厚生労働科学研究費補助金（医療技術実用化総合研究事業）
（分担）研究報告書

症候性脳放射線壊死に対する核医学的診断とベバシズマブの静脈内投与による治療

研究分担者　杉山一彦　広島大学病院がん化学療法科　教授

研究要旨
脳腫瘍患者に対する放射線治療後に生じた症候性脳放射線壊死に対して抗 VEGF 抗体であるベバシズマブの投与を行い、その有効性と安全性を検証する多施設間共同研究に参加した。

A. 研究目的
脳腫瘍放射線治療後に生じた症候性脳放射線壊死の治療におけるベバシズマブの臨床効果を検証する。

B. 研究方法
大阪医大を中心とする多施設間共同研究体制に入り、策定されたプロトコールに乗っ取り、同意を得た患者にベバシズマブによる治療を施行し、患者のフォローアップを行う。

（倫理面への配慮）
臨床研究プロトコールは広島大学病院の倫理委員会によって審議され承認済みである。患者には十分な説明を行い、同意を書面で得た後に研究参加していただく。

C. 研究結果
平成25年1月に58歳男性例の治験薬の投与が終了した。その後、神経症状の改善は乏しかったものの、腫瘍造影効果の低下、周辺T2高信号域の縮小が観察された。同年秋より嚢胞成分の増大が徐々に観察されはじめ、右片麻痺の増悪、進行を認めたために、平成26年5月、外科的介入を行い、病巣を摘出した。病理診断は広汎な壊死巣を背景にしたごく少数の異型細胞の散剤性増殖を認めた。片麻痺は改善、原発巣の肺癌も制御良好で、平成27年1月現在、存命中である。

D. 考察
本研究プロトコールに従って、慎重な経過観察をした。

E. 結論
プロトコールを順守し、登録症例の追跡に協力していく。

F. 健康危険情報
総括研究報告書参照

G. 研究発表
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(2) 杉山一彦: 脳腫瘍のガイドライン 第1版の概要: 第34回日本脳神経外科コングレス モーニングセミナーMS 2-1:平成26年5月17日: 大阪
(3) 杉山一彦: 悪性神経膠腫における bevacizumab治療、第19回日本脳腫瘍の外科学会 イブニングセミナー: 平成26年9月12日: 東京

H. 知的財産権の出願・登録状況
（予定を含む。）
1. 特許取得　　なし
2. 実用新案登録　なし
3.その他
特記事項無し

厚生労働科学研究費補助金（医療技術実用化総合研究事業）
（分担）研究報告書

症候性脳放射線壊死に対する核医学的診断とベバシズマブの静脈内投与による治療

研究分担者　阿部竜也　大分大学　準教授

研究要旨
脳腫瘍患者に対する放射線治療後に生じた症候性脳放射線壊死に対して抗 VEGF 抗体であるベバシズマブの投与を行い、その有効性と安全性を検証する多施設間共同研究に参加した。

A．研究目的
脳腫瘍放射線治療後に生じた症候性脳放射線壊死の治療におけるベバシズマブの臨床効果を検証する。

B．研究方法
大阪医大を中心とする多施設間共同研究体制に入り、策定されたプロトコールに乗っ取り、同意を得た患者にベバシズマブによる治療を施行し、患者のフォローアップを行う。

（倫理面への配慮）
臨床研究プロトコールは○○大学医学部附属病院の倫理委員会によって審議され承認済みである。患者には十分な説明を行い、同意を書面で得た後に研究参加していただいた。

C．研究結果
平成26年度は登録を行わず、前年度に投与施行した患者の経過観察を行った。
経過観察を行った患者は、浮腫、造影域体積の計測を行った結果、1年以上増大なく経過した。

D．考察
本臨床試験は症候性脳放射線壊死の治療として適切な治療効果が得られた。

E．結論
今後本臨床試験の結果を集計し、統計処理を行い、薬事承認に備えたい。

F．健康危険情報
総括研究報告書を参照

G．研究発表
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第32回日本脳腫瘍学会　千葉
2014年11月30日（日）－12月2日（火）

H．知的財産権の出願・登録状況
（予定を含む。）
1．特許取得
なし
2．実用新案登録
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3．その他
なし

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（分担）研究報告書

症候性脳放射線壊死に対する核医学的診断とベバシズマブの静脈内投与による治療

研究分担者　武笠晃丈　東京大学医学部附属病院脳神経外科　講師

研究要旨
脳腫瘍患者に対する放射線治療後に生じた症候性脳放射線壊死に対して抗 VEGF 抗体であるベバシズマブの投与を行い、その有効性と安全性を検証する多施設間共同研究に参加した。

A．研究目的
脳腫瘍放射線治療後に生じた症候性脳放射線壊死の治療におけるベバシズマブの臨床効果を検証する。

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大阪医大を中心とする多施設間共同研究体制に入り、策定されたプロトコールに乗っ取り、同意を得た患者にベバシズマブによる治療を施行し、患者のフォローアップを行う。

（倫理面への配慮）
臨床研究プロトコールは東京大学医学部附属病院の倫理委員会によって審議され承認済みである。患者には十分な説明を行い、同意を書面で得た後に研究参加していただいた。

C．研究結果
平成26年度は登録を行わず、follow-upした患者の画像を主任研究者に送付し、浮腫、造影域体積の計測を行った。

D．考察
本臨床試験は症候性脳放射線壊死の治療として適切な治療効果が得られた。

E．結論
今後本臨床試験の結果を集計し、統計処理を行い、薬事承認に備えたい。

F．健康危険情報
総括研究報告書を参照

G．研究発表
1．論文発表

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8. 武笠晃丈：グリオーマの発生・進展にかかわるエピゲノム異常（シンポジウム・指定演者）：第 37 回 日本分子生物学会 2014 年 11 月 27 日(25-7)：パシフィコ横浜（神奈川）
9. 武笠晃丈、齊藤邦昭、相原功輝、永江玄太、Brett E. Johnson、、高柳俊作、大谷亮平、田中將太、柳澤俊介、上田宏生、山本尚吾、辰野健二、Joseph F. Costello、西川亮、永根基雄、成田善孝、植木敬介、油谷浩幸、斉藤延人：神経膠腫悪性転化症例のオミクス解析から考える個別化治療戦略（ポスター）第 32 回日本脳腫瘍学会学術集会 2014.11.30 (11.30-12.2)：千葉 浦安 シェラトン・グランデ・トーキョーベイ・ホテル（浦安・千葉）
10. 武笠晃丈：がんゲノム進化、進展と治療に伴う変化の視点から（招待講演）：日経バイオテク／日経バイオテク ONLINE プロフェッショナルセミナー 創薬におけるゲノム情報の活用法：2014 年 12 月 10 日：UDX ギャラリーネクスト(秋葉原・東京)

H. 知的財産権の出願・登録状況

1. 特許取得
   なし

2. 実用新案登録
   なし

3.その他
   特記事項なし

厚生労働科学研究費補助金（医療技術実用化総合研究事業）
（分担）研究報告書

症候性脳放射線壊死に対する核医学的診断とベバシズマブの静脈内投与による治療

研究分担者　寺﨑瑞彦　久留米大学准教授

研究要旨
本研究では、神経症状を呈する脳放射線壊死に対する治療法確立を最終目的として、現存の治療にて効果不十分である症候性脳放射線壊死症例に対してベバシズマブの静脈投与の有効性を検討する単相第Ⅱ相多施設共同研究に参加した。2014年2月12日時点の久留米大学における同意取得例は1例であり、死亡イベントおよび重篤な有害事象は当院ではなかった。

A．研究目的

本研究目的は神経症状を呈する脳放射線壊死に対する新規の治療法確立である。具体的には既存の治療法にて効果不十分である症候性脳放射線壊死症例に対してベバシズマブの有効性と安全性を検証する第Ⅱ相単相臨床試験に参加した。近年、治療技術の発達に伴う生存期間の延長から増加している脳放射線壊死は現時点での標準治療が確立されておらず、欧米においてもベバシズマブに着眼した試験は行われておらず当該研究によりベバシズマブの有効性がみとめられれば多くのがん患者の福音となると思われる。

B．研究方法

原発もしくは転移性脳腫瘍もしくは隣接臓器の腫瘍に対する放射線治療後3か月以上経過したのちに症候性の脳放射線壊死を呈した症例を対象として、PETにて活動性病巣が否定され、かつ、全身状態や主要臓器評価において選択規準を満たした症例に対してベバシズマブとして1回5mg/kgに相当する用量を二週間ごとに点滴静注する。

（倫理面への配慮）

本研究は患者を対象とした介入試験である。「ヘルシンキ宣言」ならびに「臨床研究に関する倫理指針」を遵守して実施される。臨床試験実施計画書及び患者同意説明文書は久留米大学の倫理委員会　においても科学的及び倫理的な面からの審査・承認を経て、高度医療届出後に試験が開始された。被験者からの同意取得に当たっては同意説明文書を用いて試験の内容、予想される不利益・危険性、同意撤回の自由等を説明する。被験者が説明内容を十分に理解したことを確認した上で、本試験への参加について本人の自由意志による同意を文書にて取得する（インフォームドコンセント）。

C．研究結果

当該分担での研究成果は現時点で以下のごとくである。

同意取得例の内訳等

平成26年度は登録を行わず、前年度に投与した患者の経過観察を行った。

2015年2月12日時点の久留米大学における同意取得例は**1**例（登録番号**011-001**）であった。

68歳男性。2007年腫瘍摘出術を施行した髄膜腫の患者。術後の放射線照射と化学療法後、再発認めたため、2009年、2010年、2011年にガンマナイフ照射施行した。その後、症候性放射線壊死による麻痺が生じたため Methionin-PET による判定後に本臨床試験登録し、プロトコール通りにベバシズマブ投与施行した。

予定されていた 6 回までの継続投与が完遂できており、死亡イベントおよび重篤な有害事象（**SAE**）は当院ではなかった。

D．考察

本試験は2013年2月において予定登録症例の40例の登録が終了し、試験終了となっている。久留米大学における登録症例もプロトコール治療終了後1年の追跡期間終了している。

E．結論

登録症例も申請時研究計画に沿って概ね順調に経過したと評価している。今後本臨床試験の結果を集計し、統計処理を行い、薬事承認に備えたい。

F. 健康危険情報
総括研究報告書参照

G. 研究発表
1. 論文発表

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H. 知的財産権の出願・登録状況
(予定を含む。)

1. 特許取得
なし

2. 実用新案登録
なし

3.その他
特記事項なし

厚生労働科学研究費補助金（医療技術実用化総合研究事業）
（分担）研究報告書

症候性脳放射線壊死に対する核医学的診断とベバシズマブの静脈内投与による治療

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研究要旨
脳腫瘍患者に対する放射線治療後に生じた症候性脳放射線壊死に対して抗 VEGF 抗体であるベバシズマブの投与を行い、その有効性と安全性を検証する多施設間共同研究に参加した。

A. 研究目的
脳腫瘍放射線治療後に生じた症候性脳放射線壊死の治療におけるベバシズマブの臨床効果を検証する。

B. 研究方法
大阪医大を中心とする多施設間共同研究体制に入り、策定されたプロトコールに乗っ取り、同意を得た患者にベバシズマブによる治療を施行し、患者のフォローアップを行う。
なお研究分担者は平成25年4月より東北大学医学部脳神経外科・准教授の立場から現職に異動した。本研究の登録症例は東北大学における症例となる。

（倫理面への配慮）
臨床研究プロトコールは東北大学医学部附属病院の倫理委員会によって審議され承認済みである。患者には十分な説明を行い、同意を書面で得た後に研究参加していただいた。

C. 研究結果
平成26年度は登録を行わず、前年度までに投与施行した患者の経過観察を行った。
症例は2005年5月（27歳）より治療歴のある右前頭葉の退形成性乏突起星細胞腫の再発症例である。2009年11月に再発症例に対して再摘出術後追加化学療法を行っていたが、さらに摘出腔壁の造影領域と両側大脳半球に浸潤するT2/FLAIR高信号領域に対して2012年1月中性子捕捉療法を大阪医大にて行った。その一ヶ月後から急速に造影領域と浮腫の拡大を認め、bevacizumab投与を行った。これにより著しく病態は改善し、通常の生活に戻ることが可能となった。2012.12.31までこの状態を維持することを確認後、前述のように北里大学へ異動となった。

D. 考察
本臨床試験は症候性脳放射線壊死の治療として適切な治療効果が得られた。

E. 結論
今後本臨床試験の結果を集計し、統計処理を行い、薬事承認に備えたい。

F. 健康危険情報
総括研究報告書を参照

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H. 知的財産権の出願・登録状況
（予定を含む。）

1. 特許取得
なし

2. 実用新案登録
なし

3.その他
なし

研究成果の刊行に関する一覧表

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Abstract

New radiation modalities have made it possible to prolong the survival of individuals with malignant brain tumors, but symptomatic radiation necrosis becomes a serious problem that can negatively affect a patient's quality of life through severe and lifelong effects. Here we review the relevant literature and introduce our original concept of the pathophysiology of brain radiation necrosis following the treatment of brain, head, and neck tumors. Regarding the pathophysiology of radiation necrosis, we introduce two major hypotheses: glial cell damage or vascular damage. For the differential diagnosis of radiation necrosis and tumor recurrence, we focus on the role of positron emission tomography. Finally, in accord with our hypothesis regarding the pathophysiology, we describe the promising effects of the anti-vascular endothelial growth factor antibody bevacizumab on symptomatic radiation necrosis in the brain.

Key words: bevacizumab, positron emission tomography, pseudoprogression, radiation necrosis

Introduction

Most patients who develop radiation necrosis in the brain originally received radiation treatment for either brain tumors or head and neck cancers. In rare cases, radiation treatment for vascular lesions such as arteriovenous malformations may cause radiation necrosis, but the treatment modality and doses are quite different between the treatments for tumors and vascular lesions. In this review, therefore, we focus on radiation necrosis in the brain that is derived from radiation treatment for brain tumors and, head and neck cancers.

Radiation necrosis in the brain is often encountered after the treatment of metastatic brain tumors, especially by stereotactic radiosurgery, the incidence rate following stereotactic radiosurgery for such tumors is up to 68%.[1–4] Numerous reports have also linked radiation necrosis to the treatment of primary brain tumors. The incidence of radiation necrosis in the setting of focal radiotherapy has been estimated as 3–24%.[5–11] The most important factors in the risk of cerebral radiation necrosis are the radiation dose, the fraction size, and the subsequent administration of chemotherapy.[8] A smaller fraction size even with the same total radiation dose will increase the biological effective dose and subsequently the incidence of radiation necrosis. For concurrent chemotherapy for malignant gliomas, the incidence increases by threefold.[12–14] At least in patients who receive radiosurgery, the irradiated volume is also critical in terms of the risk of radiation necrosis[7,15–17] and re-irradiation or additional boost radiation treatment by stereotactic radiotherapy pose additional risk as well.[8]

There are two distinct concepts of radiation-induced injury in the brain. One is pseudoprogression and the other is radiation necrosis. Generally speaking, pseudoprogression occurs relatively earlier (i.e., 2–5 months after the initiation of adjuvant treatment), and is generally detected by contrast enhancement in neuro-imaging modalities such as magnetic resonance imaging (MRI). Pseudoprogression usually shows a self-limited course and eventual resolution, both clinically and radiographically.[12–14,18] Radiation necrosis occurs rather later than pseudoprogression, after the treatment, and often does not subside without intensive treatment. Histologically, radiation necrosis is found mainly in white matter with endothelial damage, perilesional edema, and gliosis, as described below.[19–24] Sometimes pseudoprogression also shows symptoms,[25] and occasionally it is difficult to differentiate pseudoprogression and radiation necrosis. In addition, pseudoprogression, radiation necrosis, and tumor recurrence are difficult to differentially diagnose, especially with

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neuroimaging modalities such as MRI.

Clearly, the risk of radiation-induced injury that attends radiation treatment is a significant challenge.

Pathophysiology of Radiation Necrosis

The histopathological characteristics of radiation necrosis include coagulation and liquefaction necrosis in the white matter, with capillary collapse and wall thickening and hyalinization of the vessels.[26–30] Telangiectasia is also reported to be a result of the genesis of collateral blood flow against ischemia caused by the obstruction of small venules and arterioles, as reported in a monograph by Burger and Boyko.[31] These histological changes seem to be caused by chronic inflammation and microcirculatory impairment.[19,21–23,32–34]

With respect to the cause of radiation necrosis, two hypotheses have been put forward. One postulates that the necrosis arises due to direct injury of the brain parenchyma, especially glial cells. According to this hypothesis, radiation treatment directly injures the brain parenchyma, leading to secondary damage to vessels. The primary damage is focused on glial cells, especially oligodendrocytes, creating demyelination in the white matter.[35,36] However, this hypothesis is not supported widely because even low doses of radiation that cannot result in histological necrosis cause a decrease in the number of glial cells.[30,37] The other hypothesis is that the direct primary injury to the blood vessels causes the brain parenchymal injury as secondary damage.[38] This hypothesis has been widely accepted because vascular injury was observed prior to the development of radiation necrosis in a rodent radiation necrosis model.[39–41]

We recently published our original hypothesis based on histopathological findings from human radiation necrosis surgical specimens (Fig. 1).[42] We considered that the first step in the development of radiation necrosis in a brain that has undergone radiation treatment is blood vessel damage just around the tumor. This is associated with hypoxia close to the irradiated tumor tissue, which causes the upregulation of hypoxia inducible factor-1 alpha (HIF-1α) in human glucose transporter 5 (hGLUT5)- and CD68-positive microglia. We based this hypothesis on our finding that HIF-1α is upregulated in the perinecrotic area in radiation necrosis specimens (Fig. 2).

Because HIF-1α is well known as a transactivator of vascular endothelial growth factor (VEGF) and CXCL12/CXCR4 signaling,[43,44] the upregulation of HIF-1α augments VEGF and CXCL12 expression in glial fibrillary acidic protein-positive reactive

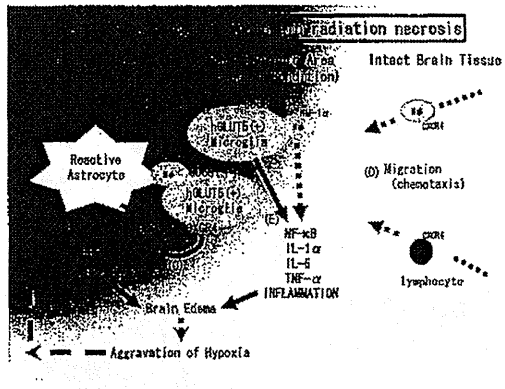

Fig. 1 The pathophysiology of brain radiation necrosis: our hypothesis. A: Vascular damage around the irradiated tumor tissue causes tissue ischemia. This hypoxia induces hGLUT5-positive microglia to express hypoxia inducible factor-1 alpha (HIF-1α) around the necrotic core. B: Under HIF-1α regulation, vascular endothelial growth factor (VEGF) is expressed in reactive astrocytes, causing leaky and fragile angiogenesis. C: CXCL12/CXCR4 signaling is also regulated by HIF-1α. D: CXCL12-expressing reactive astrocytes might draw CXCR4-expressing macrophages and lymphocytes by chemotaxis into the perinecrotic area. E: These accumulated hGLUT5-positive microglia producing NF-κB and pro-inflammatory cytokines seem to aggravate radiation necrosis. This figure was taken from our recent publication (Reference 42) with the permission of the publisher. CXCL12: C-X-C motif chemokine 12, CXCR4: C-X-C chemokine receptor type 4, hGLUT5: human glucose transporter 5, IL: interleukin, NF-κB: nuclear factor-kappa B, TNF: tumor necrosis factor.

astrocytes. The VEGF expression produces the leaky and fragile angiogenesis and the subsequent perilesional edema in radiation necrosis (Fig. 3).[45] The C-X-C motif chemokine 12 (CXCL12) expression might draw C-X-C chemokine receptor type 4 (CXCR4)-expressing hGLUT5-positive microglia and CXCR4-expressing lymphocytes by chemotaxis to the perinecrotic area. The production of pro-inflammatory cytokines [interleukin (IL)-1, IL-6 and tumor necrosis factor (TNF)-α] by these accumulated hGLUT5-positive cells seem to aggravate the perilesional edema.

However, we found that although some CD45-positive lymphocytes gathered in the perinecrotic area, they were not involved in pro-inflammatory cytokine production. Nuclear factor-kappa B (NF-κB), a key player in inflammation, would be expected to play a significant role in radiation necrosis. The aggravation of edema could lead to the further development of focal ischemia, which augments the expression of HIF-1α in the microglia in the perinecrotic area. Here, both angiogenesis and inflammation may contribute

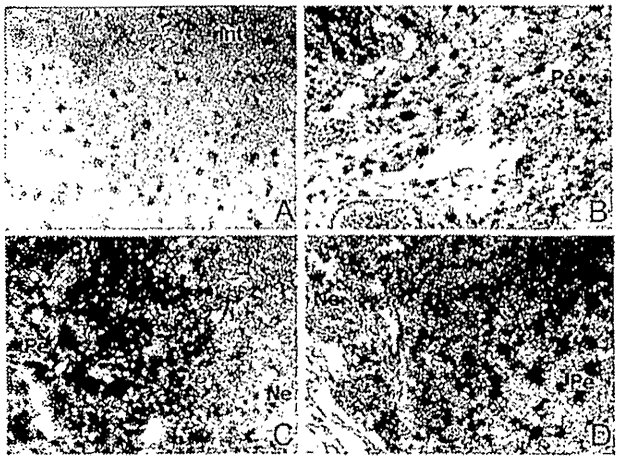

Fig. 2 Hypoxia inducible factor-1 alpha (HIF-1α) immunohistochemistry of radiation necrosis. A, B: The results of HIF-1α immunohistochemistry on the radiation necrosis in a patient with recurrent glioblastoma multiforme (GBM) who was treated by re-irradiation with boron neutron capture therapy (BNCT). The (A) intact brain area and (B) peri-necrotic area are shown. C, D: HIF-1α immunohistochemistry in patients with radiation necrosis from GBM and metastatic brain tumors, respectively. The former was treated with proton beam radiation and X-ray treatment as an initial treatment, while the latter was treated with repetitive BNCT at the recurrence. Int: intact brain, Ne: necrotic center, Pe: peri-necrotic area. The original objective magnification is ×40.

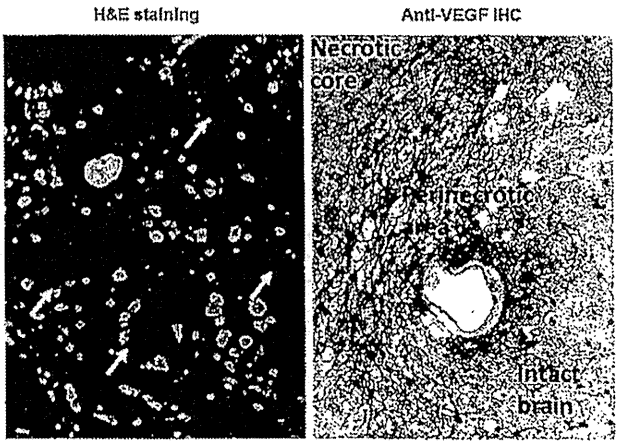

Fig. 3 Surgical specimen of radiation necrosis derived from a metastatic brain tumor caused by stereotactic radiosurgery (SRS). Hematoxylin and Eosin staining shows marked angiogenesis (indicated by *white arrows*) with perilesional edema. Anti-vascular endothelial growth factor (VEGF) immunohistochemistry shows the abundant expression of VEGF in the perinecrotic area. The VEGF-producing cells seemed to be reactive astrocytes.

to a synergistic and malignant cycle in radiation necrosis. In any case, our observations suggest that inflammation participates in the pathophysiology of brain radiation necrosis, as Yoshi suggested.[34]

Among the proinflammatory cytokines, one key upstream player is TNF-α, which regulates other cytokines to increase the blood-brain barrier's permeability, increase leukocyte adhesion, activate astrocytes, and induce endothelial apoptosis.[32,46,47] An important downstream molecule is intercellular adhesion molecule-1 (ICAM-1), which is expressed on the surface of endothelial cells and is a principal mediator of leucocyte-endothelial cell adhesion.[47–52] Our recent study provided evidence that platelet-derived growth factors (PDGFs) and their receptor families also play a significant role in cerebral radiation necrosis from the viewpoints of angiogenesis and inflammation.[53] However, to save the space of this article, we will omit the details of the participation of PDGFs and their receptor families in radiation necrosis.

Diagnosis of Radiation Necrosis

There is no question that surgical exploration including biopsy is the gold standard for the histological confirmation of radiation necrosis or tumor progression. Irradiation is generally applied to surgically inaccessible lesions. In addition, biopsies occasionally show a mixture of radiation necrosis in most parts of the specimen but some viable tumor cells in other parts. It is important for clinicians to determine the next best treatment based on the correct diagnosis of radiation necrosis or tumor progression. When we encounter increasing edema and a contrast-enhanced lesion after the radiation treatment of a brain tumor or head or neck cancer, this next best treatment must be identified. If we judge the cause of increasing edema as radiation necrosis, we can choose from among several treatment options including bevacizumab, as described below. In contrast, if we judge the cause of edema as tumor progression, re-irradiation may be preferable.[54]

I. MRI, ADC, MRS, and MR perfusion imaging

A typical characteristic of radiation necrosis in Gd-enhanced T_1-weighted MRI is called "Swiss cheese" or "soap bubble" enhancement.[6] However, conventional MRI is not sufficient to differentiate tumor progression/recurrence from treatment-related effects.[5,6,11,55]

The apparent diffusion coefficient (ADC) may be important to differentiate tumor recurrence and radiation necrosis. In tumor recurrence, the ADC is low, because high cellularity restricts water mobility.

An increased ADC is ascribed to increased water mobility in radiation necrosis.[56–58] Several research groups have attempted to differentiate radiation necrosis from tumor recurrence by magnetic resonance spectroscopy (MRS) from the viewpoint of metabolism.[11,59–61] In radiation necrosis, N-acetyl aspartate (NAA) and creatinine (Cr) generally decrease, whereas high choline (Cho) is correlated with tumor progression.[61–67] The Cho/Cr ratio and the Cho/NAA ratio have been described as good landmarks for differential diagnosis.[59,60,68] MR perfusion techniques using contrast enhancement can measure the relative cerebral blood volume (rCBV) and estimate the vascularity and hemodynamics. Hyperperfusion is seen in tumor progression, and hypoperfusion is seen in radiation necrosis.[69–71] Sugahara et al. reported that rCBV values < 0.6 suggest radiation necrosis and values > 2.6 suggest tumor progression.[72]

II. Positron emission tomography (PET)

PET scan can directly demonstrate the metabolism of the brain or lesions such as radiation necrosis or tumor progression. Several studies using fluorine-18 fluorodeoxyglucose (^{18}F-FDG) as a tracer initially suggested good sensitivity and specificity,[73–78] but there is a paucity of histological correlations in these reports. Other studies using the same tracer showed unpromising results with decreased sensitivity and specificity.[79–83]

The main reasons for this uncertainty about the utility of this tracer for the differentiation of radiation necrosis and tumor progression are as follows. The brain shows high sugar metabolism, and FDG-PET reveals a very high metabolic background in the normal brain. Moreover, FDG accumulates well in cases of inflammation.[84] However, inflammatory cells commonly infiltrate at the radiation necrosis border as well as in normal brain tissue.[26,85] It thus remains rather difficult to apply FDG-PET to discriminate between radiation necrosis and tumor progression.[86] Indeed, it has been reported that some radiation necrosis cases show good accumulation of FDG despite the absence of evidence of tumor recurrence.[87]

PET imaging using amino acids as tracers is promising for the detection of malignant tumors in the brain, because the background activity of protein metabolism in the brain is rather low compared to its sugar metabolism. ^{11}C-labeled methionine (C-MET) has been used as a tracer for amino-PET, and for analyzing the metabolism in malignant brain tumors[88,89] as well as for differentiating between radiation necrosis and tumor progression.[89] In addition, ^{18}F-labeled fluoroboronophenylalanine (F-BPA)-PET is very useful for the discrimination of radiation necrosis and tumor progression, as we have described in earlier studies.[90,91] We are currently conducting a nationwide multicenter clinical trial under the rubric of "Intravenous administration of bevacizumab for the treatment of radiation necrosis in the brain with diagnosis based on amino acid PET" as Type 3 Investigational Medical Care System and Advanced Therapy, and has been approved by Japan's Ministry of Health, Labor, and Welfare (MHLW).[92]

Treatments for Radiation Necrosis

I. Surgical treatments

The surgical excision of radiation necrosis had been a gold-standard treatment for symptomatic radiation necrosis, in order to rapidly reduce the increased intracranial pressure.[93] However, as described above, radiation treatment is often applied to surgically inaccessible lesions, and sometimes this surgical intervention worsens the patient's neurological condition, as we described previously.[45] Nonetheless, the indications for the removal of radiation necrosis should be decided carefully and strictly, and potent medical treatment should be developed for use in its stead.

II. Medical treatments other than bevacizumab

Corticosteroids have been used to treat radiation necrosis in the brain for several decades.[94,95] The rationale underlying this steroid usage is that the radiation-induced vascular endothelial damage and resulting breakdown of the blood-brain barrier must be reversed. Some inflammatory responses may also be lessened by corticosteroids. The long-term use of corticosteroids can be expected to cause numerous adverse effects such as hypertension, hyperglycemia, osteoporosis, weight changes, moon face, psychiatric disturbances, and immunosuppression, all of which can severely decrease an individual's quality of life.

As an initial step in the development of radiation necrosis, a hypoxic condition is caused by the damage to the microcirculation near a tumor treated with radiation treatment, as shown in Fig. 1. To improve such microcirculation impairments, anticoagulants and antiplatelets have been used to some effect, but not with satisfactory results.[96] Hyperbaric oxygen treatment has also been used to treat radiation necrosis in the brain to stimulate angiogenesis and the repair of the regional cerebral blood supply compromised by radiation-mediated circulatory injury.[97–99] However, there has been no large-scale study with distinct conclusions. At least one study has reported the use of hyperbaric oxygenation for the prophylaxis of radiation injury

in the treatment of metastatic brain tumors with stereotactic radiosurgery.[100]

III. Medical treatments with bevacizumab

As shown in our surgical specimen and reflected in our hypothesis (Figs. 1, 2), HIF-1α upregulation in the perinecrotic area is an initial step in the development of radiation necrosis in the brain. VEGF overproduction in reactive astrocytes then occurs; this is the most clear-cut cause of leaky and fragile angiogenesis and subsequent cerebral edema in radiation necrosis in the brain, as described above.[42,45] A reasonable strategy to reduce this overexpression of VEGF is the use of the anti-VEGF monoclonal antibody, bevacizumab.

The first report to describe the efficacy of bevacizumab for radiation necrosis was published by Gonzalez et al. in 2007.[101] In that report, bevacizumab was used as an additional chemotherapeutic agent for recurrent malignant gliomas and the authors noted retrospectively that the cases in which bevacizumab was effective seemed to be those that involved radiation necrosis. Several later studies found that bevacizumab is effective as a treatment for radiation necrosis in the brain irrespective of the original histological tumor type (including metastatic brain tumors) and the applied radiation modalities.[102–108] A placebo-controlled randomized trial of bevacizumab was published with class 1 evidence, although the number of patients was limited.[107]

We have also routinely observed the effectiveness of bevacizumab for radiation necrosis, as shown in Fig. 4. However, we also sometimes encounter the aggravation of radiation necrosis after a transient improvement in neuro-imaging and clinical neurological findings (Fig. 4). Almost all of the relevant studies have observed promising effects of bevacizumab, but one review article raised the possibility of adverse effects such as cerebral hemorrhage and thrombo-embolitic complications.[108]

In many cases, however, cerebral radiation necrosis itself has shown a trend of spontaneous hemorrhage around the lesion as a natural course.[45] Moreover, bevacizumab may be used for the prophylaxis of possible radiation necrosis in re-irradiation[109,110] and may improve the clinical results such as the overall survival after re-irradiation itself.[111] In addition to angiogenesis, we hypothesized that there is a significant role of inflammation in the pathogenesis of radiation necrosis, as shown in Fig. 1. In support of this hypothesis, preliminary reports have indicated that anti-TNF antibody may be effective for the treatment of cerebral radiation necrosis.[32,46,47]

Conclusion

Clinicians must bear in mind that radiation treatment carries a risk of radiation-induced injury. Whenever encountering an aggravation of cerebral edema after irradiation for brain tumors or head and neck cancers, it is important to remember that not only tumor progression but also radiation necrosis is possible. At that time, a correct diagnosis and prompt treatment decisions are mandatory to avoid exacerbation of the patient's condition. Re-irradiation should never be applied for possible radiation necrosis. If the lesion

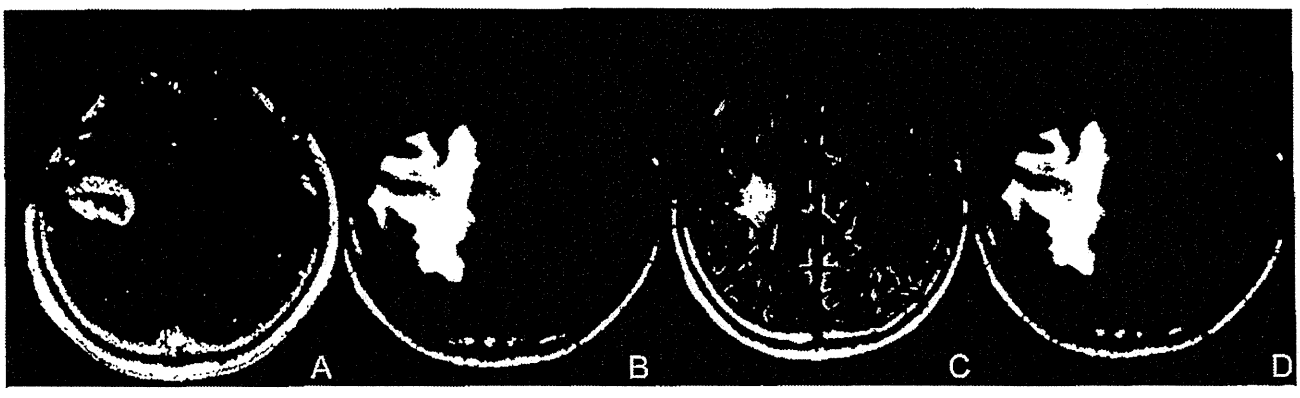

Fig. 4 A representative case of radiation necrosis treated with bevacizumab. The original disease was a metastatic brain tumor from lung cancer. The metastasis was treated with SRS. One year after the SRS, marked enhancement (A) and perilesional edema (B) were recognized on magnetic resonance imaging (MRI). At the time of the MRI, the patient could not walk by himself. After three cycles of bevacizumab treatment 5 mg/kg biweekly, an MRI showed a marked decrease of the edema (C) and he could walk again. Unfortunately, 3 months after the bevacizumab treatment, MRI showed aggravation of the edema (D) with clinical symptom deterioration. Due to financial problems, the patient could not undergo a re-challenge of bevacizumab treatment. A: Gd-enhanced T_1-weighted image. B–D: Fluid-attenuated inversion recovery images. SRS: stereotactic radiosurgery.