すると，ポータルイメージ上の座標(Portal_x, Portal_y)は，シミュレーションイメージ上の座標(Sim_x, Sim_y)を用いて(1)式と表せる．

$$\begin{pmatrix} Portal\_x \\ Portal\_y \end{pmatrix} = \begin{pmatrix} mag\_x & 0 \\ 0 & mag\_y \end{pmatrix} \begin{pmatrix} Sim\_x \\ Sim\_y \end{pmatrix} + \begin{pmatrix} shift\_x \\ shift\_y \end{pmatrix} \quad \cdots\cdots(1)$$

これらの値から両画像の画素サイズを同じにし，さらに両画像の照射野を重ね合わせることで，骨陰影などの構造物のズレが定量的に解析可能となる．処理手順を以下に示す．

(1)Fig. 6に示した座標系で，対応する基準点5点を用いて拡大率とフィルム上の照射野位置の違いを求める．ここで両者には顕著な位置依存性はないと仮定し，X，Y方向それぞれについて三つの基準点から最小二乗法を用いて算出する．X方向についての拡大率magとフィルム上の照射野位置の違いshiftを(2)～(4)式に示す．式の記号について，Sはシミュレーションイメージ上，Pはポータルイメージ上であることを表し，X，Yはそれぞれ X座標，Y座標を表す．添え字の1にはFig. 6の基準点1，2，Cが含まれる．Y方向についても同様である．

$$\begin{pmatrix} \sum SXi^2 & \sum SXi \\ \sum SXi & N \end{pmatrix} \begin{pmatrix} mag \\ shift \end{pmatrix} = \begin{pmatrix} \sum SXi \cdot PXi \\ \sum PXi \end{pmatrix} \quad \cdots\cdots(2)$$

$$mag = \frac{\begin{vmatrix} \sum SXi \cdot PXi & \sum SXi \\ \sum PXi & N \end{vmatrix}}{\begin{vmatrix} \sum SXi^2 & \sum SXi \\ \sum SXi & N \end{vmatrix}} = \frac{(\sum SXi \cdot PXi)N - (\sum SXi)(\sum PXi)}{(\sum SXi^2)N - (\sum SXi)^2} \quad \cdots\cdots(3)$$

$$shift = \frac{\begin{vmatrix} \sum SXi^2 & \sum SXi \cdot PXi \\ \sum SXi & \sum PXi \end{vmatrix}}{\begin{vmatrix} \sum SXi^2 & \sum SXi \\ \sum SXi & N \end{vmatrix}} = \frac{(\sum SXi^2)(\sum PXi) - (\sum SXi \cdot PXi)(\sum SXi)}{(\sum SXi^2)N - (\sum SXi)^2} \quad \cdots\cdots(4)$$

(2)求めた拡大率mag_x，mag_yとフィルム上の照射野位置の違いshift_x，shift_yより，シミュレーションイメージまたはポータルイメージのうち画素サイズが大きい方の画像を線形補間により拡大，移動し，両画像の照射野を一致させる．

(3)拡大率の大きさで拡大する画像を変えて処理を分ける．(a)mag_x，mag_y>1のとき，シミュレーションイメージを拡大する(Fig. 7)．(b)mag_x，mag_y<1のとき，ポータルイメージを拡大する(Fig. 8)．

2-5 コントラストの改善

Fig. 3に示したシミュレーションイメージとポータルイメージの原画像では，撮影条件の違い，特にX線エネルギーが異なるため両画像のコントラストは大きく異なっている．両画像間のズレを検出するための比較対象となる骨陰影は，70kVpのX線で撮影したシミュレーションイメージでは良好に描出されているが，6MVのX線で撮影したポータルイメージでは描出能が大きく劣っている．これ以外にも撮影条件の設定ミスなどのため，コントラストおよびフィルム濃度が不良になる場合が考えられ，これらの補正が必要となってくる．ここでは各画像のヒストグラムからその偏りを補正(一様化)し，コントラストを強調する手法(ヒストグラムの平坦化)を用いた．

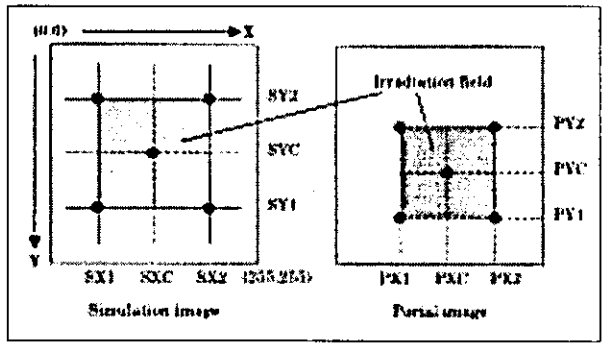

Fig. 6 Coordinate system of a simulation image and portal image.

2-6 骨陰影のエッジ抽出

コントラスト強調したシミュレーションイメージおよびポータルイメージから，両画像間のズレを検出するための比較対象となる骨陰影のエッジを抽出する．Fig. 9に示したコントラスト強調画像では階調の不連続な部分が発生しており，このままエッジ強調処理を行った場合，この部分が線状に残ってしまう可能性がある．そこで先に移動平均によりスムージング処理を行った．使用した線形平滑化フィルタを(5)式に示す．

$$g(x,y) = \frac{1}{9}\{f(x-1,y-1)+f(x,y-1)+f(x+1,y-1) + f(x-1,y)+f(x,y)+f(x+1,y) + f(x-1,y+1)+f(x,y+1)+f(x+1,y+1)\} \quad \cdots\cdots(5)$$

ここで座標(x, y)における入力画像の画素値をf(x, y)，出力画像の画素値をg(x, y)とする．

次に8近傍に対する2次微分処理を行い画像中の高周波成分を強調し，エッジ部分を抽出する．二次元空間における2次微分すなわちラプラシアンLおよびラプラシアンフィルタを(6)，(7)式に示す．

$$L = \frac{\partial^2}{\partial x^2} + \frac{\partial^2}{\partial y^2} \quad \cdots\cdots(6)$$

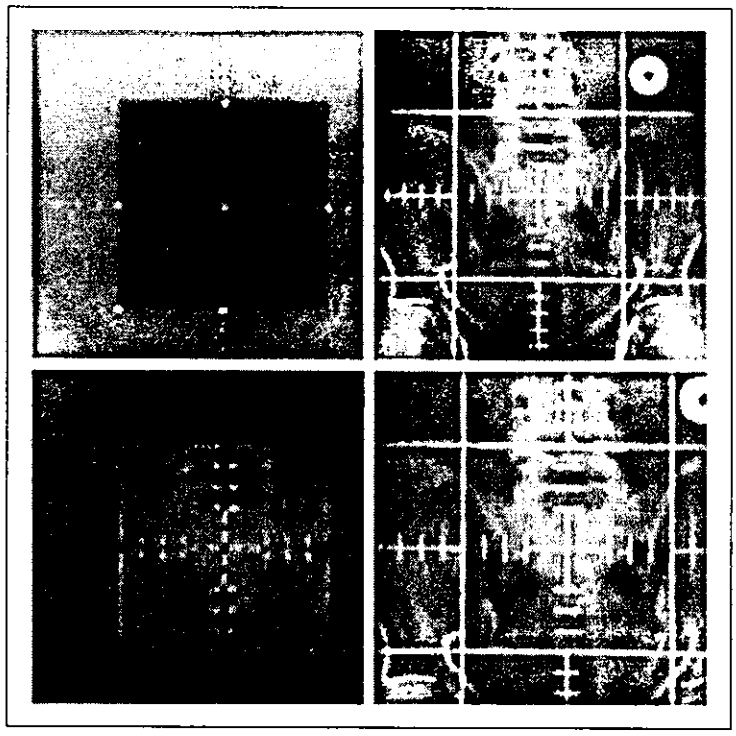

Fig. 7 Result of geometrical transformation in the case of a simulation image that is enlarged and moved.
(a) Original portal image.
(b) Original simulation image.
(b') Simulation image that is enlarged and moved.
(c) Superimposed image of the processed simulation image (b') and original portal image (a).

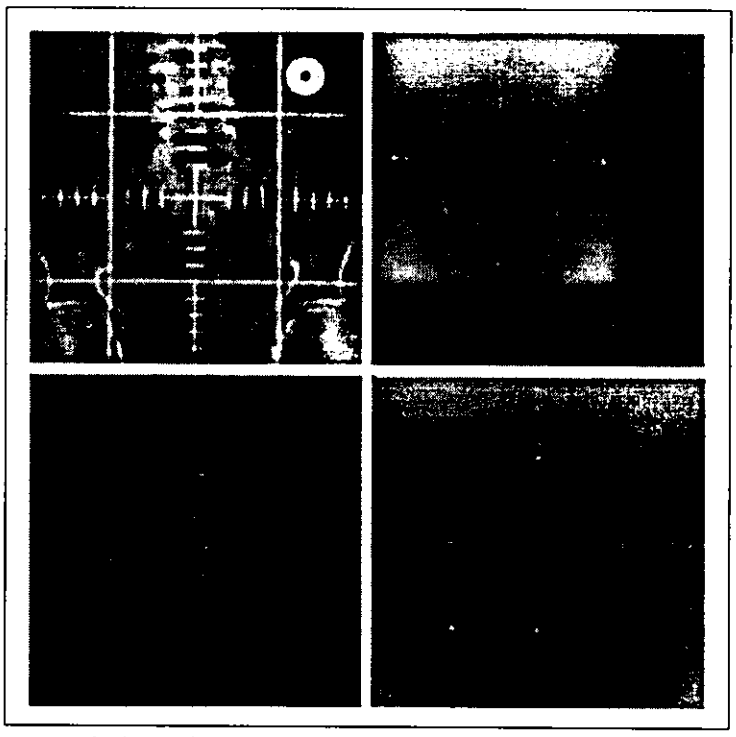

Fig. 8 Result of geometrical transformation in the case of a portal image that is enlarged and moved.
(a) Original simulation image.
(b) Original portal image.
(b') Portal image that is enlarged and moved.
(c) Superimposed image of the processed portal image (b') and original simulation image (a).

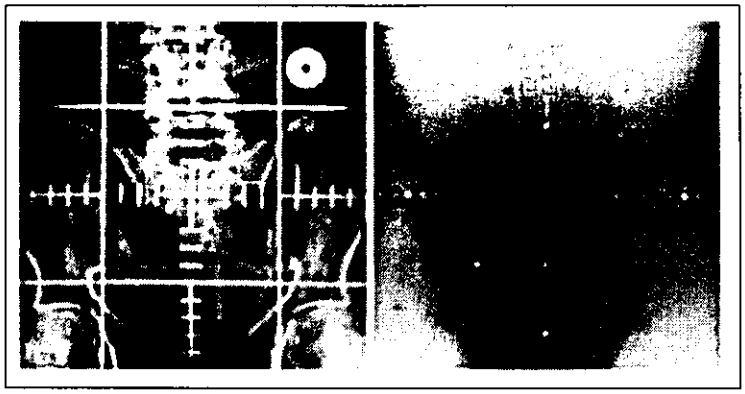

Fig. 9 Effect of contrast enhancement technique.
(a) Simulation image after processing.
(b) Portal image after processing.

a | b

$$g(x,y)=-f(x-1,y-1)-f(x,y-1)-f(x+1,y-1)$$
$$-f(x-1,y)+8f(x,y)-f(x+1,y)$$
$$-f(x-1,y+1)-f(x,y+1)-f(x+1,y+1)$$
$$\cdots\cdots\cdots\cdots\cdots\cdots(7)$$

最後に階調画像を2値化するにあたり，その閾値を決める必要があるが，ヒストグラムがなだらかに変化する(山や谷が存在しない)場合，閾値を絶対値として指定する方法では画像全体の濃淡の影響を大きく受けると考えられる．そこで，全画素数に対する2値化後の図形画素の割合を指定し2値化処理を行う，パーセンタイル法を用いた．さらに両画像上には1cm間隔の目盛りが刻まれており，これらが高い相関を示すためシミュレーションイメージ上の目盛り線に相当する部分を消去した(Fig. 10)．

2-7 ズレの方向および大きさの検出

シミュレーションイメージに対するポータルイメージのズレの方向および大きさを検出するため，両画像間の相互相関関数を求めた．(8)式に連続系，無限個のデータ系列による二次元の相互相関関数を示す．

$$R_{fg}(\kappa,\lambda)=\lim_{M\to\infty}\lim_{N\to\infty}\frac{1}{4MN}\int_{-M}^{M}\int_{-N}^{N}\{f(m,n)\cdot g(m+\kappa,n+\lambda)\}dmdn$$
$$(-\infty\le\kappa\le\infty,-\infty\le\lambda\le\infty)\quad\cdots\cdots\cdots\cdots(8)$$

ここで，(8)式のκ，λは二つのアナログ画像f(m, n)とg(m, n)の間のズレ量を表しており，相互相関値R_{fg}が最大となる(κ, λ)が両画像のズレとなる．

これを離散系，有限個のデータ系列であるディジタル画像f(x, y)，g(x, y) {x=0, 1, 2, …, Xsize−1} {y=0, 1, 2, …, Ysize−1}に対応させた二次元の相互相関関数を(9)式に示す．ただし，Xsize，Ysizeは画像f，gのマトリックスサイズであり，0≦x<Xsize，0≦y<Ysizeの範囲外ではf(x, y)=g(x, y)=0と仮定する．

$$R_{xy}(k,l)=\frac{1}{(Xsize-|k|)(Ysize-|l|)}\sum_{x=0}^{Xsize-1}\sum_{y=0}^{Ysize-1}\{f(x,y)\cdot g(x+k,y+l)\}$$
$$(k=-Xsize/2,\cdots,0,\cdots,Xsize/2\quad l=-Ysize/2,\cdots,0,\cdots,Ysize/2)$$
$$\cdots\cdots\cdots\cdots\cdots\cdots(9)$$

ここで，(9)式のk，lは二つのディジタル画像f(x, y)とg(x, y)の間のズレ量を表しており，相互相関値R_{xy}が最大となる(k, l)が両画像のズレとなる．

3. 結 果

基準点の検出(2-3節)pおよび拡大率とフィルム位置の補正(2-4節)の処理結果をFig. 7，8に示す．Fig. 7b，8bを拡大，移動処理した結果がFig. 7b'，8b'である．画素サイズはFig. 7a，8aと同じになる．両者を重ね合わせた画像がFig. 7c，8cで，シミュレーションイメージの照射野とポータルイメージの照射野が一致しているのが確認できる．

コントラストの改善(2-5節)の処理結果をFig. 9に示す．原画像(Fig. 3)と比較してコントラストが強調されたことが確認できる．

骨陰影のエッジ抽出(2-6節)の処理結果をFig. 10に示す．ここまでの処理で，シミュレーションイメージとポータルイメージの拡大率，つまり画素サイズが同じとなり，画像上の照射野位置が一致した．さらにこの状態で両画像に含まれる骨陰影のエッジ部分が抽出されていることが確認できる．

ズレの方向および大きさの検出(2-7節)の処理結果をFig. 11に示す．この例では，ポータルイメージの骨陰影がシミュレーションイメージのそれに対して，画像上で左に8pixel，上に6pixelずれていると検出した．すなわち既知のズレ量がX，Y方向ともに5.0mmであるのに対して，本手法ではX方向に6.2mm，Y方

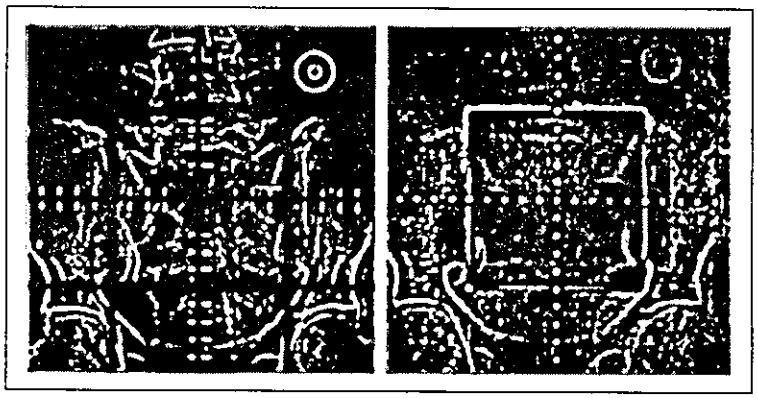

Fig. 10 Effect of edge extraction technique.
(a) Simulation image after processing.
(b) Portal image after processing.

a | b

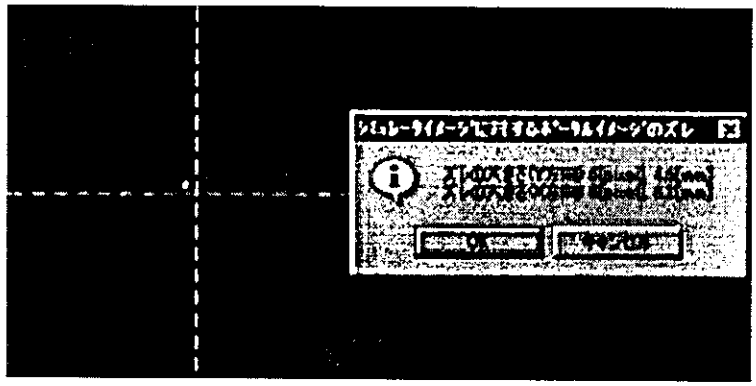

Fig. 11 Calculated values of a two-dimensional cross-correlation function.

向に4.6mmずれていると検出した.

本手法の有用性を評価するため, 1-2節に示した84対のシミュレーションイメージとポータルイメージを用いて処理を行った. 横軸に既知のズレ量と検出値の差(誤検出量)を, 縦軸に頻度を示した結果をFig. 12に示す. ズレの大きさについて, 誤検出量の絶対値として, 平均0.9mm, 標準偏差0.8mm, 最大2.7mmの誤りで検出できた. またFig. 13より既知のズレ量が0.0mmの場合では, 同5.0mmと10.0mmの場合と比べて, その平均誤検出量が有意に小さくなった.

4. 考 察

シミュレーションイメージとポータルイメージでは撮影に用いるX線エネルギーが異なるため, 被写体コントラストが大幅に異なっている. シミュレーションイメージでは約70kVpくらいであり光電効果が支配的となるため, 被写体コントラストは原子番号による影響を大きく受ける. しかしポータルイメージでは約6MVでありコンプトン効果が支配的となるため, 被写体コントラストは密度による影響を大きく受ける.

一般に両画像の比較は目視で行われており, 主に被写体コントラストの違いに起因する画像コントラストの違いが両画像の比較を困難なものとしている. 本手法では両画像に対してヒストグラムの平坦化処理を行うことで, 人為的なパラメータを用いずに画像コントラストが強調できたと考える. 2値化処理では, 対象とする部位が同じ場合では画像中に含まれる骨陰影などの割合も似たような値となるため, パーセンタイル法により間接的に閾値を決定する方が被写体の影響(個体差)を受けにくいと考えられる. 逆に対象部位が異なる場合では, 画像に含まれる骨陰影の割合が変わってしまうため, パーセンタイル法で指定する図形画素の割合を見直す必要があり, 今後の課題である.

また, X線フィルムをディジタル化する過程で画素サイズが決まるが, 本手法では照射野サイズと基準点の座標より画素サイズを計算している. ここで, 外部放射線治療装置の精度管理に関するガイドライン[7]によると, X線照射野の許容誤差は, その大きさが20cm×20cmより小さい場合では, ±2mmとなっている. 本手法の有用性の検討で用いた照射野サイズは最

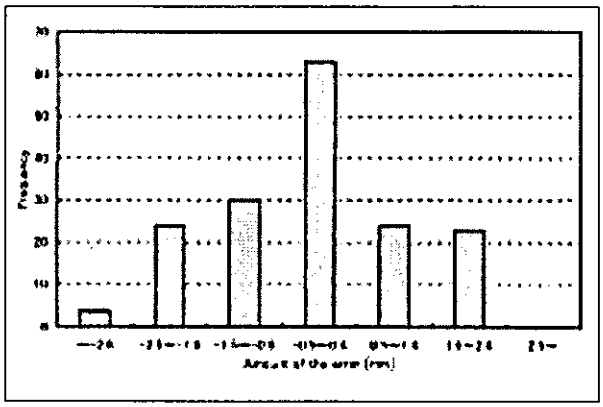

Fig. 12 Results of this method in 84 pairs of simulation images and portal images.

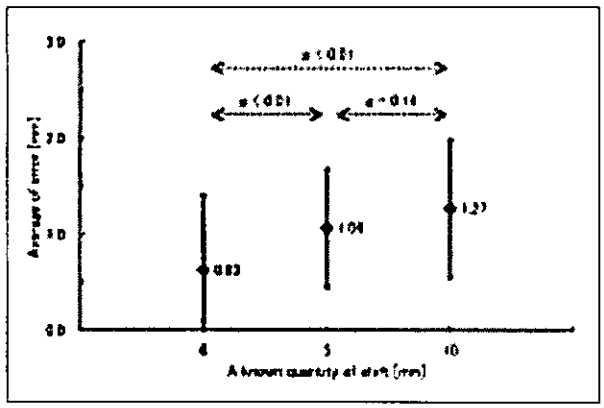

Fig. 13 Results classified according to the known quantity of shift.

小 5cm×5cmであり，このときの誤差率が最も大きく，4%となる．本手法では，ズレの大きさは画素数として検出し，これに画素サイズを乗じて実寸に変換している．そのためズレが大きい場合では，計算した画素サイズに含まれる誤差が，ズレとして検出した画素数倍されることによって，Fig. 13に示すように誤検出量が大きくなったと考えられる．さらに，最終的な精度や検出限界は，画素サイズに大きく依存するため，目標値より十分に小さい画素サイズでディジタル化する必要がある．今回，画素サイズは0.8mm程度であり，その結果は誤検出量の平均値+1SDで1.7mmとなった．この結果はAAPMレポートTG40[8]に示された患者位置決め誤差 5mm以内という報告より小さく，シミュレーションイメージとポータルイメージのズレの検出に使用可能と考える．

5. 結 語

シミュレーションイメージとポータルイメージの間のズレを，コンピュータを用いた画像処理により客観的かつ定量的に検出する方法を開発した．骨盤部人体ファントムを用い有用性を検討した結果，平均0.9mmの誤りで検出できた．また本手法では人為的なパラメータを必要としないため，処理の自動化が可能である．

謝 辞

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2004 年 1 月

図表の説明

Fig. 1　すべてのシミュレーションイメージ
上段より，アイソセンタが仙骨中央部，腸骨部，股関節部の3種類．左列より，照射野サイズが5cm×5cm，10cm×10cm，15cm×15cm，頭尾方向14cm非対称×左右方向8cm非対称の4種類．

Fig. 2　画像処理の概略

Fig. 3　シミュレーションイメージとポータルイメージの原画像
図中の丸印は五つの基準点を表す．
(a)シミュレーションイメージの原画像
(b)ポータルイメージの原画像

Fig. 4　基準点の検出(シミュレーションイメージ)
(a)原画像
(b)Y方向のプロファイルから抽出したピーク
(c)X方向のプロファイルから抽出したピーク
(d)X方向およびY方向の平均画素値のプロファイル

Fig. 5　基準点の検出(ポータルイメージ)
(a)原画像
(b)Y方向のプロファイルから抽出したピーク
(c)X方向のプロファイルから抽出したピーク
(d)X方向およびY方向の平均画素値のプロファイル

Fig. 6　シミュレーションイメージとポータルイメージの座標系

Fig. 7　幾何学変換処理(シミュレーションイメージを拡大する場合)
(a)ポータルイメージの原画像
(b)シミュレーションイメージの原画像
(b')拡大，移動処理したシミュレーションイメージ
(c)拡大，移動処理したシミュレーションイメージ(b')とポータルイメージの原画像(a)の重ね合わせ

Fig. 8　幾何学変換処理(ポータルイメージを拡大する場合)
(a)シミュレーションイメージの原画像
(b)ポータルイメージの原画像
(b')拡大，移動処理したポータルイメージ
(c)拡大，移動処理したポータルイメージ(b')とシミュレーションイメージの原画像(a)の重ね合わせ

Fig. 9　コントラスト強調処理画像
(a)処理後のシミュレーションイメージ
(b)処理後のポータルイメージ

Fig. 10　エッジ抽出処理画像
(a)処理後のシミュレーションイメージ
(b)処理後のポータルイメージ

Fig. 11　二次元の相互相関関数

Fig. 12　84対のシミュレーションイメージとポータルイメージの処理結果

Fig. 13　ズレの既知量別の処理結果

RAPID SUPERSELECTIVE HIGH-DOSE CISPLATIN INFUSION WITH CONCOMITANT RADIOTHERAPY FOR ADVANCED HEAD AND NECK CANCER

Akihiro Homma, MD, PhD,[1] Yasushi Furuta, MD, PhD,[1] Fumiyuki Suzuki, MD,[1] Nobuhiko Oridate, MD, PhD,[1] Hiromitsu Hatakeyama, MD,[1] Tatsumi Nagahashi, MD,[1] Satoshi Ushikoshi, MD,[2] Takeshi Asano, MD,[2] Takeshi Nishioka, MD, PhD,[2] Hiroki Shirato, MD, PhD,[2] Satoshi Fukuda, MD, PhD[1]

[1] Department of Otolaryngology–Head & Neck Surgery, Hokkaido University Graduate School of Medicine, Kita 15, Nishi 7, Kita-ku, Sapporo 060-8638, Japan. E-mail: ak-homma@med.hokudai.ac.jp
[2] Department of Radiology, Hokkaido University Graduate School of Medicine, Sapporo, Japan

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Abstract: *Purpose.* The purpose of this study was to evaluate the efficacy of rapid superselective high-dose cisplatin infusion with concomitant radiotherapy for previously untreated patients with advanced head and neck cancer.

Methods. Forty-three patients for whom surgery was contraindicated or who rejected radical surgery were given superselective intra-arterial infusions of cisplatin (100–120 mg/m^2/week) with simultaneous intravenous infusion of thiosulfate to neutralize cisplatin toxicity and conventional extra-beam radiotherapy (65 Gy/26 f/6.5 weeks).

Results. Thirty-nine patients had stage IV disease, and the remaining four had stage III disease. During the median follow-up period of 21 months, the 3-year locoregional progression-free rates of all patients (n = 43) and patients with unresectable disease (n = 24) were 68.9% and 56.4%, respectively. In addition, the 3-year overall survival of all patients and patients with unresectable disease was 54.0% and 39.6%, respectively. Thirty-five patients (81.4%) experienced nonhematologic grade III to IV toxicity, including mucositis (n = 16), nausea/vomiting (n = 8), and neurologic signs (n = 2). No patient died as a result of treatment toxicity. There are 29 surviving patients without evidence of disease, all of whom are able to have oral intake without feeding-tube support.

Conclusions. We confirmed the efficacy of superselective arterial infusion and concomitant radiotherapy, which can concentrate the attack of supradose cisplatin on locoregional disease. Even patients with unresectable disease can be cured. Further studies are needed to establish the indications, long-term outcome, and possible late side effects of this treatment. © 2004 Wiley Periodicals, Inc. *Head Neck* **27:** 65–71, 2005

Keywords: head and neck cancer; intra-arterial; cisplatin; chemoradiation

The main treatment for advanced head and neck cancer is surgery, with or without adjunct radiotherapy. Radical surgery is not indicated in patients with unresectable disease and is refused by some patients; generally, the prognosis with radiotherapy alone is not favorable. A recent combination of chemotherapy and radiotherapy has achieved good results in advanced cases of

Correspondence to: A. Homma

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head and neck cancer. This treatment improved local control and overall survival compared with radiotherapy alone in previously untreated patients with unresectable disease, but toxicity was severe.[1,2] Superselective arterial infusion of cisplatin with concomitant radiotherapy (RADPLAT) has also been reported to be a promising treatment.[3] RADPLAT incorporates a novel technique for infusing cisplatin directly into the tumor bed while minimizing the systemic effects of the drug and has been reported to achieve an 80% complete response rate in advanced cases.[4] In this study, we used RADPLAT in patients with unresectable disease and patients with advanced resectable disease who had refused radical surgery.

PATIENTS AND METHODS

Patient Characteristics. From October 1999 to March 2003, 43 patients with locally advanced head and neck cancer were treated at Hokkaido University Hospital (Sapporo, Japan). All patients were initially evaluated by a multidisciplinary team consisting of otolaryngologists and radiation oncologists, and tumors were classified according to the 2002 Union Internationale Contre le Cancer (UICC) staging system.[5] The stage of the tumor was determined on the basis of patient history, physical examination, chest x-rays, and CT, MRI, or both. All the patients either had disease for which radical surgery was contraindicated or had rejected radical surgery. Unresectable disease was defined as stage T4b in the 2002 UICC staging system for primary sites or disease in which neck lymph node metastases encased the common or internal carotid artery or invaded the prevertebral fascia. Medical unsuitability for resection and refusal of surgery were not included in the definition of unresectable disease.

The presence of distant metastases (M1) or prior treatment of any kind for the cancer rendered a patient ineligible for the study. The following criteria had to be satisfied for the patients to be considered eligible for entrance to the study: patients had to be no older than 75 years old with a World Health Organization performance status of 0 to 2, a white cell count of at least 4.0×10^9/L, a platelet count of at least 100×10^9/L, a hemoglobin concentration of at least 9.5 g/dL, serum glutamic oxaloacetic transaminase and serum glutamic pyruvic transaminase of less than twice the upper limit of the normal range, a total bilirubin concentration of less than 2.0 mg/dL, a serum creatinine concentration of less than 1.5 g/dL, a blood urea nitrogen concentration of less than 25 mg/dL, and a creatinine clearance of more than 60 mL/min. The disease had to be measurable or amenable to evaluation and had to be documented as precisely as possible before treatment by endoscopy, including, if possible, CT and/or MRI. Written informed consent was obtained from all patients before entry into the study. Patients who were pregnant or breast-feeding were excluded from the study.

Chemotherapy. All patients received concurrent intra-arterial cisplatin and intravenous (IV) sodium thiosulfate infusions in the following manner: cisplatin (100–120 mg/m^2 per week for 3–4 weeks) was infused through a microcatheter placed angiographically to selectively encompass only the dominant blood supply of the targeted tumor. The cisplatin was injected as rapidly as possible until it refluxed slightly into the more proximal vessels during peak systole. In patients with nodes greater than 3 cm, some of the drug (approximately 20–30 mg) was delivered to this region. Simultaneously with the cisplatin, sodium thiosulfate (20–24 g) was given intravenously, as described by Robbins et al.[4] All arterial catheterizations were accomplished transcutaneously through the femoral artery, and the catheters were removed immediately after infusion.

So that patients excreted the cisplatin rapidly, 10 L of lactated Ringer's solution were given over a period of 24 hours. A 5HT3-receptor antagonist was given to all patients before arterial infusion to minimize nausea and vomiting. Chemotherapy was completed during the first 4 weeks, provided that patients responded well in the early treatment period and had received one to three arterial infusions.

Radiotherapy. All patients received external radiotherapy (40 Gy/16 fractions/4 wk) with 4-megavolt or 6-megavolt photons from a linear accelerator to the primary sites and regional lymphatic area. The treatment was planned with a CT simulator and a three-dimensional dose calculation computer. For patients suspected of having lymph node metastases, the lower neck region and supraclavicular fossa were prophylactically irradiated with a total of 40 Gy by use of an anterior single port. Electron beams were used to boost the dose to the posterior cervical lymph nodes. The dose to the spinal cord was kept below 40 Gy in all instances.

After the initial dose of 40 Gy had been administered, an additional dose of 25 Gy was given with a shrunken field in 10 fractions over 2.5 weeks. This treatment was administered to all patients other than two patients with tongue cancer who were treated by afterloading high dose-rate radiation with iridium-192 after external radiotherapy of 40 Gy.

Management of the Neck. Patients with regional lymph node metastasis of the neck were treated with 65 Gy of radiotherapy and chemotherapy. If lymph node metastases remained or recurred, patients with resectable neck disease were referred for dissection.

Evaluation of Response and Toxicity. Responses were evaluated by clinical examination and/or CT or MRI studies at 6 to 8 weeks after the completion of therapy. Standard criteria were used to assess response. Complete response was defined as total resolution of the grossly visible tumor, and partial response was defined as 50% or greater reduction in the grossly visible tumor.

It can be impossible to differentiate between radiographic changes related to the treatment and scar tissue from persisting tumor. Over time, scar tissue will remain stable, but persistent tumor tissue will progress. We labeled patient outcomes to reflect this uncertainty: a patient with radiologic changes that remain stable over time and no signs or symptoms of disease was considered to be "progression free." Biopsy was performed only to document recurrence, if indicated. All toxicities encountered during therapy were evaluated according to the National Cancer Institute—Common Toxicity Criteria (Version 2.0, 1998).

Statistical Analysis. The major endpoint of the study was overall survival. Additional endpoints included locoregional control rate and toxicity. All patients were closely observed during follow-up. The longest follow-up period was 48 months, and the shortest was 3 months; the median and mean follow-up periods were 20 and 21 months, respectively.

Cases of persistent or recurrent primary or neck disease after completion of chemoradiotherapy were considered to be locoregional failures unless salvage was successful. Probabilities of overall survival, which included death from any cause, and locoregional control rates (locoregional progression-free rates computed from the beginning of treatment to the time of locoregional relapse) were calculated by the Kaplan-Meier method and compared by the log-rank test. P values less than .05 were considered significant. Statistical calculations were performed by use of the Stat-View software package (version 5.0, Abacus Concepts, Inc., Berkeley, CA).

RESULTS

Forty-three patients (34 men and 9 women) were enrolled in this study and could be evaluated (Table 1). Ages ranged from 25 to 73 years (median, 55 years). Among the 43 patients, 24 (55.8%) were considered to have unresectable disease, and the remaining 19 (44.2%) had refused radical surgery. Sixteen patients (37.2%) had unresectable primary disease, 10 (23.3%) had unresectable neck disease, and two had both. The histologic findings of the tumors were as follows: squamous cell carcinoma (n = 36), adenoid cystic carcinoma (n = 2), and undifferentiated carcinoma (n = 5). Primary tumor sites included the nasal and paranasal sinuses (n = 20), oropharynx (n = 9), hypopharynx (n = 8), oral cavity (n = 5), and parotid gland (n = 1).

Clinical stage is listed in Table 2. Thirty-nine patients had stage IV disease, and the remaining four had stage III disease. Thirty patients (70.0%) had T4 primary disease, and 19 (44.2%) had more than N2b neck disease.

Compliance. Thirty-seven patients (86.0%) completed therapy without interruption. Four pa-

Table 1. Clinical characteristics (n = 43).

Characteristic	No. patients (%)
Age, y	
Range	25–73 y
Median	55 y
Mean	53.86 y
Sex	
Male	34 (79.1)
Female	9 (20.9)
Primary tumor site	
Oral cavity	5 (11.6)
Oropharynx	9 (20.9)
Hypopharynx	8 (18.6)
Nasal and paranasal sinus	20 (46.5)
Parotid gland	1 (2.3)
Resectability	
Resectable	19 (44.2)
Unresectable	24 (55.8)
Histologic findings	
Squamous cell	36 (83.7)
Undifferentiated	5 (11.6)
Adenoid cystic	2 (4.7)

Table 2. T and N stage (n = 43).

T classification	No. patients by N classification						Total
	0	1	2a	2b	2c	3	
3	4			5	3	1	13
4a	9	1		1	2	1	14
4b	9	1		3	2	1	16
Total	22	2		9	7	3	43

tients had their treatment interrupted for 4 to 30 days (median, 12 days), because of pneumonia, dermatitis, mucositis, or poor general condition. Two patients did not complete radiotherapy; one stopped radiotherapy after four courses of arterial infusion and 40 Gy of radiotherapy because of a pulmonary metastasis that worsened rapidly, and the other stopped after four courses of arterial infusion and 50 Gy of radiotherapy because of quadriplegia from arterial infusion.

Toxicity. Although the treatment regimen was intensive, acute toxicity was manageable in most patients (Table 3). No patient died as a result of treatment toxicity. Thirty-five patients (81.4%) experienced grade III to IV toxicity. Nonhematologic side effects included mucositis (n = 16), nausea/vomiting (n = 8), and neurologic signs (n = 2). Hematologic toxicity consisted of leukopenia (n = 12), anemia (n = 2), and thrombocytopenia (n = 1), all of grade III. Arterial infusion had to be stopped after only one infusion in one patient who had sepsis develop because of toxicity. There was one patient with hypopharyngeal cancer who had

Table 3. Toxicity (n = 43).

Toxicity	No. patients by toxicity grade			
	I	II	III	IV
Allergic reaction	1		1	
Hearing	6	4		
Anemia	7	16	2	
Leukopenia	1	16	12	
Thrombocytopenia	3	3	1	
Arrhythmia	1			
Hypotension	1			
Fever	4	9	5	
Alopecia	6	9		
Dermatitis	5	7	1	2
Nausea/vomiting	12	9	8	
Mucositis	1	16	14	2
Diarrhea		2		
Liver dysfunction	5	2		
Neuropathy		4	1	1
Renal	1	1		

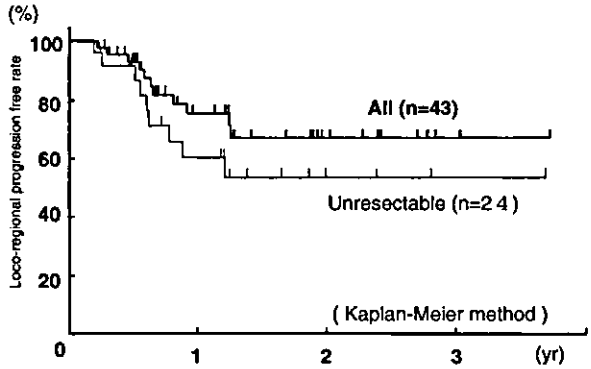

FIGURE 1. Locoregional progression-free rate.

neurologic sequela, quadriplegia. MRI revealed a spinal lesion injury. We considered the thyrocervical trunk, from which cisplatin was infused, as having communication with the anterior spinal artery. He recovered from paralysis of upper extremities but not of the lower extremities. All of the 29 surviving patients who have no evidence of disease are able to have oral intake without feeding-tube support. One patient experienced osteonecrosis of the mandible, but did not require surgical treatment.

Locoregional Response and Overall Survival. The 3-year locoregional progression-free rate was 68.9% for all patients (n = 43) and 56.4% for patients with unresectable disease (n = 24; Figure 1). The 3-year overall survival was 54.0% for all patients and 39.6% for patients with unresectable disease (Figure 2).

Response of the Primary Disease. Of the 43 patients entered into the treatment program, complete responses in the primary site were obtained in 18 (41.9%) and partial responses in 25 (58.1%).

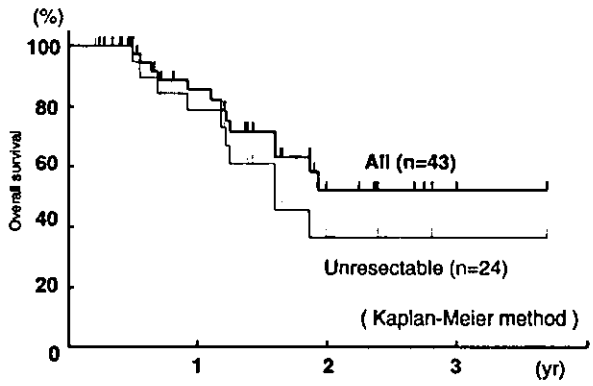

FIGURE 2. Overall survival.

Table 4. Response by primary site.

Primary tumor site	No. patients	No. patients (%) by response: Complete response	Partial response
Oral cavity	5	4 (80.0)	1 (20.0)
Oropharynx	9	5 (55.6)	4 (44.4)
Hypopharynx	8	2 (25.0)	6 (75.0)
Nasal and paranasal sinus	20	7 (35.0)	13 (65.0)
Parotid gland	1	0 (0.0)	1 (100.0)
Total	43	18 (41.9)	25 (58.1)

Response by primary site is listed in Table 4. The primary disease was well controlled by RADPLAT in 35 patients (81.4%). The remaining eight patients (18.6%) had persistent or recurrent primary disease after the completion of RADPLAT. Of these, two patients did not complete radiotherapy because of pulmonary metastasis and quadriplegia, and the other two patients had interruption to their radiotherapy of 16 and 30 days. Among the eight patients with persistent or recurrent primary disease, three patients with maxillary sinus cancer underwent salvage surgery, but this failed in each case.

Response of Neck Disease. Among the 21 patients with positive neck disease, the diseases of 14 (66.7%) were well controlled by RADPLAT without surgery. Another three patients with persistent neck disease after RADPLAT were treated successfully by salvage neck dissection. Thus, 17 patients (81.0%) had well-controlled positive neck disease. The remaining four patients were not successfully controlled; two did not complete radiotherapy, one had persistent unresectable neck disease after therapy, and the remaining patient, with N2b disease, had disease of the opposite retropharyngeal node develop.

Sites of First Recurrence. The site of first recurrence was identified whenever possible. Recurrence first occurred at distant metastases in six patients, at the primary site in six patients, and in regional lymph nodes in two patients. Two patients who did not complete RADPLAT had persistent disease.

DISCUSSION

Superselective arterial infusion of cisplatin was first reported by Robbins et al[6] in 1992. This treatment consisted of rapid superselective intra-arterial infusion of supradose cisplatin once a week combined with sodium thiosulfate for systemic cisplatin neutralization. Dose intensities of cisplatin equivalent to 10-fold that of standard IV cisplatin regimens are possible with this strategy.[7] Moreover, intratumor platinum levels were found to be twofold to 20-fold greater than in measurements obtained after IV and more conventional intra-arterial infusions.[8] In subsequent trials, the cisplatin infusion regimen has been combined with radiation therapy. We believe that the advantage of RADPLAT lies not only in the cisplatin itself but also in its established role as a radiation enhancer. Moreover, cisplatin enhances the effects of radiation on normal tissue less than other chemotherapeutic drugs. A complete response in the primary site was obtained in 171 (80%) of 213 patients with stage III to IV squamous cell carcinoma.[4] We, therefore, used RADPLAT on patients with unresectable diseases and those with resectable advanced disease who refused radical surgery.

Robbins et al[4] reported that 5-year overall survival and locoregional control were 38.8% and 74.3%, respectively, in 213 patients with stage III to IV squamous cell carcinoma. The follow-up period in this study is shorter than Robbins' study so far; therefore, it may be inappropriate to compare them. However, the results of our study were similar to those of Robbins et al despite the fact that our patients had more advanced disease. It may be that our arterial infusion procedure was more selective; Robbins et al reported that they did not permit either the guidewire or the catheter to pass beyond the origin of the occipital, lingual, or facial arteries,[9] whereas we inserted microcatheters as close as possible to the vessels feeding the tumor.

In this study, we carefully defined our patient population so our findings could be more accurately compared with those of other studies. The term "unresectable" should be clearly defined, because its use may have changed over time because of developments in surgery and diagnostic imaging technology, increased experience of treating patients with unresectable and/or borderline disease, etc. Moreover, "unresectable" was not clearly defined in previous reports[2,10,11]; in these studies, judgments of the feasibility of surgery may have been influenced by institutional practice, individual skill, and author experience. We, therefore, defined T4b primary site disease as unresectable. "T4b" is defined in the new UICC (6th edition).

Table 5. Toxicity by reporters.

Reporter (total number)	Adelstein (95)		Harrison (52)		Wendt (130)		Robbins (213)		Homma (43)	
Grade 3–5 toxicity	No.	%	No.	%	No.	%	No.	%	No.	%
Nausea/vomiting	15	15.8			14	10.8	2	0.9	8	18.6
Mucositis/dysphagia	43	45.3	52	100	50	38.5	56	26.3	16	37.2
Leukopenia	40	42.1			20	15.4			12	27.9
Thrombocytopenia	3	3.2			2	1.5			1	2.3
Anemia	17	17.9			2	1.5	17	8.0	2	4.7
Renal	8	8.4					0		0	
Skin	7	7.4			22	16.9			3	7.0
Neurologic							9	4.2	2	4.7
Cardiovascular							8	3.8	0	
All grade 3–5	85	89.5					89	41.8	35	81.4
Feeding tube	49	51.6							0	
Toxic death	4	4.2	2	3.8			6	2.8	0	

Given these caveats, our results can be compared with those of previous studies. Adelstein et al[10] reported on a phase III randomized trial in patients with unresectable squamous cell head and neck cancer. In this study, the 3-year overall survival was 37% in the group treated with single daily fractionated radiation (70 Gy at 2 Gy/d) and concurrent bolus IV cisplatin (100 mg/m^2) given on days 1, 22, and 43. Harrison et al[11] reported that the 3-year overall survival was 36%, and the 3-year local progression-free rate was 58% in patients treated by delayed accelerated radiotherapy and concomitant intravenous cisplatin (100 mg/m^2) given on days 1 and 22, among whom approximately 54% received mitomycin-C on days 1 and 22. However, Wendt et al[2] reported a 3-year overall survival of 49% and a 3-year locoregional control rate of 35% after patients were treated with three chemotherapeutic agents (cisplatin, 5-fluorouracil, and leucovorin) and conventional radiotherapy simultaneously. The reason that the overall survival rate was higher than the locoregional control rate was presumably that many patients with the disease were still alive. This study, with its 3-year overall survival of 39.6% and 3-year locoregional progression-free rate of 56.9%, therefore, had outcomes equivalent to or better than those of previous reports. If we had used the criteria for unresectability of Adelstein et al, 29 of our patients would be considered to have unresectable disease, and their 3-year overall survival would be 47.3%.

The toxicities reported in previous studies are listed in Table 5. Wendt et al[2] reported grade III to IV mucositis in 50 (38.5%) of 130 patients and dermatitis in 22 (16.9%) of 130. Adelstein et al[10] found grade III or higher mucositis (45.3%), nausea/vomiting (15.8%), and renal toxicity (8.4%); four patients (4.2%) died as a result of toxicity. Harrison et al[11] reported that grade III to IV mucositis occurred in all patients and that treatment-related toxicity resulted in the death of two patients (3.8%). In this study, however, the frequency of mucositis was not different from previous reports, and no renal toxicity or treatment-related deaths were observed. This relatively low toxicity must be due to the neutralizing effect of sodium thiosulfate on cisplatin.[12] We found a higher frequency of mucositis (grade III–IV, 38.6%) than did Robbins et al (26.3%),[4] perhaps because our arterial infusion procedure is more selective.

This study shows results equivalent or better than other reports, with a suggestion of reduced toxicity. This must be because the supradose cisplatin was infused superselectively together with sodium thiosulfate to achieve systemic neutralization of the cisplatin. However, as the overall survival rate in this study was not satisfactory because of the development of distant metastases, we plan to add systemic chemotherapy for induction or adjuvant use. Further studies are required to establish the indications, long-term efficacy, and possible late side effects of this treatment.

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CLINICAL INVESTIGATION **Brain**

IMPACT OF MARGIN FOR TARGET VOLUME IN LOW-DOSE INVOLVED FIELD RADIOTHERAPY AFTER INDUCTION CHEMOTHERAPY FOR INTRACRANIAL GERMINOMA

HIROKI SHIRATO, M.D., HIDEFUMI AOYAMA, M.D., JUN IKEDA, M.D., KENJI FUJIEDA, M.D., NORIO KATO, M.D., NOBUAKI ISHI, M.D., KAZUO MIYASAKA, M.D., YOSHINOBU IWASAKI, M.D., AND YUTAKA SAWAMURA, M.D.

Departments of Radiology, Neurosurgery, and Pediatrics, Hokkaido University School of Medicine, Sapporo, Japan

Purpose: We previously published a report stating that germinomas with elevated serum beta human chorionic gonadotropin (HCG-β) had a poor relapse rate, but these findings have not been supported by a multi-institutional trial. The margin for initial gross tumor volume (GTV) before surgery and chemotherapy of the same materials was investigated by retrospective review.

Methods and Material: The 27 patients reported on in the previous paper were analyzed. The two-dimensional margin from the initial GTV to 90% of the prescribed dose of 24 Gy was 2.0 cm for a solitary lesion in the protocol. This margin was measured retrospectively without knowledge of the serum HCG-β level. The whole ventricle field was used for patients with multifocal disease and whole central nervous system field was used for disseminated disease, respectively.

Results: Six relapses were seen in 18 patients with solitary tumors, and were treated with the minimum margin of 1.5 cm or less to the initial GTV. Five of the 6 had initially elevated serum HCG-β at the median of 7.4 mIU/mL, ranging from 0.7–233 mIU/mL. No relapses were seen in the 9 patients who were treated with whole ventricle or whole central nervous system field.

Conclusions: An inadequate margin and elevated serum HCG-β were equally determined to be candidates that caused the poor local control. The whole ventricle is recommended as the smallest target volume for germinoma with or without elevated HCG-β after induction chemotherapy. © 2004 Elsevier Inc.

Germinoma, Central nervous system, Radiotherapy, Induction chemotherapy.

INTRODUCTION

Whole ventricle or larger fields have been the standard of care for intracranial germinoma in our institution (1), as in other institutions (2–4). The possibility of reducing the dose and volume was suggested by the usage of cisplatin-based chemotherapy in the early 1990s (5). A Phase II study on induction cisplatin-based chemotherapy for germinomas followed by 24 Gy radiotherapy was conducted as a regional study in the Hokkaido district of Japan (6). The results of the Phase II study showed a higher relapse rate in germinomas with elevated serum human chorionic gonadotropin beta (HCG-β) than in those without elevated serum HCG-β (7). However, a nationwide prospective study using platinum-based induction chemotherapy followed by low-dose radiotherapy for 130 germinoma patients without elevation of HCG-β, and 34 germinoma patients with elevated HCG-β, did not show significant differences in the relapse-free rate between germinomas without elevated serum HCG-β and germinomas with elevated serum HCG-β (8). Furthermore, treatment volume was reported to be a significant prognostic factor in the nation-wide study. This discrepancy in the significance of HCG-β and the treatment volume prompted us to reevaluate the treatment results of the Hokkaido study by conducting a precise review of the treatment volume.

The purpose of this study is to investigate the impact of margins for the target volume in low-dose involved field radiotherapy after induction chemotherapy for intracranial germinoma.

METHODS AND MATERIALS

The eligibility criteria for patients receiving the induction chemotherapy followed by low-dose radiotehrapy were (*1*) 3 years old or older, (*2*) histologically proven germinoma, and (*3*) no previous chemotherapy or radiotherapy. The patients were classified into two groups as follows: (*1*) a good prognosis group, consisting of patients with a solitary

Reprint requests to: Hiroki Shirato, M.D., Department of Radiology, Hokkaido University School of Medicine, North-15 West-7, Kita-ku, Sapporo 060-8638, Japan. Tel: (+81) 11-706-5975; Fax: (+81) 11-706-7876; E-mail: hshirato@radi.med.hokudai.ac.jp

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germinoma with serum HCG-β < 0.5 mIU/mL, which was the normal upper limit in our institute, and (*2*) an intermediate prognosis group, consisting of patients with a solitary germinoma with HCG-$\beta \geq$ 0.5 mIU/mL, a multifocal germinoma (two or more lesions without evidence of dissemination), and disseminated germinoma (cytological or imaging evidence of dissemination). For the good prognosis group, 3–4 cycles of etoposide (100 mg/m^2) and cisplatin (20 mg/m^2) were given for 5 days every 4 weeks. For the intermediate prognosis group, 3–6 cycles of ifosfamide (900 mg/m^2), cisplatin (20 mg/m^2), and etoposide (60 mg/m^2) were given for 5 days every 4 weeks. After the induction chemotherapy, 24 Gy in 12 fractions in 3 weeks were given to the clinical target volume (CTV) as follows: for solitary germinomas, involved fields, or the initial gross tumor volume (GTV) with a two-dimensional (2D) margin of 2 cm; for multifocal germinoma, whole ventricles; and for disseminated germinoma, whole central nervous system (CNS). The CTV was not altered by the level of serum HCG-β. Within 2 weeks after the completion of the last course of chemotherapy, radiotherapy was started based on computed tomographic (CT) planning with slice-by-slice determination of the target volume. Magnetic resonance imaging (MRI) was used only as the reference, and no image fusion technique was used in the planning. No boost irradiation was used after the 24 Gy irradiation. First salvage treatment for the relapse was predetermined in the protocol as the same chemotherapy followed by whole brain or whole CNS irradiation of 24 Gy. Consequently, the maximum cumulative dose is then 48 Gy to the initial PTV and 24 Gy to the whole brain or whole CNS, respectively, if tumors relapse in patients who have already been treated with focal volume as the initial treatment. Six or 10 MV X-rays were used with multiple portals for the involved fields, parallel opposed fields for the whole ventricles and whole brain, and posterior tandem fields for the whole spinal irradiation, respectively.

Treatment planning was performed with Therac (NEC, Tokyo, Japan) from 1992–1995, and with Focus (CMS Japan, Tokyo, Japan) after 1995. Three-dimensional dose distribution was available for the transaxial, coronal, and sagittal views at the isocenter for patients who were treated with involved fields or whole ventricle fields. The concept of planning target volume (PTV) and CTV was not well understood at the start of this study, and CTV was covered by the isodose curve of 90% of the dose prescribed at the isocenter. In the present study, all CT and MRI slices before surgery/chemotherapy and those for radiotherapy planning were retrospectively reviewed for all the patients entered in the study. A radiation oncologist (H.A.) surveyed the 2D minimum distance between the tumor size before surgery/induction chemotherapy and the 90% isodose surface. The retrospective review was based on the careful visual correlation between planning-based CT and the diagnostic CT or MRI studies but not on image fusion techniques. The serum HCG-β was blinded to the investigator at the time of analysis. For the comparison between two categories, the chi-square test was used. Kaplan-Meier analysis and the log-rank test were used for the survival analysis.

Table 1. Information on the 6 patients who experienced tumor relapse

	Serum HCG-β (mIU/mL)	TV	Site of failure relative to TV	Spinal relapse
Elevated				
1	101	Local	Outside	
2	233	Local	Margin	
3	0.7	Local	Outside	Yes
4	5.3	Local	Outside	
5	0.7	Local	In and outside	
Nonelevated				
6	<0.5	Local	Outside	Yes

Abbreviations: HCG = human chorionic gonadotropin; TV = treated volume.

RESULTS

Between February 1992 and November 1999, 27 patients were entered in the study, as reported in the previous article (7). Age was 15.7 years old at median, distributed from 8–28 years. Twenty patients were 18 years old or younger and 7 patients were more than 18 years old. Cytology of craniospinal fluid, enhanced cranial MRI, and enhanced spinal MRI were used in staging work-up in all patients. The follow-up period was 58 months at median, ranging from 18–102 months. All but 1 patient was followed more than 24 months. Sixteen patients showed a normal serum HCG-β level, which was < 0.5 mIU/mL in our institution, and 11 patients showed elevated HCG-β with the mean at 7.4 mIU/mL, and the range from 0.7–233 mIU/mL. Serum HCG-β was elevated in 8 of the 18 patients with solitary tumors, 2 of the 6 patients with multifocal tumors, and 1 of the 3 patients with disseminated tumors. These were all treated with 24 Gy in 12 fractions in 3 weeks for the involved fields, whole ventricle, and whole CNS irradiation, respectively.

The disease-specific survival at 5 years was 100%, and the overall survival was 95%. The relapse-free survival at 5 years, according to the serum HCG-β level, was 90% for patients with normal HCG-β and 44% for patients with elevated serum HCG-β (p = 0.025). When we allowed for the first salvage treatment administered when relapse occurred, the tumor control rate was 95% at 5 years.

Details on the patients who experienced treatment failure are shown in Table 1. Five of 6 relapses were observed in patients with elevated serum HCG-β. All patients were treated with involved fields. The site of failure relative to the treated volume (TV), covered by 90% of the prescribed dose, was outside the TV in 4 (2 had spinal lesions), the marginal site in 1, and outside and in the TV (2 relapses) in 1 patient. Therefore, the local failure rate was 3.7% for the

Table 2. Relationship between the serum HCG-β, treated volume, and disease control in 27 patients with intracranial germinoma

Clinical subtype	Treated volume			
	Local	WV	WCNS	Total
Total	12/18	6/6	3/3	21/27
Serum HCG-β <0.5 mIU/mL	9/10	4/4	2/2	15/16
Serum HCG-β elevated	3/8	2/2	1/1	6/11

Abbreviations: HCG = human chorionic gonadotropin; WV = whole ventricle; WCNS = whole central nervous system.

definite in-field relapse, and 7.4% for the marginal or in-field relapse.

Table 2 shows the relationship between the serum HCG-β, treated volume, and relapse ratio. There were no relapses in 9 patients who were treated for whole ventricle or whole CNS. A small treatment volume and elevated serum HCG-β were equally considered candidates for causing the poor local control.

Even though the 2D margin for the initial GTV was determined to be 2.0 cm or more in the protocol, 12 of 27 patients were treated with < 2.0 cm, and 10 with < 1.5 cm margin. Most tumors were very small or not visible in the planning CT and MRI at the time of radiotherapy, because of the efficacy of the induction chemotherapy. All 6 relapses were treated with a 2D margin <1.5 cm. There were no relapses in 4 patients who had elevated serum HCG-β and who were treated with whole ventricle or larger fields. The whole ventricle field included the fourth ventricle. There was a statistically significant difference in the relapse ratio between patients treated with a 2D margin < 1.5 cm (median, 1.0 cm; range, 0.5–1.2 cm), and those with a 2D margin ≥ 1.5 cm (median, 2.4 cm; range, 1.5–2.8 cm; $p < 0.01$; Table 3).

The complications due to treatment were azoospermina in 1 of 4 patients examined. One patient experienced anterior pituitary hormonal replacement owing to relapse at the neurohypophyseal region. No new onset or deterioration in anterior pituitary function was noted. Three of 7 adult patients older than 18 years at the time of treatment married after treatment, and 1 fathered a child.

Table 3. Relationship between serum HCG-β, 2D margin, and relapse ratio in 27 patients with intracranial germinoma

Serum HCG-β	2D margin <1.5 cm	2D margin ≥1.5 cm
<0.5 mIU/mg	1/3	0/13
≥0.5 mIU/mg	5/7	0/4

Abbreviations: HCG = human chorionic gonadotropin; 2D = two-dimensional.

DISCUSSION

It is well known that localized treated volume results in a high relapse rate in intracranial germinoma. In a multi-institutional retrospective survey, Aoyama *et al.* (9) showed that the 5-year relapse-free rate was significantly lower in patients treated with localized volume than whole ventricle or larger volume. Because a high incidence of radiation-related late complications have been noted after large volume irradiation for pediatric patients, induction chemotherapy has been expected to reduce the amount of radiation volume and dose. There are pros and cons to this opinion (3–5, 10–14). The possible incidence of relapses using lower doses and smaller volumes is the shortcoming of this approach to this highly curable disease. Pretreatment impairment in neurocognitive function due to the tumor or surgery is also suggested to be a possible bias in the opinion against radiotherapy (15, 16). The lack of well-controlled randomized trials and the small number of patients in each institution has forced us, at present, to conduct a careful analysis of the prospective Phase II studies to speculate on the best treatment method.

Elevated serum HCG-β was reported to be a poor prognostic factor for patients with intracranial germinoma treated with chemotherapy alone in a large multi-institutional study (11). We have analyzed our data to evaluate the prognostic importance of serum HCG-β based on the previous report, and found the possible importance of serum HCG-β in our series (7). A Japanese multi-institutional cooperative group began to treat intracranial germinoma with platinum-based induction chemotherapy followed by 24 Gy irradiation 6 years ago, and treated more than 100 patients. Preliminary reports of the large Phase II study suggested that HCG-β was not a prognostic factor, and that a smaller treatment volume was associated with a higher relapse rate (8).

The small number of patients in our study prevented us from determining whether elevated serum HCG-β or an inadequate CTV margin was the predominant prognostic factor. The patients with relapsed tumors were treated with a small margin, and also had a higher serum HCG-β. Notably, there were no relapses in patients who were treated with whole ventricle or a larger volume, despite the fact that these patients had a larger tumor burden than those who were treated with involved fields. The tumor mass before chemotherapy was often massive or infiltrative, but the tumor was very small or not visible at the time of treatment planning. These differences in size and the anatomic shift of the normal brain made it difficult to determine the appropriate CTV based on the initial GTV before surgery and chemotherapy. Image fusion between the initial MRI and treatment planning CT after chemotherapy would be difficult, because of the anatomic shift of the normal brain tissues. The high incidence of violation in using 2.0 cm margins for the initial GTV may be partly due to these limitations in modern diagnostic imaging techniques rather than inadequate skills on the part of the treating physicians.

Interobserver variation must be large, even when utilizing the advanced imaging technologies available at present. Therefore, it is still difficult to achieve good quality assurance and a good quality control program for using the involved field for intracranial germinoma in a multi-institutional study.

Considering the low relapse rate in the treated volume in this study, 3.7%–7.4%, induction chemotherapy may reduce the dose required for the eradication of gross tumors. We did not use any boost dose in this study or in the Japanese multi-institutional study. Recent studies in western countries show that physicians are still using a boost dose to the tumor bed, giving 40–50 Gy in total (10, 11). Our results suggest that a prospective multi-institutional study is needed to test whether a boost dose to the tumor bed is necessary. Elimination or reduction in the boost dose after 24 Gy has a high probability of reducing vascular complications and deterioration in the anterior pituitary function. It is necessary to carefully monitor the long-term adverse effects of chemotherapy. Reduction of the radiation dose without chemotherapy would also be an important subject for a multi-institutional study.

In conclusion, the relapse rate can be unacceptably high in patients who were treated with involved fields, partly because of the difficulty in accurately determining the initial GTV before surgery and chemotherapy. Although the total tumor control rate after initial salvage treatment was high, it is obvious that tumor relapse should be avoided. In this respect, whole ventricle or larger field is still the target volume, which should be regarded as the standard both for germinoma with normal HCG-β, and for germinoma with elevated HCG-β, both in chemoradiotherapy and in radiotherapy alone.

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CLINICAL INVESTIGATION **Brain**

STEREOTACTIC IRRADIATION FOR INTRACRANIAL ARTERIOVENOUS MALFORMATION USING STEREOTACTIC RADIOSURGERY OR HYPOFRACTIONATED STEREOTACTIC RADIOTHERAPY

TA-CHEN CHANG, M.D.,* HIROKI SHIRATO, M.D.,* HIDEFUMI AOYAMA, M.D.,* SATOSHI USHIKOSHI, M.D.,* NORIO KATO, M.D.,* SATOSHI KURODA, M.D.,† TATSUYA ISHIKAWA, M.D.,† KIYOHIRO HOUKIN, M.D.,‡ YOSHINOBU IWASAKI, M.D.,† AND KAZUO MIYASAKA, M.D.*

Departments of *Radiology and †Neurosurgery, Hokkaido University Hospital, Sapporo, Japan; ‡Department of Neurosurgery, Sapporo Medical University, Sapporo, Japan

Purpose: To investigate the appropriateness of the treatment policy of stereotactic irradiation using both hypofractionated stereotactic radiotherapy (HSRT) and stereotactic radiosurgery (SRS) for arteriovenous malformations (AVMs) located in an eloquent region or for large AVMs and using SRS alone for the other AVMs.

Methods and Materials: Included in this study were 75 AVMs in 72 patients, with a mean follow-up of 52 months. Of the 75 AVMs, 33 were located in eloquent regions or were >2.5 cm in maximal diameter and were given 25–35 Gy (mean, 32.4 Gy) in four daily fractions at a single isocenter if the patient agreed to prolonged wearing of the stereotactic frame for 5 days. The other 42 AVMs were treated with SRS at a dose of 15–25 Gy (mean, 24.1 Gy) at the isocenter. The 75 AVMs were classified according to the Spetzler-Martin grading system; 21, 23, 28, 2, and 1 AVM were Grade I, II, III, IV, V, and VI, respectively.

Results: The overall actuarial rate of obliteration was 43% (95% confidence interval [CI], 30–56%) at 3 years, 72% (95% CI, 58–86%) at 5 years, and 78% (95% CI, 63–93%) at 6 years. The actuarial obliteration rate at 5 years was 79% for the 42 AVMs <2.0 cm and 66% for the 33 AVMs >2 cm. The 5- and 6-year actuarial obliteration rate was 61% (95% CI, 39–83%) and 71% (95% CI, 47–95%), respectively, after HSRT and 81% (95% CI, 66–96%) and 81% (95% CI, 66–96%), respectively, after SRS; the difference was not statistically significant. Radiation-induced necrosis was observed in 4 subjects in the SRS group and 1 subject in the HSRT group. Cyst formation occurred in 3 patients in the SRS group and no patient in the HSRT group. A permanent symptomatic complication was observed in 3 cases (4.2%), and 1 of the 3 was fatal. All 3 patients were in the SRS group. The annual intracranial hemorrhage rate was 5.5–5.6% for all patients.

Conclusion: Our treatment policy using SRS and HSRT was as effective as the policy involving SRS alone. The HSRT schedule was suggested to have a lower frequency of radiation necrosis and cyst formation than the high-dose SRS schedule. The benefit of HSRT compared with lower dose SRS has not yet been determined.

Stereotactic irradiation, Arteriovenous malformation, Hypofractionation.

INTRODUCTION

Single-fraction stereotactic radiosurgery (SRS) is an effective treatment for patients with intracranial arteriovenous malformations (AVMs) with a diameter of about ≤2.5 cm. However, AVMs >2.5 cm in mean diameter, or around 10 cm^3 in volume, and AVMs in eloquent regions are often not cured, because we cannot give an efficient dose to the AVMs without causing radiation damage to the normal tissue (1, 2).

We have used hypofractionated stereotactic radiotherapy (HSRT) as an alternative treatment for AVMs in eloquent regions or large AVMs. Single-fraction SRS was used as a basic treatment method for AVMs located in noneloquent regions or small ones. Our preliminary results have already been published, suggesting that HSRT was as effective as

Reprint requests to: Hiroki Shirato, M.D., Department of Radiology, Hokkaido University School of Medicine, North-15 West-7, Sapporo 060-8638, Japan. Tel: (+81) 11-706-7876; Fax: (+81) 11-706-5977; E-mail: hshirato@radi.med.hokudai.ac.jp

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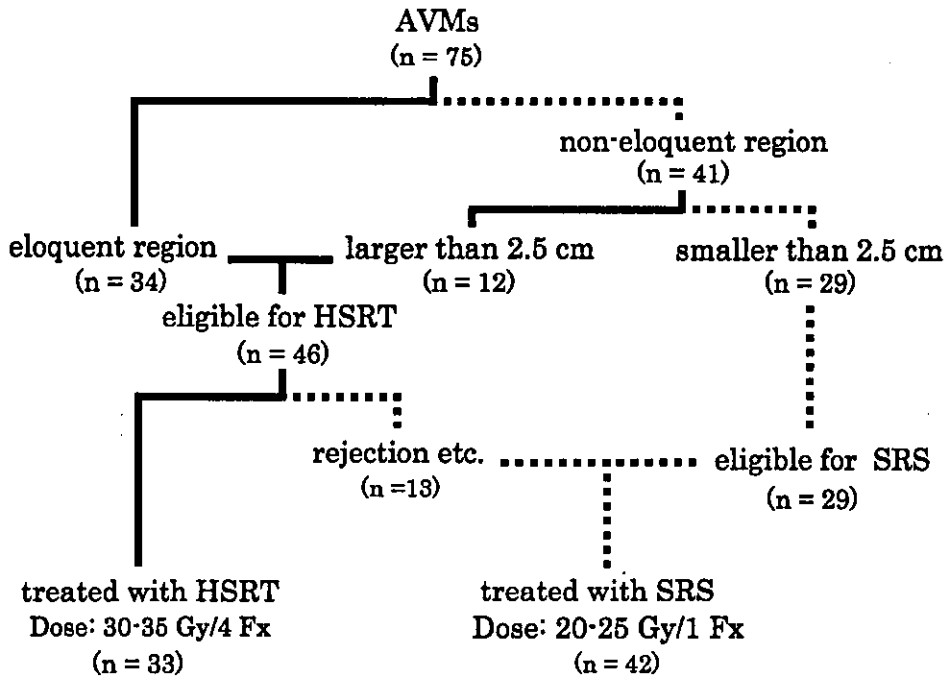

Fig. 1. Arteriovenous malformation (AVM) treatment protocol selection between stereotactic radiosurgery (SRS) and hypofractionated stereotactic radiotherapy (HSRT).

SRS, with possibly a lower complication rate (3). However, the study included only 27 SRS and 26 HSRT patients (3). The present study was not a randomized study involving SRS and HSRT. The efficacy of HSRT was investigated, taking account the selection bias of the treatment protocol. The appropriateness of our treatment policy of stereotactic irradiation (STI) using both SRS and HSRT is discussed.

METHODS AND MATERIALS

Irradiation schedule

Stereotactic irradiation was SRS or HSRT. The hypofractionation schedule in this study was determined using the linear-quadratic formula for late complications without correcting for slow repair (4). The α/β ratio of the normal brain was estimated to be 2.0, which is widely accepted with regard to late radiation effects against brain parenchyma (5). A dose of 35 Gy in four fractions and 28 Gy in four fractions would have the same effect as 18.4 Gy and 14.2 Gy, respectively, in a single exposure of radiation, assuming an α/β ratio of 2.0. An isocenter dose of 35 Gy and a peripheral dose of 28 Gy delivered in four daily fractions was prescribed as the standard dose in this study.

Patients

This study included 72 consecutive patients with angiography-proven AVMs who had agreed to undergo STI between January 1991 and December 2000. Patients initially presented with one or more of the following symptoms: episode of intracranial hemorrhage (n = 37, 51%), epileptic seizure (n = 12, 17%), and neurologic deficits (n = 46, 64%). In 19 patients, the AVM was discovered incidentally without any symptoms (n = 13), with symptoms unrelated to AVM (n = 1), or with symptoms from other disease states (subarachnoid hemorrhage in 1, facial hemangioma in 1, traffic accident in 2, and brain infarction in 1). Before STI, 11 patients had undergone surgical resection of the AVM. Embolization was performed in 7 patients before STI. Of 11 patients with coincidental intracranial aneurysms, 3 were treated by clipping the aneurysm before STI.

All patients underwent digital subtraction angiography and CT. MRI and magnetic resonance angiography were used in the patients treated since the late 1990s. The AVMs were classified according to the Spetzler-Martin grading system (6).

Treatment protocol—selection between SRS and HSRT

The recursive tree used for the selection of the treatment method in the 75 AVMs is shown in Fig. 1. If the AVM nidus was primarily located in eloquent regions, such as the sensory-motor region, language region, and visual cortex; hypothalamus and thalamus; internal capsule; brainstem; cerebellar peduncles, or deep cerebellar nuclei, HSRT was used. In addition, when the nidus was located in a noneloquent region and was >2.5 cm in maximal diameter as measured by angiography, HSRT was used. However, of those with AVMs that fulfilled the above criteria and who were eligible for HSRT, 5 patients were judged not to be suited for prolonged head-frame wearing because of physical instability or mental deficiency, and 8 patients did not agree to the prolonged head-frame wearing. These 13 patients were treated with SRS instead of HSRT. Conse-

Table 1. Patient characteristics

Characteristic	HSRT (*n*)	SRS (*n*)
Age (y)		
<20	2	7
≥20	31	35
Gender		
Male	20	23
Female	13	19
History of hemorrhage		
Yes	15	22
No	18	20
Prior resection		
Yes	6	5
No	27	37
Prior embolization		
Yes	3	4
No	30	38
Diameter (cm)		
≤2.5	18	36
>2.5	15	6
≤2.0	13	29
>2.0	20	13
Location		
Eloquent	20	14
Noneloquent	13	28
Drainage vein		
Deep	19	24
Superior	14	18
Spetzler-Martin grade		
I + II	16	28
III + IV + V	17	14

quently, 33 lesions were treated with HSRT, and 42 lesions with SRS. All 6 patients with AVMs in an eloquent area with a maximal diameter >2.5 cm were treated with HSRT. Table 1 shows the patient and AVM distribution in each treatment group.

Radiosurgery technique

All patients were treated with an invasive stereotactic head frame (RADFRAME, Mizuho Ika Kogyo, Tokyo, Japan) for use in performing CT, MRI, angiography, and RT. The RADFRAME was developed in our institution to be suitable for prolonged wearing while maintaining 1.0-mm accuracy. When SRS was used, the patients wore the stereotactic frame for 1–2 days. When HSRT was used, patients wore the stereotactic frame for 5 days. The procedure was performed with i.v. sedation when necessary. Between 1991 and April 2003, the AVM nidus was defined using biplane angiography, and the target was displayed on CT. After 1998, MRI was also used as a complementary tool for delineation (7, 8). A single isocenter and three-dimensional RT planning system (Focus, CMS, St. Louis, MO) were used. An isodose contour conforming to the entire AVM nidus was selected as the prescription isodose, and 6- or 10-mV X-ray beams from a linear accelerator were used. In general, a multileaf collimator was used for AVMs >1.5 cm, and a cone-shape collimator was used for smaller AVMs. The arc technique was used in three lesions, and the static noncoplanar multiport technique was used for 72 lesions. The number of arcs or planes ranged from three to four, and the median number of ports was 8 (range, 3–11).

Prescription

The standard total dose for SRS was 25 Gy at the isocenter of the treatment target volume, and the nidus was enclosed by an 80% isodose surface, with a minimal dose of 20 Gy. HSRT was primarily performed using 35 Gy at the isocenter, with a minimal dose of 28 Gy in four daily fractions. The total doses used for SRS and HSRT were modified depending on the size and location of the AVM, as well as patient age, with patients <20 years old receiving 90% of the dose described above. Thus, the total dose at the isocenter ranged from 15 to 25 Gy (mean, 24.1 Gy) for SRS and 25 to 35 Gy (mean, 32.4 Gy) for HSRT. In SRS, 29 AVMs <2 cm were treated with 25 Gy in one fraction. The other 13 AVMs that were >2 cm were given a lower dose to reduce the possibility of severe complications according to the isoeffect line of Kjellberg *et al.* (1) and Flickinger *et al.* (2). In HSRT, 18 AVMs received 35 Gy in four fractions, and 15 patients were treated with different doses and fractions in the early period or because of the proximity of the nidus to specifically critical structures such as the optic chiasm (4 AVMs, 25 Gy in four fractions; 1 AVM, 28 Gy in four fractions; 5 AVMs, 30 Gy in four fractions; 1 AVM, 32 Gy in four fractions; 1 AVM, 32.5 Gy in four fractions; 1 AVM, 30 Gy in eight fractions; and 2 AVMs, 35 Gy in eight fractions). The minimal dose ranged from 12 to 20 Gy (mean, 19.3 Gy) for SRS and 20 to 28 Gy (mean, 25.9 Gy) for HSRT.

Follow-up evaluation

For most of the patients who lived close enough to our institution, clinical examination and serial imaging studies (MRI or CT when MRI was contraindicated) were performed at 3- or 4-month intervals for the first year and every 6 months until complete obliteration was angiographically demonstrated. Some patients who lived far from our institution underwent the imaging studies near their homes and were evaluated by the referring physicians. Angiography was planned only when MRI demonstrated complete obliteration or when otherwise clinically indicated.

The term "complete angiographic obliteration" was defined as normal blood flow, complete absence of pathologic vessels at the site of the nidus, and the normalization of flow in the efferent veins. The date of obliteration was defined as the date of angiography demonstrating complete obliteration.

Clinical complications from STI were classified as new or aggravated neurologic symptoms or signs; complications requiring steroids, shunt placement, or surgical intervention; an imaging change suggesting radiation-induced edema (increased with a T_2-weighted signal change), radiation-induced necrosis, or cyst formation; or treatment-related death.