32

手術後の放射線療法は何のために行うのでしょうか。

A 手術後の放射線療法は，温存した乳房や乳房を切除したあとの胸壁，その周囲のリンパ節からの再発を防ぐために行います。
すべての乳房温存手術後の患者さん，および乳房切除術を受けた患者さんのうち，わきの下のリンパ節に4個以上転移があった患者さんや，しこりの大きかった(5cm以上)患者さんには，手術後の放射線療法が勧められます。

解説

乳房温存手術後の放射線療法は何のために行うのですか

乳房温存療法における手術の役割は，目にみえるがんのしこりを摘出することであり，放射線療法の役割は，手術で取りきれなかった可能性のある目にはみえないがん細胞を根絶(ねだ)やしにすることです。手術と放射線療法が揃(そろ)って初めて乳房を温存しつつ，乳がんを治療することが可能になります。

乳房温存手術後に放射線療法が必要かどうかについては，海外で多くの臨床試験が行われました。手術で切除した組織の断面を顕微鏡で詳しく調べた結果，断面およびその近くにがん細胞がみられないことが確認された(断端陰性(だんたんいんせい)といいます)患者さんに対して，放射線療法を加えた場合と，加えない場合で比べた試験では，放射線療法を加えることにより，乳房内再発が約1/3に減ることが明らかになっています。さらに乳房内再発を防ぐことにより，生存率も向上させる可能性があることが臨床試験の長期観察から示されています。ただし，放射線療法を行っても再発を100%防ぐことはできません。切除断面の間近(5mm以内)にがん病巣が迫っていた，あるいは切除断面にがん細胞があると確認された(断端陽性といいます)患者さんや，年齢の若い患者さんは乳房内再発の危険度が高くなるといわれています。また，最近では，腋窩(えきか)(わきの下の)リンパ節に転移が多数あった患者さんには温存した乳房に加えて鎖骨上窩(さこつじょうか)(首のつけ根の鎖骨の上の部分)のリンパ節にも放射線をかけることが勧められています。

乳房温存手術後に放射線療法が省略できる場合はないのですか

放射線療法は正しく行えば安全な治療ですが，時間や費用がかかり，また軽度ながら副作用もあります(☞Q34参照)。したがって，放射線療法を省略しても，乳房内再発の危険性が変わらないのであれば，それに越したことはありません。放射線療法の省略が考慮される場合としては，もともと再発する危険度が低い場合(例：高齢でホルモン療法が効くタイプ)が考えられます。最近70歳以上でホルモン療法が有効なタイプの患者さんに対して，放射線療法を加えた場合と加えなかった場合

を比べた臨床試験の結果が報告されました。やはり放射線療法を加えたほうが乳房内再発が少なかったのですが，その差はごく小さなもので，生存率にも差はありませんでした。したがって，患者さんが十分に説明を受けたうえで納得すれば，放射線療法を省略することもあります。

乳房切除術後の放射線療法は何のために行うのですか

これまでは乳房切除術に続く治療では，化学療法やホルモン療法が中心となり，放射線療法は不要といわれてきました。しかし，最近海外で行われた臨床試験の結果，乳房切除術の場合でも，胸壁やリンパ節などから再発する危険性が高い場合は，化学療法やホルモン療法に加えて，放射線療法も行ったほうがよいということがわかりました。

乳房切除術のあと胸壁や鎖骨上窩（首のつけ根の鎖骨の上の部分）のリンパ節に再発が起こると，その再発病巣から全身にがん細胞が広がる危険性があります。放射線療法を行うことにより，これらの場所の再発を減らすことができ，その結果，病気が治る可能性を高めることができると考えられています。放射線療法の技術が発達して，安全に行えるようになったこともあり，海外では積極的に実施されるようになりました。日本でも今後このような治療を受ける患者さんが増えていくと思われ，徐々にこのような患者さんに対し放射線療法を行う施設が増えてきました。

どの患者さんが放射線療法を受けたらよいかは，胸壁や鎖骨上窩のリンパ節への再発の危険度によって異なり，もともとの乳房のしこりの大きさやリンパ節への転移の状態をみて判断します。再発の危険度が高いとされる，腋窩（えきか）リンパ節に4個以上転移があった患者さんや，しこりが大きかった（5cm以上）患者さんでは，化学療法やホルモン療法の他に放射線療法を行うことで再発のリスクを下げることができます。また逆に，しこりが小さかった場合や，リンパ節への転移がなかった場合には，放射線療法を受けなくても胸壁や鎖骨上窩に再発することは少なく，放射線療法を受ける利点はあまりありません。

放射線はしこりのあった側の胸壁と鎖骨上窩に照射します。線量は施設によって若干の違いがありますが，1回線量が1.8～2.0グレイ（Gy）で，総線量は45～50グレイ程度（総治療期間約5～6週間）が最も多く行われています。

Q 33

乳房温存手術後の放射線療法の流れを教えてください。

A 手術した乳房全体に，総線量で45～50グレイ程度を照射するのが一般的です。

解説

乳房温存手術後の放射線療法では，どの範囲に照射するのが適切ですか

放射線療法の効果は，放射線を照射した部分にのみ現れます。十分な効果があり副作用が少ない放射線療法を行うためには，必要かつ十分な照射範囲を決定することが大切です。現在の標準治療は，温存した乳房全体を照射する方法（全乳房照射）です。

最近，欧米でがんのしこりのあった場所の周囲のみに短期間で集中的に照射する方法も試されています。しかし，効果や長期の副作用について，温存した乳房全体を照射する方法と同等かどうかはまだわかっていません。

術後の放射線療法の線量や治療期間はどのくらいが適切ですか

全乳房照射では，手術した乳房全体に対して1回線量1.8～2.0グレイ，総線量45～50グレイ程度を約5週間かけて行います。一度にすべての量をかけるのではなく，少しずつ分割してかけるのは，正常組織への影響を小さくして，がん細胞だけを弱らせて死滅させるためです。1回の照射時間は1～2分程度で，通院の時間以外は通常の生活が可能です。

放射線療法の効果は，どれだけの総線量を何回に分けて，どれだけの期間に照射したかで決まってきます。一般に，手術後に残っているかもしれない，目にみえない程度のがん細胞に対しては，50グレイ程度を5週間くらいかけて治療する方法が有効とされています。毎日続けて照射することにより，がん細胞が次第に少なくなっていきます。途中に長期間の休みを入れてしまうと，同じ総線量を照射しても効果が薄れます。ただし，数日程度の延長であれば問題はありません。

カナダやイギリスでは，治療期間の短縮を目的として上記とは異なった線量や照射回数での治療も行われています。1回線量2.66グレイで総線量42.56グレイを22日間かけて治療する方法で，効果と副作用は従来の方法とほぼ同等であることがわかっています。したがって，このような1回の線量を増やして回数を減らすことも，許容しうる方法です。

全乳房照射後にしこりのあった周囲に追加照射することは必要ですか

全乳房照射後にしこりのあった周囲に追加照射（ブースト照射）を行うことは，乳

房内の再発を減少させるのに有用です。

乳房全体に多くの線量を照射することは，副作用が強くなり好ましくありませんが，乳房内の再発の多くは，しこりのあった周囲に起こるので，この部分に追加照射をしておくことで再発を減らせます。

特に，切除断端陽性（☞Q32参照）の場合など，がん細胞の取り残しの可能性が高い場合は，10～16グレイの追加照射を行うことが一般的です。一方，切除断端陰性（☞Q32参照）でがんを取りきれたと思われる場合でも，追加照射によって乳房内再発が減ることがわかっています。ただしこの場合は，そもそも乳房内に再発する危険度がそれほど高くないので，追加照射による再発の減少の効果は大きいものではありません。また，この再発抑制効果は年齢が高くなるほど弱くなることもわかっています。高齢で切除断端陰性の患者さんでは，追加照射の必要性について個別の状況に応じて判断したほうがよいでしょう。

乳房以外の部分にも照射する必要はありますか

腋窩（わきの下の）リンパ節転移が4個以上あった場合は，鎖骨上窩（首の付け根の鎖骨の上の部分）への照射をお勧めします。また，リンパ節転移が1～3個の場合も，鎖骨上窩への照射を行ったほうがよい場合があります。

乳房温存療法で腋窩リンパ節への転移が4個以上あった場合には，3個以下の場合に比べて鎖骨上窩などのリンパ節転移が多いと報告されています。そのような場合，鎖骨上窩への放射線療法が有用とする報告があり，米国や日本のガイドラインでは放射線療法を勧めています。腋窩リンパ節への転移が1～3個の場合には，病理学的悪性度などのその他の危険因子によって，照射をお勧めする場合があります。また，胸骨のわきにある胸骨傍リンパ節への転移はまれですが，腫瘍の位置などの病状によって照射をお勧めすることがあります。

なお，腋窩リンパ節の郭清後，さらに腋窩に放射線療法を追加しても生存率は改善せず，かえって腕の腫れや肩の副作用が増えるのでお勧めしません。

Q34

手術後の放射線療法の際にみられる副作用はどのようなものですか。また，対処法はありますか。

A

手術後の放射線療法中または治療終了後数カ月のうちに現れる副作用としては皮膚炎，倦怠感，放射線肺臓炎などがあります。皮膚炎はほとんどの患者さんでみられますが，重篤なものではありません。それ以外の副作用も頻度は少なく，大きな問題になることはほとんどありません。
乳房切除術後の照射では，胸壁に加えて周囲のリンパ節を照射することが多く，副作用は乳房温存手術後の放射線療法の場合より，やや増加します。

解説

放射線療法中と終了後まもなく現れる副作用

放射線照射による副作用が現れるのは照射した部位に限られますので，乳がんの場合は，胸壁，周囲のリンパ節領域です。頭髪の脱毛やめまいなどはなく，吐き気や白血球減少もほとんど起こりません。放射線を当てている間に痛みや熱さを感じることもありません。放射線がからだに残ることもありませんので，家に帰った後，乳幼児などを抱いても安全です。照射期間中に，疲れやだるさを感じる患者さんもいますが，基本的には日常生活や仕事をしながら受けることが可能です。

開始して3～4週間後くらいで，放射線が当たっている範囲内の皮膚が日焼けのように赤くなり，ひりひりすることがあります。このような場合に皮膚を冷やすほうがよいかどうかについては，よくわかっていません。症状が楽になるようであれば冷やしていただいても構いませんが，あまり冷やしすぎないようにご注意ください。照射部位は皮膚が弱くなっているので，絆創膏などを貼らないでください。また，からだを洗うときにも強くこすったりしないよう気をつけてください。場合によっては皮がむけたり，水ぶくれのようになることもありますが，治療が終了すれば1～2週間で軽快します。照射後は皮膚が黒ずみ，汗腺や皮脂腺の働きが一時的に衰え，手で触れると暖かく感じたり，皮膚もカサカサすることがあります。乳房温存手術後の照射の場合は乳房全体が少し腫れて硬くなったり，痛んだりすることもあります。多くの患者さんでは，これらの症状は数年以内にかなりの程度回復するので，日常生活で苦になることはありません。

放射線療法終了後しばらくして現れる副作用

放射線療法が終了して，数カ月～数年後に出る副作用を晩期の副作用といいます。放射線が肺にかかることによって起こる肺炎はまれですが，治療後数カ月以内に100人に1人くらいの割合でみられることがあります。咳や微熱が長く続くときは病院（できれば照射を受けた病院）を受診してください。「放射線療法を受けた」

という情報が重要ですので，医師にその旨を伝えてください。放射線による肺炎は適切な治療により治癒します。

治療後数カ月以降にみられる副作用の頻度は少なく，あまり問題となりません。乳房に放射線を当てることによって乳汁をつくる機能は失われるので，放射線療法後に赤ちゃんを産んだ場合は，照射した乳房から母乳が出ることはほとんどありませんが，反対側の乳房からは授乳できます。

また，腕がむくむことがありますが，頻度や程度は手術方法によって異なり，大きな手術を受けた場合ほどリスクは高くなります。かつては，放射線が心臓に当たってしまうことによる心筋梗塞（しんきんこうそく）などの心臓障害も心配されましたが，現在は放射線療法の技術が高くなったため，ほとんど問題になりません。

放射線療法で他のがん（二次がん）が発生することはありませんか

この場合の二次がんというのは，乳がんの治療後に治療が原因で別の部位（例えば反対側の乳房や肺や大腸など）にがんが発生することをいいます。乳がんを経験された患者さんは，乳がんの病歴がない女性に比べると，二次がんを生じる割合が高いことが知られています。原因はいろいろで，遺伝，環境因子，化学療法や放射線療法などが考えられます。

しかし，リスクが増加するといっても，二次がんになる患者さんの数は，わずかであり，放射線療法による利益は二次発がんの危険性を上回ると考えられています。

Q35

放射線療法は早く受けたほうがよいのでしょうか。

A 乳房温存手術後に，特別な理由もなく放射線療法の開始を遅らせることは望ましくありません。しかし，放射線療法と抗がん剤治療（化学療法）の両方を受ける必要がある場合には，抗がん剤治療が終わってから放射線療法を開始するのが一般的です。

解説

乳房温存療法の場合

乳房温存手術を受けた患者さんは，年齢や病気の性質，病気の進み具合などによって，放射線療法だけを受ければよい場合と，放射線療法と抗がん剤治療の両方を受けなければならない場合があります。前者では，①放射線療法はいつ頃までに始めたほうがよいか，後者では，②放射線療法と抗がん剤治療のどちらを先にしたらよいか，③抗がん剤治療を先に始めた場合，放射線療法は遅くともいつ頃までに開始しないといけないのかが気にかかるところです。実はこうした問いに対する明快な答えは用意されていないのですが，いくつか明らかになっていることもありますので順に説明します。

抗がん剤治療を受けない場合，放射線療法はいつ頃までに始めたほうがよいでしょうか

放射線療法だけを行う場合は，手術の傷がよくなった時点で直ちに治療を始めるのが普通です。しかし，ときには手術後の合併症（傷の治りが悪い場合や炎症など）や年末・年始のお休み，個人的な理由などで治療の開始が遅れることがあります。これまでの研究によると，放射線療法をいつまでに始めるべきかという区切りはなく，治療開始が遅れるほど手術の傷跡近く（局所）の再発が増える可能性が示されています。とくに手術から放射線療法の開始までが20週を超えると，生存率も下がる可能性があると報告されています。したがって，特別な理由がない限り，手術後の放射線療法はなるべく早期に（とくに手術後20週以内に）始めることが勧められます。

放射線療法と抗がん剤治療のどちらを先にしたらよいでしょうか

抗がん剤治療と放射線療法の両方が必要な場合，両者の順序には，抗がん剤治療を先行させる場合，放射線療法を先行させる場合，放射線療法と抗がん剤治療を同時に行う場合の3通りが考えられます。どの方法が最も治療効果が高いかを調べた研究では，放射線療法と抗がん剤治療はどちらを先に行っても局所再発や遠隔転

移，死亡率に差がないことが報告されています。しかし最近では，遠隔転移は生死にかかわる可能性があるので，これを減らす目的で数カ月間の抗がん剤治療を先に行い，その後で放射線療法を行うことが一般的となっています。抗がん剤治療と放射線療法を同時に行う治療については，副作用に問題はなく安全に行えたとする報告と，見過ごすことのできない急性の副作用がみられたとする報告があり，現時点では十分観察の行き届いた臨床研究においてのみ行われるべきであると考えられます。

抗がん剤治療を先に始めた場合，放射線治療は遅くともいつ頃までに開始しないといけませんか

抗がん剤の投与法にも種類があり，どの投与法を採用するかで放射線療法の開始時期も異なります。標準的な術後の抗がん剤治療は3～6カ月かかり，その副作用からの回復期間（1カ月程度）を含めると放射線療法の開始は手術後おおよそ4～7カ月後になります。手術前に抗がん剤治療を行った場合は，手術後から放射線療法までの期間は，抗がん剤治療をしていない場合と同じように考えてよいでしょう。したがって，放射線療法は，予定していた標準的な抗がん剤治療が終わり，副作用がある程度落ち着いた時点（約1ヵ月）で始めても差し支えないと考えてよいでしょう。

乳房切除術の場合

乳房切除後に抗がん剤治療と放射線療法の両方を受けることが勧められる場合，どちらを先に行えばよいかについては，よくわかっていません。

乳房切除後の放射線療法は乳房を切除した手術部位（胸壁）とその近辺（周囲のリンパ節領域）の再発を予防するために行われ，乳房から離れた部位（遠隔）の再発を予防するためには抗がん剤治療が行われます。両者とも必要な治療ですが，どちらを先に行ったらよいかという問題が生じます。この問題についていくつかの研究が行われてきましたが，まだはっきりした結論は得られていません。ただし，通常は抗がん剤治療を先に行っている場合が多いようです。

また，他のがん腫（食道がん・肺がん・膵臓がんなど）では，放射線療法と抗がん剤治療を同時に行うことで治療成績が高まったという信頼できる報告があります。乳がんでも抗がん剤を放射線療法と同じ期間に行うことについて研究されていますが，副作用が多くみられるという報告もあり，今のところ標準治療としてはこのような方法はお勧めできません。

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Original Article

Validation of Nomogram-based Prediction of Survival Probability after Salvage Re-irradiation of Head and Neck Cancer

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Objective: Treatment outcomes after salvage re-irradiation in patients with recurrent head and neck cancer vary widely due to heterogeneous patient characteristics, and it is difficult to evaluate optimal re-irradiation schedules. This study aimed to validate a nomogram, originally developed by Tanvetyanon et al., used to predict the survival probability of patients with recurrent head and neck cancer after re-irradiation.

Methods: Twenty-eight patients with recurrent head and neck cancer who underwent salvage re-irradiation between June 2007 and November 2011 were evaluated. The median total dose used for initial radiotherapy was 60 Gy (range, 22–72). Re-irradiation sites included the nasopharynx or Rouviere's node ($n = 14$), external ear ($n = 4$), neck lymph node ($n = 3$) and other sites ($n = 7$). Overall survival after re-irradiation was calculated using the Kaplan–Meier method, and the 2-year survival probability was estimated using Tanvetyanon's nomogram.

Results: Twenty-two patients were treated with stereotactic body radiotherapy using a median total dose of 30 Gy (range, 15–40) in 1–7 fractions and six patients were treated with conventional external beam radiotherapy using 45 Gy (range, 23.4–60) in 10–30 fractions. The 2-year overall survival was 21.7% (95% confidence interval: 9.3–41.3), and the 2-year survival probability was 16.8% (95% confidence interval: 9.9–23.6). The 2-year overall survival in 20 patients with unfavorable prognosis (median 2-year survival probability, 5.5%) and in 8 patients with favorable prognosis (median 2-year survival probability, 45%) were 11.0 and 45.7%, respectively ($P = 0.05$).

Conclusions: Our findings show that Tanvetyanon's nomogram accurately estimates the survival probability in patients with recurrent head and neck cancer after re-irradiation.

Key words: salvage re-irradiation – head and neck cancer – nomogram – stereotactic body radiotherapy

INTRODUCTION

About 500 000 patients with head and neck cancer (HNC) are diagnosed each year worldwide (1). Despite comprehensive treatment strategies including surgery, radiotherapy and chemotherapy, approximately half of the patients with HNC die due to locoregional failure, distant metastases and second

primary neoplasms (2). Recurrent HNC (rHNC) and second primary neoplasms in the previously irradiated area represent a clinical challenge, and are normally treated with salvage surgical resection as this method offers the greatest probability for long-term survival (3–4). However, the population of candidates for curative salvage surgery is relatively small, and some patients require chemotherapy or re-irradiation in addition to surgery. The survival time after salvage chemotherapy has been estimated to be ~6 months (5). Re-irradiation using a full dose is associated with severe toxicities including tissue necrosis, bleeding and infection, and treatment-related deaths due to carotid hemorrhage (6–8). Recent studies using intensity modulated radiotherapy (IMRT), stereotactic body radiotherapy (SBRT), twice-daily radiotherapy and concurrent chemotherapy reported the feasibility and effectiveness of re-irradiation in patients with rHNC (2,7,9). These studies also reported locoregional control rates after re-irradiation ranging from 19 to 64%, and median survival times (MST) ranging from 8.5 to 28 months (1,8,10–12). Treatment outcomes vary widely due to heterogeneous patient characteristics and diverse treatment schedules. Moreover, an optimal salvage re-irradiation schedule has not yet been established (1,8). Optimal sub-classification according to a confidential prognostic index is essential to rigorously compare treatment outcomes. Tanvetyanon et al. (13) developed a nomogram to predict 2-year survival probability in patients with rHNC after salvage re-irradiation. The nomogram includes the following: the presence of comorbidities, organ dysfunction, presence or absence of isolated neck recurrence, tumor bulk and time interval between the previous radiotherapy and start of re-irradiation. The overall goal of the present study was to validate this nomogram in patients with rHNC who were mainly treated with SBRT.

PATIENTS AND METHODS

Twenty-eight consecutive patients with local rHNC who underwent salvage re-irradiation between June 2007 and November 2011 were evaluated. The male-to-female ratio was 20:8, with a median age of 65 years (range, 43–90). Patients were treated for nasopharyngeal cancer ($n = 8$), external ear cancer ($n = 4$), hypopharyngeal cancer ($n = 3$) and other cancers ($n = 13$). Patient characteristics are shown in Table 1. Initial radiotherapy included treatment with definitive radiotherapy ($n = 22$), postoperative radiotherapy ($n = 5$) and salvage radiotherapy ($n = 1$) for recurrent disease after surgery. Twenty-three patients were treated with conventional three-dimensional external beam radiotherapy using Clinac iX or Trilogy (Varian Medical Systems, Inc., Palo Alto, CA) with a photon energy of 4 or 6 MV. Treatment plans included lateral opposed field, wedged pair field or multiple-field techniques. The radiation field covered the primary site, surrounding the lymph node area, and/or the prophylactic regional lymph node area. The prescribed dose was calculated at the center of the radiation field or from the planning target volume (PTV). The median total

Table 1. Patient characteristics

	Patient number	Median	Range
Age (years)		67	43–90
Gender			
Male	20		
Female	8		
Performance status			
0	20		
1	4		
2–4	4		
Initial diagnosis			
Nasopharyngeal cancer	8		
External ear cancer	4		
Hypopharyngeal cancer	3		
Tongue cancer	2		
Paranasal cavity cancer	2		
Others	9		
Pathology			
Squamous cell carcinoma	24		
Leiomyosarcoma	1		
Neuroblastoma	1		
Round cell sarcoma	1		
Salivary duct carcinoma	1		
Initial radiotherapy			
Total dose (Gy)		60	22–72
Fraction size (Gy)		2	1.8–22
Site of re-irradiation			
Nasopharynx or Rouviere's node	14		
External ear	4		
Neck lymph node	3		
Oropharynx	2		
Paranasal cavity	2		
Others	3		
Maximum diameter of recurrent disease			
Stereotactic radiotherapy (cm)		2.9	1.0–6.0
Conventional radiotherapy (cm)		3.8	2.5–10.0
Interval between initial treatment and salvage re-irradiation			
1–6 (months)	10		
Over 6 (months)	18		
Re-irradiation			
Stereotactic radiotherapy	22		
Total dose (Gy)		30	15–40
Fraction size (Gy)		8	5–23
Conventional radiotherapy	6		
Total dose (Gy)		45	23.4–60
Fraction size (Gy)		2	1.8–3

dose was 60 Gy (range, 48–72) in 24–36 fractions over a 5- to 7-week period. Five patients were treated with using robotic image-guided radiotherapy (Cyberknife Robotic Radiosurgery System; Accuracy, Inc., Sunnyvale, CA) with a median total dose of 38 Gy (range, 22–39) in one to six fractions over a 1- to 6-day period. The prescribed dose for SBRT was defined as the dose covering at least 80% of the PTV. Sixteen patients received systemic chemotherapy concurrently or sequentially, which included platinum-based or 5-fluorouracil (5-FU) regimens (Table 2).

The median interval from initial radiotherapy to salvage re-irradiation was 9 months (range, 3–40). Twenty-two patients had comorbidities and nine had organ dysfunction (e.g. tracheostomy and dysphagia) at the start of salvage re-irradiation. The median maximum diameter of recurrent disease was 3.4 cm (range, 1–10). Re-irradiation sites included the nasopharynx or Rouviere's node ($n = 14$), external ear ($n = 4$), neck lymph node ($n = 3$) and other sites ($n = 7$). Twenty-two patients were treated with SBRT and six were treated with conventional external beam radiotherapy. The median total dose administered during salvage re-irradiation using SBRT was 30 Gy (range, 15–40) in one to seven fractions over a 1- to 9-day period. The median total dose of salvage re-irradiation using conventional external beam radiotherapy was 45 Gy (range, 23.4–60) in 10–30 fractions over a 2- to 6-week period. Both re-irradiation techniques adopted narrow field margins without prophylactic regional lymph node irradiation. Three patients who were treated with conventional external beam radiotherapy received chemotherapy (i.e. platinum-based or 5-FU regimens) concurrently with radiotherapy.

The OS was calculated using the Kaplan–Meier method, and the median 2-year survival probability was estimated using the nomogram developed by Tanvetyanon et al. (13) The OS was measured from the start of re-irradiation and calculated using death due to any cause as an event. Tumor responses were classified as complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD) according to the revised Response Evaluation Criteria in Solid Tumors (revised RECIST guideline version 1.1) (14). In-field recurrence was defined as an increase in the tumor size or appearance of new lesions in the re-irradiation area from diagnostic images, and out-field recurrence was defined as an increase in the tumor size or appearance of new lesions in the non-irradiated head and neck area. Distant metastases were defined as the appearance of new lesions beyond the head and neck area. Toxicity was assessed using the Common Terminology Criteria Adverse Event (CTCAE version 4.0). Statistical analyses were performed using JMP version 5.1J (SAS Institute, Inc.).

Table 2. Patient characteristics in the favorable and unfavorable groups

	Favorable group	Unfavorable group
Age (years)	59.0 (44–72)	69.5 (43–90)
Gender		
Male	7	13
Female	1	7
Performance status		
0	8	12
1	0	4
2–4	0	4
Pathology		
Squamous cell carcinoma	8	16
Others	0	4
Initial radiotherapy		
Total dose (Gy)	60	57
Fraction size (Gy)	2	2
Site of re-irradiation		
Nasopharynx or Rouviere's node	5	9
External ear	1	3
Neck lymph node	1	2
Oropharynx	1	1
Paranasal cavity	0	2
Others	0	3
Maximum diameter of recurrent disease		
Stereotactic radiotherapy (cm)	1.6	3.6
Conventional radiotherapy (cm)	N/A	3.8
Interval between initial treatment and salvage re-irradiation		
1–6 (months)	3	7
Over 6 (months)	8	10
Organ dysfunction		
No	7	11
Yes	1	9
Re-irradiation		
Stereotactic radiotherapy	8	14
Total dose (Gy)	26	30
Fraction size (Gy)	9.4	8
Conventional radiotherapy	0	6
Total dose (Gy)	N/A	45
Fraction size (Gy)	N/A	2

RESULTS

The median follow-up time in the present study was 7.3 months (range, 1.7–25.3). After re-irradiation, 5 patients (18%) achieved CR, 8 (28%) achieved PR and 15 (54%) showed SD or PD. In addition, two patients achieving PR received salvage surgery and one patient achieving PR and three showing SD received systemic chemotherapy (i.e. Tegafur Gimeracil Oteracil Potassium, S-1). The other patients were carefully monitored and received supportive

care. The median progression-free survival time after re-irradiation was 5.5 months [95% confidential interval (CI), 3.3−7.2]. Among the patients with re-progressive disease after re-irradiation, 15 (83%) developed in-field recurrence with or without out-field recurrence and/or distant metastases, two (11%) developed distant metastases alone and one (6%) developed recurrence in the field margin. However, no patients developed regional recurrence alone. The sites of distant metastases included the lung and mediastinal lymph nodes. Thirteen patients (46%) achieved a relative response (RR), which included CR and PR, and had a median maximum tumor diameter of 2.7 cm (range, 1.0−6.0). In patients who did not achieve RR, the median maximum tumor diameter was 3.7 cm (range, 1.5−10.0; $P = 0.03$). MST after re-irradiation of patients who achieved RR was 13.3 months (95% CI, 6.0–N/A) and 7.3 months for those who did not achieve RR (95% CI, 3.8–14.9; $P = 0.03$).

Univariate analyses revealed that MST and 2-year OS of 19 patients with small recurrent disease <4 cm were 13.0 months (95% CI, 6.0–N/A) and 26.6%, and those of 9 patients with large recurrent disease 4 cm or larger were 7.3 months (95% CI, 1.7–N/A) and not applicable, respectively ($P = 0.39$). MST and 2-year OS of 8 patients who developed recurrence within 6 months from the initial treatment were 7.9 months (95% CI, 1.7–N/A) and 20.2%, and those of 18 patients who developed it beyond 6 months were 8.6 months (95% CI, 7.3–18.9) and not applicable, respectively ($P = 0.62$). MST and 2-year OS of 24 patients with good performance status (PS = 0–1) were 13.3 months (95% CI, 7.3–N/A) and 24.9%, and those of 4 patients with poor PS (PS = 2–4) were 3.9 months (95% CI, 1.7–N/A) and 0%, respectively ($P = 0.02$).

The 2-year OS estimated using the Kaplan–Meier method was 21.7% (95% CI, 9.3–41.3), and the MST was 8.6 months (95% CI, 6.0–14.9; Fig. 1). The median 2-year survival probability estimated by Tanvetyanon's nomogram was 16.8% (95% CI, 9.9–23.6). The 2-year OS in 20 patients with unfavorable prognosis whose 2-year survival probability was <15% (median, 5.5; range, 1−11) and the 2-year OS in eight patients with favorable prognosis whose 2-year survival probability was >15% (median, 45; range, 15−55) was 11.0 and 45.7%, respectively ($P = 0.05$; Fig. 2).

Two patients (7.1%) developed adverse events (Grades 2−3), which included tumor bleeding (Grade 2) and oral bleeding (Grade 3). In addition, three patients (10.7%) developed severe adverse events (Grade 5). All three patients developed local progression after re-irradiation, with two of them developing local infection and soft tissue necrosis in the submandibular area and paranasal cavity. These two patients died due to tumor progression and infection. The third patient was initially treated with whole neck conventional radiotherapy (60 Gy in 30 fractions) followed by adjuvant chemotherapy, and also received salvage SBRT (25.6 Gy in 5 fractions) to treat left-neck lymph node recurrence. Despite these treatments, the patient developed in-field recurrence 6 months later, which was treated with re-salvage SBRT (24 Gy in two fractions); however, recurrence was not controlled and the patient died eight months later due to a carotid artery rupture. Four patients who developed severe adverse events (Grades 3−5) were treated with

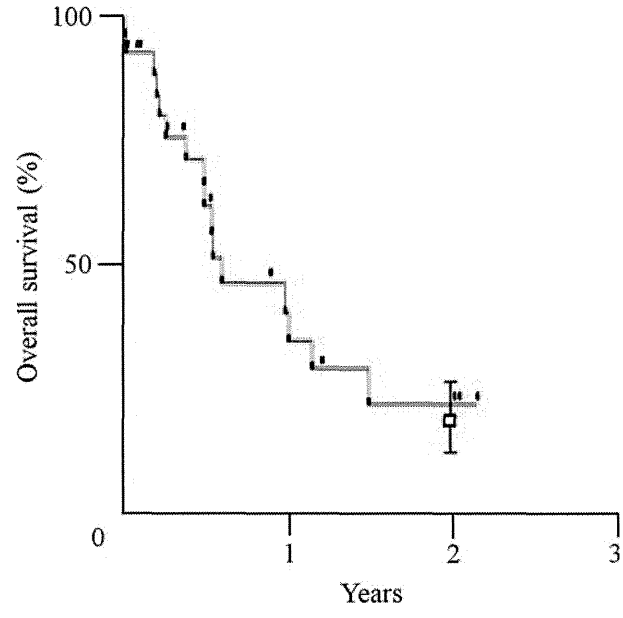

Figure 1. The overall survival curve (OS) of 28 patients with recurrent head and neck cancer (rHNC) was estimated using the Kaplan–Meier method. The white box shows the 2-year survival probability (16.8%) estimated using Tanvetyanon's nomogram. The vertical line indicates the 95% confidence interval of the 2-year OS rate (95% CI, 9.9–23.6%). This figure shows approximate values for the 2-year OS calculated by the Kaplan–Meier method and the 2-year survival probability estimated by Tanvetyanon's nomogram.

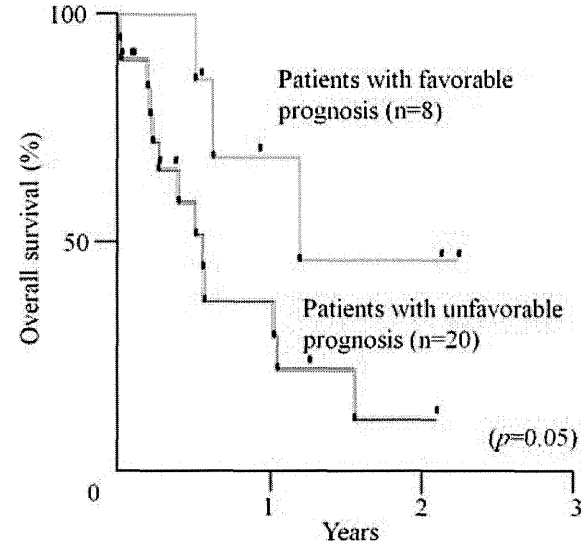

Figure 2. OS curves of patients with rHNC with favorable and unfavorable prognoses. The 2-year OS in 20 patients with unfavorable prognosis whose 2-year survival probability was <15% and the 2-year OS in eight patients with favorable prognosis whose 2-year survival probability was >15% were 11.0 and 45.7%, respectively ($P = 0.05$).

re-irradiation using SBRT; however, there was no difference between re-irradiation modalities ($P = 0.25$).

DISCUSSION

The American College of Radiology (ACR) Expert Panel on Head and Neck Cancer reviewed relevant literature on re-irradiation after definitive radiotherapy and evaluated its appropriateness, including radiation technique, treatment volume, doses and treatment schedule (3). The ACR Expert Panel emphasized the importance of patient selection and recommended careful evaluation and treatment by a comprehensive cancer team. Furthermore, they recommended considering re-irradiation with and without chemotherapy in patients with favorable prognosis and with relatively long estimated survival times. They also recommended performing a computed tomography (CT) scan of the chest and positron emission tomography/CT to determine the presence of metastatic disease, and evaluating patient conditions such as comorbidities, performance status, speech and swallowing function, and nutritional status. Moreover, a multi-disciplinary cancer care team should decide on the appropriate treatment strategy (e.g. salvage surgery, intensive re-irradiation with or without chemotherapy, chemotherapy alone and palliative care). The total absolute radiation dose to critical organs such as the spinal cord, carotid artery and optic pathways should be estimated using previous radiation dosimetry and latest patient images (8). Another important consideration is the interval between previous radiotherapy and start of salvage re-irradiation. One study showed that a longer interval was associated with a lower probability of severe adverse events due to re-irradiation and lower occurrence rates of distant metastases (15). In Tanvetyanon's nomogram, the interval is an important component used to estimate 2-year survival probabilities after re-irradiation (13). Previously published clinical trials have used intervals of >6 months to determine the eligibility for re-irradiation (6,7). Hoebers et al. (15) reported that an interval of over 3 years was associated with a favorable OS. However, the appropriate interval between previous radiotherapy and re-irradiation remains unknown.

The Fox Chase Cancer Center conducted a phase I study (FCCC 96-006) combining twice-daily radiotherapy (1.5 Gy per fraction bid; 5 days every other week; four cycles) with concurrent cisplatin and paclitaxel administration during salvage therapy (16). The MST was 9.5 months, and the 1- and 2-year OS were 41 and 27%, respectively. Hematologic toxicities were feasible, and grade 3 mucositis occurred in only 6% of patients. Given these encouraging results, the Radiation Therapy Oncology Group (RTOG) conducted a phase II study (RTOG 9911) to evaluate the efficacy and toxicity of twice-daily radiotherapy (1.5 Gy per fraction bid; 5 days every other week; four cycles) with concurrent cisplatin and paclitaxel administration (6). One-hundred and five patients were enrolled into the study, and 1- and 2-year OS were 50.2 and 25.9%, respectively. These findings suggest that this strategy is a promising treatment option; however, eight treatment-related deaths (8%), including acute neutropenic sepsis and late carotid hemorrhage, were noted. Spencer et al. (17) conducted a phase I study on previously irradiated patients with rHNC who received hydroxyurea and 5-FU in combination with daily radiotherapy (2 Gy per fraction) during a 2-week period followed by a 1-week break. These patients then received hyperfractionated radiotherapy on weeks 4 and 5 (total dose 50 Gy). The 1- and 2-year OS were 41 and 15%, respectively, and one patient died 3 weeks after the study due to pneumonia. Furthermore, two patients acquired soft tissue ulcers, and one developed trismus and a non-healing clavicular fracture. Therefore, concurrent chemoradiotherapy using twice-daily regimens are not considered ideal strategies for re-irradiation (18).

Hoebers et al. (15) evaluated 58 patients who had received re-irradiation at a median cumulative dose of 119 Gy (range, 76 − 140) with or without chemotherapy. The group reported a 2-year OS of 42%, and that higher re-irradiation doses and concurrent chemoradiation were associated with severe adverse events. They also reported that re-irradiation alone (compared with concurrent chemo-re-irradiation), a longer interval between initial radiotherapy and salvage re-irradiation, and a lower cumulative radiation dose were associated with better local control rates. Lee et al. (4) reported a study of 105 patients with rHNC who received re-irradiation with or without chemotherapy. The multivariate analyses revealed that non-nasopharynx and non-IMRT were associated with an increased risk of locoregional failure. Administration of chemotherapy could not be used to predict improved locoregional control rates and OS. The role of concurrent or sequential chemotherapy remains uncertain for re-irradiation in patients with rHNC. In the present study, 83% of patients with progressive disease after re-irradiation developed in-field recurrence with or without distant metastases. Lee et al. (4) reported the occurrence of locoregional failure with or without distant metastases in 65% of patients who developed progressive disease after re-irradiation. They also emphasized that future efforts for maximizing tumor control in a recurrent setting, including dose escalation with IMRT and effective chemotherapy, were warranted. The median re-irradiation dose of 45 Gy in our conventional radiotherapy is low compared with previously published doses. We could not use IMRT then for head and neck cancers in our institute, and thus relatively low re-irradiation doses were used to avoid the risk of high radiation exposure of organs. As it is now possible to use IMRT, more aggressive radiation therapy should be tried in the salvage setting.

Stereotactic radiotherapy, such as single fraction stereotactic radiosurgery (SRS) and fractionated SBRT using concave dose distributions, is useful since it protects critical organs (e.g. carotid artery, spinal cord, brain stem and optic pathway). The University of Pittsburgh conducted a phase I dose-escalation study in patients with rHNC. The results revealed that 44 Gy in five fractions over a 2-week period was

well tolerated (2). Vargo et al. (1) reported a retrospective study which included 34 patients with rHNC who received SBRT at a median dose of 40 Gy in five fractions (range, 30–44) as a strategy for salvage therapy. The report showed that local control was significantly improved for small tumors (i.e. <25 cc), and that late grade 3 adverse events occurred only in 6% of patients. Lee et al. (4) reported that IMRT was better suited to predict locoregional tumor control. New technologies such as stereotactic radiotherapy (SRT), SBRT and IMRT might be useful tools to increase the prescribed dose without incrementing the exposure to critical organs. In our study, 79% of patients received SRT/SBRT and the majority developed minor recurrent disease. The most frequent recurrence after re-irradiation occurred within the re-irradiation field. However, our findings did not highlight the superiority of SRT/SBRT, and it did not clarify what the appropriate modality and radiation schedule should be. Unger et al. (19) reported a study on 65 patients who received a median initial radiotherapy of 67 Gy and a median re-irradiation SBRT dose of 30 Gy (range, 21−35) in two to five fractions. They reported that the 2-year OS and locoregional control rates were 41 and 30%, respectively. In addition, they showed by multivariate analysis that a higher total dose, surgical resection and naopharynx site were significantly associated with an improved locoregional control rate. Surgical resection and non-squamous histology were also associated with an improved OS (19). However, 11% of patients in that study experienced severe toxicities due to re-irradiation. Lee et al. (4) reported that a nasopharyngeal site and IMRT technique were associated with a good locoregional progression-free survival (LRPFS) in patients with rHNC who received re-irradiation. Finally, they concluded that achieving locoregional control was crucial to improve OS and that radiation doses >50 Gy were associated with better LRPFS and OS.

The present study has a few limitations worth noting. First, this study is a retrospective review of patients from a single institution, and thus selection- and physician-based biases may exist. In addition, it is important to note that the results are based on a small number of patients who underwent diverse radiotherapy schedules. Secondly, a minority of patients received conventional external beam re-irradiation, whereas no patients received IMRT. Finally, the median follow-up time in the study was only 7.3 months (range, 1.7−25.3). Longer follow-up periods are needed to clarify the long-term complications associated with re-irradiation.

CONCLUSION

Our results suggest that Tanvetyanon's nomogram accurately estimates survival probability after salvage re-irradiation in patients with rHNC. This nomogram is a practical tool for optimal sub-classification of patients with rHNC to evaluate treatment outcomes. Future prospective studies using this nomogram should be performed to establish the appropriate re-irradiation schedule for these patients.

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Conflict of interest statement

None declared.

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Treatment Outcome of Elderly Patients With Glioblastoma who Received Combination Therapy

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Objectives: Large population-based registries in Western countries show that the treatment strategy for glioblastoma multiforme (GBM) in elderly patients is likely less intensive. The purpose of this study was to clarify the treatment outcome of elderly patients with GBM and to explore appropriate treatment strategies.

Methods: We analyzed records from 86 patients (median age, 59 y; range, 9 to 77 y) diagnosed and histologically confirmed to have GBM, between January 1991 and June 2006 at our institutions; 14 elderly patients (range, 71 to 77 y) and 72 younger patients (range, 9 to 70 y). Fifty-two patients underwent total or subtotal resection and 34 patients underwent partial resection or biopsy. The median radiation dose was 54 Gy and 79 patients (92%) received anticancer agents.

Results: Among the 51 patients in recursive partitioning analysis (RPA) classes 5 and 6, the median survival time of the 12 elderly and 39 younger patients were 10.5 months [95% confidence interval, 5.8-12.8] and 11.7 months (95% confidence interval, 9.3-13.0), respectively ($P = 0.32$). Multivariate analysis showed only RPA class as an independent prognostic factor for overall survival rate ($P = 0.009$), whereas age ($P = 0.85$), total radiation dose ($P = 0.052$), and treatment with anticancer agents ($P = 0.32$) were not.

Conclusions: After adjustment for RPA class, the treatment outcome of patients aged >70 years was equal to that of younger patients. Definitive treatment should not be withheld based on age alone.

Key Words: glioblastoma, prognostic factor, radiotherapy, elderly patients

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Glioblastoma multiforme (GBM) is the most common glioma, occurring more often in patients in their 60s and 70s.[1,2] GBM is a rapidly progressive brain tumor, and the standard of care includes surgery, postoperative radiotherapy, and systemic chemotherapy.[1,3–6] In most clinical trials, the optimal treatment has been offered to only a selected subgroup of patients with GBM, such as those aged <70 years and with a good performance status (PS).[4,7] There is little information to define the standard of care for elderly patients with GBM.[6,8,9] Large population-based cancer registries in Western countries show that the treatment strategy for GBM in patients aged >70 years is likely to be less intensive and more palliative.[1,10] Data from the United States National Cancer Institute's Surveillance, Epidemiology, and End Results program showed that a total of 1412 patients with GBM (35%) received neither radiation nor chemotherapy, and patients who were elderly, unmarried, or had more comorbidities were less likely to receive radiotherapy and chemotherapy.[10,11] The cancer registry in Switzerland showed that although 56% of patients with GBM, aged 65 to 74 years, underwent surgery followed by radiotherapy, radiotherapy alone, or surgery alone, only 25% of the patients aged ≥75 years underwent surgery and/or radiotherapy.[12]

Some retrospective studies have shown that aggressive treatment is associated with prolonged survival in elderly patients with GBM. A study at the Memorial Sloan-Kettering Cancer Center demonstrated that, similar to studies in younger patients with GBM, age, PS, and extension of surgery were independent prognostic factors for treatment outcome of elderly patients, and emphasized that age alone should not disqualify patients from aggressive-combined treatment.[10] Results from the Cleveland Clinic showed that elderly patients aged >70 years with good PS, treated aggressively with maximal resection and definitive radiotherapy survived longer than those who received palliative radiotherapy and biopsy.[8] More prospective and retrospective studies are needed to establish the standard of care for elderly patients with GBM.

The purpose of this retrospective study was to clarify the treatment outcome of patients with GBM aged >70 years who received combination therapy, and to explore appropriate treatment strategies for elderly patients.

MATERIALS AND METHODS

We analyzed records from 86 patients (median age, 59 y; range, 9 to 77 y) who were diagnosed and histologically confirmed to have GBM between January 1991 and June 2006 at our institutions. Fourteen patients were aged >70 years (elderly patients; range, 71 to 77 y) and 72 patients were aged ≤70 years (younger patients; range, 9 to 70 y). Forty-six patients (53%) had good PS scores (0 to 1), whereas 40 (47%) had poor PS scores (2 to 4). The median preoperative tumor size was 4.5 cm (range, 1.4 to 8 cm; Table 1). Fifty-two patients (60%) underwent total or subtotal resection, and 34 (40%) underwent partial resection or biopsy. There was no difference in extension of surgery between elderly and younger patients ($P = 0.55$). O^6-methylguanine-DNA methyltransferase (MGMT) promoter methylation status was not assessed in all patients.

Radiotherapy started within 6 weeks postoperatively. As a basic procedure, clinical target volume was based on

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TABLE 1. Patient Characteristics

	Younger Patients (n = 72)		Elderly Patients (n = 14)	
	No. Patients (%)	Median (range)	No. Patients (%)	Median (range)
Age		57 y (9-70)		74 y (71-77)
Performance status				
0-1	44 (61%)		2 (14%)	
2-4	28 (39%)		12 (86%)	
RPA				
Class 3	14 (19%)		0 (0%)	
Class 4	19 (26%)		2 (14%)	
Class 5	25 (35%)		6 (43%)	
Class 6	14 (20%)		6 (43%)	
Tumor size		4.5 cm (1.4-8.0)		4.0 cm (3.0-6.5)
Surgery				
Total or subtotal resection	44 (61%)		8 (57%)	
Partial resection or biopsy	28 (39%)		6 (43%)	
Systemic therapy				
Chemotherapy	66 (92%)		9 (64%)	
Interferon-β	62 (86%)		8 (57%)	
External radiotherapy				
Fraction size		2 Gy (1.8-2)		2 Gy (2-3)
Total dose		54 Gy (42-66)		60 Gy (30-70)

RPA indicates recursive partitioning analysis proposed by the Radiation Therapy Oncology Group.

preoperative computed tomography (CT) and magnetic resonance imaging (MRI) studies, and included the enhanced tumor and peritumoral edema with 1.5 to 2 cm margins. The planning target volume (PTV) was based on clinical target volume with a 0.5 cm margin. If the PTV included critical organs, such as the brainstem, optic chiasm, optic nerve, or retina, PTV was reduced to a 1 to 1.5 cm margin of the preoperative gross tumor volume after a radiation dose of 50 Gy. A photon energy of 4 MV, 6 MV, or 10 MV was used. Treatment plans included lateral-opposed fields, wedged-pair fields, rotation techniques, or multiple-field techniques. Computer-aided treatment planning was performed after the late 1990s. The prescribed dose was calculated at the center of the radiation field or that of the PTV. A 74-year-old man with poor PS, who was grouped into class 6 by recursive partitioning analysis (RPA), was treated with 30 Gy in a fraction size of 3 Gy over 2 weeks. The remaining 85 patients were treated with 42 to 70 Gy in a fraction size of 1.8 to 2 Gy over 4 to 7 weeks. The median and mean radiation doses were 60 and 55 Gy (range, 30 to 70 Gy) in elderly patients, and 54 and 54 Gy (range: 42 to 66 Gy) in younger patients. There was no difference between the total radiation dose in elderly and younger patients ($P = 0.22$).

Seventy-nine patients (92%) received anticancer agents, including cytotoxic agents and/or interferon-β, during or after radiotherapy. Sixty-nine younger patients (96%) and 10 elderly patients (71%; P=0.008) received anticancer agents. Nitrosourea alone or nitrosourea-containing combination chemotherapy was administered to 75 patients, usually concomitant with radiotherapy and/or in a postradiotherapy adjuvant setting. Seventy patients received intravenous interferon-β at a dose of 3,000,000 IU daily during radiotherapy and weekly in a postradiotherapy adjuvant setting. As a basic procedure, patients received these anticancer agents until disease progression or development of severe adverse events. Temozolomide, an oral alkylating agent, was not used in the initial treatment of all patients. Temozolomide was approved for clinical use by the Ministry of Health, Labor, and Welfare of Japan in July 2006. Only a 59-year-old man, who was grouped into RPA class 4, was treated with temozolomide after local progression.

Overall survival time and progression-free survival (PFS) was measured from the date of treatment initiation. PFS was calculated using disease progression and death due to any cause such as events, and overall survival was calculated using death due to any cause such as an event. Disease progression was defined as an increase in tumor size compared with the initial tumor volume visualized on CT/MR images or the appearance of a new lesion separate from the initial tumor volume. Local progression was defined as a tumor size increase or new lesion in the surgical cavity seen on CT/MR images, and distant progression was defined as the appearance of new lesions separated from the initial tumors by at least 2 cm on CT/MR images. We used the Kaplan-Meier method to estimate survival distributions for each group and the log-rank test to compare survival distributions using a significance level of <0.05. The Mantel-Haenszel χ^2 test was used to compare patients and tumor characteristics at baseline. We carried out a multivariate analysis of prognostic factors using the Cox proportional hazards model. Statistical analysis was carried out using JMP version 5.1J (SAS Institute Inc.).

RESULTS

The median follow-up for all patients was 11.6 months (range, 1.4 to 105.8 mo). The median PFS and median survival time (MST) of all 86 patients were 5.8 months [95% confidence interval (CI), 4.7-7.4] and 12.8 months (95% CI, 10.8-14.9), respectively. One-year and 2-year overall survival rates of all patients were 53% and 16%, respectively. Thirteen patients (15%) showed disease progression at the end of radiotherapy. Twelve younger patients (17%) and 1 elderly patient (7%) showed local progression at the end of radiotherapy (P=0.36). The MST of the 35 patients in classes 3 and 4 was 16.9 months (95% CI, 14.2-22.7), and that of the 51 patients in classes 5 and 6 was 11.0 months (95% CI, 9.3-12.6; $P < 0.001$; Fig. 1).

Among the patients in classes 3 and 4, the MST of 2 elderly patients was 14.8 months (95% CI, 10.5-N/A), and that of 33 younger patients was 18.1 months (95% CI, 14.2-24.4;

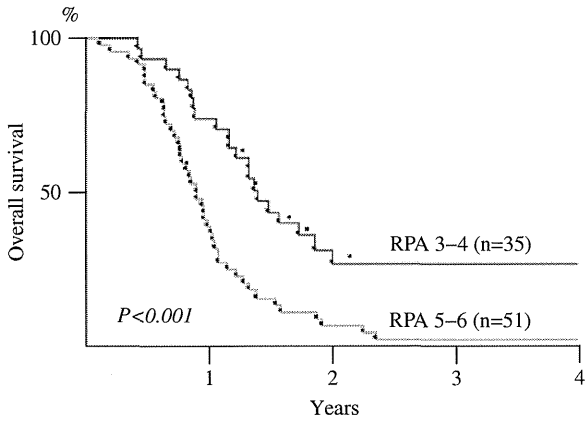

FIGURE 1. Comparison of overall survival rates based on recursive partitioning analysis (RPA) classes.

$P = 0.10$). Twelve elderly patients (86%) and 39 younger patients (54%) were grouped in RPA classes 5 and 6 (P=0.01). Among these patients, the MST of the 12 elderly patients was 10.5 months (95% CI, 5.8-12.8), and that of 39 younger patients was 11.7 months (95% CI, 9.3-13.0; P=0.32; Fig. 2). The 2-year overall survival rates of elderly and younger patients in classes 5 and 6 were 0% and 9%, respectively. The MST of the 20 middle-aged patients (61 to 70 y) in classes 5 and 6 was 8.8 months (95% CI, 6.7-12.0), and the 2-year overall survival rate was 0%. There was no difference between the MST of middle-aged patients and that of elderly patients (>70 y) ($P = 0.48$). The median PFS of elderly patients in classes 5 and 6 was 5.3 months (95% CI, 1.1-9.4), and that of younger patients was 5.8 months (95% CI, 3.2-7.2; $P = 0.74$). The median PFS of middle-aged patients in classes 5 and 6 was 3.6 months (95% CI, 1.7-7.2), and there was no difference between that of the middle-aged patients and that of elderly patients ($P = 0.70$). Among patients in classes 5 and 6, there was no difference between the extension of surgery and total radiation dose between elderly and younger patients ($P = 0.36$ and 0.69). However, younger patients received anticancer agents more frequently than elderly patients ($P = 0.03$).

We carried out a multivariate analysis including RPA class (3 to 4 vs. 5 to 6), age (60 to 70 y vs. >70 y), total radiation dose, and treatment with anticancer agents (yes vs. no). Only RPA class was an independent prognostic factor for overall survival rate ($P = 0.009$), whereas age ($P = 0.85$), total radiation dose (P=0.052), and treatment with anticancer agents ($P = 0.32$) were not. We also carried out a multivariate analysis including these prognostic factors for PFS, but found no independent prognostic factors (RPA classes, P=0.67; age, $P = 0.25$; total radiation dose, $P = 0.11$; anticancer agents, $P = 0.13$).

Sixty-five patients (75%) showed disease progression during the follow-up period: 54 patients (83%) had local progression, 8 (12%) had both local and distant progression, and 3 (5%) had only distant progression. Salvage therapies, including chemotherapy or best supportive care (BSC), were performed according to each physician's policy.

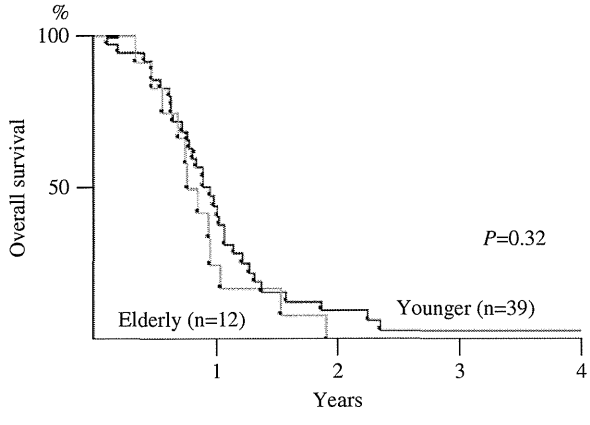

FIGURE 2. Overall survival rates of the 12 elderly patients and 39 younger patients in recursive partitioning analysis classes 5 and 6.

DISCUSSION

Data from the cancer registry in Switzerland demonstrated that 27% of patients with GBM aged 55 to 64 years, 44% of the patients aged 65 to 74 years, 75% of the patients aged >75 years received BSC alone without effective treatment.[12] The Surveillance, Epidemiology, and End Results-Medicare linked data demonstrated that increased age was associated with noneffective treatment and hence, worse prognosis.[13] Although these large population-based cancer registries demonstrate that an increase in age is associated with less intensive treatment, there is little information to define the standard of care for elderly patients with GBM.[9] In particular, there are no prospective randomized studies that evaluate the effectiveness and safety of combination therapy, including postoperative radiotherapy and chemotherapy, for patients aged $\geq$70 years.

Adjuvant systemic chemotherapy after surgery prolongs survival in patients with GBM.[6,14] A meta-analysis of 12 randomized controlled trials, including more than 3000 patients, compared postoperative radiotherapy alone with postoperative radiotherapy and chemotherapy, and demonstrated that the addition of chemotherapy decreased the risk of death by 15% (hazard ratio, 0.85; 95% CI, 0.78-0.91).[5] The European Organisation for Research and Treatment of Cancer/the National Cancer Institute of Canada Intergroup conducted a randomized clinical trial for patients aged 18 to 70 years with newly diagnosed GBM, and reported that the 2-year survival rate was 26% for the temozolomide and radiotherapy group compared with only 10% for the radiation only group.[4] This trial demonstrated the clinical benefit of temozolomide in patients with GBM, but subset analysis showed that the benefit was not statistically significant in patients undergoing diagnostic biopsy only or those with poor PS.[4,15] The 5-year analysis of this trial demonstrated that patients aged 60 to 70 years benefited from combined therapy (hazard ratio for overall survival, 0.7; range, 0.5 to 0.97).[16] Grant et al[17] retrospectively analyzed 148 patients with malignant gliomas or recurrent astrocytomas who received nitrosourea-based chemotherapy, and reported that age was strongly predictive of the likelihood of responding to chemotherapy, time to progression, and survival, and patients aged $\geq$60 years had a lower chance of benefiting from chemotherapy. On the other hand, Combs et al[18] conducted a retrospective study including 43 patients aged $\geq$65 years (range, 65 to 76 y) who received postoperative radiotherapy and chemotherapy, and reported that radiochemotherapy was safe and effective in this population. Prospective studies are required to clarify the benefit of chemotherapy for elderly patients with GBM.

The Medical Research Council conducted a randomized trial comparing 45 Gy in 20 fractions over 4 weeks with 60 Gy

in 30 fractions over 6 weeks for patients aged 18 to 70 years with grade 3 or 4 malignant glioma, and reported that the 60 Gy course produced a modest lengthening of PFS and overall survival.[19] Keime-Guibert et al[6] conducted a randomized trial that compared BSC only with radiotherapy (50 Gy in daily fractions of 1.8 Gy over 5 wk) in patients with GBM aged ≥70 years. Radiotherapy improved MST from 16.9 weeks to 29.1 weeks, and the hazard ratio for death in the radiotherapy group was 0.47 (95% CI, 0.29-0.76; P=0.002). Roa et al[20] conducted a prospective randomized trial that compared standard radiation therapy (60 Gy in 30 fractions over 6 wk) and a short course of radiotherapy (40 Gy in 15 fractions over 3 wk) in patients aged ≥60 years. There was no difference in survival between the 2 groups, and short-course radiotherapy led to a decrease in posttreatment corticosteroid dosage. Although radiotherapy has been effective and safe in elderly patients, it is unclear whether a total dose of 60 Gy represents the standard dose for these patients.[6,19] A limitation of this study is that the median radiation dose for younger patients was <60 Gy. However, there was no statistical difference between the radiation dose in elderly, middle-aged, and younger patients and multivariate analysis showed that total radiation dose was not associated with overall survival. This study is also limited due to the lack of evaluation of MGMT methylation status, quality of life, and long-term neurotoxicity.

Although age is an important factor for predicting survival of patients with GBM, there is a room for discussion as to whether less intensive therapy is suitable for the majority of elderly patients.[8,9] RPA proposed by the Radiation Therapy Oncology Group has been a useful tool for predicting the prognosis of patients with malignant glioma.[21] RPA includes age, histology, mental status, PS, and the extent of surgical excision. The median survival time was 4.7 to 58.6 months for the 12 subgroups resulting from this analysis. This study showed that the MST of the 35 patients in classes 3 and 4 was superior to that of 51 patients in classes 5 and 6 (P < 0.001). However, a limitation of the RPA classification is that it requires the extent of surgical excision, which cannot be assessed before treatment, and this prognostic system is not used for the initial pretreatment decision-making process. The Organisation for Research and Treatment of Cancer/the National Cancer Institute of Canada Clinical Trials Group developed nomograms for predicting survival in patients with GBM. The nomograms include methylated MGMT promoter status, age, PS, extension of surgical excision, and Mini-Mental State Examination score.[7] Patients with GBM with a methylated MGMT promoter benefit from temozolomide and have a good prognosis.[22] This additional molecular information may be useful for estimating the treatment outcome of patients with GBM, and other molecular characteristics and predictive markers may facilitate individually tailored therapy.

In this study, the majority of elderly patients were grouped in RPA classes 5 and 6. However, an analysis adjusting for RPA classification showed that the treatment outcome of patients aged >70 years in classes 5 and 6 and that of younger patients in classes 5 and 6 was likely to be equal. Treatment decision-making should be performed in the same manner in elderly patients as for younger patients, and definitive treatment should not be withheld based on age alone.

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Phase II study of concurrent chemoradiotherapy with high-dose-rate intracavitary brachytherapy in patients with locally advanced uterine cervical cancer: Efficacy and toxicity of a low cumulative radiation dose schedule ☆

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ABSTRACT

Objective. A multicenter phase II trial was conducted to assess the efficacy and toxicity of concurrent chemoradiotherapy (CCRT) with high-dose-rate intracavitary brachytherapy (HDR-ICBT) using a low cumulative prescribed dose schedule in patients with locally advanced uterine cervical cancer.

Methods. The Japanese Gynecologic Oncology Group (JGOG) study JGOG1066 enrolled patients with FIGO stages III–IVA uterine cervical cancer who had no para-aortic lymphadenopathy (>10 mm) assessed by CT. Patients received definitive radiotherapy (RT) consisting of external beam whole pelvic RT and HDR-ICBT. The cumulative linear quadratic equivalent dose (EQD2) was 62–65 Gy prescribed at point A. Cisplatin 40 mg/m^2 weekly was administered concurrently with RT for 5 courses.

Results. Of the 72 patients registered, 71 were eligible. With a median follow-up of 28 months, the 2-year progression-free survival rate and pelvic disease progression-free rate were 66% (95% CI, 54% to 76%) and 73% (95% CI, 61% to 82%), respectively. Progression-free survival decreased significantly with increased central tumor size (P=0.036). The 2-year cumulative late complication rates were 24% for all grades, 9% for grade 1, 12% for grade 2, 3% for grade 3, and 0 for grades 4/5.

Conclusions. The JGOG1066 demonstrated that CCRT using HDR-ICBT with a low cumulative RT dose schedule achieved comparable outcome as those achieved with global dose schedules (EQD2=85 Gy) with a lower incidence of late toxicity for locally advanced uterine cervical cancer in a Japanese population.

Introduction

Concurrent chemoradiotherapy (CCRT) has been shown to be superior to definitive radiotherapy (RT) alone in several randomized controlled trials (RCTs), and is now the standard of care for locoregionally advanced uterine cervical cancer [1]. Standard definitive RT consists of whole pelvic external beam RT (EBRT) and either high or low dose rate intracavitary brachytherapy (ICBT). The previously mentioned RCTs utilized only low dose-rate ICBT (LDR-ICBT) [1]. High dose-rate ICBT (HDR-ICBT) has become widely used in Japan [2], and many centers worldwide are also shifting to HDR-ICBT [3].

Several RCTs have demonstrated clinical equivalence in terms of both local control and toxicity between HDR-ICBT and LDR-ICBT in the setting of definitive RT (without chemotherapy) [4]. In CCRT, many investigators also reported favorable treatment results using HDR-ICBT in single institutional retrospective series [5–13]. The Gynecologic Oncology Group (GOG) and the Radiation Therapy Oncology Group (RTOG) now allow the use of HDR-ICBT as well as LDR-ICBT in recent clinical trials of CCRT for cervical cancer [14–18]. In these

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