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特集　固形腫瘍の新しい治療

# 小児固形腫瘍・脳腫瘍の放射線治療

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## 要旨

放射線治療の技術的進歩としての三次元放射線治療（Three-dimensional conformal radiotherapy：3D-CRT）について，その構成要素および治療計画について紹介する．さらに，応用としての脳腫瘍や軟部組織腫瘍に対する臨床試験における放射線治療の実際を紹介する．



**Key Words**

**radiation therapy**
**three-dimensional conformal radiotherapy**
**clinical trial**
**pediatric**

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## はじめに

放射線治療の歴史は1895年のレントゲンによるX線の発見に始まるとされる．その後の放射線生物学・物理学の研究の発展と治療技術・装置の開発により，悪性腫瘍治療の3本柱のひとつとして広く応用されている．その特徴としては，①機能・形態の温存，②治療対象部位の制限が少ない，③合併症を有する患者や高齢者など対象患者の制限が少ない，の3点があげられている．しかし，これらの特徴はさらなる局所制御率の向上と有害反応の軽減があってこそ，臨床においてその有用性を発揮すると考えられる．

本稿では，放射線治療の技術的進歩として三次元放射線治療（Three-dimensional conformal radiotherapy，以下3D-CRTと略す）について述べる．さらに，その応用としての脳腫瘍や，軟部組織腫瘍に対する臨床試験における放射線治療の実際を紹介する．

## 三次元放射線治療計画

3D-CRTとは，放射線腫瘍医の追究する理想をCTやMRI，PETなどの放射線診断学と治療装置に関するテクノロジーの進歩が支え，実現した治療方法といえよう．その応用と成果は重

要臓器に囲まれた，従来の二次元放射線治療では正常組織の有害反応ゆえに，放射線治療にとって困難の多かった領域，脳腫瘍・頭頸部腫瘍や骨盤腫瘍などの治療で，まずその成果が報告され，諸臓器の治療でその応用が進行している．

3D-CRTとは，永田らによれば[1]“薄い間隔で撮像された複数のCT画像に基づいて，正確なターゲット領域とリスク臓器体積（organs at risk volume）の幾何学的配置を決定する．それらを画像処理した種々の三次元画像を用いたうえで，適切な三次元線量計算に基づき正確な放射線治療計画を行う”と定義している．従来の放射線治療が“照射方向と照射野辺縁の設定をしてからターゲット内の線量分布を確認する”のに対し，“ターゲットと関連正常臓器の輪郭を設定してから，計算された三次元画像を利用することによって，照射方向や照射門数を決定する”ように，治療計画は大きな変化をとげた．

さらに，強度変調放射線治療（Intensity-Modulated Radiotherapy：IMRT）では“ターゲットの内部の詳細な照射線量と各種関連リスク臓器の詳細な容積線量を定義（prescribe）した後に，治療計画装置によって最適な照射方法を決定する”こととなり，望ましい線量分布の実現が，治療計画装置の進歩により可能となりつつある．

もっとも重要であるターゲットの決定において，治療計画を施行する放射線腫瘍医間における認識の差異を最小化するために，国際的な用語の統一が行われてきた．現在使用されているICRU Report 62[2]による表記では**表1**に示す用語が使用されている．放射線治療にかかわるターゲットの決定においては，ICRU Report 62に従い対象を決定していくが（図），その容積はGTV＜CTV＜ITV＜PTVの順に大きくなり，対象とする疾患やその組織型・分化度，臨床病期などにより異なる設定が必要となった．たとえば，聴神経腫瘍など良性腫瘍や動静脈奇形，転移性脳腫瘍に対する定位放射線照射においては，CTVはGTVに限りなく近づくこととなる．ターゲットの決定において重要な役割を果すのは画像診断であり，CTやMRI，PETにとどま

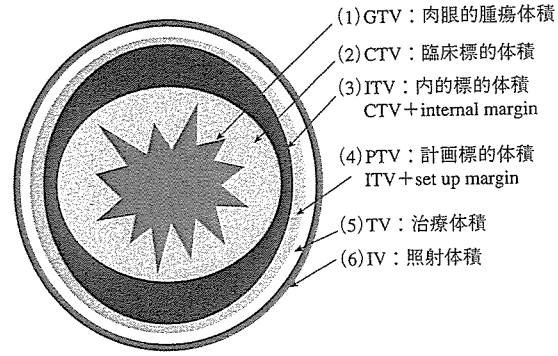


**図　ICRU Report 62に基づく放射線治療にかかわるターゲットの決定**

**表1　放射線治療にかかわるターゲットの決定**

| | |
|---|---|
| GTV：Gross Tumor Volume<br>肉眼的腫瘍体積 | 画像や触診で明らかに腫瘍が存在すると判断される領域の体積 |
| CTV：Clinical Target Volume<br>臨床標的体積 | GTV＋顕微鏡的進展範囲 |
| ITV：Internal Target Volume<br>内的標的体積 | CTVに臓器移動に対するmarginを加えた標的体積<br>CTV＋IM |
| PTV：Planning target volume<br>計画標的体積 | ITVに患者およびビームの位置合わせに関する不正確さを考慮した領域<br>ITV＋SM |

**IM：internal margin**：呼吸移動や腸管のガスによる影響など体内臓器の移動にかかわる**margin**
**SM：set up margin**：毎回の治療における設定誤差にかかわる**margin**

らずMolecular ImagingやFunctional Imagingの応用で腫瘍の浸潤・残存範囲や正常組織の機能を考慮した治療計画の可能性が実現されている．

治療計画の選択においては，従来は治療計画を行って線量分布を計算し（forward planning），その比較により最適治療計画を選択していた．近年，線量を設定したあとに治療計画を最適化するinversed planningが実現している．治療計画の比較には，線量分布図以外に容積線量ヒストグラム（Dose-Volume Histogram：DVH）が使用され，ターゲットや周囲の重要なリスク臓器の全容積中の照射線量が表示されている．TCP（tumor control probability）やNTCP（normal tissue complication probability）の計算も可能である．

3D-CRTは，ターゲットへの線量の集中を可能とし有害反応の軽減をもたらしうるが，総線量の増加により局所制御率の向上が望みうる領域においては，局所制御率をも期待させることとなった．3D-CRTには日本で開発された原体照射や，定位放射線照射，non-coplanar固定多門三次元照射，わが国で開発された歳差運動照射，アメリカで開発されたCyber-knifeなども含まれる．森田ら[3]によれば原体照射とは，“光子線ないし粒子線ビームを用いた二次元ないし三次元方向からの回転運動照射で，どの照射方向から見ても照射野形状がターゲット形状に一致している照射法”と定義されている．CT-simulator，治療計画装置，照射野形状を作成するためのマルチリーフコリメーター（Multi-leaf Collimator：MLC）を搭載した治療装置とネットワークの構築により，原体照射は可能となり，多くの施設に普及している．non-coplanar固定多門三次元照射は，体軸と垂直な方向以外から照射する三次元照射方法で，体軸にそって重要な臓器がとりまくように存在する脳腫瘍や骨盤内腫瘍では，リスク臓器体積の照射線量の軽減に有用である．

定位放射線照射（stereotactic irradiation：STI）とは，小病変に対し多方向から放射線を集中させる方法であり，通常の放射線治療に比較し周囲正常組織の線量を極力減少させつつ，病巣に高線量を集中させる治療である．定位放射線治療は，ガンマナイフに代表される1回で照射する定位手術的照射（stereotactic radiosurgery：SRS）と，分割して照射する定位放射線治療（stereotactic radiotherapy：SRT）に大別される．定位的であるという条件としては，①患者あるいはそれに固定された座標系において照射中心を固定精度内に納めるシステムであること，②定位型手術枠または着脱式固定具を用いた方法であること，③固定装置の照射中心精度が1～2 mm以内であること，④治療中を通じて上記固定精度を保つこと，などが考えられている．脳以外の体幹部定位放射線治療に関しては，①照射装置の照射中心精度が±1 mm以内であること，②治療セットアップの精度が左右，背腹方向それぞれに±5 mmを保ち，頭尾方向に±10 mmを保つ機能を有することが，体幹部定位放射線照射研究会から提言されている．

ガンマナイフは201個の$Co^{60}$より出る$\gamma$線がその中心に集束するよう設計されている．頭部固定用のLeksell stereotactic frameを用い，機械的精度を0.1 mmとする高精度の放射線治療である．SRSは一般放射線治療用の直線加速器（Linac）を用いることにより普及し，より均一な線量分布や大きな照射野が可能となった．Lars Leksellらの治療体積が小さければ逆比例して耐容線量が上り，高線量1回投与が可能となる[4]という理論がSRSの裏づけとなっている．よってその特徴を活かすためにも，対象病変は3 cm以下とされる場合が多い．

SRTは分割照射により治療可能比（正常組織の耐容線量/腫瘍の致死線量）が高まるという放射線生物学のLQ（linear quadratic）モデルを背景としている．1回線量や照射回数などの治療

スケジュールが腫瘍により適切に設定可能であるが，精度がSRSより劣る可能性があり，さまざまな工夫が精度管理のためになされている．

定位放射線照射の治療成績は，局所制御において手術と同等と考えられている．有害反応はFlickingerら[5]の動静脈奇形に関する検討より，その発生頻度が照射部位によることが明らかとなり，照射部位や脳神経との位置関係により1回線量の低減が推奨されている．脳転移の治療は，全脳照射と手術に加え定位放射線照射の登場により，その選択の多様性と妥当性に関する検討がさまざまに行われている．

## 脳腫瘍の三次元放射線治療計画

小児の脳腫瘍ではAstrocytoma星細胞腫がもっとも多く，ついでMedulloblastoma髄芽腫，上衣腫やGerm Cell Tumorが続く．小児の脳腫瘍においては，手術や化学療法の併用による集学的治療の一環として放射線治療が応用されるが，遅発性放射線反応の軽減が重要な課題である．神経機能と神経内分泌機能の発達への影響を軽減するために，照射体積と照射線量の最適化をめざした試みがなされている．

Children's Oncology Group（COG）のLow-

**表2　Intergroup Rhabdomyosarcoma Study Groupの臨床試験における横紋筋肉腫の放射線治療Guidelines**

| 臨床試験 | 総線量 | 1回線量/ターゲット/タイミング | 化学療法と結果 |
|---|---|---|---|
| IRS Ⅰ<br>(1972～78) | age < 3yrs = 40 Gy<br>age < 6yrs and < 5 cm = 50 Gy<br>age > 6 yrs or > 5 cm = 55 Gy<br>age > 6 yrs and > 5 cm = 60 Gy | 1.5～2.25 Gy/Fr/day<br>whole muscle bundle or tumor + margin<br>no difference in local control<br>Immediately: Groups Ⅰ and Ⅱ<br>Week 6: Groups Ⅲ and Ⅳ | VAC, VA, VACA<br>Overall 5-year survival 55% |
| IRS Ⅱ<br>(1978～84) | Group Ⅰ = no RT.<br>Group Ⅱ = 40-45 Gy.<br>Group Ⅲ：age < 6yrs and < 5 cm = 40-45 Gy<br>age > 6 yrs or > 5 cm = 45-50 Gy<br>age > 6 yrs and > 5 cm = 50-55 Gy | 1.5～2.25 Gy/Fr/day<br>GTV + 2 cm<br>Week 0: Group Ⅱ<br>Week 6: Groups Ⅲ and Ⅳ | VAC, VA, VadrC-VAC<br>Overall 5-year survival 63%<br>Botryoid89%,<br>Embryonal 68%,<br>Alveolar 52%, Other 55% |
| IRS Ⅲ<br>(1984～88) | Grp Ⅰ FH-no RT.<br>Grp Ⅰ UH/Ⅱ-41.4 Gy.<br>Group Ⅲ varied by age, size but all < 50.4 Gy. | GTV + 2 cm<br>Day 0: PM with CN palsy, BOS erosion, intracranial extension.<br>Week 2: Group Ⅱ FH/Group Ⅲ orbit and H/N.<br>Week 6: all others | VAC, VA, VadrC-VAC, VAadr<br>CDDP/VP16<br>VadrC-VAC + CDDP<br>Overall 5-year survival 71% |
| IRS Ⅳ<br>(1991～97) | Group Ⅰ, Stage 1/2-no RT.<br>Group Ⅰ, Stage3/Ⅱ-41.4 Gy CRT.<br>Group Ⅲ randomized to<br>50.4 Gy CRT vs 59.4 Gy HRT（1.1 Gy BID） | GTV + 2 cm<br>Day 0: PM with CN palsy, BOS erosion, intracranial extension.<br>Week 12: all others | VA, VAC, VAI, VIE<br>Overall 3-yr FFS 77%<br>No difference in local control with CRT vs HRT. |
| IRS Ⅴ<br>(1999～04) | Experimental dose reductions for selected patients:<br>Group Ⅰ alveolar/undifferentiated 36 Gy<br>Group Ⅱ N0: 36 Gy<br>Group Ⅲ orbit/eyelid: 45 Gy<br>Group Ⅲ second look surgery<br>negative margins: 36 Gy<br>microscopically + margins: 41.4 Gy<br>Group Ⅲ requiring 50.4Gy:<br>volume reduction to initial GTV + 5 mm<br>at 36 Gy if N0, and at 41.4 Gy if N+ | GTV + 2 cm<br>Day 0: PM with intracranial extension only<br>Week 3: low risk,<br>week 12: intermediate,<br>week 15: high risk | Low risk: VA, VAC<br>Intermediate Risk:<br>VAC vs VAC/VTC |

Grade Glioma に対する臨床試験においては[6)~7)]，3D-CRT が応用され線量分布の改善による遅発性放射線反応の軽減が図られている．小児の Glioma の治療においては，発達への影響を考慮して放射線治療の適応を躊躇する傾向にあったが，3D-CRT による正常組織への影響の軽減によって，放射線治療のより積極的な応用が検討されており，今後の臨床試験結果が注目される．

Medulloblastoma の集学的治療においては，Craniospinal Irradiation（CSI）が標準治療であり，high risk 群で 36 ～ 40 Gy，average risk 群で 18 ～ 24 Gy 程度の CSI と，54 Gy 前後の後頭蓋窩への照射が組み合せて施行されている．Children's Cancer Group（CCG）で施行された CCG9892 では，化学療法の併用により CSI の線量を低減する臨床試験が施行され，その効果が確認された[8)]．その後の CCG9961 では average risk 群では，化学療法併用で 23.4Gy の CSI と 54 ～ 55.8 Gy の後頭蓋窩への照射が施行された．さらに COG では，average risk 群で CSI の線量の低減とともに，3D-CRT を応用して原発巣への追加照射の照射野を，後頭蓋窩より腫瘍床＋margin へ限局する臨床試験が提案されている．総線量や照射野以外に考慮されるべき放射線治療因子として，治療期間の延長が治療効果に与える影響が delCharco らにより報告されている[9)]．5 年後頭蓋窩制御率が照射期間 45 日以内で 89％であったのに対し，45 日を超えると 68％と低下し（$p = 0.01$），5 年無再発生存率が照射期間 45 日以内で 76％であったのに対し，45 日を超えると 43％と低下していた（$p = 0.004$）．放射線治療の中断の治療効果への影響は，International Society of Paediatric Oncology（SIOP）と United Kingdom Children's Cancer Study Group（UKCCSG）の臨床試験でも指摘されており[10)]，今後臨床試験を検討する際に十分認識すべきと考える．

## 軟部組織腫瘍の三次元放射線治療計画

横紋筋肉腫の治療は，1970 年代より集学的治療が積極的に進められており，臨床試験の結果により治療成績の改善が進められてきた分野の一つである．**表 2** に，Intergroup Rhabdomyosarcoma Study Group により計画されてきた集学的治療の経過を示す[11)~15)]．放射線治療は，化学療法の併用薬剤の変化とともに総線量の軽減が図られた．一方で，IRS-Ⅳでは Group Ⅲにおいて，50.4 Gy の通常分割照射と 59.4 Gy の多分割照射（1.1 Gy を 1 日 2 回照射）が比較検討された．Donaldson らの報告では[16)]，failure-free survival（FFS）および overall survival（OS）と

**表 3　IRS-V 放射線治療 Guidelines による正常組織の耐容線量と DVH による評価**

| 正常組織 | 通常照射による上限 | DVH |
|---|---|---|
| 頭部　脳 | 全脳 3 歳未満 23.4Gy | 不要 |
| | 全脳 3 歳以上 30.6Gy | 不要 |
| 左右網膜 | | 必要 |
| 左右視神経 | 46.8Gy | 必要 |
| 視神経交叉 | 46.8Gy | 必要 |
| 下垂体 | | 必要 |
| 角膜 | 41.4Gy | 不要 |
| 水晶体 | 14.4Gy | 不要 |
| 涙腺 | 41.4Gy | 不要 |
| 鼓牛 | | 必要 |
| 頸部　甲状腺 | | 必要 |
| 胸部　肺 | 両肺 14.4Gy | 必要 |
| 心臓 | 全心臓 30.6Gy | 必要 |
| 腹部　肝臓 | 全肝 23.4Gy | 必要 |
| 腎臓 | 両側で 14.4Gy | 必要 |
| 消化管 | 一部 45Gy | 不要 |
| 全腹―骨盤 | 30Gy（1.5Gy/回） | 不要 |
| 骨盤　膀胱 | | 必要 |
| 直腸 | | 必要 |
| 脊髄　脊髄 | 45Gy | 必要 |

この耐容線量は化学療法と併用した場合の有害事象の増強することが考慮されていない．大量化学療法併用時の耐容線量はさらに低いことが予想され，両側腎，肝臓全体，両側肺，全脳，脊髄，心臓全体への照射の場合はさらに 5 Gy 程度低い線量を上限とすることが望ましいと考えられる

もに通常分割照射と多分割照射で有意差を認めなかった．現在進行中のIRS-Vでは，1日1回1.8 Gy/回の通常分割照射が採用され，新たにIMRTを含む3D-CRTが推奨されており，小線源治療や陽子線治療を含む正常組織の線量を軽減した放射線治療が，放射線治療ガイドラインに取り入れられている．表3にIRS-Vの放射線治療Guidelinesにおいて示されている正常組織の耐容線量とDVHによる評価が必要な正常組織を示す．今後，臨床試験の結果によるevidenceの蓄積により，さらに適切な照射線量の設定が可能となることが期待されている．

## おわりに

小児の悪性腫瘍において，放射線治療の技術的進歩により応用範囲が拡大してきている．小児に対する放射線治療は，リスク臓器の線量に細心の注意をはらった治療が実施されるべきであり，さらに有害事象の経過観察が長期に必要である．

今後，線量分布の最適化による治療成績の向上と有害事象の軽減や，分割照射方法や化学療法や手術との併用の工夫に関するevidenceの蓄積が求められている．

●文　献


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## 軟部腫瘍の病理とスライドセミナーのお知らせ

会　期　2004年11月20日(土) 午前9時30分～午後6時30分（懇親会　午後7時～）
21日(日) 午前9時～午後5時
会　場　浜松市楽器博物館内研修室
対　象　軟部腫瘍の診断，治療に従事する臨床検査技師，病理医，放射線科医，整形外科医，形成外科医，小児科医，皮膚科医およびこの領域に関心のある方
講　師　Antonio G Nascimento　Professor, Mayo School of Medicine, Rochester, USA
Angelo P Dei Tos　Director, Regional Hospital of Treviso, Treviso, Italy
参加費　15,000円（ハンドアウト代2,000円を含む）懇親会は別途5,000円
申込締切　2004年10月（定員が150名ですのでお早めに申し込みください）

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# Pro-Gastrin–Releasing Peptide as a Factor Predicting the Incidence of Brain Metastasis in Patients with Small Cell Lung Carcinoma with Limited Disease Receiving Prophylactic Cranial Irradiation

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**BACKGROUND.** Prophylactic cranial irradiation (PCI) reduces the incidence of brain metastasis with an effect on overall survival in patients with small cell lung carcinoma (SCLC). In spite of multidisciplinary intensive treatment approaches, many patients still experience brain metastasis. The authors retrospectively analyzed the characteristics of the first failure event due to brain metastasis (FBM) in patients treated with PCI.

**METHODS.** Between January 1990 and April 2004, 71 patients with limited disease SCLC were treated with PCI after completing systemic treatment at the National Cancer Center Hospital (Tokyo, Japan). Univariate and multivariate analyses were used to identify factors related to FBM and survival.

**RESULTS.** The FBM and overall incidence of brain metastasis (OBM) were 16.9 % (12 of 71) and 26.8% (19 of 71), respectively. Median time to progressive disease and median survival were 8.4 months and 21.6 months, respectively. Elevation of pro-gastrin–releasing peptide (Pro GRP) level before PCI was found to be a significant predictive and prognostic factor for FBM, OBM, and survival on multivariate analysis ($P = 0.007$, $P = 0.025$, and $P = 0.009$, respectively).

**CONCLUSIONS.** An elevated Pro GRP level before PCI was found to be significantly related to FBM and survival, and should be considered before PCI is performed. *Cancer* **2005;104:811–6.** © *2005 American Cancer Society.*

**KEYWORDS: prophylactic cranial irradiation, small cell lung carcinoma, limited disease, predictive factor, pro-gastrin–releasing peptide.**

Small cell lung carcinoma (SCLC) accounts for approximately 20% of all lung carcinomas.[1] Although SCLC rapidly develops distant metastasis, it is very sensitive to chemoradiotherapy, unlike non-SCLC. Limited disease SCLC is clinically confined to the hemithorax, and chemoradiotherapy is the standard treatment. In patients with limited disease SCLC, chemotherapy combined with thoracic radiotherapy yields complete remission (CR) rates of 50–85%, with a median survival time of 12–20 months.[2–4] The 5-year survival rate is reported to be 26% for patients who have CR.[4] Because chemoradiotherapy reduces the risk of intrathoracic disease recurrence, distant metastasis in the brain has been the main cause of disease recurrence. Although only 10% of patients have brain metastasis at the time of diagnosis, the cumulative incidence at 2 years is > 50%.[5,6] As many as 73% of patients develop clinically apparent central nervous system metastases before death,[7,8] and even higher rates are documented in autopsy series.[9] The brain is the initial site of disease recurrence in 5–

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33% of patients, and is the only site of disease recurrence in ≤ 20% of patients.[10,11]

Although several randomized trials of prophylactic cranial irradiation (PCI) have attempted to reduce the risk of brain metastasis and to improve survival, to our knowledge its role in the management of patients with SCLC has remained controversial according to the results of each trial.[12–14]

Recently, the metaanalysis of these trials comparing PCI with no-PCI found that PCI led to a small but significant absolute reduction in mortality (5.4%), and that PCI not only significantly reduced the risk of brain metastasis, but also improved both overall survival (OS) and disease-free survival among patients with SCLC in CR.[15] These results suggest that PCI should be considered as a part of the standard treatment for patients with limited disease SCLC who achieved CR or good partial remission (PR).

Although PCI was performed for patients who achieved CR or good PR as part of the combined treatment that consisted of chemotherapy and thoracic radiotherapy, brain metastasis occurred in 4–24% of the treated patients.[6,12–14] Whole-brain irradiation (WBRT) for brain recurrence was often difficult because these patients had already received PCI to the whole brain. Therefore, we should strictly consider PCI for patients who could achieve a true CR, as assessed with diagnostic imaging. In addition, we should be careful to follow the patients who have a high risk of brain recurrence after PCI.

To our knowledge, there are no previous reports that describe the characteristics of patients with brain metastasis after PCI. In the current study, we analyzed retrospectively predictive factors for brain metastasis in patients with limited disease SCLC treated with PCI.

## MATERIALS AND METHODS

### Patients

A total of 71 patients with limited disease SCLC were treated with PCI after chemoradiotherapy for primary disease between January 1990 and April 2004 at the National Cancer Center Hospital (Tokyo, Japan). Fifty-four patients were male, and the median age was 62 years old (range, 40–75 years).

Histologic or cytologic examination confirmed the diagnosis of SCLC in all patients. Before the initiation of systemic treatment, staging was performed using computed tomography (CT) or magnetic resonance imaging (MRI) scans of the chest, abdomen, and brain, as well as radionuclide bone scanning and bone marrow aspiration and biopsy. Limited disease was defined as being limited to one hemithorax, mediastinal, hilar, or supraclavicular area, which could be encompassed within a reasonable single radiation portal. Patients with pleural effusion found on chest films or CT scan were excluded.

Tumor response was classified in accordance with the World Health Organization (WHO) criteria.[16] After systemic treatment, including thoracic radiotherapy, PCI was administered to patients with CR or good PR according to the results of chest radiography and CT or MRI scans of the head, chest, and abdomen.

### Thoracic Radiotherapy

The majority of patients ($n$ = 55 [77.5%]) received accelerated twice-daily thoracic radiotherapy comprised of 45 gray (Gy) in 1.5-Gy fractions. The remaining patients ($n$ = 16 [22.5%]) received once-daily radiotherapy, 50 Gy in 2-Gy fractions. Radiotherapy was performed 5 days per week, excluding weekends and holidays. Sixty of the 71 patients received concurrent chemoradiotherapy, which began on Day 2 of the first cycle of combination chemotherapy as cisplatin (80 mg/m$^2$, Day 1) plus etoposide (100 mg/m$^2$, Days 1, 2, and 3). The other patients received sequential thoracic radiotherapy after the forth cycle of chemotherapy.

The initial field included the primary tumor volume with a 1.5-cm margin around the mass, the ipsilateral hilum, the entire width of the mediastinum, and the supraclavicular lymph nodes (only if there was tumor involvement).

### Chemotherapy

All patients received cisplatin combination chemotherapy. After concurrent chemoradiotherapy, 34 patients received 3 cycles of cisplatin plus etoposide, 17 patients received CODE therapy (cisplatin at a dose of 25 mg/m$^2$ weekly for 6 weeks; vincristine at a dose of 1 mg/m$^2$ during Weeks 2, 4, and 6; and doxorubicin at a dose of 40 mg/m$^2$ and etoposide at a dose of 80 mg/m$^2$ for 3 days during Weeks 1, 3, and 5), and 9 patients received 3 cycles of cisplatin (60 mg/m$^2$, Day 1) plus irinotecan (60 mg/m$^2$, Days 1, 8, 15). In patients treated with sequential radiotherapy, five patients received four cycles of cisplatin plus etoposide, four patients received four cycles of cisplatin plus irinotecan, and two patients received four cycles of cisplatin containing combination chemotherapy, optimized for each patient.

### Prophylactic Cranial Irradiation

All patients who achieved CR ($n$ =40 [56.3%]) or good PR ($n$ = 31 [43.7%]) were treated with PCI. The median time between the initiation of systemic induction treatment and the initiation of PCI (duration) was 3.7 months (range, 2.6–7.5 months).

The target volume was the entire intracranial site. Individual shaped ports with multileaf collimators

were used to define the irradiation target volume. Patients were treated using a megavoltage linear accelerator with 4–6 megavolt (MV) photons. Treatment was delivered with equally weighted right and left lateral fields, with the dose calculated on the central ray at mid-separation of the beams.

Of the 71 patients who received PCI, the majority of patients (52 of 71 [73.2%]) received 25 Gy in 2.5-Gy fractions daily, 12 patients received 30 Gy in 2-Gy fractions daily, 6 patients received 24 Gy in 1.5-Gy fractions twice daily, and 1 patient received 36 Gy in 2-Gy fractions daily. All PCI was performed a total of 5 days per week. The treatment was administered with a linear accelerator of 6 MV ($n$ = 53 patients) or 4 MV ($n$ = 18 patients). The median follow-up time after PCI was 16.3 months (range, 1.4–113.6 months).

### Statistical Analysis

The first failure event due to brain metastasis (FBM) was defined as brain metastasis as a first event after PCI, and the overall incidence of brain metastasis (OBM) was defined as the overall incidence of brain metastasis found throughout the clinical course after PCI. Clinical and laboratory variables before PCI were chosen by considering possible factors indicated by our own experience. We determined the predictive factors for FBM and OBM using both univariate (Pearson chi-square test/Fisher exact test) and multivariate analysis.

Before PCI, 9 categorized variables for multivariate analysis were selected, as follows: gender (male vs. female), age (< 60 vs. ≥ 60 years), response to systemic treatment (CR vs. good PR), time between the start of systemic treatment and the start of PCI (duration: < 4 months vs. ≥ 4 months), hemoglobin level (< 10 g/dL vs. ≥ 10 g/dL), lactate dehydrogenase level (≤ 229 U/L vs. > 229 U/L), C-reactive protein (≤ 0.1 mg/dL vs. > 0.1 mg/dL), neuron-specific enolase (NSE) (≤ 10 ng/mL vs. > 10 ng/mL), and pro-gastrin–releasing peptide (Pro GRP) (≤ 46 pg/mL vs. > 46 pg/mL).

Time to progressive disease (PD) was measured from the first day of PCI until PD or the last day of follow-up without PD, and OS time was measured from the first day of PCI until death or the last day of follow-up. Median time to PD and median OS were estimated using the Kaplan–Meier method. Prognostic factors were evaluated by multivariate analysis. All statistical analyses were performed using SPSS version 12.0J (SPSS Inc., Chicago, IL).

## RESULTS

### Incidence of Brain Metastasis

FBM and OBM were observed in 16.9% (12 of 71; 95% confidence interval [95% CI], 8.2–17.3%) and 26.8% (19 of 71; 95% CI, 16.5–27.3%) of patients, respectively. Nine patients with FBM had multiple brain metastases and the others had solitary lesions. Among these patients, six were reirradiated with WBRT or stereotactic multiarc radiotherapy, five were treated with systemic chemotherapy, and one received best supportive care. The median times to FBM and OBM were 9.4 months (range, 1.1–23.5 months) and 12.0 months (range, 1.1–92.9 months), respectively. In univariate analysis, an elevated Pro GRP level was found to be significantly related to FBM and OBM (Table 1) ($P$ = 0.007 and $P$ = 0.029, respectively). Using a complete dataset from

TABLE 1
Univariate Analyses of Pretreatment Variables for FBM and OBM

| Variables | No. of patients | No. of FBM | $P$ value | No. of OBM | $P$ value |
|---|---|---|---|---|---|
| Gender | | | 0.27 | | 0.99 |
| Male | 54 | 11 | | 15 | |
| Female | 17 | 1 | | 4 | |
| Age (yrs) | | | 0.71 | | |
| ≥ 60 | 38 | 7 | | 11 | 0.66 |
| < 60 | 33 | 5 | | 8 | |
| Energy (MV) | | | 0.99 | | 0.36 |
| 4 | 18 | 3 | | 3 | |
| 6 | 53 | 9 | | 16 | |
| Total dose (Gy) | | | 0.99 | | 0.08 |
| ≤ 25 | 58 | 10 | | 13 | |
| > 25 | 13 | 2 | | 6 | |
| Hyperfraction | | | 0.27 | | 0.33 |
| Twice daily | 6 | 2 | | 3 | |
| Once daily | 65 | 10 | | 16 | |
| Response | | | 0.63 | | 0.70 |
| Good PR | 31 | 6 | | 9 | |
| CR | 40 | 6 | | 10 | |
| Duration (mos)[a] | | | 0.61 | | 0.86 |
| ≥ 4 | 25 | 5 | | 7 | |
| < 4 | 46 | 7 | | 12 | |
| Hemoglobin level (g/dL) | | | 0.75 | | 0.79 |
| < 10 | 43 | 8 | | 12 | |
| ≥ 10 | 28 | 4 | | 7 | |
| LDH level (U/L) | | | 0.99 | | 0.99 |
| > 229 | 6 | 1 | | 1 | |
| ≤ 229 | 65 | 11 | | 18 | |
| CRP level | | | 0.75 | | 0.50 |
| > 0.1 mg/mL | 42 | 8 | | 10 | |
| ≤ 0.1 mg/dL | 29 | 4 | | 9 | |
| NSE level (ng/mL) | | | 0.63 | | 0.99 |
| > 10 | 8 | 2 | | 2 | |
| ≤ 10 | 59 | 10 | | 16 | |
| Pro GRP level (pg/mL) | | | 0.007 | | 0.029 |
| > 46 | 12 | 5 | | 5 | |
| ≤ 46 | 37 | 2 | | 4 | |

FBM: first failure event due to brain metastasis, OBM: overall incidence of brain metastasis, MV: megavolt; Gy: grays; PR: partial remission, CR: complete remission; LDH: lactate dehydrogenase, CRP: C-reactive protein; NSE: neuron- specific enolase; Pro GRP: pro-gastrin-releasing peptide.
[a] Duration indicates the time between the initiation of systemic induction treatment and the initiation of prophylactic cranial irradiation.

TABLE 2
First Progressive Disease Sites after PCI

| Site | No. of patients | % of all patients |
|---|---|---|
| Local failure (inside the thorax) | 20 | 28.2 |
| Distant metastasis[a] | 26 | 36.6 |
| Abdominal organ | 7 | 9.9 |
| Bone | 9 | 12.7 |
| Spinal cord | 1 | 1.4 |
| Brain | 12 | 16.9 |
| Total | 46 | 64.8 |

PCI: prophylactic cranial irradiation.
[a] Three patients had more than one progressive disease site in distant metastasis.

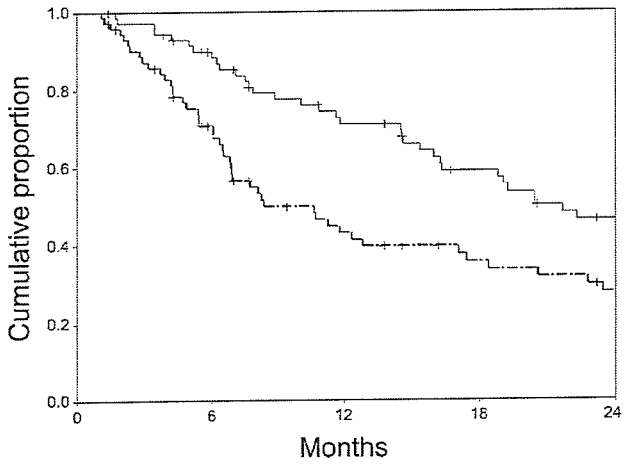


**FIGURE 1.** Kaplan–Meier analysis of time to disease progression (dotted line) and overall survival (solid line).

49 patients, a multivariate logistic regression model disclosed that an elevated Pro GRP level was a significant predictive factor for both FBM (hazard ratio [HR], 12.5; 95% CI, 2.00–77.9 [$P$ = 0.007]) and OBM (HR, 5.89; 95% CI, 1.25–27.7 [$P$ = 0.025]).

### Time to Progressive Disease and Survival

In the current series, the majority of patients (46 of 71 [64.8%]; 95% CI, 53.7–65.4%) experienced PD in their clinical courses. The first sites of PD are listed in Table 2. The median time to PD and the median survival time were 8.4 months ( 95% CI, 3.9–12.8 months) (Fig. 1)and 21.6 months (95% CI, 14.1–29.2 months) (Fig. 1), respectively. A multivariate Cox regression model indicated that elevated Pro GRP level before PCI was a prognostic factor (HR, 2.97; 95% CI, 1.31–6.75 [$P$ = 0.009]).

## DISCUSSION

It is suggested that PCI eradicates subclinical brain metastasis that is protected from cytotoxic drugs by the blood-brain barrier as a pharmacologic sanctuary.[17] A recently reported metaanalysis of seven prospectively randomized trials demonstrated both an OS and disease-free survival advantage for patients with limited disease SCLC who received PCI compared with patients who did not receive PCI.[15] However, the metaanalysis included various trials and often insufficient systemic chemotherapy regimens, different PCI techniques, and a mixed population of patients with limited and extensive disease.[12–15] Therefore, Kotalik et al.[18] found there was insufficient evidence to make a definitive recommendation in terms of the total dose, fractionation, indication, and timing of PCI according to this metaanalysis.

In the current study, 16.9% of patients had brain metastasis as a first site of failure, which is consistent with previous reports of 4–24%.[6,12–14] The salvage treatment for brain metastasis after PCI would be restricted by the number of brain metastases, patient condition, and previous irradiation. To our knowledge, no report has described the predictive or prognostic factors for outcomes after PCI. Therefore, our results could provide useful information concerning the indication of PCI and close follow-up in patients with limited disease SCLC with CR or good PR who received intensive multidisciplinary treatment.

We found that elevated Pro GRP level before PCI was a significant predictive factor for FBM and for OBM ($P$ = 0.007 and $P$ = 0.025, respectively). The other pretreatment variables such as clinical and laboratory parameters had no influence on FBM or OBM. Among tumor markers, NSE is known to have a high false-positive rate due to hemolysis, whereas Pro GRP is a stable and reliable tumor marker for SCLC.[19] In addition Pro GRP is found to have higher specificity than NSE, and its serum level was frequently elevated at an earlier stage compared with that of the NSE level in patients with SCLC at the time of diagnosis.[20,21] It is reported that Pro GRP reflects tumor volume and the effect of treatment more sensitively than does NSE, and that it is useful in detecting PD because Pro GRP levels increase before disease recurrence becomes evident.[19,21,22] From the results of the current study, the elevation of Pro GRP before PCI might reflect the existence of residual viable tumor cells after a series of induction treatments, even if CR or good PR is indicated by imaging. A PCI would be recommended for patients with limited and extensive disease SCLC with CR.[15] However, PCI might not be sufficiently beneficial for decreasing the incidence of brain metastasis in patients with an elevated Pro GRP level. Therefore, by the completion of whole therapy, we should completely eliminate residual subclinical intracranial

and/or extracranial disease that causes the brain recurrence.

Several evidence-based guidelines for limited disease SCLC described uncertainty in terms of the optimal regimen, schedule of drug administration, duration of chemotherapy, and maintenance chemotherapy.[23,24] Although there is a guideline that recommends a maximum of six cycles of chemotherapy,[23] the trend in clinical trials and practice, including the current study, has been to use only four cycles of cisplatin-based chemotherapy. In patients with CR with elevated Pro GRP after four cycles of chemotherapy, two additional cycles of chemotherapy might be possible to eliminate tumor cells, to normalize Pro GRP levels, and to reduce the risk of brain recurrence.

A previous study suggested that there may be a dose-response relation for PCI, and that higher doses were more effective in reducing the risk of brain metastasis.[14] If currently ongoing trials that compare 25 Gy in 10 fractions with 36 Gy in 18 fractions[18] indicate the superiority of high-dose PCI, this will be another option to optimize the PCI procedure for controlling the subclinical disease at pharmacologic sanctuary.

The previous WHO criteria for evaluation of tumor response[11] did not consider the value of tumor markers. However, the Response Evaluation Criteria in Solid Tumors (RECIST) include tumor markers for assessment of CR.[25] Serum laboratory methods more accurately evaluate the evidence of viable tumor cells, and have a complementary role to the imaging studies when macroscopic tumor disappears or residual scar remains. In SCLC, tumor markers are well correlated to the response and tumor volume,[19,21,22] as was observed with Pro GRP in the current study. Therefore, CR according to the RECIST guidelines might be more appropriate in the evaluation of patients with SCLC for PCI.

Several authors reported many prognostic factors of clinical and laboratory parameters for patients with SCLC.[26] Almost all the analyses in the previous reports showed pretreatment factors before the initiation of systemic therapies. We analyzed pretreatment parameters for patients with CR or good PR receiving PCI. In our study, most of the laboratory parameters fell within normal limits before PCI, except for Pro GRP as a prognostic factor.

Local failure occurred in approximately one-half of the patients with disease recurrence, in addition to distant failure. The Southwest Oncology Group reported the pattern of failure in 114 patients with limited disease SCLC treated with cisplatin plus etoposide and concomitant thoracic radiotherapy followed by PCI. Local failure and distant metastasis occurred in 49% and 35% of patients, respectively.[27] These results also suggested that the main cause for disease recurrence was local or distant failure. Therefore, it is crucial to develop new drugs or regimens for improving local and distant control, which achieve a high rate of CR without elevation of tumor markers such as Pro GRP before PCI.

The results of the current study demonstrate that elevation of Pro GRP before PCI is a significant predictive factor for the first failure event due to brain metastasis. With regard to the indication of PCI, the assessment of clinical response according to RECIST might be evaluated more accurately using Pro GRP together with conventional imaging studies.

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# A multidisciplinary treatment strategy that includes high-dose chemotherapy for metastatic retinoblastoma without CNS involvement

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**Summary:**

**The prognosis of patients with metastatic retinoblastoma is poor with conventional chemotherapy and radiation. Since retinoblastoma is highly chemosensitive, dose-escalation of chemotherapeutic agents with stem cell support should be promising. We report our experience with high-dose chemotherapy (HDC) and autologous stem cell transplantation (SCT) in patients with metastatic retinoblastoma. Five patients with metastatic retinoblastoma underwent HDC with autologous SCT following conventional chemotherapy and local radiation therapy. Stem cells (bone marrow in four and peripheral blood stem cells in one) were collected after marrow involvement was cleared. Melphalan was a key drug in all patients, and was administered in combination with other agents such as cisplatin, cyclophosphamide, carboplatin or thiotepa. Three patients are currently alive disease-free at 113, 107 and 38 months, respectively, from the time of SCT. They had no central nervous system (CNS) involvement. The two patients who died of disease had CNS involvement. No long-term sequelae of HDC have been noted. Our treatment strategy using HDC appears to be effective for treating metastatic retinoblastoma without CNS involvement.**

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Retinoblastoma, the most common ocular malignancy in childhood, develops in infants, and the incidence is one in 160 000–20 000 births in Japan.[1] Many therapeutic modalities have been employed, and retinoblastoma has become one of the curable pediatric solid tumors. Nevertheless, the prognosis of extraocular retinoblastoma with metastasis to bone/bone marrow (BM) or the central nervous system (CNS) remains very poor.[2] Such high-risk populations include involvement of the cut end of the optic nerve, extrascleral spread into the orbit, lymphatic or hematogenous dissemination, CNS involvement and trilateral retinoblastoma. The overall occurrence of extraocular retinoblastoma was 4.8% of all patients at an institution.[3] Since retinoblastoma is highly chemosensitive, a treatment strategy that includes the dose-escalation of chemotherapeutic agents and stem cell support should be promising. We treated five patients with metastatic retinoblastoma using high-dose chemotherapy (HDC) followed by autologous stem cell transplantation (SCT), and three patients are currently alive and disease-free. Although our experience is very limited, our experience suggests the feasibility of a prospective study.

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## Patients and methods

Five patients received HDC for extraocular retinoblastoma between March 1986 and November 2000 at the National Cancer Center Hospital of Japan (NCCH), and the data reported reflect the last patient contact as of January 2004. All patients originally were treated with radiation therapy and/or enucleation for intraocular disease at NCCH. The clinical characteristics of the patients are described in Table 1. After completion of the initial series of local ophthalmic therapies in NCCH, four of the five patients developed metastatic recurrence, as reported elsewhere.[4–6] Only one patient had BM metastasis at the initial diagnosis. Staging studies included computed tomography and magnetic resonance imaging of orbits and brain, histopathologic evaluation of BM aspiration and cytologic examination of cerebrospinal fluid (CSF). All patients were classified as having stage III/IV disease by the grading system of Grabowski and Abramson.[7] After the diagnosis of metastatic diseases was established, all patients were treated with conventional chemotherapy with or without radiotherapy and surgical enucleation (Table 2). Systemic chemotherapy included courses of vincristine, cyclophosphamide and doxorubicin with or without cisplatin alternating with cisplatin and cyclophosphamide, or

**Table 1** Patients characteristics

| *UPN* | *Sex* | *Age at diagnosis* | *Involvement* | *Metastases at diagnosis* | *Treatment* | *Metastases after therapy* |
|---|---|---|---|---|---|---|
| 1 | F | 3 months | Bilateral | None | Right: 50.7 Gy radiation<br>Left: enucleation | Brain (optic chiasm), spinal cord (L1) |
| 2 | M | 10 months | Bilateral | None | Right: 49.4 Gy radiation<br>Left: enucleation | Brain (ethmoid and sphenoid sinus), bilateral cervical LNs |
| 3 | F | 41 months | Left | None | Left: 46 Gy radiation + HIT | Right temporal bone, marrow (70%) |
| 4 | F | 16 months | Right | Marrow | Right: enucleation + 6 Gy radiation + chemotherapy | |
| 5 | F | 18 months | Right | None | Right: 46 Gy radiation + enucleation + HIT + PC + CTT + IVI | Right orbit, marrow (50%) |

UPN = unique patient number; HIT = heat-inducing thermotherapy; PC = photocoagulation; CTT = chemothermotherapy; IVI = intravitreal injection.

**Table 2** Therapy and outcome

| *UPN* | *Cx. after Mets* | *Rx. after Mets* | *SCT from relapse (mos)* | *Conditioning (mg/m²)* | *Stem cell source* | *Result* | *Meta. after SCT (mos)* | *Sequelae* |
|---|---|---|---|---|---|---|---|---|
| 1 | VCR/CY/ADR × 2<br>CY/CDDP × 1 | Spine 40 Gy, cranium 25 Gy + boost 15 Gy | 5 | CDDP 90, CY 120 mg/kg, L-PAM180 | BM | DOD | Spinal cord at Th12-L1 level (24 mos) | NE |
| 2 | VCR/CY/ADR × 3<br>CDDP/ETO × 2 | Cranium 40 Gy + boost 20 Gy, spine 21 Gy, cervical LNs 40 Gy | 5 | CDDP 90, CY 120 mg/kg, L-PAM180 | BM | DOD | Rt. cervical LN (4 mos) | NE |
| 3 | VCR/CY/ADR × 4<br>CDDP/ETO × 2 | Focal site 40 Gy | 7 | L-PAM 180, VP-16 800, CBDCA 1600 | BM | NED (113+) | None | None |
| 4 | VCR/CY/ADR × 3<br>CDDP/ETO × 3 | — | 6 | L-PAM 180, VP-16 800, CBDCA 1600 | BM | NED (107+) | None | None |
| 5 | VCR/CY/ADR/<br>CDDP × 3 CBP/<br>ETO × 4 | — | 7 | L-PAM 160, CY 120 mg/kg, TEPA 500 | PBSC | NED (38+) | None | None |

SCT = stem cell transplantation; BM = bone marrow; CNS = central nervous system; LN = lymph node; NED = no evidence of disease; DOD = dead of disease; NE = not evaluable; VCR/CY/ADR = vincristine 1.5 mg/m²/day × 1, cyclophosphamide 600 or 800 mg/m²/day × 2, doxorubicin 40 mg/m²/day × 1; CDDP/CY = cisplatin 90 mg/m²/day × 1, cyclophosphamide 1200 mg/m²/day × 1; CDDP/ETO = cisplatin 20 mg/m²/day × 5, etoposide 100 mg/m²/day × 5; VCR/CY/ADR/CDDP = vincristine 1.5 mg/m²/day × 1, cyclophosphamide 1200 mg/m²/day × 1, doxorubicin 40 mg/m²/day × 1, cisplatin 18 mg/m²/day × 5; CBP/ETO = carboplatin 120 mg/m²/day × 5, etoposide 100 mg/m²/day × 5; L-PAM = melphalan; VP-16 = etoposide; CBDCA = carboplatin; TEPA = thiotepa.

cisplatin and etoposide, or carboplatin and etoposide. After complete response of tumor involvement in the BM, autologous BM cells were collected from four patients, autologous blood stem cells from one patient, respectively. The nonpurged stem cells were cryopreserved. All patients also received one to five intrathecal injections of methotrexate at a variable dose of 5–12.5 mg/dose, concomitant with systemic chemotherapy. Radiation therapy was given in four patients to sites that had harbored bulky disease at early stage after the diagnosis of metastasis. All patients were prepared for HDC with SCT after achieving complete remission, which was evaluated by imaging studies, BM aspiration and/or CSF examination. We harvested BM cells or peripheral blood stem cells, if a BM aspirate had no tumor cells on morphologic analysis before harvesting. We did not apply minimum residual disease (MRD) studies on BM cells or peripheral blood stem cells. Conditioning regimens for all patients contained melphalan 180 mg/m² as a key drug. Concomitant agents were cisplatin 90 mg/m² and cyclophosphamide 120 mg/kg (case 1, 2), etoposide 800 mg/m² and carboplatin 1600 mg/m² (case 3, 4), or thiotepa 500 mg/m² and cyclophosphamide 120 mg/kg (case 5). The collected BM cells (1.0–1.7 × $10^8$ total nucleated cells/kg) or peripheral blood stem cells (4.7 × $10^6$ CD34+ cells/kg), which were unmanipulated, were infused approximately 24 h after completion of the conditioning chemotherapy. Granulocyte-colony stimulating factor was administrated intravenously once daily from day +5 or +7, and was continued until engraftment of neutrophils was established (case 3–5).

## Results

### *Engraftment*

Engraftment of neutrophils, defined as the first of two consecutive days of an absolute neutrophil count of at least 0.5 × $10^9$/l, occurred 18, 26, 10, 14 and 11 days, respectively, after stem cell rescue. Platelet engraftment, defined as the first of 2 consecutive days of an absolute platelet count of at least 50 × $10^9$/l sustained without transfusion, occurred 67, 32, 11, 51 and 16 days, respectively, after stem cell rescue.

### *Toxicities*

All patients developed severe mucositis with oropharyngeal pain (WHO grade 3) after SCT. Only one patient had elevated transaminase levels greater than five times normal (case 5). All patients developed febrile neutropenia without a detectable pathogen, which subsided within 7 days by antibiotic treatment. No other acute toxicities associated with SCT were observed.

### *Patient survival*

All three patients without CNS metastasis are alive disease-free at 113, 107 and 38 months, respectively, from the time of SCT (case 3–5). They are alive without complications, except for orbital growth retardation because of local irradiation and surgical enucleation. Two patients died of recurrent diseases 4 and 48 months, respectively, after SCT (case 1, 2). There was no second malignancy in this series.

## Discussion

The prognosis of patients with metastatic retinoblastoma is poor with conventional chemotherapy and radiation therapy.[2,8] Honavar *et al*[9] have shown that postenucleation adjuvant therapy is safe and effective in significantly reducing the occurrence of metastasis in patients with retinoblastoma manifesting high-risk histopathologic characteristics.[9] Several centers have used conventional-dose chemotherapy and radiation therapy for hematogenously spread extraocular disease. Despite some reports of long-term event-free survival,[7,10] the bulk of the evidence suggests that the prognosis remains poor with such an approach.[11]

A limited number of studies and case reports have suggested that HDC with autologous stem cell rescue might be beneficial for patients with metastatic retinoblastoma (Table 3).[12–20] Namouni *et al*[14] conducted a study of HDC consisting of carboplatin, etoposide and cyclophosphamide (CARBOPEC) followed by autologous SCT in 25 patients, including 12 patients with distant metastases. Among eight children with bone and BM metastases, five survived between 11 and 70 months disease free, while three patients with CNS metastases relapsed in the CNS after HDC and died. Thus, the CARBOPEC regimen appeared to be effective only for patients with bone and/or BM involvement of retinoblastoma. Dunkel *et al*[16] reported four retinoblastoma patients with orbit and BM metastases who underwent HDC consisting of carboplatin and thiotepa with or without etoposide. All patients survived event-free for 46–80 months after the diagnosis of metastatic disease. They concluded that this treatment strategy is effective for metastatic retinoblastoma without CNS involvement. Rodriguez-Galindo *et al*[19] reported four retinoblastoma patients with bone and BM metastases, treated by intensive systemic therapy. Although they did not mention an effectiveness of HDC, they concluded that the use of intensive multimodal approach in patients with metastatic retinoblastoma without CNS involvement could achieve long-term survival.

The important component in HDC is the alkylating agents, which have favorable toxicity profile. There are some reports that thiotepa is effective for high-risk retinoblastoma and other malignancies.[16,19,21,22] As it penetrates well into the brain, as demonstrated by similar drug levels in CSF and in serum after intravenous injection bolus use, we should consider the high-dose thiotepa in the attempts of HDC in disseminated retinoblastoma, particularly with CNS involvement. However, we used not thiotepa but melphalan for HDC. High-dose melphalan and SCT have been used to treat neuroblastoma, rhabdomyosarcoma and Ewing's sarcoma in children.[23–26] In addition, Inomata and Kaneko[27] suggested that retinoblastoma was most sensitive to melphalan based on a colony assay on double agar layers. Kaneko treated six patients with intraocular retinoblastoma that recurred after irradiation therapy by injecting 40 mg/m$^2$ of melphalan into the ipsilateral intracarotid artery, and by applying ocular hyperthermia (45°C, 1 h).[5] Two patients were cured (no recurrence for more than 10 years) with a single treatment procedure while preserving adequate visual function. Based on their observation, we selected melphalan as a key drug for HDC. We should consider that not only thiotepa but also melphalan is an effective agent of HDC for retinoblastoma. As other agents, busulfan and nitrosurea drugs

**Table 3** High-dose chemotherapy for retinoblastoma

| *Author (year)* | *n* | *Marrow involvement (+/−)* | *Bone Metastasis (+/−)* | *CNS Metastatsis (+/−)* | *High-dose chemotherapy* | *Result* |
|---|---|---|---|---|---|---|
| Namouni *et al* (1997)[14] | 12 | 1/11 | 7/5 | 4/8 | CARBOPEC | 6 alive |
| Dunkel *et al* (2000)[16] | 4 | 3/1 | 4/0 | 0/4 | CTE 3, TC 1 | 4 alive |
| Kremens *et al* (2003)[19] | 5 | 4/1 | 2/3 | 0/5 | CTE 4, BCyE 1 | 5 alive[a] |
| Rodriguez-Galindo *et al* (2003)[20] | 4 | 4/0 | 4/0 | 0/4 | CE 1, BuCyM 1, CyE 1, CyTopo 1 | 2 alive |
| Jubran *et al* (2004)[3] | 4 | 1/3 | 2/0 | 1[b]/3 | CTE | 2 alive |
| Our cases | 5 | 2/3 | 2/3 | 2/3 | CDDP-CyM 2, MEC 2, TCyM 1 | 3 alive |

[a]One alive after relapse.
[b]Pineal.
CARBOPEC = carboplatin + etoposide + cyclophosphamide; CTE = carboplatine + thiotepa + etoposide; TC = thiotepa + carboplatin; BcyE = busulfan + cyclophosphamide + etoposide; CE = carboplatin + etoposide; BuCyM = busulfan + cyclophosphamide + melphalan; CyE = cyclophosphamide + etoposide; CyTopo = cyclophosphamide + topotecan; CDDP-CyM = cisplatin + cyclophosphamide + melphalan; MEC = melphalan + etoposide + carboplatin; TCyM = thiotepa + cyclophosphamide + melphalan; DOD = dead of disease.

(nimustine, ranimustine), which are effective because of their capacity to cross the blood–brain barrier, have been used for retinoblastoma.[28,29]

We conclude that our treatment strategy that includes high-dose melphalan with autologous SCT and local irradiation is effective in patients with metastatic retinoblastoma without involvement of the CNS, although a wide variation in the HDC regimen made it difficult to judge the objective safety and efficacy of autologous SCT. A safer and more effective modality is required to better control CNS involvement. The possible risk of late sequelae secondary to additive toxicity by HDC and cranial radiation should be critically evaluated. Since metastatic retinoblastoma is a rare disease, a larger cooperative study is needed to clarify the safety and efficacy of this HDC strategy.

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特集 骨転移痛治療の新たな展開

# 骨転移痛に対する放射線療法の現状と新しい試み

伊藤芳紀* 加賀美芳和* 角美奈子* 今井 敦* 池田 恢*

疼痛緩和を目的とした放射線療法において，近年報告された大規模なランダム化比較試験やメタアナリシスの結果，病的骨折や骨折のリスクがなく，脊髄麻痺兆候や神経因性疼痛がない症例に対する明らかな線量-効果関係は示されなかった．しかしこれまでの臨床試験は評価方法が一定でないなどの問題点もあり，今後実施される骨転移に関する放射線療法の臨床試験のエンドポイントをまとめた「国際的コンセンサス(international consensus)」が提示された．再照射や新しい照射方法などの骨転移に対する放射線療法の課題はまだ残されており，今後のより正確な臨床試験での評価が望まれる．

## はじめに

骨転移による疼痛，病的骨折，脊髄圧迫などは患者のQOL(quality of life)を著しく低下させ，そのうち疼痛が主症状である．骨転移の治療には外部放射線治療，整形外科的手術，鎮痛薬，化学療法，内分泌療法，内部照射，骨吸収抑制薬などがあり，予後，病状，一般活動状態（performance status：PS）などを考慮して種々の組み合わせで治療がおこなわれる．骨転移に対する放射線療法の目的としては，①疼痛の軽減，②病的骨折の予防，③脊髄への直接浸潤あるいは腫瘍の圧迫に伴う麻痺の予防と治療であり，このうち疼痛の軽減を目的とすることが最も多く，鎮痛薬と並び放射線療法は有痛性骨転移の一般的な治療である．至適な照射スケジュールを決めるため，これまでさまざまな分割法の違いによるランダム化比較試験がおこなわれ，一定の見解が得られるようになった．しかし再照射などの骨転移に対する放射線療法の課題は残されている．また，近年の骨転移による疼痛発生機序の分子生物学的研究の進歩や放射線療法における物理工学的進歩はめざましいものがあり，骨転移に対してどのようなアプローチができるのかも今後の課題である．

本稿では，骨転移痛に対する外部放射線治療に

KEY WORDS
有痛性骨転移
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再照射
臨床試験

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