INTRODUCTION

Several advanced radiotherapy technologies have been introduced over the last decade, and their use has contributed to both reductions in the rates of treatment-related complications and improvements in patients' quality of life after cancer treatment (1–3). In the USA, the proportion of intensity-modulated radiotherapy (IMRT) used for patients with prostate cancer rose from 28.7% in 2002 to 81.7% in 2005 (4), and the proportion of IMRT for head and neck cancers rose from 1.3% in 2000 to 46.1% in 2005 (5). Pan et al. (6) conducted a survey on the use of advanced radiotherapy technologies in the USA, and they found that the cumulative adoption of stereotactic body radiotherapy (SBRT) for the treatment of any disease site was <5% in 2000 versus >60% in 2010. The percentage of physicians using SBRT was 63.9%, but nearly one-half of the physicians reported that they first used SBRT in 2008 or later. IMRT and SBRT have rapidly become widely adopted among American radiation oncologists (ROs).

The Japanese government enacted the Basic Act for Anti-Cancer Measures in June 2006 to promote comprehensive strategies against cancer. The government set basic guidelines and founded a system of designated cancer care hospitals (DCCHs). The prefectural DCCH (P-DCCH) is defined as the coordinating hospital of each prefecture (the 47 prefectures in Japan are akin to the states in the USA), and the regional DCCHs (R-DCCHs) are mainly cardinal hospitals in the secondary medical care area of prefecture. The DCCHs are required to cooperate with each other to deliver comprehensive cancer care, including adequate radiotherapy, surgical treatment, systemic chemotherapy and palliative care to all citizens.

We conducted the present study to survey the current situation regarding the use of novel radiotherapy technologies such as IMRT and SBRT at all of the DCCHs in Japan.

PATIENTS AND METHODS

There are currently two national cancer centers: 51 P-DCCHs and 344 R-DCCHs in Japan (total, 397 DCCHs). We included the two national cancer centers in the grouping of P-DCCHS for a total of 53 hospitals that are defined as P-DCCHs in this analysis. We obtained the institutional information of the DCCHs from the Center for Cancer Control and Information Services of the National Cancer Center, Japan. The data from each DCCH were submitted to the Ministry of Health, Labor and Welfare of Japan in October 2011, and that of each DCCH has been updated on a regular basis.

We collected the data of all 397 DCCHs, which included the number of medical staff working in radiotherapy departments, such as ROs, medical physicists (MPs), radiotherapy quality managers (RQMs) and radiation therapists (RTs), the number of linear accelerators, the number of patients who were treated with radiotherapy per year and radiotherapy use for each disease site in detail (e.g. SBRT, IMRT and brachytherapy) as of November 2012. We calculated the proportion of implementation of the advanced radiation techniques for IMRT for head and neck and prostate cancers, and SBRT for lung cancer according to each kind of DCCH. The proportion of implementation means that of institutions which have potential availability of advanced radiation technologies.

Differences between the two sample medians for continuous variables were analyzed using Pearson's chi-squared test. P values of <0.05 were considered significant. Multivariate analyses were performed using the logistic regression model. Statistical analyses were performed using JMP version 10.0.0 (SAS Institute, Inc.).

RESULTS

Institute's Qualification for Advanced Radiotherapy Technologies

Japanese health insurance providers cover the cost of SBRT and IMRT only at hospitals which satisfy the institute's qualification including the number and year of experience of full-time ROs, appropriate treatment machine and planning systems for these advanced radiotherapy techniques and adequate radiotherapy quality control (QC) system. The institute's qualification for IMRT includes (i) two or more full-time ROs, (ii) at least one of them who has over 5 years experience in radiotherapy, (iii) at least one full-time RT who has over 5 years experience in radiotherapy, (iv) appropriate treatment machine and inverse planning systems for IMRT and (v) adequate radiotherapy QC system. The institute's qualification for stereotactic radiotherapy (SRT) includes (i) at least one full-time RO, (ii) appropriate treatment machine for SRT and (iii) appropriate treatment system for SRT. Thirty P-DCCHs (57%) satisfy the institute's qualification for IMRT, and 76 R-DCCHs (22%) satisfy it ($P < 0.001$). Forty-seven P-DCCHs (89%) with institute's qualification for SRT, and 175 R-DCCHs (51%) satisfy it ($P < 0.001$).

IMRT for Head and Neck Cancers

In November 2012, only 53% P-DCCHs and 16% R-DCCHs had been using IMRT for head and neck cancers. The results of our univariate analyses of the implementation of IMRT for head and neck cancers, which included the number of linear accelerators, those of medical staff such as ROs, RTs, RQMs and MPs are shown in Table 1 according to the types of DCCH. We analyzed the 30 P-DCCHs which satisfy the institute's qualification for IMRT, and the multivariate analysis including the five factors listed above revealed that there was no factor associated with IMRT implementation for head and neck cancers (Table 2). But there was a trend to correlate the number of ROs with IMRT implementation for head and neck cancers ($P = 0.08$). We analyzed the 76 R-DCCHs with institute's qualification for IMRT, and the multivariate analysis revealed that there was no factor associated with IMRT implementation for head and neck cancers (Table 2).

Table 1. Univariate analysis of implementation of IMRT and SBRT according to the type of designated cancer care hospital

	Prefectural designated cancer care hospitals			Regional designated cancer care hospitals		
	Implementation, median (range)	Non-implementation, median (range)	*P* value	Implementation, median (range)	Non-implementation, median (range)	*P* value
IMRT for head and neck cancer						
No. of linear accelerators	3 (2–4)	2 (1–4)	0.07	2 (1–3)	1 (1–3)	0.0001
No. of ROs	4 (1–11)	2 (0–5)	0.06	2 (0–36)[b]	1 (0–8)	0.0001
No. of radiation therapists	6.5 (2–15)	4 (1–18)	0.33	4 (1–11)	2 (1–10)	0.0001
No. of radiation quality managers	2 (1–18)	2 (1–5)	0.26	2 (1–8)	2 (1–9)	0.28
No. of medical physicists	1 (0–5)	1 (0–3)	0.41	1 (0–7)	0 (0–4)	0.0001
IMRT for prostate cancer[a]						
No. of linear accelerators	3 (1–4)	2 (1–4)	0.16	2 (1–3)	1 (1–3)	0.0001
No. of ROs	4 (1–11)	3 (0–7)	0.38	2 (0–36)[b]	1 (0–8)	0.0001
No. of radiation therapists	7 (2–15)	4 (2–18)	0.01	4 (1–11)	2 (1–10)	0.0001
No. of radiation quality managers	2 (1–13)	1 (1–18)	0.49	2 (1–8)	2 (1–9)	0.20
No. of medical physicists	1 (0–5)	0.5 (1–4)	0.57	1 (0–7)	0 (0–4)	0.0001
SBRT for lung cancer						
No. of linear accelerators	3 (1–4)	2 (1–4)	0.14	1 (1–3)	1 (1–3)	0.0001
No. of ROs	3 (1–11)	2 (0–5)	0.12	1 (0–9)[b]	1 (0–36)	0.0001
No. of radiation therapists	6 (1–18)	4 (1–12)	0.11	3 (1–11)	2 (1–8)	0.0001
No. of radiation quality managers	2 (1–18)	1.5 (1–5)	0.73	2 (1–8)	2 (1–9)	0.15
No. of medical physicists	1 (0–5)	0.5 (0–4)	0.16	1 (0–7)	0 (0–4)	0.007

Data are expressed as median (range) values unless otherwise specified.
ROs, radiation oncologists; IMRT, intensity-modulated radiotherapy; SBRT, stereotactic body radiotherapy.
[a]The data of three hospitals were not available.
[b]A part of hospitals which have full-time radiation oncologists seem to submit under-reporting of them in error.

IMRT for Prostate Cancer

Only 62% P-DCCHs and 23% R-DCCHs had been using IMRT for prostate cancer. The results of the univariate analysis of IMRT for prostate cancer, which included the five factors listed above, are shown in Table 1 according to the types of DCCHs. We analyzed the 30 P-DCCHs with institute's qualification for IMRT, and the multivariate analysis revealed that the number of ROs ($P = 0.01$) and that of RTs ($P = 0.003$) were significantly correlated with IMRT implementation for prostate cancers (Table 2). Our multivariate analysis of the 76 R-DCCHs with institute's qualification for IMRT revealed no factor associated with IMRT implementation for prostate cancer.

SBRT for Lung Cancer

At the time of our survey, 74% P-DCCHs and 40% R-DCCHs were using SBRT for lung cancer. The results of the univariate analysis of SBRT for lung cancer are shown according to the types of DCCH (Table 1). We analyzed the 47 P-DCCHs with institute's qualification for SBRT, and the multivariate analysis including the five factors listed above revealed that the number of ROs was significantly correlated with SBRT implementation for lung cancers ($P = 0.02$) (Table 2). There was a trend to correlate the number of MPs with SBRT implementation for lung cancers ($P = 0.07$). We analyzed the 175 R-DCCHs with institute's qualification for SBRT, and the multivariate analysis revealed that there was no factor associated with SBRT implementation for lung cancers at these hospitals.

Quality Assurance/Quality Control (QA/QC) System

The freedom of information act data from the Center for Cancer Control and Information Services showed that only nine P-DCCHs (17%) and 46 R-DCCHs (13%) had a radiotherapy quality assurance (QA) committee, and the output dose of linear accelerators was evaluated by a third party in only 26 P-DCCHs (49%) and 150 R-DCCHs (44%).

DISCUSSION

IMRT reduces the dose to the organ at risk while maintaining good coverage of the target (1), and it has rapidly become a

Table 2. Multivariate analysis of implementation of IMRT and SBRT according to the type of designated cancer care hospital that has institute's qualification for advanced technologies

IMRT	Prefectural designated cancer care hospitals (n = 30)		Regional designated cancer care hospitals (n = 76) [a]	
Head and neck cancer	Implementation (n = 23), median (range)	*P* value	Implementation (n = 40), median (range)	*P* value
No. of linear accelerators	3 (2–4)	0.86	2 (1–3)	0.64‘
No. of radiation oncologists	4 (2–11)	0.08	2.5 (1–36)	0.46
No. of radiation therapists	8 (2–15)	0.62	5 (1–11)	0.31
No. of radiotherapy quality managers	2 (1–18)	0.29	2 (1–8)	0.49
No. of medical physicists	2 (0–5)	0.99	1 (0–7)	0.64
Prostate cancer	Implementation (n = 28)		Implementation (n = 61)	
No. of linear accelerators	3 (2–4)	0.99	2 (1–3)	0.69
No. of radiation oncologists	4 (2–11)	0.01	2 (1–36)	0.59
No. of radiation therapists	7 (2–15)	0.003	5 (1–11)	0.19
No. of radiotherapy quality managers	2 (1–13)	0.99	2 (1–8)	0.86
No. of medical physicists	1.5 (0–5)	0.99	1 (0–7)	0.90
SBRT	Prefectural designated cancer care hospitals (n = 47)		Regional designated cancer care hospitals (n = 175)[b]	
Lung cancer	Implementation (n = 37)	*P* value	Implementation (n = 116)	*P* value
No. of linear accelerators	3 (1–4)	0.52	1 (1–3)	0.30
No. of radiation oncologists	4 (1–11)	0.02	2 (0–9)[c]	0.70
No. of radiation therapists	7 (1–18)	0.29	3 (1–11)	0.24
No. of radiotherapy quality managers	2 (1–18)	0.73	2 (1–8)	0.70
No. of medical physicists	1 (0–5)	0.07	1 (0–7)	0.31

Data are median (range) unless otherwise specified.
[a]The data of four hospitals were not available.
[b]The data of three hospitals were not available.
[c]A part of hospitals which have full-time radiation oncologists seems to submit under-reporting of them in error.

widely adopted treatment approach among American ROs. This increase in the use of IMRT could be attributed in part to the fact that multiple investigators have reported dosimetric advantages and consequent improvement in the xerostomia rate, rectal toxicity rate and quality of life measures following the use of IMRT (3,7,8).

In the UK, Mayles et al. performed a survey and found that in 2008 only 6.7% of the patients with head and neck cancers and 7.5% of the patients with prostate cancers received IMRT (9). Their survey included questions about the reasons for not using IMRT, and the respondents' answer showed that the main reasons for the lack of progress in using IMRT in the UK were the inadequate availability of MPs, the lack of funding, the lack of equipment and the inadequate availability of ROs. The present IMRT situations in the UK is thus similar in some ways to those in Japan, with the need for more ROs and other types of medical staff in the department of radiation oncology for the establishment of a training system for IMRT. In particular, in Japan's R-DCCHs, the proportion of implementation of IMRT is very small, and the insufficient number of medical staff working in radiotherapy departments and the small number of R-DCCHs with institute's qualification for IMRT have been serious problems. The high fee for IMRT might lead to its prevalence, but it causes the unnecessary implementation for the patients who do not receive its benefit. The appropriate indication of advanced radiation technologies should be established.

In contrast, in the USA, the rapid adoption of IMRT in the wider clinical practice has shown that there is great variability in IMRT delivery such as incorrect contouring and the various margins, dose and techniques used for anal cancer and other malignancies (10,11). The establishment of adequate IMRT requires not only sufficient number of operating staff, but also the preparation of IMRT training programs for each type of operating staff in the radiation department (12). Routsis et al. (13) proposed that the reason for the slow adoption of IMRT in the UK is associated with insufficient understanding and skills concerning IMRT among the operating staff. The Radiotherapy Development Board in the UK has begun education and training programs for IMRT for each type of medical staff in the radiation department. Our survey revealed that the proportion of IMRT for head and neck cancers in Japan was small. Especially, head and neck anatomy is complex, and the physical examination, image evaluation and radiation treatment of this region are technically demanding. Rosenthal et al. (14) emphasized the importance of the patient examination in the clinical quality assurance of head and neck radiotherapy, and they observed that a co-examination by a second head and neck cancer specialist—typically a RO or a head and neck surgeon—improved the accuracy of the radiation plan, including the target volume. The adequate IMRT for head and neck cancers requires not only a sufficient system of radiation oncology department, but also experienced head and neck surgeon's team.

SBRT uses an advanced technology to deliver a potent ablative high dose of radiation to deep-seated tumors, in a limited number of fractions to extracranial targets such as lung, liver, spine, pancreas, kidney and prostate (15). But the Japanese health insurance providers cover the cost of SBRT for only primary lung cancer, metastatic lung tumor, primary hepatic cancer, metastatic liver tumor and arteriovenous malformation of spinal cord. Accurate SBRT requires an immobilization system to prevent patient movement, accurate repositioning in each treatment, rigorous accounting of organ motion, stereotactic registration in the treatment system of the tumor targets and the normal-tissue avoidance structures and ablative high doses delivered to the patient with sub-centimeter accuracy. The implementation of accurate SBRT also requires sufficient understanding and skills among the operative staff, including ROs, MPs, RTs and RQMs. Pan et al. (6) performed an online SBRT survey for the American Society for Radiation Oncology members, and the results revealed that ROs in academic centers were more likely to cite clinical research as a motivation for SBRT adoption (59 versus 18%; $P < 0.0001$) compared with those in private practice. The other common reasons for adopting SBRT were to allow the delivery of doses higher than conventional radiation doses and retreatment. SBRT for small-sized lung cancer seems to be one of the optional treatments for medically inoperative patients (2). The rapidly aging society of Japan is a serious problem, and SBRT may be an important treatment option for elderly patients with comorbidities.

The UK guidelines emphasized the importance of QA/QC systems in the safe delivery of advanced radiotherapy technologies (12). In Japan, only $\sim$15% of the DCCHs have radiotherapy QA committees. Within each hospital, QA committees should hold regular meetings not only to manage the quality of radiotherapy, but also to maintain the safety of patients and working staff in the department of radiation oncology at all times (16–19). The QA committee should make concrete QA/QC manuals, work flow of plans for radiotherapy and educational programs for radiotherapy staff (11,17,18,20). The linear accelerator output dose was evaluated by a trusted third party in less than one-half of the DCCHs in Japan. The International Atomic Energy Agency and World Health Organization have measured the output dose of linear accelerators, and >60% of institutions worldwide which have linear accelerators are evaluated by these trusted third-party organizations (18). From an international viewpoint, the QA/QC systems in Japanese hospitals are insufficient. An adequate QA/QC system should be established in each hospital for the use of advanced radiotherapy technologies.

Our survey has some limitations. The patient's choice of hospitals is associated with high-volume hospitals and implementation of advanced radiation technologies, and the use of advanced radiation technologies might be based on the sufficient manpower in the department of radiation oncology, physicians' abilities and the radiation treatment systems, including high-quality linear accelerator and radiation planning machine, which are appropriate for the advanced technologies, and QA/QC systems. Our survey mainly focused on the number of medical staff in the department of radiation oncology. We could not ascertain the subspecialties, license and years of experience of the medical staff, or the quality of the linear accelerators and radiation planning systems. Surveys including the year of experience of the medical staff and the details of the radiotherapy treatment systems will be helpful to clarify the problems regarding the advanced radiation technologies in Japan. We could not analyze the role of nurse in the radiotherapy department because of lack of information. A part of P-DCCH and R-DCCHs seem to have submitted wrong data to the Ministry of Health, Labor and Welfare of Japan (e.g. number of full-time ROs) in error. There are some discrepancies between the number of hospitals with the institute's qualification for advanced radiotherapy technologies and those of hospitals which used these techniques. But we could not check all of them because of large volume of data. We performed analyses using the original data.

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Conflict of interest statement

None declared.

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IMRT/ブラキセラピーの登場による前立腺癌治療方針のパラダイムシフト

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■ はじめに

前立腺癌に対する放射線治療は，コンピュータ技術の発達とともに近年急速に進歩している。本邦においても，三次元原体放射線治療（three-dimensional conformal radiotherapy：3D CRT），強度変調放射線治療（intensity-modulated radiotherapy：IMRT），画像誘導放射線治療（image-guided radiotherapy：IGRT）などの最新の技術が多くの施設に導入され，普及期を迎えている。また，2003年にヨウ素125密封小線源永久挿入療法（ブラキセラピー）が本邦でも使用可能となり，急速に全国へ普及した。前立腺に対する線量増加の有用性に関する臨床試験の結果が次々と明らかとなり，臨床現場へフィードバックされることにより，前立腺癌に対する放射線治療の照射法，線量等は急速に変化しつつある。これらの導入により大きなパラダイムシフト（PS）が起こりつつある。

本項では，高精度放射線技術およびブラキセラピーの導入により，前立腺癌放射線治療がどのように変化し，将来どのように変化していこうとしているかについて考察する。

① 前立腺癌の治療方針のPSへのIMRTの役割は?

1）線量増加

前立腺癌の外部照射におけるIMRTの重要性は明らかである。すなわち，IMRTを実施することによって，直腸の線量を低減することができ，有害事象の頻度を低下させることができる。それゆえに，安全に前立腺への投与線量を増加することが可能となる。前立腺癌は投与線量が大きいほどPSA非再発率が向上することが知られているため[1]，IMRTを実施することにより，有害事象を増加させることなくPSA非再発率を向上させることが可能となる。

これらのエビデンスの蓄積をふまえ，米国のNCCN（National Comprehensive Cancer Network）guidelineでは，2005年の時点で低リスクでは70～75 Gyが，中および高リスクについては75～80 GyがPSA非再発率を向上させるらしい（appear to be appropriate）と婉曲的な表現が用いられていた。しかし，2013年では低リスク群では75.6～79.2 Gy，中および高リスク群では最大81 Gyまでの線量増加によりPSA非再発率の改善が得られる（are appropriate）と断定的な表現が用いられており[2]，IMRTやIGRTなどを併用して，高線量を投与することがすでに標準となっている。

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〔索引用語：前立腺癌，IMRT，ブラキセラピー〕

2) 本邦の現状

コンピュータ技術が飛躍的に発展する以前は，直腸などの重要臓器に対する線量低減は，矩形の照射野に置かれた鉛ブロックで行われていたため，どうしても正常組織の線量を低減することに限界があった。しかし，前述の様に，3D CRT，IMRT などの高精度放射線技術が開発されることにより，安全により多くの線量が投与されるようになり，それに伴い，前立腺への投与線量も増加してきている。本邦における放射線治療の実態調査は，厚生労働省の研究助成金による医療実態調査研究（Patterns of Care Study：PCS）にて実施されてきた。その調査によれば，照射線量の中央値は，65 Gy（1996～1998 年）から 70 Gy（2003～2005 年）と上昇しており，より高精度な照射方法の普及に伴い，経年的に高い線量が投与される傾向にあることを示している[3) 4)]（図 1）。一方，米国での PCS 研究からの報告では，1999 年の時点ですでに前立腺への投与線量の中央値は 70 Gy を超えており[5)]，投与線量からみれば，本邦では米国と比べて数年の遅れがあった。しかし，2010 年に行われた全国アンケート調査では，3D CRT での線量の中央値は 70 Gy であったのに対して，IMRT での線量の中央値は 76 Gy であり，現在では IMRT を行う場合にはかなりの高線量が投与されているということがいえる[6)]。米国では 1 回 1.8 Gy が用いられることも多く，1 回 2 Gy が標準的に用いられる本邦との比較は慎重であるべきだが，もし仮に，前立腺癌の α/β 値が 1.5 と仮定すると，1 回 2 Gy での 76 Gy は，1 回 1.8 Gy での 80.6 Gy に相当し，本邦でも米国なみの線量増加がなされていると考えてよいであろう。

3) 有害事象

前立腺癌に対する外部照射では，線量増加によりどの程度有害事象が増加するのであろうか。Cahlon らのレビューによると[7)]，3D CRT では，70 Gy 程度の通常照射による消化器系の grade 2 以上の有害事象は 10～15%程度であるが，75～78 Gy まで線量増加を行うと 15～25%程度と増加する傾向にあることが報告されている。泌尿器系の有害事象についても，10～20%から 15～25%と同様な傾向にある。一方，IMRT にて線量増加を行う場合には，消化器系の有害事象は 3～10%程度と 3D CRT と比べて有害事象の頻度が有意に低下している報告が多い。興味深いことに，泌尿器系の有害事象の頻度は 3D CRT，IMRT のどちらで実施しても大きな差はなく，IMRT による低減効果はみられていない。一般的には IMRT を用いて線量増加を図った場合，消化器系の有害事象は低減できるが，泌尿器系の有害事象を低下させることは難しいと考えられている[7)]。このひとつの理由として，IMRT では明かに物理的に直腸線量を低減できるが，尿道などの線量低下は難しいことが挙げられる。これが通常の IMRT での線量増加の限界であろう。

❷ 前立腺癌の治療方針の PS への IGRT の役割は？

1) IGRT

放射線治療のターゲットとなる前立腺の位置は，毎回の治療ごとに変動することが知られている。前立腺の位置は，日々のセットアップエラーに加えて，直腸，膀胱容量などによっても影響される。さらに体位によっては前立腺の呼吸性移動も無視できなくなる。もし，この治療ごとの位置変動を小さくすることができれば，より小さい照射野で照射でき，有害事象を低減化できる可能性がある。

このような放射線治療時の不確定要素を低減するために，治療直前または治療中のターゲットの位置を確認して照射する，いわゆる画像誘導放射線治療（IGRT）が近年急速に普及してきた。IGRT の方法としては，金属マーカーを前立腺周囲に挿入し，治療直前に X 線透視等でマーカーの位置を確認する方法，治療装置に連携した超音波装置や CT 等により位置確認を行う方法などがある。

2010 年に実施された，本邦における IGRT，IMRT の実施状況に関するアンケート調査では，117 施設の回答のうち，71 施設にて IGRT が実施されていた[6)]。IGRT の方法は kVCT，MVCT，透視装置，超音波装置，金属マーカー等，様々な手法で行われていたが，前立腺癌の放射線治療では，前立腺または金属マーカーでの位置合わせが 37 施設（52.1%），骨情報での位置合わせが 33 施設（46.5%）であった。このうち，直腸側の PTV マージンでは，前立腺または金属マーカーでの位置合わせでは中央値 5mm（3

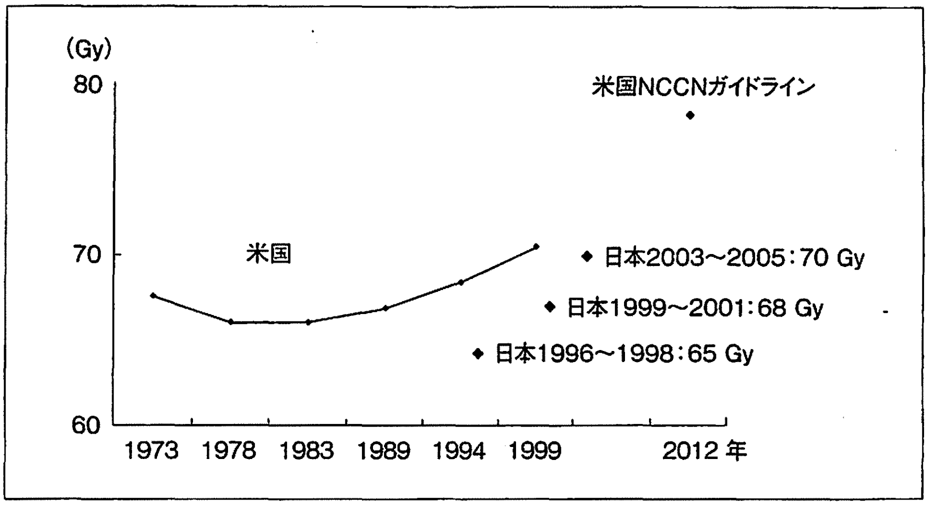

図1 前立腺癌への投与線量の年次的推移（米国および日本の医療実態調査研究の結果から）

〜7mm），骨情報での位置合わせでは中央値 6mm（3〜10mm）と，前立腺または金属マーカーでの位置合わせで小さい傾向にあった。

このように，前立腺癌の外部照射にて IGRT を実施することにより，より小さい照射野を用いることができ，それによって有害事象を低減化できる可能性がある。

2）寡分割

上述のように，IGRT を実施することのメリットのひとつは，毎回の治療ごとのセットアップエラー等による位置変動を小さくすることにより，照射野を縮小でき，有害事象低減に貢献することである。もちろん，照射野を縮小できる分，投与線量を増加させることも可能である。しかし，IMRT だけでも grade 2 以上の消化器系の有害事象は 3〜10%程度で，grade 3 以上では 1%以下である。一方，IMRT や IGRT を利用して直腸側のマージンを縮小したからといって，尿道の線量を低減することは難しく，泌尿器系の有害事象の発生頻度を改善することは困難であろう。

実は，IGRT のもうひとつの利点として，1 回線量を増加させ，治療回数を減らす（寡分割照射，hypofractionation）ことにより治療成績向上につながる可能性が指摘されている。

放射線に対する感受性の指標として α/β 比が知られており，通常の悪性腫瘍は 10 程度，直腸などの正常組織では 2〜3 程度とされている。通常の腫瘍に対する放射線治療では，1 回線量を大きくすると，α/β 比の小さい正常組織の有害事象の可能性が高くなり，腫瘍のコントロール率向上のメリットよりもマイナス面のほうが大きいとされている。よって歴史的には 1 回線量を 1.8〜2 Gy とし，総線量 60〜70 Gy を照射するスケジュールが選択されてきた。しかし，前立腺癌細胞は増殖速度が遅いため，前立腺癌の α/β 比は通常の腫瘍に比べて非常に小さいと推測されている[8]。もしこの予想が正しく，前立腺癌の α/β 比が直腸や尿道などよりも小さいのであれば，1 回線量をより大きくし，分割回数を少なくすればするほど治療可能比が高くなることが推測される。たとえば，正常組織の α/β 比を 3 と仮定し，前立腺癌の α/β 比が 1.5 であるとすれば，1 回 2 Gy，総線量 70 Gy での有害事象が起こる確率は，1 回 7 Gy での総線量 35 Gy と同等と推定されるが，1 回 7 Gy，総線量 35 Gy の前立腺癌に対する治療効果は，2 Gy での 85 Gy 程度に相当すると計算できる。すなわち，1 回線量を増加させることにより，有害事象の危険性は増加させずに，治療効果のみを高めることが可能となるのである。

しかし，ここで問題となるのが，位置精度である。通常分割での前立腺癌に対する照射回数は 37〜40 回程度であり，セットアップエラー，呼吸性移動や直腸容積などによる前立腺位置の変動があっても，多数回の照射により平均化されるため，それほど治療成績に影響しない。しかし，照射野のマージンが小さい

場合，1回線量をより大きくし，分割回数を小さくすればするほど，前立腺の位置の不確定要素が治療成績に大きく関係してくるようになる[9]。すなわち，前立腺の位置の不確定要素を解決しない限り，回数を減らすことによってかえって治療成績が低下する危険性がある。よって，毎回の前立腺の位置の不確定要素を低減させるIGRTを用いてこそ，寡分割照射を安全にかつ効果的に実現できると考えられている。

前立腺癌に対する寡分割照射についての後ろ向きの報告は数多くなされている。Kupelianらは，超音波装置を使ったIGRTにて前立腺の位置を同定し，IMRTにて1回2.5 Gy，total 70 Gyを照射した770例についての後ろ向きの治療成績を報告している[10]。5年PSA無再発率は82%と良好であり，grade 2以上の直腸障害，尿路系障害はそれぞれ4.5%，5.2%と通常分割法と同程度であったとしている。

現在，寡分割照射の有効性を確認するために，IGRT，IMRTを使った寡分割照射の臨床試験が数多く実施されている[11]。

本邦でも，厚生労働科学研究費補助金がん臨床研究事業「放射線治療期間の短縮による治療法の有効性と安全性に関する研究」の援助により，前立腺癌に対するIMRT/IGRT併用寡分割照射法の第Ⅱ相臨床試験が開始されている。これは，前立腺癌に対して前立腺合わせでのIGRTを用いて，IMRTによる少数分割法70 Gy/28回（1回2.5 Gy）が有効かつ安全であるかを探索的に検討する試験であり，Primary endpointを5年遅発性有害事象発生割合としている。対象は低・中リスク（T1-2c and PSA =＜20 and G =＜7）または高リスク因子で危険因子（T3a，20＜PSA =＜30，G = 8，9）がひとつのみの症例で，2012年6月より症例登録が開始されている。これらの結果次第によっては，寡分割照射がスタンダードのひとつとなる可能性を秘めている。

また，前立腺癌に定位的に放射線治療を行い，さらに少ない回数で，1回大線量を投与する試みもある。Katzらは，前立腺癌304例（低リスク211例，中リスク81例，高リスク12例）に対して，サイバーナイフにより定位的に35～36.5 Gy/5分割を照射し，5年PSA無再発率は低リスク97%，中リスク90.7%，高リスク74.1%と良好な治療成績であったと報告している[12]。サイバーナイフでは，さらに尿道の線量も低減することができ，高線量率組織内照射のような線量分布を形成できることが特徴である。このような大線量，少数分割はいまだ研究的な治療法であるが，欧米を中心に臨床試験が進行している。

❸ 前立腺癌の治療方針のPSへのブラキセラピーの役割は？

前立腺癌に対する低線量率線源を用いた密封小線源永久挿入療法（ブラキセラピー）は，欧米では古くから実施されていたが，ようやく本邦でも2003年にヨウ素125による治療が可能となった。2006年により保険収載されてからは急速に全国へ普及している。従来，ブラキセラピーは，低リスクおよび中リスク前立腺癌が主な適応であり，一般的には高リスク前立腺癌は適応とはなっていなかった。前述のNCCN guidelineによれば，2004年では低リスクにはブラキセラピー単独，中リスクにはブラキセラピーと外部照射40～50 Gyが推奨され，高リスクはブラキセラピーには適さない（are poor candicates）とされていた。しかし，2007年には，高リスクの一部の患者には外部照射とホルモン療法とを併用することによって効果的かもしれない（it may be effective ）との表現に変わり，2013年では，高リスク例は，ブラキセラピーと外部照射40～50 Gy，ホルモン療法にて治療されるかもしれない（may be treated ）との表現になっている[2]。

このように，ガイドラインが変化してきたのは，高リスク前立腺癌でも十分な高線量を投与すればPSA非再発率の改善が期待できるエビデンスが蓄積されてきたからである。Grimmらは，過去に報告された，前立腺癌に対する手術，外部照射，ブラキテラピーの膨大な論文を調査し，高リスク前立腺癌においても，ブラキテラピー + 外部照射 ± ホルモン療法が，手術，ブラキテラピー，外部照射単独と比較して，優れている傾向にあったことを報告している[13]。

本邦も，高リスク前立腺癌に対してブラキテラピーにて治療される症例は増加しており，また，高リスク前立腺癌に対する小線源・外照射併用放射線療法における補助ホルモン治療の有効性に関する臨床研究（TRIP試験）も進行している。この試験結果が明

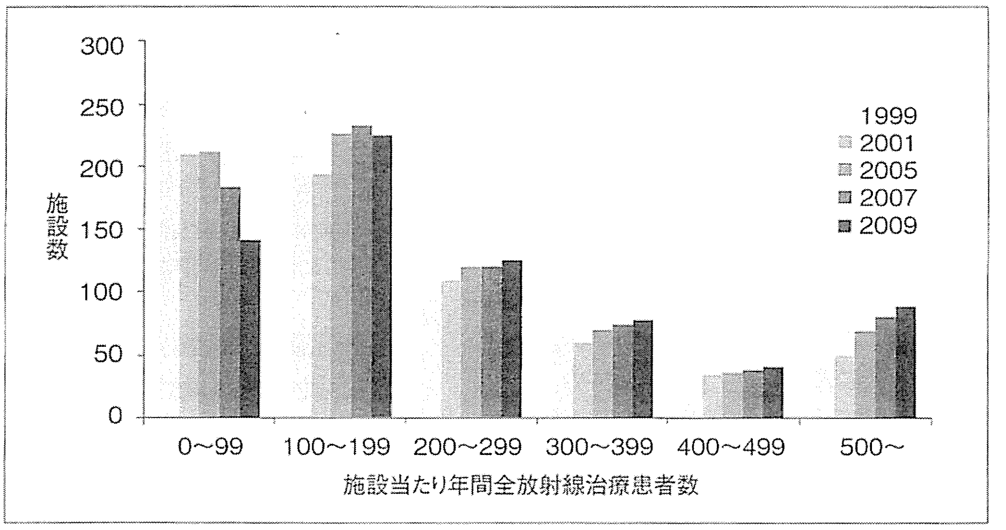

図2　施設当たり年間全放射線治療患者数の推移

かとなれば，高リスク前立腺癌に対するブラキテラピーの有用性が確立するであろう。

❹ 高精度放射線治療やブラキテラピーの普及と質の担保への課題

前立腺癌のブラキテラピーに関しては，2003年に治療が開始されて以来，一施設当たりの年間治療数がどのように変化しているかの調査が施行されている[14]。治療を開始してから1年以上が経過した施設数は，2004年ではわずか2施設で計269例が治療されていたが，2005年には23施設で1,412例が治療され，2008年には83施設で2,783例，2011年には109施設で3,793例が治療されていた。しかし，一施設当たりの年間治療患者数の中央値は2005年では42例，2008年では25例，2011例では24例と年々低下し，特に年間治療数が24例以下（月2例以下），12例以下（月1例以下）の施設は急増していたが，年間48例以上を治療する施設数は大きな変化はなかった[14]。一般的に悪性腫瘍の治療においては年間治療数と治療成績との相関があるとの報告もある[15]。しかし，日本泌尿器科学会，日本放射線腫瘍学会の協力のもと，安全講習会，技術講習会などが数多く行われ，その臨床的質を保つ多大な努力が払われており，本邦での前立腺癌のブラキテラピーに関しては，年間治療数と治療成績との相関関係ははっきりとは証明されていない。

一方，前立腺癌の外部照射では，詳細なデータについて報告されたものはない。そこで，日本放射線腫瘍学会から定期的に公表されている構造調査から，各年ごとの一施設当たり年間全放射線治療患者数の推移を求めて示したものが図2である。前立腺癌の治療数は不明であるため，単に全放射線治療患者数をみたものではあるが，1999～2009年までに治療数が年間100例に満たない施設数は減少している一方，年間500例以上を治療している施設数は増加している。しかし，これらの施設におけるIMRTなどの高精度放射線治療がどのように実施されているかなどについての質的な評価は今後正しくなされていくべきであろう。

■ おわりに

これまで述べてきたように，外部照射については，線量増加そして寡分割照射へ，ブラキテラピーについては高リスクへの適応拡大へと大きなPSが起きている。今後はさらに陽子線治療，炭素線治療などの粒子線治療が加わってくる。

2007年に定められたがん対策基本計画では，癌医療の均てん化の促進がうたわれ，放射線療法および化学療法の推進並びに医療従事者の育成の方向性が定められた。2012年度にはその見直しが行わ

れ，放射線療法の質を確保し，地域格差を是正し均てん化を図るとともに，人員不足を解消する取組に加えて，一部の疾患や強度変調放射線治療などの治療技術の地域での集約化を図る，とされた。今後は単に，高精度放射線治療が実施できるというだけではなく，高い質を保つために，集約化も含めた放射線治療の効率化を模索していく必要があろう。

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Summary

A paradigm shift in radiation treatment strategy for prostate cancer by intensity-modulated radiotherapy and brachytherapy

A paradigm shift in radiation treatment strategy for prostate cancer has been stimulated by precise radiotherapy including intensity-modulated radiotherapy (IMRT) and brachytherapy. Using IMRT technique, dose escalation has been achieved without increasing late gastrointestinal toxicities. Hypofractionation treatment protocols for prostate cancer with IMRT and image-guided radiotherapy may have a therapeutic advantage. Low dose rate brachytherapy may offer a better outcome for high-risk prostate cancer. However, in addition to the introduction of new technologies, it is also important to evaluate the quality of new treatment techniques in each institution.

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Diffusion pattern of low dose rate brachytherapy for prostate cancer in Japan

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Permanent implant brachytherapy for prostate cancer using iodine-125 seeds was adopted in Japan in 2003. Here, we report on the diffusion pattern of this treatment in Japan since 2003. We examined the annual numbers of prostate cancer patients per hospital in Japan, who were treated with iodine-125 seed implant brachytherapy with or without external beam radiation therapy between 2003 and 2011. The hospitals were excluded from the count if brachytherapy was begun in a hospital within the given year, and thus was only available for part of the year. In 2004, 269 patients were treated by brachytherapy at only two hospitals. However, the numbers increased rapidly. A total of 1412 patients were treated at 23 hospitals in 2005, 2783 patients were treated at 83 hospitals in 2008, and 3793 patients were treated at 109 hospitals in 2011. The mean/median numbers of patients treated per hospital were 61.4/42 in 2005, 33.5/25 in 2008, and 35.0/24 in 2011. The number of hospitals where 24 or fewer patients were treated in a year increased. On the other hand, the number of hospitals with a volume of >48 patients per year was stable. Because a relationship between provider volume and outcomes following oncological procedures was shown, a careful evaluation of the effectiveness of permanent implant brachytherapy for prostate cancer is needed. (*Cancer Sci*, doi: 10.1111/cas.12168, 2013)

When a medical technology, the usefulness of which has been established, is adopted in a country, how does the technology diffuse into medical practice? The speed and degrees of the diffusion depend upon many factors: consumer demand, promotional efforts of technology manufacturers, medical education, health insurance and payment systems, and governmental regulatory policies.[(1)]

Permanent implant brachytherapy for prostate cancer using iodine-125 (I-125) seeds was adopted in Japan in 2003.[(2)] The advantages of brachytherapy had been well recognized,[(3)] and the expectation for treatment was very high among Japanese urologists and radiation oncologists. In addition, the Cancer Control Act was approved in June 2006. Based on this law, the Basic Plan to Promote Cancer Control Programs was approved. One of its basic concepts is the equalization of cancer medical services including radiation therapy. This basic plan has stimulated the installation of new radiation therapy equipment at core hospitals.

In this study, we report on the diffusion pattern of permanent implant brachytherapy for prostate cancer in Japan since 2003, focusing in particular on the changes in the annual numbers of patients treated by brachytherapy per hospital since 2003.

Materials and Methods

We examined the annual numbers of prostate cancer patients per hospital in Japan, who were treated with I-125 seed implant brachytherapy with or without external beam radiation therapy. The use of palladium-103 (Pd-103) seeds, which is common in the United States, is not permitted in Japan. To elucidate the actual number of patients treated in a year, the hospitals were excluded from the count if brachytherapy was begun in a hospital within the given year, and thus was only available for part of the year. Because brachytherapy using I-125 seeds was adopted in Japan in 2003, the annual numbers of patients treated with brachytherapy between 2004 and 2011 were examined. These data were estimated from the database by Japanese Prostate Permanent Seed Implantation Study Group.[(4)] In Japan, I-125 seeds are supplied from two radiation source supply companies to medical institutions via the Japan Radioisotope Association (JRIA). Their database was also used to confirm the estimation.

Results

The total estimated number of patients treated with brachytherapy at hospitals where more than 1 year had passed since brachytherapy was first made available is shown in Table 1. In 2004, 269 patients were treated by brachytherapy only in two hospitals. However, the numbers increased rapidly. A total of 1412 patients were treated at 23 hospitals in 2005, 2783 patients were treated at 83 hospitals in 2008, and 3793 patients were treated at 109 hospitals in 2011.

Figure 1 shows the number of patients treated per hospital in 2005, 2008, and 2011. The mean/median number of patients treated per hospital was 61.4/42 in 2005, 33.5/25 in 2008, and 35.0/24 in 2011. Almost half of the patients in Japan were treated at the top six hospitals in 2005, at the top 18 hospitals in 2008, and at the top 22 hospitals in 2011. The number of hospitals in which 24 or fewer patients were treated in a year (i.e., two patients per month) was four in 2005, 40 in 2008, and 60 in 2011.

Figure 2 shows the distribution of the annual number of patients treated with brachytherapy per hospital from 2004 to 2011. The percentage of hospitals is also shown according to the number of patients per year in Table 1. The number of hospitals where 24 or fewer patients were treated in a year increased rapidly, in particular after 2006. On the other hand, the number of hospitals with a volume of >48 patients per year was stable.

Discussion

Although the advantages of brachytherapy were well recognized among Japanese urologists and radiation oncologists, low dose rate brachytherapy for prostate cancer using I-125 or Pd-103 seeds had not been allowed in Japan, because of the

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Table 1. Total number of hospitals/patients and the breakdown of hospitals according to the number of patients per year, among hospitals where more than 1 year has passed since brachytherapy was first made available

	2004	2005	2006	2007	2008	2009	2010	2011
Total number of hospitals	2	23	38	60	83	94	102	109
Estimated total number of patients	269	1412	1795	2516	2783	3112	3442	3793
Percentage of hospitals								
>96 patients/year	50.0	17.4	7.9	5.0	4.8	7.4	6.9	6.4
48–96 patients/year	50.0	30.4	28.9	23.3	10.8	10.6	11.8	11.9
24–48 patients/year	0.0	34.8	36.8	35.0	36.1	31.9	24.5	26.6
12–24 patients/year	0.0	17.4	10.5	18.3	32.5	28.7	35.3	33.9
≤ 12 patients/year	0.0	0.0	15.8	18.3	15.7	21.3	21.6	21.1

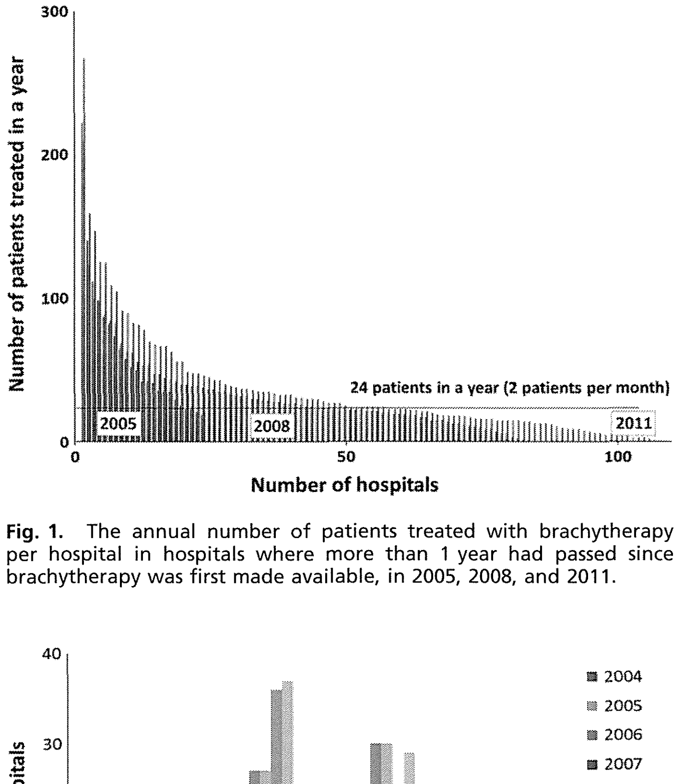

Fig. 1. The annual number of patients treated with brachytherapy per hospital in hospitals where more than 1 year had passed since brachytherapy was first made available, in 2005, 2008, and 2011.

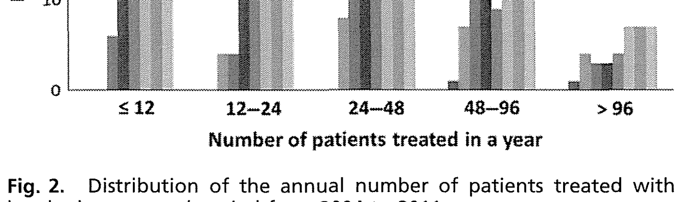

Fig. 2. Distribution of the annual number of patients treated with brachytherapy per hospital from 2004 to 2011.

strict Japanese laws on radiation safety.[2] However, after long discussions between members of the Japanese Society for Therapeutic Radiology and Oncology (JASTRO), the Japanese Urological Association (JUA), the Ministry of Health, Labor, and Welfare, and the Ministry of Education and Science, permanent implant brachytherapy for prostate cancer using I-125 seeds was approved in July 2003.[2] Even after permanent implant brachytherapy was permitted in Japan, only a limited number of institutions started the treatment, in part because of the very low price fixed by the Japanese health insurance system.[2] However, after a higher price for brachytherapy was approved by the Japanese health insurance system in April 2006, many institutes started providing the treatment, as shown in Figures 1 and 2. In particular, the number of hospitals with a low volume of patients increased.

Oncological procedures may have better outcomes if performed by high-volume providers. Killeen *et al.*[5] revealed that high-volume providers have significantly better outcomes for complex cancer surgery, in particular for pancreatectomy, esphagectomy, gastrectomy and rectal resection. In Japan, influences of hospital procedure volume on cancer survival have been under intense investigation using The Osaka Cancer Registry's data.[6–10] As for localized prostate cancer, Jeldres *et al.*[11] examined the effect of annual and cumulative provider volume on the rate of use of secondary therapies using a cohort of 3907 patients treated with definitive external-beam radiation therapy. They demonstrated lower rates of secondary therapy for providers with an annual provider volume >10 cases and for those with a cumulative provider volume >200 cases. Taussky *et al.*[12] showed that seed migration in prostate brachytherapy depended on experience and technique. Chen *et al.*[13] concluded that patients treated with brachytherapy by higher-volume physicians were at lower risk for recurrence and prostate cancer death. Interestingly, they showed that there was no significant association between hospital volume and recurrence, prostate cancer death or all deaths.

Japanese urologists and radiation oncologists have made a great effort to maintain the safety and quality of permanent implant brachytherapy for prostate cancer. JASTRO, JUA, and the Japan Radiological Society (JRS) have published guidelines for brachytherapy (in Japanese).[2,14] These guidelines require physicians involved in this treatment to attend an education course held by JRIA. The guidelines also strongly recommend that each institution administering this treatment should have a urologist certified by the JUA and a radiation oncologist certified by JASTRO and/or JRS in full-time employment.[2] In addition, training workshops have been held at regular intervals to maintain or improve the technical level of permanent implant brachytherapy for prostate cancer. It is not still clear whether the provider volume is associated with outcomes following brachytherapy for prostate cancer in Japan.

The diffusion of a new medical technique depends upon many factors including consumer demand and health insurance and payment systems.[1] In Japan, although health care is under the management of an obligatory insurance system, it is within the framework of a capitalist economy.[15] Given this situation, a new "Basic Plan to Promote Cancer Control Programs" was

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approved in 2012. In addition to the further promotion of radiation therapy and the training of doctors/staff members specializing in this area, the plan recommends the centralization of high-precision radiation therapy including intensity-modulated radiation therapy (IMRT) in each medical region.

There are several new options for patients with clinically localized prostate cancer including robotic surgery, brachytherapy, and IMRT. The majority of the published papers have shown similar treatment results in large-scale institutions. However, after the diffusion of a new medical technique, evaluation of the quality remains an important issue. Therefore, a nationwide multi-institutional cohort survey for prostate brachytherapy focusing on the effect of provider volume on treatment efficacy and safety is needed.

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Disclosure Statement

The authors have no conflict of interest.

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Review Article

Stereotactic Body Radiation Therapy for Stage I Non-small-cell Lung Cancer: A Historical Overview of Clinical Studies

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Because of difficulties with stabilization, breathing motion and dosimetry, stereotactic body radiotherapy for lung cancer has only been practiced for the past 15 years. However, a large amount of case data has rapidly been accumulated in recent years. Stereotactic body radiotherapy for Stage I non-small-cell lung cancer has been actively investigated in inoperable patients since around 1995, and a number of clinical trials have been undertaken. Early studies from 2001 presented a 3-year local control rate of 94% and a 3-year overall survival rate of 66% for patients receiving 50–60 Gy in 10 fractions. Another study in 2005, using 48 Gy in four fractions, presented a 3-year local control rate of 98% and 3-year overall survival rates of 83% for Stage IA patients and 72% for Stage IB patients. A multi-institutional study showed favorable local control and survival rates in a group receiving a biologically effective dose of 100 Gy. A dose-escalation study in the USA suggested a maximum tolerated dose of 60 Gy in three fractions. A Phase II clinical trial (RTOG0236) followed, with a reported 3-year local control rate of 98% and a 3-year overall survival rate of 56% for patients who received 60 Gy in three fractions. A Japanese Phase II clinical trial (JCOG0403) investigated a dose of 48 Gy in four fractions among 165 Stage IA patients, showing a 3-year survival rate of 76% and a 3-year locally progression-free survival rate of 69% for the operable group. An overview of past clinical trials in stereotactic body radiotherapy for Stage I non-small-cell lung cancer and current issues is presented and discussed.

Key words: stereotactic radiotherapy – non-small-cell lung cancer – Stage I – clinical study – review

INTRODUCTION

Lung cancer is one of the most prevalent cancers in the world and is the leading cause of cancer deaths in Japan for both men and women. In recent years, detection rates for early-stage lung cancer have improved as computed tomography (CT) examination has become more common. At present, the standard treatment for early-stage lung cancer is surgery. However, as the rapidly aging population increases the number of medically inoperable cases, the efficacy and safety of stereotactic radiotherapy, a less invasive treatment, have attained critical importance. This paper presents an overview of past clinical trials in stereotactic body radiotherapy (SBRT) for Stage I non-small-cell lung cancer (NSCLC) and current issues.

DEFINITION AND HISTORY OF SBRT

The use of stereotactic radiotherapy to treat extracranial tumors began with 40 years of using stereotactic radiosurgery with a gamma knife on cranial tumors. If stereotactic radiotherapy can be substituted for surgical resection of a solitary brain metastasis (1), then logically a similarly sized primary lesion could also be efficiently controlled using the same method. SBRT allows for the application of large doses of radiation to the tumor with minimal exposure of surrounding organs. Rapid advances in the capabilities of radiotherapy equipment during the 1990s enabled three-dimensional irradiation. Stereotactic irradiation methods were gradually trialed for lung cancer from around 1995, with increases in stability and precision, and the development of related technologies such as image-guided navigation. Blomgren et al. (2) first reported how to perform stereotactic radiotherapy on body tumors. Uematsu et al. began clinical trials of stereotactic radiotherapy on body tumors in Japan with the development of a combined CT and linear accelerator unit (3) in 1996. Shirato et al. developed a method for tracing a fiducial marker placed near a tumor, installing a device that allowed real-time observation during irradiation in the irradiation room, and applied this method to SBRT (4). As a result of developments like these, SBRT is now showing promise as a radical treatment modality, mainly for lung cancers. Numerous clinical trials are currently underway. SBRT is being applied not only to lung cancers, but also to diverse other body tumors, including the liver, pancreatic, prostate and metastatic cancers, as well as to spinal arteriovenous malformations. Radiotherapy has recently achieved higher levels of accuracy in covering tumors, thanks to advances in respiratory motion management (5) and various image-guidance techniques (6). The cyberknife, originally designed for use on cranial lesions, is now good enough to also be applied to cervical and body lesions (7).

In 2004, Japanese health insurance policies began to cover SBRT using linear accelerators. Since then, the number of patients receiving SBRT has increased substantially. The specified treatment cost was 630 000 yen (~8000 USD), which covered medical services for the entire process, starting from treatment planning. The four conditions the radiotherapy must fulfill are as follows: (1) stability and reproducibility of the focal position of irradiation within 5 mm between treatment planning and actual treatment; (2) measures for preventing respiratory motion error (additionally approved for coverage by Japanese health insurance from 2012 in Japan); (3) dose concentration on the tumor by multi-directional, three-dimensional convergence of multiple beams and (4) short treatment period (generally <2 weeks) with a single high-dose treatment (generally ≥5 Gy). For lung cancer, coverage by the Japanese health insurance system is applied for: primary lung cancer with no metastatic lesions and diameter ≤5 cm; and up to three masses of metastatic lung cancer each ≤5 cm in diameter, with no other foci. According to a national survey conducted by Nagata et al., SBRT was being performed at 53 institutions in Japan as of 2005. Overall, 2104 patients had received treatment for lung cancer using stereotactic radiotherapy (including for primary lung cancer in 1111 patients, metastatic lung cancer in 702 patients and unknown histology in 291 patients) (8).

PHASE I (DOSE ESCALATION) STUDY

No rigorous Phase I clinical trial to identify the maximum tolerated dose of SBRT for lung cancer has been conducted in Japan. The results of retrospective study, discussed below, have suggested sufficient local control with biologically effective dose (BED) >100 Gy (9). The prescribed dose for clinical trials or medical practice was established with this trial in Japan. The most frequent SBRT dose fractionation for Stage I NSCLC in the previous survey by Nagata et al. was 12 Gy, administered four times (8).

However, in the USA, the maximum tolerated dose was set at 20 Gy, administered three times, based on a dose escalation study that started from 8 Gy, administered three times (10,11). The dose-limiting toxicities reported at the time included dermatitis, pericarditis, pneumonitis and bronchial necrosis. Some reports have described decreased local control using the Japanese standard SBRT dose for larger lesions (12,13), and a dose escalation study (JCOG0702) is being conducted in Japan for T2N0M0 NSCLC.

RETROSPECTIVE STUDY FOR MEDICALLY INOPERABLE PATIENTS

Needless to say, the standard treatment for Stage I NSCLC is surgery. SBRT was used only for inoperable patients in early phase. Table 1 shows the results of retrospective studies of SBRT for mostly inoperable patients (12,14–17). These studies showed variations in irradiation techniques and prescribed doses, but the results suggested that local control exceeded 90% when treatment doses were sufficient. However, the survival time was not long enough, as discussed below, and insufficient information was obtained regarding local control rates in the long-term follow-up. Survival rates appeared highly variable and were generally inferior to surgical outcomes. This may be partly attributable to a high number of deaths due to other causes, because of the poor health condition of inoperable elderly patients.

RETROSPECTIVE STUDY FOR OPERABLE PATIENTS

A certain proportion of patients are operable but choose to undergo SBRT. One retrospective study extracted operable cases from accumulated multi-institutional data in Japan (13,18). Doses achieving BED >100 Gy showed more favorable local control and survival rates than doses <100 Gy. The 87 operable cases in the group with BED >100 Gy (median age, 74 years) displayed 5-year locally progression-free and 5-year overall survival rates of 90% and 74% for Stage IA and 89% and 58% for Stage IB, respectively, at a median follow-up duration of 58 months. Other illnesses were a major cause of death. Grade 3 toxicity or above was found in only 2% of patients, but the true level of toxicity

Table 1. Results of retrospective studies of stereotactic body radiotherapy for mainly inoperable patients with T1-3N0M0 non-small-cell lung cancer

Author	Pt. no	Age min–max (median)	Dose Gy/fraction (fx)	Median follow-up (months)	Overall survival rate	Local control	Toxicity
Uematsu (14)	50	54–86 (71)	50–60 Gy/5–10 fx	36	66% (at 3 year)	94%	Rib fracture: 2%
Wulf (15)	20	58–82 (68)	26–37.5 Gy/1–3 fx	11	32% (at 2 year)	92%	No complications > RTOG grade 2
Onishi (16)	35	65–92 (71)	60 Gy/10 fx	13	64% (at 2 year)	88%	NCI-CTC (V2) grade 3 penumonia: 9%
Onimaru (12)	28	52–85 (76)	48 Gy/4 fx	27	IA 82% IB 32% (at 3 year)	64%	NCI-CTC (V3.0) grade 3 pneumonia: 4%
Takeda (17)	63	56–91 (78)	50 Gy/5 fx	31	IA 90% IB 63% (at 3 year)	95%	NCI-CTC (V3.0) grade 3 pneumonia: 3%

might not have been sufficiently evaluated due to the retrospective nature of the study.

PHASE II CLINICAL STUDY FOR MEDICALLY INOPERABLE PATIENTS

Many Phase II clinical trials for medically inoperable regular patients were conducted one after the other based on favorable local control results in early retrospective studies, as shown in Table 1. Table 2 shows the major results of various Phase II trials (19–25). Prescribed doses differ between Japan and the West, but variations in survival rates and local control rates were generally the same as those from retrospective research. A multi-institutional clinical trial undertaken in the USA (Radiation Therapy Oncology Group (RTOG)-0236) found a local control rate of 98%, a 3-year survival rate of 56% and grade 3 or 4 toxicity in 16.3% (24). Some studies showed a higher proportion of grade 3 toxicity and above than the retrospective research. This may be due to regular follow-ups with no missing values in prospective research. In particular, a study of SBRT with 60–66 Gy in three fractions for subjects including patients with centrally located lung tumors near the trachea or lobar bronchus found that 14 of 70 cases (20%) experienced toxicity of grade 3 or above, 6 cases showed grade 5 toxicity (pneumonia, 4 cases; pericarditis, 1 case; hemoptysis, 1 case) and 4 of these 6 cases had centrally located cancers (20). Accordingly, a dose escalation study has been conducted with the prescribed dose for centrally located lung cancer starting from 7.5 Gy administered eight times (JROSG10–1) in Japan and 10 Gy administered five times (RT0G0813) in the USA.

PHASE II STUDY FOR MEDICALLY OPERABLE PATIENTS

In 2004, a Japanese Radiation Treatment Group (representative: Masahiro Hiraoka) was first created in the Japan Clinical Oncology Group (JCOG) and a Phase II clinical trial of SBRT was initiated for NSCLC in clinical Stage IA (JCOG0403). All cases were pathologically confirmed, and two groups were registered, comprising patients with medially operable and inoperable tumors for standard surgery. The medically operable group reached the target number of registrations early and Nagata et al. presented preliminary results after a 3-year follow-up in 2010 at the annual meetings of the American Society for Therapeutic Radiology and Oncology (26) and the Japan Lung Cancer Society. This was the first Phase II clinical trial in the world for a medically operable case group. In JCOG0403, 48 Gy administered in four fractions was prescribed for the isocenter. Sixty-five patients were included between July 2004 and January 2007. The mean age of participants was 79 years (range, 50–91 years), with 45 men and 20 women. The mean tumor diameter was 21 mm (range, 10–30 mm), and histological examination revealed 40 adenocarcinomas, 21 squamous cell carcinomas and 4 others, with performance status (PS) 0 in 43, PS 1 in 20 and PS 2 in 2. The median observation period was 45 months, the 3-year overall survival rate was 76% and the 3-year locally progression-free rate was 69%. Treatment-related toxicities of grade 3 and above included one case of chest pain, two cases of dyspnea, one case of hypoxia and two cases of radiation pneumonitis. No cases of toxicity of grade 4 or above were identified.

PHASE III RANDOMIZED STUDY COMPARING SBRT WITH SURGERY

Two randomized multi-institutional studies comparing SBRT with surgery on operable patients preceded the announcement of JCOG0403. One was a randomized study comparing CyberKnife treatment to surgical resection for Stage I NSCLC (STARS) based in MD Anderson Cancer Center in the United States (27), while the other was a randomized Phase III trial, Radiosurgery or Surgery for operable Early-stage (Stage IA) non-small-cell Lung cancer (ROSEL) based in VU University Medical Center in Netherlands (28). These experimental studies did not have sufficient rationales affirming the randomization process between surgery and SBRT and the registration of patients has encountered difficulties.

Table 2. Results of prospective Phase II trials of stereotactic body radiotherapy for mainly inoperable patients with Stage I non-small-cell lung cancer

Author	Pt. no	Age min–max (median)	Dose Gy/fraction (fx) (prescription)	Median follow-up (months)	Three-year overall survival rate	Three-year local control	Toxicity
Nagata (19)	42	51–87 (77)	48/4 (tumor center)	30	IA 83%, IB 72%	98%	NCI-CTC (V2) grade 2 pneumonia: 4%
Timmerman (20)	70	51–86 (70)	60–66 Gy/3 fr	17	55% (at 2 year)	95% (at 2 year)	NCI-CTC (V2) grade 3–5: 20% grade 5: 8.5%
Zimmermann (21)	68	59–92 (76)	37.5 Gy/3–5 fx (60% isodose)	18	53%	94%	RTOG grade 3 pneumonia: 6% rib fracture: 3%
Fakiris (22)	70	not shown	T1: 60 Gy/3 fx T2: 66 Gy/3 fr (80% isodose)	50	43%	94%	peripheral; NCI-CTC (V2) grade 3–5: 10% central; NCI-CTC (V2) grade 3–5: 27%
Baumann (23)	57	59–87 (75)	45 Gy/3 fx (67% isodose)	35	60%	92%	NCI-CTC (V2) grade 3: 28%
Timmerman (24)	55	48–89 (72)	60 Gy/3 fx (D95)	34	56%	98%	grade 3 NCI-CTC (V3.0): 12.7% grade 4 NCI-CTC (V3.0): 3.6%
Ricardi (25)	62	53–83 (74)	45 Gy/3 fx (80% isodose)	28	57%	92%	pneumonia > RTOG grade 3: 3% rib fracture 2%

CURRENT CLINICAL TRIALS

Over 50 clinical trials on SBRT for early lung cancer are now underway around the world. The major studies are listed in Table 3. RTOG0618 is a Phase II study for medically operable patients with T1-3N0M0 NSCLC, RTOG0813 and JROSG10-1 are dose escalation studies regarding doses for centrally located lung cancer in close proximity to the trachea and lobar bronchus, RTOG0915 is an investigation into the safety and efficacy of single-fraction and four-fraction SBRT for Stage I NSCLC, and the American College of Surgeons Oncology Group (ACOSOG) Z4099/RTOG1021 is a randomized trial comparing SBRT with partial lung resection with or without brachytherapy in cases with a high risk for receiving lobectomy.

DISCUSSION

The processes used in radiation oncology can be divided into three successive steps: (1) treatment simulation, in which all relevant information on target definition is incorporated; (2) treatment planning, which involves selection of delivery technique and approach for optimizing target coverage and normal tissue avoidance; and (3) radiation delivery and treatment verification. Many technological developments have been made to enable SBRT for small lung tumor, including the following: (a) high precision and speed in calculation algorithms for treatment plans; (b) high dose rate and smaller size of irradiation equipment; and (c) increased precision in respiratory motion management.

Table 3. Major prospective studies of SBRT for lung cancer

Trial name	Protocol
RTOG0236 (closed)	Phase II study for inoperable T1-3N0M0 NSCLC (60 Gy/3 fx)
JCOG0403 (closed)	Phase II study for operable and inoperable T1N0M0 NSCLC (48 Gy/4 fx)
RTOG0618	Phase II study for operable T1-3N0M0 NSCLC (60 Gy/3 fx)
JCOG0702	Dose escalation study for T2N0M0 NSCLC (started from 40 Gy/4 fx)
RTOG0813	Dose escalation study for centrally located Stage I NSCLC (started from 50 Gy/5 fx)
JROSG10-1	Dose escalation study for centrally located Stage I NSCLC (started from 60 Gy/8 fx)
RTOG0915	Randomized study (34 Gy/1 fx versus 48 Gy/4 fx for inoperable Stage I NSCLC)
ACOSOG Z4099/ RTOG1021	Randomized study (SBRT versus surgery ± brachytherapy) for high risk patients)
STARS	Randomized study (SBRT versus surgery) for operable Stage I NSCLC)
ROSEL	Randomized study (SBRT versus surgery) for operable Stage I NSCLC)

New dose-calculation programs more accurately predict the doses to which normal tissues are exposed, thereby overcoming the limitations of older software that over- or underestimated dose distributions in inhomogeneous tissues such as the lungs by more than 10% (29). Accurate dose estimation using these new algorithms will allow for better correlation of dose with toxicity, allowing higher doses to be delivered more safely (30).

Since 2003, four-dimensional (4D) CT scanners have become commercially available, and are increasingly replacing conventional CT for treatment simulation. The use of 4DCT allows organ motions to be observed and quantified (31). When 4DCT information is combined with daily patient position verification, safety margins around tumors can be significantly reduced, thereby decreasing target volumes. In addition, 4DCT allows for the evaluation of strategies such as respiration-gated radiation therapy to minimize target volumes in individual patients (32). When tumors show significant movement, enlargement of the planning target volume (PTV) can be circumvented by limiting treatment to only specific phases of respiration (33) or tracking the beam to the moving tumor (34).

Current approaches to image-guided radiation therapy aim to monitor patient and tumor positions during the course of treatment, an approach that is mandatory when using very small safety margins. Many commercial imaging systems are available for installation in treatment rooms, and are used to verify patient positioning using kilovoltage or megavoltage imaging devices, cameras, external markers or laser tracking systems. Tumor positions can be verified using kilovoltage or megavoltage imaging devices integrated into linear accelerator. The combined use of optimal pretreatment imaging with 4DCT-based target delineation, modern planning techniques and the use of linear accelerators equipped with cone-beam CT scanners allows for smaller safety margins around the tumor (35). In-room imaging in image-guided radiotherapy (IGRT) using CT-on rail (36) or cone-beam CT allows for variations in patient or tumor positions to be identified on a routine basis, and can identify trends in tumor volume and shape, increases or decreases in atelectasis, or changes in patient anatomy due to excessive weight loss.

Although there has been increasing evidence regarding the efficacy and safety of SBRT for patients with Stage I NSCLC, recruitment of further cases and sufficient follow-ups is currently required to create a fair evaluation of treatment outcomes for SBRT. We also have to pay special attention to patients with centrally located tumors or pulmonary fibrosis. SBRT is becoming established as a radical treatment strategy for medically inoperable Stage I NSCLC. Investigation of whether SBRT can also provide a surrogate treatment for surgery in medically operable patients would therefore be meaningful. It is necessary to both wait for progress in ongoing clinical trials and to formulate new clinical trials to more fully elucidate the position of SBRT among other treatment modalities for Stage I NSCLC. If the JCOG0403 study shows long-term, stable, positive outcomes for the operable group, a study of SBRT versus minimal surgery may be justified for patients who have some risks on standard lobectomy, such as due to poor pulmonary condition or overall physical state (the group for whom minimal surgery is considered). A major problem with SBRT is that it does not allow pathological diagnosis of resected subclinical lymph node metastases to determine the necessity of adjuvant chemotherapy. If subjects with a low risk of lymph node metastases can be clarified through the results of the trials currently underway by the lung cancer surgery group in Japan (JCOG0804/WJOG 4507L: case recruitment complete), then groups can be offered SBRT without adjuvant chemotherapy.

Table 4. Unsolved issues of SBRT

Tolerable dose of normal structures
Effect of pulmonary fibrosis on SBRT-induced pneumonitis
Justice of SBRT for histologically unproven lung tumors
Optimal dose fractionation
Adjuvant therapy
Salvage treatment after recurrence
Long-term prognosis (over 10 years)
Comparison with surgery

Furthermore, many issues (Table 4) remain unresolved and ought to be investigated through long-term follow-up of past clinical trials and the creation of new clinical trials.

CONCLUSION

Stereotactic radiotherapy administers a concentrated large dose in 3D, over a short time span, with precise targeting of the locations of small tumors. This treatment has been used more widely in recent years on a growing number of cases. Since 1995, SBRT for patients with Stage I NSCLC has mainly seen clinical use on inoperable patients. In addition, various clinical trials have been conducted and have found improved local control and survival rates compared with conventional radiation treatments. SBRT is considered the standard treatment for medically inoperable patients and is selected as a surrogate treatment for operable patients who reject surgery. However, the number of cases and observation periods remain insufficient and many uncertainties need to be clarified related to the tolerable dose to at-risk organs and appropriate dose-fractionation, and several issues related to oncology, such as adjuvant therapy or surgery, etc. It is hoped that SBRT will be used in clinics more properly through obtaining new clinical and long-term follow-up data for Stage I NSCLC.

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Conflict of interest statement

None declared.

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