食道

浅井佳央里[*1]／塩山善之[*2]

九州大学大学院医学研究院 臨床放射線科学分野[*1]／同 重粒子線がん治療学講座[*2]

Points

①Golden standardとなったFP療法併用の根治的化学放射線療法を上回る治療効果を期待して、照射技術の向上、新規抗癌剤・分子標的薬の開発が進められている。
②根治的化学放射線療法後の再発時のサルベージ手術の安全性を念頭において、欧米並みの総線量50.4Gyへの移行も検討されている。
③副作用低減のため、予防的リンパ節領域を省略する照射野（IFRT）も選択肢の1つとなっている。
④頸部・胸部上部食道癌では、IMRTによる線量分布改善の恩恵が大きい。
⑤正常組織への大幅な線量低減が可能な粒子線治療にも期待がもてる。

はじめに

食道癌診療における放射線治療の役割は大きく、食道癌に対する放射線治療は、根治治療から緩和目的の治療まですべての病期において適応となる。放射線治療の最も大きな利点は、食道を温存して根治をめざすことができる点であり、化学放射線療法が確立して以降、T4症例に対しては標準治療となった。Ⅰ期（T1b）、Ⅱ期、T4を除くⅢ期症例に対しては手術が標準治療と考えられているが、手術を希望しない症例や医学的手術困難例に対する有効な治療選択肢に挙げられている。また、手術後の局所再発やリンパ節再発例に対する救済治療としても有効な治療法として汎用されている。さらに、内科的合併症や高齢のために手術はもとより化学放射線療法も困難な場合においては、根治性はやや下がるものの、放射線治療単独療法が選択される。

近年、3次元原体照射法や強度変調放射線治療など放射線治療技術の進歩は著しく、また一方で、陽子線や重粒子線（炭素線）といった従来のX線とは異なる性質をもつ放射線を用いた治療（粒子線治療）の有用性も注目されている。本稿では局所進行症例に対する術前治療および根治的治療を中心に食道癌治療における放射線治療の進歩について概説する。

化学放射線療法の進歩

食道癌においては、放射線治療単独と比較して化学放射線療法にて有意に生存率が向上することが証明されており（RTOG8501）、非外科的治療の場合は化学放射線療法が標準となっている[1]。現在の併用化学療法の標準レジメンはシスプラチン（CDDP）と5-FUの2剤併用（FP療法）である。投与法については放射線照射日に低容量のCDDPと5-FUを連日投与する、いわゆるlow dose FP療法が本邦では広く行われてきた。しかし、JCOG0303にて標準投与法と比較された結果、low dose FP療法の優越性は証明できず、むしろ生存率がわずかに下回っていたことから、標準投与法が現時点での標準治療と考えられている。

腎機能不良な症例では、CDDPに代えて本邦で開発された白金製剤であるCDGPが選択肢となる。ただし、放射線治療単独と比較して化学放射線療法では血液毒性や粘膜炎といった有害事象が増強するので、年齢や合併症の程度によっては放射線治療単独が選択される場合もある。

根治的化学放射線療法では食道温存が得られ、治療後の摂食嚥下機能も手術と比較すると良好であり、QOLを保つ意味での患者への恩恵は大きいと考えられる。特に、Ⅰ期(T1N0M0)食道癌に対する治療成績は良好で、外科的治療との比較試験が進行中である(JCOG0502)。しかし、局所進行食道癌に対する根治的化学放射線療法の治療成績は3年生存率で40%程度であり、いまだ満足いくものではない。治療強度を高めるため、T4および遠隔リンパ節転移陽性(M1a)例に対しては現在、ドセタキセル、シスプラチン、5-FUの3剤(DCF療法)を併用した化学放射線療法の安全性と有効性を確認するための臨床試験が行われている。新規抗癌剤としてはそのほかにも、切除可能食道癌に対し、CDDP＋S-1併用化学放射線療法の第Ⅰ/Ⅱ相試験も進行中である(JCOG0604)。分子標的薬としては、cetuximabやtrastuzumabが注目されている。

腺癌の20～30%がHer2陽性で、化学療法にtrastuzumabを加えることで奏功率、生存率ともに改善することが報告されており[2]、海外では術前化学放射線療法にtrastuzumabを併用する第Ⅲ相試験が進行中である。

切除可能局所進行食道癌についてはJCOG9907以降、術前化学療法後の根治術が標準治療とされ、本邦にて広く施行されている[3]。しかし、本邦で圧倒的に頻度の高い扁平上皮癌においては、手術単独に対して術前化学放射線療法は優位性を認めたものの、術前化学療法では証明できなかったとのメタアナリシスもあり[4]、今後計画されている術前化学療法と術前化学放射線療法の比較試験の結果次第では、術前化学放射線療法が標準治療となる可能性もある。術前化学放射線療法により少なからずpCR例が得られることが知られており、フランスおよびドイツで施行された臨床試験でも術前化学放射線療法の奏功例では、根治的化学放射線療法と手術で治療成績に差がなかったと報告されている[5,6]。これらの事実は化学放射線療法により食道を温存した根治治療が可能な患者群が潜在的に存在することを示しており、今後、このような症例の抽出を適切に行い、治療の個別化を図ることが重要と考えられる。

3D-CRT

現在、多くの施設で行われている方法は、予防的リンパ節領域も含めて前後対向2門照射で40～46Gy程度照射の後、局所および転移リンパ節に照射野を縮小して斜入対向2門照射で脊髄を遮蔽して総線量60Gy程度まで照射するというものである。このような従来型の放射線治療の問題点として、照射野が広くなる傾向があり、重篤な晩期有害事象(特に心・肺)が起こり得ること、正常組織の耐用線量の問題から局所への線量増加が困難なこと、治療後の遺残・再発癌に対する救済治療が確立されていないことなどが挙げられる。

有害事象の軽減を図るため、照射野の工夫として、3D-CRTを用いた多門照射による心毒性の軽減や、原発巣および転移リンパ節のみを照射野に含み予防的リンパ節領域への照射を省略する、いわゆるinvolved field radiotherapy(IFRT)が挙げられる。根治的放射線治療後の再発形式が、局所および遠隔転移が主体であり、領域リンパ節単独再発は比較的まれであることから、IFRTを妥当とする報告がある。一方で、T1a-MM以深ではリンパ節転移の可能性があることから、所属リンパ節領域を予防的に照射野に含めるべきという意見もある。どのリンパ節領域までを含むべきかに関してのコンセンサスはまだなく、各施設の裁量によっており、照射技術の発達した現在においての至適照射野が検討されている。

また局所進行癌においては、根治照射後の遺残がいまだ認められ、再発例の約半数は局所再発であることから、局所線量増加は考慮される選択肢の1つと思われる。しかしINT0123試験の結果、50.4Gyから64.8Gyへの線量増加の有効性が証明できず、むしろ高線量において全生存率が低い傾

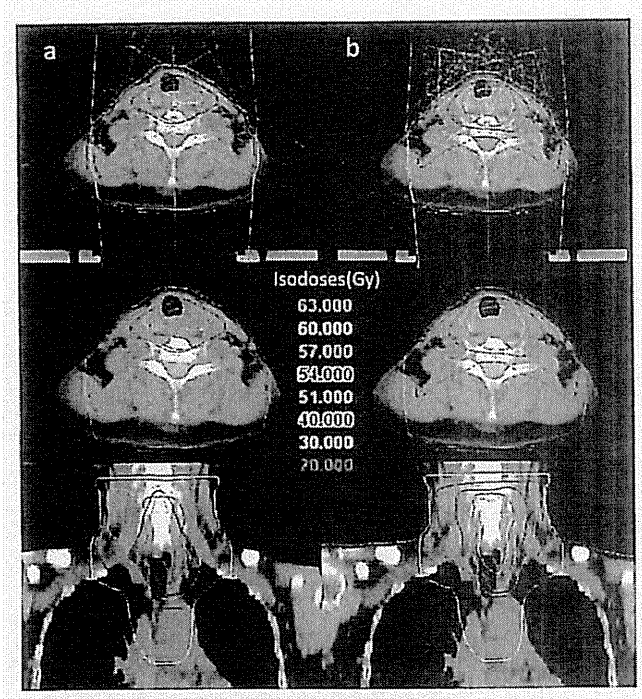

図1　頸部食道癌に対する線量分布の比較
頸部食道癌に対して、予防的リンパ節領域を含めて前後対向2門照射で40Gy/20Fr照射後、ブースト照射(20Gy/10Fr)を3D-CRT 4門照射で行った場合とIMRTで行った場合の線量分布を比較した。IMRTではPTVへの線量集中性が改善している(参考文献8を参考にして作成)。

IMAGE PREVIEW 参照

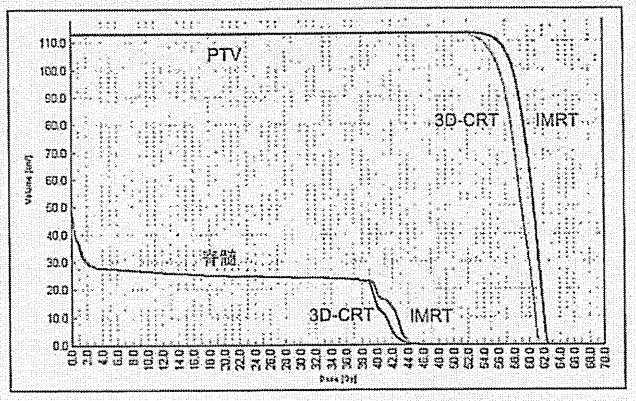

図2　DVHの比較
図1のそれぞれの照射法についてDVHの比較を行った。IMRTでは脊髄線量は耐容線量内に納めながら、PTVの線量を確保することが可能となっている。

IMAGE PREVIEW 参照

向にあったことから、欧米では根治線量は50.4Gyが標準線量となっている[7]。放射線治療後の遺残・再発時のサルベージ手術を念頭においた場合は、放射線治療後の線維化や癒着による非治癒切除率や術後合併症の増加が懸念されるため、本邦においても欧米並みの50.4Gyへの線量低下も検討されている。しかし、照射技術の発達した現在では、3D-CRTやIFRTなどを用いた照射法で正常組織への線量低減が得られる可能性もあり、局所線量増加の意義が本当にないのか、再度検証する必要があると思われる。

IMRT

食道癌の放射線治療においては、食道周囲に肺・脊髄・気管/気管支・大血管といったリスク臓器が近接しており、特に重篤な晩期有害事象が問題となる。正常組織への線量低減と病変部への線量増加を図る新たな照射技術である強度変調放射線治療(Intensity-modulated radiation therapy)は、前立腺や頭頸部領域では臨床応用されて久しいが、食道癌においても臨床報告がみられるようになっている[8,9]。

M.D.アンダーソンがんセンターからの報告では、2D-CRTと比較してIMRTにより心臓・肺の平均線量をそれぞれ30%、23%低減し、24.8%のGTVへの線量増加が図れたとしている[9]。特に頸部食道癌や胸部上部食道癌では、頸部から縦隔にかけて非常に複雑な領域を合わせて照射する必要があり、3D-CRTでも計画標的体積(PTV)へ十分な線量投与しつつ脊髄への線量を耐容量以下に抑えることが困難な場合が少ないことから、IMRTが非常に有用な領域と考えられている(図1、2)。

頸部・胸部上部食道癌に対する治療の場合には、シェルにより一定の固定精度が得られること、呼吸や心臓による動きも少ないといったこともIMRTを行う上で有利な点である。

IMRTの問題点の1つとして低線量被爆の増加が挙げられ、特に胸部中部食道癌で広範なリンパ節転移を伴う場合などでは、肺への照射容積拡大が問題となる。下部および腹部食道癌の治療においては肝臓などの腹部臓器への線量低減といった有用性も報告されてはいるが、セットアップエラーや呼吸性の動きが大きいことなどから、その適応には十分注意が必要である。今後は、IMRTによる局所線量の増加の安全性と有効性について前向きな臨床試験によるエビデンスの蓄積とともに、呼吸移動対策や画像誘導放射線治療技術を用いた安全な照射法の確立が望まれる。

粒子線治療

線量集中性のさらなる向上のため、粒子線治療にも期待がもたれている。Welshらは、IMRTと比較して強度変調粒子線治療(Intensity Modulated Particle Therapy：IMPT)によってより心・肺・肝といったリスク臓器への線量低減が図れたとし、心合併症のある症例に対しては後直交2門で心臓の線量低減、CTVの広い症例では前後対向2門で肺線量の低減を図るなど、症例によってbeam arrangementを使い分けることが可能であると報告している[10]。

治療成績では、Mizumotoらが陽子線単独にて5年生存率21.1%と照射単独としては比較的良好な成績を報告している。有害事象としては一般的な化学放射線療法と比較すると低減されるとしているが、80GyE以上の照射では食道潰瘍のリスクが高く、食道潰瘍からの出血による治療関連死が1例あったとも報告されており[11]、至適線量の決定と化学療法の併用によるさらなる治療成績の改善が望まれる。

炭素線イオン治療については、放射線医学総合研究所・重粒子医科学センター病院で胸部食道扁平上皮癌に対する術前炭素イオン線治療の第Ⅰ/Ⅱ相試験が行われており、近々その結果が報告される見込みである。また、Ⅰ期胸部食道扁平上皮癌に対する根治的な炭素イオン線治療の第Ⅰ/Ⅱ相試験も進行中であり、その結果もまたれる。

画像診断の寄与

食道癌診療における画像診断の役割は、正確な病期診断と治療効果判定と考えられる。従来の形態診断による画像診断法に加えて、昨今では細胞の糖代謝を捉えたFDG-PETが日常診療で用いられる機会が増えてきている。しかし、食道癌の術前病期診断についてのメタアナリシスでは、FDG-PET/CTは感度51%、特異度84%と報告されており、役割は限定的といわざるを得ない[12]。

他のモダリティでは同定し得ない遠隔転移の診断に最も威力を発揮すると期待されているが、通常の画像診断を行った術前症例199例のうち、FDG-PETを追加することで予期しない遠隔転移を検出出来た症例はわずか8例(4%)であり、不必要な手術を予防できた症例はわずか3%であったとの報告がある。また偽陽性率が7.5%と高く、これらの症例では追加精査が必要であったとしている[13]。病期診断においてはFDG-PETにより付加的情報が得られる可能性はあるが、結果の解釈については他のmodalityと合わせて慎重に判断する必要がある。

術前治療の効果判定におけるFDG-PETの有用性については有用とする報告とそうでないとする報告があり、コンセンサスはまだ得られていない。ただし、EUSなどの従来の診断法を凌駕するものではないものの相補的な役割があり、術前治療中に行った効果判定が終了後に行った効果判定と相違しなかったという報告もあり、治療効果の早期判定に有用な可能性がある[14,15]。いずれにしても、FDG-PETの臨床的有用性については、大規模な比較試験によりその有用性と限界を明らかにする必要があろう。CT・MRIに関しても、化学放射線治療効果と画像パラメータとの関係が種々の癌に対してさかんに研究され、灌流画像や拡散強調画像から計算されるパラメータが有望視され

ている。

治療法の個別化の観点から治療効果判定や予測といった研究も非常に重要であるが、今後の放射線治療においては、副作用低減の観点で限局的な照射野（IFRT）が採用される傾向が今後いっそう強まると思われることから、リンパ節転移を含めた治療前診断精度の更なる向上を目的とした研究がもっと精力的に行われることが望まれる。

最後に

食道癌の化学放射線療法の治療成績は、現時点では手術を凌駕するものではない。現在の根治的放射線治療後の局所再発については、サルベージ手術の安全性を重視して欧米並みの50.4Gyへの線量低下や照射野の縮小が検討されている。一方、X線3D-CRTでは頭打ちであった局所制御率の向上を図る手段として、正常組織への線量を低減しながら局所線量を増加させ得るIMRTや粒子線治療への期待も強く、長期的な治療成績が待たれる。

食道癌治療においては集学的な治療法開発が重要であることはいうまでもないが、そのなかで近年の放射線治療技術の進歩が今後大きく寄与することが期待される。

参考文献

1) Cooper JS et al: Chemoradiotherapy of locally advanced esophageal cancer: long-term follow-up of a prospective randomized trial (RTOG 85-01). JAMA 281(17): 1623-1627, 1999
2) Bang YJ et al: Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. Lancet 376(9742): 687-697, 2010
3) Ando N et al: A Randomized Trial Comparing Postoperative Adjuvant Chemotherapy with Cisplatin and 5-Fluorouracil Versus Preoperative Chemotherapy for Localized Advanced Squamous Cell Carcinoma of the Thoracic Esophagus (JCOG9907). Ann Surg Oncol 2011 (Epub ahead of print)
4) Gebski V et al: Survival benefits from neoadjuvant chemoradiotherapy or chemotherapy in oesophageal carcinoma: a meta-analysis. Lancet Oncol 8(3): 226-234, 2007
5) Bedenne L et al: Chemoradiation followed by surgery compared with chemoradiation alone in squamous cancer of the esophagus: FFCD 9102. J Clin Oncol 25(10): 1160-1168, 2007
6) Stahl M et al: Chemoradiation with and without surgery in patients with locally advanced squamous cell carcinoma of the esophagus. J Clin Oncol 23(10): 2310-2317, 2005
7) Minsky BD et al: INT 0123 (Radiation Therapy Oncology Group 94-05) phase III trial of combined-modality therapy for esophageal cancer: high-dose versus standard-dose radiation therapy. J Clin Oncol 20(5): 1167-1174, 2002
8) 西村恭昌ほか：食道がんの最新放射線治療　強度変調放射線治療（IMRT）—化学放射線療法の治療成績向上と晩期合併症の低減に向けて. INNERVISION 26(3): 37-38, 2011
9) Welsh J et al: Esophageal Cancer Dose Escalation using a Simultaneous Integrated Boost Technique. Int J Radiat Oncol Biol Phys, 2011 (Epub ahead of print)
10) Welsh J et al: Intensity-Modulated Proton Therapy further reduces normal tissue exposure during definitive therapy for locally advanced distal esophageal tumors: a dosimetric study. Int J Radiat Oncol Biol Phys, 2011 (Epub ahead of print)
11) Mizumoto M et al: Clinical results of proton-beam therapy for locoregionally advanced esophageal cancer. Strahlenther Onkol 186(9): 482-488, 2010
12) Van Westreenen HL et al: Systematic review of the staging performance of 18F-fluorodeoxyglucose positron emission tomography in esophageal cancer. J Clin Oncol 22(18): 3805-3812, 2004
13) Van Westreenen HL et al: Limited additional value of positron emission tomography in staging oesophageal cancer. Br J Surg 94(12): 1515-1520, 2007
14) Ngamruengphong S et al: Assessment of response to neoadjuvant therapy in esophageal cancer: an updated systematic review of diagnostic accuracy of endoscopic ultrasonography and fluorodeoxy-glucose positron emission tomography. Dis Esophagus 23(3): 216-231, 2010
15) Kwee RM et al: Prediction of tumor response to neoadjuvant therapy in patients with esophageal cancer with use of 18F FDG PET: a systematic review. Radiology 254(3): 707-717, 2010

Clinical Results of Definitive Chemoradiotherapy for Patients With Synchronous Head and Neck Squamous Cell Carcinoma and Esophageal Cancer

Makoto Shinoto, MD, Yoshiyuki Shioyama, MD,† Tomonari Sasaki, MD,* Katsumasa Nakamura, MD,‡ Hiroki Ohura, AS,* Yasushi Toh, MD,§ Yuichiro Higaki, MD,¶ Toshihiro Yamaguchi, MD,‖ Kayoko Ohnishi, MD,† Kazushige Atsumi, MD,† Hideki Hirata, MD,** and Hiroshi Honda, MD†*

Objectives: To assess the efficacy and toxicity of radical chemoradiotherapy for patients with synchronous head and neck squamous cell carcinoma (HNSCC) and esophageal cancer (EC).

Methods: Thirty-four patients with synchronous HNSCC and EC were treated mainly with radical chemoradiotherapy at the same time. Median external radiation dose for HNSCC and EC was 70 Gy (range, 60–70.5 Gy), except for 2 patients with tongue cancer, who underwent brachytherapy and 60 Gy (range, 45–70 Gy), respectively. Thirty-one patients were treated with concurrent chemoradiotherapy with cisplatin and/or 5-fluorouracil or TS-1 (oral anticancer agent that combines tegafur, a metabolically activated prodrug of 5-fluorouracil, with 5-chloro-2, 4-dihydoroxypyridine, and potassium oxonate).

Results: Thirty-three patients completed the intended treatment. The response rate was 94%, with 26 complete responses (76%) and 6 partial responses (18%). At a median follow-up of 17.3 months, 2-year rates of overall survival, cause-specific survival, and disease-free survival were 44%, 52%, and 33%, respectively. Initial failure patterns were local failure in 14 patients (63%), regional progression in 3 patients (13%), and distant metastasis in 6 patients (27%). The most common acute toxicity was myelosuppression, with 8 patients experiencing grade 3–4 toxicity. Three patients experienced grade 3 mucositis and pharyngitis. No patients experienced late morbidity of grade 3 or higher.

Conclusions: Definitive chemoradiotherapy for patients with synchronous HNSCC and EC is feasible with a low mortality rate and acceptable morbidity.

Key Words: radiotherapy, synchronous, head and neck squamous cell carcinoma, esophageal cancer

(*Am J Clin Oncol* 2011;34: 362–366)

Multiple squamous cell carcinomas often arise in the upper aerodigestive tract.[1–3] The association of multiple tumors in that area has been explained by the concept of field cancerization.[4,5] Neoplasms of the head and neck (HN) and the esophagus area are seen most frequently, although other combinations occur.[6–8] In patients with head and neck squamous cell carcinoma (HNSCC), routine endoscopy of the esophagus at diagnosis results in more frequent detection of second primary esophageal cancer (EC) at an early stage.[9,10] The management and clinical course of these patients with multiple squamous cell carcinomas are poorly documented. The poor prognosis of each carcinoma and their anatomic proximity complicate the therapeutic strategy and limit the treatment options for each location.[11] In the past, patients with synchronous HNSCC and EC were thought to be candidates for palliative treatment.[12] This was partly because surgical resection for synchronous HNSCC and EC was thought to be too definitive and inappropriate for these patients and to offer only a small chance of cure.[12] There have been very few studies focusing on definitive therapeutic strategies for such patients, and treatment options are controversial.[13,14] In contrast to several studies on surgical treatment[13,15] for patients with synchronous HNSCC and EC, the feasibility, efficacy, and toxicity of definitive chemoradiotherapy for the treatment of these patients has not been evaluated enough yet. Thus, we retrospectively analyzed clinical findings, particularly clinical outcomes including cause of death, for patients with synchronous HNSCC and EC who had been treated with definitive chemoradiotherapy.

MATERIALS AND METHODS

Patient Characteristics

A total of 34 patients underwent definitive radiotherapy for synchronous HNSCC and EC at the National Kyushu Cancer Center and Kyushu University Hospital from 1995 to 2007. The median age of these patients was 64 years (range, 49–85 years). The median Karnofsky Performance Status was 90 (range, 70–100). The primary sites of HNSCC were as follows: larynx, 3 (9%); mesopharynx, 9 (26%); hypopharynx, 19 (56%); oral floor, 1 (3%); and tongue, 2 (6%). All patients were evaluated according to the 1997 International Union Against Cancer tumor, node, metastasis classification. T and N stages of HNSCC and EC are listed in Table 1. Pretreatment diagnostic evaluations consisted of barium swallow, endoscopy with Lugol's iodine, cervical and abdominal ultrasound, computed tomography (CT), magnetic resonance imaging (MRI) of HN area, and bone scintigraphy. Whole-body fluorodeoxyglucose-positron emission tomography (FDG-PET) scan was not routinely performed.

Treatment Planning

Radiotherapy for HNSCC and that for EC were performed simultaneously. Twenty patients were treated with a 2-dimensional (2D) technique, whereas 14 patients received three-dimensional conformal radiotherapy (3D-CRT). The initial radiotherapy fields included the HN and mediastinal region for 32 patients, and HN and mediastinal and upper abdominal region for 2 patients. For HN treatment, external radiotherapy was performed using a cobalt-60 or 4 to 6 MV photon beam. Thirty-two of the 34 patients received external beam radiation therapy (EBRT) alone and 2 patients received EBRT and brachytherapy. The target volume was defined by means of endoscopic evaluation, physical examination, CT, MRI, and/or PET. The radiotherapy tech-

From the *Departments of Radiology, National Kyushu Cancer Center, Fukuoka, Japan; †Department of Clinical Radiology, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan; ‡Department of Radiology, Kyushu University Hospital at Beppu, Oita, Japan; §Department of Gastroenterological Surgery, National Kyushu Cancer Center, Fukuoka, Japan; ¶Division of Head and Neck Surgery, National Kyushu Cancer Center, Fukuoka, Japan; ‖Department of Radiology, Kitakyushu Municipal Medical Center, Fukuoka, Japan; and **School of Health Sciences, Kyushu University, Fukuoka, Japan.

The authors declare no conflicts of interest.

Reprints: Makoto Shinoto, MD, Departments of Radiology, National Kyushu Cancer Center, 3-1-1 Notame, Minami-ku, Fukuoka, 811-1359, Japan. E-mail: shinoto@nirs.go.jp.

ISSN: 0277-3732/11/3404-0362
DOI: 10.1097/COC.0b013e3181e84b4b

niques mainly used a standard 3-field arrangement, 2 lateral fields to treat the primary tumor and upper neck and 1 AP field to treat the lower neck. A single field or 2 lateral fields were also used depending on the case. The daily fractional EBRT dose was 1.5 to 2 Gy, administered 5 days per week, for all patients. Median total radiation dose for HNSCC was 70 Gy (range, 60–70.5 Gy), except for 2 patients with tongue cancer who were treated with brachytherapy after EBRT. In one of these 2 patients, permanent radioactive seeds, ^{198}Au grains, were used for the treatment of tongue cancer and 20 Gy was prescribed to the marginal line after EBRT of 19.8 Gy in 11 fractions. The other patient was treated with afterloaded high-dose-rate brachytherapy with plastic tubes and the prescribed dose was 50 Gy in 10 fractions per 5 days after EBRT of 30 Gy in 20 fractions. Five patients, who were evaluated as CR for primary sites and as PR for neck nodal involvement, were offered neck dissection followed by chemoradiotherapy.

TABLE 1. Sites and Stages of HNSCC and EC

HNSCC	
T stage	
T1	8
T2	12
T3	3
T4	11
N stage	
N0	14
N1	3
N2	14
N3	3
Location	
Larynx	3
Mesopharynx	9
Hypopharynx	19
Oral Floor	1
Tongue	2
EC	
T stage	
T1	24
T2	3
T3	4
T4	3
N stage	
N0	27
N1	7

Staging was defined according to UICC (1997).

For esophageal treatment, radiotherapy was performed using a cobalt-60 or 6 to 21 MV photon beam. Median dose for EC was 60 Gy (range, 45–70 Gy) with conventional fraction sizes (1.5–2 Gy). After the initial anterior/posterior field included the primary tumor and metastatic lymph nodes at 30 to 40 Gy, simulation was performed to reduce the RT field and exclude the spinal cord by using an oblique opposed field.

Chemotherapy was performed concurrently with radiotherapy in 31 patients (91%). The other 3 patients did not receive chemotherapy because of advanced age, renal dysfunction, or refusal. Chemotherapy consisted of 2 courses of cisplatin in 9 patients, 2 courses of 5-fluorouracil/cisplatin in 11 patients, or TS-1 (oral anticancer agent that combines tegafur, a metabolically activated prodrug of 5-fluorouracil, with 5-chloro-2, 4-dihydoroxypyridine, and potassium oxonate) for 4 weeks in 10 patients. In 1 patient, carboplatin was selected instead of cisplatin because creatinine clearance was <60 mL/min. The choice of chemotherapy regimen depended on the managing physician.

Criteria for Response and Toxicity

A complete response was defined as disappearance of the tumor mass on endoscopy, CT, MRI, and/or PET. A partial response was defined as more than 30% regression based on one-dimensional measurement by means of endoscopy, CT or MRI, and no response was defined as less than 30% regression or less than 20% progression.

Acute and late toxicities were graded using National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0).

Statistical Analysis

Overall survival (OS), cause-specific survival (CSS), and disease-free survival (DFS) rates were calculated by using the

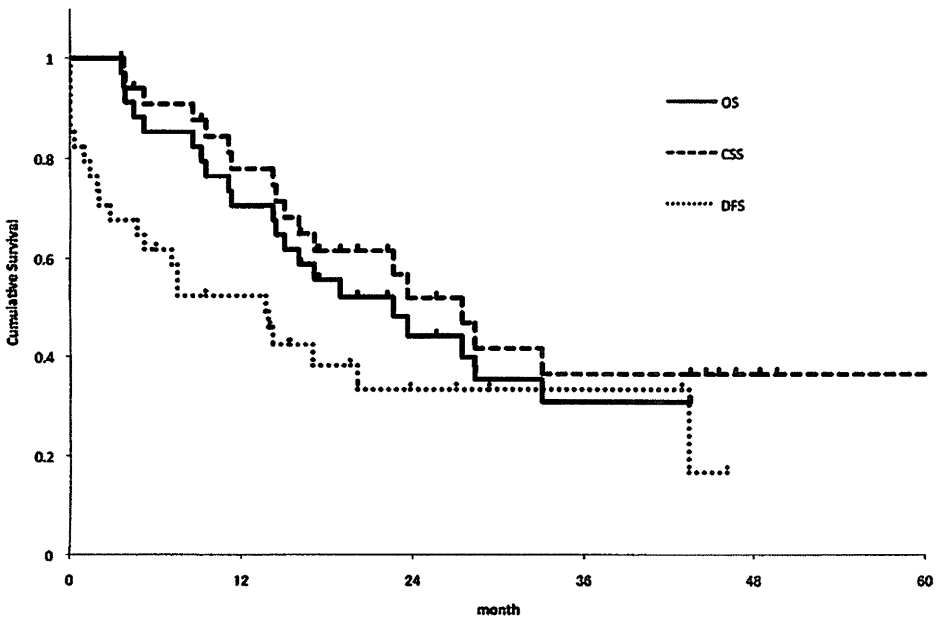

FIGURE 1. Overall survival, cause-specific survival and disease-free survival for all patients.

Kaplan-Meier method. When calculating CSS, patients who were alive at the last follow-up or had died of causes other than HNSCC or EC were censored. DFS was defined as the absence of disease in HNSCC and EC. All time points were calculated from the initiation of chemoradiotherapy. Statistical difference in survival was compared with log-rank tests. A P of less than 0.05 was regarded as statistically significant.

RESULTS

Of the 34 patients, 33 completed the intended treatment. The treatment was tolerated well in all but 1 patient, who could not complete chemoradiotherapy because of impaired Performance Status. Eighteen patients (53%) required a treatment break for 1 to 4 weeks. Treatment was discontinued for 2 to 4 weeks in 7 of those patients due to toxicity such as myelosuppression, mucositis, and/or pharyngitis. A period of 1 to 4 weeks was needed to determine whether to continue chemoradiation or switch to surgery in 11 patients.

All patients were evaluated for toxicity. The most common acute toxicity was myelosuppression, with 7 (21%) of the patients experiencing grade 3–4 toxicity. In addition, grade 3 mucositis and pharyngitis occurred in 3 patients and 1 patient, respectively. Seven patients required treatment breaks because of these toxicities.

No patient experienced late morbidity of grade 3 or higher. Three patients had feeding disorder due to esophagostenosis with grade 2, and 1 patient required thyroid hormone treatment because of hypothyroidism.

The median period of overall treatment was 67 days (range, 50–104 days) except for 1 patient in whom treatment was discontinued at 16 days. For the 34 patients with synchronous HNSCC and EC, the response rate was 94% with 26 complete responses (CR) (76%) and 6 partial responses (PR) (18%). Five patients, who were evaluated as CR for primary sites and as PR for neck nodal involvement, were offered neck dissection followed by chemoradiotherapy. Of those 5 patients, 2 had no evidence of pathologic residual carcinoma. At a median follow-up of 17.3 months (range, 4–65 months), 2-year rates of OS, CSS, and DFS were 44%, 52%, and 33%, respectively (Fig. 1).

At the last evaluation, 12 patients were still alive and 5 of them with locoregional recurrence underwent salvage surgery such as pharyngolaryngectomy or esophagectomy. Ten patients died of HNSCC, 5 died of EC, 3 died of other cancers, and 2 died of noncancer-related causes such as pneumonia or disseminated intravascular coagulation. For the remaining 2 patients, the exact cause of death could not be determined retrospectively.

Twenty-two patients experienced recurrence of HNSCC or EC. Fourteen patients had local progression as a component of initial failure (63%), and local progression occurred in the setting of distant failure in 1 patient. In 3 patients (13%), local progression was initially in the regional lymph nodes, all cases being HN lesions. Six patients (27%) had distant metastasis as a first site of failure (Table 2). Three patients with local recurrence had salvage surgery such as laryngectomy or esophagectomy and were still alive at the last evaluation.

Figure 2 shows the OS curves in our series according to the stage of EC. OS in patients with stage I–II EC was significantly better than in patients with stage III–IV EC (P = 0.0001). The 2-year rate of OS in the 27 patients with HNSCC and stage I–II EC was 56%. Survival of patients with stage I–II HNSCC tended to be better than that of patients with stage III–IV HNSCC. However, the survival difference was not statistically significant (P = 0.06) (Fig. 3). Among the 27 patients who had stage I–II EC, survival was significantly better in patients with stage I–II HNSCC comparing to those with stage III–IV HNSCC (P = 0.02) (Fig. 4). The 2-year rate of OS was 86% in the 8 patients with stage I–II HNSCC and stage I–II EC. No statistical significance in overall survival was observed in patient age and treatment duration.

TABLE 2. Patterns of Initial Disease Progression

Origin	HN	Esophageal	Both	
Local	5	6	2	
Regional	3			
Distant	4	1		
Local +distant	1			
Unknown				2

DISCUSSION

We showed the efficacy and feasibility of simultaneous definitive chemoradiotherapy for patients with HNSCC and EC. To the best of our knowledge, though many reports recommend surgical

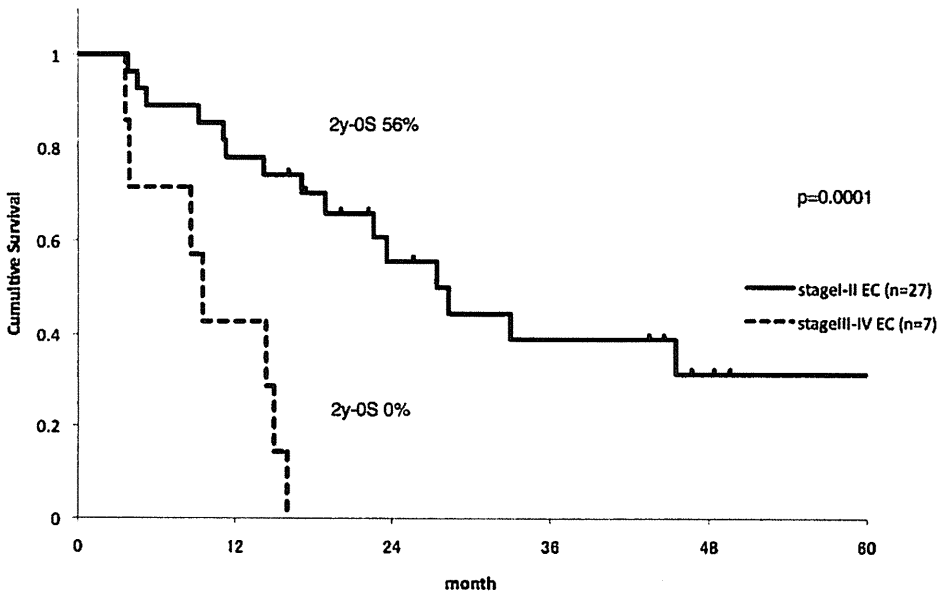

FIGURE 2. Overall survival according to stages of EC. The group of stage I–II EC (n = 27) includes HNSCC with stage I-II (n = 8) and stage III-IV (n = 19). The group of stage III–IV EC (n = 7) includes HNSCC with stage I-II (n = 3) and stage III-IV (n = 4).

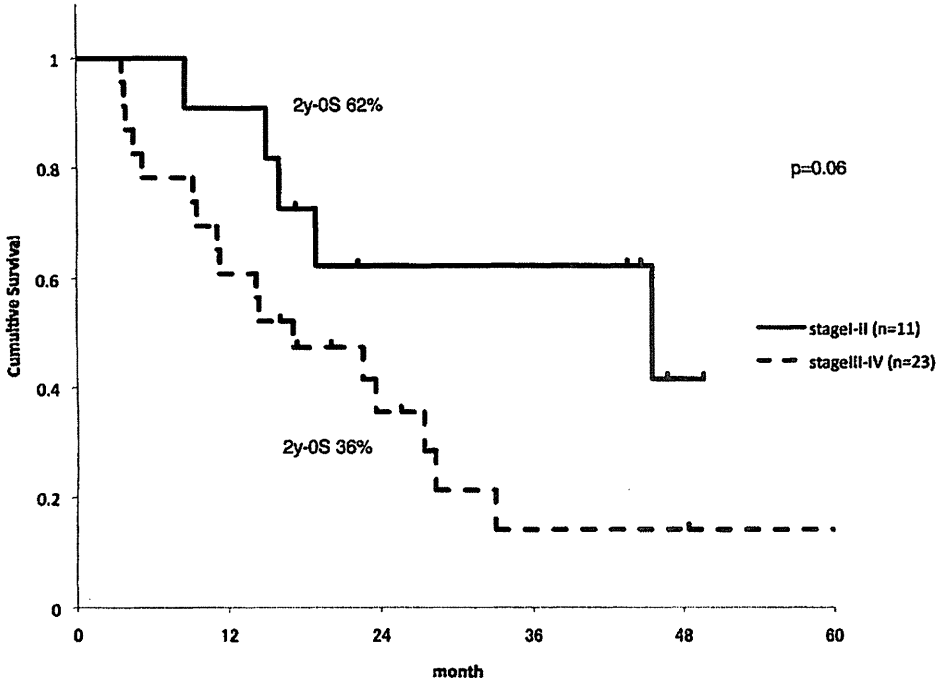

FIGURE 3. Overall survival according to stage of HNSCC.

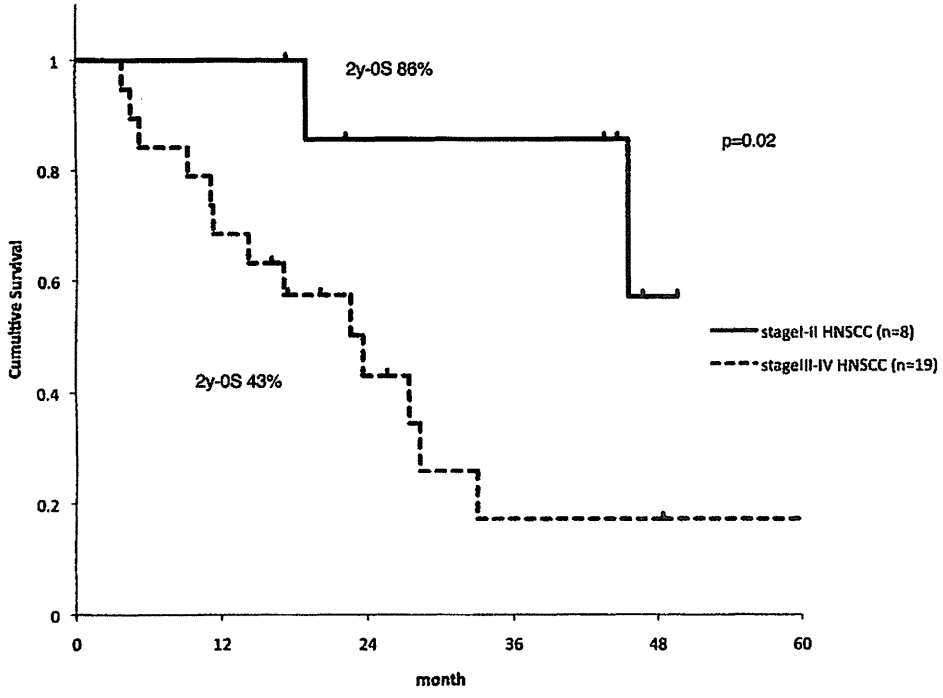

FIGURE 4. Overall survival according to stages of HNSCC with only stage I-II EC.

resection as a standard treatment policy,[16–19] there have been only a few previous studies in which the outcome of patients with HNSCC and EC mainly treated with radiotherapy was analyzed.

Guillot et al[20] retrospectively reviewed 22 patients with multiple synchronous squamous cell carcinomas of the upper aerodigestive tract who had been treated with neoadjuvant chemotherapy followed by radiotherapy or surgery. Twelve patients were free of disease after locoregional treatment and mean survival was 17 months. Nguyen et al[21] evaluated neoadjuvant chemotherapy and irradiation in 24 patients with synchronous squamous cell carcinoma of the upper aerodigestive tract. Sixteen patients (66%) had complete remission in both cervical and mediastinal sites. The median survival was 12 months and survival rate was 5% at 24 months. Welz et al[22] treated 24 patients with synchronous HNSCC and EC by a radiation based curative approach, and they reported that the median overall survival was 37 months.

In our series, 14 patients (64%) had a complete response and 5 of them were still alive at the time of evaluation. The median survival was 19 months and the 2-year survival rate was 44%. These results are comparable to results of previous studies.[20–22] The 2-year survival rate

in patients with EC of stage I–II was 56%. Thus, favorable prognosis can be expected by definitive chemoradiotherapy in patients with synchronous HNSCC and EC if the coexisting EC is early stage (stage I–II). Furthermore, survival of patients with stage I-II diseases for both HNSCC and EC was excellent (2-year OS = 86%). Chemoradiotherapy is considered to be an effective treatment option for synchronous early-stage HNSCC and EC.

Although acute toxicity of grade 3 or higher was observed in 7 patients (21%), 33 of the 34 patients completed the treatment and no patient experienced late severe toxicity of grade 3 or higher. Our results indicate that definitive chemoradiotherapy for synchronous HNSCC and EC is feasible and effective.

The impact synchronous double primary cancer on survival of cancer patients has not been clear. Robinson et al[23] reported that survival of HNSCC patients without second primary cancer (SPC) was better than that of HNSCC patients with second primary cancer. The presence of EC was found to have an adverse effect on the survival of patients with HNSCC.[24] With regard to the effect of SPC on the of patients with EC, Kagei et al reported that the survival outcome of EC was not different between patients with SPC and those without SPC.[25] Poon et al[8] also reported that survival rates of patients with EC did not significantly differ between patients with and those without SPC. These results suggest that the dismal prognosis of EC overshadows the moderate effect of SPC on survival. The difference in the impact of SPC on survival of patients with HNSCC and survival of patients with EC might be due to the presentation of most patients with EC at an advanced stage, and their prognosis was poor regardless of whether another primary cancer was present or not.[8] In fact, Kagei et al[25] showed that the overall survival rate of patients with early-stage EC was better for patients without synchronous SPC than for patients with synchronous SPC. For synchronous HNSCC and EC, treatment should be selected in consideration of the prognosis of the disease. The present study showed that the survival of patients with synchronous HNSCC and EC was significantly affected by the stage of EC (stage I–II vs. stage III–IV). The results of our study and previous studies suggest that the stage of EC is more important for predicting survival of patients with synchronous HNSCC and EC. We found that the stage of coexisting HNSCC also significantly influenced the survival of patients with early-stage EC.

Past studies showed that patients with HNSCC had higher rates of early-stage EC than did only EC patients, and a significant difference was found between the 2 groups in terms of tumor, node, metastasis stage groupings.[26,27] In our series, 27 patients (79%) with EC had stage I–II disease, and their survival rate was significantly better than that of patients in stage III-IV. This suggests that intense screening and surveillance resulted in high detection rates for cases of early-stage EC, which have a chance of cure with definitive treatment.

CONCLUSION

Definitive chemoradiotherapy in the presence of synchronous HNSCC and EC can be performed safely without increase in morbidity and mortality rates. Although there is no standard approach for this group of patients, definitive chemoradiotherapy is a good curatively intended treatment option if comorbid EC is in stage I–II.

REFERENCES

1. McGuirt WF, Matthews B, Koufman JA. Multiple simultaneous tumors in patients with head and neck cancer: a prospective, sequential panendoscopic study. *Cancer*. 1982;50:1195–1199.
2. Shibuya H, Wakita T, Nakagawa T, et al. The relation between an esophageal cancer and associated cancers in adjacent organs. *Cancer*. 1995;76:101–105.
3. Grossman TW. The incidence and diagnosis of secondary esophageal carcinoma in the head and neck cancer patient. *Laryngoscope*. 1989;99:1052–1056.
4. Slaughter DP, Southwick HW, Smejkal W. Field cancerization in oral stratified squamous epithelium; clinical implications of multicentric origin. *Cancer*. 1953;6:963–968.
5. Yasuda M, Kuwano H, Watanabe M, et al. p53 expression in squamous dysplasia associated with carcinoma of the oesophagus: evidence for field carcinogenesis. *Br J Cancer*. 2000;83:1033–1038.
6. Kumagai Y, Kawano T, Nakajima Y, et al. Multiple primary cancers associated with esophageal carcinoma. *Surg Today*. 2001;31:872–876.
7. Fogel TD, Harrison LB, Son YH. Subsequent upper aerodigestive malignancies following treatment of esophageal cancer. *Cancer*. 1985;55:1882–1885.
8. Poon RT, Law SY, Chu KM, et al. Multiple primary cancers in esophageal squamous cell carcinoma: incidence and implications. *Ann Thorac Surg*. 1998;65:1529–1534.
9. Winn DM, Blot WJ. Second cancer following cancers of the buccal cavity and pharynx in Connecticut, 1935–1982. *Natl Cancer Inst Monogr*. 1985;68:25–48.
10. Tepperman BS, Fitzpatrick PJ. Second respiratory and upper digestive tract cancers after oral cancer. *Lancet*. 1981;2:547–549.
11. Tachimori Y, Watanabe H, Kato H, et al. Treatment for synchronous and metachronous carcinomas of the head and neck and esophagus. *J Surg Oncol*. 1990;45:43–45.
12. Takita H, Vincent RG, Caicedo V, et al. Squamous cell carcinoma of the esophagus: a study of 153 cases. *J Surg Oncol*. 1977;9:547–554.
13. Elias D, Mamelle G, el Malt O, et al. Synchronous cancers of the esophagus and of the ORL area: results of combined treatments with esophagectomy (28 cases) [in French]. *Bull Cancer*. 1991;78:173–178.
14. Sun K, Matsubara T, Ueda M. Surgical treatment for primary esophageal cancer developing after pharyngolaryngectomy for head and neck cancer. *Surgery*. 1997;122:15–19.
15. Erkal HS, Mendenhall WM, Amdur RJ, et al. Synchronous and metachronous squamous cell carcinomas of the head and neck mucosal sites. *J Clin Oncol*. 2001;19:1358–1362.
16. Wind P, Roullet MH, Quinaux D, et al. Long-term results after esophagectomy for squamous cell carcinoma of the esophagus associated with head and neck cancer. *Am J Surg*. 1999;178:251–255.
17. Lo OS, Law S, Wei WI, et al. Esophageal cancers with synchronous or antecedent head and neck cancers: a more formidable challenge? *Ann Surg Oncol*. 2008;15:1750–1756.
18. Wind P, Roullet MH, Douard R, et al. Experience in the treatment of synchronous and metachronous carcinoma of the oesophagus and the head and neck. *J Surg Oncol*. 2000;73:138–142.
19. Natsugoe S, Matsumoto M, Okumura H, et al. Multiple primary carcinomas with esophageal squamous cell cancer: clinicopathologic outcome. *World J Surg*. 2005;29:46–49.
20. Guillot T, Spielmann M, Kac J, et al. Neoadjuvant chemotherapy in multiple synchronous head and neck and esophagus squamous cell carcinomas. *Laryngoscope*. 1992;102:311–319.
21. Nguyen TD, Panis X, Legros M, et al. Neoadjuvant chemotherapy and irradiation in multiple synchronous squamous cell carcinoma of the upper aero digestive tract. *Radiother Oncol*. 1989;16:283–288.
22. Welz S, Schmid A, Hehr T, et al. Treatment-outcome for synchronous head-and-neck and oesophageal squamous cell carcinoma. *Radiother Oncol*. 2005;77:267–270.
23. Robinson E, Zauber A, Fuks Z, et al. Clinical characteristics of patients with epidermoid carcinoma of the upper aerodigestive tract who develop second malignant tumors. *Cancer Detect Prev*. 1992;16:297–303.
24. Gluckman JL, Crissman JD. Survival rates in 548 patients with multiple neoplasms of the upper aerodigestive tract. *Laryngoscope*. 1983;93:71–74.
25. Kagei K, Hosokawa M, Shirato H, et al. Efficacy of intense screening and treatment for synchronous second primary cancers in patients with esophageal cancer. *Jpn J Clin Oncol*. 2002;32:120–127.
26. Sugimachi K, Kitamura K, Baba K, et al. Endoscopic diagnosis of early carcinoma of the esophagus using Lugol's solution. *Gastrointest Endosc*. 1992;38:657–661.
27. Natsugoe S, Baba M, Yoshinaka H, et al. Mucosal squamous cell carcinoma of the esophagus: a clinicopathologic study of 30 cases. *Oncology*. 1998;55:235–241.

J. Radiat. Res., 52, 522–530 (2011)

Regular Paper

Prediction of Local Failures with a Combination of Pretreatment Tumor Volume and Apparent Diffusion Coefficient in Patients Treated with Definitive Radiotherapy for Hypopharyngeal or Oropharyngeal Squamous Cell Carcinoma

Kayoko OHNISHI[1], Yoshiyuki SHIOYAMA[1]*, Masamitsu HATAKENAKA[1], Katsumasa NAKAMURA[2], Koichiro ABE[1], Takashi YOSHIURA[1], Saiji OHGA[1], Takeshi NONOSHITA[1], Tadamasa YOSHITAKE[1], Torahiko NAKASHIMA[3] and Hiroshi HONDA[1]

Diffusion-weighted magnetic resonance imaging/Apparent diffusion coefficient/Hypopharyngeal squamous cell carcinoma/Oropharyngeal squamous cell carcinoma.

Purpose: The purpose of this study was to investigate the clinical factors for predicting local failure after definitive radiotherapy in oropharyngeal or hypopharyngeal squamous cell carcinoma. **Materials and Methods:** Between July 2006 and December 2008, 64 consecutive patients with squamous cell carcinoma of the hypopharynx or the oropharynx treated with definitive radiotherapy were included in this study. Clinical factors, such as pretreatment hemoglobin (Hb) level, T-stage, gross tumor volume of primary tumors (pGTV), and maximum standardized uptake value (SUV_{max}) on FDG-PET, were evaluated for the correlation with local failure. A subset analysis of 32 patients with MR images including diffusion-weighted images (DWI) as a pretreatment evaluation was also performed. The Kaplan-Meier curves, the log-rank test, and the Cox proportional hazards model were used to evaluate these clinical factors. **Results:** Eleven of 64 patients experienced local recurrence, with a median follow-up time of 15 months. In the univariate analysis, Hb level ($p = 0.0261$), T-stage ($p = 0.012$), pGTV ($p = 0.0025$), and SUV_{max} ($p = 0.024$) were significantly associated with local failure. In the multivariate analysis, pGTV ($p = 0.0070$) remained an adverse factor for local control. In the subset analysis of 32 patients with DWI, the median apparent diffusion coefficient (ADC) value of primary tumors on DWI was 0.79×10^{-3} mm^2/s (range, $0.40–1.60 \times 10^{-3}$ mm^2/s). Patients with a high ADC value ($> 0.79 \times 10^{-3}$ mm^2/s) had a significantly lower local control rate than patients with a low ADC value (100% vs. 44%, $p = 0.0019$). The rate of local failure among patients with a large pGTV and a high ADC value was 55% (6/11), whereas no local failures occurred (0%, 0/21) among patients with a small pGTV or a low ADC. **Conclusions:** These results suggest that a combination of a large tumor volume and a high ADC value could be predictive of local recurrence after definitive radiotherapy in hypopharyngeal or oropharyngeal squamous cell carcinoma.

INTRODUCTION

Primary radiotherapy, typically with concurrent chemotherapy, has recently been accepted as a standard management option for the organ-sparing treatment of head and neck squamous cell carcinoma (HNSCC).[1–5] However, treatment outcomes achieved thus far with definitive radiotherapy have remained unsatisfactory, especially in cases of locally advanced disease. Treatment failure after chemoradiotherapy (CRT) is primarily related to locoregional tumor recurrence, whereas isolated distant metastases occur less frequently. Moreover, locally recurrent tumors not only threaten patient survival but also seriously impair quality of life, as most patients with such recurrences die with symptomatic local tumor progression. Therefore, it is essential to investigate factors that exert an influence on local control. Various clinical factors, such as hemoglobin (Hb) level,[6–10] T-stage,[11] tumor volume,[12–19] and comorbidity,[11,12] have

*Corresponding author: Phone: +81-92-642-5695,
Fax: +81-92-642-5708,
E-mail: shioyama@radiol.med.kyushu-u.ac.jp
[1]Department of Clinical Radiology, Graduate School of Medical Sciences, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka city, Fukuoka, 812-8582, Japan; [2]Department of Radiology, Kyushu University Hospital at Beppu, 4546 Tsurumihara, Beppu city, Oita, 874-0838, Japan; [3]Department of Otorhinolaryngology, Graduate School of Medical Sciences, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka city, Fukuoka, 812-8582, Japan.
doi:10.1269/jrr.10178

been reported to be correlated with local control. Despite careful evaluation of these known clinical factors, it remains difficult to reliably predict outcomes after radiotherapy. If an outcome can be predicted prior to treatment, patients who are unlikely to be cured with CRT could be selected for alternative treatments.

Advances in imaging technologies such as perfusion computed tomography (CT), diffusion-weighted magnetic resonance imaging (DWI), and positron emission tomography (PET), have made it possible to assess the functional aspects of tumor physiology. These new approaches to imaging are considered to improve the accuracy of radiation response assessment for HNSCC. Several studies have suggested that the degree of pretreatment ^{18}F-flurodeoxyglucose (FDG) uptake can be used as a predictor of local control, in that patients with high FDG uptake generally exhibit less local control.[20–23] However, due to the large overlap between responders and non-responders, a reliable method of predicting tumor response based on FDG uptake has not yet been established.

Diffusion-weighted magnetic resonance imaging (MRI) is used to measure differences in tissue microstructure that are based on the random displacement of water molecules.[24] These differences in water mobility are quantified by using the apparent diffusion coefficient (ADC). To date, DWI has been demonstrated to possess the potential to prospectively predict the success of certain treatments for a number of different tumor types.[25–34] One study identified strong negative correlation between the pretreatment tumor ADC in patients with rectal cancer and changes in tumor size after chemotherapy and chemoradiotherapy.[30] The application of DWI to HNSCC has recently been investigated.[35–37] It was reported that the pretreatment ADC of metastatic nodal masses and changes in the ADC within the first week of CRT can be used as markers for early detection and prediction of a response to concurrent CRT.[35] More recently, the pretreatment ADC of primary tumor was reported to have a potential indicator of local failure in HNSCC treated with radiotherapy.[38] On the other hand, there is another study that found no correlation between pretreatment ADC and local failure in HNSCC treated with radiotherapy.[39] Therefore, the role of the pretreatment ADC as a predictor of local control still has been controversial.

In the present study, we investigated the role of previously reported prognostic factors for predicting local control after definitive radiotherapy had been administered to patients with hypopharyngeal or oropharyngeal squamous cell carcinoma. In addition to these reported prognostic factors, we also evaluated the utility of ADC in pretreatment DWI to predict local control.

MATERIALS AND METHODS

Patient population and treatment

This retrospective study was approved by the Committee for Clinical Studies at our institution; the requirement for informed consent was waived. Between July 2006 and December 2008, 82 consecutive patients with newly diagnosed squamous cell carcinoma of the hypopharynx or the oropharynx were treated with definitive radiotherapy at our institution. Sixty-four of these patients were included in this study. The inclusion criteria were as follows: *(a)* histologically confirmed squamous cell carcinoma, *(b)* availability of pretreatment FDG-PET for the initial evaluation, *(c)* sufficient dose of radiotherapy (> 60 Gy), and *(d)* no combination therapy involving radiotherapy and surgery. We excluded 18 patients due to the unavailability of FDG-PET (n = 8) and preoperative radiotherapy (n = 10). Of the 64 patients included, 39 underwent MRI including DWI. To estimate the usefulness of DWI for predicting local failures, 32 of these 39 patients were identified for a subset analysis. Of the 39 patients who underwent MRI with DWI, 7 were excluded for the subset analysis due to the presence of a small and unevaluable primary lesion (n = 6) or a severe artifact (n = 1) on DWI.

Radiation treatment was planned on a CT-based three-dimensional treatment planning system (Eclipse; Varian medical systems, Palo Alto, CA). Each patient was immobilized with a custom-made thermoplastic cast in the supine position, and 3-mm thick CT was performed. Target volumes and organs at risk were delineated on CT images. All patients were treated according to a conventional radiotherapy schedule, i.e., 5 days per week at 1.8 to 2.0 Gy per fraction. Typically, the total dose of 65.4–69.4 Gy in 35–37 fractions was prescribed to treat the primary tumor and involved nodes, whereas the prophylactic dose administered to the adjacent nodal regions was 41.4–45.0 Gy in 23–25 fractions. The median total dose targeted to the primary tumor and involved nodes was 65.4 Gy (range, 61.4 to 71.4 Gy). Chemotherapy was administered concurrently in 60 of 64 patients (94%). The regimen of concurrent chemotherapy was S-1 (Taiho Pharmaceutical Co., Ltd, Tokyo, Japan) in 50 patients (78%) and cisplatin-based in 10 patients (22%). Planned neck dissection was performed in 16 patients who had suspected persistent disease in the neck after radiotherapy, as assessed clinically or by imaging study.

Patients underwent routine post-treatment follow-up examination every 1 to 3 months. The follow-up evaluation included physical examination, fiberoptic pharyngolaryngoscopy, and radiographic imaging (CT and/or PET-CT), if needed. Persistent or recurrent primary disease was confirmed by histologic and/or physical examination, radiographic imaging, and by clinical course.

Diffusion-weighted MRI study and image interpretation

MRI studies were performed with a 1.5-T scanner (Intera Achieva; Philips Medical System, Best, the Netherlands) by using a neurovascular coil. Conventional MRI, including T2-weighted turbo spin-echo images, T1-weighted spin-echo images, and contrast-enhanced T1-weighted spin-echo images, were obtained in the transverse plane, a slice thickness of 4–5 mm, a slice gap of 1–1.5 mm, and a 20 × 20 cm – 23 × 23 cm field of view. A T2-weighted turbo spin-echo sequence was performed with the following parameters: matrix, 512 × 288; and repetition time/echo time (TR/TE) = 4467 ms/100 ms. A T1-weighted spin-echo sequence was performed with the following parameters: matrix size, 512 × 288; and TR/TE = 572 ms/10 ms. A contrast-enhanced T1-weighted sequence was obtained after the administration of 0.1 mmol/kg of gadopenatate dimeglumine (Magnevist; Schering, Berlin, Germany). Coronal or sagittal images were obtained when needed.

Diffusion-weighted images were acquired in the transverse plane using a single-shot spin-echo echo-planar imaging sequence with a spectral presaturation of inversion recovery for fat suppression, with diffusion gradient encoding in three orthogonal directions. The parameters used to obtain the diffusion-weighted images were as follows: matrix size, 112 × 79; TR/TE = 3000 ms/73 ms; and bandwidth, 1645.9 Hz/pixel. The following three different *b*-values were applied: 0, 300, and 1,000 sec/mm^2. Diffusion-weighted imaging was performed prior to the administration of the contrast media injection.

The ADC values were calculated according to the following formula: $ADC = \ln[S_1/S_2]/b_2 - b_1$, where S_1 and S_2 are the signal intensities measured on diffusion-weighted images obtained with a lower *b* factor (b_1) and a higher *b* factor (b_2). We used *b* factors of 300 and 1,000 sec/mm^2 for calculation of ADC values. The ADC maps were calculated on a pixel-by-pixel basis using software integral to the MRI unit. For the ADC calculation, solid tumor components with T2-weighted and contrast-enhanced images were retrospectively identified by consensus between two radiologists (M.H. and T.Y.) with over 20 years of experience in head and neck radiology, both of whom were blinded to the clinical information. The region of interest (ROI) was designated as the primary tumor in the ADC map created on the console at the level of the largest tumor diameter to cover most of the lesion while avoiding cystic and/or necrotic areas that could have influenced the ADC values. Then the mean ADC values were selected for analysis.

Statistical analysis

Local control was measured from the first day of radiotherapy to the time of local failure or last follow-up. We estimated the relationship between the clinical and radiographic data and local control. Adverse factors included pretreatment Hb level, T-stage according to the classification system of the American Joint Committee on Cancer (2002), gross tumor volume of the primary tumor (pGTV) calculated using the above mentioned radiation treatment-planning system, overall treatment time, maximum standardized uptake value (SUV_{max}) on FDG-PET, and mean ADC of the primary tumor on DWI. Due to the lack of an established cutoff level for these factors, we used the median of the SUV_{max} and the mean ADC value as the cutoff levels. Local control rates were calculated according to the Kaplan-Meier method, and the log-rank test was used to analyze differences between local control curves. The multivariate Cox proportional hazards model was used to adjust for the influence of local control factors. All statistical analyses were performed using computer software (JMP 7; SAS institute, Cary, NC). For all analyses, $p < 0.05$ was considered to be significant.

RESULTS

Patient characteristics

The patient characteristics are shown in Table 1. Fifty-eight (91%) of the patients were men, and the median age was 65 years (range, 37–87 years). The primary sites were the oropharynx in 30 patients (47%), and the hypopharynx in 34 patients (53%). The T-stage classifications were T1 in 12 patients (19%), T2 in 27 (35%), T3 in 17 (27%), and T4 in 12 (19%). The pretreatment Hb ranged from 8.6 to 16.3 g/dl (median, 13.4 g/dl). The pGTV ranged from 0.4 to 86.8 cm^3 (median, 9.98 cm^3). The SUV_{max} of the primary lesion ranged from 2.9 to 28.2 (median, 12.0).

Univariate and multivariate analysis of local failure

At the last follow-up, 52 patients were alive and 12 had died of the disease. The median follow-up time for all patients was 15 months (range, 3–42 months). Over the entire follow-up period, 11 of 64 patients (17%) experienced a local recurrence. Local failure occurred within 12 months after the completion of radiotherapy in all but one patient. The 2-year local control rate for all 64 patients was 80% (Fig. 1). Factors associated with poor local control were low pretreatment Hb level ($p = 0.0261$), advanced T-stage ($p = 0.012$), high pGTV ($p = 0.0025$), and high SUV_{max} ($p = 0.024$). The results of the univariate analysis are shown in Table 2.

Factors significantly influencing local control in the univariate analysis were included in the multivariate analysis using the Cox proportional hazards model. A high pGTV remained a significant adverse factor (hazard ratio, 6.12, $p = 0.0470$) for local control. Regarding pretreatment Hb level, the statistical significance was marginal (hazard ratio, 3.34, $p = 0.0530$). However, other two factors (T-stage and SUV_{max}) were not significantly associated with local failure in the multivariate analysis. The hazard ratios associated

Table 1. Patient characteristics and treatment details.

Characteristics	Total (n = 64)
Age (year), median(range)	65 (37–87)
Gender, n (%)	
Male	58 (91)
Female	6 (9)
Hb value (g/dl), median (range)	13.4 (8.6–16.3)
Tumor site, n (%)	
Oropharynx	30 (47)
Hypopharynx	34 (53)
Maximum SUV, median (range)	12.0 (2.9–28.2)
2002 AJCC T-stage, n (%)	
T1	12 (19)
T2	23 (35)
T3	17 (27)
T4	12 (19)
2002 AJCC stage, n (%)	
I	6 (9)
II	6 (9)
III	9 (14)
IV	43 (67)
Radiotherapy	
pGTV (cm^3), median (range)	9.98 (0.35–86.81)
Total dose (Gy), median (range)	65.4 (61.4–71.4)
OTT (day), median (range)	60 (48–110)
Chemotherapy	
None	4 (6)
Concurrent	43 (67)
Concurrent and adjuvant	17 (27)
Concurrent chemotherapy regimen	
S-1	50 (83)
Platinum-based	10 (17)

Abbreviations: SUV = Standardized uptake value; AJCC = American Joint Committee on Cancer; pGTV = Gross tumor volume of the primary tumor; OTT = Overall treatment time.

with local control are listed in Table 3.

Local failure and pretreatment ADC value

We performed a subset analysis of 32 patients who underwent DWI during the pretreatment evaluation in order to assess the usefulness of the ADC value as a factor predictive of local control in addition to that of the pGTV, which is the most sensitive predictor among the conventionally considered factors. Local recurrence occurred in 6 of the 32 patients (19%), and the 2-year local control rate was 80%.

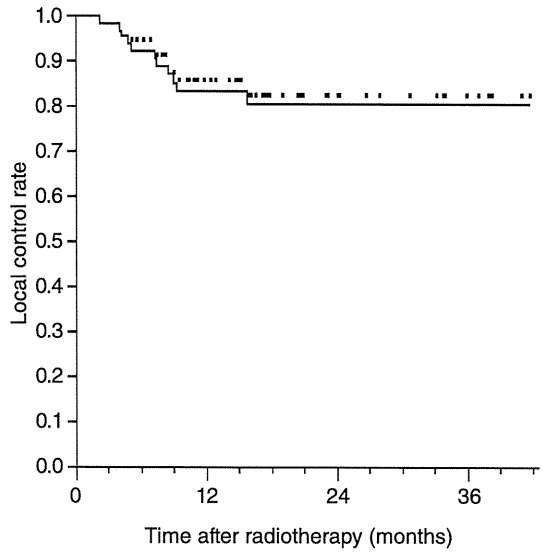

Fig. 1. Kaplan-Meier estimate of local control probabilities in all 64 patients.

Table 2. Univariate analysis of local control (n = 64)

Factors	Patients (n)	2-year Local control	*p* value
Hb value (g/dl)			
≥ 12.5	44	88%	0.0261
< 12.5	20	59%	
T-stage			
T1-2	35	94%	0.0120
T3-4	29	64%	
pGTV (cm^3)			
< 10	33	97%	0.0025
≥ 10	31	64%	
OTT (days)			
< 60	32	80%	0.7848
≥ 60	32	80%	
Maximum SUV			
< 12.0	32	93%	0.0240
≥ 12.0	32	66%	

Abbreviations: pGTV = Gross tumor volume of the primary tumor; OTT = Overall treatment time; SUV = Standardized uptake value.

Table 3. Multivariate analysis of local control (n = 64)

Factors	HR (95% CI)	*p* value
Hb value (g/dl; ≥ 12.5 vs. < 12.5)	3.34 (0.98, 11.80)	0.0530
T-stage (T1-2 vs. T3-4)	2.39 (0.57, 16.37)	0.2501
pGTV (cm^3; < 10.0 vs. ≥ 10.0)	6.12 (1.02, 118.21)	0.0470
Maximum SUV (< 12.0 vs. ≥ 12.0)	2.32 (0.54, 16.26)	0.2790

Abbreviations: HR = hazard ratio; CI = confidence interval.

These subset analysis results were similar to those of the large-group analysis, suggesting that the 32 patients included in the ADC value analysis were representative of the entire group. Also in the univariate analysis of the 32 patients, patients with a high pGTV (≥ 10 cm^3) had significantly lower rates of local control compared to those with a low pGTV (< 10 cm^3) (66% vs. 100%, $p = 0.0358$) (Fig. 2).

The mean ADC of the primary tumors in the 32 patients ranged from 0.401 × 10^{-3} mm^2/s to 1.636 × 10^{-3} mm^2/s (mean ± S.D. 0.798 ± 0.207 × 10^{-3} mm^2/s; median, 0.794 × 10^{-3} mm^2/s). The median ADC values of the primary tumors in the 6 patients with local failure was significantly higher than that of the 26 patients without local failure (0.9288 vs. 0.7628, $p = 0.0013$, two-tailed Mann-Whitney U test) (Fig. 3). Due to the lack of an established ADC cutoff value, the median value was used to establish two groups, i.e., one with a high ADC (≥ 0.79 × 10^{-3} mm^2/s) and the other with a low ADC (< 0.79 × 10^{-3} mm^2/s). In the univariate analysis, patients with a high ADC value had a significantly lower local control rate than patients with a low ADC value (100% vs. 44%, $p = 0.0019$) (Fig. 4).

Between patients with a large pGTV (≥ 10 cm^3) and those with a small pGTV (< 10 cm^3), there was no significant difference of the pretreatment ADC (0.8162 vs. 0.8229, $p = 0.1345$, two-tailed Mann-Whitney U test). A scatter plot for

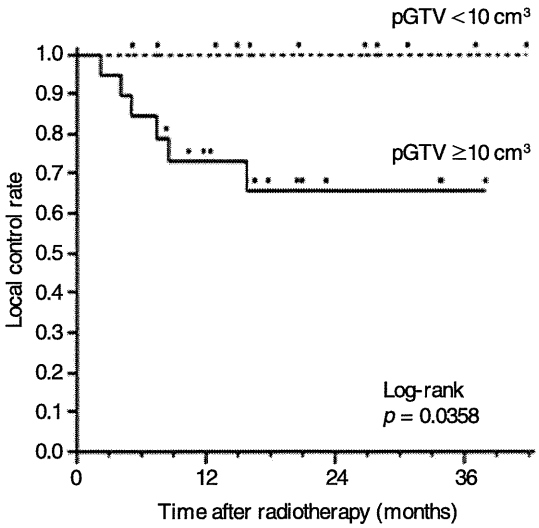

Fig. 2. Kaplan-Meier estimate of local control probabilities in 32 patients by gross tumor volume of primary tumor (pGTV) with respect to time after radiotherapy.

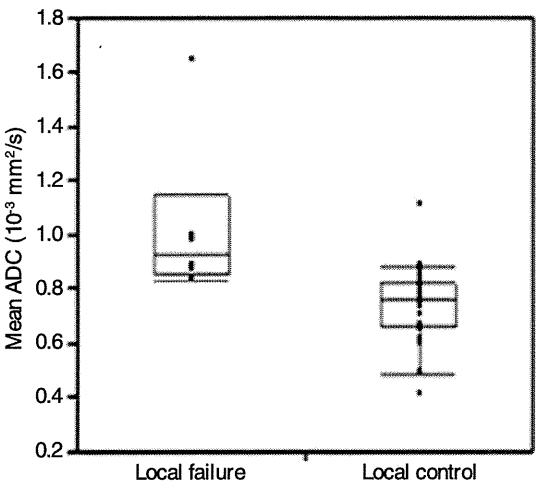

Fig. 3. Comparison of mean ADC values of primary tumors between patients with local failure and those with local control.

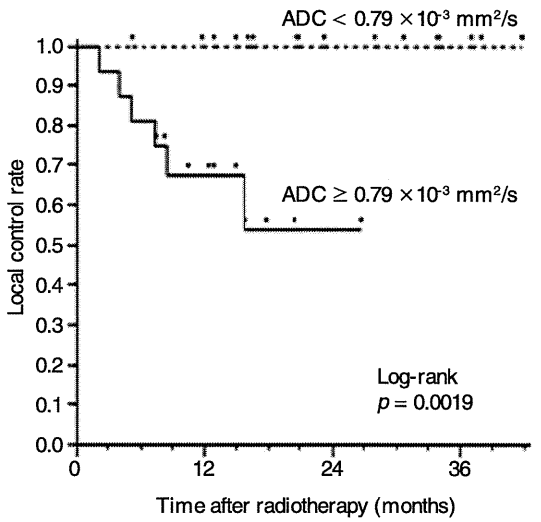

Fig. 4. Kaplan-Meier estimate of local control probabilities by ADC value with respect to time after radiotherapy.

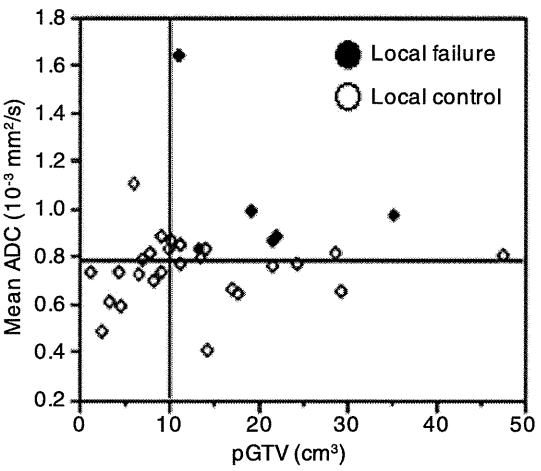

Fig. 5. A scatter plot of the incidence of local failure with respect to the relationship between the apparent diffusion coefficient (ADC) and the gross tumor volume of primary tumors (pGTV). The entire area of interest is divided into subsections (lines) at a pGTV of 10 cm^3 and at an ADC of 0.79 × 10^{-3} mm^2/s. Closed diamonds indicate local failure and open diamonds indicate local control.

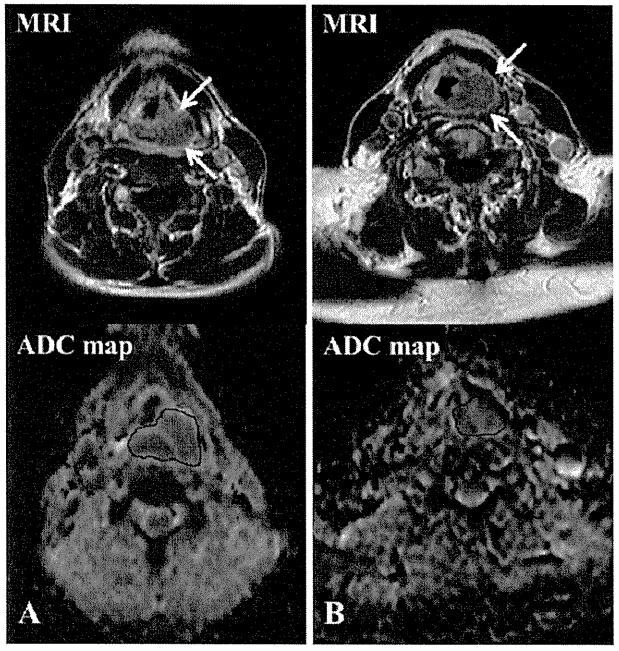

Fig. 6. MR images of the two patients with squamous cell carcinoma of the hypophaynx. Contrast-enhanced T1-weighted images (*upper images*) show primary tumors (*arrows*). ADC values were calculated using region-of-interest on ADC maps (*lower images*). (A) A 50-year-old man with T3N0M0 disease. The gross tumor volume of the primary tumor (pGTV) was 21.7 cm^3. The ADC value was 0.86×10^{-3} mm^2/s. The patient experienced local failure 7 months after the treatment. (B) A 80-year-old man with T3N2bM0 disease. The pGTV was 21.6 cm^3. The ADC value was 0.75×10^{-3} mm^2/s. The patient has local control 13 months after the treatment.

the incidence of local failure with respect to the relationship between pGTV and ADC values is shown in Fig. 5. All local failures occurred in patients with a high pGTV and a high ADC value (pGTV $\geq$ 10 cm^3 and ADC $\geq 0.79 \times 10^{-3}$ mm^2/s). The rate of local failures among patients with a high pGTV and a high ADC value was 55% (6/11), whereas no local failures occurred (0%, 0/21) among patients with a low pGTV or a low ADC value. Representative images of MRI before the treatment in two patients with a high pGTV of hypopharyngeal squamous cell carcinoma treated with definitive radiotherapy were shown in Fig. 6. One patient had a T3 primary tumor (pGTV = 21.7 cm^3) with a high ADC value (0.86×10^{-3} mm^2/s). This patient experienced local failure 7 months after the treatment (Fig. 6A). On the other hand, another patient also had a similar volume of a T3 tumor (pGTV = 21.6 cm^3) with a low ADC value (0.75×10^{-3} mm^2/s). This patient had local control 13 months after the treatment (Fig. 6B).

DISCUSSION

In this study, we investigated the usefulness of ADC as a possible factor to be considered together with other clinical factors in the prediction of local control with radiation therapy for hypopharyngeal or oropharyngeal squamous cell carcinoma. Primary tumor volume was found to be the most sensitive predictive factor of local control among the traditionally considered clinical factors. In addition, a high ADC was significantly associated with less local control in a group of patients with large primary tumors. These results suggest that a combination of large tumor volume and high ADC value is predictive of local recurrence after definitive radiotherapy.

Various factors for predicting outcome in HNSCC have been described in previous clinical studies. Pretreatment Hb level,[6–10] T-stage,[11] primary tumor volume,[12–19] and overall treatment time[40–44] have been widely reported to be factors related to local control. Recently, the potential value of FDG-PET has been demonstrated in several studies.[20–23] In the present study, only primary tumor volume was a significant factor associated with local failure in both univariate and multivariate analyses, whereas pretreatment Hb level, T-stage, and SUV_{max} were significantly associated with local failure in the univariate analysis. The 2-year local control rates for tumor volumes < 10 cm^3 compared with those $\geq$ 10 cm^3 were 97% and 64%, respectively. It remains difficult to directly compare our results with those of the preceding studies, because other studies of various tumor sub-sites have been reported in which each factor was evaluated separately. However, we collectively analyzed such predictive factors in a relatively homogenous group of patients with primary tumors in the hypopharynx and the oropharynx treated with definitive radiotherapy. The result of multivariate analysis in the present study shows that primary tumor volume is more predictive for local control than pretreatment Hb level, T-stage and SUV_{max} on FDG-PET in our patient group. Therefore, primary tumor volume is considered to be one of the most useful predictors for local control after definitive radiotherapy in patients with hypopharyngeal or oropharyngeal squamous cell carcinoma. Primary tumor volume measured by CT for HNSCC has been shown to be variable within T-stage in several studies.[45–47] In addition, it has been reported that primary tumor volume is more important to predict local control after radiotherapy compared to T-stage in the studies of nasopharyngeal carcinoma, and hypopharyngeal carcinoma.[15,48] Regarding to the FDG-PET, maximum SUV was reported to be not independent prognostic factor after radiotherapy for HNSCC by several authors.[49–51] Instead of maximum SUV, metabolic tumor volume was reported to be an adverse prognostic factor in patients with HNSCC.[51] Primary tumor volume combined with metabolic activity may be useful to predict local control after definitive radiotherapy. In the present study, pretreatment Hb level was associated with local failure with a marginal significance in the multivariate analysis. This result of an influence of pretreatment Hb level on local failure is

thought to be not contradicted to those of the previous reports.[6–10] Pretreatment Hb level should be considered to have an important role in local control of hypopharyngeal or oropharyngeal squamous cell carcinoma with definitive radiotherapy as a factor in the host.

To date, ADC values have been studied as a potential marker for predicting treatment outcome; some studies have demonstrated that a high ADC value is an adverse factor in patients who undergo chemotherapy or chemoradiotherapy. In a rectal cancer study, Dzik-Juraz *et al.* found strong negative correlations between mean pretreatment tumor ADC and changes in tumor size after chemotherapy and chemoradiation.[30] Koh *et al.* reported that a high pretreatment mean ADC of colorectal hepatic metastatic lesions was predictive of a poor response to chemotherapy.[52] Moreover, in the case of cervical squamous cell carcinomas, McVeigh *et al.* reported that the 90th percentile of ADC values was lower in responders than in non-responders to chemoradiation.[53] Although the biophysical basis for an association between a high ADC and poor outcome is not yet fully understood, there is some accounting for this relationship. A negative correlation between ADC and cell density has been observed in certain primary and secondary malignancies.[54–57] Therefore, it appears that tumors with a lower ADC are more likely to have viable proliferative cells, which exhibit a better response to chemoradiotherapy. On the other hand, the presence of necrosis, inflammatory changes, and/or submucosal fibrosis was associated with high ADC values, which correlates with an increased interstitial water content and low cell density on histologic samples.[58] This observation indicates that tumors with a high ADC exhibit a poor response to chemoradiotherapy.

In a study of HNSCC, Kim *et al.* reported that the pretreatment ADC value in the metastatic lymphnodes of complete responders was significantly lower than in those of partial responders.[36] Kato *et al.* also reported that tumors responded to neo-adjuvant therapy tended to have lower ADC values.[37] Our observation of an association between high local control and low primary-tumor ADC values is consistent with the findings of these previous studies. Moreover, in patients with large-volume primary tumors, a significant difference in local control rate was observed between those with low and high primary-tumor ADC values. Since sample size of the present study was too small to arrive at definitive conclusions, further study will be needed in order to define the associated mechanisms of action and the potential role for the ADC value in predicting local failure. However, it appears likely that a high primary-tumor ADC value is an adverse factor related to local control of large-volume tumor.

New biomarkers (e.g., human papilloma virus (HPV) infection,[59–61] epidermal growth factor receptor expression (EGFR),[62] and p53 overexpression[63]) potentially predictive of or able to detect treatment outcomes in HNSCC patients have been recently reported. In the present study, no analysis was performed to investigate the biological basis of this disease. Nevertheless, our results demonstrated a significant correlation between ADC value and local failure, which suggests the great predictive potential of the ADC value.

In conclusion, our results indicate that a combination of the tumor volume and the ADC value, calculated using diffusion-weighted MRI, can predict local failure in patients with squamous cell carcinoma of the hypopharynx or oropharynx. The inclusion of diffusion-weighted MRI during pretreatment evaluation will provide useful information for the selection of patients appropriate for definitive radiotherapy. In particular, function may be preserved with definitive radiotherapy in cases involving primary tumors with a low ADC value.

ACKNOWLEDGEMENT

The authors thank to Drs. Kazushige Atsumi, Kotaro Terashima, Kaori Asai, and Keiji Matsumoto for cooperating with treatment planning of radiotherapy. We are also very grateful to Prof. Shizuo Komune and Prof. Yoshinao Oda for their helpful discussions and other many support pertaining to this work.

REFERENCES

1. Pignon JP, *et al* (2000) Chemotherapy added to locoregional treatment for head and neck squamous-cell carcinoma: Three meta-analyses of updated individual data. MACH-NC Collaborative Group. Meta-Analysis of Chemotherapy on Head and Neck cancer. Lancet **355**: 949–955.
2. Browman GP, *et al* (2001) Choosing a concomitant chemotherapy and radiotherapy regimen for squamous cell head and neck cancer: A systemic review of the published literature with subgroup analysis. Head and Neck **23**: 579–589.
3. Forastiere AA, *et al* (2003) Concurrent chemotherapy and radiotherapy for organ preservation in advanced laryngeal cancer. N Eng J Med **349**: 2091–2098.
4. Nguyen N, *et al* (2002) Combined chemotherapy and radiation therapy for head and neck malignancies. Cancer **94**: 1131–1141.
5. Adelstein DJ, *et al* (2003) An intergroup phase III comparison of standard radiation therapy and two schedules of concurrent chemoradiotherapy in patients with unresectable squamous cell head and neck cancer. J Clin Oncol **21**: 92–98.
6. Fein DA, *et al* (1995) Pretreatment hemoglobin level influences local control and survival of T1–T2 squamous cell carcinoma of the glottis larynx. J Clin Oncol **13**: 2077–2083.
7. Lee WR, *et al* (1998) Anemia is associated with decreased survival and increased locoregional failure in patients with locally advanced head and neck cancer: A secondary analysis of RTOG 85-27. Int J Radiat Oncol Biol Phys **42**: 1069–1075.
8. Grant DG, Hussain A and Hurman D (1999) Pre-treatment anemia alters outcome in early squamous cell carcinoma of the larynx treated by radical radiotherapy. J Laringol Otol **113**: 829–833.

9. Glaser CM, *et al* (2001) Impact of hemoglobin level and use of recombinant erythropoietin on efficacy of preoperative chemoradiation therapy for sqaumous cell carcinoma of the oral cavity and oropharynx. Int J Radiat Oncol Biol Phys **50**: 705–715.
10. Bhide SA, *et al* (2009) Anemia during sequential induction chemotherapy and chemoradiation for head and neck cancer: the impact of blood transfusion on treatment outcome. Int J Radiat Oncol Biol Phys **73**: 391–398.
11. Mendenhall WM, *et al* (2003) Parameters that predict local control after definitive radiotherapy for sqaumous cell carcinoma of the head and neck. Head Neck **25**: 535–542.
12. Broek GB, *et al* (2004) Pretreament probability model for predicting outcome after intraarterial chemoradiation for advanced head and neck carcinoma. Cancer **101**: 1809–1817.
13. Pameijer FA, *et al* (1997) Can pretreatment computed tomogr aphy predict local control in T3 squamous cell carcinoma of the glottis larynx treated with definitive radiotherapy? Int J Radiat Oncol Biol Phys **37**: 1011–1021.
14. Chau DTT, *et al* (1997) Volumetric analysis of tumor extent in nasopharyngeal carcinoma and correlation with treatment outcome. Int J Radiat Oncol Biol Phys **39**: 711.
15. Pameijer FA, *et al* (1998) Evaluation of pretreatment computed tomography as a predictor of local control in T1/T2 pyriform sinus carcinoma treated with definitive radiotherapy. Head Neck **20**: 159–168.
16. Grabenbauer GG, *et al* (1998) Nodal CT density and total tumor volume as prognostic factors after radiation therapy of Stage III/IV head and neck cancer. Radiother Oncol **47**: 175–183.
17. Nathu RM, *et al* (2000) The impact of primary tumor volume on local control for oropharyngeal sqaumous cell carcinoma treated with radiotherapy. Head Neck **22**: 1–5.
18. Studer G, *et al* (2007) Volumetric staging is superior to TNM and AJCC staging in predicting outcome of head and neck cancer treated with IMRT. Acta Oncologica **46**: 386–394.
19. Chen SW, *et al* (2009) Prognostic impact of tumor volume in patients with Stage III–IVA hypopharyngeal cancer without bulky lymph nodes treated with definitive concurrent chemoradiotherapy. Head Neck **31**: 709–716.
20. Allal AS, *et al* (2002) Standardized uptake value of 2-[(18)F] fluoro-2-deoxy-D-glucose in predicting outcome in head and neck carcinoma treated by radiotherapy with or without chemotherapy. J Clin Oncol **20**: 1398–1404.
21. Allal AS, *et al* (2004) Prediction of outcome in head-and-neck cancer patients using the standardized uptake value of 2-[^{18}F]fluoro-2-deoxy-D-glucose. Int J Radiat Oncol Biol Phys **59**: 1295–1300.
22. Schwartz DL, *et al* (2004) FDG-PET prediction of head and neck squamous cell cancer outcomes. Arch Otolaryngol Head Neck Surg **130**: 1361–1367.
23. Torizuka T, *et al* (2009) Prognostic value of ^{18}F-FDG PET in patients with head and neck squamous cell cancer. AJR **192**: W156–W160.
24. Le Bihan D, *et al* (1988) Separation of diffusion and perfusion in intravoxel incoherent motion MR imaging. Radiology **168**: 497–505.
25. Thoeny HC, *et al* (2005) Diffusion-weighted MR imaging in monitoring the effect of a vascular targeting agent on rhabdomyosarcoma in rats. Radiology **234**: 756–764.
26. Theilmann RJ, *et al* (2004) Changes in water mobility measured by diffusion MRI predict response of metastatic breast cancer to chemotherapy. Neoplasia **6**: 831–837.
27. Mardor Y, *et al* (2003) Early detection of response to radiation therapy in patients with brain malignancies using conventional and high b-value diffusion-weighted magnetic resonance imaging. J Clin Oncol **21**: 1094–1100.
28. Zabaren P, Weidner S and Thoeny HC (2008) Laryngeal and hypopharyngeal carcinomas after (chemo) radiotherapy: a diagnostic dilemma. Curr Opin Otolaryngol Head Neck Surg **16**: 147–153.
29. Thoeny HC, *et al* (2005) Diffusion-weighted magnetic resonance imaging allows noninvasive in vivo monitoring of the effects of combretastatin a-4 phosphate after repeated administration. Neoplasia **7**: 779–787.
30. Dzik-Jurasz A, *et al* (2002) Diffusion MRI for prediction of response of rectal cancer to chemoradiation. Lancet **360**: 307–308.
31. Devries AF, *et al* (2003) Tumor microcirculation and diffusion predict therapy outcome for primary rectal carcinoma. Int J Radiat Oncol Biol Phys **56**: 958–965.
32. Chenevert TL, *et al* (2000) Diffusion magnetic resonance imaging: an early surrogate marker of therapeutic efficacy in brain tumors. J Natl Cancer Inst **92**: 2029–2036.
33. Galons JP, *et al* (1999) Early increase in breast tumor xenograft water mobility in response to paclitaxel therapy detected by non-invasive diffusion magnetic resonance imaging. Neoplasia **1**: 113–117.
34. Yamasaki F, *et al* (2010) Glioblastoma treated with postoperative radio-chemotherapy: Prognostic value of apparent diffusion coefficient at MR imaging. Europ J Radiol **73**: 532–537.
35. Vandecaveye V, *et al* (2008) Detection of head and neck squamous cell carcinoma with_diffusion-weighted MRI after (chemo) radiotherapy: correlation between radiologic and histopathologic findings. Int J Radiat Oncol Biol Phys **72**: 1551–1559.
36. Kim S, *et al* (2009) Diffusion-weighted magnetic resonance imaging for predicting and detecting early response to chemoradiation therapy of squamous cell carcinoma of the head and neck. Clin Cancer Res **15**: 986–994.
37. Kato H, *et al* (2009) Head and neck squamous cell carcinoma: usefulness of diffusion-weighted MR imaging in the prediction of a neoajuvant therapeutic effect. Eur Radiol **19**: 103–109.
38. Hatakenaka M, *et al* (2010) Pretreatment apparent diffusion coefficient of the primary lesion correlates with local failure in head and neck cancer treated with chemoradiotherapy or radiotherapy. Int J Radiation Oncology Biol Phys (in press).
39. King AD, *et al* (2010) Squamous cell carcinoma of the head and neck: diffusion-weighted MR imaging for prediction and monitoring of treatment response. Eur Radiol (published online).
40. Bese NS, *et al* (2007) Effects of prolongeation of overall treatment time due to unplanned interruptions during radiotherapy of different tumor sites and practical methods for compensation. Int J Radiation Oncology Biol Phys **68**: 654–661.

41. Groome PA, *et al* (2006) Compromised local control due to treatment interruptions and late treatment breaks in early glottis cancer: Population-based outcomes study supporting need for intensified schedules. Int J Radiat Oncol Biol Phys **64**: 1002–1012.
42. Fowler JF and Lindstrom MJ (1992) Loss of local control with prolongation in radiotherapy. Int J Radiat Oncol Biol Phys **23**: 457–467.
43. Robertson AG, *et al* (1998) Effect of gap length and position on results of treatment of cancer of the larynx in Scotland by radiotherapy: A linear quadratic analysis. Radiother Oncol **48**: 165–173.
44. McClosley SA, *et al* (2009) Radiation treatment interruptions greater than one week and low hemoglobin levels (12g/dL) are predictors of local regional failure after definitive concurrent chemotherapy and internsity-modulated radiation therapy for squamous cell carcinoma of the head and neck. Am J Clin Oncol **32**: 587–591.
45. Johnson CR, *et al* (1995) The influence of quantitative tumor volume measurements on local control in advanced head and neck cancer using concomitant boost accelerated superfractionated irradiation. Int J Radiat Oncol Biol Phys **32**: 635–641.
46. Pameijer FA, *et al* (1997) Variability of tumor volumes in T3-staged head and neck tumors. Head Neck **19**: 6–13.
47. Lee WR, *et al* (1993) Can pretreatment computed tomography findings predict local control in T3 squamous cell carcinoma of the glottic larynx treated with radiotherapy alone? Int J Radiat Oncol Biol Phys **25**: 683–687.
48. Chen MK, *et al* (2010) Better prediction of prognosis for patients with nasophayngeal carcinoma using primary tumor volume. Cancer **10**: 2160–2166.
49. Greven KM, *et al* (2001) Serial positron emission tomography scans following radiation therapy patients with head and neck cancer. Head Neck **23**: 942–946.
50. Vernon MR, *et al* (2008) Clinical outcomes of patients receiving integrated PET/CT-guided radiotherapy for head and neck carcinoma. Int J Radiat Oncol Biol Phys **70**: 678–684.
51. La TH, *et al* (2009) Metabolic tumor volume predicts for recurrence and death in head-and-neck cancer. Int J Radiat Oncol Biol Phys **74**: 1335–1341.
52. Koh DM, *et al* (2007) Predicting response of colorectal hepatic metastasis: Value of pretreatment apparent diffusion coefficients. AJR **188**: 1001–1008.
53. McVeigh PZ, *et al* (2008) Diffusion-weighted MRI in cervical cancer. Eur Radiol **18**: 1058–1064.
54. Humphries PD, *et al* (2007) Tumors in pediatric patients at diffusion-weighted MR imaging: apparent diffusion coefficient and tumor cellularity. Radiology **245**: 848–854.
55. Squillaci E, *et al* (2004) Correlation of diffusion-weighted MR imaging with cellularity of renal tumors. Anticancer Res **24**: 4175–4179.
56. Manenti G, *et al* (2008) Malignant renal neoplasms: correlation between ADC values and cellularity in diffusion weighted magnetic resonance imaging at 3 T. Radiol Med **113**: 199–213.
57. Sugahara T, *et al* (1999) Usefulness of diffusion-weighted MRI with echo-planar technique in the evaluation of cellularity in gliomas. J Magn Reson Imaging **9**: 53–60.
58. Mukherji SK, *et al* (1994) Radiologic appearance of the irradiated larynx. Part I. Expected changes. Radiology **193**: 141–148.
59. Fakhry C, *et al* (2008) Improved survival of patients with human papillomavirus-positive head and neck squamous cell carcinoma in a prospective clinical trial. J Natl Cancer Inst **100**: 261–269.
60. Ragin CC and Taiolo E (2007) Survival of squamous cell carcinoma of the head and neck in relation to human papillomavirus infection: Review and meta-analysis. Int J Cancer **121**: 1813–1820.
61. Nichols AC, *et al* (2009) HPV-16 infection predicts treatment outcome in oropharyngeal squamous cell carcinoma. Otolaryngol Head Neck Surg **140**: 228–234.
62. Grandis JR, *et al* (1998) Levels of TGF-α and EGFR protein in head and neck squamous cell carcinoma and patient survival. J Natl Cancer Inst **90**: 824–832.
63. Narayana A, *et al* (2000) P53 overexpression is associated with bulky tumor and poor local control in T1 glottic cancer. Int J Radiat Oncol Biol Phys **46**: 21–26.

Received on December 10, 2010
Accepted on February 24, 2011
J-STAGE Advance Publication Date: June 2, 2011

Japanese Structure Survey of Radiation Oncology in 2007 with Special Reference to Designated Cancer Care Hospitals

Hodaka Numasaki[1], Hitoshi Shibuya[2], Masamichi Nishio[3], Hiroshi Ikeda[4], Kenji Sekiguchi[5], Norihiko Kamikonya[6], Masahiko Koizumi[7], Masao Tago[8], Yutaka Ando[9], Nobuhiro Tsukamoto[10], Atsuro Terahara[11], Katsumasa Nakamura[12], Michihide Mitsumori[13], Tetsuo Nishimura[14], Masato Hareyama[15], Teruki Teshima[1] and Japanese Society of Therapeutic Radiology and Oncology Database Committee

Background and Purpose: The structure of radiation oncology in designated cancer care hospitals in Japan was investigated in terms of equipment, personnel, patient load, and geographic distribution. The effect of changes in the health care policy in Japan on radiotherapy structure was also examined.

Material and Methods: The Japanese Society of Therapeutic Radiology and Oncology surveyed the national structure of radiation oncology in 2007. The structures of 349 designated cancer care hospitals and 372 other radiotherapy facilities were compared.

Results: Respective findings for equipment and personnel at designated cancer care hospitals and other facilities included the following: linear accelerators/facility: 1.3 and 1.0; annual patients/linear accelerator: 296.5 and 175.0; and annual patient load/full-time equivalent radiation oncologist was 237.0 and 273.3, respectively. Geographically, the number of designated cancer care hospitals was associated with population size.

Conclusions: The structure of radiation oncology in Japan in terms of equipment, especially for designated cancer care hospitals, was as mature as that in European countries and the United States, even though the medical costs in relation to GDP in Japan are lower. There is still a shortage of manpower. The survey data proved to be important to fully understand the radiation oncology medical care system in Japan.

Key Words: Structure survey · Radiotherapy facility · Radiotherapy personnel · Radiotherapy equipment · Caseload · Medical care system

Strahlenther Onkol 2011;187:167–74
DOI 10.1007/s00066-010-2205-3

Japanische Strukturerhebung zur Radioonkologie im Jahr 2007 unter besonderer Berücksichtigung von auf Krebsbehandlung spezialisierten Krankenhäusern

Hintergrund und Ziel: Es wurde die Struktur der Radioonkologie in auf Krebsbehandlung spezialisierten Krankenhäusern in Japan untersucht, und zwar im Hinblick auf Ausrüstung, Personal, Patientenaufkommen und geografische Verteilung. Ebenso

[1]Department of Medical Physics and Engineering, Osaka University Graduate School of Medicine, Suita, Osaka, Japan,
[2]Department of Radiology, Tokyo Medical and Dental University, Tokyo, Japan,
[3]Department of Radiology, National Hospital Organization Hokkaido Cancer Center, Sapporo, Hokkaido, Japan,
[4]Department of Radiology, Sakai Municipal Hospital, Sakai, Osaka, Japan,
[5]Department of Radiation Oncology, St. Luke's International Hospital, Tokyo, Japan,
[6]Department of Radiology, Hyogo College of Medicine, Nishinomiya, Hyogo, Japan,
[7]Oncology Center, Osaka University Hospital, Suita, Osaka, Japan,
[8]Department of Radiology, Toho University Omori Medical Center, Tokyo, Japan,
[9]Department of Medical Informatics, Heavy Ion Medical Center, National Institute of Radiological Sciences, Chiba, Japan,
[10]Department of Radiation Oncology, Saitama Medical University International Medical Center, Saitama, Japan,
[11]Department of Radiology, University of Tokyo Hospital, Tokyo, Japan,
[12]Department of Radiology, Kyushu University Hospital at Beppu, Oita, Japan,
[13]Department of Radiation Oncology and Image-applied Therapy, Graduate School of Medicine Kyoto University, Kyoto, Japan,
[14]Division of Radiation Oncology, Shizuoka Cancer Center, Shizuoka, Japan,
[15]Department of Radiology, Sapporo Medical University, Hokkaido, Japan.

Received: August 13, 2010; accepted: October 7, 2010
Published Online: February 21, 2011