悪性神経膠腫

井垣　浩／作美　明／中川恵一

東京大学医学部附属病院 放射線科

Points

①脳定位放射線照射は、転移性脳腫瘍に対する治療の意義が示されており、現在普及している体幹部高精度放射線治療の基盤になっている。
②悪性神経膠腫に対する術後化学放射線療法は標準治療となっているが、その成績はいまだ十分とはいえない。
③強度変調放射線治療は、悪性神経膠腫に対しても近年積極的に行われているが、その有効性を示す報告はまだ少ない。
④悪性神経膠腫に対して粒子線（陽子線・炭素イオン線）治療の臨床試験が行われており、有望な成績が報告されている。
⑤ホウ素中性子捕捉療法も、限られた施設のみではあるが多形性膠芽腫に用いられており、近年急速に治療成績が向上している。
⑥分子マーカによる予後予測を取り入れたテーラーメイド治療も、今後は放射線治療に求められるようになるかもしれない。

はじめに

体幹部と比較すると頭頸部では、ガントリと治療寝台の干渉によって照射方向の制約を受ける可能性が比較的少ないこと、セットアップにおいてinternal marginを考慮する必要がほとんどないことなどから、他臓器の放射線治療に比較して脳腫瘍に対しては古くからいろいろな方法による集光的照射が行われてきた。その結果、脳定位放射線照射が転移性脳腫瘍治療の流れを大きく変えたといっても過言ではない。この技術が確立したからこそ体幹部定位放射線治療の普及が可能になったのであり、全身の腫瘍に適応が広がりつつある粒子線治療やホウ素中性子捕捉療法（boron neutron capture therapy：BNCT）も、脳および頭頸部の病変が初期の対象疾患の中心であった。つまり、現在さかんに行われている高精度放射線治療のほとんどは、脳腫瘍への応用という視点を盛り込みながら進歩してきた歴史があるのだ。それにもかかわらず、放射線治療技術の進歩の成果が脳腫瘍領域に対して十分に結実しているとはいえない。

実際、転移性脳腫瘍では、全脳照射に定位放射線治療を加えることで生存期間が延長することが示されて以降は、新たな技術導入による生存期間の延長は得られていない。悪性神経膠腫治療においては定位放射線治療の意義すら認められておらず、いまだ根治がきわめてむずかしい悪性腫瘍である。そのような状況下ではあるが、加療後のquality of lifeの保持を重視した集学的治療の一部として、腫瘍の局所制御と正常脳組織の保護という2つの相反する目標が放射線治療には期待されており、さまざまな試みがなされ続けている。

表　悪性神経膠腫に対するIMRTのおもな報告

報告者（文献）	線量（PTV1/PTV2/PTV3）	分割回数	症例数（WHO grade Ⅲ/grade Ⅳ）	中間生存期間（ヵ月）	化学療法
Sultanemら[5]	40Gy/60Gy/-	20	0/25	9.5	なし
Floydら[6]	30Gy/50Gy/-	10	0/18	7	なし
Iuchiら[7]	32Gy/40Gy/48～68Gy	8	2/23	2年生存率55.6%	19症例で施行（詳細記述なし）
Nakamatsuら[8]	56Gy/70Gy/-	28	5/8	2年生存率31%	11症例で施行（ACNU、VCR、IFNβ）
Panet-Raymondら[9]	40Gy/60Gy/-	20	0/35	14.4	TMZ
Morgantiら[10]	45Gy/60～65Gy/-	25	0/19	20	TMZ
Choら[11]	50Gy/60Gy/-	25	14/26	14.8	TMZ

本稿では、近年の新規放射線治療技術のうち、悪性神経膠腫に対して用いられているものを中心に記載し、その将来性や問題点についても議論する。

古典的な放射線治療の意義と標準治療

定位放射線治療の普及以前から、古典的な放射線治療（2次元放射線治療もしくは3次元原体照射）は、悪性神経膠腫だけでなく他の脳腫瘍に対しても行われてきた。悪性神経膠腫に対する術後放射線治療は、複数のランダム化比較試験結果に基づいて1980年代には標準治療の地位をすでに確立しており[1～4]、化学療法もメタアナリシスによってその意義は示されていた。

しかし、標準治療である術後化学放射線療法を行っても悪性神経膠腫の生存期間は十分とはいえず、特に多形性膠芽腫（glioblastoma multiforme：GBM）では多くの症例で腫瘍中心部からの再発がみられる。このため、3次元原体照射や定位放射線照射による線量増加が試みられてきたものの、60Gyを超える線量増加は悪性神経膠腫の予後の改善に寄与しないとするデータが大半であった。現在でも、悪性神経膠腫に対する術後照射の標準治療は、粒子線治療や強度変調放射線治療、BNCTなどの方法が試みられており、第Ⅰ/Ⅱ相試験段階ではあるが良好な成績も報告されつつある。

1）悪性神経膠腫に対する強度変調放射線治療

中枢神経系は、泌尿器、頭頸部領域に続いてIMRTが普及している臓器であり、悪性神経膠腫に対するIMRTの臨床成績も近年多く報告されている。施設によって線量分割方法がまちまちであり、現時点では悪性神経膠腫に対するIMRTの有効性を評価するのは困難といえる。

Simultaneous integrated boost法によって腫瘍中心部は2.4～6Gy/回以上の加速照射とし、放射線生物学的には標準治療よりも実質的な線量増加をしている施設が多いが[5～11]、生存期間延長を示唆する報告は残念ながらまだ少ない（表）。また、線量だけでなく、標的の決め方までもが施設ごとに異なっており、IMRTの意義や成績を比較するのも現時点では困難である。今後、線量分割方法を標準化した上で、その有効性と安全性を示す報告がまたれる。

一方、加速照射を行っても治療成績の低下や有害事象頻度の明らかな増加がみられない点は着目に値する。期待される生存期間が短い患者に対する治療と考えれば、従来6週間を要していた放射線治療期間がIMRTの導入によって短縮できるという意義は大きいといえるだろう。

これまでは、CTやMRIで描出可能な臓器や領域のみが臨床腫瘍容積やリスク臓器として治療計

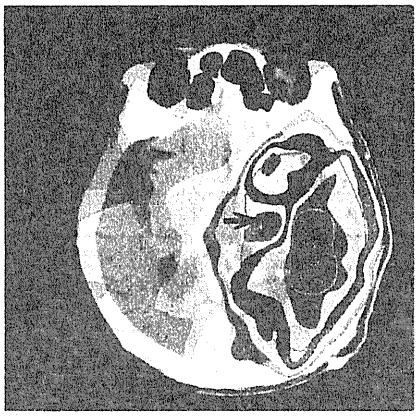

図1　悪性神経膠腫に対する皮質脊髄路（→）保護IMRTの線量分布図

IMAGE PREVIEW 参照

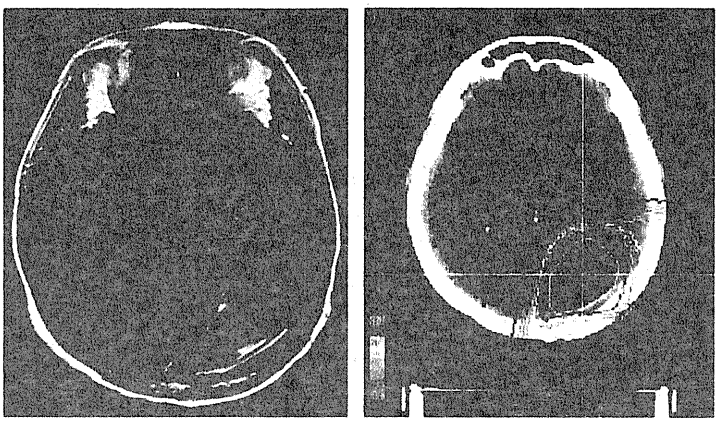

図2　左後頭葉原発のGBM症例の陽子線治療計画

術後MRIで腫瘍は亜全摘されており（左）、X線による拡大局所照射の後に陽子線boost局所照射（右）を行った。陽子の飛程が決まっているので、正常脳組織の線量はきわめて少なく照射することができる。

IMAGE PREVIEW 参照

画上に設定されてきたが、近年は機能画像によってCTやMRIだけでは描出できない脳の特定領域の輪郭を設定する試みも行われている[12]。そのうち、最も普及しているのはFDG-PETやメチオニンPETによって腫瘍組織の中でも増殖活性の高い部位を特定し、その領域に線量増加をするものである。一般に術後MRI画像のガドリニウム増強域は残存病変に相当すると考えられているが、実際にはFDGやメチオニンの集積域と必ずしも一致せず、PET画像に基づいてGTVの代わりにbiological target volumeを設定して放射線治療を行う研究も既に多く報告されている。

また、MR spectroscopyによって脳の一次運動野を特定し、これをリスク臓器として線量を落とし、放射線障害による運動麻痺リスクを下げる試みも報告されている[13]。当科では、拡散テンソルトラクトグラフィをfusionし、皮質脊髄路をリスク臓器として線量を落とすIMRT計画の研究を行っている（**図1**）。

2）悪性神経膠腫に対する粒子線治療

重荷電粒子は、多くのエネルギーを飛程の停止直前に放出してブラッグピークを形成する。重荷電粒子の入射エネルギーを適切に調節することで、X線治療と比較して臨床標的体積に集中してエネルギー付与できるのが粒子線治療の特徴である（**図2**）。現在わが国には、陽子線治療6施設と炭素イオン線治療3施設で計8施設（1施設は陽子線・炭素イオン線両方あり）が稼働している。炭素イオン線の場合にはRBEが2～3と高く、放射線低感受性腫瘍に対する治療効果も期待される。

放射線医学総合研究所では、ACNU化学療法併用にてX線治療50Gy/25分割後の追加照射に炭素イオン線を用いた第Ⅰ/Ⅱ相線量増加試験を行い、炭素イオン線の線量効果関係が認められ、最大線量である24.8GyE/8分割の治療をしたGBM症例は5例と症例数は少ないが26ヵ月の中間生存期間を得たとしている[14]。筑波大学では、ACNU化学療法併用でX線治療50.4Gy/28分割と陽子線治療46.2GyE/28分割の加速過分割照射の第Ⅰ/Ⅱ相線量増加試験を行い、21.6ヵ月の中間生存期間を報告している[15]。

粒子線治療を実施するには、粒子を加速する巨大な加速器が必要であり、予算的・敷地的な部分が普及の障壁となっている。ただし、近年は加速器の小型化と低価格化が同時に実現されつつあり、他臓器腫瘍領域における粒子線治療への注目もあり、導入予定の施設も増加傾向にある。また、保険診療化への強い要望はあるが、本稿執筆時点では保険適応となっておらず、先進医療として約300万円の自己負担が必要なことも患者の視点か

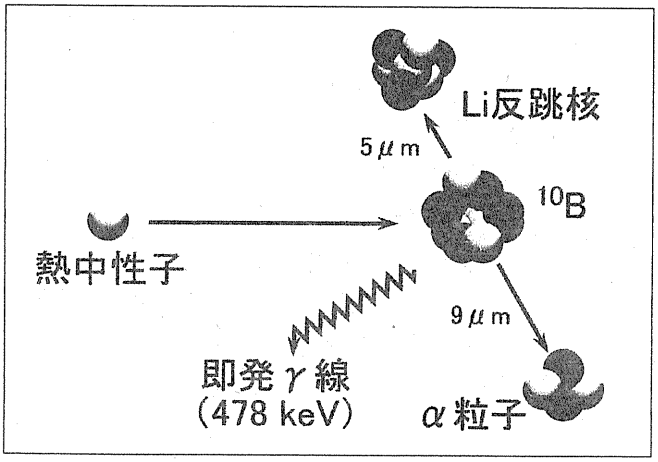

図3　BNCTの原理
熱中性子が^{10}B原子核に衝突すると、α粒子とLi反跳核に分裂する原子核反応が起きる。α粒子はRBEが高く、その飛程は細胞の直径とほぼ等しいので、ホウ素化合物を腫瘍細胞特異的に取り込ませれば腫瘍細胞特異的な放射線治療が実現できる。

らは大きな問題である。

3）悪性神経膠腫に対するBNCT

BNCTは、質量数10のホウ素原子核（^{10}B）に中性子が照射された際に起きる核反応で生じた、生物学的効果比が高く飛程が約9μmと短いα線を用いる治療である（**図3**）。腫瘍細胞に効率よく集積するBSH（sodium borocaptate）やBPA（boronophenylalanine）といったホウ素化合物を中性子照射前に投与しておくことによって、腫瘍細胞特異的で殺細胞効果の高い治療が期待できる。

ホウ素化合物の腫瘍組織への薬剤送達が障壁となり、この治療法の発祥の地アメリカでは一時衰退したが、わが国では地道な研究が続けられ、近年急速にその治療成績が伸びた。現在では、X線治療との併用によって生存期間中央値はGBMでも2年を超える成績も報告されている[16, 17]。

治療には熱外中性子がおもに用いられるが、高強度の中性子束が必要なため、中性子源として研究用原子炉が用いられてきた。わが国では現時点で、京都大学原子炉実験所および日本原子力研究開発機構でしか行われていない。しかし、中性子源となる加速器の開発が現在進んでおり、これが実用化されれば治療のために研究用原子炉まで行く必要がなくなるため、病院でBNCTを行うことが可能となり、本治療の普及が期待できる。

また、腫瘍組織への十分な薬剤送達は本治療のカギを握る。わが国以外では薬剤送達に関する基礎研究やプロトコル検討が十分に行われていないことも、いまだ海外でのBNCTの成績がふるわない原因の1つとなっている。

おわりに

悪性神経膠腫治療においては、現在行われているX線治療の改良というだけではこれ以上の成績向上は見込めないのかもしれない。他領域では積極的に行われているIMRTについても、悪性神経膠腫に関する限りにおいては、生存期間の改善が期待できるデータは今のところ十分にはそろっていない。しかしそのぶん、粒子線治療やBNCTといった"特殊な治療"を用いた挑戦が積極的に続けられていることも事実である。

もともと化学療法に対する反応性の予測因子として注目されるようになったMGMT遺伝子プロモーターメチル化や1p/19q欠失といった分子マーカが、放射線単独治療後の予後予測因子にもなることも示唆されている[18〜20]。また、VEGF阻害剤であるbevacizumabは、GBMに対する抗腫瘍活性が期待されているばかりでなく、血管新生阻害によって血管透過性を減少させることによって放射線脳壊死治療薬としての意義も最近ランダム化比較試験によって示された[21]。すでによく用いられている臨床的予後因子だけでなく、分子マーカも考慮に入れて予後や治療反応性を予測し、それに基づいて方針や線量も決めてゆくテーラーメイド治療が、悪性神経膠腫の放射線治療にも期待されるようになりつつある。

通常のX線治療や化学療法に対する反応が期待しにくい症例に対しては、放射線脳壊死を恐れすぎずに、粒子線治療やBNCTも用いて線量増加を積極的に考慮することによって[22]、悪性神経膠腫全体としての治療成績の向上が見込めるようになるかもしれない。

参考文献

1) Andersen AP: Postoperative irradiation of glioblastomas. Results in a randomized series. Acta Radiol Oncol Radiat Phys Biol 17(6): 475-484, 1978

2) Walker MD et al: Evaluation of BCNU and/or radiotherapy in the treatment of anaplastic gliomas. A cooperative clinical trial. J Neurosurg 49(3): 333-343, 1978

3) Chin HW et al: Survival response of malignant gliomas to radiotherapy with or without BCNU or methyl-CCNU chemotherapy at the University of Kentucky Medical Center. Cancer Treat Rep 65(1-2): 45-51, 1981

4) Kristiansen K et al: Combined modality therapy of operated astrocytomas grade Ⅲ and Ⅳ. Confirmation of the value of postoperative irradiation and lack of potentiation of bleomycin on survival time: a prospective multicenter trial of the Scandinavian Glioblastoma Study Group. Cancer 47(4): 649-652, 1981

5) Sultanem K et al: The use of hypofractionated intensity-modulated irradiation in the treatment of glioblastoma multiforme: preliminary results of a prospective trial. Int J Radiat Oncol Biol Phys 58(1): 247-252, 2004

6) Floyd NS et al: Hypofractionated intensity-modulated radiotherapy for primary glioblastoma multiforme. Int J Radiat Oncol Biol Phys 58(3): 721-726, 2004

7) Iuchi T et al: Hypofractionated high-dose irradiation for the treatment of malignant astrocytomas using simultaneous integrated boost technique by IMRT. Int J Radiat Oncol Biol Phys 64(5): 1317-1324, 2006

8) Nakamatsu K et al: Treatment outcomes and dose-volume histogram analysis of simultaneous integrated boost method for malignant gliomas using intensity-modulated radiotherapy. Int J Clin Oncol 13(1): 48-53, 2008

9) Panet-Raymond V et al: Accelerated hypofractionated intensity-modulated radiotherapy with concurrent and adjuvant temozolomide for patients with glioblastoma multiforme: a safety and efficacy analysis. Int J Radiat Oncol Biol Phys 73(2): 473-478, 2009

10) Morganti AG et al: A phase I dose-escalation study (ISIDE-BT-1) of accelerated IMRT with temozolomide in patients with glioblastoma. Int J Radiat Oncol Biol Phys 77(1): 92-97, 2010

11) Cho KH et al: Simultaneous integrated boost intensity-modulated radiotherapy in patients with high-grade gliomas. Int J Radiat Oncol Biol Phys 78(2): 390-397, 2010

12) Lammering G et al: The use of FDG-PET to target tumors by radiotherapy. Strahlenther Onkol 186(9): 471-481, 2010

13) Chang J et al: Feasibility study of intensity-modulated radiotherapy (IMRT) treatment planning using brain functional MRI. Med Dosim 33(1): 42-47, 2008

14) Mizoe JE et al: Phase Ⅰ/Ⅱ clinical trial of carbon ion radiotherapy for malignant gliomas: combined X-ray radiotherapy, chemotherapy, and carbon ion radiotherapy. Int J Radiat Oncol Biol Phys 69(2): 390-396, 2007

15) Mizumoto M et al: Phase Ⅰ/Ⅱ trial of hyperfractionated concomitant boost proton radiotherapy for supratentorial glioblastoma multiforme. Int J Radiat Oncol Biol Phys 77(1): 98-105, 2010

16) Yamamoto T et al: Boron neutron capture therapy for newly diagnosed glioblastoma. Radiother Oncol 91(1): 80-84, 2009

17) Kawabata S et al: Boron neutron capture therapy for newly diagnosed glioblastoma. J Radiat Res (Tokyo) 50(1): 51-60, 2009

18) Cairncross G et al: Phase Ⅲ trial of chemotherapy plus radiotherapy compared with radiotherapy alone for pure and mixed anaplastic oligodendroglioma: Intergroup Radiation Therapy Oncology Group Trial 9402. J Clin Oncol 24(18): 2707-2714, 2006

19) van den Bent MJ et al: Adjuvant procarbazine, lomustine, and vincristine improves progression-free survival but not overall survival in newly diagnosed anaplastic oligodendrogliomas and oligoastrocytomas: a randomized European Organisation for Research and Treatment of Cancer phase Ⅲ trial. J Clin Oncol 24(18): 2715-2722, 2006

20) Stupp R et al: Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomised phase Ⅲ study: 5-year analysis of the EORTC-NCIC trial. Lancet Oncol 10(5): 459-466, 2009

21) Levin VA et al: Randomized double-blind placebo-controlled trial of bevacizumab therapy for radiation necrosis of the central nervous system. Int J Radiat Oncol Biol Phys 79(5): 1487-1495, 2011

22) Sköld K et al: Boron neutron capture therapy for newly diagnosed glioblastoma multiforme: an assessment of clinical potential. Br J Radiol 83(991): 596-603, 2010

Surg Radiol Anat (2012) 34:85–88
DOI 10.1007/s00276-011-0837-3

ANATOMIC VARIATIONS

Thyrolingual trunk arising from the common carotid artery identified by three-dimensional computed tomography angiography

Toshinori Iwai · Toshiharu Izumi · Tomio Inoue · Jiro Maegawa · Nobukazu Fuwa · Kenji Mitsudo · Iwai Tohnai

Received: 4 April 2011 / Accepted: 26 May 2011 / Published online: 9 June 2011

Abstract It is well-known that the branches of the external carotid artery (ECA) can show anatomical variation, but it is extremely rare that thyrolingual trunk originates from common carotid artery (CCA). Here we report a case of the thyrolingual trunk arising from the CCA on the right side in a 73-year-old female as revealed by three-dimensional computed tomography angiography for vascular mapping of the carotid vessels before head and neck microsurgical reconstruction. The thyrolingual trunk arose from the anterior surface of the right CCA, with an origin 14.5 mm (difference between the carotid bifurcation and upper border of the origin 12.7 mm) below the carotid bifurcation. The inner diameter of origin of the thyrolingual trunk was 3.5 mm, and the angle between the thyrolingual trunk and the CCA was 130°. After a 10.2-mm course, the thyrolingual trunk divided into the superior thyroid artery (STA) and lingual artery (LA). The inner diameters of the origins of the STA and LA were 1.7 and 1.9 mm, respectively, and the angle between the branches was 94°. It is important to recognize this anatomic variation of the branches of the ECA before the microsurgical reconstruction or super-selective intra-arterial chemotherapy for head and neck cancer.

Keywords Variation · Thyrolingual trunk · Common carotid artery · Three-dimensional computed tomography angiography

T. Iwai (✉) · K. Mitsudo · I. Tohnai
Department of Oral and Maxillofacial Surgery,
Yokohama City University Graduate School of Medicine,
3-9 Fukuura, Yokohama, Kanagawa 236-0004, Japan
e-mail: iwai104oams@yahoo.co.jp

T. Izumi · T. Inoue
Department of Radiology, Yokohama City University Hospital,
3-9 Fukuura, Yokohama, Kanagawa 236-0004, Japan

J. Maegawa
Department of Plastic and Reconstructive Surgery,
Yokohama City University Hospital, 3-9 Fukuura,
Yokohama, Kanagawa 236-0004, Japan

N. Fuwa
Department of Radiation Oncology,
Southern Tohoku Proton Therapy Centre,
Southern Tohoku Research Institute of Neuroscience,
7-172 Yatsuyamada, Koriyama, Fukushima 963-8052, Japan

Introduction

It is well-known that the branches of the external carotid artery (ECA) can show variation, which is usually asymptomatic and discovered incidentally, and a common trunk is occasionally found. However, it is extremely rare that thyrolingual trunk originates from common carotid artery (CCA) [5, 7]. Here we report a case of the thyrolingual trunk arising from the CCA as identified by three-dimensional computed tomography (CT) angiography (3D-CTA).

Case report

A 73-year-old female was referred to our department for recurrence of right mandibular gingival carcinoma 3 years after the marginal mandibulectomy via an extraoral approach. Head and neck reconstruction was necessary due to the advanced cancer invasion of the skin. CTA was performed for vascular mapping of the carotid vessels before microsurgical reconstruction. A 64-detector spiral CT scanner (Aquilion 64; Toshiba Medical, Tokyo, Japan)

was used. Nonionic contrast medium (100 ml) was injected at a rate of 4.0 ml/s through an antecubital vein with an automatic power injector. A bolus tracking technique was used to select the individual start delay for the arterial phase. Repetitive low-dose scans were performed at a level inferior to the carotid bifurcation (CB) with a delay of 8 s. The region of interest was placed in the CCA to measure the bolus arrival time. The scanning procedure started automatically once the enhancement level of 90 HU was reached. The scan volume included the inferior margin of the thyroid cartilage/bottom of C6 to the superior margin of the orbit for arterial phase scan. The scanner settings were 120 kV, 250 mA, 64 × 0.5 mm slice collimation, table speed 20.5 mm/rotation (pitch 0.641), and rotation time 0.75 s. The patient was adviced to hold the breath and avoid swallowing during the arterial phase scan. Image processing was done on a workstation (Ziostation, Ziosoft, Tokyo, Japan) using the volume rendering technique. Rotational images of the bilateral three-dimensional vascular architecture were produced and viewed from different angles. 3D-CTA revealed that the thyrolingual trunk arose from the anterior surface of the right CCA, with the point of origin located 14.5 mm (difference between the CB and upper border of the origin 12.7 mm) below the CB (Fig. 1). The inner diameter of origin of the thyrolingual trunk was 3.5 mm and the angle between the thyrolingual trunk and CCA was 130°. After a 10.2 mm course, the thyrolingual trunk divided into the superior thyroid artery (STA) and lingual artery (LA), the inner diameters of origin of which were 1.7 and 1.9 mm, respectively. The angle between the two arteries was 94°. The CB was located 11.2 mm above the tip of the greater horn of the hyoid bone, and the thyrolingual trunk was located 2.7 mm (difference between upper border of the origin and tip: 0.4 mm, difference between lower border of the origin and tip: 4.7 mm) below it (Fig. 2). The right facial artery could not be detected for ligation during the primary operation. On the left side, the STA arose from the CCA and linguofacial trunk originated from the ECA. The occipital artery was located between the CB and the origin of the linguofacial trunk.

Discussion

The STA is the first branch of the ECA, but sometimes it arises from the CCA [6]. The incidence of the STA arising from the CCA is reported to range widely between 1 and 54% [1, 5, 6, 14]. Toni et al. [14] reviewed that the STA more frequently originated from the ECA on the right side and from the CCA on the left side. In the present case, the left STA originated from the CCA. The LA commonly arises from the ECA above the STA and it is rare for the LA to arise from the CB level [8]. Furthermore, there are few reports of the LA originating from the CCA [2]. Although Kaneko et al. [2] reported just such an LA arising from the CCA, their case had no ECA. When there is no ECA, the LA naturally originates from the CCA or ICA. Therefore, the LA arising from the CCA is extremely rare if the ECA is present. In our case with the ECA, the LA and

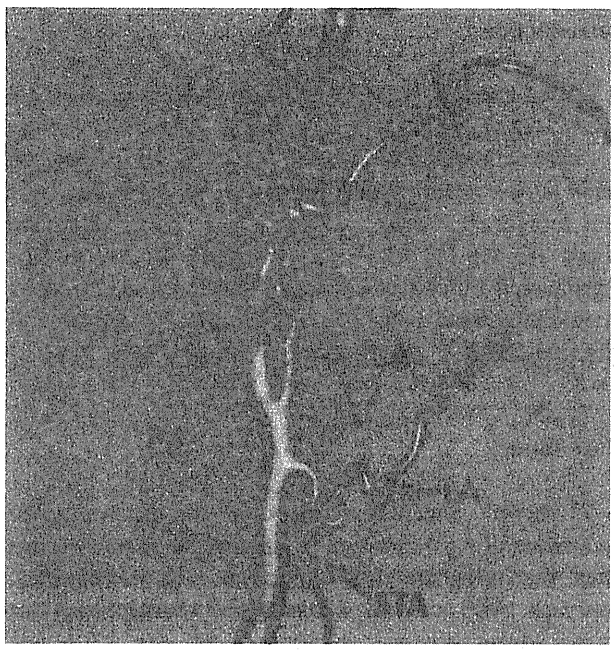

Fig. 1 3D-CTA image of the right carotid artery. *LA* lingual artery, *STA* superior thyroid artery, *TLT* thyrolingual trunk, *CCA* common carotid artery, *ECA* external carotid artery, *ICA* internal carotid artery

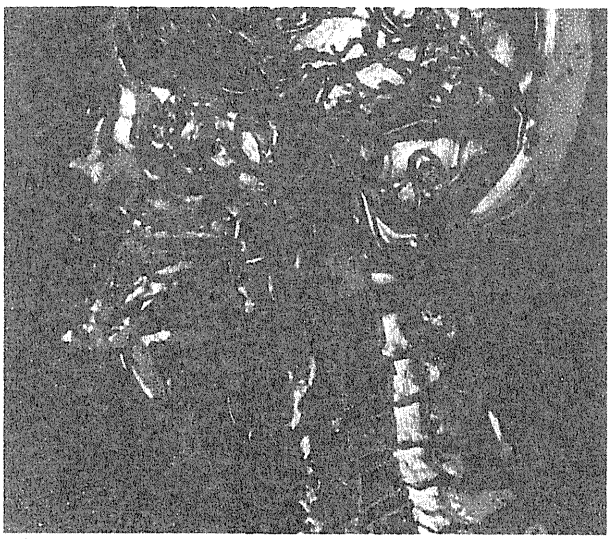

Fig. 2 3D-CTA image of the right carotid artery and hyoid bone. *TLT* thyrolingual trunk, *HB* hyoid bone, *ECA* external carotid artery, *ICA* internal carotid artery

STA originated from the CCA as common trunk on the right side.

The incidence of the thyrolingual trunk arising from the ECA is reported as 0.7–3% by Ozuger et al. [9] and that from the CCA is even rarer [5, 7] with an incidence of less than 0.1% reported by Lippert et al. [7]. In our institution, CTA was performed for 265 head and neck cancer patients between June 2006 and December 2010, and of these cases, only present case showed the thyrolingual trunk arising from the CCA, for an incidence of 0.38%. Lemaire et al. [5] reported the thyrolingual trunk arising from the CCA in 2 cases, in which the origin of the thyrolingual trunk (5.2 and 10 mm long) was 30 mm below the CB in both the cases, compared to a thyrolingual trunk in our case that was 10.2 mm long with an origin 14.5 mm below the CB.

The CB is commonly located at the superior border of the thyroid cartilage, and the incidence of it being located at a higher level opposite to the superior border of the hyoid bone is reported to be 12.5% [8]. Although Lemaire et al. [6] reported that the CB was located 13.2 ± 5.6 mm below the tip of the greater horn of the hyoid bone, in our case the CB was located 11.2 mm above it. Moreover, they reported the origin of the STA 13 ± 4.5 mm below the tip of the greater horn of the hyoid bone and the origin of the LA at −0.5 ± 4.4 mm on the vertical axis of the tip [6], while in the present case the thyrolingual trunk was located 2.7 mm below the tip of the greater horn of the hyoid bone. Therefore, in our case the thyrolingual trunk seemed to originate from the CCA because the patient had a higher CB and the STA arose from a higher position as the common trunk. During the embryonic period, the LA springs from the ECA and the STA develops later from the CB [11]. As the origins of the LA and STA separate during the development, the thyrolingual trunk may be considered in light of the fact that the STA springs ectopically from the LA.

Both radiologic diagnosis and the surgical approach depend on anatomical knowledge of the patient, and knowledge and understanding of the patterns of individual variability in the course of the ECA and its branches are vital for the surgery and interventional radiologic procedures in the head and neck region. Any lack of knowledge or experience regarding the possible variations could lead to fatal errors if one blood vessel is mistaken for the another [8]. Without the knowledge of present anatomic variation or preoperative information on the origin of the LA, the vessel may be ligated needlessly during the surgery. Retrograde super-selective intra-arterial infusion via the STA cannot be applied in the treatment of tongue cancer [13] in the cases with the LA arising from the CCA given the high risk for cerebral infarction. Therefore, any anomalous branches of the ECA including the LA or the STA must be precisely determined before head and neck cancer treatment. Although various different techniques including digital subtraction angiography (DSA), ultrasonography (US), magnetic resonance imaging (MRI), and CT are currently available to assess extracranial arterial vessels, CTA is the latest way of minimally invasive imaging and has advantages over US and MRI [12]. Recently, 3D-CTA has been used for vascular mapping before head and neck microsurgical reconstruction [3, 4, 10, 12], and the images of 3D-CTA proved to be a reliable alternative to invasive DSA [3, 4]. Therefore, we routinely perform 3D-CTA as well as the contrast enhanced CT at once for vascular assessment before head and neck surgery or super-selective intra-arterial catheterization for head and neck cancer, as the findings can alert us to the existence of unusual carotid arteries and its branches. To avoid cerebral infarction during the interventional radiological procedures and decrease the potential injury during the surgery, we recommend the use of 3D-CTA, which carries no risk of cerebral infarction compared with the DSA, to assess the patterns and course of the branches of the ECA three dimensionally.

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Akyol MU, Koç C, Ozcan M, Ozdem C (1997) Superior thyroid artery arising from the common carotid artery. Otolaryngol Head Neck Surg 116:701
2. Kaneko K, Akita M, Murata E, Imai M, Kohji Sowa (1996) Unilateral anomalous left common carotid artery; a case report. Ann Anat 178:477–480
3. Kramer M, Vairaktaris E, Nkenke E, Schlegel KA, Neukam FW, Lell M (2008) Vascular mapping of head and neck: computed tomography angiography versus digital subtraction angiography. J Oral Maxillofac Surg 66:302–307
4. Lell M, Tomandl BF, Anders K, Baum U, Nkenke E (2005) Computed tomography angiography versus digital subtraction angiography in vascular mapping for planning of microsurgical reconstruction of the mandible. Eur Radiol 15:1514–1520
5. Lemaire V, Jacquemin G, Medot M, Fissette J (2001) Thyrolingual trunk arising from the common carotid artery: a case reprot. Surg Radiol Anat 23:135–137
6. Lemaire V, Jacquemin G, Nelissen X, Heymans O (2005) Tip of the greater horn of the hyoid bone: a landmark for cervical surgery. Surg Radiol Anat 27:33–36
7. Lippert PabstR (1985) Arterial variations in man: classification and frequency. JF Bergmann, Munich
8. Lucev N, Bobinac D, Maric I, Drescik I (2000) Variations of the great arteries in the carotid triangle. Otolaryngol Head Neck Surg 122:590–591
9. Ozgur Z, Govsa F, Ozgur T (2008) Assessment of origin characteristics of the front branches of the external carotid artery. J Craniofac Surg 19:1159–1166
10. Tan O, Kantarci M, Parmaksizoglu D, Uyanik U, Durur I (2007) Determination of the recipient vessels in the head and neck using

multislice spiral computed tomography angiography before free flap surgery: a preliminary study. J Craniofac Surg 18:1284–1289
11. Tandler J (1902) Zur Entwicklungsgeschichte der Kopfarterien bei den Mammalia. Morphol Jahrb 30:274–373
12. Thurmüller P, Kesting MR, Hölzle F, Retzgen H, Wolff KD (2007) Volume-rendered three-dimensional spiral computed tomographic angiography as a planning tool for microsurgical reconstruction in patients who had operations or radiotherapy for oropharyngeal cancer. Br J Oral Maxillofac Surg 45:543–547
13. Tohnai I, Fuwa N, Hayashi Y, Kaneko R, Tomaru Y, Hibino Y, Ueda M (1998) New superselective intra-arterial infusion via superficial temporal artery for cancer of the tongue and tumour tissue platinum concentration after carboplatin (CBDCA) infusion. Oral Ocncol 34:387–390
14. Toni R, Della Casa C, Castirina S, Malaguti A, Mosca S, Roti E, Valenti G (2004) A meta-analysis of superior thyroid artery variations in different human groups and their cliniccal implications. Ann Anat 186:255–262

PHASE I STUDY OF WEEKLY DOCETAXEL AND CISPLATIN ARTERIAL INFUSION FOR RECURRENT HEAD AND NECK CANCER

Tatsuya Nakamura, MD, Nobukazu Fuwa, MD, Kanako Takayama, DDS, Haruo Inokuchi, MD, Takuya Tomoda, MD, Akinori Takada, MD, Chiyoko Makita, MD, Miho Shiomi, MD, Jun-ichi Yokouchi, MD, Kazuo Watanabe, MD

Department of Radiation Oncology, Southern Tohoku Proton Therapy Center, 7-172 Yatsuyamada, Koriyama, Fukushima 963-8052, Japan. E-mail: tatsuya.nakamura@nifty.com

Accepted 8 September 2011
Published online in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/hed.21983

Abstract: *Background.* We planned a phase I study of weekly arterial infusion of docetaxel and cisplatin via a superficial temporal artery for recurrent head and neck cancer to determine the optimal dose.

Methods. The dose of cisplatin was fixed and the dose of docetaxel was escalated from 8 mg/m^2, with an increase of 2 mg/m^2 per step, to identify the maximum tolerated dose (MTD). In total, 4 courses of weekly chemotherapy were administered.

Results. Twelve patients were recruited to this trial. The MTD of docetaxel was 14 mg/m^2. At this dose level, dose-limiting toxicity was observed in 2 of 3 patients. One patient experienced grade 3 leukopenia, while the other experienced grade 3 leukopenia. Myelosuppression was the dose-limiting toxicity for this regimen.

Conclusion. The recommended dose for weekly arterial infusion of docetaxel was identified as 12 mg/m^2 combined with weekly cisplatin at 40 mg/m^2, with 4 courses of each.
 Head Neck **00:** 000–000, 2011

Keywords: head and neck cancer; docetaxel; cisplatin; arterial infusion; chemotherapy

The choice of therapy for recurrent head and neck cancers depends on the location, size or extent of the tumor, presence, or absence of distant metastases, previous therapy, and performance status of the patient.[1–5] For the most part, chemotherapy is selected in patients for whom radiotherapy was used previously, and in patients for whom surgery would be difficult or who show distant metastases. Unless the patient has distant metastases, intraarterial infusion seems ideal, because the local concentration of antitumor drugs can be maximized at the tumor bed with less toxicity.[6] As an intraarterial chemotherapeutic regimen for head and neck cancers, cisplatin (CDDP) or carboplatin are usually recommended,[6–9] but these drugs have often been used previously for neoadjuvant or concurrent chemotherapy, and drug resistance might have developed in such cases.[1,2,4] Thus, exploring the use of other anticancer agents together with platinum-containing drugs is important. Taxoid cytotoxic agents, such as docetaxel and paclitaxel, have recently been used for head and neck cancers and have shown good response rates when given intravenously.[10,11] Moreover, according to the latest reports, the combination of CDDP and either docetaxel or paclitaxel shows higher response rates than the use of either docetaxel or paclitaxel alone.[12,13] Yabuuchi et al[14] found combined CDDP and docetaxel intraarterial infusion therapy to be effective and safe. However, those reports on intraarterial chemotherapy have used a femoral artery approach. Intraarterial infusion via a superficial temporal artery (STA) can easily provide repeated chemotherapy for patients with head and neck cancer. To the best of our knowledge, no phase I studies of intraarterially infused chemotherapy via an STA have been described using taxoids for head and neck cancer. The present phase I study of intraarterial infusion via an STA was performed using CDDP and docetaxel in patients with recurrent head and neck cancer to determine the recommended dose in combination with radiotherapy.

PATIENTS AND METHODS

Eligibility. Patients with histologically confirmed head and neck cancer, excluding thyroid cancer, were enrolled in this trial. Written informed consent was obtained from each patient before enrollment. All patients were diagnosed as having recurrence with a measurable legion after the initial treatment. Previous treatments, including chemotherapy, radiotherapy, and surgery, were allowed if the treatment had finished at least 1 month before registration for the

Correspondence to: T. Nakamura

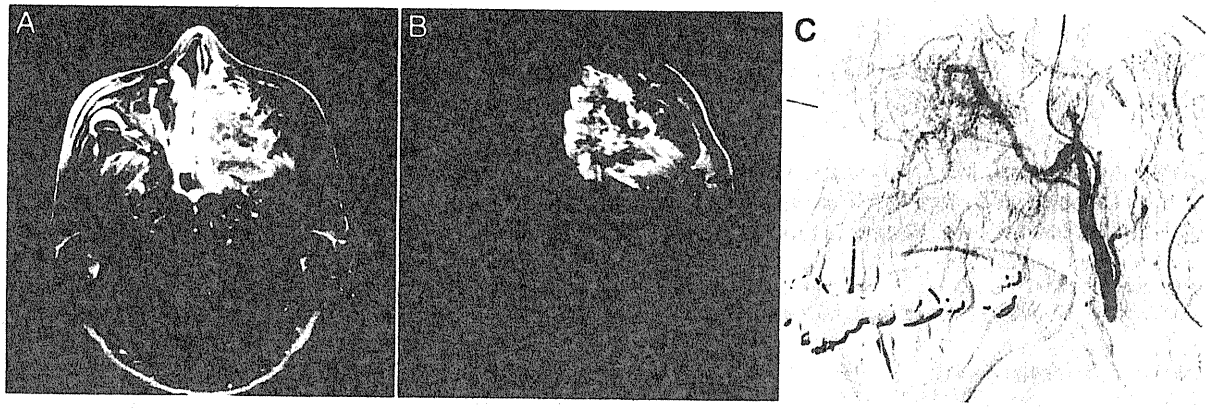

FIGURE 1. A patient with recurrence of left maxillary sinus carcinoma. **(A)** Contrast-enhanced MR image. **(B)** MR image after infusion of a small amount of contrast medium through the catheter for arterial injection. **(C)** Angiography after catheterization via the superficial temporal artery.

present study. Specific eligibility criteria were: age, ≥20 years and <75 years old; Eastern Cooperative Oncology Group performance status, 0 or 1; adequate hematological, hepatic, and renal functions (white blood cells, >3500/μL; neutrophils, >2000/μL; platelet count, >100,000/μL; hemoglobin, >9 g/dL; AST and ALT, <3 times the upper limit of normal; total bilirubin, <1.5 mg/dL; and creatinine clearance >60 mL/minute); and life expectancy ≥3 months.

Intraarterial Infusion Procedure via Superficial Temporal Artery. Before treatment, 3-dimensional CT angiography of the carotid artery was necessary to identify the main tumor-feeding arteries and determine the morphology and course of the tumor feeding artery from the external carotid artery. Catheterization from the STA was performed as previously reported,[15,16] with the anterior ear on the affected side incised under local anesthesia to expose the STA. During fluoroscopy, a catheter was placed into the external artery. When the lesion also involved the contralateral side beyond the median line, another catheter was inserted into the contralateral side for bilateral arterial injection.

We confirmed the extent of arterial injection by dyeing the tumor with a pigment, using angiography, or using an MRI with an extremely low dose of contrast medium slowly infused by way of the catheter for arterial injection (Figure 1).

Treatment Schedule and Dose Escalation. CDDP was administered as an intraarterial infusion at fixed doses of 40 mg/m^2 over 5 hours on day 2, once a week, with a total of 4 courses. During arterial infusion of CDDP, a CDDP-neutralizing agent, sodium thiosulfate, was also administered intravenously at 8 g/m^2 for 8 hours, starting 1 hour before starting arterial infusion of CDDP.

Docetaxel was administered as an intraarterial infusion over 4 hours on day 1, once a week, for a total of 4 courses. The starting dose was 8 mg/m^2 (Figure 2).

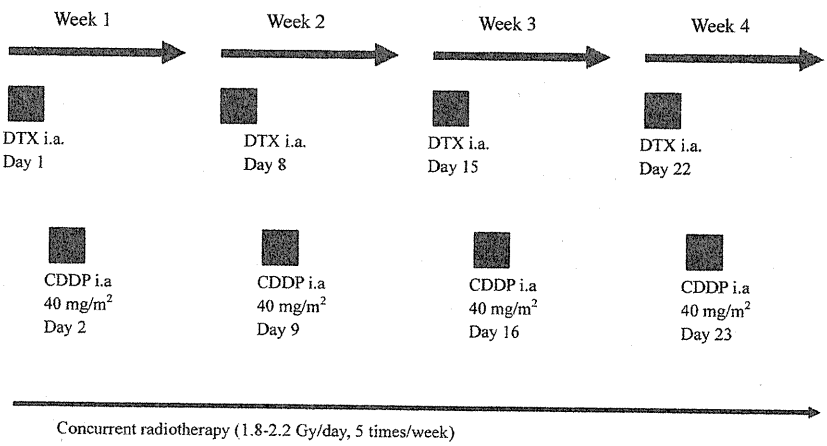

FIGURE 2. Treatment schedule for intraarterial infusion (i.a.) of docetaxel (DTX) and cisplatin (CDDP). External irradiation focused on the tumor was also performed, with a median dose of 43 gray (Gy). The starting dose of docetaxel was 8 mg/m^2/week.

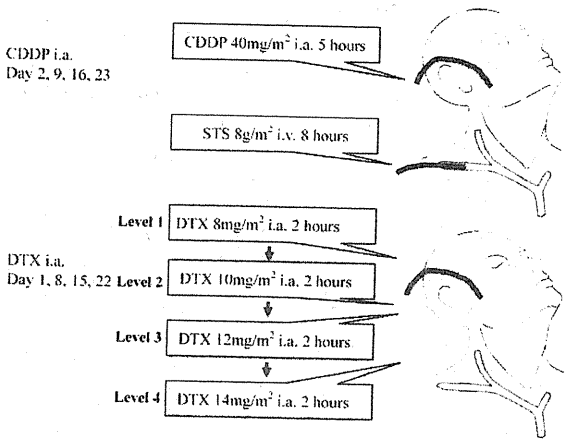

FIGURE 3. Study design was done using a modified fibonacci method. There is no dose-limiting toxicity (DTX) observed in the level 1, step-up level 2. If dose-limiting toxicity was observed in 1/3 of the candidates, we added 3 candidates and continued the study. If dose-limiting toxicity was observed in 2/6 of candidates, we stopped the study and defined the level as maximum tolerated dose (MTD). (Weekly cisplatin [CDDP] 40 mg/m^2 i.a. was fixed.) i.a., intraarterial infusion; STS, sodium thiosulfate; i.v., intravenously.

Concurrent use of antiemetics, antibiotics, sedatives, steroids, hematopoietic growth factors, and gastric protectors was permitted. An additional increase by 2 mg/m^2 up to the maximum tolerated dose (MTD) was permitted. At least 3 patients were treated at each dose level. Dose-limiting toxicity was defined as grade 3 according to the Common Terminology Criteria for Adverse Events, version 3.0, for hematological toxicities and grade 4 for nonhematological toxicities, especially oral mucotitis and radiation dermatitis. When a dose-limiting toxicity appeared, 3 patients were added in at the same dose level. Endpoints to close the study were dose-limiting toxicity with hematological or nonhematological toxicity if observed in 2 of 3 or in 3 of 6 patients at the same dose levels. The previous dose level before the MTD was considered as the recommended dose (Figure 3).

Radiotherapy was used concurrent with chemotherapy. All patients showed recurrence, so the irradiation field was focused on the local tumor or lymph node metastasis only. If the patients had not previously undergone radiotherapy for this cancer, they received 60 to 74 gray (Gy) in 30 to 37 fractions. Conversely, for patients who had previously undergone radiotherapy, the prescribed dose was 36 to 40 Gy in 18 to 20 fractions because Nakamura et al[17] reported it is high risk for fetal late complications to prescribe 110 Gy totally. We selected proton beam therapy for this study to reduce radiation exposure of normal tissue compared to photon therapy, and expected reduction of late complications, especially for reirradiation (Figure 4).

The ethics committee of our institute approved all protocols for this clinical trial.

Evaluation and Follow-up. Baseline evaluation included a complete medical history, physical examination, complete blood cell count, serum chemistry, and positron emission tomography-CT. Blood biochemistry and symptoms/signs of toxicity were monitored on a 2-weekly basis during treatment. Clinical response was evaluated 8 weeks after the completion of the radiotherapy. The response was judged according to Response Evaluation Criteria in Solid Tumors guidelines, complete response was defined as the disappearance of all clinically evident tumors and no new disease. Partial response was defined as a >30% reduction in products of perpendicular tumor measurements with no new disease. Stable disease was defined as less than a partial response and a <20% increase in all dimensions of measurable disease. Progressive disease was defined as a ≥20% increase in all dimensions of measurable disease or appearance of new sites of disease.[18] We used the Kaplan–Meier method for the overall survival and progression-free survival analyses.

RESULTS

Patient Characteristics. Twelve patients (8 men, 4 women) received this protocol from April 2009 to June 2010. Details of these patients are shown in Table 1. Median age at the time of recurrence was 60 years (range, 29–72 years).

The catheters were put in the external carotid artery. The tip of the catheter was put at the proximal to lingual artery in case of tongue cancer and oropharyngeal cancer, put at the proximal maxillary artery in case of maxillary sinus cancer or maxillary gingival cancer and external auditory canal cancer. There were no central nerve complications and infections.

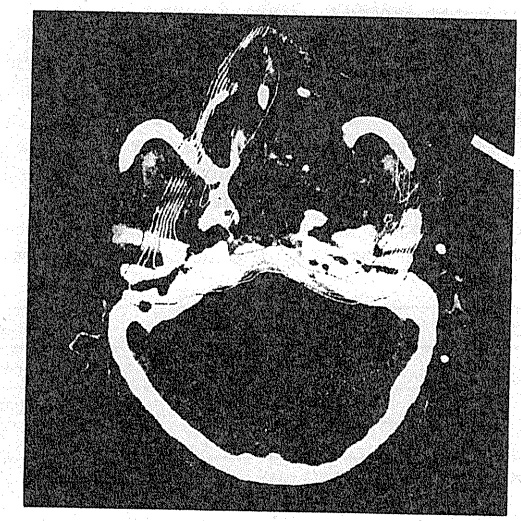

FIGURE 4. The dose distribution map of proton therapy. The outside line shows under 10% of prescription dose.

Table 1. Patient characteristics.

Characteristic	Value
Patients enrolled	12
Sex	
Male	8
Female	4
Age, y	19–72 (median, 60)
Performance status	
1	12
Previous treatment	
Chemoradiotherapy	4
Chemoradiotherapy and surgery	5
Surgery	3
Primary tumor location	
Tongue	4
Maxillary gingiva	3
Maxillary sinus	2
Oropharynx	2
External auditory canal	1
Histopathology	
Squamous cell carcinoma	9
Adenoid cystic carcinoma	1
Ameloblastic carcinoma	2
Recurrent TN factor	
rT0N2	1
rT2N0	1
rT2N1	1
rT3N2	1
rT4N0	7
rT4N1	1
Radiotherapy, Gy	36–74.8 (median, 43)

Abbreviation: Gy, gray.
Note: Values represent number of patients, except as otherwise stated.

All patients underwent proton beam therapy concurrent with arterial infusion chemotherapy under the described protocol. The median dose of irradiation was 43 Gy (range, 36 Gy–74.8 Gy). Nine patients had an irradiation career before this therapy, so their irradiation dose had to be reduced, 3 patients could be prescribed definitive radiotherapy.

Dose-Limiting Toxicity. Table 2 shows the hematological toxicities observed at each dose level. No patient experienced grade 3 or higher hematological toxicity at levels I to III (docetaxel, 8–12 mg/m^2/week). At level IV (docetaxel, 14 mg/m^2/week), 2 of 3 patients experienced dose-limiting toxicity. One patient experienced grade 3 leukopenia and grade 3 anemia, while the other had grade 3 leukopenia.

Table 3 shows the nonhematological toxicities observed at each dose level. The most significant toxicity was dermatitis within the radiation field. Of the 12 patients, 10 developed grade 3 dermatitis and had grade 3 mucotitis. None of the patients experienced grade 3 or higher toxicities of the liver or kidney, or anorexia or vomiting.

Response and Status. Seven patients achieved complete response and 5 patient achieved partial response after arterial infusion and proton beam therapy, respectively. The response rate to this treatment was 100%. All patients could receive a minimum of 4 cycles of CDDP and 4 cycles of docetaxel arterial infusion. The median follow-up period was 17.4 months (range, 5.5–24.6 months); 5 patients had died of disease progression, 3 patients died of multiple lung metastases, and 2 patients died of local recurrence progression. No carotid blowouts were seen. One-year overall survival was 75%, and 1-year progression-free survival was 50% (Figures 5, 6).

DISCUSSION

Intraarterial chemotherapy for head and neck cancers has the advantage of allowing delivery of a high concentration of chemotherapeutic agents to the tumor bed with fewer systemic toxic effects than systemic chemotherapy. Intraarterial infusion via the STA has become feasible for daily concurrent radiotherapy and chemotherapy. The superficial temporal approach is technically simple and probably the easiest method of inserting a catheter into the target artery.[15] In addition, due to the relatively low daily dose, this method can be used in elderly patients or patients with poor performance status. Transfemoral catheterization is also easy and enables catheter insertion into the target artery, but can sometimes cause serious problems such as a cranial nerve disorder.[19] In the present study, major complications such as neurological complications or massive bleeding were not encountered. Thus, this method is safe and suitable for intraarterial therapy to treat head and neck cancer.

For intraarterial chemotherapy via the femoral artery with high-dose CDDP infusion, CDDP alone is given at many institutions and provides high efficacy.[20–22] Fuwa et al[16,23–25] reported good results for selective intraarterial infusion therapy via the STA for head and neck cancer using carboplatin or CDDP. All those studies used a carcinostatic substance,

Table 2. Hematological toxicity.

	No. of patients by dose level (I–IV) and toxicity grade (1–4)															
	I (8 mg/m^2)				II (10 mg/m^2)				III (12 mg/m^2)				IV (14 mg/m^2)			
	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
Hemoglobin	3	0	0	0	1	0	0	0	2	0	0	0	0	2	1	0
Leukocytes	1	2	0	0	0	0	0	0	0	1	0	0	0	1	2	0
Neutrophils	0	1	0	0	0	0	0	0	1	0	0	0	1	2	0	0
Platelets	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Table 3. Nonhematological toxicity.

	No. of patients by dose level (I–IV) and toxicity grade (1–4)															
	I (8 mg/m^2)				II (10 mg/m^2)				III (12 mg/m^2)				IV (14 mg/m^2)			
	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
Dermatitis	0	0	3	0	0	1	2	0	0	0	3	0	0	1	2	0
Mucitis	0	0	3	0	0	1	2	0	0	0	3	0	0	1	2	0
Liver	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
Kidney	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Anorexia	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Vomiting	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

typically CDDP. The combination of docetaxel and CDDP is known to offer enhanced clinical activity in various types of tumors, including head and neck carcinoma.[26] CDDP and docetaxel have different mechanisms of action as either cytotoxic agents or radiosensitizers. Furthermore, in vitro data have demonstrated not only that cell lines with acquired resistance to CDDP are still sensitive to docetaxel, but also that docetaxel enhances the cytotoxicity of CDDP by modification of intracellular platinum metabolism.[27,28] Treatment with docetaxel followed by CDDP demonstrates synergistic effects on inhibition of cancer cell survival, with increased intracellular platinum accumulation compared to CDDP followed by docetaxel, and docetaxel improves the multidrug resistance induced by single treatment with CDDP.[28]

The dose of CDDP was set at 40 mg/m^2/week in this study based on reports of chemoradiotherapy for cervical carcinoma of the uterus treated using weekly CDDP.[29–32] Even though those studies used intravenous infusion of CDDP at 40 mg/m^2/week for 5 courses and the whole pelvis was irradiated, few hematological toxicities over grade 4 were encountered. In addition, we used a CDDP-neutralizing agent, sodium thiosulfate for intravenous administration during arterial injection of CDDP to reduce toxicities.

In head and neck cancer, Kodaira et al[33] reported the safety of weekly docetaxel at 12 mg/m^2 in combination with radiation in a phase I study. We referred to that report and started with 8 mg/m^2/week of docetaxel via arterial infusion, increasing by 2 mg/m^2 with each step up.

Radiation mucotitis and dermatitis grade 3 were often seen from level I in this study. Combination of radiotherapy and concurrent arterial chemotherapy might have increased mucotitis and dermatitis, but patients with mucotitis and dermatitis under grade 3 could recover in 4 to 8 weeks after the therapy. The incidence of osteoradionecrosis of the mandible and maxilla after radiotherapy for head and neck cancer has declined in recent decades. Since 1997, pooled studies have shown even lower incidences of 3.0%.[34] Eisbruch et al[35] assessed the results of a multiinstitutional study of intensity-modulated radiation therapy for early oropharyngeal cancer. Osteoradionecrosis was observed in 6% of 69 patients at 14 institutions. Ben–David et al[36] reported the use of a strict prophylactic dental policy, and intensity-modulated radiation therapy resulted in no cases of clinical osteoradionecrosis. At our institute, all patients underwent panoramic radiography, and the periodontal condition was evaluated before treatment. Dental prophylactic care was a major factor to prevent osteoradionecrosis. In addition, a smaller total dose of irradiation to the tumor is preferable. In case the anticancer agent spread from the proper lesion including tumor in arterial infusion chemotherapy, the irradiation dose might be able to be controlled to <60 Gy.[37] Intraarterial

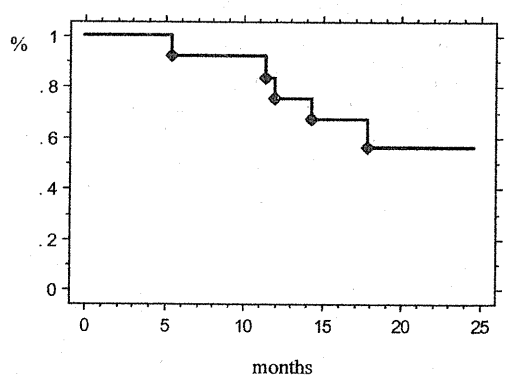

FIGURE 5. Overall survival curve. One year overall survival was 75%.

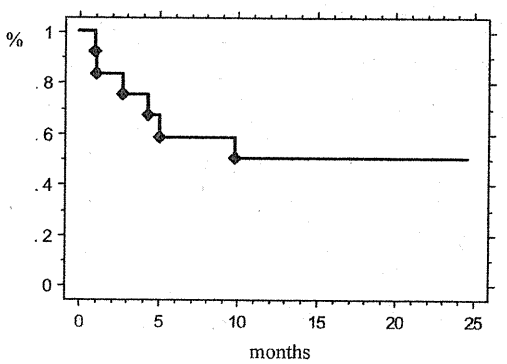

FIGURE 6. Progression-free survival curve. One year progression-free survival was 50%.

infusion via the STA has recently become feasible, but the proper total dose and infusion rate of drugs remains controversial.

The purpose of this study was to clarify the efficacy and toxicities of intraarterial infusion therapy using docetaxel and CDDP in patients with recurrent head and neck cancer. Our results demonstrate that combination therapy by intraarterial infusion of docetaxel and CDDP is effective and safe for patients with recurrent head and neck cancer. Using the results of this study, we are planning a phase II study of the clinical outcome of intraarterial infusion of docetaxel and CDDP combination with concurrent radiotherapy.

REFERENCES

1. Khuri FR, Shin DM, Glisson BS, Lippman SM, Hong WK. Treatment of patients with recurrent or metastatic squamous cell carcinoma of the head and neck: current status and future directions. Semin Oncol 2000;27(4 Suppl 8):25–33.
2. Lamont EB, Vokes EE. Chemotherapy in the management of squamous-cell carcinoma of the head and neck. Lancet Oncol 2001;2:261–269.
3. Spencer SA, Wheeler RH, Peters GE, et al. Concomitant chemotherapy and reirradiation as management for recurrent cancer of the head and neck. Am J Clin Oncol 1999;22:1–5.
4. Vokes EE, Weichselbaum RR, Lippman SM, Hong WK. Head and neck cancer. N Engl J Med 1993;328:184–194.
5. Watson JC, Ridge JA. Surgical management of local and regional recurrent head and neck squamous cell carcinoma. Curr Opin Oncol 1998;10:207–212.
6. Lee YY, Wallace S, Dimery I, Goepfert H. Intraarterial chemotherapy of head and neck tumors. AJNR Am J Neuroradiol 1986;7:343–348.
7. Imai S, Kajihara Y, Munemori O, et al. Superselective cisplatin (CDDP)-carboplatin (CBDCA) combined infusion for head and neck cancers. Eur J Radiol 1995;21:94–99.
8. Korogi Y, Hirai T, Sakamoto Y, et al. Intravascular ultrasound imaging of peripheral arteries as an adjunct to atherectomy: preliminary experience. Br J Radiol 1995;68:110–115.
9. Robbins KT, Storniolo AM, Kerber C, Seagren S, Berson A, Howell SB. Rapid superselective high-dose cisplatin infusion for advanced head and neck malignancies. Head Neck 1992;14:364–371.
10. Dreyfuss AI, Clark JR, Norris CM, et al. Docetaxel: an active drug for squamous cell carcinoma of the head and neck. J Clin Oncol 1996;14:1672–1678.
11. Forastiere AA, Shank D, Neuberg D, Taylor SGt, DeConti RC, Adams G. Final report of a phase II evaluation of paclitaxel in patients with advanced squamous cell carcinoma of the head and neck: an Eastern Cooperative Oncology Group trial (PA390). Cancer 1998;82:2270–2274.
12. Schöffski P, Catimel G, Planting AS, et al. Docetaxel and cisplatin: an active regimen in patients with locally advanced, recurrent or metastatic squamous cell carcinoma of the head and neck. Results of a phase II study of the EORTC Early Clinical Studies Group. Ann Oncol 1999;10:119–122.
13. Thödtmann F, Theiss F, Kemmerich M, et al. Clinical phase II evaluation of paclitaxel in combination with cisplatin in metastatic or recurrent squamous cell carcinoma of the head and neck. Ann Oncol 1998;9:335–337.
14. Yabuuchi H, Kuroiwa T, Tajima T, Tomita K, Ochiai N, Kawamoto K. Efficacy of intra-arterial infusion therapy using a combination of cisplatin and docetaxel for recurrent head and neck cancers compared with cisplatin alone. Clin Oncol (R Coll Radiol) 2003;15:467–472.
15. Fuwa N, Ito Y, Matsumoto A, et al. A combination therapy of continuous superselective intraarterial carboplatin infusion and radiation therapy for locally advanced head and neck carcinoma. Phase I study. Cancer 2000;89:2099–2105.
16. Fuwa N, Kodaira T, Furutani K, Tachibana H, Nakamura T. A new method of selective intra-arterial infusion therapy via the superficial temporal artery for head and neck cancer. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2008;105:783–789.
17. Nakamura T, Kodaira T, Tachibana H, et al. Chemoradiotherapy for locally recurrent nasopharyngeal carcinoma: treatment outcome and prognostic factors. Jpn J Clin Oncol 2008;38:803–809.
18. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228–247.
19. Gemmete JJ. Complications associated with selective high-dose intra-arterial cisplatin and concomitant radiation therapy for advanced head and neck cancer. J Vasc Interv Radiol 2003;14:743–748.
20. Balm AJ, Rasch CR, Schornagel JH, et al. High-dose superselective intra-arterial cisplatin and concomitant radiation (RADPLAT) for advanced head and neck cancer. Head Neck 2004;26:485–493.
21. Homma A, Furuta Y, Suzuki F, et al. Rapid superselective high-dose cisplatin infusion with concomitant radiotherapy for advanced head and neck cancer. Head Neck 2005;27:65–71.
22. Robbins KT, Kumar P, Harris J, et al. Supradose intra-arterial cisplatin and concurrent radiation therapy for the treatment of stage IV head and neck squamous cell carcinoma is feasible and efficacious in a multi-institutional setting: results of Radiation Therapy Oncology Group Trial 9615. J Clin Oncol 2005;23:1447–1454.
23. Fuwa N, Kodaira T, Furutani K, Tachibana H, Nakamura T. Treatment results of continuous intra-arterial CBDCA infusion chemotherapy in combination with radiation therapy for locally advanced tongue cancer. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2008;105:714–719.
24. Fuwa N, Kodaira T, Furutani K, et al. Intra-arterial chemoradiotherapy for locally advanced oral cavity cancer: analysis of therapeutic results in 134 cases. Br J Cancer 2008;98:1039–1045.
25. Fuwa N, Kodaira T, Furutani K, et al. Arterial chemoradiotherapy for locally advanced tongue cancer: analysis of retrospective study of therapeutic results in 88 patients. Int J Radiat Oncol Biol Phys 2008;72:1090–1100.
26. Inohara H, Inoue T, Akahani S, et al. Concurrent chemoradiotherapy with cisplatin and docetaxel for advanced head and neck cancer. A phase I study. Anticancer Res 2004;24:4135–4140.
27. Hill BT, Whelan RD, Shellard SA, McClean S, Hosking LK. Differential cytotoxic effects of docetaxel in a range of mammalian tumor cell lines and certain drug resistant sublines in vitro. Invest New Drugs 1994;12:169–182.
28. Maeda S, Sugiura T, Saikawa Y, et al. Docetaxel enhances the cytotoxicity of cisplatin to gastric cancer cells by modification of intracellular platinum metabolism. Cancer Sci 2004;95:679–684.
29. Keys HM, Bundy BN, Stehman FB, et al. Cisplatin, radiation, and adjuvant hysterectomy compared with radiation and adjuvant hysterectomy for bulky stage IB cervical carcinoma. N Engl J Med 1999;340:1154–1161.
30. Pearcey R, Brundage M, Drouin P, et al. Phase III trial comparing radical radiotherapy with and without cisplatin chemotherapy in patients with advanced squamous cell cancer of the cervix. J Clin Oncol 2002;20:966–972.
31. Rose PG, Bundy BN, Watkins EB, et al. Concurrent cisplatin-based radiotherapy and chemotherapy for locally advanced cervical cancer. N Engl J Med 1999;340:1144–1153.
32. Whitney CW, Sause W, Bundy BN, et al. Randomized comparison of fluorouracil plus cisplatin versus hydroxyurea as an adjunct to radiation therapy in stage IIB-IVA carcinoma of the cervix with negative para-aortic lymph nodes: a Gynecologic Oncology Group and Southwest Oncology Group study. J Clin Oncol 1999;17:1339–1348.
33. Kodaira T, Fuwa N, Furutani K, Tachibana H, Yamazaki T. Phase I trial of weekly docetaxel and concurrent radiotherapy for head and neck cancer in elderly patients or patients with complications. Jpn J Clin Oncol 2005;35:173–176.
34. Wahl MJ. Osteoradionecrosis prevention myths. Int J Radiat Oncol Biol Phys 2006;64:661–669.
35. Eisbruch A, Harris J, Garden AS, et al. Multi-institutional trial of accelerated hypofractionated intensity-modulated radiation therapy for early-stage oropharyngeal cancer (RTOG 00–22). Int J Radiat Oncol Biol Phys 2010;76:1333–1338.
36. Ben–David MA, Diamante M, Radawski JD, et al. Lack of osteoradionecrosis of the mandible after intensity-modulated radiotherapy for head and neck cancer: likely contributions of both dental care and improved dose distributions. Int J Radiat Oncol Biol Phys 2007;68:396–402.
37. Mitsudo K, Shigetomi T, Fujimoto Y, et al. Organ preservation with daily concurrent chemoradiotherapy using superselective intra-arterial infusion via a superficial temporal artery for T3 and T4 head and neck cancer. Int J Radiat Oncol Biol Phys 2011;79:1428–1435.

Oral Oncology 47 (2011) 387–390

Contents lists available at ScienceDirect

Oral Oncology

journal homepage: www.elsevier.com/locate/oraloncology

A new method using MRI to delineate areas of head and neck cancer targeted by intra-arterial infusion via a superficial temporal artery

Tatsuya Nakamura *, Nobukazu Fuwa, Kanako Takayama, Takuya Tomoda, Akinori Takada, Chiyoko Makita, Miho Shiomi, Jun-ichi Yokouchi, Kazuo Watanabe

Department of Radiation Oncology, Southern Tohoku Proton Therapy Center, 7-172 Yatsuyamada, Koriyama, Fukushima 963-8052, Japan

ARTICLE INFO

Article history:
Received 18 December 2010
Received in revised form 8 March 2011
Accepted 10 March 2011
Available online 27 March 2011

Keywords:
Chemotherapy
Perfusion
Malignant tumor
Recurrence
MRI

SUMMARY

To determine whether anticancer drugs delivered via arterial infusion can permeate entire tumors using a new MRI flow check method. We infused 20 ml of contrast medium (2 ml of Gd-GDPA plus 18 ml of normal saline) over a period of 10 min using a continuous injection pump, then immediately performed MRI using a 1.5 T unit. Images were obtained in 5-mm-thick continuous sections in two or three planes (axial, coronal, and sagittal) depending on the extent of the tumor, and enhanced fast gradient echo 3 D (EFGRE3D) images with a special inversion at lipids were photographed using a neurovascular array coil. The new MRI flow check method delineated an area of tongue cancer perfused with drugs more accurately than conventional methods.The MRI flow check method provides accurate information about areas of arterial infusion.

Introduction

Arterial infusion therapy for head and neck cancer has been applied for many years, particularly since 1990s, when a more effective technique for the selective insertion of a catheter into an artery nourishing a tumor was established.[1–5] Intra-arterial administration might result in increased levels of anticancer agents being delivered to tumors compared with intravenous administration and thus they could exert more potent antitumor effects.

To ascertain whether arterial infusion of anticancer drug actually permeates the entire tumor is important for successful arterial infusion therapy. Conventional methods to achieve this include using a pigment or CT angiography.[6,7] However, the internal area of the tumor cannot be confirmed using pigment and artifacts that arise due to crowned teeth render CT evaluation difficult in many patients with head and neck cancer. We developed an MRI method to delineate the area reached by arterial infusion more accurately and thus overcome these problems. This paper describes the procedure involved in this new method, and discusses its value to the treatment of patients with cancer of the head and neck.

Methods

Arterial injection therapy

We inserted a catheter into the target artery feeding a tumor through the superficial temporal artery during fluoroscopy as described.[1,2,5,8,9] The targets comprised the lingual artery for carcinoma of the tongue and base of the tongue, the facial artery for carcinoma of the buccal mucosa and lower gum, and the superior thyroid artery for carcinoma of the larynx and hypopharynx. When several arteries nourished one tumor, or when arteriosclerosis caused difficulties with selective insertion of a catheter into a target artery, we catheterized the external carotid artery.

We check the position of the catheter whether the catheter was put on the proper position in the artery before MRI.

MRI flow check method

We performed several trials to determine the optimal volume and method of delivering of contrast medium. We found that administering 20 ml of contrast medium (a mixture of 2 ml of Gd-GDPA and 18 ml of normal saline) over a period of 10 min using a continuous injection pump was optimal when immediately followed by MRI using a 1.5 T unit (Signa ver.9.0; General Electric Medical Systems, Milwaukee, WI, USA). Images obtained in continuous 5-mm sections in two or three planes (axial, coronal, and sagittal) depending on the extent of the tumor using enhanced 3 D fast

* Corresponding author. Tel.: +81 24 934 3888; fax: +81 24 934 5393.
E-mail address: tatsuya.nakamura@nifty.com (T. Nakamura).

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doi:10.1016/j.oraloncology.2011.03.010

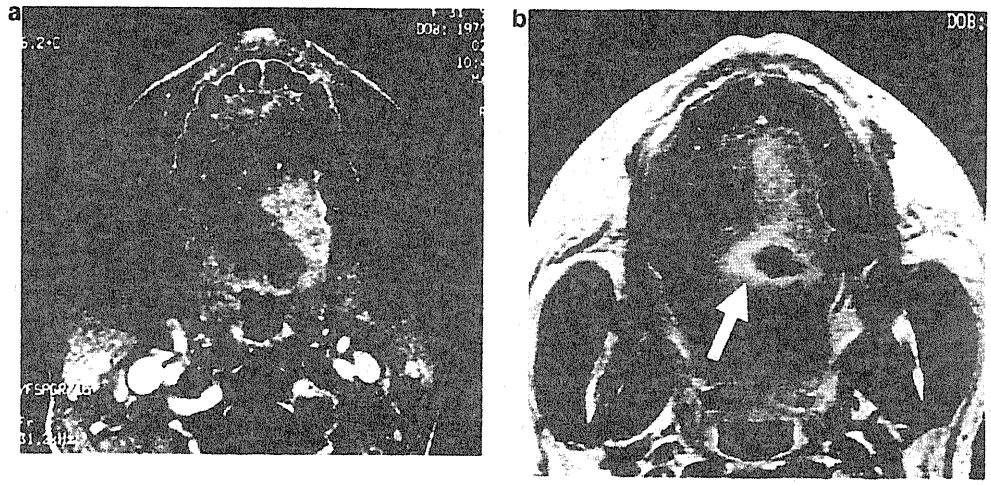

Figure 1 Axial views of MRI enhanced T1 images before (a) and after (b) intra-arterial infusion. Tumor extends from left to middle of the tongue (a). Recurrent tumor extends from middle to both sides of the tongue (b).

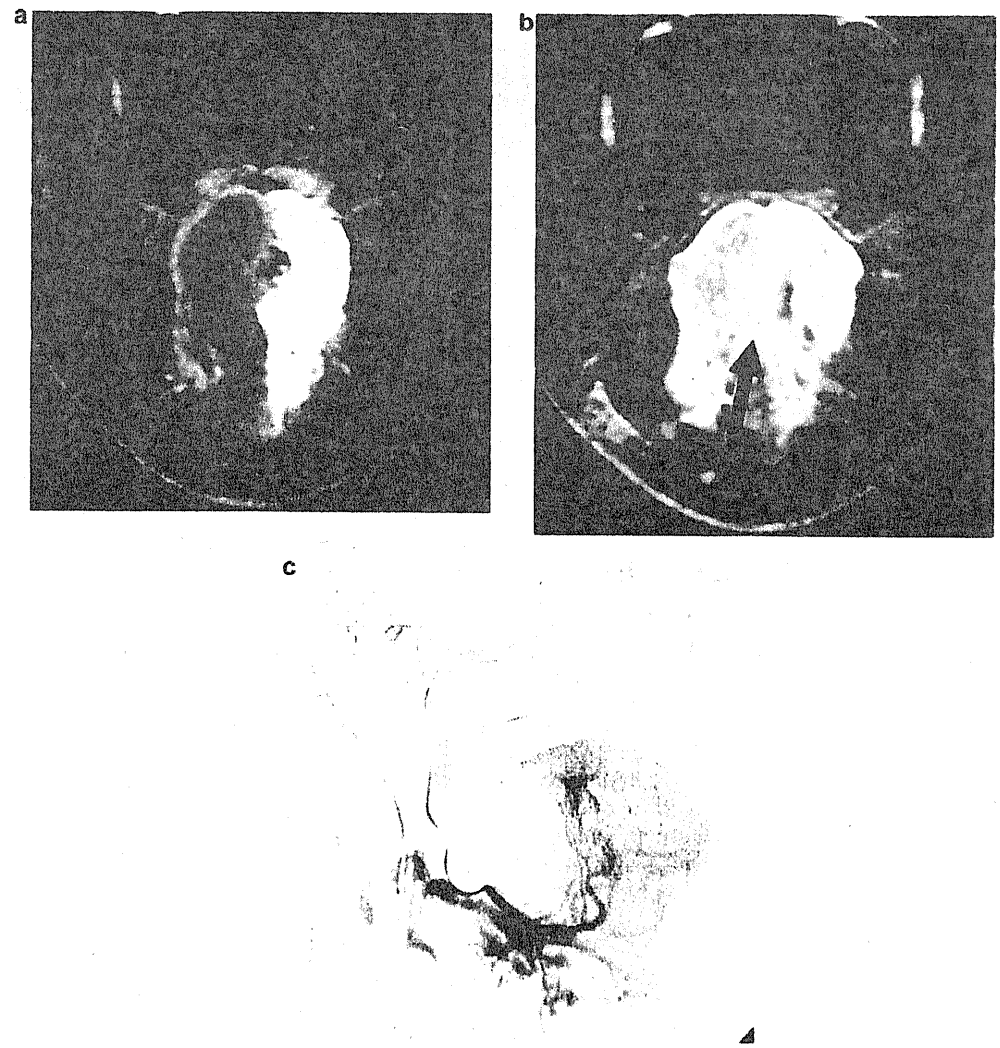

Figure 2 Coronal views of MRI flow check image from left lingual and right facial arteries after recurrence and digital subtraction angiography (DSA) of right facial artery. The middle of the tongue is not visualized from the left lingual artery (a) but is visible from the right facial artery (b). Anterior two-thirds of the right tongue are visualized from the right facial artery (c).

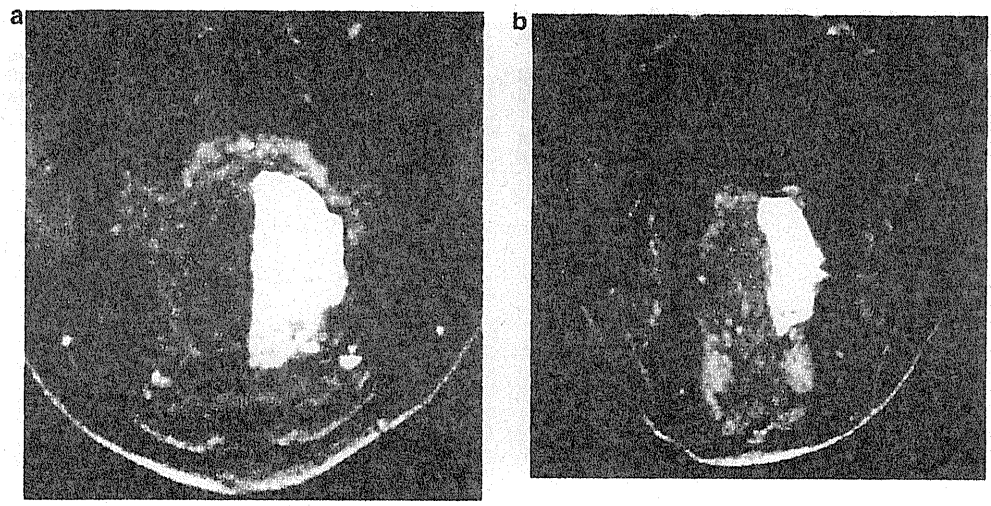

Figure 3 Coronal views of MRI flow check image at level of the tongue root and center before treatment. Region as far as middle of the tongue is visualized at level of tongue root (a). Center of the tongue is not visible in image at level of tongue center suggesting recurrence (b). This area was later confirmed as a site of cancer recurrence.

gradient echo (EFGRE3D) with special inversion at lipids were photographed (36 s) using a neurovascular array coil.

The photographic conditions were as follows: TE/TR, 1.4/5.6 ms; prep time, 40 ms; flip angle, 15°; and width, 31.25 Hz; FOV, 22 cm; slice thickness, 5.0 mm; Locs per slab, 16; 256 × 256 matrix and 1 NEX.

Case presentation

A 35-year-old woman was treated by radiotherapy and left lingual arterial infusion with the anticancer drug using CBDCA for cancer that had invaded the left side of the tongue up to the midline (T3N0M0; Fig. 1a). Since the MRI flow check method verified that left lingual arterial infusion alone had covered the entire tumor, we did not infuse the right lingual artery. Although this strategy resolved the cancer, the patient developed recurrence in the area from the midline slightly to the left (Fig. 1b). Since she declined surgery, we reinserted an arterial catheter via the left occipital artery into the left lingual artery. Coronal MR images obtained as described showed that the perfusion area of the left lingual artery was limited to the left-sided portion of the tumor (Fig. 2a). Coronal MR images (Fig. 2b) obtained as described after inserting a catheter via the right superficial temporal artery into the right facial artery (Fig. 2c), revealed that the right portion of the tumor was perfused by the right facial artery (the right lingual artery perfused only the right portion of the tongue base).

Discussion

The following conditions must be satisfied to establish the clinical usefulness of arterial injection therapy in the treatment of head and neck as well as other cancers: (1) a stable, highly reproducible and safe procedure; (2) arterially injected drugs permeating the entire tumor can be confirmed; (3) anticancer agents are appropriate for arterial injection therapy, and an optimal dose is established; and (4) more advantageous than other approaches such as surgery, radiotherapy alone and chemoradiation involving systemic chemotherapy and radiotherapy.

Although the extent of arterial injection has been examined using a pigment or CT angiography, a pigment cannot confirm the internal area of the tumor and CT imaging is hampered by artifacts related to crowned teeth in many patients with head and neck cancer.

The MRI flow check method presented here allows the acquisition of images from various directions, thereby delineating the perfusion area by arterial infusion more accurately than conventional methods.

Re-interpretation of the image acquired by MRI flow check at the first arterial infusion showed that delivery via the left lingual artery perfused the tongue up to the midline at the level of the tongue base (Fig. 3a), but not the recurrent tumor (Fig. 3b), confirming that the tumor had recurred in the non-perfused area. Six years have now passed since the recurrent tumor was controlled by the second arterial infusion together with radiotherapy using a small radiation source. The present case reaffirmed the value of the MRI flow check method and simultaneously highlighted the need for meticulous attention to the interpretation of images acquired by MRI flow check.

To ascertain whether the area reached by infusion of an arterial anticancer drug covers the entire tumor is critically important. The MRI flow check method provides accurate information about whether or not a tumor is supplied by arteries other than that into which a catheter is selectively inserted. Thus, this procedure is essential for successfully treating head and neck cancer by arterial infusion therapy.

Conflict of interest statement

None declared.

References

1. Furutani K, Fuwa N, Kodaira T, Matsumoto A, Kamata M, Tachibana H, et al. Continuous selective intraarterial chemotherapy in combination with irradiation for locally advanced cancer of the tongue and tongue base. *Oral Oncol* 2002;**38**(2):145–52.
2. Fuwa N, Kodaira T, Furutani K, Tachibana H, Nakamura T, Nakahara R, et al. Intra-arterial chemoradiotherapy for locally advanced oral cavity cancer: analysis of therapeutic results in 134 cases. *Br J Cancer* 2008;**98**(6):1039–45.
3. Robbins KT, Kumar P, Wong FS, Hartsell WF, Flick P, Palmer R, et al. Targeted chemoradiation for advanced head and neck cancer: analysis of 213 patients. *Head Neck* 2000;**22**(7):687–93.
4. Robbins KT, Storniolo AM, Kerber C, Vicario D, Seagren S, Shea M, et al. Phase I study of highly selective supradose cisplatin infusions for advanced head and neck cancer. *J Clin Oncol* 1994;**12**(10):2113–20.
5. Tohnai I, Fuwa N, Hayashi Y, Kaneko R, Tomaru Y, Hibino Y, et al. New superselective intra-arterial infusion via superficial temporal artery for cancer of the tongue and tumour tissue platinum concentration after carboplatin (CBDCA) infusion. *Oral Oncol* 1998;**34**(5):387–90.

6. Goodman DN, Hoh BL, Rabinov JD, Pryor JC. CT angiography before embolization for hemorrhage in head and neck cancer. *AJNR Am J Neuroradiol* 2003;**24**(1):140–2.
7. Yokoyama J. Usefulness of CT-angiography for superselective intra-arterial chemotherapy for advanced head and neck cancers. *Gan To Kagaku Ryoho* 2002;**29**(12):2302–6.
8. Fuwa N, Kodaira T, Furutani K, Tachibana H, Nakamura T. Treatment results of continuous intra-arterial CBDCA infusion chemotherapy in combination with radiation therapy for locally advanced tongue cancer. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2008;**105**(6):714–9.
9. Fuwa N, Kodaira T, Furutani K, Tachibana H, Nakamura T. A new method of selective intra-arterial infusion therapy via the superficial temporal artery for head and neck cancer. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2008;**105**(6):783–9.