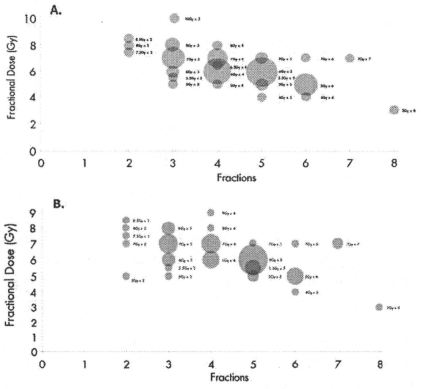

Fig. 1. Cervical cancer high-dose-rate brachytherapy fractionation patterns by dose in Gray (Gy) and number of brachytherapy fractions prescribed. (A) Respondents' answers regarding the fractionation pattern prescribed for Stages IB–IIA cervical cancer. (B) Fractionation pattern recommended for Stages 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.

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 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 international standard of 80 Gy, must be further analyzed, including comparison of recurrence rates and toxicities; an upcoming abstract shows reasonable rates of local control (17). The Japanese regimen, in use for several decades, was implemented

Table 1. Routine high-dose-rate brachytherapy fractionation regimens for cervical cancer as used by Gynecologic Cancer Intergroup surveyed physicians

Standard fractionation for Stages IB–IIA cervical cancer				Standard fractionation for Stages IIB–IVA cervical cancer			
% Respondents (*n*)	Dose/fraction	Fractions (*n*)	EQD2	% Respondents (*n*)	Dose/fraction	Fractions (*n*)	EQD2
18% (11)	6	5	40	23% (14)	6	5	40
15% (9)	6	4	32	10% (6)	7	4	40
12% (7)	7	3	29.75	10% (6)	7	3	30
8% (5)	5	6	37.5	8% (5)	6	4	32
8% (5)	7	4	39.7	7% (4)	5.5	5	35.5
5% (3)	5	5	31.25	5% (3)	5	6	37.5
5% (3)	5.5	5	35.52	5% (3)	7	6	59.5
3% (2)	8	3	36	5% (3)	6	3	24
1.6% (1)	3	8	26	5% (3)	8	3	36
1.6% (1)	4	5	23.3	3% (2)	7	7	69.4
1.6% (1)	4	6	28	3% (2)	5	5	31.3
1.6% (1)	5	3	18.75	1.6% (1)	3	8	26
1.6% (1)	5	4	25	1.6% (1)	4	6	28
1.6% (1)	5.5	3	21.3	1.6% (1)	7	5	49.6
1.6% (1)	6	3	24	1.6% (1)	8	4	48
1.6% (1)	6.5	4	35.75	1.6% (1)	9	4	57
1.6% (1)	7	5	49.6	1.6% (1)	5	3	18.8
1.6% (1)	7	6	59.5	1.6% (1)	5.5	3	21.3
1.6% (1)	7	7	69.4	1.6% (1)	5	2	12.5
1.6% (1)	7.5	2	21.9	1.6% (1)	7.5	2	21.9
1.6% (1)	8	2	24	1.6% (1)	8	2	24
1.6% (1)	8	4	48	1.6% (1)	8.5	2	26.2
1.6% (1)	8.5	2	26.2				
1.6% (1)	10	3	50				

Abbreviation: EQD2 = Equivalent dose in 2 Gy fractions.
Results indicate the diversity of responses.
The EQD2 formula was used to convert the high-dose-rate dose and number of fractionations.

upon the observation that Japanese women, potentially because of their small body size, had very high bowel and bladder toxicity rates when treated with higher pelvic EBRT doses (18). The current Japanese regimen begins HDR intracavitary brachytherapy once per week after 20 Gy. Whether a genetic difference in sensitivity to radiation exists is unknown, but one implication of the successful outcomes in Japanese women is that brachytherapy may be the more critical component for treatment to the cervix, particularly for early stage disease with a lower risk of nodal spread.

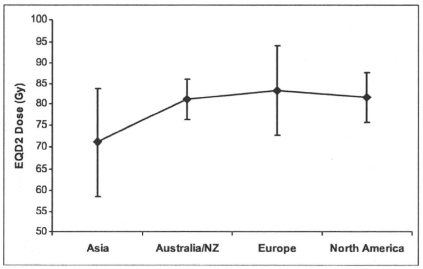

Fig. 2. The sum external beam plus brachytherapy dose with the error bars indicating the standard deviation (SD), converted using the equivalent dose in 2-Gy fractions (EQD2) assuming an $\alpha/\beta = 10$, by region of the world. The mean EQD2 dose was 80.9 Gy (SD 10.14).

A previously unassessed difference in brachytherapy administration was identified with regard to the proportional relationship of brachytherapy to the sum total dose. For early-stage patients, the Japanese respondents administer a significantly higher proportion of the dose using brachytherapy than practitioners from other countries. The reliance on HDR brachytherapy fractionation may indicate that a large dose given with HDR can compensate for a lower external beam dose in patients with small tumors. This assumption of proportionality must be corroborated with recurrence information.

For all respondents (including those from Japan), the mean EBRT plus brachytherapy cumulative EQD2 dose was 80.4 Gy, with a standard deviation of 10 Gy. Patients with higher-stage disease (Stage IIB–IVA) received a significantly higher dose than did those with earlier-stage cervical cancer. Therefore, a dose of 80 Gy may be considered the universally accepted international baseline dose overall, with on average 79 Gy for Stage IB–IIA and 84 Gy for Stage IIB–IVA cases. A dose of 80 Gy is approximately equivalent to 45 Gy delivered with EBRT and 5.5 Gy for five fractions delivered with HDR brachytherapy. A dose of 84 Gy is approximately equivalent to 45 Gy with EBRT and 6 Gy for five fractions or 7 Gy for four fractions of HDR.

Standardization of HDR brachytherapy on an international level will assist institutions in terms of comparing toxicities and outcomes in patients with cervical cancer, and will also allow for the exchange of information and uniformity in a multi-institutional international randomized clinical trial that permits HDR brachytherapy. A cumulative dose of 80 Gy should be considered an achievable goal for patients with locally advanced cervical cancer. Analysis of the outcomes in Japanese patients treated with a lower total dose is necessary. Future randomized trials in the era of chemoradiation may attempt radiation dose variation based on response and on improved sparing of normal tissues with 3D imaging, to determine the acceptable safe threshold level that results in equivalent eradication of disease while minimizing toxicities.

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Regular Paper

Intracavitary Combined with CT-guided Interstitial Brachytherapy for Locally Advanced Uterine Cervical Cancer: Introduction of the Technique and a Case Presentation

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Interstitial brachytherapy/Cervical cancer/Radiotherapy/CT-guided brachytherapy/Intracavitary brachytherapy.

We report a new technique of brachytherapy consisting of intracavitary combined with computed tomography (CT)-guided interstitial brachytherapy for locally advanced cervical cancer. A Fletcher-Suit applicator and trocar point needles were used for performing high-dose rate brachytherapy under in-room CT guidance. First, a tandem and ovoids were implanted into the patient's vagina and uterus by conventional brachytherapy method. Based on clinical examination and MRI/CT imaging, operating radiation oncologists decided the positions of insertion in the tumor and the depth of the needles from the upper surface of the ovoid. Insertion of the needle applicator was performed from the vaginal vault inside the ovoid within the tumor under CT guidance. In treatment planning, dwell positions and time adaptations within the tandem and ovoids were performed first for optimization based on the Manchester system, and then stepwise addition of dwell positions within the needle was continued. Finally, dwell positions and dwell weights were manually modified until dose-volume constraints were optimally matched. In our pilot case, the dose of D90 to high-risk clinical target volume was improved from 3.5 Gy to 6.1 Gy by using our hybrid method on the dose-volume histogram. D1cc of the rectum, bladder and sigmoid colon by our hybrid method was 4.8 Gy, 6.4 Gy and 3.5 Gy, respectively. This method consists of advanced image-guided brachytherapy that can be performed safely and accurately. This approach has the potential of increasing target coverage, treated volume, and total dose without increasing the dose to organs at risk.

INTRODUCTION

The combination of external beam radiotherapy (RT) and intracavitary brachytherapy (ICBT) is a standard treatment technique of RT for uterine cervical cancer, and concomitant chemotherapy is combined for locally advanced cases.[1–5] ICBT plays an important role because the brachytherapy system allows a much higher dose to the cervix while sparing adjacent bladder and bowels. Local control rates of cervical cancer have been reported at 80–90% for early stages.[6–8] However, those for advanced stages show a range of 67–75% and further improvement is needed.[4,5,9] One of the reasons for local failure is inadequate dose coverage to bulky and/or irregular-shape tumors.

In order to realize adequate dose coverage to cervical tumors, intracavitary combined with computed tomography (CT)-guided interstitial brachytherapy was developed at Gunma University. We introduce the new technique of hybrid-brachytherapy with a pilot case.

PATIENT

The patient was a 53-year-old woman with stage IIIB squamous cell carcinoma of the uterine cervix according to the International Federation of Gynecology and Obstetrics (FIGO) staging system.[10] On image diagnosis, CT detected a bulky tumor at the uterine cervix with left hydronephrosis. MRI before treatment revealed a cervical mass measuring $60 \times 58 \times 70$ mm^3. The tumor extension reaching the pelvic side-wall before RT still existed at the time of brachytherapy (Fig. 1).

The patient was treated with a combination of external

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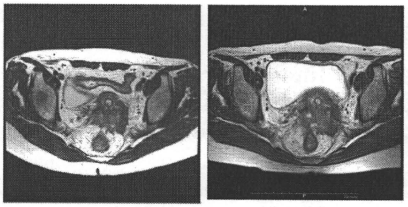

Fig. 1. MRI images before treatment and after 30 Gy.

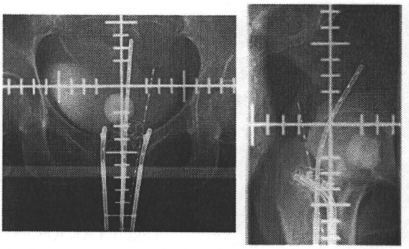

Fig. 2. X-ray photographs of needle placement after implantation of a tandem and ovoids.

beam RT and high-dose rate (HDR) brachytherapy. She did not receive concurrent chemotherapy because of renal dysfunction. External irradiation to the whole pelvis was performed with antero-posterior and postero-anterior parallel-opposed ports with a total dose of 30 Gy at 2 Gy per fraction, 5 times per week. This was followed by a central shielding pelvis field up to a total pelvis irradiation dose of 50 Gy at 2 Gy per fraction, 5 times per week. Along with the central shielding irradiation, she was given HDR brachytherapy by HDR-remote afterloading system (RALS) 5 times using an iridium-192 source. In the first three sessions, she received ICBT without interstitial brachytherapy administered once per week at fraction doses of 7.5, 7 and 7 Gy at Point A, with a total dose of 21.5 Gy. In the remaining two sessions, the hybrid method was used because the tumor showed poor response to radiotherapy. Written informed consent was obtained from the patient before this brachytherapy.

METHODS

In-Room CT Imaging

Brachytherapy was delivered in our unit, comprising HDR-RALS (microSelectron HDR; Nucletron, The Netherlands) coupled to a CT scanner and X-ray imager sharing a common couch. The couch rotates 230° at the CT-scanning position or 50° at the X-ray imaging position. During CT scanning, the gantry moves along rails on the floor while the table remains stationary. Applicators are implanted into the patient's vagina and uterus on the couch, and all processes including application, imaging, and irradiation can be performed on the same couch using the in-room CT brachytherapy system.[11,12]

Brachytherapy application

A set of Fletcher-Suit Asian Pacific applicator (tandem and half-size ovoids) and trocar point needles (Nucletron) was used. This hybrid application was done without general anesthesia or spinal anesthesia. The tandem and ovoids were implanted into the vagina and uterus by the procedure of conventional brachytherapy. After implantation, CT scans were generated on the same couch at 3-mm slice thickness. Magnetic resonance images (MRI) were taken before brachytherapy and used as reference images of the tumor. Based on clinical examination and MRI/CT imaging, operating radiation oncologists decided the positions of insertion in the tumor and the depth of the needles from the upper surface of the ovoid.

The CT-guided insertion of the needle applicator was performed along the inside of the half-size ovoid into the tumor (Fig. 2). After tumor location and needle position were confirmed, anterior and posterior vaginal packing was done in a manner similar to the non-interstitial procedure. CT scans were generated again and used for treatment planning. Then, X-ray images were also taken in the same position while rotating the couch. After completion of irradiation, the applicator was removed in the order of tandem and ovoids, followed by the needles.

Treatment Planning

The applicator geometry was digitized, reconstructed and registered to the X-ray and CT images. Image registration was performed with the evaluation module of the PLATO Brachytherapy Planning System v14.3.6 (Nucletron).

The current brachytherapy planning process starts with a conventional pattern for tandem and ovoids planning based on the Manchester system. Point A was defined on the X-ray as being 2 cm superior to the external os, and 2 cm lateral from the axis of the intrauterine tandem. At first, the dose of point A at the opposite side of needle placement was normalized to 6 Gy. A dwell position and time adaptation were established first to optimize the initial standard dose distribution, and then continued with 2.5-mm stepwise additions as dwell positions within the needle. Dose distribution by the resulting treatment plan was confirmed on CT images for the high-risk clinical target volume (HRCTV), which is