ウ　三次元放射線治療計画システム
エ　患者ごとの治療計画にそった自動設定機構を有する照射野形成装置
オ　標準状態および患者ごとの吸収線量及び線量分布を測定するための装置
(7) 当該保険医療機関において、粒子線治療に関する機器の精度管理に 関する指針が策定されており、実際の線量測定等の精度管理が当該指針に沿って行われているとともに、公開可能な精度管理に係る記録が保存されていること。

*日本医学放射線学会専門医もしくは日本放射線腫瘍学会認定医
**文部科学省委託事業
***医学物理士認定機構が認定する医学物理士

C-2) コミッショニング

1．吸収線量の外部監査

パッシブ法を採用している群馬大学では、空気カーマで校正されたリファレンス線量計が使用された。線量5回測定時の繰り返し再現性は、ファーマ電離箱で0.05%程度と極めて良好であった。また放医研の二次標準線量計で水吸収線量を評価したところ、施設間比較でσ =0.5%程度で一致し、以前の陽子線線量相互比較実験と同程度の良い一致がみられた。

一方、スキャニング法を採用している放医研新治療研究棟では、空気カーマで校正された施設の線量計と、水吸収線量で校正された二次標準線量計が使用された。繰り返し再現性は、0.1-0.2%程度とパッシブ法には及ばないものの、水吸収線量についてはσ =0.1%程度の極めて良好な一致が得られた。また水吸収線量で校正された線量計を使用することにより、水吸収線量の絶対値の不確かさを3.2%から2.8%へ低減できた。

この結果、線量モニタの校正については、スキャニング法の場合においても、パッシブ法と同様のクライテリアを設定することが妥当であることが明らかとなった。

2．コミッショニングリスト

放医研新治療研究棟でのコミッショニング項目をリストアップした。基本的には「陽子線・重イオン線治療装置の物理・技術的ＱＡシステムガイドライン」を踏襲し、さらにスキャニング法やロボット治療台等の新技術に係る項目を追加した。

具体的項目は以下の通りである。

I. 治療線量に関係しない項目
- QAファントム
- X線撮影装置
- 照射模擬ポート
- 治療台装置
- CT装置
- レーザー装置
- 治療計画装置

II. 治療線量に関係する項目
- ビーム性状確認
- ビーム位置校正・精度検証
- 線量モニタ
- 位置モニタ
- 照射装置総合確認
- 照射装置・治療計画装置組合せ試験
- 照射線量インターロック

これらの各項目について検査内容とクライテリアを設定した上で、検査結果についてQA分科会にてピアレビューが行われ

た。その結果、臨床研究の開始は妥当との評価を得た。

C-3) QA/QCガイドライン

次の9つの章からなるQA/QCガイドライン案を策定した。関連学会等とも連携を図り今後ホームページや印刷物等によりガイドラインを公開する計画である。

1． はじめに
2． 品質管理体制
3． 粒子線治療のQAとながれ
4． 照射体積と線量の定義
  4.1 臨床標的体積と計画標的体積
  4.2 標準照射体積の定義
  4.3 線量の評価
5． 粒子線治療の精度を担保する項目
  5.1 標準照射体積の形成
  5.2 粒子線治療照射
  5.3 患者位置決め
  5.4 患者の固定法・補助具
  5.5 治療計画装置
  5.6 呼吸同期照射
6． 設定マージンの計算
7． 治療照射システム受け入れ時の試験
8． 装置のQA項目と許容誤差
  8.1 出力系
  8.2 メカニカル系
  8.3 画像系
  8.4 呼吸同期系
  8.5 安全装置系
9． おわりに

D． 考察

本研究により、粒子線治療施設の実態や新技術の導入状況等を踏まえ、施設基準案、コミッショニング、ＱＡ／ＱＣガイドラインについて成案を得ることができた。

これまでは各施設毎に品質管理の取組が個別になされてきたが、本研究を通してその標準化の方向性が明らかになったと言える。

本研究の成果は、ＩＥＣ国際規格ドラフト、国際放射線防護委員会（ＩＣＲＰ）レポート等の策定にあたって、日本発の参考資料となりうるものであり、ひいては薬事審査や施設認定等の判断基準にも活用が期待される。

E． 結論

国内の粒子線治療施設の協力を得て、各施設の経験や実態を踏まえ、また実際のコミッショニング等を通して、施設基準、コミッショニング、ＱＡ／ＱＣガイドライン等について成案をとりまとめた。これにより、粒子線治療の品質管理の標準化が図られ、粒子線治療の一層の普及に資するものと期待される。

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分担研究報告書【総合】

放射線療法と粒子線治療の比較

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研究要旨：
強度変調原体照射法が、臓器移動を伴う前立腺癌患者に対して、どの程度の精度を保証できるか、また腫瘍の呼吸性移動を伴う肺癌患者に対しても実現可能か臨床的実証研究を行い、適正に強度変調放射線治療が施行できることが示された。強度変調原体照射法は、粒子線治療の有用性を比較する重要な対象であり、粒子線治療も今後も更に簡便化を図る必要があることが明らかとなった。

A. 研究目的

回転型強度変調放射線治療中における臓器の移動量の定量的な検証を行うための技術を開発する。この技術を用いて、臓器移動や腫瘍の呼吸性移動を伴う症例に対する回転型強度変調放射線治療の実現の妥当性を臨床的に実証する。

B. 研究方法

普及型の強度変調放射線治療として期待される強度変調原体照射法（Volumetric Modulated Arc Therapy; 以下 VMAT）中に、治療装置に併設されたコーンビーム CT を同時に撮影できる方法を開発した。その技術を用いて、臓器移動を伴う前立腺癌患者や腫瘍の呼吸性移動を伴う肺癌患者を対象として、腫瘍の移動量を定量的に検証し、臨床的実証研究を行った。

C. 研究成果

対象とした 15 人の前立腺患者全てにおいて、VMAT 中の前立腺重心の移動量は、PTV マージン 5 mm の範囲内にあることが確認された。また、体幹部定位放射線治療が適応となる肺癌患者を対象として、VMAT による定位照射をする、臨床的実証研究を行った。VMAT 中には呼吸波形を取得しながら同時コーンビーム CT を撮影した。得られた呼吸波形を用いて、コーンビーム CT 画像を 4 つの呼吸位相（終末吸気相、呼出相、終末呼気相、吸入相）に分けたところ、いずれの位相のコーンビーム CT 画像にも腫瘍陰影が描出できた。腫瘍の位置は、呼吸位相ごとに異なっており、VMAT 中の腫瘍の呼吸性移動を反映したコーンビーム CT 画像が得られたものと考えられる。また、コーンビーム CT 画像を用いて beam's eye view を作成したところ、腫瘍はいずれの呼吸位相においても、治療計画上の ITV 内に入っていたことが示され、肺癌に対しての VMAT による体幹部定位放射線治療が適正に施行可能であることが示された。

また、VMAT 中にコーンビームと同時に治療ビームによる投影画像から呼吸波形を取得し、位相ごとの再構成画像を得ることに成功した。この治療ビームによる再構成画像から、照射野と腫瘍の相対位置関係を直接把握でき、それぞれの呼吸位相において腫瘍が照射野内に入っていたことを確認できた。この結果は、治療中の腫瘍の動きのモニタリングを治療ビームそのもので行うことができ、コーンビーム CT による余計な被曝を低減で

きる可能性を示唆している。

D. 考察

VMAT は、検証が簡便で装置の占有時間が短く、わが国の医療体制に見合った強度変調放射線治療法と言える。2010 年度は前立腺癌症例を対象として、VMAT における品質保証や治療手順の簡便化を実現した。前立腺癌に対する VMAT は、当施設では一般臨床の一部分として行うことが既に可能となっている。2011 年度はそれを更に進めて、呼吸性移動を伴う腫瘍である肺癌に対しても VMAT における品質保証や治療手順の簡便化が可能であることが示された。

現在、徐々に普及してきている VMAT がどこまで簡便化しながら治療成績を上げることができるかを追求することによって、粒子線治療の有用性を議論するうえでの重要な比較対象となる。

E. 結論

VMAT は、呼吸性移動を伴う腫瘍に対しても、安全かつ簡便な強度変調放射線治療として実施が可能である。全身の腫瘍に対して VMAT が適応可能となり、治療成績がその他の強度変調放射線治療と遜色ないことが実証されれば、医療経済的にも粒子線治療の強いライバルになることが見込まれる。

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総合研究報告書

放射線療法と粒子線治療の比較

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研究要旨：
各癌種の診療・治療ガイドラインの記載を調査し、放射線療法・粒子線治療の適応を明確にした。また、トラクトグラフィを用い、皮質脊髄路をリスク臓器として強度変調放射線治療計画をする新規技術を開発した。

A. 研究目的

放射線療法と粒子線治療との臨床的適応を比較するため、各癌種に対してこれまでに発行されている診療・治療ガイドラインにおける、放射線治療と粒子線治療に関する記載を調査し、放射線療法・粒子線治療の適応を明確にする。また、新規技術による強度変調放射線治療計画法を開発する。

B. 研究方法

1) 現在までに我が国で編集出版されている各癌種の診療・治療ガイドラインの記載内容を調査し、記載内容の比較を行った。

2) 肝細胞癌に対する放射線療法のエビデンスについてシステマティックレビューを行い、放射線療法の適応についての肝癌診療ガイドラインの作成に携わった。

3) 拡散テンソル画像を用いて脳内の皮質脊髄路線維束をトラクトグラフィとして描出し、この皮質脊髄路をリスク臓器として強度変調放射線治療の計画作成を試みた。トラクトグラフィの描出は、拡散テンソル画像上で小脳脚にシードを、一次運動野にターゲットを設定し、Fractional anisotropy < 0.18 で中止するという条件で行った。

C. 研究成果

1) 粒子線治療に関する Clinical question が設定されていたのは、前立腺癌のみであった。肝癌のガイドラインでは、放射線療法の Clinical question に対する解説中で、粒子線治療が安全で有効性の高い治療である可能性を指摘している。

それぞれのガイドラインは、編集方針の点で多様であり、エビデンスを重視したガイドラインばかりでなく、実地臨床での適用頻度を重視したガイドラインも見られた。放射線治療についての記載は一切見られないガイドラインや、一般に知られている治療方法をすべて均等に扱い、放射線治療に関する記載が非常に豊富なガイドラインも見られた。

2)「科学的根拠に基づく肝癌診療ガイドライン 2009 年版」（日本肝臓学会・編）および Clinical Practice Guidelines for Hepatocellular Carcinoma - The Japan Society of Hepatology 2009 update として英文誌 Hepatology Research の特別号に掲載された。肝細胞癌に対する放射線治療および粒子線治療の意義を明確にし、ガイドライン中に記載をした。

3) 画像処理ソフトウェア Dr.View（AJS 株式会社, 東京）を用い、T1 強調画像もしくは T2 強調画像を皮質脊髄路トラクトグラフィにブレンドした画像を使用す

ることで皮質脊髄路線維束の輪郭抽出が可能となり、皮質脊髄路をリスク臓器としたIMRTの計画作成が可能であった。

D. 考察

診療・治療ガイドラインに記載されている内容を今回比較調査したところ、放射線療法は概して、世界的なエビデンスと比較して過小評価されて記載されているものが多く、粒子線治療についても大半のガイドラインでは記載がされていなかった。放射線療法も粒子線治療も、ますます高いレベルのエビデンスを作り出してゆく必要があると思われた。また、既存の診療・治療ガイドラインの検討だけでは放射線療法と粒子線治療の包括的な比較は困難であり、新たに粒子線治療の適応に関するガイドラインの作成が必要と考えられた。

脳機能画像を用いた新たなIMRT計画技術が開発され、特定の神経線維束をリスク臓器としたIMRT計画作成が可能であることが示された。また、本方法は粒子線治療においても応用可能である。

E. 結論

我が国の各癌種の診療・治療ガイドラインは、それぞれの編集方針が互いに大きく異なり、包括的な比較は困難であるため、新たに粒子線治療の適応に関するガイドラインの作成が必要と考えられる。新たに導入される技術も勘案しながら、今後も更に詳細に放射線療法と粒子線治療の有用性を比較する必要がある。

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Ⅲ．研究成果の刊行に関する一覧表

研究成果の刊行に関する一覧表

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Ⅳ. 研究成果の刊行物・別刷
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CLINICAL OUTCOME OF SACRAL CHORDOMA WITH CARBON ION RADIOTHERAPY COMPARED WITH SURGERY

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Purpose: To evaluate the efficacy, post-treatment function, toxicity, and complications of carbon ion radiotherapy (RT) for sacral chordoma compared with surgery.

Methods and Materials: The records of 17 primary sacral chordoma patients treated since 1990 with surgery ($n = 10$) or carbon ion RT ($n = 7$) were retrospectively analyzed for disease-specific survival, local recurrence-free survival, complications, and functional outcome. The applied carbon ion dose ranged from 54.0 Gray equivalent (GyE) to 73.6 GyE (median 70.4).

Results: The mean age at treatment was 55 years for the surgery group and 65 years for the carbon ion RT group. The median duration of follow-up was 76 months for the surgery group and 49 months for the carbon ion RT group. The local recurrence-free survival rate at 5 years was 62.5% for the surgery and 100% for the carbon ion RT group, and the disease-specific survival rate at 5 years was 85.7% and 53.3%, respectively. Urinary-anorectal function worsened in 6 patients (60%) in the surgery group, but it was unchanged in all the patients who had undergone carbon ion RT. Postoperative wound complications requiring reoperation occurred in 3 patients (30%) after surgery and in 1 patient (14%) after carbon ion RT. The functional outcome evaluated using the Musculoskeletal Tumor Society scoring system revealed 55% in the surgery group and 75% in the carbon ion RT group. Of the six factors in this scoring system, the carbon ion RT group had significantly greater scores in emotional acceptance than did the surgery group.

Conclusion: Carbon ion RT results in a high local control rate and preservation of urinary-anorectal function compared with surgery. © **2011 Elsevier Inc.**

Chordoma, sacrum, carbon ion radiotherapy, surgery.

INTRODUCTION

Chordomas are rare malignant tumors arising from embryonic notochordal remnants. They account for only 1–4% of all primary malignant bone tumors (1, 2) and 17.5% of primary malignant tumors of the axial skeleton, with a reported incidence of 0.5 to 0.8/1,000,000 persons (3, 4). Lesions can arise from the sacrococcygeal region (47%), skull base (38%), and vertebral bodies (15%) (5, 6). Many sacral chordomas are quite large at diagnosis and can involve adjacent neurovascular structures and vital organs owing to their deep location within the pelvic cavity. Surgery is the mainstay treatment of chordomas because the tumor has a poor sensitivity to conventional radiotherapy (RT) and chemotherapy (5, 7, 8). Although many investigators have reported surgical resection margins to be the most important predictor of survival and local recurrence, recurrence is not uncommon (6, 9). Moreover, neurogenic dysfunction is a frequent consequence of surgery with adequate surgical margins, and these complications strongly depend on the resection level.

Chordomas have been shown to be refractory to conventional photon RT at doses <60 Gy. The RT can be facilitated with the use of heavy charged particles such as protons or carbon ions, which provide greater physical selectivity. Also, the carbon ion beam possesses unique physical and biologic properties. It has a well-localized energy deposition

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(high-dose peak) at the end of the beam path, called the Bragg peak, leading to improved dose distributions and permitting dose escalation within the target and sparing of adjacent normal tissues. Recently, several investigators have reported on the efficacy of carbon ion RT against sacral chordoma, describing a markedly high local control rate and low toxicity (10–12). However, no studies have focused on the differential oncologic and functional outcomes between surgery and carbon ion RT from identical institutions and using consecutive series of patients. In the present study, the local recurrence-free and disease-specific survival, postoperative complications, and ambulatory, urinary-anorectal, and musculoskeletal function were retrospectively analyzed in patients with sacral chordomas treated with surgery or carbon ion RT at our institutions.

METHODS AND MATERIALS

Between 1990 and 2007, patients with tumors originating from the sacrum that had been histologically proven to be chordomas by experienced pathologists were reviewed. The therapeutic indications varied between before and after 1999. Before 1999, surgical resection was considered the treatment of choice. After 1999, however, patients in whom an adequate surgical margin would be difficult to achieve have undergone carbon ion RT. After 2004, patients were allowed to choose their preferred modality after a detailed explanation of the expected complications and functional impairments after the specific treatment. Carbon ion RT was provided by the National Institute of Radiological Sciences in Chiba, Japan. The specific technique of carbon ion RT used at the National Institute of Radiological Sciences has been previously published (10, 11, 13, 14). In brief, we used dosages from 54.0 to 73.6 Gray equivalent (GyE) on the basis of the results from previous trials of bone and soft tissue tumors. Carbon ion RT was performed once daily, 4 d/wk, for a total of 16 fixed fractions within 4 weeks. Generally, we used fraction doses of 4.4 GyE and 4.6 GyE. The bowel was removed from the treatment area for carbon ion RT. All patients signed an informed consent form.

A total of 17 patients referred to the orthopedic units of our institutions (Nagoya University Hospital, Nagoya Memorial Hospital, and Aichi Cancer Center Central Hospital) participated in the present study. Data regarding age, gender, location, tumor size, American Joint Committee on Cancer staging (15), treatment, surgical margin, local and systemic relapse, follow-up period, and oncologic and functional outcome were obtained. Lower extremity function after treatment was evaluated according to the scoring of Enneking *et al.* (16) at the postoperative point at which functional scores have been shown to plateau. The Musculoskeletal Tumor Society (MSTS) score consists of six items: pain, overall function, emotional acceptance, walking ability, walking supports, and gait handicap or limp. Each item is rated on a scale of 1–5, with 5 the most favorable score. The total score is calculated by summing the individual items. Patients treated with surgery or carbon ion RT were followed up with physical examinations, computed tomography, and magnetic resonance imaging at the outpatient unit of orthopedic surgery in our institutions. In the analysis, the patients lost to follow-up were included to the point at which their health status was last known.

We used the Kaplan-Meier product limit method to estimate the overall and local recurrence-free survival for the group and to illustrate the effect of the individual factors. The log–rank test was used to evaluate the differences between survival curves. The chi-square test or Fisher's exact test was used for the comparison of proportions. In cases of skewed distribution, nonparametric Mann-Whitney tests were used. Statistical analysis was done using Statistical Package for Social Sciences, version 15.0, for Windows (SPSS, Chicago, IL).

RESULTS

No patients had undergone previous RT with photons. No patients presented with recurrent tumor after surgery at other institutions. A total of 18 patients had sacral chordomas. One patient who refused any medical treatment was excluded, for a total of 17 patients included in the present study. No patients had distant metastasis at their initial referral for treatment. Of the 17 patients, 9 were men and 8 were women. According to the American Joint Committee on Cancer Staging System, of the 17 tumors, 4 were Stage IA, 12 were Stage IB, and 1 was Stage IIB. The most proximal tumor extension was L5 in 1 patient, S1 in 5, S2 in 7, S3 in 2, and S4 and S5 in 1 each. No patients received chemotherapy or photon RT. Of the 17 patients, 10 underwent surgery and 7 underwent carbon ion RT. The surgical margins were wide in 8 patients and intralesional in 2. All 17 patients were followed up at the orthopedic units of our institutions. The median follow-up was 56 months (range, 7–118) for all patients. Only 1 patient underwent RT (50 Gy) postoperatively. A total of 3 patients each developed local recurrence and distant metastasis. A total of 3 patients died of disease and 1 of pneumonia unrelated to the chordoma. The clinical data of all 17 patients are listed in Table 1.

The disease-specific and local recurrence-free survival rate for all 17 patients was 73.8% and 77.4% at 5 years, respectively. For the 10 patients who underwent surgery, the 5-year disease-specific and local recurrence-free survival rate was 85.7% and 62.5%, respectively. For the 7 patients who underwent carbon ion RT, the disease-specific and local recurrence-free survival rate at 5 years was 53.3% and 100%, respectively (Fig. 1). However, statistical analysis using the log–rank test revealed no significant difference between the surgery and carbon ion RT groups in either disease-specific ($p = .19$) or local recurrence-free ($p = .14$) survival. Also, no significant factors were noted that influenced the prognosis, except for gender, which showed a marginally significant result for local recurrence-free survival ($p = .043$; Table 2). No difference was found in overall survival for the patients treated before vs. after 1999, when carbon ion RT was introduced for patients with sacral chordoma (Fig. 2).

The mean patient age was 55 years in the surgery group and 65 years in the carbon ion RT group ($p = .28$). The mean major axis of the tumor was 8.2 cm in the surgery group and 10.1 cm in the carbon ion RT group ($p = .13$). The median follow-up was 76 months (range, 7–118) and 49 months (range, 35–72) in surgery and carbon ion RT groups, respectively ($p = .29$). Of the 17 patients, 9 were able to walk without an assistive device, 7 used a single cane, and 1 relied on a wheelchair. In the surgery group, the ability to walk was reduced in 6 of 7 patients with tumor extending above S2

Table 1. Clinical patient data

Pt. No.	Age (y)	Gender	Major axis	Tumor extension	Treatment	Surgical margin	CIRT dose	Local recurrence	Metastatic site	Follow-up period (mo)	Survival
1	75	Male	8	S5	Surgery	Wide	NA	No		93	CDF
2	43	Female	8	S1	Surgery	Intralesional	NA	Yes	Femur, spine	56	DOD
3	67	Male	10	S2	Surgery	Wide	NA	No		105	CDF
4	19	Female	8	S1	Surgery	Wide	NA	No		22	CDF
5	71	Male	11	S1	CIRT	NA	73.6	No		48	DOD
6	31	Female	10	S2	Surgery	Wide	NA	Yes		89	NED
7	60	Female	3	S4	Surgery	Wide	NA	Yes	Lung	87	AWD
8	54	Male	10	S1	CIRT	NA	70.4	No		72	CDF
9	68	Male	12	S2	Surgery	Intralesional	NA	No		7	DOOD
10	66	Male	11	S2	CIRT	NA	70.4	No	SC, spine	56	DOD
11	30	Male	11	L5	CIRT	NA	70.4	No		64	CDF
12	61	Female	11	S2	Surgery	Wide	NA	No		64	CDF
13	80	Female	12	S1	CIRT	NA	70.4	No		42	CDF
14	64	Male	5	S3	Surgery	Wide	NA	No		53	CDF
15	67	Male	7	S3	CIRT	NA	70.4	No		49	CDF
16	86	Female	9	S2	CIRT	NA	54	No		35	CDF
17	60	Female	7	S2	Surgery	Wide	NA	No		12	CDF

Abbreviations: CIRT = carbon ion radiotherapy; NA = not available; CDF =; DOD = dead of disease; NED =; AWD = alive with disease; DOOD: dead of other disease; SC = subcutaneous.

level, a statistically significant difference ($p = .033$, Fisher's exact test). In contrast, the level of tumor extension did not have a significant effect on the ability to walk in the patients undergoing carbon ion RT ($p = 1$). Although 4 of 7 patients already had had neurologic disabilities at their initial referral to our institutions (Grade 2 in 2 and Grade 3 in 2), no patient developed late neurologic toxicity after carbon ion RT.

All 7 patients who underwent carbon ion RT maintained their urinary-anorectal function after treatment. In contrast, 6 (60%) of 10 patients in the surgery group had worsened function postoperatively (Table 3). Probably because 9 (90%) of the 10 patients in the surgery group had urinary anorectal dysfunction, greater resection levels did not show significantly poorer function.

The results of the MSTS functional score in 9 patients are listed in Table 4. The mean MSTS score was 19.8 (66%), 16.5 (55%), and 22.4 (75%) for all patients, the surgery group, and carbon ion RT group, respectively. No significant difference was found in the MSTS score between the surgery and carbon ion RT groups ($p = .32$). However, surgery was significantly associated with a low score of emotional

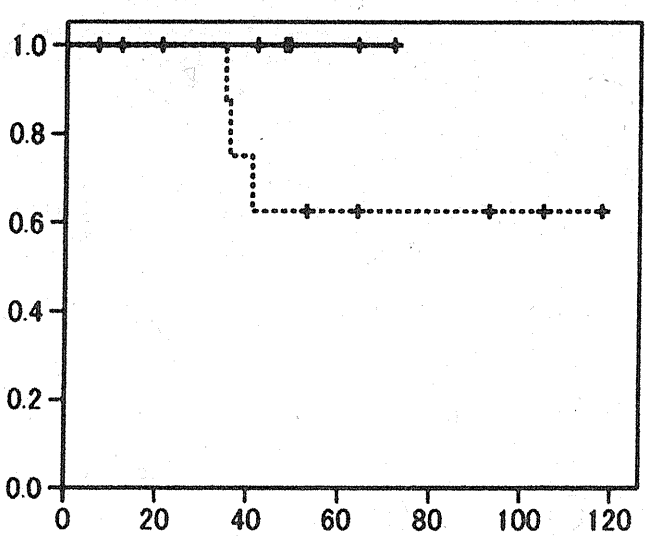

Fig. 1. Kaplan-Meier curves showing local recurrence-free survival of patients who underwent carbon ion radiotherapy (solid line) vs. surgery (dotted line).

Table 2. Disease-specific survival and recurrence-free survival at 5 years

Variable	Patients (n)	DSS (%)	p*	LRFS (%)	p*
All	17	73.8		77.4	
Age (y)			.23		.074
≥ 64	9	55.6		100	
< 64	8	85.7		57.1	
Gender			.64		.043
Male	9	70		100	
Female	8	80		51.4	
Tumor size (cm)			.75		.47
≥ 10	9	71.4		85.7	
< 10	8	75.0		68.6	
Tumor extension			.32		
L5–S1	6	60.0		83.3	.73
S2–S5	11	83.3		71.4	
Treatment			.19		.14
Surgery	10	85.7		62.5	
CIRT	7	53.3		100	
Study period			.89		.80
Before 1999	4	75.0		75	
After 1999	11	74.1		77.8	

Abbreviations: DSS = disease-specific survival; LRFS = local recurrence-free survival; CIRT = carbon ion radiotherapy.
* Log–rank test.

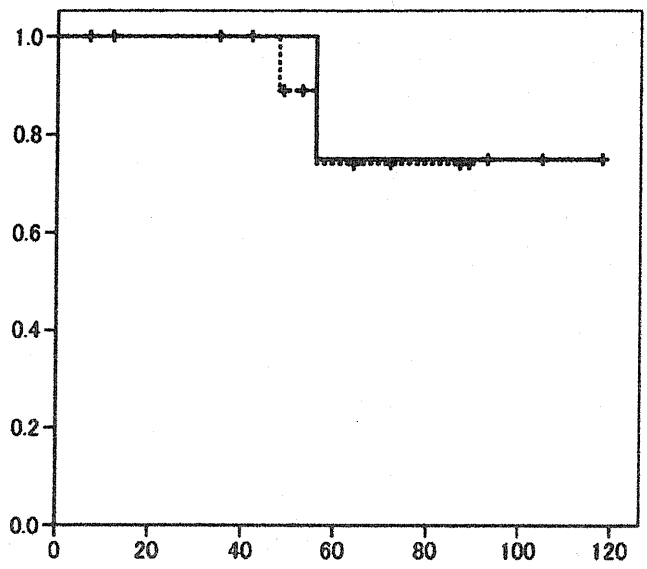

Fig. 2. Kaplan-Meier curves showing overall survival of patients diagnosed with chordomas before (solid line) and after (dotted line) 1999.

acceptance compared with carbon ion RT ($p = .005$). Because the already reduced preoperative function resulting from extensive tumor extension would correlate with low scores at the postoperative evaluation, excluding Patients 10 and 13 from the analysis, revealed a significant difference in the postoperative MSTS score between the 2 groups ($p = .031$ overall; pain, function, emotional acceptance, supports, walking, gait; $p = .026$, $p = .026$, $p = .014$, $p = .386$, $p = .046$, and $p = .026$, respectively).

In the surgery group, 5 patients had wound complications, which ranged from superficial infections in 2 patients that did not require operative intervention to deep wound infection, seroma, and wound dehiscence that required one or more additional operations in 3 patients. Only 1 patient had a wound complication in the carbon ion RT group (Patient 5). This patient had received a total dose of 73.6 GyE and subsequently developed a postoperative deep wound infection and dehiscence that required reoperation and resulted in death, probably of infectious causes. The other 6 patients had received ≤70.4 GyE of carbon ion RT and had no postoperative wound complications.

DISCUSSION

Resection has generally been considered to be the mainstay of treatment of sacral chordoma. Complete resection with adequate surgical margins contributes to a high local control rate, which has been associated with better survival (5, 17–20). Kaiser *et al.* (21) reported a 28% recurrence rate in patients with en bloc resection but a 64% recurrence rate in patients in whom the tumor capsule had been breached intraoperatively. Fuchs *et al.* (22) reported a 5% local recurrence rate with wide surgical margins vs. 71% with inadequate margins. Although several studies have indicated the importance of surgical margins for local control, not a few local failures (5–60%) have occurred, even with wide surgical margins (17, 20, 22–25). In the present study, a 70% local control rate was obtained in the surgery group with mostly adequate surgical margins. However, ensuring adequate margins can be at the expense of normal adjacent neurovascular structures and associated function. Previously, the local control rate for sacral chordoma after carbon ion RT was shown to be 96% at 5 years (10). In the present study, the local control rate after carbon ion RT was 100%, consistent with that noted in a previous study and superior to those from reports of surgery and/or other RT. Conventional RT has been reported to be a useful adjunct to surgery but has not been sufficient as a stand alone therapy (8, 20, 26). Charged particle beam RT, other than carbon ion RT, has been reported for sacral chordoma. Schoenthaler *et al.* (27) reported a 55% 5-year local control rate in 14 patients with helium and neon. Schulz-Ertner *et al.* (12) reported that with carbon ion as a boost therapy followed by surgery and postoperative intensity-modulated RT, the actuarial 3-year local control rate was 81% for spinal and sacral chordomas. DeLaney *et al.* (28)

Table 3. Comparison of clinical characteristics and outcome between groups

Treatment	Tumor extension	Mean age (y)	Mean major axis (cm)	Median follow-up (mo)	LR	DM	Postoperative gait	Urinary-anorectal dysfunction		Postoperative MSTS
								Preoperative	Postoperative	
Surgery ($n = 10$)										
	S1: 2 S2: 5 S3: 1 S4: 1 S5: 1	55	8.2	76	3/10	2/10	A: 5 B: 4 C: 1	3/10	9/10	17 (57%, 4 cases)
CIRT ($n = 7$)										
	L5: 1 S1: 3 S2: 2 S3: 1	65	10.1	49	0/7	1/10	A: 4 B: 3 C: 0	4/7	4/7	22 (73%, 5 cases)

Abbreviations: MSTS = Musculoskeletal Tumor Society (functional score); LR = local recurrence; DM = distant metastasis; A = gait without support; B = gait with a cane; C = nonambulatory; CIRT = carbon ion radiotherapy.

Table 4. Functional evaluation with MSTS scoring system

Pt. No.	Pain	Function	Emotional acceptance	Supports	Walking	Gait	Total
Surgery group							
Overall	2.3	2.8	2	4	3.3	2.8	16.5 (55%)
4	2	2	2	1	2	1	10
6	2	3	2	5	4	4	20
14	2	3	2	5	3	3	18
17	3	3	2	5	2	3	18
CIRT							
Overall	3.8	3.2	5*	3.2	3.4	3.8	22.4 (75%)
8	4	5	5	5	4	5	28
10	5	0	5	1	2	1	14
13	1	2	5	0	1	3	12
15	4	4	5	5	5	5	28
16	5	5	5	5	5	5	30

Abbreviations: Pt. No. = patient number; CIRT = carbon ion radiotherapy.
* $p = .005$ (vs. surgery, Mann-Whitney U test).

reported a 100% local control rate in 23 primary chordomas treated with high-dose photon/proton RT with or without surgery. Of the 9 patients treated without surgery and high-dose photon/proton, only 1 developed local recurrence, a patient with local recurrence after previous surgery, a group notoriously difficult to treat with any salvage therapy (28). Rutz *et al.* (29) reported postoperative proton RT in extracranial chordomas, including seven sacrococcygeal chordomas. They showed a 3-year actuarial local control rate of 86% for chordomas at all locations (29).

The occurrence of distant metastases in the published data has ranged from 5% to 40% and is generally more delayed than the occurrence of local relapse (18, 21, 26, 30). Local recurrence is of great concern because of its inverse relationship with survival (17–20). However, Ahmed (31) recently reported that 2 (40%) of 5 patients with distant metastasis had no local relapse. The results from the present study showed that 1 of the 7 patients who underwent carbon ion RT developed distant metastasis without local relapse, in agreement with the report by Ahmed (31). However, the effect of carbon ion RT on the control of distant metastasis should be analyzed further. The 5-year survival rate of patients with carbon ion RT was 53.3%, lower than the 85.7% rate after surgery. One explanation might be that 1 patient died, probably of local infection after RT with 73.6 GyE, reducing the survival rate among the 7 patients receiving carbon ion RT. The disease-related death rate in the present study was 10% and 29% in the surgery and carbon ion RT groups, respectively. Two patients in the carbon ion RT group died. One patient died of metastatic spread of the chordoma to the lung, and the other died of local infection in an area of skin breakdown after carbon ion RT, as described in the "Results" section. Considering that the reported disease-related death rates have ranged from 33% to 55% (17, 20, 22–25, 30), the results of the present study were more favorable for both surgery and carbon ion RT. This is attributable in part to the adequate surgical margins obtained even in those in whom the tumor had invaded the more proximal levels.

As reported by Gunterberg *et al.* (32) and Stener and Gunterberg (33), ambulatory impairment is related to the number of preserved nerve roots. The loss of bilateral S1 markedly diminishes the ability to ambulate. The results of the present study have indicated that the ability to walk was significantly reduced in 6 of the 7 patients with tumor extending above the S2 level in the surgery group. This was in accordance with a previous report in which only 3 patients were able to walk without the use of an assistive device and the remaining 13 had to use a cane, walker, wheelchair (25). In contrast, the tumor extension level did not affect the ability to walk of the patients undergoing carbon ion RT, one of the most striking results of the present study. Previous studies concerning charged particle RT did not describe ambulatory function in detail (12, 28, 29).

In the present study, 60% of the patients with surgery had worsened urinary anorectal function postoperatively. This is in accordance with a previous report by Hulen *et al.* (25) in which only 1 (6%) of 16 patients had normal bowel and bladder control postoperatively. Previous studies have shown that urinary and fecal continence are impaired when at least one S2 root has been transected (32, 33). Todd *et al.* (34) reported that unilateral resection of the sacral roots or preservation of at least one S3 root will preserve bowel and bladder function in most patients. To obtain a better local control rate (30%) with surgery might have required sacrifice of the critical roots for urinary anorectal function in the present series. In contrast to the outcome with surgery, bowel and bladder function were preserved with carbon ion RT in all patients. Although 4 of 7 patients in the carbon ion RT group already had some degree of urinary anorectal dysfunction at their initial referral to our institutions, the function was also maintained in these 4 cases.

The most common complications were infection and delayed wound healing, which required reoperation in 3 (30%) of 10 patients in the surgery group. Wuisman *et al.* (35) reported the prevalence of wound complications to be 45.5%. Fuchs *et al.* (22) described that local wound breakdown occurred in 33% of patients postoperatively. The rate

of postoperative wound complications in these reports was comparable to that in the present surgery cohort. Considering that only 1 of 7 patients had undergone postoperative RT in the present study, wound complications can occur, irrespective of RT, in patients with sacral chordoma. In contrast to the surgery group, only 1 patient (14%), who had received 73.6 GyE, developed a wound complication in an area of skin breakdown after carbon ion RT. Given that patients who had received 70.4 GyE developed no wound complications and obtained perfect local control, physicians should explain the low complication and high local control rates with 70.4 GyE of carbon ion RT to patients with sacral chordomas.

Serizawa *et al.* (36) reported that 5 (21%) of 24 patients developed Grade 2 late neurologic toxicity after carbon ion RT with 52.8–73.6 GyE. However, 3 of the 5 patients had the disabilities before carbon ion RT (36). DeLaney *et al.* reported that 2 patients with Grade 3 sacral neuropathy had received 77.4 GyE. In contrast, no patients developed neural injuries at doses <70.2 GyE (28). Imai *et al.* (10) reported that 73.6 GyE is a dose level that might cause neurologic toxicity in sacral nerve function. The results of their study also revealed that chordomas above the S2 level resulted in neurologic complications, but that patients with S3-S4 tumors had no adverse reactions (37). We could not compare the results from Imai *et al.* (10) with those from the Massachusetts General Hospital studies by DeLaney *et al.* (28) owing to the difference in the fraction doses. In the present study, carbon ion RT (range, 54.0–73.6 GyE; median, 70.4) did not result in late neurologic toxicity. The neurologic toxicity after 70.4 GyE carbon ion RT (fraction doses of 4.4–4.6 GyE) is considered acceptable for neurologic function.

Although the number of patients was small in both groups, the MSTS score was obtained and compared between the patients in each group. We did not find a difference in the total MSTS score between the 2 groups. However, 5 patients in the carbon ion RT group had 5 points for emotional acceptance compared with 3 patients in the surgery group had only 2 points. One of the limitations of the present functional analysis was the lack of a preoperative evaluation. Because many patients with sacral chordomas will have pain and/or functional dysfunction at their initial referral, the alteration of functional scores should be analyzed between the pre- and postoperative points. Two patients with huge tumors experienced great pain and ambulatory dysfunction before treatment. Excluding these 2 patients from the analysis, the carbon ion RT group had significantly greater MSTS scores compared with the surgery group. These results suggest that carbon ion RT could be a well-accepted modality for sacral chordoma patients.

Because the function and complications, in addition to oncologic outcome, are obviously affected by the treatment modality in patients with sacral chordomas, more detailed informed consent should be required. Since 2004, we have explained the possible impairment of ambulatory and urinary anorectal function and complications after surgery and carbon ion RT according to the previous reports and experience in our institutions.

CONCLUSION

A greater local control rate was achieved after carbon ion RT than after surgery. Fewer wound complications and less post-treatment urinary anorectal dysfunction occurred after carbon ion RT. The functional outcome evaluated using the MSTS scoring system revealed emotional acceptance to be significantly superior in the carbon ion RT group. Although overall survival should be investigated further and late complications should be evaluated, carbon ion RT represents an excellent treatment modality for patients with sacral chordomas.

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Endobronchial Ultrasound-Guided Transbronchial Needle Aspiration for Lymph Node Staging in Patients with Non-small Cell Lung Cancer in Nonoperable Patients Pursuing Radiotherapy as a Primary Treatment

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Introduction: Carbon ion radiotherapy (CIRT) is a promising modality with excellent localization and significant biologic effects on tumors. Nevertheless, success depends primarily on accurate staging before radiotherapy. Surgical interventions should be avoided in patients considered for CIRT because they usually have multiple comorbidities. The aim of this study was to evaluate the effectiveness of endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) for lymph node staging in patients with non-small cell lung cancer before CIRT.

Methods: From April 2005 to December 2007, 49 patients with non-small cell lung cancer considered for CIRT with abnormal positron emission tomography-computed tomography (PET-CT) accumulations in the mediastinum and/or hilum were evaluated by EBUS-TBNA. The convex probe EBUS was used for EBUS-TBNA.

Results: There were 38 men and 11 women. Their mean age was 75.2 years (range: 55–87). Based on PET-CT, clinical staging was four with N1 disease, 42 with N2 disease, and three with N3 disease. By histology, 26 patients had adenocarcinoma, 19 had squamous cell carcinoma, and four had other histologies. All positive lymph nodes on PET-CT were aspirated (range: 1–5; average 2.55 lymph nodes/patient). EBUS-TBNA diagnosed 43 cases as N0 disease and as a result underwent CIRT. Forty of the 43 cases remained in stable condition without local recurrences (follow-up 6–46 months). The diagnostic accuracy of EBUS-TBNA for lymph node staging was 93.9%.

Conclusions: EBUS-TBNA offers accurate minimally invasive lymph node staging in patients who are candidates for CIRT. EBUS-TBNA can be safely performed with a high diagnostic accuracy before CIRT.

Key Words: Endobronchial ultrasound-guided transbronchial needle aspiration, Lymph node staging, Carbon ion radiotherapy.

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Lung cancer is the leading cause of death for men and ranks second for women in Japan. In 2002, 73,635 new lung cancer cases were diagnosed, and 46,566 were older than 70 years.[1] This is a situation similar to the United States, where more than 90,000 patients died of lung cancer and more than 20% of them were older than 80 years.[2] A less invasive but effective treatment is required for patients with lung cancer of advanced age, diminished pulmonary functions, and chronic diseases, such as cardiovascular disorders. Carbon ion radiotherapy (CIRT) has been used for inoperable patients with stage I lung cancer since 1994 in the National Institute of Radiologic Science (NIRS) in Chiba. From previous reports for CIRT by the NIRS, we have achieved high local control with low complication rates.[3–5] In contrast to standard stereotactic radiotherapy (SRT) and proton beam radiotherapy, which show good local control rate in T1 tumors, CIRT has been shown to be effective even in T2 tumors with a local control rate of more than 85%.[6–10] CIRT is a promising modality for stage I lung cancer as an alternative to surgical resection.[11]

Accurate mediastinal and hilar lymph node staging is one of the most important factors that determine the outcome and indications for CIRT. Positive findings in mediastinal or hilar lymph nodes on positron emission tomography-computed tomography (PET-CT) before CIRT should be confirmed by invasive staging. Surgical interventions such as mediastinoscopy[12,13] should be avoided in potential CIRT

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