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I. RFA

1. 乳癌に対する熱凝固療法の適応と限界—RFAを中心に—

Feasibility study on radiofrequency ablation for small breast carcinomas and future study

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Summary

乳癌の外科治療は乳房温存手術やセンチネルリンパ節生検法がすでに標準化している。本邦においても乳癌の罹患率が上昇するとともに，マンモグラフィ検診の普及や画像診断法の進歩により，早期乳癌の発見機会の割合が増加してきている。このような時代的背景と患者の要望に応えるため，さらなる低侵襲局所治療であるnon surgical ablation療法が注目されはじめた。実臨床で乳癌に応用されているのは凍結療法（cryoablation），MRガイド下集束超音波療法（MRgFUS），ラジオ波熱凝固療法（radiofrequency ablation：RFA）であるが，装置の普及度と簡便さからRFAが急速に普及していった。一方，われわれの施設では2006年より高度医療評価制度下に早期乳癌に対するRFAの多施設臨床試験を実施し，その適応と限界を明らかにしてきたので紹介する。

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Key Words　乳癌，ラジオ波熱凝固療法，高度医療評価制度，安全性試験

はじめに

早期乳癌の局所療法としての乳房温存療法は，本邦では1980年代から慎重な適応基準をもって導入されたが，術前化学療法を併用するなどにより徐々に適応を拡大し，現在では約6割の患者が恩恵を受けている。一方，究極の乳房温存療法としてのnon surgical ablation therapyが試みられてきている。RFAの原理は交流電流により電極周囲の組織にイオンの変動が起き，その結果として生じる摩擦熱により癌細胞を凝固，壊死させるものである。本稿では，高度医療評価制度下に実施している当院でのRFA安全性試験の

◆メモランダム◆

クールチップRFシステムの原理と機能

AMラジオに近い周波数の電流を組織に流し，通電加熱の原理にてジュール熱を発生して組織を焼灼する。組織における熱の影響は50℃で不可逆的組織変性が始まり，100℃にて組織炭化・蒸散発生する。RFAの最終目標組織温度は60℃以上である。

本システムの特徴を以下に示す。

・針先の温度センサーにより，焼灼後の組織温度を測定できる。ただし，焼灼中は，針の中を水が通るため（炭化防止），測定不能。

・インピーダンスコントロールモード（※）により，焼灼効果を高めることができる。

※抵抗値が，初期抵抗より20Ωあがったとき，自動的に出力が0.005Aになる状態が15秒間続く（ブレイクまたはロールオフと呼ばれる）。ブレイク後は，ふたたびブレイク前の出力で再開。焼灼により高まった組織抵抗をいったん抑え，さらなる焼灼効果を狙う。

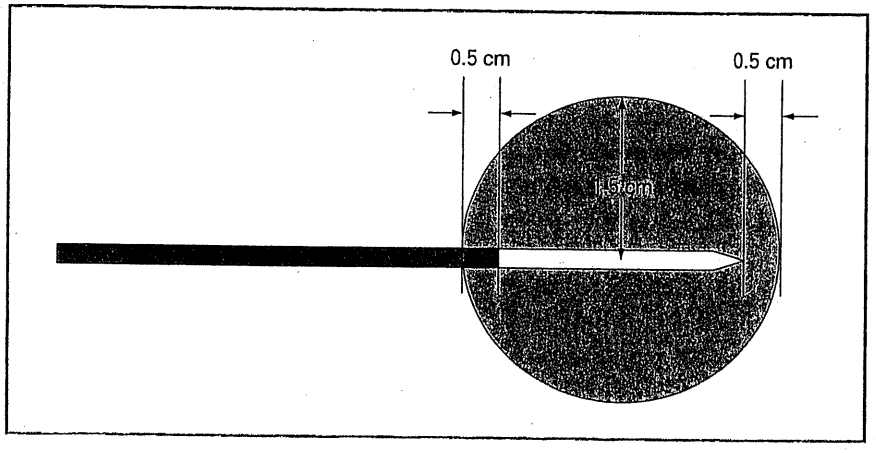

図1　肝臓癌でのRFA — Cool-tip ニードルの焼灼範囲（参考：肝臓）

17G の Cool-tip RF システムシングルニードルは，症例の焼灼径に合わせ，exposure size（白色部）を 1 cm，2 cm，3 cm と選択できる。グレーが焼灼範囲。

概要と今後の問題点について解説する。

本邦における RFA の現状

RFA は国内では肝臓癌の治療として用いられている。Cool-tip ニードル（17G）での肝臓における焼灼モデルを図1に示した。exposure size 1.5 cm を選択した場合，直径 3 cm の範囲が焼灼されることになる。この手技を乳癌に応用したもので，当初，肝臓と同じ7本の展開針型ニードルが用いられていたが，乳腺組織が肝臓と比べて硬く，穿刺しにくいこと，皮膚への熱伝搬のコントロールが難しいことなどから，現在ではシングルニードルで熱コントロールも容易な Cool-tip RF System（COVIDIEN, energy-based devices, Interventional Oncology, Boulder, CO, USA）が主に用いられている。

本法の利点としては，肝臓癌治療ですでに普及している機器を使用するため，機器を有する施設ではニードルの購入のみで実施できるので，わが国では普及する可能性が高い。欠点としては，局所の疼痛が強いため全身麻酔下での実施が推奨されること，治療中に組織内に水蒸気（バブル）が発生するため超音波検査での治療領域の観察が困難であること，局所反応が強いため局所の一過性の浮腫や硬結の残存を認めることなどが挙げられる。

2010 年度に日本乳癌学会にて実施されたアンケート調査によると，乳癌に対する RFA は国内 29 施設が実施し，症例数は 1,049 症例であることが判明した。ただし適応や標準的手技，管理体制がまちまちで，臨床試験として実施していない施設も少なからず認められた。これに対して日本乳癌学会では乳癌 RFA は臨床試験として実施するようにと警告した。また，乳癌低侵襲治療研究会では，患者のフォローアップデータや QOL に関しても検証の必要があると考え，調査を行っている。

当院における RFA の実際

当院では，2006 年 6 月より倫理審査委員会の承認の下に，RFA の安全性と RFA 施行後に切除標本にて病理組織学的に評価を行う安全性試験を開始した。primary endpoint は手術手技の確立と有害事象の評価，secondary endpoint を抗腫瘍効果の評価方法として，目標症例数は 40 例として開始した。本研究は，厚生労働省の臨床的使用確認試験として開始し，高度医療（第三項先進医療）へと引き継がれて実施された。最終的に 50 例登録され，49 例に対して治療が行われた。対象症例を表1に示した。試験開始当初は，施術後，乳房切除の症例を対象としたため腫瘍径 3 cm までを適応としている。画像診断では，超音波検査（US）および MRI を必須として，腫瘍径の計測は US を基本とした。

当院での手技は，US ガイド下に経皮的に Cool-tip ニードル（17G）を腫瘍の中心部に留置する（図2）。皮膚熱傷の予防のために，RFA 前に腫瘍の皮膚側と筋肉側に 5 % ブドウ糖液を注入し，さらに施術中は氷嚢にて十分に皮膚を冷却する。施術中は US にて適

表1　患者背景

	症例数
年齢（歳）	
中央値	61
レンジ	36～82
診断方法	
マンモグラフィ検診（症状なし）	32(65%)
自覚症状あり	17(35%)
T分類	
Tis	1(2%)
T1	34(69%)
T2	14(29%)
占拠部位	
C	18(37%)
D	5(10%)
A	18(37%)
B	7(14%)
E	1(2%)
US腫瘍径（cm）	
中央値	1.70
レンジ	0.5～3.0
MRI腫瘍径（cm）	
中央値	1.50
レンジ	0.7～4.5
臨床的リンパ節転移（N）	
N0	44(90%)
N1	5(10%)

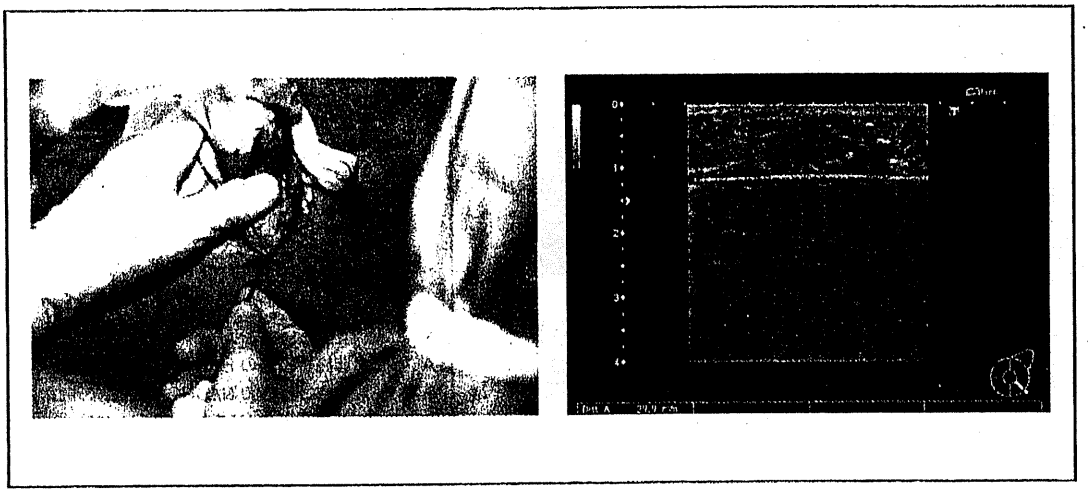

図2　電極針をUSガイド下に穿刺

超音波ガイド下にCool-tipニードルを腫瘍の中心を貫くように穿刺する。その際にニードルの先端から腫瘍の両側端（近位，遠位）までの距離を計測し，記録しておく。

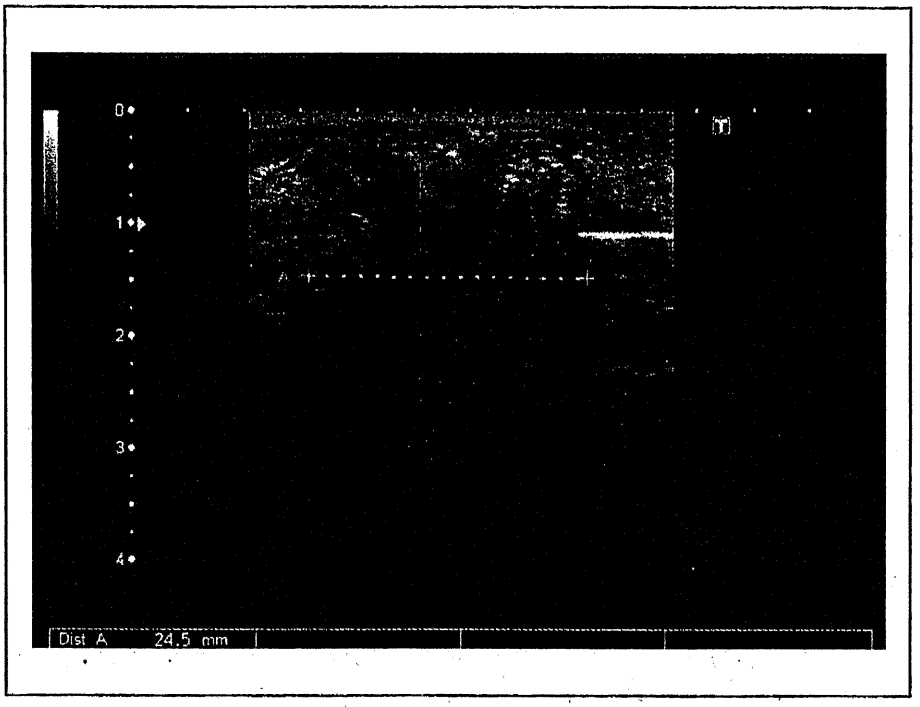

図3　RFA 終了時の腫瘍超音波像
RFA 終了後，腫瘍影は熱変性したバブル像に置き換わる。この熱変性領域を計測しておく。

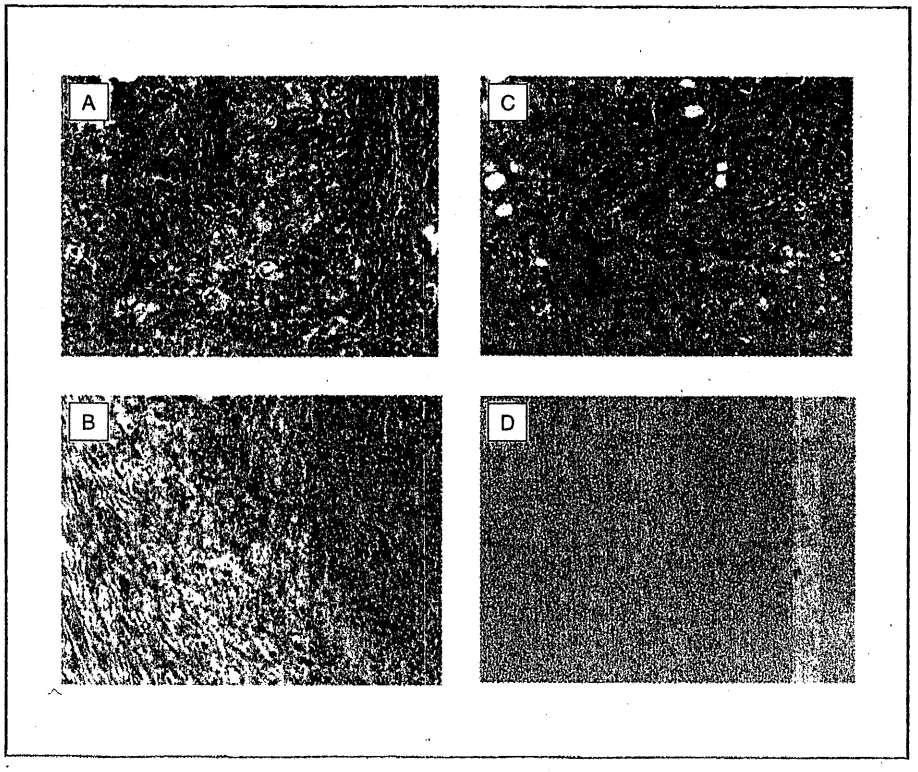

図4　RFA 施行，非施行腫瘍の病理像
A：RFA 非施行腫瘍の H&E 染色像（× 400）
B：RFA 非施行腫瘍の NADH 染色像（× 400）
C：RFA 施行腫瘍の H&E 染色像（× 400）
D：RFA 施行腫瘍の NADH 染色像（× 400）
（カラーグラビア p2　写真 1 参照）

表2　病理組織学的結果

	症例数
組織型	
浸潤性乳管	43(88%)
浸潤性小葉	1(2%)
粘液	2(4%)
髄様	2(4%)
非浸潤性乳管	1(2%)
組織学的グレード	
1	22(45%)
2	16(33%)
3	11(22%)
リンパ節転移 (n)	
陰性	39(80%)
陽性	10(20%)
病理学的全腫瘍径 (cm)	
中央値	1.7
レンジ	0.1～8
extended intraductal component (EIC)	
あり	23(47%)
なし	26(53%)
RFA の病理組織学的効果判定	
変性径 / 長径 (cm)	
中央値	3.0
レンジ	0～6.6
変性径 / 短径 (cm)	
中央値	2.2
レンジ	0～6.6
不完全焼灼例	18(37%)
浸潤部遺残	7(14%)
非浸潤部遺残	11(23%)

宜，腫瘍の焼灼状態をモニタリングする。当院での RFA 治療時間の中央値は 8.7 分で，施術終了時には US 上，腫瘍影は発生したバブル陰影により観察不能となる（図 3）。このバブル像を US 上の熱変性範囲と想定し記録しておく。RFA 終了時のニードルの先進部と腫瘍中心部の温度も記録しておき，RF 目標温度に達しているかを記録しておく。

施術終了時に合併症の有無を確認し，予定されている乳房切除術を実施する。このとき，予定されていた手術が安全に実施できたかどうか，手術後の合併症，入院期間などに関しても記録しておく。切除標本はただちに病理組織検室にて nicotinamide adenine dinucleotide（NADH）-diphorase 染色用の凍結保存用検体が採取され，通常の H&E 染色および NADH 染色にて抗腫瘍効果の判定がなされた。

RFA 施行腫瘍と非施行腫瘍の H&E 染色および NADH 染色像を図 4 に示した。RFA 施行腫瘍では NADH 染色

表3　病理組織学的腫瘍径とRFAの成績

病理学的腫瘍径 (t)*	患者数	完全焼灼 (%)	不完全焼灼 (%)
≦2 cm	29	25(86%)	4(14%)
＞2 cm	20	6(30%)	14(70%)

＊：浸潤部，非浸潤部を含んだ全腫瘍径

表4　EICの有無とRFAの成績

	患者数	完全焼灼 (%)	不完全焼灼 (%)
EIC(＋)	23	9(39%)	14(61%)
EIC(－)	26	22(85%)	4(15%)

表5　RFA後腫瘍切除を伴う安全性試験の報告

報告者 (年)	患者数	腫瘍径 (T)	使用装置	Power (W)	治療時間・中央値 (分)	完全焼灼率 (%)	合併症
Jeffery ら[1] (1999)	5	T2-3	LeVeen	20～60	30	80	なし
Izzo ら[2] (2001)	26	T1-2	LeVeen	25～80	15	96	皮膚熱傷×1
Burak ら[3] (2003)	10	T1	LeVeen	-	13.8	90	なし
Singletary ら[4] (2003)	29	T1-2	RITA	-	-	86	皮膚熱傷×1
Hayashi ら[5] (2003)	22	T1	RITA	-	15	64	皮膚熱傷×1 創感染×4
Fornage ら[6] (2004)	20	T1	RITA	-	15	95	なし
Noguchi ら[7] (2006)	10	T1	RITA	-	15	100	なし
Khatri ら[8] (2007)	15	T1	Cool-Tip	7～36	21	93	皮膚変形×2 創感染×1
Medina-Franco ら[9] (2008)	25	T1-2	Elektrotorm	-	11	76	皮膚熱傷×3 創感染×1
Garbay ら[10] (2008)	10	IBTR, ≦3 cm	LeVeen	25～32	11	70	-
Imoto ら[11] (2009)	30	T1	LeVeen	5～42	18	85	皮膚熱傷×2 大胸筋熱傷×7
present study	49	T1-2, ≦3 cm	Cool-Tip	5～118	8.7	63	皮膚熱傷×2 大胸筋熱傷×3

陰性で，細胞死が示唆された。NADH染色陰性標本のH&E染色での特徴は，①細胞核の淡明粗造化，線状化，濃縮，②間質の列隙形成，③無構造化した間質内の細胞が挙げられた。NADH染色とH&E染色を併用した細胞死判定により主腫瘍ばかりでなく離れた部位の娘結節や乳管内病変 (extended intraductal component：EIC) の効果判定も可能となった。

病理組織学的な結果を表2に示した。浸潤部と非浸潤部を合わせた病理学的全腫瘍径の中央値は1.7 cm（レンジ0.1～8 cm）でEICを認めた症例が23例（47％）であった。乳房でのCool-

tip システム（17G）での RFA 焼灼範囲は中央値で 3.0 × 2.2 cm であった。US 腫瘍径 3 cm 以下の全 49 例中，18 例（37 %）が不完全焼灼で 7 例（14 %）に浸潤部での非焼灼残存が確認された。US 腫瘍径 2 cm 以下の全 38 例中，10 例（26 %）が不完全焼灼で 6 例（16 %）に浸潤部での非焼灼残存が確認された。

一方，浸潤部，非浸潤部を含んだ病理学的全腫瘍径 2 cm 以下の症例では，29 例中 25 例（86 %）に完全焼灼が確認された（表 3）。さらには EIC の有無での治療成績は，EIC（−）26 例中，22 例（85 %）に完全焼灼が確認された（表 4）。当院での結果より，病理学的腫瘍径 2 cm 以下で EIC（−）の症例が RFA の良い適応となることが確認された。ただし，術前の画像診断で対象の絞り込みができるかどうかが鍵となる。

プライマリーエンドポイントである本手技の合併症は，皮膚熱傷が 2 例，大胸筋熱傷が 3 例でいずれも保存的に軽快，治癒しており，入院期間の延長なども認めていない。本試験により RFA 手技の安全性は確認されたものと考える。

海外での RFA 試験と今後

1999 年から今日までの RFA 後腫瘍切除試験の報告を表 5 にまとめた[1)-11)]。すべてが単施設からの報告で，適応やデバイスは異なり，完全焼灼率も 64 ～ 100 %である。症例数も少数であり保険収載の承認を獲得するための十分なエビデンスとなる報告は見当たらない[12)]。

乳癌に対するマイクロ波熱凝固療法

ラジオ波とマイクロ波はともに電磁波の一種であり，腫瘍の凝固能に関しては各々特徴があるが，治療に供される周波数はラジオ波が 460 kHz，マイクロ波が 2,450 MHz である。オープン MR システムを利用して使用する場合にはラジオ波は干渉し合うことになり，マイクロ波が使用可能となる。乳癌に対してはオープン MR システム下での肝転移に対する治療が報告されているが[13)]，原発巣に対しては少数例の報告にとどまっている。

おわりに

乳癌の低侵襲局所療法である RFA などの non surgical ablation 療法は正しい適応や手技のもとに実施されれば，従来の外科的切除に劣らない成績を残せるものと期待する。本邦では薬事法上承認されている RFA が一番の近道と考え，その評価を開始した。結論は，ターゲットにした腫瘍は安全に，完全に細胞死に至らせることが可能であることは確認されたが，乳房温存療法と同様に画像診断では検出できない乳管内病変の遺残が問題となる。引き続きデバイスや手技の開発，改善とともに本治療の中～長期的安全性，整容性，局所制御能を評価していく必要がある。エビデンスが不十分な現状では，十分なインフォームドコンセントと確立されたモニタリングシステムのもと，臨床試験としてのみ実施されるべき治療であると考える。

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ORIGINAL ARTICLE

Radiotherapy quality assurance of the Japanese Gynecologic Oncology Group study (JGOG1066): a cooperative phase II study of concurrent chemoradiotherapy for uterine cervical cancer

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Abstract
Background To assess radiotherapy protocol compliance in a multi-institutional phase II study of concurrent chemoradiotherapy for patients with locally advanced cancer of the uterine cervix (JGOG1066).
Methods For study protocol development, various radiotherapy parameters were examined and consensus was reached by Japanese radiation oncologists with cervical cancer treatment expertise. Quality assurance (QA) was also discussed and included in the protocol. A credentialing process was used to select institutions for participation in the study. Individual case reviews referring to 18 QA items were undertaken for each patient. Radiotherapy data were submitted to the Japanese Gynecologic Oncology Group (JGOG) data center and reviewed by the members of the radiotherapy committee. The QA evaluation was classed as per protocol, deviation, and violation.
Results Individual case reviews were performed on 69 of 72 patients entered in the study. In 24 patients (35%), there

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were no deviations for any QA items. There were also no deviations seen for 5 of the 18 items in 69 patients evaluated. Deviations of 64 QA items were seen in 45 cases, and violations were seen in 4 cases (4 items). The most common deviation concerned appropriate application for the external beam radiotherapy (EBRT) boost to involved nodes or parametrium (32 cases). The 4 violations were identified in the QA items regarding high-dose rate intracavitary brachytherapy.

Conclusions Radiotherapy protocol compliance was favorable except for the EBRT boost indications. The results of this study validate the quality of radiotherapy in JGOG1066, and indicate that the final analysis will provide meaningful results.

Keywords Carcinoma of the uterine cervix · Radiation therapy · Chemoradiotherapy · Intracavitary brachytherapy · High dose rate

Introduction

Concurrent chemoradiotherapy (CCRT) is a standard treatment for patients with locoregionally advanced uterine cervical cancer [1]. However, some Japanese physicians remain cautious about employing CCRT as a standard treatment, for 2 reasons. The first concerns the feasibility of using the standard chemotherapy of weekly 40 mg/m^2 cisplatin concurrently with radiotherapy. There have been several reports that Japanese cervical cancer patients frequently experienced severe toxicities, and investigators concluded that CCRT using weekly 40 mg/m^2 cisplatin may not be feasible for Japanese patients [2, 3]. The second is that there are limited data on CCRT using high-dose-rate intracavitary brachytherapy (HDR-ICBT) [4, 5]. In addition, total radiation doses to the primary tumor seem to be extremely low compared with doses for definitive radiotherapy or CCRT in the United States [4–7]. A large amount of data concerning excellent outcomes and toxicity have been reported for patients treated with the Japanese standard schedules, but most of this information was derived from retrospective analyses, and CCRT data were limited [8]. Therefore, the 2007 Japanese treatment guidelines for uterine cervical cancer recommended a B grade for CCRT [9]. We undertook a prospective study (JGOG1066) to evaluate toxicities and outcomes in patients treated with CCRT using the standard dose/schedule of cisplatin and the standard Japanese radiotherapy dose schedules for HDR-ICBT.

For scientifically valid CCRT clinical trial results, it is essential to develop an adequate protocol and assure compliance with the radiotherapy protocol. In developing the JGOG1066 protocol, several Japanese radiation oncology experts on cervical cancer undertook extensive deliberations on radiotherapy methods. In addition, effective quality assurance (QA) for radiotherapy was also discussed. In this paper, we describe the process for QA and present results of independent case reviews (ICRs) from the CCRT study.

Patients and methods

Summary of the JGOG1066

The Japanese Gynecologic Oncology Group (JGOG) conducted a phase II trial (JGOG1066) to evaluate the feasibility, toxicity and efficacy of CCRT using the standard global schedule for cisplatin (40 mg/m^2 weekly, 5 courses) and standard Japanese dose schedules for HDR-ICBT. Table 1 summarizes the trial, listing the criteria for patient eligibility, the endpoints, and treatments.

Protocol development

Radiotherapy parameters were examined and consensus was reached by Japanese radiation oncologists with expertise in the treatment of cervical cancer. A nationwide questionnaire on radiotherapy methods including treatment schedules, delivery of an external beam radiotherapy (EBRT) boost to lymph nodes and the parametria, and bladder/rectum dose calculations (ICRU38) was first distributed to radiation oncologists. Treatment schedule queries included total and fractional doses of whole-pelvis EBRT (with/without midline block) and also total and fractional doses of HDR-ICBT. In developing protocols for radiotherapy methods, data from the questionnaire and from previous published reports were extensively discussed, and a consensus was reached.

To determine location of point A, a rule was established based on the topographical relationships between tandem and ovoid. Basically, a coordinate at the external os (usually equivalent to the position of the tandem flange) was selected as the geographic origin of point A. In cases where the external os was located caudally to the cranial ovoid

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Table 1 Summary of JGOG1066

Eligible patients			
1. FIGO stage III/IVA uterine cervical cancer			
2. Squamous cell carcinoma, adenosquamous cell carcinoma, adenocarcinoma			
3. ECOG performance status 0–1			
4. Age 20–70 years			
5. No para-aortic lymphadenopathy (≥10 mm assessed by CT)			
6. No prior treatment			
7. Adequate organ (bone marrow, hepatic, renal, heart) functions			
8. Written informed consent			
Endpoints			
Primary: 2-year progression-free survival rate			
Secondary: treatment completion rate, toxicity rates (acute and late), complete response rate, 2-year survival rate, 2-year pelvic progression-free rate, 2-year distant metastases-free rate			
Planned sample size and accrual duration:			
70 within 2 years			
Treatment			
Concurrent chemoradiotherapy (CCRT)			
Chemotherapy			
Cisplatin 40 mg/m^2, weekly, 5 courses			
Radiotherapy			
External beam radiotherapy (EBRT) and high-dose-rate intracavitary brachytherapy (HDR-ICBT)			
Radiotherapy schedules			
WP	WP + MB	HDR-ICBT[a]	BED (WP + HDR-ICBT)[a]
30 Gy/15f	20 Gy/10f	24 Gy/4f	74.5Gy$_{10}$
30.6 Gy/17f	19.8 Gy/11f	24 Gy/4f	74.4Gy$_{10}$
40 Gy/20f	10 Gy/5f	18 Gy/3f	76.8Gy$_{10}$
41.4 Gy/23f	9 Gy/5f	18 Gy/3f	77.8Gy$_{10}$

WP whole pelvic radiotherapy, *MB* midline block, *BED* biologically effective dose, *f* fraction

[a] Prescribed at point A

surface (i.e. patients with roomy vaginal vaults), a coordinate at the vaginal vault was selected as the origin of the vertical level with the point A. The concept behind the latter definition is essentially the same as that of point H proposed by the American Brachytherapy Society (ABS) [6]. Four radiotherapy schedules were provided for the protocol (Table 1). Because these schedules have almost biologically equivalent doses, the treating radiation oncologist was allowed to apply one of the schedules at their discretion. The protocol stated that enlarged pelvic node(s) (greater than 10 mm in the shortest diameter) visualized by pretreatment computed tomography (CT)/ magnetic resonance imaging (MRI), and palpable nodular parametrium(s) fixed to the wall(s) should received an EBRT boost, with a total dose of 6–10 Gy/3–5 fractions.

To maintain radiotherapy quality, methods for QA were also examined. A credentialing process for participating institutions and independent case reviews (ICRs) of all treated patients were adopted for the QA. A description of the QA process was included in the protocol.

Credentialing

For institutional participation in this study, credentialing was required. The participating institutions had to meet the following 3 criteria:

1. Institution was certified by the Japanese Society for Therapeutic Radiology and Oncology (JASTRO) with JASTRO-certified radiation oncologist(s).
2. All HDR-ICBT procedures (i.e., applicator insertions, calculations, and evaluations) were carried out by JASTRO-certified radiation oncologist(s) or their colleagues.
3. At least 10 cervical cancer cases per year were treated by definitive radiotherapy using HDR-ICBT.

Meeting the first requirement indicated that the institution had a specified accuracy of external beam radiation dose delivery, since JASTRO-certified institutions must regularly undertake output measurements and calibrations of their linear accelerators. The second and third

requirements aid in ensuring that the HDR-ICBT procedure is performed with a reliable degree of skill.

Credentialing was undertaken by the JGOG radiotherapy committee. First, the committee identified JASTRO-certified institutions from 237 JGOG member institutions. Next, the committee asked those institutions if they would like to participate in the study. Institutions responding "yes" were subsequently requested to submit applications providing the following information: name of radiation oncologist(s) performing HDR-ICBT, name of radiologic technician(s) and physicist(s) responsible for HDR-ICBT, number of cervical cancer patients treated by definitive radiotherapy with HDR-ICBT per year, models and manufacturers of the HDR-ICBT machine and planning computer, source strength verification at the time of source replacement, and verification of source positioning in the catheter. With this information, the committee arrived at a consensus on whether or not an institution could participate in the study.

ICR summary

Participating institutions were requested to submit radiotherapy data for all treated patients. Table 2 lists the submitted items. Radiotherapy charts describing daily treatment records and treatment parameters were submitted as hard copies. Other graphical data (including simulation, digitally reconstructed radiography) and figures (including dose distributions) were submitted in digital formats on CD-ROMS. The radiotherapy committee performed ICRs on 18 QA items according to predefined evaluation criteria (Table 3). The QA assessment was classed as per protocol, deviation, and violation. QA evaluation criteria for ICRs were not included in the protocol description, but prepared separately.

Preliminary evaluations were performed by the study chair (T.T.). The preliminary evaluations were reviewed and approved by other JGOG radiotherapy committee members at the time of the QA meetings. The QA meetings were held twice (April 24, 2009, and May 7, 2010).

Table 2 Data submitted for ICR

External beam radiotherapy
Treatment charts (beam energy, SAD, gantry angle, field size, MU, plan summary sheets from RTPS, and daily treatment record)
Simulation films or DRRs
Verification portal films or EPIDs
Isodose distributions (central axis plane)
HDR-ICBT
Treatment charts for all sessions (activity, dwell times, dwell positions, and point doses)
AP and lateral orthogonal films or images for all sessions
AP and lateral isodose distributions for all sessions

ICR individual case review, *SAD* source-axis distance, *MU* monitor unit, *RTPS* radiotherapy treatment planning system, *DRR* digitally reconstructed radiographs, *EPID* electronic portal imaging devices, *HDR-ICBT* high dose-rate intracavitary brachytherapy, *AP* anterioposterior

Results

From March 2008 to January 2009, 72 patients from 25 institutions were enrolled. One patient who did not meet the eligibility requirements and 2 patients who stopped protocol treatment because of toxicities were excluded, leaving 69 patients who were considered eligible for the ICRs. Table 4 summarizes the ICR results. In 24 patients (35%), there were no deviations of any of the 18 ICR items. There were also no deviations seen in 5 of the 18 items (i.e., QA-1, -2, -3, -4, -8) in any of the 69 patients evaluated. Deviations were seen in 45 cases, and violations were observed in 4 cases. Table 5 lists the number of cases and number of ICR items assessed with a deviation or violation. Deviations were observed most frequently for QA-7, which evaluated the appropriateness of delivering an EBRT boost.

Details of QA evaluations

QA-1 EBRT beam energy: No deviations were seen. Beam energies included the following: 6 MV in 1 patient, 10 MV in 40 patients, 15 MV in 14 patients, 18 MV in 12 patients, and 20 MV in 2 patients.

QA-2 EBRT method: No deviations were seen. There were 28 patients treated with anteroposterior–posteroanterior (AP–PA) ports, and the remaining 41 patients were treated with the four-field box technique.

QA-3 Daily EBRT dose fraction: No deviations were seen. In 40 patients, 1.8 Gy was used, and in 29 patients, 2 Gy was used.

QA-4 Total EBRT dose of the whole pelvis (WP) with/without midline block (MB): No deviations from the protocol description were seen.

QA-5 MB set-up timing: One patient whose MB was set at 32 Gy received 24 Gy/4 fractions of HDR-ICBT; this was judged as a deviation. The remaining patients were all evaluated as per protocol. The MB was set at 30 Gy in 11 patients, 30.6 Gy in 33 patients, 40 Gy in 15 patients, and 41.4 Gy in 7 patients. There were 2 patients who

Table 3 Radiotherapy quality assurance items and criteria for ICR

Items	Evaluation		
	Per protocol	Deviation	Violation
QA-1: EBRT beam energy	≥6MV	<6MV or cobalt	–
QA-2: EBRT methods	AP–PA or 4-field box	Other methods	All ports not delivered each day
QA-3: EBRT daily fraction dose (prescribed)	1.8 or 2 Gy and 5 fractions/week	Other fraction dose and 5 fractions/week	4 fractions/week
QA-4: EBRT total dose (prescribed)	<±5%	5–10%	>±10%
QA-5: MB set-up timing	1. 30/30.6/40/41.4 Gy	1. 30–41.4 Gy, but not 30/30.6/40/41.4 Gy	Before 30 Gy
	2. after 41.4 Gy with certain clinical validity	2. after 41.4 Gy without certain clinical validity	
QA-6: EBRT treatment portals	WP with proper coverage	WP with improper coverage	Extended fields (covering para-aortic nodes)
QA-7: EBRT boost	Performed properly/not applicable	Not performed even applicable/performed but improperly	–
QA-8: EBRT dose homogeneity within PTV[a]	95–107%	<95 or >107%	–
QA-9: Divergence between simulation and verification	≤5 mm and no difference in shape	≥6 mm or different shape	No verification
QA-10: Timing of the first HDR-ICBT	After 30–41.4 Gy and within 7 days from MB insertion	After 30–41.4 Gy but over 7 days from MB insertion	Before 30 Gy
QA-11: EBRT and HDR-ICBT on same day	No	–	Yes
QA-12: HDR-ICBT planning for each fraction	Yes	–	No
QA-13: HDR-ICBT fraction dose (at point A, prescribed)	6 Gy and once a week	Other than 6 Gy (<7.5 Gy) or ≥twice a week	≥7.5 Gy
QA-14: HDR-ICBT total dose (at point A, prescribed)	18 or 24 Gy	Other than 18 or 24 Gy	≥30 Gy
QA-15: Determination of point A	As stated in protocol	Not as stated in protocol	–
QA-16: Dose calculation at OARs (rectum, bladder; ICRU 38)	Yes	No	–
QA-17: Total EBRT and HDR-ICBT dose (prescribed, BED at point A)	As stated in protocol (74–78 Gy_{10})	Not as stated in protocol but 70–80 Gy_{10}	<70 Gy_{10} or >80 Gy_{10}
QA-18: Overall treatment time	≤8 weeks	8–10 weeks	>10 weeks

ICR individual case review, *EBRT* external beam radiotherapy, *AP–PA* anteroposterior–posterioanterior, *MB* midline block, *WP* whole pelvis, *PTV* planning target volume, *HDR-ICBT* high-dose-rate intracavitary brachytherapy, *OAR* organ at risk, *BED* biological effective dose

[a] At level of field isocenter

received 50 Gy of whole-pelvis EBRT without MB, in whom the treating radiation oncologists thought that adequate shrinkage of the primary tumor had not been achieved for effective ICBT. This situation had been described as "clinically appropriate" in the protocol, and was judged per protocol.

QA-6 EBRT treatment portals: There were 6 patients with deviations. These were all from a single institution, and planning was based on clinical target volume (CTV) contouring on CT images.

QA-7 EBRT boost: In 32 patients, the EBRT boost was not applied appropriately as stated in the protocol. These were judged as deviations.

QA-8 EBRT dose homogeneity within planning target volume (PTV): No deviations were seen.

QA-9 Geometrical divergence between simulation and verification: There were 3 patients from a single institution for whom a geometrical divergence ≥5 mm was seen. These were judged as deviations.

QA-10 Timing of the first HDR-ICBT. There were 2 patients whose first HDR-ICBT was delayed for ≥7 days, which was judged as a deviation. There

Table 4 Radiotherapy ICR summary: JGOG1066

Items	Evaluation		
	Per protocol	Deviation	Violation
QA-1: EBRT beam energy	69	0	–
QA-2: EBRT method	69	0	0
QA-3: EBRT daily fraction dose (prescribed)	69	0	0
QA-4: EBRT total dose (prescribed)	69	0	0
QA-5: MB set-up timing	68	1	0
QA-6: EBRT treatment portals	63	6	0
QA-7: EBRT boosts	37	32	0
QA-8: EBRT dose homogeneity within PTV	69	0	–
QA-9: Divergence between simulation and verification	66	3	–
QA-10: Timing of the first HDR-ICBT	65	2	2
QA-11: EBRT and HDR-ICBT on same day	68	–	1
QA-12: HDR-ICBT planning for each fraction	68	–	1
QA-13: HDR-ICBT fraction dose (prescribed)	66	3	0
QA-14: HDR-ICBT total dose of (prescribed)	65	4	0
QA-15: Determination of point A	64	5	–
QA-16: Dose calculation of OARs (ICRU38)	66	3	–
QA-17: Total EBRT and HDR-ICBT dose (prescribed)	67	2	0
QA-18: Overall treatment time	66	3	0

ICR individual case review, *EBRT* external beam radiotherapy, *MB* midline block, *PTV* planning target volume, *HDR-ICBT* high-dose-rate intracavitary brachytherapy, *OAR* organ at risk

were 2 patients who received their first HDR-ICBT before 30 Gy of EBRT had been administered, which was judged as a violation.

QA-11 Prohibition against same-day delivery of EBRT and HDR-ICBT: There was 1 patient who received both EBRT and HDR-ICBT on the same day, which was judged as a violation.

QA-12 HDR-ICBT planning for each fraction: The protocol stated that dose calculations should be performed for every HDR-ICBT session. There was 1 patient who received her second and third HDR-ICBT based on planning data from her first application. This was judged as a violation.

QA-13 HDR-ICBT fraction dose: There were 2 patients who received HDR-ICBT with an incorrectly prescribed point A dose, which was judged as a deviation. Another patient received HDR-ICBT using an inappropriate reference point instead of point A, which was also judged as a deviation.

QA-14 HDR-ICBT total dose: The 3 patients with QA-13 deviations and 1 patient who did not receive the last HDR-ICBT because of acute toxicity were judged as deviations.

QA-15 Determination of point A: There were 5 patients who received HDR-ICBT at an incorrectly defined point A. These were judged as deviations. One of those patients also had deviations for QA-13 and -14. In 4 of these patients, the external os was selected as the geometrical origin for point A instead of the vaginal vault level (which was the correct definition), although the external os was located caudally to the cranial ovoid applicator surface.

Table 5 Numbers of cases and quality assurance items with deviations or violations

Number of deviations	Number of cases[a]
0	24
1	36 (2)
2	6 (1)
3	0
4	1 (1)
5	1
6	0
7	1

[a] Parentheses include number of cases also having violations

QA-16 Organs at risk (OAR) dose calculation [10]: Bladder dose calculations were not performed in 3 patients, which were judged as deviations.

QA-17 Total EBRT and HDR-ICBT dose: Two of 3 patients who had deviations in QA-13 were also assessed with deviations for this.

QA-18 Overall treatment time (OTT): There were 3 deviations in OTT. The OTTs of these 3 patients were 56, 57, and 65 days. The longest OTT was

caused by a delayed starting time of the EBRT boost to the parametrium.

Discussion

This study determined that there was favorable radiotherapy compliance with the JGOG1066 protocol. Based on our findings, we expect the final results of this study on long-term outcomes and complications to be scientifically valid.

A credentialing process was used to select the participating institutions in this study. Our credentialing consisted of a review of questionnaires received from institutions and an assessment of radiotherapy QA, especially with regard to HDR-ICBT. The credentialing process has been adopted for some recent clinical trials performed by the Gynecologic Oncology Group (GOG). Lowenstein and colleagues reported that major protocol deviations were more frequently seen in non-certified institutions than in certified institutions [11]. We believe that the credentialing process in this study may be one of the reasons that favorable protocol compliance was achieved.

Favorable radiotherapy compliance was observed for EBRT, especially with regard to parameters defined by numerically prescribed values, such as beam energy and prescribed dose, which had 100% compliance. Regarding EBRT port arrangements, deviations were observed in 6 patients. These were all from a single institution and were based on CTV delineation-based treatment planning. Only 2-dimensional (2D) treatment planning was prescribed in the protocol. Some clinical study groups have published consensus guidelines for CTV delineation of the pelvic node region [12, 13], and the Radiation Therapy Oncology Group (RTOG) has also released a guideline for primary cervical cancer tumors [14]. For future clinical trials, it will be essential to include detailed descriptions of 3-dimensional (3D) treatment planning, including the definition of CTV contouring. In this study, frequent deviations were observed for EBRT boosts. Most deviations were omissions at the discretion of the treating physicians, despite indications for a boost. These physicians might have prioritized their clinical impressions and experiences over the protocol. We believe that there was a discrepancy between the protocol and current daily clinical practice. At present, there is no obvious evidence that an EBRT boost provides therapeutic value [15]. In ongoing Gynecology Oncology Group (GOG) and RTOG trials, EBRT boosts have been optional. Therefore, for trials in the near future, it is reasonable to keep the EBRT boost as an option.

Although protocol compliance was also favorable for HDR-ICBT administration, 4 violations were seen. Two were in patients who received their first HDR-ICBT application before they received 30 Gy of EBRT. Eligible patients in this study all had extensive cervical disease. It is thought that locoregionally advanced disease should receive adequate doses of EBRT before HDR-ICBT application, and it is essential to deliver an adequate HDR-ICBT dose to the entire cervical tumor [16]. There was 1 patient who received EBRT and HDR-ICBT on the same day, which was judged as a violation. In accordance with the ABS guidelines [6], concurrent delivery of EBRT and HDR-ICBT was strictly prohibited in the protocol. In 1 patient, treatment planning for the first HDR-ICBT was also applied during the subsequent HDR-ICBT sessions. We believe that these types of violations should be strictly avoided, because they could cause poor treatment outcomes and decrease safety [6].

Only 4 deviations were observed for the designation of point A. We adopted 2 alternative determination methods for point A from a previous prospective study (JAROG0401/JROSG04-2) [17]. In that study, 10 of 60 patients were assessed with deviations regarding the definition of point A [17]. We think that compliance with this definition has improved over the previous study. To further improve compliance with point A determination, a dummy run may be effective. This would also be effective for CTV delineation on EBRT treatment planning. While image-guided brachytherapy is becoming popular, especially in the United States [18], point A is still widely used for dose prescription along with DVH parameters [19]. We think that our system can provide consistent and clinically appropriate point A determinations [20].

The theoretical weakness of our present QA process is lack of physics QA, including an external dosimetry audit and independent dose calculation of HDR-ICBT. In the GOG and RTOG studies, an independent HDR-ICBT dose calculation was performed and revealed some variation of actual doses compared with prescribed doses [20]. We need to establish an effective QA system for physics by ensuring active participation of medical physicists in the CCRT studies of cervical cancer. Our QA assessments regarding deviations and violations may be considered subjective. We classified the cases into 3 QA categories based on previously decided criteria. Our QA criteria were developed with reference to those used in other clinical study groups, such as GOG [11]. Development of standard QA criteria, including those pertaining to physics which can be used globally, should be encouraged.

In conclusion, compliance with the radiotherapy protocol in JGOG1066 was favorable, except for indications for the EBRT boost. The results of this compliance study validate the quality of radiotherapy in JGOG1066 and indicate that the final analysis will provide meaningful results.

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Conflict of interest No author has any conflict of interest.

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Original Article

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

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

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

INTRODUCTION

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

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

PATIENTS AND METHODS

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

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

RESULTS

General Information

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

Treatment Planning

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

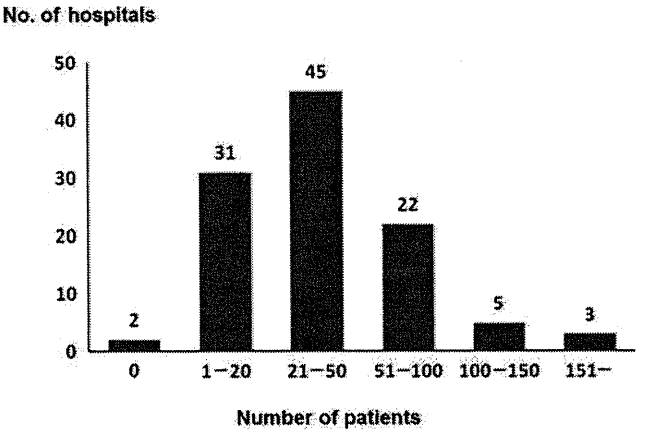

Figure 1. Total number of patients with prostate cancer treated with external-beam radiation therapy at facilities in 2009. Because some data were missing, the total numbers of patients were less than the actual number.

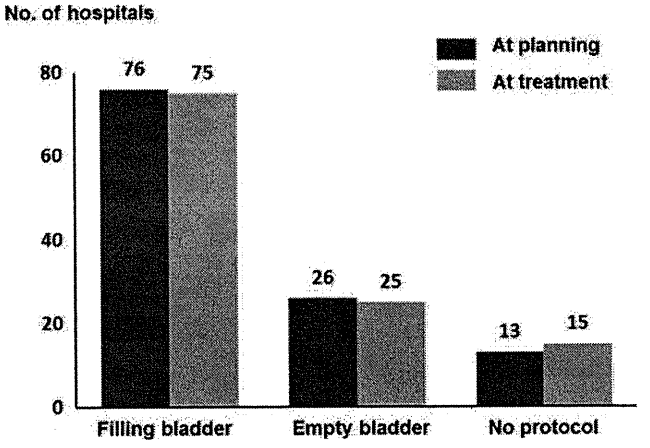

Figure 2. Condition of the bladder at the treatment planning stage and during treatment.

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

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

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

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

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

Treatment

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

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

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

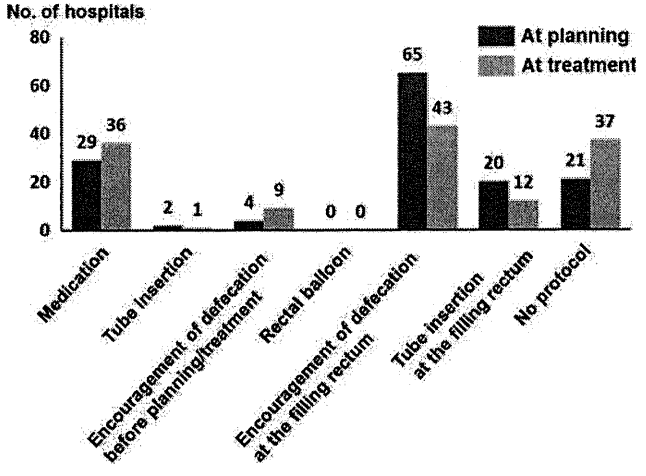

Figure 3. Condition of the rectum at the treatment planning stage and during treatment. Multiple answers allowed.

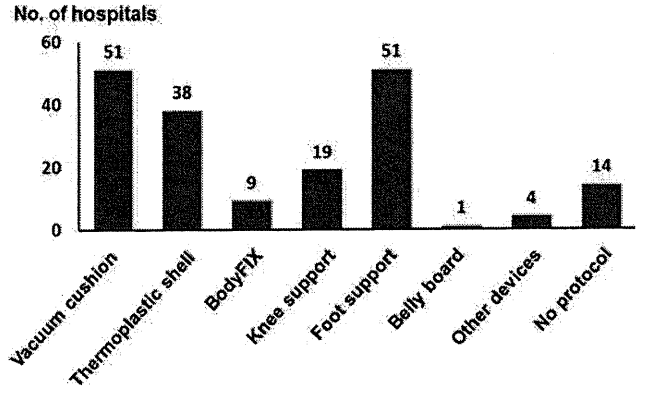

Figure 4. Fixation of the patients at the treatment planning stage and during treatment. Multiple answers allowed.

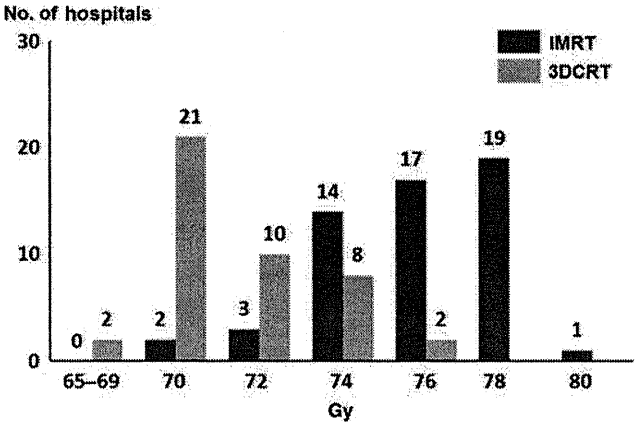

Figure 5. Total dose to the prostate.

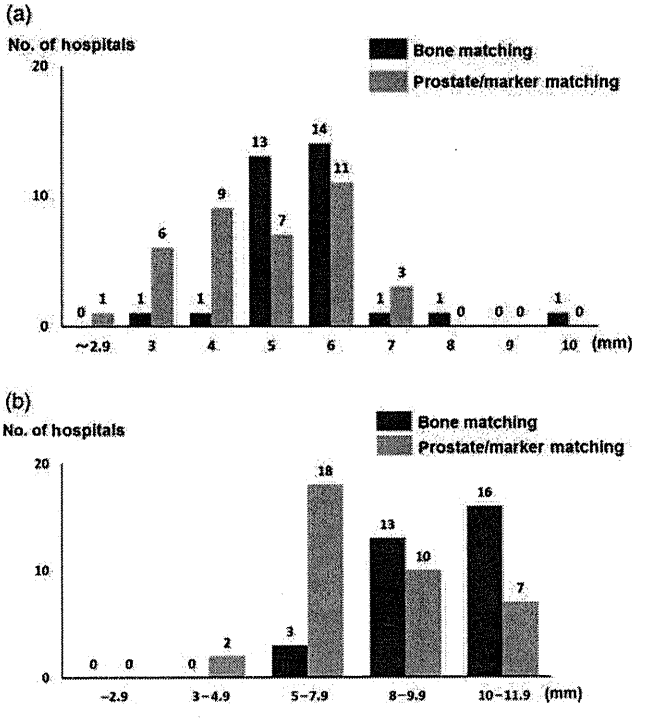

Figure 6. Margins from the prostate to planning target volume for patients with T1–2 tumors treated with IGRT: (a) rectal side and (b) other sides.