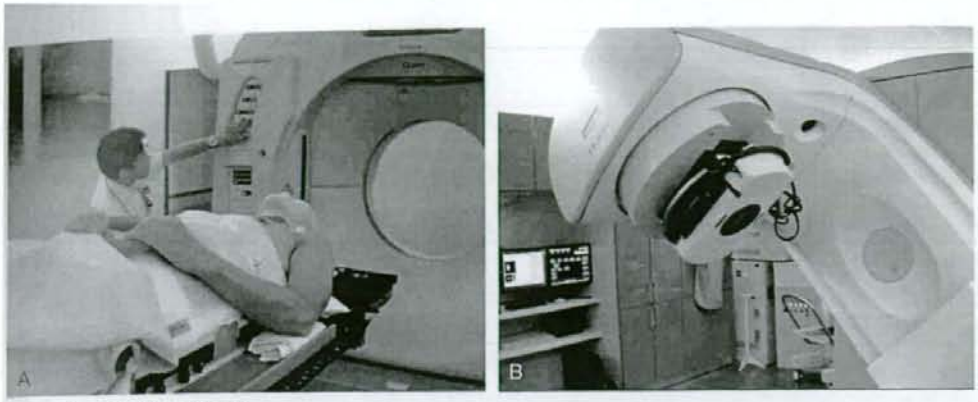

図1　治療装置と患者の固定
A　患者の体幹部と頭部を固定。この状態でCTシミュレーションを行う。B　マイクロマルチリーフコリメータをリニアックに装着する。

幅となるブレインラボ社製マイクロマルチリーフコリメータ（micro-multi leaf collimator：m-MLC）をリニアックヘッドに外付けして，照射野を形成している。体幹部定位照射においては，体位の固定は吸引式バッグと体幹部のシェルを用いて固定を行っている（図1）。今回，脊椎病変へIMRTを適応するにあたり，頭蓋内病変への治療経験をいかし，m-MLCを用いた照射野形成を行い，体幹部病変への治療経験を生かして体位の保持・固定，アイソセンターの確認を行うという方法で治療を施行することとした。強度変調にはstep and shoot法を使用した。治療計画装置はブレインラボ社製Brain SCANであり，計算アルゴリズムはpencil beam法で不均質補正が行われた。

治療の実施が決定された後，まずシミュレーションを行う。患者の体位の保持と，固定を行った後，CT撮影を行う。疼痛のため同一体位が保持できない場合，本治療は適用不可能となるため，事前に十分なペインコントロールを行っておく。

治療計画は，磁気共鳴画像を参考にしながら，シミュレーション時に撮影したCT画像をもとに行う。その際，ウインドウとレベルを調整して，軟部条件と骨条件との両方を観察する。その上で明らかな溶骨性変化がみられる領域を肉眼的腫瘍体積（gross tumor volume：GTV），CTの骨条件で変化がみられる領域を加えたものを臨床標的体積（clinical target volume：CTV），計画標的体積（planning target volume：PTV）はCTVと同一とした。一方，リスク臓器（organs at risks：OAR）として，脊髄と食道，咽頭，口腔，頸動脈等を設定した。またPTVにはOARと重複する体積は含めなかった（脊髄については，PTVに脊柱管を含めないようにした）。

ビームは，固定多門照射法で5門以上を原則とした。ビームの角度については，リニアックに外付けされたm-MLCと，治療寝台や固定具との干渉する角度を避けて設定した。この干渉は，腫瘍の位置や，アイソセンターの深さ，体型などによって異なるため，シミュレーション時，症例毎にあらかじめ設定可能な角度を検討した。

OARの線量制限としては，脊髄については1回あたり2 Gyが処方される体積を可能なかぎり最小化すること，その他については1回あたり3 Gyが処方される体積を可能なかぎり最小化することを目標とした。PTVの90%体積（D90）を，90%等線量曲線（5.4 Gy/回）でカバーすることを目標としたが，OARに対する線量制限を優先させた。分割回数は，原則5回としたが，症例により増減を行った。

治療計画が立案され，承認された後に治療計画の検証作業に入る。IMRTの線量分布は非常に複雑になり，PTVとOARが近接していることが多いため，検証作業を行い計画通りの線量分布が実現できるのか，確認する必要がある。IMRTを実施する上で，放射線治療装置（リニアック，マルチリーフコ

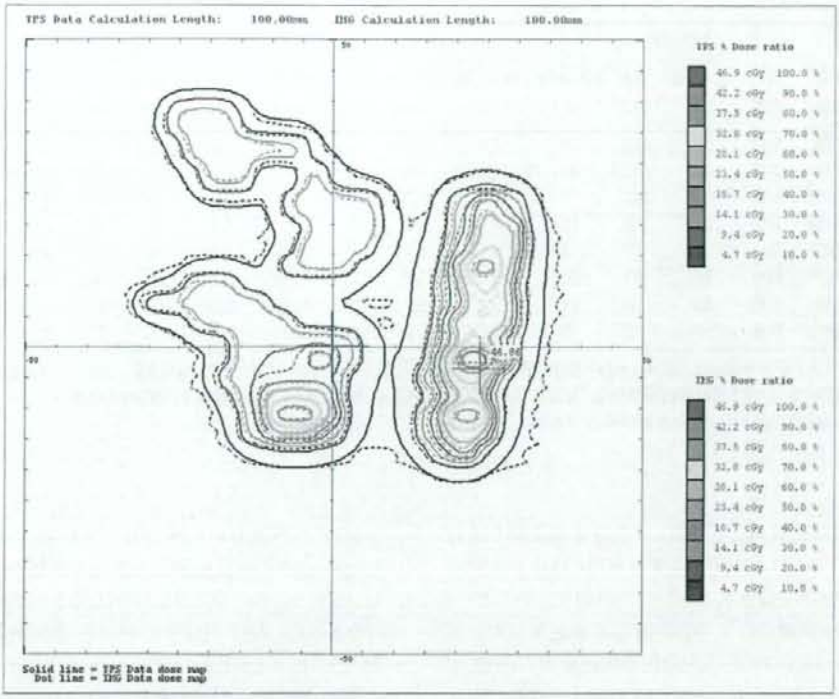

図2　解析ソフトによる検証
ファントムに照射を行って得たフルエンスマップ（破線）と，治療計画装置が出力したフルエンスマップ（実線）との誤差を検証する。

リメータ等）の日常的な精度管理の実施は必須であり，IMRT 実施の大前提であるが本稿では省略する。以下，当院での検証方法の実際について述べる。

検証の方法は，各種勧告に準拠した形で行うことを基本原則としている[4,5]。IMRT 検証用に患者用計画を IMRT ファントムに写しこみ，検証に必要な線量分布の作成，ポイント線量算出を行う。IMRT の検証作業は大きく分けると，1）各ポートの線量評価，2）全ポート合算の線量評価の 2 つに分けられる。各ポートの線量評価では，主にフルエンスマップの評価を行う。各ポートのガントリ角度を 0 度にし，測定深の厚さの板ファントムをフィルム上に置き，ポートごとにフィルムに照射する。当院における m-MLC の動作は step and shoot 方式のため，各ポートの照射野は複数の形状の異なるセグメントと呼ばれるサブフィールドからなり，セグメントを重ね合わせることで強度変調されたモザイク状の線量分布（フルエンスマップ）が作成される。フィルムから得られたフルエンスマップと治療計画装置から得られたフルエンスマップとを解析ソフトを用いて解析し，相対線量の評価を行う。各ポートの最大線量に対して 50 ～ 100%の線量分布の error ratio（該当領域内の平均線量の差）がおおむね± 3%以内，30%以上の領域でおおむね ±5%以内であることを当院の基準としている（図 2）。m-MLC が計画通りの動作をしていなければ当然良い結果は得られない。すなわち，各ポートのフルエンスマップの評価は主に m-MLC の動作確認・位置精度確認と言える。本来ならば各ポート毎に，電離箱を用いた絶対線量評価も合わせて行うべきであるが，BrainSCAN ではポートごとの計画が作成できないので省略している。

次に全ポート照射の線量評価を行う。フィルムによ

表1　各症例の詳細

症例番号	原発臓器	照射部位	初回照射 処方線量(Gy)	初回照射 分割回数	照射間隔(月)	IMRT D95/回(Gy)	IMRT D90/回(Gy)	IMRT 照射回数	脊髄(1回あたり) 総線量(Gy)	脊髄(1回あたり) 最大線量(Gy)	脊髄(1回あたり) V2Gy(cc)	疼痛改善	麻痺 前→後	観察期間(月)
1	乳腺	胸椎	39	13	74	4.6	4.9	5	23	2.5	0.2	あり	なし→なし	12
2	乳腺	胸椎	40	20	40	4.4	4.9	3	20	2.6	0.4	あり	あり→なし	10**
3	甲状腺	胸椎	39	13	3	4.8	5.0	5	24	2.3	0.1	あり	あり→なし	12
4	甲状腺	胸椎	30	10	18	4.4	4.5	5	22	2.4	0.3	あり	なし→あり*	6
5	下咽頭	頸椎	39	13	7	4.5	4.7	5	22.5	1.9	0	あり	なし→なし	2**
6	舌	胸椎	40	20	24	5.4	5.7	4	21.6	2.2	0.3	あり	なし→あり	3**
7	胆管	胸椎	30	10	14	5.0	5.2	5	25	2.2	0.1	あり	なし→なし	11
8	肺	胸椎	40	20	6	4.7	4.9	5	23.5	2.8	0.7	あり	なし→あり	10**

注）IMRT：intensity modulated radiotherapy（強度変調放射線治療），D95：PTVの95%体積が照射される線量，D90：PTVの90%体積が照射される線量，V2Gy：2 Gy以上照射される脊髄体積，総線量：D95線量で表示。症例2は8 Gy/4回の後方1門照射との合算。
*：IMRT施行部位は制御されたが，他椎体の悪化による麻痺，**：死亡。

る相対線量評価と電離箱による絶対線量評価を行う。フィルムによる相対線量評価は，IMRTファントムにフィルムをはさみ，全ポートの照射を行い各ポートの評価と同様に行う。電離箱による絶対線量の評価では，IMRTファントム内の任意の測定ポイントとしてアイソセンターを含めPTV内で2～3点，治療計画装置上でそれぞれに電離箱のROI（region of interest）を設定し，平均線量を算出しておく。測定はFarmer型電離箱を用い，治療計画で設定したポイントに電離箱をセットし，全ポートの照射を行う。治療計画装置で算出した線量と比較し，おおむね± 3%以内の差であることを当院の基準としている。以上の検証結果が，放射線治療担当医へ報告され，最終的に臨床適応することの妥当性が判断される。

❹ 結　果

各症例の詳細を表1に示す。初回の放射線治療は，30 Gy/10回，39 Gy/13回，あるいは40 Gy/20回で施行されているが，他院で初回治療を受けた症例については，線量分布図など照射の詳細が不明な部分があり，脊髄の既照射線量については10%内外の誤差はあるものと推測される。初回の照射から，本治療までの間隔は，3～74か月（中央値16か月）であり，1例を除き，6か月以上経過後に再照射を施行した。

PTVへの処方線量はD90で5.4 Gy/回を目標としたが，OARの線量制限を優先したため，実際には4.5～5.7 Gy/回となり，1例を除き5.4Gyには達しなかった。D95（PTVの95%体積が照射される線量）は，4.4～5.4 Gy/回となった。OARである脊髄への線量は，2 Gyを超えるvolume（V2 Gy）で評価した。結果はV2 Gyで0～0.7ccであり，全例で1cc未満とした。全例において，治療計画が検証されいずれも臨床適応するに妥当であると判断され，計画された照射を完遂した。シミュレーション実施から，治療開始までの期間はおおむね2週間であった。

疼痛は全例で，鎮痛剤の増量無い条件下で早期に緩和された。治療開始時点で，2例でFrankel分類Cの麻痺[6]（筋力は残存するも歩行できない）が出現していたが，治療後麻痺が改善し，歩行可能となった。照射回数は，8例中6例で5回照射とした。1例では，PTVへの処方線量が目標以上となったため（D90 = 5.7 Gy/回，D95 = 5.4 Gy/回），照射回数は4回とした。もう1例は，図3に示す乳癌胸椎転移の50歳代の女性で，当初麻痺症状はなかったものの治療計画作成・検証期間中に，脊髄圧迫による下肢麻痺症状が出現した。このため直ちにステロイド治療と通常照射法（後方1門照射）による照射を開始した。8 Gy/4回の緊急照射後，IMRTの検証が終了し治療可能となったため，引き続きIMRTを3

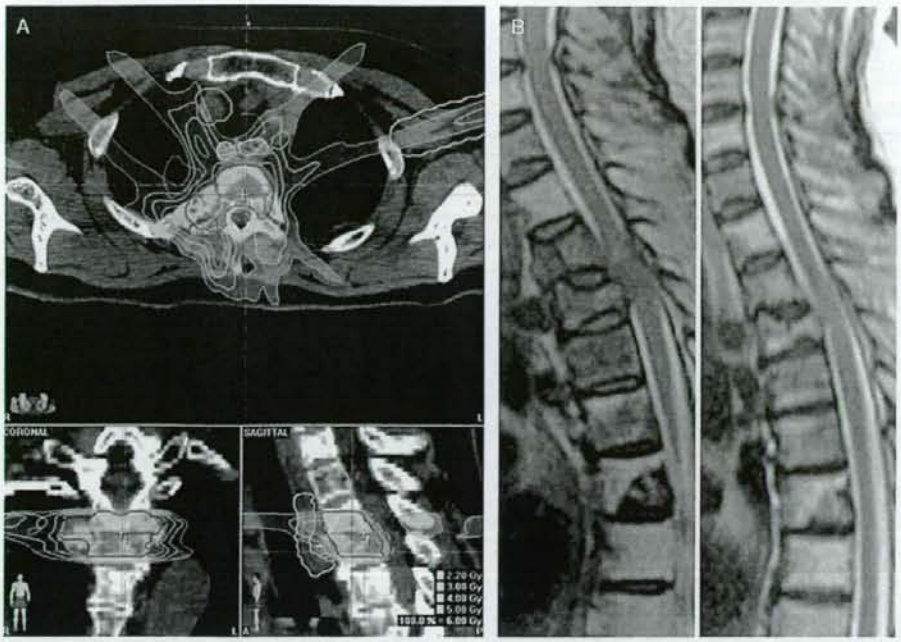

図3　乳癌胸椎転移例
A　IMRTの線量分布　B　MRI（左：治療前，右：治療後7か月）

回追加した。徐々に麻痺は改善し歩行可能となった。治療後7か月時点のMRIでは，治療前に認めた腫瘍による脊髄圧迫が解除されていた。治療後10か月で原病死する直前まで歩行が可能であった。

2008年8月時点で，4例が原病死し，3例が担癌生存中，1例が転院によって追跡終了となっている。観察期間中において，放射線脊髄症を含め晩期有害事象は発生しなかった。

しかし2例では，照射部位の腫瘍再増悪がみられそれぞれ2か月後と3か月後に脊髄横断麻痺となった。1例では，照射部位は制御されたものの他椎体転移による増悪で脊髄横断麻痺となった。

❺ 考　察

放射線脊髄症は回避すべき晩期毒性として，通常は耐容線量未満の線量となるように治療計画がされる。このため従来，照射部位の再増悪に対しては，手術など侵襲的な処置が可能な一部の例外を除いて，よい方法がなかった。予後が限られた症例においては，晩期有害事象である脊髄症について実際には問題となることがないために，状況に応じて適切な線量にて再照射が行われている。しかし，個別の症例の予後を予測するのは困難であること，全身療法の進歩にて生存期間の延長がみられてきており，再照射による晩期有害事象が発生する危険は逆に増大してきているともいえる。特に脊髄症については一度発症すると根本的な治療がないため，初回治療では必ず耐容線量以下となるような治療が行われるが，再照射の場合の許容線量について明確な基準はない。

脊髄耐容線量は，Emamiらの報告[7]によると，5年間に5%の確率で脊髄症を発症する線量は47～50 Gyとされている。これは通常分割照射（1日1回1.8～2.0 Gy）による場合であるが，しばしば骨転移の照射では1回3Gy以上の線量が処方されるこ

とが多く，これをこのまま適応することはできない。異なる線量分割による治療を比較するため，Linear Quadratic model（LQモデル）が提唱されている[8]。急性反応臓器に対してはα/β= 10 Gy，晩期反応臓器に対してはα/β= 2 ～ 3Gyを用いることが多い。脊髄症は晩期障害であり，α/β= 2 Gyとすると日本で標準とされている30 Gy/10回の照射は，1回2 Gy換算にて，37.5 Gyに相当する。

再照射の安全性について検討したNiederらの報告[9]によると，初回照射と再照射との間隔が6か月以上あり，それぞれの生物学的等価線量（biological effective dose：BED）が98 Gy_2以下である場合には脊髄症発症のリスクは低く，かつ累積BEDが135.5 Gy_2以下では，脊髄症の発症はなかったとされる。これを日本の実臨床にあてはめて考えると，30 Gy/10回の照射後，30 Gy/15回で再照射を行った場合，BED（α/β= 2 Gy）の合計は135 Gy_2となる。2002 ～ 2006年に脊椎再照射を行った15例18部位において自験例を検討したところ，初回治療と再照射との合計BEDは中央値139.5 Gy_2であり，放射線脊髄症は発生しなかった。しかし，再照射後の生存期間の中央値は155日と必ずしも長期間の観察によるものではない点や，再照射にもかかわらず腫瘍進展による脊髄横断症状が5例に発生するなどの点が課題としてあげられた。ある程度の予後が期待される症例では，再照射による障害発生の危険があり，放射線感受性が高くない腫瘍では，再照射後の再増悪が問題となる。こうした問題を解決するためには，新たな照射方法を開発する必要があるが，IMRTによる再照射は計画どおりに治療が行われれば脊髄線量を軽減させることができるはずである。

IMRTによる再照射を実施する上で，解決すべき点として，1）臨床的に許容できる治療計画が作成できるか，2）治療計画の検証作業が可能か，3）必要十分な体位の固定が可能か，4）アイソセンターの固定精度が確保できるか，などが挙げられる。我々は，治療計画を作成するにあたり，脊髄に1回2 Gy以上が照射される線量を極力最小化するように努めた。これは，初回照射において通常分割照射換算で37.5 ～ 40 Gy相当が照射されていることから，5回分割照射としてIMRTを施行した場合の脊髄照射線量（1回2 Gyとして計10 Gy/5回）とを単純に加算した場合に，累積線量が通常分割照射換算で50 Gy相当となることを想定したからである。つまり連続で照射した場合の脊髄耐容線量に相当し，少なくとも放射線脊髄症の発症リスクが5%以上にはならない線量である。椎体前方の咽頭，食道についても高線量が照射されないような治療計画を心がけた結果，現在まで晩期毒性は観察されていない。

治療計画の検証作業については，ほぼ滞りなく実施することができ，計画と測定値との誤差も，臨床使用するにあたり許容範囲にあると判断された。ただし，リニアック室の当日の治療業務が終了した後に測定業務を行わざるを得ないため，治療現場に負荷がかかることも事実である。体位の固定については，体幹部定位照射と同様の固定を行うことで，再現性をもって照射中の体動を軽減させることが可能になった。毎回，アイソセンターを確認するために治療寝台同一CTを使用した。固定具や皮膚マークによって設定された仮のアイソセンター位置からの修正が平均2mm程度必要であった。椎体は動きがない臓器のため，CTを使用することでアイソセンターをほぼ計画どおりの位置に設定することが可能であった。

病変部位での疼痛は全例で緩和された。さらに麻痺症状を呈していた2例も，歩行可能にまで回復するなど（Frankel分類C → D）効果が得られた症例がある一方で，局所の腫瘍増大によって麻痺となった症例が2例，他部位で腫瘍が増大し麻痺となった症例が1例あった。PTVへの処方線量は，OARである脊髄線量によって制約を受け1回あたりおおむねD90で4.5 ～ 5.7 Gy，D95で4.4 ～ 5.4 Gyが処方された。しかしながら，脳転移症例に対する5回分割照射による定位放射線治療の報告では[10]，1回あたり6 ～ 7 Gyが処方され，定位手術的照射と同等の効果であると述べている。またWrightら[11]は，脊椎病変への再照射をIMRTで施行した成績を報告している。初期症例では20 Gy/5回の照射が施行され，局所制御率は60%であったが，その後30 Gy/5回に線量増加させている。これらと比べると，今回の検討症例は十分な線量であるとはいえない。

局所で増悪した2例ではいずれも，腫瘍が脊柱管内に進展している部分が増悪していた。本治療では，脊髄線量を最小化するために，PTVと脊柱管が重複した体積についてはPTVに含めなかった。IMRT

において，腫瘍部分である椎体・椎弓の線量とリスク臓器である脊髄との境界部分は線量勾配が存在し，当然十分な線量が処方されない体積となる。この領域に存在する腫瘍細胞には不十分な照射となったために，増悪したものと考えられた。こうした症例において，手術で腫瘍の減量が可能であれば望ましいが[12]，実際には全身状態や多発骨転移の存在などによって困難なことが多い。こうした症例に対しては，麻痺のリスク，期待される予後と腫瘍制御の可能性などを総合的に勘案し，脊髄線量制限を緩和する必要があると考えられた。

既照射脊椎転移へのIMRTによる再照射は，実行可能であり初期効果はおおむね良好であった。今後の課題として，さらなる経過観察によって晩期毒性の発生がないかどうかを確認していくこと，一定の安全性が確認された後には，局所制御を得るために至適な線量を検討していく必要があると考えている。

〔本論文の要旨は，第67回日本医学放射線学会総会（2008年4月，横浜）にて発表した。なお，本治療を施行するにあたり，多忙な業務にもかかわらず治療計画の検証作業ならびに治療の実施に協力いただいた当院放射線治療科診療放射線技師（半村勝浩，伊藤哲，郷昌明，深井智章，古宮泰三，松谷直樹，明保桂太，金澤謙太，富田哲也，後藤弘徳・順不同，敬称略）に深謝いたします。〕

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Summary

Re-irradiation for spine metastasis using intensity modulated radiotherapy

We present our initial experience of 8 patients with re-irradiation for recurrent spine metastases using intensity modulated radiotherapy (IMRT).

We evaluated dose volume parameters and clinical outcomes. Median Dose to 95% volume of plannning target volume was 23 Gy in 5 fractions. Maximum spinal cord dose was median 2.3 Gy per fraction. Pain was relieved in all patients. Local recurrence was occurred in 2 patients. No radiation myelitis has been identified.

In conclusions, re-irradiation using IMRT is feasible and further follow-up is needed.

Hideyuki Harada et al
Division of Radiation Oncology
Shizuoka Cancer Center

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CLINICAL INVESTIGATION **Esophagus**

CONCURRENT CHEMORADIOTHERAPY FOR ESOPHAGEAL CANCER WITH MALIGNANT FISTULA

RYUTA KOIKE, M.D., YASUMASA NISHIMURA, M.D., PH.D., KIYOSHI NAKAMATSU, M.D., PH.D., SHUICHI KANAMORI, M.D., PH.D., AND TORU SHIBATA, M.D., PH.D.

Department of Radiation Oncology, Kinki University School of Medicine, Osaka, Japan

Background: We reviewed clinical results of chemoradiotherapy (CRT) in the treatment of patients with advanced esophageal cancer with fistulae that developed before or during CRT.
Methods and Materials: The study group included 16 patients with fistulous esophageal cancer treated by means of CRT between 1999 and 2006. Nine patients had fistulae before CRT, whereas 7 developed fistulae during CRT. The group included 12 men and four women with a median age of 55 years (range, 37–77 years). There were 9 patients with Stage III disease and 7 with Stage IV disease. All tumors were squamous cell carcinomas. Two courses of concurrent chemotherapy were combined with radiation therapy; 60 Gy/30 fractions/7 weeks (1-week split). For 15 patients, low-dose protracted chemotherapy with 5-fluorouracil (250–300 mg/m^2 × 14 days) and cisplatin (7 mg/m^2 × 10 days) was administered, whereas full-dose cisplatin and 5-fluorouracil were administered to the remaining patient.
Results: The planned dose of 60 Gy was delivered to 11 patients (69%), whereas radiation therapy was terminated early in 5 patients (40–58 Gy) because of acute toxicities, including two treatment-related deaths. Disappearance of fistulae was noted during or after CRT in 7 patients (44%). All three esophagomediastinal fistulae were closed, but only four of 13 esophagorespiratory fistulae were closed by CRT. For patients with Stage III, 1- and 2-year survival rates were 33% and 22%, respectively. Median survival time was 8.5 months.
Conclusion: Despite significant toxicity, concurrent CRT appears effective at closing esophageal malignant fistulae. © **2008 Elsevier Inc.**

Esophageal cancer, Chemoradiation, Esophageal fistulae.

INTRODUCTION

In patients with esophageal or pulmonary malignancies, formation of an esophagorespiratory (ER) fistula, including esophagotracheal and esophagobronchial (EB) fistulae, is a serious complication with a dismal prognosis. If a malignant ER fistula is left untreated, the patient soon develops pulmonary infection and sepsis with a median survival time (MST) from diagnosis of 1 to 6 weeks (1, 2). The presence of a malignant esophageal fistula historically was considered a relative contraindication to radiation therapy (RT), and RT alone rarely was used for the treatment of a patient with a malignant esophageal fistula. However, in one large retrospective analysis, RT significantly improved the survival rate compared with supportive care only for patients with malignant ER fistulae (2). In addition, transient closure of fistulae and occasional long-term survivors with a reduced fraction size and protracted RT were reported (3, 4).

For patients with locally advanced esophageal cancer, a significant improvement in local control and overall survival was achieved with concurrent chemoradiotherapy (CRT) compared with RT alone (5, 6). CRT was also effective for patients with unresectable T4 esophageal cancer. Ohtsu *et al.* (7) reported a 3-year survival rate of 14% for patients with T4 esophageal cancer treated with definitive CRT of 60 Gy. Our previous study of concurrent CRT with the protracted infusion of cisplatin and 5-fluorouracil (5-FU) for patients with T4 esophageal cancer with or without a fistula showed a 2-year survival rate of 27% for patients with Stage III disease (8). In that study, two of five T4-fistulous tumors showed disappearance of the fistula, although worsening or development of an esophageal fistula was noted in 5 of 25 patients. Muto

Reprint requests to: Yasumasa Nishimura, M.D., Ph.D., Department of Radiation Oncology, Kinki University School of Medicine, 377-2, Ohno-Higashi, Osaka-Sayama, Osaka 589-8511, Japan. Tel: (+81) 72-366-0221 (ext. 3130); Fax: (+81) 72-368-2388; E-mail: ynishi@med.kindai.ac.jp

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et al. (9) reported promising results of concurrent CRT for patients with malignant ER or esophagomediastinal (EM) fistulae. Closure of fistulae after CRT was observed in 17 of 24 patients (71%) with an MST from diagnosis of the fistulae of 198 days. They concluded that the presence of malignant fistulae did not contraindicate CRT to give the best chance for survival and palliation of dysphagia.

Based on our own experience and reports of the promising effects of CRT on malignant esophageal fistulae, we treated patients with advanced esophageal cancer with ER or EM fistulae aggressively by using concurrent CRT. Here, we review clinical results of CRT for the treatment of patients with esophageal cancer with malignant fistulae that developed before or during treatment.

METHODS AND MATERIALS

Patient population

From January 1999 to May 2006, a total of 16 patients with advanced esophageal cancer with malignant fistulae were treated by using CRT at Kinki University Hospital (Osaka, Japan). Seven patients were included in a previous report of CRT for patients with T4 esophageal cancer with or without fistulae (8). Of 16 patients, 9 had fistulae at presentation (Group A) and 7 developed fistulae during CRT (Group B). There were 12 men and 4 women with a median age of 55 years (range, 37–77 years). Thirteen patients had ER fistulae and the remaining 3 patients had EM fistulae. According to the 2002 International Union Against Cancer tumor, node, metastasis (TNM) classification,all patients had T4N1 disease, whereas 9 had Stage III, 3 had Stage IVa, and 4 had Stage IV disease. All tumors were squamous cell carcinomas in terms of histologic characteristics. Performance status (PS) for most patients was PS1 or PS2. Sites of the primary tumor were the cervical esophagus in 1 patient, upper thoracic esophagus in 6 patients, middle thoracic esophagus in 8 patients, and lower thoracic esophagus in 1 patient. Lengths of the primary tumors ranged from 6–14 cm, with a median of 9.5 cm. Five patients had multiple esophageal lesions. One patient received systemic chemotherapy before the start of RT.

All patients underwent physical examination, computed tomography (CT) of the chest and abdomen, an upper gastrointestinal series, and endoscopy of the esophagus. Assessment of fistulae was based on leakage in the barium study or an apparent fistula on endoscopy. For some patients with poor PS, only chest CT findings of the mediastinum and/or a lung abscess adjacent to the primary esophageal tumor were regarded as indicative of fistulae formation.

RT and chemotherapy

Two courses of concurrent chemotherapy were combined with RT of 60 Gy/30 fractions/7 weeks (1-week split at Week 4). Chemotherapy was given for patients with a serum creatinine level less than 1.5 mg/dl, creatinine clearance greater than 50 ml/min, white blood cell count greater than 4,000/μl, and platelet count greater than 100,000/μl. For patients with fistulae, the possibility of worsening of the fistula because of CRT and severe toxic effects associated with CRT were fully explained before starting or continuing CRT. For these patients, CRT was started or continued with total parenteral nutrition or nasogastric tube feeding.

For 15 patients, low-dose protracted infusion chemotherapy, cisplatin 7 mg/m^2 × 10 days and 5-FU 250–300 mg/m^2 × 14 days, was given, whereas full-dose chemotherapy, cisplatin 70 mg/m^2 × 1 day and 5-FU 700 mg/m^2 × 5 days, was given to the remaining patient with distant metastasis. This schedule was repeated twice every 4 weeks concurrently with RT. The RT was administered within 1 hour after administration of cisplatin for patients treated with low-dose protracted infusion chemotherapy. After CRT, 2 courses of adjuvant chemotherapy with full-dose cisplatin/5-FU were given to 4 patients in whom fistulae had disappeared.

Either a 6-MV or 10-MV X-ray was used. The daily fractional dose of RT was 2 Gy administered 5 days a week. Total RT dose was 60 Gy in 30 fractions. Because a 1-week split was inserted after a dose of 30 Gy, overall treatment time was 7 weeks. The initial anterior/posterior field for patients with Stages III and IVa esophageal cancer included the supraclavicular fossa and mediastinum, except for tumors originating in the lower thoracic esophagus. For tumors originating in the lower thoracic esophagus, the initial RT field included the superior mediastinum to the perigastric region. For patients with Stage IV disease, the initial RT field included the primary tumor and nearby involved lymph nodes with a 2–3-cm margin. At 40 Gy, CT simulation was performed to reduce the RT field and exclude the spinal cord, usually by using oblique opposed fields. For primary tumors and involved lymph nodes, a margin of 1.0–2.0 cm in the craniocaudal direction or 0.5–1.0 cm in the axial plane was added.

Chemotherapy was stopped if Grade 3 leukocytopenia or thrombocytopenia was noted. The RT was stopped if Grade 4 leukocytopenia or thrombocytopenia, Grade 4 esophagitis with a fever greater than 38°C, or worsening of PS was observed. For patients who developed fistulae during CRT (Group B), the possibility of worsening of the fistula because of CRT was fully explained. When the patient's consent was obtained, RT was not stopped for development of fistula.

Criteria for response and toxicity

Local response was evaluated 2 to 4 weeks after CRT by means of esophageal endoscopy and chest CT with contrast enhancement. When endoscopy or chest CT indicated closure of fistulae, a barium study was added. A complete response was defined as disappearance of the tumor mass on the barium study, endoscopy, and chest CT. A partial response was defined as 50–99% regression based on two-dimensional measurement by means of CT, and no response, less than 50% regression. Esophagography and/or endoscopy were performed every 2 to 4 months for asymptomatic patients, and any clinically suspected tumor recurrence required biopsy and histopathologic confirmation. The CT scans were obtained at 2 to 6-month intervals and used to evaluate recurrence of primary tumors and regional lymph nodes.

Acute toxicity was graded using National Cancer Institute Common Toxicity Criteria (version 2.0).

Statistical methods

Overall survival was calculated from the first date of external RT. Overall survival considered deaths from any cause. Survival was plotted using the Kaplan-Meier method, with statistical significance assessed by using log-rank test.

RESULTS

Table 1 lists clinical courses of patients with malignant esophageal fistulae. When fistula formation was noted, all except 2 patients had fever with or without pneumonia. All patients reported severe dysphagia caused by locally advanced tumors, and only liquid or semisolid food could be ingested. The planned dose of 60 Gy was delivered to 11 patients (69%), whereas RT was terminated early for 5 patients

Table 1. Clinical course of patients with malignant esophageal fistulae

Patient no.	Age (y)/ Sex	PS	Group	Stage	Fistula site	Symptoms at fistula formation	RT dose (Gy)	CT cycles	Fistula closure	Oral intake after treatment	Survival (mo)	Status
1	37/M	2	A	3	EB	Fever, pneumonia	60	2	No	Possible by a covered stent	4	DOD
2	49/M	1	A	4a	ET	Fever	40	1	No	Possible by a covered stent	6	DOD
3	62/M	3	A	4	EB	Fever	40	1	No	Impossible	2	TRD
4	68/M	1	A	3	ET	No fever, uGIS only	60	2	No	Solid	13	DOD
5	47/M	1	A	3	EM	Fever, pneumonia	60	2+2*	Closed	Solid	61	NED
6	55/M	1	A	4a	EM	Fever	60	2+2*	Closed	Solid	11	DOD
7	55/F	2	A	3	EB	Fever	60	2	Closed	Semisolid	10.5	DOD
8	58/M	1	A	3	EB	Fever, pneumonia	60	2	Closed	Solid	5	DOD
9	59/M	1	A	3	EB	Fever	60	2+2*	Closed	Solid	8.5	DOD
10	55/M	1	B	3	EB	Fever, pneumonia	60	2	No	Impossible	6	DOD
11	55/M	0	B	4	EB	Fever	60	2*	No	Impossible	3	DOD
12	58/M	1	B	4	ET	Fever, pneumonia	60	2	No	Impossible	4	DOD
13	60/F	1	B	4a	ET	Fever, pneumonia	42	1	No	Impossible	3.5	DOD
14	51/F	2	B	4	EB	Fever, pneumonia	58	1	No	Impossible	2	TRD
15	50/M	1	B	3	EM	Fever, pneumonia	60	2+2*	Closed	Solid	6.5	DOD
16	67/F	2	B	3	ET	No fever, uGIF only	50	2	Closed	Solid	14	NED

Abbreviations: PS = performance status; RT = radiotherapy; CT = chemotherapy; ET = esophagotracheal; EB; esophagobronchial; EM = esophagomediastinal; uGIS = upper gastrointestinal series; uGIF = upper gastrointestinal fiber scopy; DOD = dead of disease; TRD = treatment-related death; NED = no evidence of disease.

* Full-dose chemotherapy.

(40–58 Gy) because of acute toxic effects, including 2 patients with treatment-related deaths (TRDs; 13%). For 12 patients (75%), two courses of planned chemotherapy were combined concurrently with RT.

Table 2 lists acute toxic effects associated with CRT. Hematologic toxicities were mild, and no patient showed Grade 4. The incidence of esophageal dysphagia related to RT was high, and Grade 3 or greater toxicities were noted in 9 patients, including 2 with Grade 5. In terms of pulmonary toxicity, Grades 4 and 5 lung abscesses related to EB fistulae were noted in 1 patient each. One patient showed Grade 4 hepatic toxicity related to 5-FU therapy.

In the present study, worsening of esophageal fistulae was noted in 5 of 16 patients, including 2 with TRDs (13%). In Group B, esophageal fistulae occurred between 14 and 58 Gy of CRT (median, 22 Gy), and worsening of fistulae and general condition as CRT continued were noted in 3 patients, including 1 with TRD. In Group A, worsening of esophageal fistulae and general condition were noted in 2 patients, including 1 with TRD. Both patients with TRD had Stage IV disease (T4N1M1) and died of worsening of EB fistulae with or without lung abscess. Both patients underwent one cycle of low-dose protracted infusion chemotherapy concurrent with RT of 40 or 58 Gy.

Local response could not be evaluated for 3 patients for whom RT was terminated at 40–58 Gy. Of the remaining 13 patients, 3 (23%) showed complete response, 9 (69%) showed partial response, and 1 (8%) showed no response.

Disappearance of fistulae during or after CRT was observed in 7 patients (44%). Five of 9 patients in Group A and 2 of 7 patients in Group B showed disappearance of fistulae by CRT. Similarly, 6 patients with Stage III disease and 1 with Stage IVa disease showed disappearance of fistulae. Regarding the site of fistulae, all three EM fistulae closed, but only four of 13 ER fistulae closed by using CRT (Table 1).

Of 7 patients with closure of fistulae, complete regression and local control were achieved in 2 patients at 14 and 61 months. For the remaining 5 patients, local recurrence with or without fistulae was noted 1 to 5.5 months after closure of fistulae. These 7 patients whose fistulae closed could eat solid or semisolid food after CRT (Table 1). In addition, 2 patients without closure of fistulae could eat food after insertion of a covered esophageal stent. One patient ate solid food after CRT by his own responsibility, although the fistula was not closed by using CRT.

All 16 patients were evaluated in terms of survival. Figure 1 shows survival curves for patients with Stages III and IV disease. As of July 2007, 14 patients died of the disease and 2

Table 2. Acute toxicities: National Cancer Institute Common Toxicity Criteria, version 2

	Grade					
Toxicities	0	1	2	3	4	5
White blood cells	2	2	8	4	0	0
Hemoglobin	3	4	7	2	0	0
Platelet	13	1	1	1	0	0
Dysphagia*	5	1	1	5	2	2
Lung	6	3	5	0	1	1
Liver	15	0	0	0	1	0
Kidney	15	0	1	0	0	0
Skin	16	0	0	0	0	0
Oral mucosa	15	0	1	0	0	0

* Dysphagia = esophageal dysphagia related to radiation.

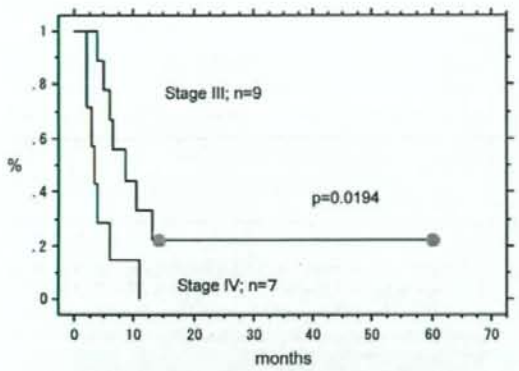

Fig. 1. Overall survival curves after chemoradiotherapy (CRT) for patients with esophageal cancer with malignant fistulae according to stage. Median survival times (MSTs) for patients with Stages III and IV were 8.5 and 3.5 months, with a significant difference by means of log-rank test ($p = 0.0194$), respectively.

were alive without evidence of disease. Follow-up periods for surviving patients were 14 and 61 months. The 1-year and 2-year survival rates for 9 patients with Stage III disease were 33% and 22%, respectively. The MSTs for patients with Stages III and IV were 8.5 and 3.5 months, respectively. There was a significant difference by means of log-rank test ($p = 0.0194$). Figure 2 shows survival curves for patients with closed fistulae and those without closure of fistulae. A significantly better overall survival rate was observed for patients with than without closure of fistulae ($p = 0.0168$). Two of 7 patients with closure of fistulae survived more than 1 year.

DISCUSSION

Most CRT trials for patients with advanced esophageal cancer excluded tumors with fistulae (5–7, 10), and only a few studies reported results of CRT for patients with T4-fistula esophageal cancer (8, 9, 11). For patients with T4 esophageal cancer, a high incidence of esophageal perforation was reported for RT or CRT. Ishida *et al.* (10) reported that 6 of 45 patients (13%) with T4 tumors and/or M1 lymph nodes developed EB fistulae during CRT, and CRT was terminated for these patients. The risk of esophageal perforation may be inevitable when patients with T4 esophageal tumors are treated with RT or CRT.

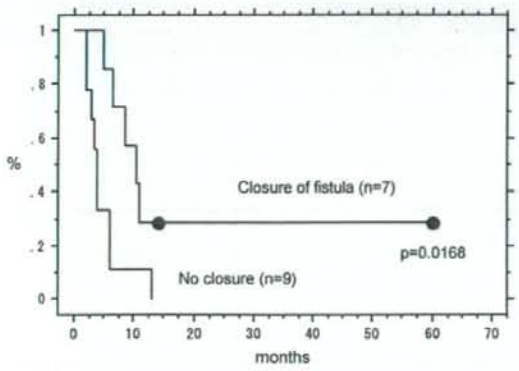

Fig. 2. Overall survival curves for patients with closed fistulae and those without closure of fistulae. A significantly better overall survival rate was observed for patients with than without closure of fistulae ($p = 0.0168$).

Ohtsu *et al.* (7) reported that three of five esophageal perforations observed during CRT were eventually closed by continuing CRT. The same group reported the closure of esophageal malignant fistulae after CRT in 17 of 24 patients (71%) (9). In the present analysis, effects and toxicities of CRT for patients with T4-fistula esophageal squamous cell carcinomas were evaluated, and seven (44%) of the 16 tumors with fistulae were closed. In addition, the overall survival rate was good enough for patients with closure of fistulae (Fig. 2). Thus, it seems apparent that CRT is not contraindicated for patients with T4 esophageal cancer with fistulae. Although most patients died of local recurrence thereafter, they could eat for several months when the fistulae closed, which improved their quality of life.

In the present analysis, all three EM fistulae were closed, but only four of 13 ER fistulae (31%) were closed by using CRT. Similarly, Muto *et al.* (9) reported that closure rates for EM and ER fistulae were 86% (six of seven fistulae) and 65% (11 of 17 fistulae), respectively. Thus, EM fistulae may be more controllable by using CRT than ER fistulae.

In addition, fistulae observed before treatment (Group A) had a better rate of closure than those that developed during treatment (Group B). This trend was also observed by Muto *et al.* (9). Similarly, fistulae in patients with Stage III disease had a better rate of closure than those in patients with Stage IV disease. In this analysis, no patient with distant metastasis showed fistulae closure by using CRT. This may be related to the poor general condition of patients with Stage IV disease.

In the present study, low-dose protracted infusion of 5-FU and cisplatin were combined with full-dose RT of 60 Gy for most patients. The purpose of the protracted infusion chemotherapy was to obtain a maximum radiosensitizing effect without rapid depopulation of massive T4 tumors by full-dose chemotherapy (8, 12, 13). Muto *et al.* (9) also used protracted infusions of 5-FU and cisplatin. Ahmed *et al.* (11) reported that malignant esophagotracheal fistulae disappeared completely in 4 of 5 patients treated with 5-FU (400 to 600 mg/m^2) by protracted continuous infusion and RT of 60 Gy. To avoid rapid depopulation of massive T4 fistulous tumors, this protracted infusion method may be effective.

In addition, a 1-week split was inserted after 30 Gy was delivered in our protocol. Muto *et al.* (9) used a 2-week split of RT. The rate of compliance in the present series was relatively high, considering that it included patients with Stage IV disease and poor PS. This high compliance rate may be attributable to the split period of RT. For RT alone, it was reported that a reduced fraction size and protracted RT might

be effective for closure of fistulae (3, 4). This somewhat protracted treatment period may contribute to the closure of fistulae.

In the present study, both patients with TRDs had distant metastasis at presentation, and their general condition was poor (PS2 and PS3). We believe that such deteriorated patients should not be treated with concurrent CRT, and use of a covered esophageal stent may be appropriate for them (14).

Despite its significant toxicity, this concurrent CRT protocol involving protracted infusion of 5-FU and cisplatin appears feasible and effective at closing esophageal malignant fistulae, especially in patients in a good general condition and without metastasis.

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ORIGINAL ARTICLE

Kiyoshi Nakamatsu · Minoru Suzuki
Yasumasa Nishimura · Shuichi Kanamori · Ryuta Koike
Toru Shibata · Naoya Shintani · Masahiko Okumura
Kaoru Okajima · Fumiharu Akai

Treatment outcomes and dose-volume histogram analysis of simultaneous integrated boost method for malignant gliomas using intensity-modulated radiotherapy

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Abstract

Background. The aim of this article is to report the treatment outcomes, toxicities, and dosimetric feasibility of our simultaneous-boost intensity-modulated radiotherapy (SIB-IMRT) protocol.

Methods. Thirteen patients with malignant gliomas treated between December 2000 and September 2004 were enrolled in this study. Two planning target volumes (PTVs) were defined in the present study. Our IMRT regimen delivered 70 Gy/28 fractions (fr)/daily; 2.5 Gy to the gross tumor volume (GTV) with a 0.5-cm margin, defined as the PTV-G, and 56 Gy/28 fr/daily, with 2.0 Gy to the surrounding edema, defined as the planning target volume annulus (PTV-a). Eleven of the 13 patients received one or two courses of nimustine hydrochloride (ACNU) (100 mg/m^2) and vincristine (1.2 mg/body) and interferon-β (3×10^6 units) three times weekly during the period of radiotherapy. Adjuvant chemotherapy, ACNU (100 mg/m^2) and vincristine (1.2 mg/body), was repeated every 6 weeks and interferon-β was repeated every 2 weeks. The treatment outcomes, toxicity, and dosimetric feasibility were assessed.

Results. All the patients experienced tumor recurrence. The median progression-free survival times for patients with grade III tumors and glioblastome were 7.5 and 8.0 months, respectively. The 1-year and 2-year overall survival rates for all the patients were 77% and 31%, respectively. Four patients experienced acute grade 1/2 toxicities during the treatment. No late toxicity related to radiotherapy has been seen. Analyses with dose-volume histograms confirmed excellent conformity of dose distributions in the two target volumes, PTV-G and PTV-a, with the sparing of organs at risk.

Conclusion. Our IMRT regimen did not prevent tumor progression. However, the ability of IMRT to deliver highly conformative doses to two contiguous targets, GTV and the surrounding edema, justifies its application to malignant gliomas.

Key words Intensity-modulated radiotherapy · Simultaneous integrated boost technique · Malignant glioma

K. Nakamatsu · M. Suzuki · Y. Nishimura · S. Kanamori · R. Koike · T. Shibata
Department of Radiation Oncology, Kinki University School of Medicine, Osaka, Japan

M. Suzuki (✉)
Particle Oncology Research Center, Research Reactor Institute, Kyoto University, 2-1010 Asashiro-nishi, Kumatori-cho, Osaka 590-0494, Japan
Tel. +81-72-451-2390; Fax +81-72-451-2627
e-mail: msuzuki@rri.kyoto-u.ac.jp

N. Shintani · M. Okumura
Department of Central Radiological Service, Kinki University School of Medicine, Osaka, Japan

K. Okajima
Department of Radiology, Kinki University School of Medicine Nara Hospital, Nara Japan

F. Akai
Department of Neurosurgery, Kinki University School of Medicine, Osaka, Japan

Introduction

Postoperative external radiotherapy has been recommended as standard treatment for malignant glioma. However, most patients experience local recurrence, and the prognosis of patients with this tumor remains dismal.[1]

Intensity-modulated radiotherapy (IMRT) has proved itself to have many advantages over conventional radiotherapy. The ability of IMRT to deliver a highly conformative dose of irradiation to the target while sparing surrounding tissues has promoted its application to dose-escalation studies for patients with prostate cancer.[2,3] Another unique application of IMRT is the simultaneous-boost (SIB) technique, which can deposit a dose gradient between regions of gross tumor involvement and regions of microscopic tumor involvement or a lymph node chain. At many cancer centers, head and neck cancers have been treated with IMRT using this dose-painting technique (SIB-IMRT).[4,5] In the ongoing protocol Radiation Therapy

Oncology Group (RTOG) 0022, with each fraction, the lymph node groups or surgical neck levels at risk of subclinical metastases received 1.8 Gy, for a total of 54 Gy, and the primary tumor and lymph nodes containing clinical or radiographic evidence of metastases at the same time received 2.2 Gy, for a total of 66 Gy.

We used SIB-IMRT to deliver an entire course of treatment to patients with malignant glioma. Our initial experience with six patients showed local recurrence in five patients within 7 months of the start of radiotherapy, although, concerning dosimetry and early toxicity, the feasibility of our protocol was confirmed.[6] The clinical outcomes of SIB-IMRT for malignant glioma have been reported.[7-10] In a study reported by Iuchi et al.,[7] the following hypofractionation regimen was used; in 8 fractions, 48–68 Gy was delivered to the area of enhancing lesion with a 5-mm margin, 40 Gy was delivered to the area with a 15-mm margin, and 32 Gy was delivered to the area of the peritumoral edema. In a study by Sultanem et al.,[8] 60 Gy was delivered to the gross tumor volume (GTV) and 40 Gy to the planning target volume (PTV), defined as the GTV + 1.5-cm margin by SIB-IMRT.

There have been few studies of SIB-IMRT for malignant glioma. In addition, in those studies that have been published, the total doses and number of fractions varied. To evaluate the feasibility and efficacy of SIB-IMRT for treating malignant glioma, more prospective studies are needed. Therefore, we have reported the updated results of a prospective trial for treating malignant glioma using SIB-IMRT.

Patients and methods

Eligibility criteria

The eligibility criteria included 20–75 years of age and Eastern Cooperative Oncology Group performance status of 0–2. Patients previously treated with radiotherapy were excluded. Patients with major heart or infectious disease were also excluded. This pilot study was reviewed and approved by the Institutional Review Board, Kinki University School of Medicine, Japan. Written informed consent was obtained from all the patients.

Patient characteristics

Between December 2000 and September 2004, 13 patients with histologically confirmed malignant gliomas underwent IMRT at the Department of Radiation Oncology, Kinki University School of Medicine. Patient characteristics are summarized in Table 1. There were seven men and six women with a median age of 56 years (range, 20–71 years) at the time of IMRT. Tumors included glioblastome (GBM; $n = 8$), anaplastic astrocytoma (AA; $n = 4$), and anaplastic oligodendroglioma (AO; $n = 1$). Except for 2 of the patients with AA who were diagnosed by biopsy, all patients had pathologically diagnosed malignant gliomas and were treated with IMRT following tumor resection. A gross total resection was performed in 8 patients and a subtotal resection in 3 patients.

Table 1. Patient and tumor characteristics

Total number of patients	13
Sex	
Male	7
Female	6
Age (years)	27–71 (median, 56)
Histology	
Glioblastome	8
Anaplastic astrocytoma	4
Anaplastic oligodendroglioma	1
Performance status (ECOG)	
0	2
1	4
2	7

Target volume delineation

Following the recommendations of the International Commission on Radiation Units and Measurements (ICRU) report number 50,[11] the gross tumor volume (GTV) and the clinical target volume (CTV) were delineated on axial computed tomography (CT) images. The GTV was defined using contrast-enhanced tumors on contrast-enhanced CT images. If the gross tumor was resected, the area where the brain tumor had existed on the contrast-enhanced magnetic resonance imaging (MRI) scan obtained before surgery was outlined as the GTV. The CTV was defined as the GTV plus a 2-cm margin. The margin was expanded to include edema beyond 2 cm from the GTV or contracted to the anatomical defense such as intracerebral fissures or tentorium cerebelli.

Two planning target volumes (PTVs) were defined in the present study. The PTV-G was defined as the GTV plus a 0.5-cm margin. The PTV-annulus (PTV-a) was delineated by subtracting the PTV-G from the CTV plus a 0.5-cm setup margin. In the present study, the PTV-G and the PTV-a were treated as two separate targets with IMRT at different fraction sizes. We have already reported the details of the target volume delineation in this clinical trial, in which the contouring of PTV-G and PTV-a was graphically demonstrated.[6,12]

Treatment planning

A commercial treatment-planning system (Cadplan Helios ver.6.01; Varian Associates, Palo Alto, CA, USA) was used. The IMRT beam arrangements consisted of five coplanar beams. The five beams were equally spaced at 72° intervals following gantry angles of 20°, 92°, 164°, 236°, and 308°. The prescribed doses delivered to the PTV-G and the PTV-a were 70 Gy in 28 fractions (fr) and 56 Gy in 28 fr, respectively. Daily fractions of 2.5 Gy and 2.0 Gy were prescribed for the PTV-G and the PTV-a, respectively. The treatment goals were as follows; (1) the doses delivered to 95% volume

Table 2. Starting template for dose constraints and penalties for targets and organs at risk

Targets	Dose constraints and penalties	
	Max (Gy)/Penalty	Min (Gy)/Penalty
PTV-G	71.4/100	68.6/100
PTV-a	64–70/100	53.2/100
OARs		
Brain	Max 54/80	ND
	D_{33} 45/80	
	D_{66} 45/81	
Brain stem	Max 54/80	ND
	D_{33} 42/80	
	D_{66} 38/80	
Eye (retina) Optic nerve	40/90	ND
Lens	6/90	ND
Pituitary gland	30/90	ND

Max, maximum; Min, minimum;
PTV, planning target volume; OARs, organs at risk;
D_{33}, dose delivered to 33% of the brain or brain stem;
D_{66}, dose delivered to 66% of the brain or brain stem; ND, not defined

(D_{95}) of the PTV-G and PTV-a were greater than the prescribed doses, (2) the dose delivered to 5% volume (D_{05}) of the PTV-G was less than 77 Gy, i.e., 110% of the prescribed dose delivered to the PTV-G, and (3) the D_{05} of the PTV-a was less than the prescribed dose delivered to the PTV-G (70 Gy).

The optimization process in inverse planning is the automated generation of beam intensity distributions by adjusting the difference between the planner-defined dose constraints for the targets or the organs at risk (OARs) and the actual dose according to the weighted penalties.[13] The first step determined by the treatment planner was to input the maximum and minimum dose constraints for the targets and the maximum dose constraints or the dose-volume constraints for the OARs. Table 2 shows the starting template for the dose constraints and the penalties of the targets and the OARs. The maximum and minimum dose constraints for the PTV-G were 71.4 Gy and 68.6 Gy (±2% of the prescribed dose to the PTV-G), respectively. The maximum dose constraint for the PTV-a was adjusted with a range of 64–70 Gy in each case to accomplish the treatment goal. The minimum dose constraint for the PTV-a was 53.2 Gy (95% of the prescribed dose). The final step of the treatment planning was the normalization of the dose intensity. The treatment plan was normalized to enable delivery of the prescribed dose to 95% volume (D_{95}) of the PTV-G according to the treatment goal. If the treatment plan did not fulfill the other treatment goals or a dose higher than that tolerable was delivered to the OARs, the optimization process was repeated with modification of the dose constraints or penalties of the targets and OARs.

Treatment delivery

Treatment was delivered using dynamic multileaf collimation (DMLC) on a Clinac-600C accelerator (Varian Associates) equipped with a 40-leaf dynamic multileaf collimator. A beam energy of 4-MV X-rays was used. The daily treatment time was about 15–20 min. Details of the quality assurances (QA) in the present study have been described in our previous report.[6]

Chemotherapy

Eleven of the 13 patients received one or two courses of nimustine hydrochloride (ACNU) (100 mg/m^2) and vincristine (1.2 mg/body) and interferon-β (3×10^6 units) three times weekly during the radiotherapy. Adjuvant chemotherapy, ACNU (100 mg/m^2) and vincristine (1.2 mg/body), was repeated every 6 weeks and interferon-β was repeated every 2 weeks.

Dose-volume histogram (DVH) analysis

Dose-volume histograms of the PTV-G, PTV-a, and OARs, including the brain, eye (retina and optic nerve), and lens were analyzed. For the PTV-G and PTV-a, the D_{95} and D_{05} were recorded to evaluate conformity and homogeneity of the targets, and the mean doses were also evaluated. For the OARs, the maximum doses were evaluated.

Endpoints and follow-up

The primary endpoint in this pilot study was the progression-free survival (PFS) time. Secondary endpoints included treatment toxicity, failure patterns (local or distant), and overall survival (OS) times. All the patients were evaluated at least once per week during radiotherapy. The patients were followed every 1–2 months for the first 6 months, and every 3 months thereafter. MRI with contrast enhancement was usually evaluated every 3 months. Radiation Therapy Oncology Group (RTOG) neurotoxicity scores were used to evaluate acute and late toxicities.[9] In addition, other acute toxicities were graded using the National Cancer Institute Common Toxicity Criteria (version 2.0). Survival was calculated from the start of IMRT until death or last follow-up, according to the Kaplan-Meier method.

Results

Treatment outcome

Time to disease progression and OS time were measured from the first day of the IMRT treatment. At the time of this analysis, 29 months had passed since the first day of the treatment of the last-enrolled patient in the present study. The median follow-up time for all the enrolled patients was 17 months. Two patients with GBM and one with AA remain alive, with follow-up times of 30 months, 48 months, and 41 months, respectively. All the patients experienced tumor recurrence. The PFS curves for all the patients are demonstrated in Fig. 1. The 1-year PFS times for patients

Table 3. Dose-volume histogram (DVH) analyses for planning target volumes (PTVs)

	PTV-G		PTV-a	
	Average ± SD	(Range)	Average ± SD	(Range)
Volume (cc)	106.2 ± 50.6	(31.6–184.1)	240.9 ± 89.4	(93.1–394.4)
Maximum dose (Gy)	76.5 ± 1.5	(74.8–79.4)	72.7 ± 1.1	(71.3–74.2)
Mean dose (Gy)	72.4 ± 0.5	(71.3–73.1)	61.9 ± 1.1	(59.6–63.2)
Minimum dose (Gy)	65.1 ± 2.7	(57.0–67.0)	51.5 ± 2.1	(47.7–56.0)
D_{05} (Gy)	74.5 ± 0.8	(73.1–75.9)	68.0 ± 0.8	(66.4–69.5)
D_{95} (Gy)	69.9 ± 0.2	(69.3–70.1)	57.1 ± 1.1	(55.4–58.9)
V_{95} (%)	99.9 ± 0.4	(98.5–100.0)	99.9 ± 0.1	(99.5–100.0)

D_{05}, the dose delivered to 5% of the PTV-G or PTV-a;
D_{95}, the dose delivered to 95% of PTV-G or PTV-a; V_{95}, the volume that receives 95% of the prescribed dose

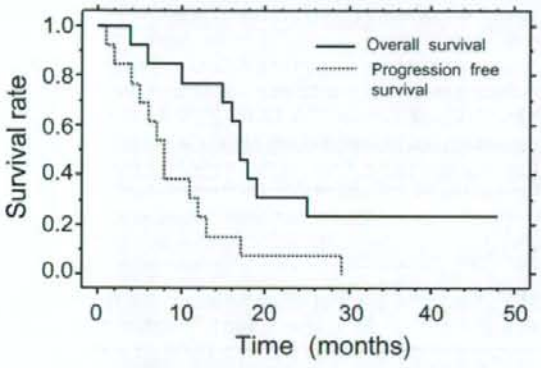

Fig. 1. Progression-free and overall survival rates in all the patients with high-grade gliomas

with grade III tumors (AA; $n = 4$ and AO; $n = 1$) and GBM ($n = 8$) were 20% and 25%, respectively. The 2-year PFS times for those with grade III tumors and GBM were 0% and 13%, respectively. The median PFS times for those with grade III tumors and GBM were 7.5 months (range, 4–13 months) and 8.0 months (range, 0–29 months), respectively. Twelve patients (92%) experienced local recurrence in the radiation field. Local recurrence arose in nine patients with PTV-G and in three patients with PTV-a. Recurrence in the brain outside the radiated region was noted in one patient.

In this pilot study, because no restriction was imposed on the treatment of the recurrent tumors, seven patients (54%) received further treatment. Four patients received gamma-knife radiosurgery; two, boron neutron capture therapy (BNCT) following surgical resection; and one, surgical resection alone. The OS curves for all the patients are shown in Fig. 1. The 1-year and 2-year OS rates for all the patients were 77% and 31%, respectively. The 1-year and 2-year OS rates for GBM patients were 75% and 25%, respectively. The 1-year and 2-year OS rates for patients with grade III tumors were 80% and 40%, respectively.

Toxicity

One patient's treatment was interrupted for 47 days due to loss of consciousness following the PTV-G; this patient had received 37.5 Gy (15 fr). A causal relationship between this adverse event and the radiotherapy was unclear. Twelve patients completed the scheduled radiotherapy without interruption. Four patients experienced acute grade 1/2 toxicities during the treatment. One patient experienced headaches scored as grade 1 toxicity, and three patients experienced grade 2 toxicity, including seizures and vomiting, and required medication with a steroid and antiseizure agent. No late toxicity related to the radiotherapy has been seen. No radiation-induced necrosis was observed in any of the patients.

Dose-volume histogram (DVH) analyses

Table 3 summarizes the treatment volumes and DVH parameters, including the maximum, mean, minimum, D_{05}, and D_{95} doses, and V_{95}% for the PTV-G and PTV-a. Because the treatment goal was that 95% volumes of the PTV-G and PTV-a be received as prescribed doses (70 Gy for the PTV-G, 56 Gy for the PTV-a), the average D_{95} doses for the PTV-G and PTV-a were 69.9 and 57.1 Gy, respectively. The DVHs for the PTV-G, PTV-a, and brain of a representative patient are shown in Fig. 2.

Table 4 shows the DVH parameters for organs at risk. The average DVH parameters delivered to the organs at risk were lower than the dose constraints (Table 2), except for the left lens. However, the average maximum dose delivered to the left lens, 7.0 Gy, was acceptable in the clinical situation, and no toxicity related to visual acuity was observed.

Discussion

Our regimen, delivering 70 Gy in 28 fr to PTV-G and 56 Gy in 28 fr to PTV-a, provided no advantage in preventing recurrence of the tumor. The median progression-free sur-

Table 4. Dose-volume histogram (DVH) analyses for organs at risk (OARs)

		Average ± SD	Range
Brain			
	Mean dose (Gy)	25.7 ± 6.1	(15.1–37.8)
	D_{05} (Gy)	52.2 ± 2.5	(47.8–55.8)
	D_{33} (Gy)	32.5 ± 7.2	(21.0–46.3)
	D_{66} (Gy)	17.1 ± 9.0	(2.1–32.9)
Brain stem			
	Maximum dose (Gy)	42.9 ± 20.9	(21.3–60.8)
Right eye (retina and optic nerve)			
	Maximum dose (Gy)	16.9 ± 8.1	(1.2–30.4)
Right lens			
	Maximum dose (Gy)	5.2 ± 2.9	(1.3–9.0)
Left eye (retina and optic nerve)			
	Maximum dose (Gy)	21.6 ± 15.5	(2.1–48.3)
Left lens			
	Maximum dose (Gy)	7.0 ± 4.3	(1.3–12.0)

D_{05}, dose delivered to 5% of the brain;
D_{33}, dose delivered to 33% of the brain; D_{66}, dose delivered to 66% of the brain

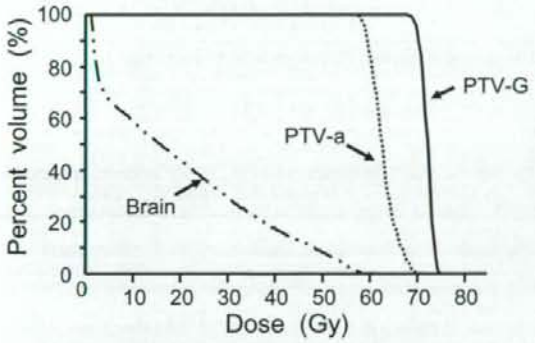

Fig. 2. Dose-volume histograms for the planning target volume (*PTV*)-G, PTV-a, and brain of a representative patient. See text for definitions of PTV-G and PTV-a

vival (PFS) times for patients with grade III tumors and GBM were 7.5 and 8.0 months, respectively. For 12 patients (92%), the tumors recurred in the radiation field. There have been few available reports on IMRT for malignant glioma.[7-10] The treatment outcomes published from five institutes, including ours, are summarized in Table 5. In four studies, SIB-IMRT was carried out to deposit a dose gradient between the GTV and its peripheral region including edema. The given doses per fraction ranged from 1.8 Gy to 8.5 Gy. In four of the five studies, including ours, the SIB-IMRT failed to improve local control and the survival rate. One regimen, that used by Iuchi et al.,[7] provided excellent local control (1-year PFS, 71.4%; 2-year PFS, 53.6%) and survival advantages (1-year OS, 71.4%; 2-year OS, 55.6%).

According to the report of Iuchi et al.,[7] the PFS and OS in the IMRT group compared favorably, in their experience, with conventional fractionation (60–72 Gy in 2.0-Gy fractions); as shown in Table 5, the total equivalent doses delivered to the GTV with their regimen were much higher than those in the other studies. When calculating the effective dose equivalent to standard fractionation (2.0 Gy per fraction), the value of the α/β coefficient should be determined with caution. As Floyd et al.[9] discussed in their report, malignant gliomas are relatively radioresistant and respond like a late-responding tissue. They adopted an α/β coefficient of 1.5 for malignant glioma and made a comparison of effective doses between their study and other studies. We agree with using an α/β coefficient of 1.5 for malignant glioma, and we calculated the equivalent dose in the 2.0-Gy fraction, as shown in Table 5. The calculated total equivalent dose of 103–194 Gy-Eq in the 2.0-Gy fraction in the study of Iuchi et al.[7] was much higher than that in the other studies (range, 56–93 Gy-Eq); the marked intensification of dose delivered to the GTV in their study may explain their excellent treatment outcomes.

Our DVH analysis confirmed excellent conformity in target coverage for both PTV-G and PTV-a, while sparing organs at risk. As shown in Table 3, the calculated DVH parameters for the two target volumes in all the patients were distributed within a small range and with small SDs. As discussed in the report of Narayana et al.,[10] an oval or spherical-shaped glioma may exhibit excellent conformity and dose uniformity compared to the concave or complicated target volumes in head and neck tumors; although the SIB method was not adopted in their study, the results of our study confirmed the advantage of IMRT in delivering the prescribed dose to the two contiguous targets with good conformity and uniformity. According to the report of Narayana et al.,[10] IMRT contributes to a moderate decrease in the dose delivered to critical structures in the brain compared to three-dimensional (3D) conformal radiotherapy (CRT). Chan et al.[14] demonstrated that SIB-IMRT could deliver a higher dose to the GTV compared to 3D-CRT without elevating the dose delivered to organs at risk.

In our study using the 2.5-Gy fraction dose, no radiation-induced necrosis was observed. The large fractionated doses, 5.0-Gy and 8.0–8.5-Gy, used in the studies of Floyd et al.[9] and Iuchi et al.,[7] caused necrosis in 12%–15% of the patients. However, necrosis may not be a dose-limiting toxicity (DLT) in the treatment of malignant gliomas with

Table 5. Treatment outcomes of IMRT for malignant gliomas

Series	*n*		Radiation dose	Equivalent dose ($\alpha/\beta = 1.5$, in 2-Gy fractions)	Treatment outcomes
Sultanem et al.[8]	25	GBM, 25	60 Gy/20 fr (GTV) 40 Gy/20 fr (peripheral volume: within 1.5 cm from GTV)	77 Gy-Eq	1-Year OS, 40%; 2-year OS, 0% MST, 9.5 months
Floyd et al.[9]	20	GBM, 20	50 Gy/10 fr (GTV) 30 Gy/10 fr (edema)	93 Gy-Eq 39 Gy-Eq	MST, 7 months
Narayana et al.[10]	58	GBM, 41; grade III 17	59.4–60 Gy/30–33 fr (GTV + 2.0 cm)	56–60 Gy-Eq	GBM: 1-year PFS, 0%; 2-year PFS, 0% 1-Year OS, 30.0%; 2-year OS, 0% Grade III: 1-year PFS, 21.8%; 2-year PFS, 10.8% 1-Year OS, 86.3%; 2-year OS, 61.6%
Iuchi et al.[7]	25	GBM, 23; grade III 2	48–68 Gy/8 fr (GTV + 0.5 cm)	103–194 Gy-Eq	GBM: 1-Year PFS, 71.4%; 2-year PFS, 53.6%
			40 Gy/8 fr (peripheral volume: within 2.0 cm from GTV) 32 Gy/8 fr (edema)	74 Gy-Eq 50 Gy-Eq	1-Year OS, 71.4%; 2-year OS, 55.6%
Currrent study	13	GBM, 8; grade III, 5	70 Gy/28 fr (GTV + 0.5 cm)	80 Gy-Eq	GBM: 1-year PFS, 25.0%; 2-year PFS, 13.0%
			56 Gy/28 fr (peripheral volume: within 2.0 cm from GTV)	56 Gy-Eq	1-Year OS, 75.0%; 2-year OS, 25% Grade II:I 1-year PFS, 20.0%; 2-year PFS, 0% 1-Year OS, 80.0%; 2-year OS, 40.0%

GBM, glioblastome; GTV, gross tumor volume; OS, overall survival; MST, median survival time; PFS, progression-free survival

radiotherapy, because long-term survivors exist among patients who experience radiation-induced necrosis.[9,15]

In conclusion, our treatment regimen, the delivery of 70 Gy in 28 fractions to the GTV and 56 Gy in 28 fractions to the peripheral region, did not prevent tumor progression. However, IMRT can deliver prescribed doses to two contiguous targets with almost the same distribution and uniformity and can keep the doses to organs at risk (OARs) below the tolerable doses. Although our fractionation schedule was not effective for malignant gliomas, hypofractionated SIB-IMRT with a large fraction for GTV seems to be a promising strategy for malignant gliomas.

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ORIGINAL ARTICLE

Static and moving phantom studies for radiation treatment planning in a positron emission tomography and computed tomography (PET/CT) system

Mitsuru Okubo · Yasumasa Nishimura
Kiyoshi Nakamatsu · Masahiko Okumura
Toru Shibata · Shuichi Kanamori · Kouhei Hanaoka
Makoto Hosono

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Abstract
Objective To determine an appropriate threshold value for delineation of the target in positron emission tomography (PET) and to investigate whether PET can delineate an internal target volume (ITV), a series of phantom studies were performed.
Methods An ellipse phantom (background) was filled with 1028 Bq/ml of [^{18}F] fluoro-2-deoxyglucose (^{18}FDG), and six spheres of 10 mm, 13 mm, 17 mm, 22 mm, 28 mm, and 37 mm in diameter inside it were filled with ^{18}FDG activity to achieve source-to-background (S/B) ratios of 10, 15, and 20. In static phantom experiments, an appropriate threshold value was determined so that the size of PET delineation fits to an actual sphere. In moving phantom experiments with total translations of 10 mm, 20 mm, and 30 mm and a period of oscillation of 4 s, the maximum size of PET delineation with the appropriate threshold value was measured in both the axial and sagittal planes.
Results In the static phantom experiments, the measured maximum ^{18}FDG activities of spheres of less than 22 mm were lower than 80% of the injected ^{18}FDG activity, and those for the larger spheres ranged from 90% to 110%. Appropriate threshold values determined for the spheres of 22 mm or more ranged from 30% to 40% of the maximum ^{18}FDG activity, independent of the S/B ratio. Therefore, we adopted an appropriate threshold value as 35% of the measured maximum ^{18}FDG activity. In moving phantom experiments, the maximum ^{18}FDG activity of spheres decreased significantly, dependent on the movement distance. Although the sizes of PET delineation with 35% threshold value tended to be slightly smaller (<3 mm) than the actual spheres in the axial plane, the longest sizes in the sagittal plane were larger than the actual spheres.
Conclusions When a threshold value of 35% of the measured maximum ^{18}FDG activity was adopted, the sizes of PET delineation were almost the same for static and moving phantom spheres of 22 mm or more in the axial plane. In addition, PET images have the potential to provide an individualized ITV.

Keywords Phantom experiments · Appropriate threshold values · Positron emission tomography (PET) · Radiation treatment planning · Internal target volume (ITV)

M. Okubo (✉) · Y. Nishimura · K. Nakamatsu · T. Shibata · S. Kanamori
Department of Radiation Oncology, Kinki University School of Medicine, 377-2 Ohno-Higashi, Osaka-Sayama 589-8511, Japan
e-mail: ohkubo@rad.med.kindai.ac.jp

M. Okumura · K. Hanaoka
Department of Central Radiological Service, Kinki University School of Medicine, Osaka-Sayama, Japan

M. Hosono
Department of PET, Kinki University School of Medicine, Osaka-Sayama, Japan

Introduction

Positron emission tomography (PET) is used for various purposes including the staging of tumors and prediction of a tumor's response to irradiation [1–5]. Notably, for staging in non-small-cell lung cancers (NSCLCs), PET/computed tomography (CT) imaging is now considered to be the most accurate method [1, 2]. In recent years, there have been many reports that PET/CT is diagnosti-

cally significantly more accurate than PET alone because PET/CT can correlate functional images and anatomical structures more precisely than PET alone [6–10].

Positron emission tomography/computed tomography is also useful for radiation treatment planning (RTP) in patients with NSCLC, esophageal carcinoma, head and neck cancer, etc. [11–17]. In the delineation of the gross tumor volume (GTV), [^{18}F] fluoro-2-deoxyglucose (^{18}FDG)-PET/CT images can significantly reduce inter-observer variation [18]. Faria et al. [11] and Erdi et al. [19] reported that RTP based on CT and PET fusion images was useful for delineating tumors from atelectasis in patients with NSCLC. PET/CT also has a major impact on decisions regarding the management of the patient with NSCLC [20].

The size of PET delineation changes significantly dependent on its threshold value, and the PET image affects the target delineation clinically. There have been many clinical and phantom studies on appropriate threshold values for PET images [21–32] (Table 1). Erdi et al. [21] reported that 36%–44% of the maximum FDG activity was appropriate for delineating target volumes larger than 4 ml in a static phantom study. Recently, thresholds calculated by more complex algorithms containing the mean activity of spheres and background activity were proposed [26–28] (Table 1).

The planning target volume (PTV) contains margins for internal motion and setup error. For lung tumors, respiratory motion is the major contributor to internal motion. At the present time, CT simulation is standard for RTP. Because CT provides only snapshot images of a moving tumor, conventional CT images cannot reflect the internal motion. On the other hand, it takes a few minutes to acquire PET images. Thus, PET images are influenced by internal motion, and have the potential to delineate an internal target volume (ITV). Although there are several reports on moving phantom experiments [22, 23, 29], only one study described the benefit of PET images to delineate ITV [23]. However, appropriate threshold values for moving phantom have never been reported. In the present study, to determine an appropriate threshold value for target delineation in PET images and to investigate whether PET can delineate a real ITV, a series of experiments using static and moving phantom spheres were performed.

Materials and methods

Phantom object

In this study, the NEMA IEC Body Phantom Set (Data Spectrum, Chapel Hill, NC, USA) was used. This phantom is composed of an ellipse and six spheres. The volume of the ellipse is 10.3 l, and the ellipse phantom has six spheres inside it. The inner diameters of spheres ranged from 10 mm to 38 mm (10 mm, 13 mm, 17 mm, 22 mm, 28 mm, and 37 mm). At our institution, 3 MBq/kg of [^{18}F] fluoro-2-deoxyglucose (^{18}FDG) is injected into patients, and a PET image is taken 1 h later. At the time of image acquisition, 1 standardized uptake value (SUV) is equivalent to 2.055 MBq/kg. This ^{18}FDG activity was defined as 1 SUV-p (2055 Bq/ml) in the phantom experiments. The ellipse phantom was filled with a positron emitter of 0.5 SUV-p (1028 Bq/ml) ^{18}FDG activity as the background. This activity is close to that seen commonly

Table 1 Literature review of thresholds for contouring phantoms or gross tumor volumes with positron emission tomography (PET)

Authors	No. of patients or phantom	Thresholds
Erdi et al. [21]	Static phantom	42%[a]
Nagel et al. [22]	Moving phantom	34%[a]
Caldwell et al. [23]	Moving phantom	15%[a]
Deniaud-Alexandre et al. [24]	101 pts (NSCLC)	50%[a]
Ford et al. [25]	Static phantom 8 pts (head and neck cancer)	42%[a]
Nestle et al. [26]	25 pts (NSCLC)	$(0.15 \times I_{mean}) + I_{background}$
Black et al. [27]	Static phantom	0.307 × (mean target SUV) + 0.588
Davis et al. [28]	Static phantom	Bgd + 0.41 × (Sig_{max} − Bgd)
Yaremko et al. [29]	Static and moving phantom	Static: 50%[a] Moving: 25%[a] Gated breath hold
Biehl et al. [30]	20 pts (NSCLC)	<3 cm; 42%[a] 3–5 cm; 24%[a] >5 cm; 15%[a]
Hong et al. [31]	19 pts (NSCLC)	2.5 SUV
Ashamalla et al. [32]	19 pts (NSCLC)	Visual interpretation

NSCLC non-small-cell lung cancer, *pts* patients
[a] Percentage of maximal [^{18}F] fluoro-2-deoxyglucose activity

in normal lungs, measured in 40 patients with lung tumors at our institution.

In the static phantom experiments, the six spheres were filled with ^{18}FDG to get source-to-background (S/B) ratios of 10, 15, and 20, namely, the ratios observed in lung carcinomas. For each S/B ratio, a PET/CT scan was taken, and these images were transferred to RTP system (Eclipse, Varian Medical Systems, Palo Alto, CA, USA) and analyzed. The maximum ^{18}FDG activity (SUV-p-max) was measured in each sphere, and the threshold for target delineation in PET images was expressed as the percentage of measured SUV-p-max for each sphere. The appropriate threshold values for each sphere were determined so that the sizes of the PET delineation in an axial plane become closest to those of each sphere.

In the moving phantom experiments, the background was filled with 0.5 SUV-p ^{18}FDG and spheres were filled with 10 SUV-p ^{18}FDG, which resulted in an S/B ratio of 20:1. This value was observed most commonly in lung tumors at our institution. To simulate a moving lung tumor, a moving device of our own making was used. This device is composed of a mounting unit and a motor unit, allowing oscillatory movement in one dimension. The NEMA phantom was placed on the mounting unit, and moved along the longitudinal plane, which corresponds to the cranio-caudal plane in clinical images. Total translations of 10 mm, 20 mm, and 30 mm were selected as representative of the range of motions reported for lung tumors in the literature [33–35]. A period of oscillation of 4 s was selected, the cycle time typically observed in normal respiration. The experimental setup is shown in Fig. 1. PET and CT images were taken five times, and all data were transferred to the RTP system and analyzed. The maximum size of PET delineation with an appropriate threshold value determined from static experiments was measured in both the axial and sagittal planes, and compared with the corresponding values in that of CT delineation and real ITV distance including an actual sphere size plus movement distance.

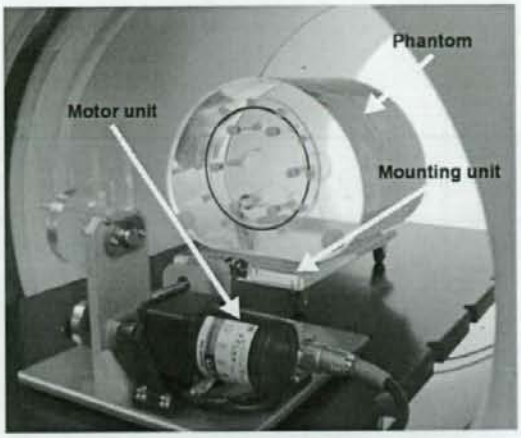

Fig. 1 Experimental setup. The NEMA phantom was placed on a mounting unit, and moved along the longitudinal plane with a period of oscillation of 4 s. The total translation was 10 mm, 20 mm, and 30 mm

Data acquisition

Positron emission tomography/computed tomography scanning was performed with an integrated PET (Biograph)/CT (Somatom Emotion Duo) unit (Siemens Medical Solutions, Hoffmann Estates, IL, USA). The data for the phantom experiments were acquired using a protocol employed for simulating PET/CT at our institution.

Positron emission tomographic scans were acquired in the three-dimensional mode using an axial field of view (FOV) of 163 mm (one bed position). The time for a one bed position scan is 100 s. All PET images were acquired using a matrix of 128 × 128 pixels. At a distance of 10 cm from the center of the FOV, the full-width at half maximum reached 7.4 mm × 7.4 mm × 7.1 mm, in the x, y, and z directions, respectively. A Fourier rebinning algorithm was combined with an ordered subsets expectation-maximization reconstruction (eight subsets, two iterations). The voxel dimensions were 4.5 mm × 4.5 mm × 2.0 mm.

Computed tomographic scans were acquired in the spiral mode, with a slice thickness of 2 mm, a pitch of 6 mm, 130 kv, and 55 mAs. The translation speed of the couch was 7.4 mm/s. All CT images were acquired using a matrix of 512 × 512 pixels. The voxel dimensions were 0.9 mm × 0.9 mm × 2.0 mm.

Results

^{18}FDG activity

Figure 2 shows the mean measured SUV-p-max of six spheres derived from the five measurements in static phantom experiments. For spheres of 22 mm or more, the measured SUV-p-max ranged from 90% to 110% of the injected ^{18}FDG activity, independent of the S/B ratio. In contrast, for spheres of less than 22 mm, the measured SUV-p-max was lower than 80% of the injected ^{18}FDG activity and decreased dependent on the size of the sphere. For the small spheres of less than 22 mm, the