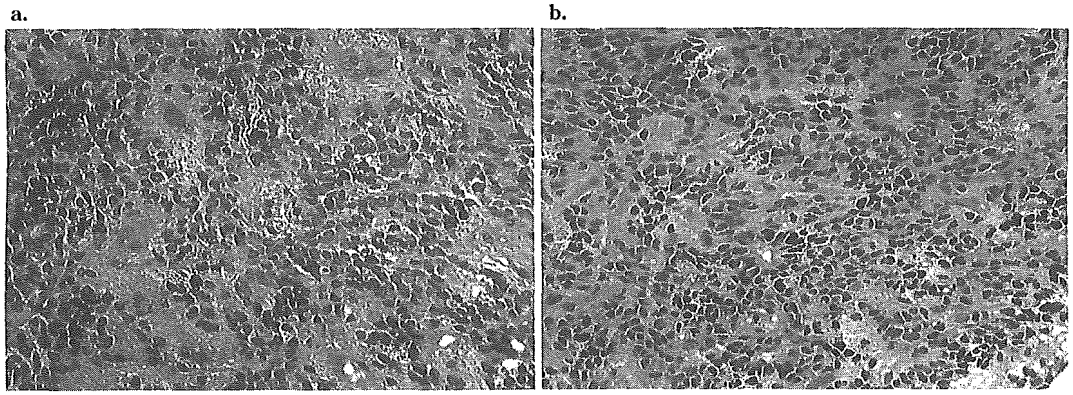


**図1 上衣腫**
a: 血管周囲性偽ロゼット．腫瘍細胞が血管周囲を取り囲むように，細胞突起を伸ばし，その結果，核のみられない無核帯を形成する．
b: 上衣ロゼット．管腔を囲む上衣様細胞配列が認められる．
(HE染色)(写真提供 東北大学脳神経外科 池田秀敏先生)

**e. 病理所見**

**1) 肉眼所見**

脳室内に突出する腫瘤を形成することが多い．周囲組織との境界は星細胞腫に比較して明瞭である[9]．充実性，灰白色の柔らかい腫瘤で，出血や壊死は目立たない．部分的な嚢胞形成や石灰沈着をみることもある．

**2) 光顕所見**

組織学的にはよく分化した中等度の細胞密度を有するグリオーマである．核は類円形あるいは楕円形で異型に乏しく核分裂像は少ないか認められない．典型的な所見としては血管周囲性偽ロゼット(**図1-a**)，上衣ロゼット(**図1-b**)があげられるが，この2つのロゼットの性質は根本的に異なる．血管周囲性偽ロゼットは腫瘍細胞が血管に向かって長い細胞突起を伸ばして配列したものであり，本腫瘍の大多数で認められる．したがって，血管周囲には細胞突起のみからなる無核帯が形成される．一方で上衣ロゼットは上衣腫に最も典型的な構造であり，管腔を囲む上皮様細胞配列であるが，実際に認められる症例は少ない．免疫組織化学的にはGFAP，vimentin，S100，cytokeratinが陽性である．GFAPは細胞質，特に突起の部分が陽性となる．管腔に面する細胞質表面はEMAが線上に陽性となる．MIB-1陽性率は数%以下であり，WHO grade IIに分類される．

(1) 細胞性上衣腫(cellular ependymoma)：上衣腫の中で細胞密度が高いが，核分裂像は乏しく，その他の悪性所見も，認められないものを細胞性上衣腫と呼んでいる．

(2) 乳頭状上衣腫(papillary ependymoma)：乳頭状細胞配列の目立つ上衣腫である．腫瘍の細胞突起はGFAP陽性のことが多い．鑑別診断として，脈絡叢乳頭腫，乳頭状髄膜腫，転移性脳腫瘍などがあり，GFAP，EMAなどが鑑別に有用である．

(3) 明細胞上衣腫(clear cell ependymoma)：細胞質が淡明で類円形の核をもつ腫瘍細胞からなる上衣腫である．この亜型はoligodendroglioma，central neurocytoma，hemangioblastomaなどと類似しており鑑別する必要がある．血管周囲の細胞がGFAP陽性のことが多く，鑑別に重要である．最終的には電顕像で診断を決定することが多い．

(4) 伸長細胞性上衣腫(tancytic ependymoma)：まれな特殊型であり，脊髄に多い．繊細な細長い突起を伸ばす双極性細胞が流れるような線維束を作りながら増殖する腫瘍である．pilocytic astrocytomaとの鑑別を要する．

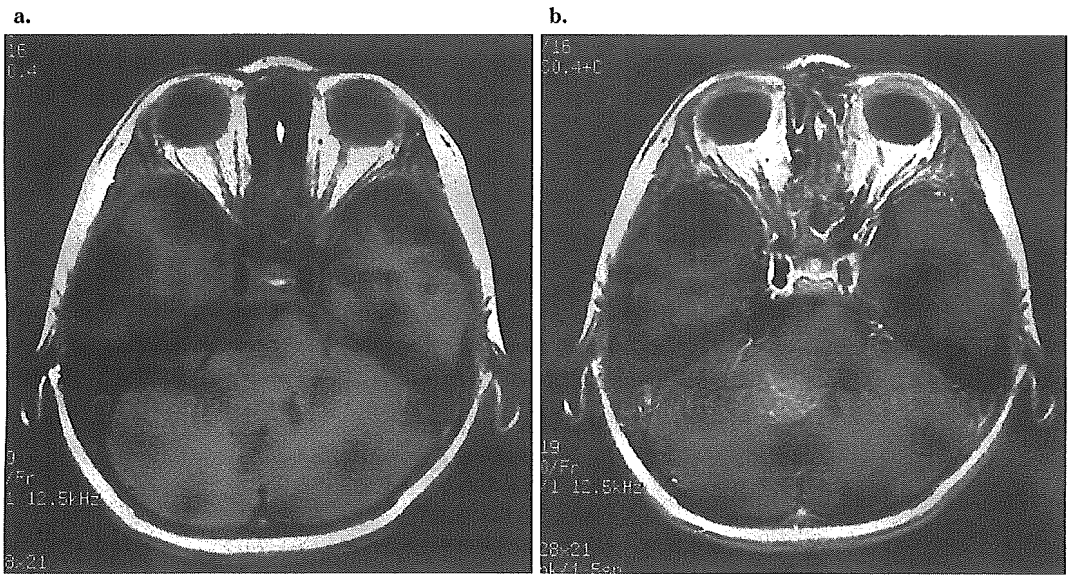


**図2 上衣腫のMRI像**
T1強調画像(a)では髄液より低信号で，白質よりやや低信号域を呈し，Gd増強MRIでは強く増強される．T2強調画像(b)では淡い高信号域で，腫瘍周囲に拡張した第4脳室を認める．

**3）電顕所見**

上衣腫においても上衣細胞の特徴を残している．すなわち，細胞はmicrorosetteを形成し腔内にはmicrovilliとciliaが塊をなしている．細胞間はjunctional complexes(zonula adherentesやgap junction)が発達している．

**f. 検　査**

**1）CT**

単純CTでは脳実質と等吸収値あるいは高吸収値で石灰化を約半数に認める．テント上上衣腫では嚢胞を伴うことが多いが，テント下病変ではほとんどが充実性である．造影剤増強効果は中等度で，均一あるいは不均一に増強されるが，髄芽腫，星細胞腫より軽度な傾向がある．

**2）MRI**

基本的にT1WIで低信号，T2WIでは高信号となるが，内部構造により不均一な信号強度を示すことが多い．T1WI，ガドリニウム増強像では強く増強を受けることが多い(図2)．髄液腔に沿って広がることより，小脳橋角槽，中脳水道，上部頸椎管にまで進展している場合は上衣腫が疑われる．テント上上衣腫は脳室内にとどまるものは少なく，多くは脳実質内に進展することから，画像から他の神経膠腫と鑑別することは困難である．

**3）血管撮影**

腫瘍血管は認められないことが多い．

**g. 診断，鑑別診断**

第4脳室発生例では，小児後頭蓋窩に好発する髄芽腫との鑑別が問題となる．鑑別点としては，上衣腫は発生母地が第4脳室底であり，髄芽腫は小脳虫部であるという点があげられる．

**h. 予後，転帰**

上衣腫の予後に関しては多くの報告があるが，おおむね5年生存率は60–70％前後である[10]．明らかに予後に影響を与える因子は手術による摘出率である[11,12]．ほぼ全摘出されたものの5年生存率は80％程度であるが，全摘出率は低く，この場合は追加照射が必要となる．ほかに予後因子として，年齢があげられており，成人例は小児例に比較し，予後良好である．また補助療法としての放射線治療の有無は，予後因子の一つである．

## 2. 退形成上衣腫(anaplastic ependymoma)

**a. 概念，定義**

上衣細胞由来の悪性グリオーマであり，急速な増大を示し，特に小児において転帰不良である．

**b. 分類，頻度**

脊髄の上衣系腫瘍には悪性のものはまれであり，頭蓋内発生がほとんどである．

**c. 病因，病態生理**

退形成上衣腫に特徴的な遺伝子異常は知られていない．

**d. 臨床症状**

基本的には上衣腫と似た症状を呈するが，症状の進行は，上衣腫より急速であり，早期に頭蓋内亢進症状を呈する[8]．

**e. 病理所見**

上衣腫の特徴である血管周囲性偽ロゼットが認められ診断に有用であるが，上衣ロゼットなどの上衣様細胞配列はほとんどみられない．退形成所見として細胞密度の増加，多数の核分裂像，組織壊死巣，血管内皮の増殖，pseudopalisading necrosis などがみられる．MIB-1陽性率は10％以上の高値を示し，WHO grade III に分類される．

**f. 検　　査**

**1) MRI**

MRI では典型的な造影効果を呈する．

**g. 診断，鑑別診断**

テント上発生の場合は多形性膠芽腫，松果体芽腫，PNET，テント下発生の場合は髄芽腫などがあげられる．いずれも確定診断は病理診断で行われる．

**h. 予後，転帰**

組織学的な悪性度が予後に影響を及ぼすという報告はほとんどなく，生存率と組織学的悪性度に関連性は認められなかった[13]．一方で，細胞密度と細胞分裂像が予後に影響するとの報告や，3歳以下の上衣腫では，腫瘍の摘出率，組織学的悪性度，髄腔内播種の有無が予後に影響するとの報告もある[14]．

## 3. 粘液乳頭状上衣腫(myxopapillary ependymoma)

**a. 定　　義**

若年成人の脊髄終糸に特異的に発生する．組織学的には血管周囲に粘液性間質を伴った腫瘍が乳頭状に配列する．

**b. 分類，頻度**

上衣系腫瘍の13％を占める．成人の馬尾から発生する腫瘍の83％を占める．平均年齢は36.4歳で男性に多い[15]．

**c. 病因，病態生理**

脊髄終糸の上衣グリア細胞から発生すると考えられている．

**d. 臨床症状**

長い経過の背部痛を呈することが多い．

**e. 病理所見**

**1) 肉眼所見**

ゼラチン様の腫瘤としてみられる．性状は分葉状で柔らかく灰色である．

**2) 光顕所見**

立方状ないし細長い腫瘍細胞が豊富な粘液性基質を伴って血管の周囲に乳頭状に配列するものである．血管外膜に著明な硝子様肥厚が認められることもある．WHO grade I．免疫組織学的にはGFAP，S-100，vimentin が陽性で，cytokeratin は陰性である．MIB-1陽性率は0.4-1.6％と低値を示す．

**f. 検　　査**

**1) MRI**

T1強調画像では房状の低信号域として，T2強調画像では境界明瞭な高信号域として，描出される．T1強調-ガドリニウム増強像では均一に造影される．

**g. 髄液所見**

髄液蛋白値の上昇が特徴的で，報告例の平均は2,000 ng/dl になる．

**h. 診断，鑑別診断**

鑑別としては chordoma などの馬尾に発生する腫瘍があげられる．GFAP陽性，cytokeratin陰性などの免疫組織学的所見より確定診断がされる．

**i. 予後，転帰**

全摘出あるいは部分摘出されたものは，10年以上の生存が期待できる．再発や播種は極めてまれである．

## 4. 上衣下腫（subependymoma）

**a. 定　義**

脳室壁に付着した極めて成長の緩徐な良性腫瘍．

**b. 分類，頻度**

成人に発生する比較的まれな腫瘍で，第4脳室発生が58.4％で最も多く，次いで側脳室発生が多い．性差はなく，あらゆる年齢で発生するが，中年あるいは高齢の男性に多い．

**c. 病因，病態生理**

家族発症の報告もあるが，一般的には孤発例である．

**d. 臨床症状**

第4脳室の小さいものはほとんど無症状である．側脳室発生例はしばしば増大し，閉塞性水頭症を呈し，頭蓋内圧亢進症状を呈する．ときに無症状でも腫瘍内出血で発症することがある．

**e. 病理所見**

**1）肉眼所見**

脳室壁から腔内に突出する，やや白色で比較的柔らかい充実性の腫瘍である．

**2）光顕所見**

グリア細胞の突起からなる密な線維性基質の中に小型細胞が集簇し，基質には嚢胞形成がみられる．細胞密度は低く，核は小型の類円形で，分裂像は乏しい．石灰沈着あるいは出血を認めることもある．免疫組織学的には細胞質がGFAP陽性である．MIB-1陽性率は1％以下で極めて低く，WHO grade Iに分類される．

**f. 検　査**

**1）MRI**

上衣下腫は成人に多く，T2WIでは高信号で，T1WIで造影効果を認めないことが多い．第4脳室発生例では石灰化や，不均一に増強効果を認めることが多いが，側脳室発生例ではまれである．

**g. 診断，鑑別診断**

他の脳室内発生腫瘍との鑑別は画像診断からは困難であり，確定診断は摘出術後の病理組織学的診断でなされる．

**h. 予後，転帰**

上衣下腫の予後は良好で，手術により治癒が期待できる．上衣腫と上衣下腫の成分が混在している場合，臨床経過は上衣腫に準ずる．

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# Treatment of low-grade oligodendroglial tumors without radiotherapy

Yoshinori Higuchi, MD; Yasuo Iwadate, MD; and Akira Yamaura, MD

**Abstract**—The authors prospectively treated 18 consecutive patients with low-grade oligodendroglial tumors without postoperative radiotherapy. The treatment strategy was as follows: follow-up after total resection and chemotherapy after subtotal resection or biopsy. All patients were alive and 17 patients (94%) were progression-free after a median follow-up of 4.7 years. The results suggested that radiotherapy could be postponed until clinical progression in the treatment of low-grade oligodendroglial tumors.

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Oligodendroglioma is a rare intracranial tumor, which is conventionally treated with surgery with postoperative radiotherapy or follow-up.[1] Although many retrospective studies suggest that postoperative radiotherapy for oligodendrogliomas has some benefit,[2-5] the efficacy of radiotherapy is still unsettled. Radiation-induced toxicities, including dementia and radiation necrosis in particular, may occur in long-term survivors.

It has been recently reported that oligodendrogliomas including low-grade tumors respond to chemotherapy.[6] Since low-grade oligodendrogliomas can be indolent for years, some researchers recommend starting chemotherapy first to postpone radiotherapy until clinical progression.[1] In the present study, we prospectively treated patients with low-grade oligodendroglial tumors without radiotherapy. As a rule, chemotherapy was used to treat the incompletely resected tumors. We estimated the outcome of the patients as compared with the published reports, and discussed the necessity of radiotherapy for patients with low-grade oligodendroglial tumors.

**Methods.** Since 1995, we have treated patients with oligodendroglial tumors without postoperative radiotherapy according to the following protocol: follow-up after total resection and chemotherapy (ACNU 75 mg/m$^2$ for day 1, vincristine 1 mg/m$^2$ for days 8 and 29, procarbazine 100 mg/day for days 8 to 21; four cycles a year for 2 years) after subtotal/partial resection. In this study, the outcome of the patients was evaluated. The primary endpoints of our study were progression-free survival time and overall survival time. Patients were enrolled in this study if their tumors had been histologically confirmed as newly diagnosed low-grade oligodendroglioma or oligoastrocytoma. The patients were required to provide informed consent. The age, sex, original pathologic diagnosis, initial symptom, tumor location, imaging findings, and extent of resection were recorded. A minimum of 1 year of clinical follow-up information was required. The date of diagnosis was the date of initial surgery in 11 patients. However, in 7 patients abnormal imaging findings consistent with low-grade brain tumors were documented more than 1 year before obtaining pathologic material. In these patients, the initial imaging date was used as the date of diagnosis; and subsequently the diagnosis was pathologically confirmed as oligodendroglial tumor. The median interval from onset of symptoms to tissue diagnosis was 6 years for the seven patients. Tumor progression was defined as a change in the radiographic characteristics such as increased tumor size or new enhancement with or without clinical worsening. The progression-free and overall survival distributions were estimated using Kaplan-Meier methodology.

**Results.** Eighteen patients were treated and followed up for a median period of 4.7 years. There was no patient who was excluded from the analysis because of early recurrence within 1 year. Fifteen patients had oligodendrogliomas (grade 2) and three had oligoastrocytoma (grade 2). There were 13 men and 5 women. The tumors were frontal in eight patients, multilobular in four, temporal in five, and parietal in one. The patients' characteristics are summarized in table 1.

The initial presenting symptom was seizure in 7 (39%), headache in 4 (22%), memory disturbance in 2 (11%), and other neurologic deficits in 4. During this study, seizures developed in a total of 10 patients (56%). MRI and CT were obtained in all patients. Contrast enhancement was noted in 9 patients (50%). Calcification was noted in 10 patients (56%).

Five patients (27.8%) underwent total resection (postoperative MRI ensured tumor-free margin), and eight patients (44.4%) underwent subtotal tumor resection. Biopsy was carried out for five patients (27.8%) to avoid severe neurologic deficits after resection. No patient received radiotherapy.

Twelve patients received the chemotherapy immediately following the surgical resection. Although the patients who underwent biopsy or subtotal tumor removal were essentially candidates for adjuvant chemotherapy, one patient refused receiving chemotherapy after subtotal tumor removal. We estimated the tumor response to chemotherapy using MRI after the chemotherapy. We classified the response into three categories as follows: 1) responder, more than 50% reduction in volume; 2) nonresponder, more than 25% increment in volume; 3) no change, all other situations. Among the 12 tumors treated with chemotherapy, 7 (58.3%) including 2 oligoastrocytomas were responders and the other 5 cases were catego-

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*Table 1* *Patient characteristics*

| Characteristics | Values |
|---|---|
| n | 18 |
| M:F | 13:5 |
| Age at diagnosis, y, mean (range) | 45.8 (9–69) |
| Age at operation, y, mean (range) | 48.3 (23–69) |
| Follow-up period, y, median (range) | 4.65 (1.0–15.6) |
| Tumor site | |
| Frontal | 8 |
| Temporal | 5 |
| Multilobular | 4 |
| Parietal | 1 |

rized as no change. The chemotherapy was well tolerated. Although the primary toxicity experienced by patients during the chemotherapy was myelosuppression, grade 3 or 4 leukopenia that mandated treatment delay occurred only in two patients (11%).

All the patients were alive and did not have uncontrolled tumor progression (figure, A). Recurrence occurred in one patient with oligodendroglioma (5.6%) that had been completely resected, and the time for tumor progression was 2.5 years (figure, B). This patient had not received chemotherapy immediately after surgical resection. The recurrent tumor shrank after chemotherapy and was well controlled.

**Discussion.** We demonstrated that 94% of oligodendroglial tumors could be controlled without radiotherapy during a median follow-up of 4.7 years in our series. Although this follow-up period is not enough to give a definite conclusion, the 5-year survival rate in our study was favorable as compared with those in the previous reports[2-5] (table 2). It was suggested that radiotherapy could be postponed when tumor recurrence or progression occurred following surgical resection and chemotherapy. Large-scale clinical follow-up is required for determining the role of adjuvant radiotherapy in control of oligodendroglial tumors.

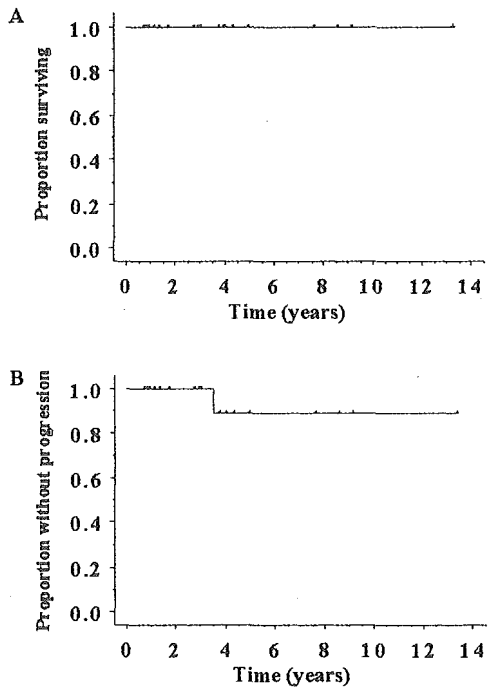


*Figure. Kaplan-Meier curve shows overall (A) and progression free survival (B) of 18 patients. Tick mark indicates last follow-up.*

*Table 2* *Five-year survival rates of patients with oligodendroglial tumor in previous reports*

| | | 5-year survival rate, % | |
|---|---|---|---|
| Reference | n | With RT | Without RT |
| 2 | 170 | 36 | 27 |
| 3 | 81 | 46 (<50 Gy) | 63 |
| | | 61 (>50 Gy) | |
| 4 | 137 | 70 | 45 |
| 5 | 52 | 89 | 63 |

RT = radiotherapy.

Although many authors have suggested some benefit of radiotherapy in the treatment of oligodendrogliomas,[1-5] all those studies are retrospective. There are two prospective randomized studies on low-dose and high-dose fractionated radiotherapy for low-grade gliomas.[7,8] The authors demonstrated that the survival was significantly better in the patients with oligodendroglioma and oligodendroglioma-dominant histology, and that the low-dose radiotherapy is as effective as the high-dose for low-grade gliomas. The efficacy of early postoperative radiotherapy for patients with low-grade gliomas was also investigated.[9] The authors reported that early postoperative conventional radiotherapy improved the time to tumor progression, but not overall survival. Thus, the efficacy of early postoperative radiotherapy for oligodendrogliomas has not been established.

Patients with oligodendroglioma need care for radiation-related complications because they are relatively long survivors as compared with those with high-grade gliomas. It was reported that high frequency of radiation-induced toxicity, such as radiation necrosis and cognitive dysfunction, follows radiotherapy.[1] Since low-grade tumors can be indolent for years, the risk-benefit relationship of radiotherapy needs to be considered.

It has been demonstrated that anaplastic oligodendroglioma may be remarkably chemosensitive when associated with allelic loss of 1p/19q.[10] The molecular genetic analysis would be helpful to determine the therapeutic strategy especially for tumors with anaplastic components. Our results suggest that surgical resection and chemotherapy for residual tumors are generally enough for the initial treatment of low-grade oligodendrogliomas. It would be

better to postpone radiotherapy until tumor progression after chemotherapy becomes uncontrolled.

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process. As the scar matures, the continuous vascular regression may eventuallly transform the richly vascularized granulation tissue into a pale and avascular scar. Thus, the neomembrane of the fibrous capsule may not be seen if the time for vascular regression is long enough. In general, the capsules of chronic ICHs were commonly shown as ring enhancement after contrast medium injection,[1,2,7] but only faint enhancement was seen in our case. This may be attributed to vascular regression in the neomembrane.

How did the fibrous capsule undergo calcification and ossification? Based on the encephalomalacia changes in brain tissue adjacent to the haematoma, the patient might have suffered a severe brain trauma which caused progressive cell death and necrosis. Heterotopic bone formation tends to occur in necrotic tissue. The calcification of dead and necrotic tissue is frequently encountered and known as dystrophic calcification.[13] The membrane phospholipids of necrotic tissue, collagen fibrils or denatured proteins have been proven to be the centre for initiation of calcification.[13,14] Through the model of membrane-facilitated calcification,[15] the necrotic tissue around the hematoma underwent dystrophic calcification. Similar calcification phenomena could be found in chronic epidural and subdural haematomas.[10,11,16] The hematoma of the present case was a mixture of necrotic debris, cholesterol cleft, haemosiderin and sand-like calcification. The unabsorbed haematoma may be decomposed and degradation of red blood cells (RBCs) and white blood cells (WBCs) may occur over time causing deposition of haemosiderin and cholesterol, the latter being a component of cell membranes. The cholesterol cleft, haemosiderin and sand-like calcification of the semiliquid contents may be the result of insufficient degradation or clearance of RBCs, lipids and minerals.

The calcified chronic ICH in the present case was originally considered to be an extra-axial lesion. However, a thin layer of brain cortex covering over the lesion could be detected on the brain MRI (Fig. 1B). This was verified during surgery. The presentation of the intra-axial lesion as an extra-axial one on brain MRI may be attributed to the encephalomalacia changes in the surrounding brain tissue, which caused widening of the subarachnoid space. Comparing the MR images and skull plain film with the resected specimen, the upper and major portion of the mass showing intermediate signal intensity on T1WI and low signal intensity relative to the gray matter on T2WI was a mixture of necrotic debris, cholesterol cleft, haemosiderin and sand-like calcification (Figs. 1B and C and Fig. 2). The middle part of the lesion demonstrated low signal intensity on T1WI and high signal intensity on the T2WI, indicative of water contents (Figs. 1B and C and Fig. 2). The calcification, shown on the peripheral and lower portions of the mass in the skull plain film, appeared as high signal intensity on T1WI and T2WI (Fig. 1B–D and Fig. 2). The image characteristics are compatible with the gross appearance of the lesion and have not been reported previously.

In conclusion, in the present case, head injury or occult vascular malformation may be the cause of the initial intracerebral haemorrhage, and repeated haemorrhages from the fragile vessels of the neomembrane may have played a role in the expansion of the ICH. The neomembrane vessels may regress after a long period such as over the 28 years in our case. Calcification and ossification of the capsule were produced through the process of dystrophic calcification. It is recommended that in patients with encapsulated ICH, that the removed lesion and the adjacent brain tissue should be thoroughly examined to rule out the presence of any vascular malformation.

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# A rare case of metastatic renal cell carcinoma resembling a nerve sheath tumor of the cauda equina


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**Summary** We present a rare case of solitary metastasis to the cauda equina from the kidney. The patient was a 68-year-old man with a two-year history of low back pain. His past medical history revealed a renal cell carcinoma diagnosed seven years earlier. His lumbosacral MR imaging showed a well-demarcated, intradural extramedullary mass at the L3 level. He underwent an L2-4 laminectomy. The operative findings of the tumor quite resembled that of a nerve sheath tumor. It did not infiltrate into the subarachnoid space and involved only one spinal nerve. Pathology of the tumor was a metastasis of the renal cell carcinoma. Only 10 cases with such a metastasis to the cauda equina have been reported in the English

literature. We added the 11th and reviewed the literature with reference to tumor pathologies, clinical findings and route of metastasis to the cauda equina.



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## INTRODUCTION

The majorities of cauda equina tumors are of glial or nerve sheath origin,[3,5,7,15] and metastases from outside the central nervous system are extremely rare. We present a case of solitary metastasis to the cauda equina. His past medical history included renal cell carcinoma; nevertheless, the radiographic and the operative findings suggested a nerve sheath tumor. To our knowledge, only 10 cases with metastatic tumor of the cauda equina from outside the central nervous system have been reported in detail in the English literature.[1,2,4,6,8–12,14] The literature is reviewed with reference to tumor pathologies, clinical findings and route of metastasis to the cauda equina.

## CASE REPORT

A 68-year-old male had a two-year history of low back pain, which worsened in recumbency or at sneezing and became progressively severe. His medical history revealed a renal cell carcinoma diagnosed seven years earlier and treated by a right nephrectomy. He had then three times undergone partial pneumonectomies for metastatic lung tumors from the primary lesion five years (left S1+2 resection), three years (right S2 resection) and one year (left S6 resection) prior to admission. On admission, he complained of low back pain projecting into the right L5 region. He had full muscle strength and intact sensation as to light touch, pinprick, and joint position sense. Deep tendon reflex showed no laterality. Straight leg raising test was limited on the right side. Plain X-ray films showed no abnormality. Lumbosacral MR imaging revealed an intradural extramedullary mass measured 2.5 cm craniocaudally by 1.3 cm anteroposteriorly at the L3 level (Fig. 1). The mass was well demarcated and demonstrated homogeneous enhancement. Abdominal MR images and radioisotope images revealed no tumor recurrence of the primary lesion and no tumor invasion to the intrapelvic or paraspinal organs.

He underwent an L2-4 laminectomy. Dural opening revealed an ocher-color ovarian-shape tumor. The tumor was elastic hard, well demarcated and did not infiltrate into the subarachnoid space. It involved only one spinal nerve that fanned out over the surface of the tumor. We resected the nerve proximal and distal to the tumor and could remove the tumor easily (Fig. 2). Pathology of the tumor was a metastatic renal cell carcinoma (Fig. 3). His postoperative course was excellent. He noticed a complete relief of radicular pain and left hospital on the twelfth postoperative day without neurological deficits. No recurrence was observed with a follow-up period of two years after surgery.

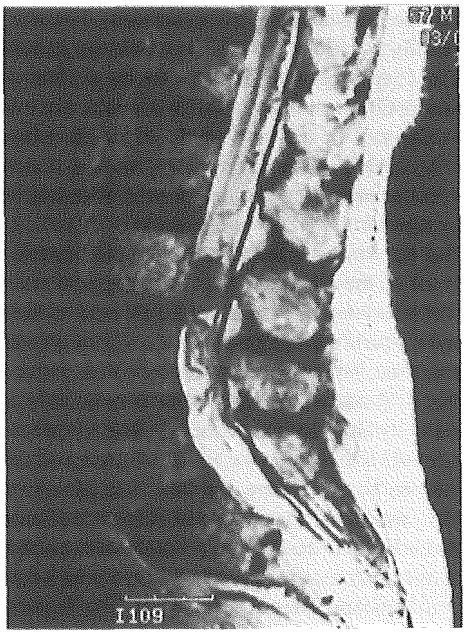


**Fig. 1** Lumbosacral MR imaging (heavy T2 weighted image in sagittal plane) showing an intradural extramedullary mass located at L3 level.

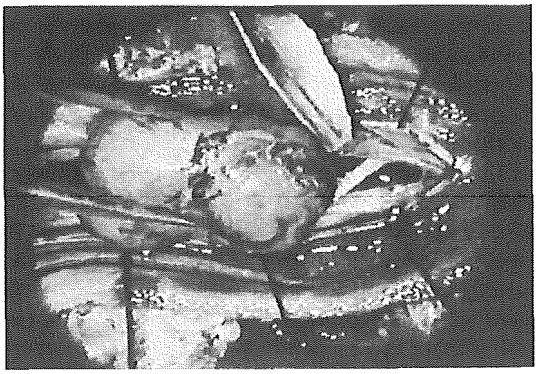

**Fig. 2** An operative view showing well demarcated tumor. The tumor did not infiltrate into the subarachnoid space and involved only one spinal nerve. It could be easily removed after resecting the nerve.

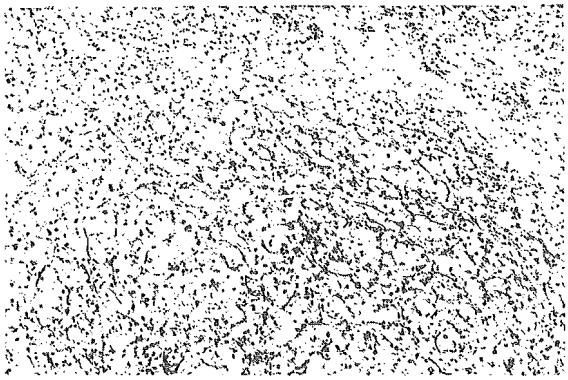

**Fig. 3** Photograph showing the interface between the tumor and nerve root. Tightly packed clear cells are typical for renal cell carcinoma.

## DISCUSSION

Spinal metastasis occurs in 10–60% of all carcinomas. However, intradural spinal metastasis is less common and represents only

0–6% of all spinal metastases.[1] Ependymomas and neurinomas are dominant around the cauda equina.[4] Metastatic tumor from outside the central nervous system in this region is very rare and, to our knowledge, only 11 cases including the present case (eight males, three females) have been reported in detail in the English literature.[1,2,4,6,8–12,14] The ages of the patients averaged 59.3 years (44–84 years). Wippold et al.[15] reported that the mean age of the patients with neurinoma was 49.7 years and that with ependymoma was 38.3 years. Metastatic cauda equina tumors seem to appear later in life than neurinoma and ependymoma of this region.

The pathologies and primary lesions of the metastases to the cauda equina were adenocarcinoma[4,10,11] (one case from prostate, one case from ovarium, one case from endometrium), renal cell carcinoma[6,8,14] (four cases including the present case from kidney), squamous cell carcinoma[1] (one case from anus), undifferentiated carcinoma[2] (1 case from lung), nasopharyngeal carcinoma[12] (one case), and lymphosarcoma[9] (one case from mediastinum). These tumors metastasized to the cauda equina three to six years (mean 4.6 years) after surgery of the primary lesions. According to the Stark's series[13] with 131 metastatic spinal tumors, the lung (43 cases) and breast (37 cases) were the most common primary lesion sites, whereas metastases from the kidney occurred in only four cases. The kidney, however, seemed to be relatively a common primary lesion site of metastasis to the cauda equina. In four out of 11 cases, renal cell carcinomas were the primary malignancy. The prevalence of brain metastasis ranges from the kidney 5.7–9.7% in autopsy studies and 3.0–32% in clinical studies.[14]

The symptoms of cauda equina lesions are known to be nonspecific.[3,15] Low back pain was the most common symptom, followed by sciatic pain, sensory disturbance, motor weakness, and bladder dysfunction.[3,5,7,15] Of 11 patients with metastatic tumors, four showed only low back pain with or without sciatica, and the remainder complained of multiple neurological symptoms. A remarkable feature of the clinical course of primary cauda equina lesions was the longstanding preoperative history with a mean time of years.[5,7] The preoperative histories of the metastatic tumors varied from two to 36 months (mean 12.6 months). Metastatic tumors seem to evolve symptoms more rapidly than primary cauda equina tumors.

Five routes have been hypothesized for metastatic intradural spinal tumor from outside the central nervous system;[11] (a) haematogenous, via the arterial system, (b) through the rich venous plexus, (c) through perineural lymphatics, (d) spread via subarachnoid space, and (e) seeding from the involved osseous structure to the cerebrospinal fluid through the dura mater.[6] Arterial embolism through the lung seems to explain the unusual metastasis to the cauda equina in our case. He had been diagnosed as having metastatic lung tumors prior to admission. Some authors have suggested venous embolism through the venous channels between the pelvis and the spinal cord. This could be the mechanism, though it is unlikely. Metastasis through the perineural lymphatics is also unlikely. Neuroradiological examinations including abdominal MRI, CT scan and radioisotope images revealed no local tumor recurrence and no metastasis to the intrapelvic or paraspinal organs. Other authors have proposed that seeding via the subarachnoid space formed the metastasis around the cauda equina as drop metastasis.[10,12] This seems unlikely because brain MRI showed no metastatic brain tumor and his surgical findings revealed no evidence of subarachnoid dissemination of the tumor. Despite a radiological work-up, we could not diagnose correctly before surgery. Fifty-seven percent of clear cell renal carcinomas demonstrate mutations of the Hippel-Lindau locus at 3p25. Globoganglio-sides acting as adhesion molecules have been shown to be increased in renal cell carcinoma metastasis. A new approach directed towards the molecular biology of renal cell carcinoma metastasis may offer more options for the treatment of this condition.[8]

The tumor in our case was elastic hard, well demarcated and did not infiltrate into the subarachnoid space. It involved a single spinal nerve that fanned out over the surface of the tumor. We could remove the tumor easily after resecting the nerve proximal and distal to the tumor. These surgical findings are typical for nerve sheath tumors but are extremely exceptional for metastatic tumors. All of the metastatic cauda equina tumors seemed to have involved several spinal nerves or disseminated in the subarachnoid space[8–12] with the exception of Takahashi's case,[14] where the operative findings resembled those of our case. Both cases had renal cell carcinoma. The postoperative course of our patient was satisfactory. He noticed complete relief of his radicular pain. He also showed no sensory and motor disturbance after surgery. The tumor might have metastasized to one of the sensory roots, and the function of the affected root might have been compensated by the adjacent sensory roots during tumor growth.

## CONCLUSION

We reported a rare case of the metastatic tumor of the cauda equina from the kidney. The radiographic and the operative findings of the tumor quite resembled that of a nerve sheath tumor. Only 10 cases with solitary metastasis to the cauda equina were reported in the English literature and we added the 11th case.

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# Gamma knife surgery for brain metastases: indications for and limitations of a local treatment protocol

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## Summary

*Objective.* The purpose of this retrospective study was to evaluate results of a local treatment protocol using gamma knife surgery (GKS) for brain metastases without upfront whole brain radiation therapy (WBRT).

*Methods.* Results for 521 consecutive patients satisfying the following 3 criteria were analysed: 1) a maximum of 3 tumours with a diameter of 25 mm or more; 2) no prior WBRT; 3) no surgically inaccessible large (>30 mm) tumours. Large tumours were surgically removed and all smaller lesions were treated by GKS without upfront WBRT. New lesions, detected with follow-up MRI, were appropriately treated with repeat GKS. Overall survival (OS), neurological survival (NS), qualitative survival (QS) and new lesion-free survival (NLFS) curves were calculated and the prognostic values of covariates were obtained. OS and NS were compared according to tumour number.

*Results.* In total, 1023 separate sessions were required to treat 4562 lesions. The primary organs were lung in 369 patients, gastrointestinal tract in 70, breast in 33, urinary tract in 24, and others/unknown in 25. The median OS period was 9.0 months. On multivariate analysis, the significant prognostic factors for OS were found to be extracranial disease (risk factor: active), Karnofsky performance status (KPS) score (<70) and gender (male). NS and QS at one year were 85.6% and 73.0%, respectively. The only significantly poor prognostic factor for NS was carcinomatous meningitis. NLFS at 6 months was 68.9%. For both OS and NS, the differences between a few (≤3) and many (4–10) brain lesions were not significant (OS: $p = 0.3128$, NS: $p = 0.5509$). Patients with numerous (>10) tumours had a significantly poorer prognosis than those with ≤10.

*Conclusion.* Our protocol, aggressively applying GKS, provides excellent results in selected patients with ≤10 brain lesions and no carcinomatous meningitis.

*Keywords:* Brain metastasis; stereotactic radiosurgery; gamma knife surgery; whole brain radiation therapy.

## Introduction

Excellent results have been reported using radiosurgery for a few small metastatic brain tumours resulting from various systemic cancers [2, 3, 5–7, 13]. However, most previous studies were small or multi-institutional and followed inhomogeneous management protocols, and few prospective randomised studies comparing radiosurgery alone and radiosurgery plus WBRT have been reported [2, 3, 5–7, 9, 14, 15]. Furthermore, they evaluated only OS, which depended mainly on the extracranial disease and pre-treatment KPS score. NS and QS should be considered in discussing the results of treating brain metastases. In this retrospective study, we carefully reviewed a very large series of results of GKS without upfront WBRT for brain metastases, treated according to the same protocol, at a single institute with special attention paid to NS and QS, and discuss the indications and limitations herein.

## Patients and methods

Among 550 cases with brain metastases treated by GKS at Chiba Cardiovascular Center from January 1998 through December 2002, 521 consecutive patients who satisfied the following 3 criteria were enrolled: 1) a maximum of 3 tumours with a diameter ≥25 mm; 2) no prior WBRT; 3) no surgically inaccessible large (>30 mm) tumours. Patients with miliary cerebral dissemination (>25) were excluded in this study. All metastatic lesions were diagnosed on gadolinium-enhanced MRI (1.5 Tesla, Magnetom Vision, Siemens) with a 5-mm thickness and no gaps. At diagnosis of brain metastases, the primary physician evaluated

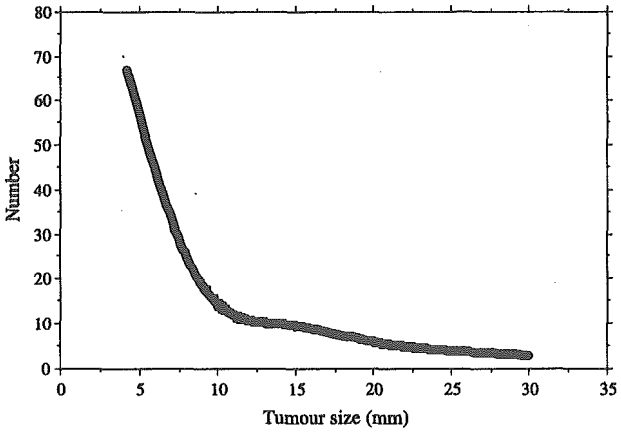


Fig. 1. Limits of lesion number and size for gamma knife surgery: The curve indicates a 3 Gy mean whole brain radiation dose calculated using the GammaPlan with 20 Gy (50%) peripheral doses. Within these limits, we assume that 25 tiny (8 mm), 10 small (14 mm) or 4 medium-sized (25 mm) lesions can be safely irradiated at a single GKS session

the status of extracranial disease using x-ray films, CT scanning and radionuclide scanning. According to the protocol of this study, large tumours (>30 mm) were surgically removed, and smaller lesions (≤30 mm) were treated by GKS without upfront WBRT. Additional GKS to the tumour bed was performed with 18–20 Gy when neurosurgeons judged the lesion to have been incompletely resected. New distant lesions detected by gadolinium-enhanced MRI were appropriately treated with repeat GKS, if the patient's condition allowed. For all GKS procedures, the mean whole brain radiation dose calculated with the Leksell GammaPlan™ (Elekta Instruments, Atlanta, GA) was kept below 3 Gy, thus preventing acute brain swelling, as previously reported [10, 11]. According to our criteria, if the lesions are scattered and similar in size, the upper simulated numerical limit is approximately 25 for tiny (8 mm), 10 for small (14 mm) and 3 for medium-sized (25 mm) lesions, with 20 Gy at the periphery, as presented in Fig. 1. Chemotherapy was administered by the primary physician.

Neurological and neuroradiological evaluations were performed every one to three months after initial GKS. Control of the GKS-treated lesion was defined as the absence of any significant increase in tumour diameter (<10%), as confirmed by axial or coronal MRI. To differentiate tumour recurrence from radiation injury, thallium-201 Chloride (Tl) SPECT was employed, as previously reported [12]. With these measurement methods, a high (>5.0) Tl index indicates tumour recurrence, a low (<3.0) index radiation injury. In lesions with an intermediate (≥3.0, ≤5.0) index, the Tl SPECT studies were repeated until the index exceeded 5.0 or was less than 3.0. Neurological death was defined as death due to all forms of intracranial disease, including tumour recurrence, carcinomatous meningitis, cerebral dissemination, and other unrelated intracranial disease. Impaired activity of daily life (ADL) was defined as an impaired neurological status as reflected by a Karnofsky performance status (KPS) score <70 (functionally dependent). A new lesion was defined as the appearance of a new brain metastasis at a site different from the original one.

The intervals from the date of initial referral to our center until the date of death (overall survival, OS), neurological death (neurological survival, NS), impaired ADL (qualitative survival, QS), and appearance of new distant lesions (new-lesion-free survival, NLFS) were calculated by the Kaplan-Meier method. The tumour-progression-free survival for all lesions treated with GKS was also analysed. Prognostic values of the individual covariates for OS, NS, QS and NLFS were obtained with the Cox proportional hazards model. The following 11 dichotomised covariates were entered: age (≥65 years versus <65 years); gender (male versus female); pre-treatment KPS score (≥70 versus <70); extracranial disease (controlled versus active); diagnostic timing of brain metastasis with primary site (synchronous versus metachronous); primary organ (lung cancer versus non-lung cancer); brain lesion number (>10 versus ≤10); maximum lesion size (≥25 mm versus <25 mm); presence of carcinomatous meningitis at initial MRI (yes versus no); chemotherapy (yes versus no) and craniotomy (yes versus no). Covariates revealed to be significant by univariate analyses were included in the multivariate model verified by stepwise methods in the final model. According to tumour number (a few: ≤3, many: 4–10, numerous: >10), OS and NS were also compared by logrank test. A probability value <0.05 was considered statistically significant.

## Results

The distributions of dichotomised covariates are summarised in Table 1. In total, 1023 separate GKS

Table 1. *Distribution of patient characteristics*

| Characteristics | Number of patients |
|---|---|
| Age (years) | |
| <65 | 252 |
| ≥65 | 269 |
| Gender | |
| male | 322 |
| female | 199 |
| Extracranial disease | |
| controlled | 68 |
| active | 453 |
| Initial KPS score | |
| <70 | 94 |
| ≥70 | 427 |
| Primary organ | |
| lung | 367 |
| non-lung | 154 |
| Brain lesion number | |
| ≤10 | 433 (single 121) |
| >10 | 88 |
| Maximum lesion size | |
| <25 mm | 343 |
| ≥25 mm | 178 |
| Carcinomatous meningitis | |
| yes | 45 |
| no | 476 |
| Chemotherapy | |
| yes | 148 |
| no | 373 |
| Craniotomy | |
| yes | 97 |
| no | 424 |
| Diagnostic timing | |
| synchronous | 358 |
| metachronous | 163 |

*KPS* Karnofsky performance status.

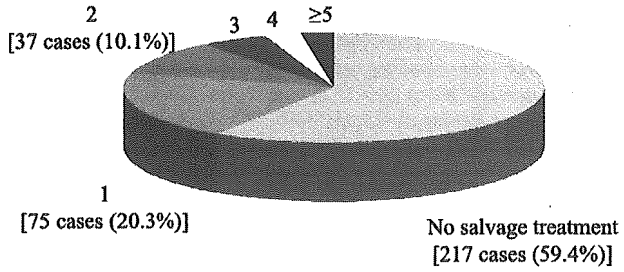


Fig. 2. Number of salvage treatments: There were zero salvage treatments by gamma knife surgery in 217 cases (59.4%), one in 74 (20.3%), two in 37 (10.1%), three in 19 (3.6%), and ≥5 in 19 (3.6%)

procedures were required to treat 4562 lesions. The median number of lesions treated by the initial GKS was 3, range 1 to 25. During follow-up, the number of GKS procedures averaged 1.7 ± 1.3, varying between 1 and 9 (Fig. 2), and the mean total number of lesions treated per patient with GKS was 8.9 ± 11.4, range 1 to 77. The mean calculated tumour volume was 1.0 ± 2.8 $cm^3$. The minimum dose applied to the tumour margin was 13.3 to 33.3 Gy (mean ± SD 20.8 ± 2.4 Gy, median 20 Gy) with a 59.5% isodose contour (range 30–95%). The whole brain radiation dose was 0.1 Gy to 3.0 Gy (mean ± SD 1.2 ± 0.6 Gy, median 1.1 Gy). In 57 incompletely resected lesions of 97 operations (58.8%), the tumour bed was additionally irradiated with 18–20 Gy using GKS. The primary cancers were in the lung in 369 patients (72.1%), gastro-intestinal tract in 70 (13.4%), breast in 33 (6.3%), urinary tract in 24 (4.6%), and others/unknown in 25 (4.8%). The tumour-progression-free survival rates were 95.7% at one year and 91.1% at 2 years. The median OS period was 9.0 months (Fig. 3a). In multivariate analysis, significant prognostic factors for OS were active extracranial disease ($p < 0.0001$), low pre-treatment KPS score ($p < 0.0001$) and male gender ($p = 0.0028$), as shown in Table 2. NS and QS at one year were 85.6% and 73.0%, respectively (Fig. 3b, c). Of the 365 mortalities, 66 (18.1%) were attributed to neurological death. Causes of neurological death were carcinomatous meningitis in 26, cerebral

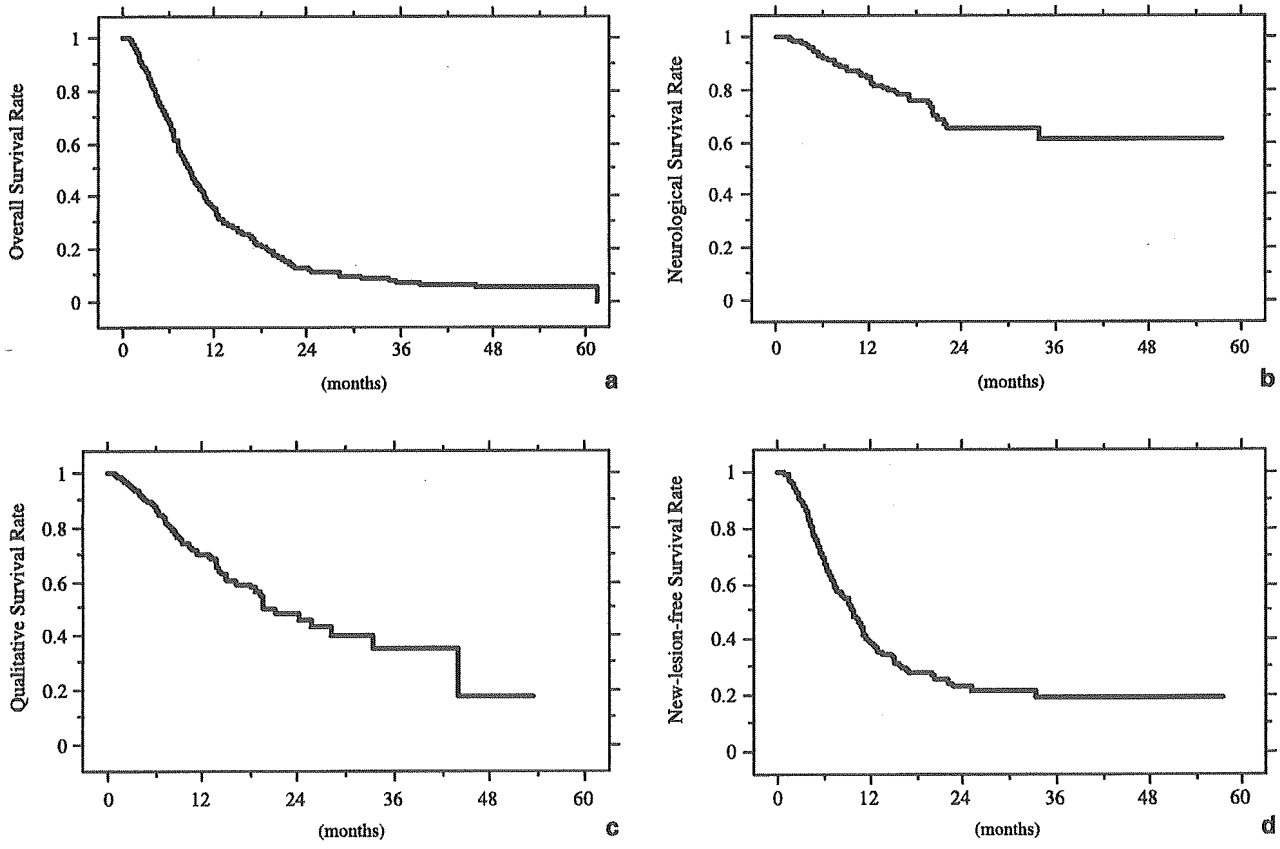


Fig. 3. (a) Overall survival: The overall survival (*OS*) curve is presented. The median OS period was 9.0 months. (b) Neurological survival: The neurological survival curve is shown. The neurological death free rate following GKS was 85.6% at one year. (c) Qualitative survival: The qualitative survival (*QS*) curve is presented. The functional-dependent-free rate was 73.3% at one year. (d) New-lesion-free survival: The new-lesion-free survival (*NLFS*) curve is shown. The NLFS rate was 68.9% at 6 months, 38.9% at 1 year

Table 2. *Prognostic variables for overall survival*

| Variables | High risk group | P-value* | HR* | P-value** | HR** |
|---|---|---|---|---|---|
| Age | ≥65 | 0.9995 | 1.000 | | |
| Gender | male | 0.0027 | 1.389 | 0.0028 | 1.392 |
| Extracranial disease | active | <0.0001 | 4.098 | <0.0001 | 3.969 |
| Initial KPS score | <70 | <0.0001 | 1.845 | <0.0001 | 1.864 |
| Primary organ | non-lung | 0.0242 | 1.290 | | |
| Brain lesion number | >10 | 0.0010 | 1.580 | | |
| Maximum lesion size | ≥25 mm | 0.2281 | 1.142 | | |
| Presence of CM | yes | 0.0494 | 1.434 | | |
| Chemotherapy | no | 0.1246 | 1.189 | | |
| Microsurgery | no | 0.1214 | 1.225 | | |
| Diagnostic timing | synchronous | 0.4133 | 1.098 | | |

* Monovariate analysis, ** Multivariate analysis (Cox's proportional hazard final model), *HR* hazard ratio, *KPS* Karnofsky performance status, *CM* carcinomatous meningitis.

Table 3. *Prognostic variables for neurological survival*

| Variables | High risk group | P value* | HR* | P value** | HR** |
|---|---|---|---|---|---|
| Age | <65 | 0.2631 | 1.339 | | |
| Gender | male | 0.3039 | 1.314 | | |
| Extracranial disease | active | 0.0113 | 2.577 | | |
| Initial KPS score | <70 | 0.1622 | 1.628 | | |
| Primary organ | non-lung | 0.5436 | 1.186 | | |
| Brain lesion number | >10 | 0.0009 | 2.681 | | |
| Maximum lesion size | ≥25 mm | 0.2818 | 1.326 | | |
| Presence of CM | yes | <0.0001 | 8.013 | <0.0001 | 8.013 |
| Chemotherapy | no | 0.3366 | 1.311 | | |
| Microsurgery | yes | 0.9206 | 1.030 | | |
| Diagnostic timing | synchronous | 0.4857 | 1.209 | | |

* Monovariate analysis, ** Multivariate analysis (Cox's proportional hazard final model), *HR* hazard ratio, *KPS* Karnofsky performance status, *CM* carcinomatous meningitis.

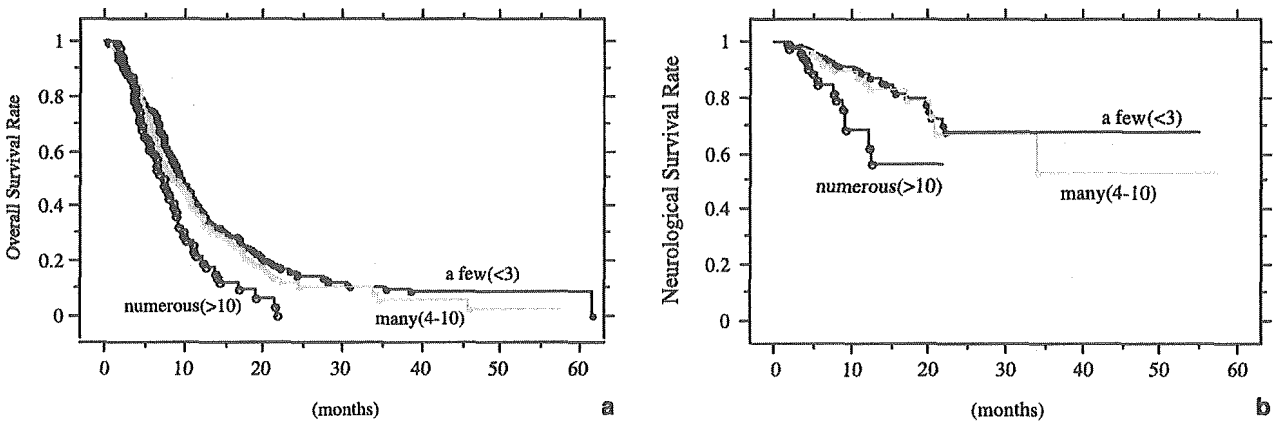


Fig. 4. Overall and neurological survival curves according to tumour number: (a) Overall survival curves according to tumour number: The difference between a few (≤3) and many (4–10) lesions was not statistically significant (p = 0.3128). The outcome of patients with numerous (>10) lesions was significantly poorer than that of those with a few (p = 0.0025) or many (p = 0.0144). (b) Neurological survival curves according to tumour number: Neurological survival curves according to tumour number are shown. The difference between a few (≤3) and many (4–10) lesions was not statistically significant (p = 0.5509). Patients with numerous (>10) lesions had a significantly poorer outcome than those with a few (p = 0.0017) or many (p = 0.0098)

dissemination in 18, recurrence of the treated lesion in 14, progression of an untreated lesion in 7 and other in 1. Among 105 cases with functional dependence due to brain lesions, the causes were radiation injury in 31, carcinomatous meningitis in 28, cerebral dissemination in 20, recurrence of the treated lesion in 16, progression of an untreated lesion in 9, and other in 1. The only significantly poor prognostic factor for NS was carcinomatous meningitis ($p < 0.0001$), as depicted in Table 3. Extracranial active disease ($p = 0.0008$), poor pre-treatment KPS score ($p = 0.0002$) and carcinomatous meningitis ($p < 0.0001$) were confirmed to be significant factors influencing QS in multivariate analysis. NLFS at 6 months was 68.9% (Fig. 3d). New lesions emerged more frequently in patients with active extracranial disease ($p = 0.0017$) and numerous (>10) brain metastases ($p = 0.0365$). OS and NS curves, according to tumour number, are shown in Fig. 4a and b, respectively. For both OS and NS, the differences between a few ($\leq 3$) and many (4–10) were not statistically significant (OS: $p = 0.3128$, NS: $p = 0.5509$), but the outcome of patients with numerous (>10) lesions was significantly poorer that of those with $\leq 10$ (ON: $p = 0.0144$, NS: $p = 0.0017$).

## Discussion

Patients with many (>4) lesions have been considered to have a poorer prognosis than those with a few ($\leq 3$). This study revealed the differences in OS and NS between a few ($\leq 3$) and many (4–10) to be statistically not significant and suggests that the limit of lesion numbers for GKS is around 10, as previously reported [10, 11]. GKS in a single session is limited not only by lesion number, but also lesion size. However, most earlier investigators focused solely on number [2, 3, 5–9, 13–15]. Both the number and the size of lesions affect the mean whole brain radiation dose, which provides information on the limits for GKS in a single session [10, 11]. With a mean skull radiation dose of 3 Gy or less, our calculations indicate 25 tiny (8 mm), 10 small (14 mm) or 4 medium-sized (25 mm) to be the numerical limits for a single session of GKS, if the peripheral dose is 20 Gy with the GammaPlan. Adverse early radiation effects such as acute brain swelling were not observed in our series. Research groups of Yamamoto and Yang, using higher radiation doses than allowed by the criteria employed herein, reported the safety of GKS for numerous brain metastases [16, 17]. From the viewpoint of our large series and routine WBRT use, a mean whole brain radiation dose of 3 Gy seems to be quite safe, if lesions are diffusely scattered in the brain. Furthermore, this study found patients with carcinomatous meningitis to have significantly poorer NS and QS. In conclusion, our present criteria indicating GKS alone to be suitable for treating metastatic brain tumours are 1) no surgically inaccessible large (>30 mm) tumours, 2) 10 or fewer lesions, 3) a maximum of 3 tumours with a diameter $\geq 25$ mm, and 4) no findings of carcinomatous meningitis on MRI. NS and QS for one year of patients with these criteria were 91.5% and 81.6%, respectively.

It has become widely accepted, since the advent of CT scanning, that even patients with only a single metastatic lesion have microscopic metastases [8]. Modern high-quality MRI can detect metastatic tumours only a few millimeters in diameter. The survival period may be too short for invisible metastases or true new lesions to be identified on follow-up MRI or to cause neurological symptoms and signs. Chemotherapy may, of course, play an additional role in controlling microscopic lesions. Our treatment policy for metastatic brain tumours is that verifiable local control is the first priority, while treating invisible metastases is the second. Indeed, almost 60% of patients in our series did not require salvage treatment. Upfront WBRT need not be introduced and appropriate salvage treatment, taking the patient's condition into consideration, may be warranted, if new lesions are detected. The current study demonstrates that a local GKS treatment protocol without upfront WBRT can provide highly satisfactory results in selected patients with close observation and appropriate salvage treatment.

## Conclusions

From the viewpoints of NS and QS, GKS without upfront WBRT for brain metastases from various primary tumours provides satisfactory palliation considering the patients' short life expectancies. Brain metastases could be managed according to our local treatment protocol by GKS alone without upfront WBRT, if the following 4 criteria were satisfied 1) no surgically inaccessible large (>30 mm) tumours, 2) 10 or fewer lesions, 3) a maximum of 3 tumours with a diameter of $\geq 25$ mm, and 4) no findings of carcinomatous meningitis on MRI. However, careful follow-up MRI and appropriate salvage treatment are essential to preventing neurological death and maintaining favorable ADL.

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## Comment

This is an interesting and potentially important paper. As some other authorities have done before them, the authors have challenged the traditional wisdom of limiting gamma knife surgery to the maximum of 3 lesions. Inclusion criteria for this study were patients with a maximum of 3 tumours with a diameter $\geq$25 mm, no cerebral dissemination ($\leq$25 micrometastases) and no surgically inaccessible large (>30 mm) tumours. This reviewer from the United Kingdom read with great interest, that in several of their patients salvage treatment was carried out, in nine cases five times or more. This raises an interesting question about healthcare funding.

They have, very usefully, extended the outcome measures from overall survival to include death from neurological causes, qualitative survival, new lesion free survival, progression free survival etc.

They have shown that there is no significant reduction in outcome up to 10 lesions when a wide variety of outcome measures are considered. They have truly tested the technique, by going up to 77 lesions in one case.

The observations made are sound if not particularly surprising. Active extracranial disease, poor pretreatment Karnofsky score and carcinomatous meningitis were confirmed to be significant factors influencing outcome. At this stage of our knowledge their recommendations: no surgically inaccessible large tumours, 10 or fewer lesions, a maximum of 3 tumours with a diameter of $\geq$25 mm, and no carcinomatous meningitis, appear sensible.

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# Diagnostic value of thallium-201 chloride single-photon emission computerized tomography in differentiating tumor recurrence from radiation injury after gamma knife surgery for metastatic brain tumors

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*Object.* The authors assessed the diagnostic value of $^{201}$Tl Cl single-photon emission computerized tomography (SPECT), performed after gamma knife surgery (GKS) for metastatic brain tumors in differentiating tumor recurrence from radiation injury.

*Methods.* Of 6503 metastatic brain tumors treated with GKS, $^{201}$Tl SPECT was required in 72 to differentiate between tumor recurrence and radiation injury. When the Tl index was greater than 5, the lesion was diagnosed as a tumor recurrence. When the index was < 3.0 it was called radiation injury. In cases with a Tl index between 3 and 5, $^{201}$Tl SPECT was repeated once per month until the Tl index was greater than 5 or less than 3. If the Tl index fluctuated between 3 and 5 for 2 months, the lesion was diagnosed as radiation injury. The final diagnosis was based on histological examination or clinical course.

The sensitivity of the method was 91%; thus $^{201}$Tl SPECT is effective for differentiating between tumor recurrence and radiation injury in metastatic brain tumors treated with GKS. Caution is necessary, however, for the following reasons: 1) simple interinstitutional comparisons of Tl indices are not possible because measurement methods are institute specific; 2) steroid administration decreases the Tl index to a variable degree; and 3) a severe radiation injury lesion, as is often seen after repeated GKS or very high dose GKS, may have a Tl index greater than 5.

*Conclusions.* Used with critical insight $^{201}$Tl Cl SPECT can be useful in distinguishing between tumor regrowth and radiation necrosis in patients with cerebral metastases.

KEY WORDS • **gamma knife surgery** • **metastatic brain tumor** • **radiation injury** • **tumor recurrence** • **thallium-201** • **single-photon emission computerized tomography**

EXCELLENT tumor control has been reported using GKS for metastatic brain tumors that result from various systemic malignancies; however, tumor regrowth with surrounding edema can occur after GKS.[8,10] In this situation, differentiating between tumor recurrence and radiation injury may be difficult using only MR imaging. The purpose of this prospective study was to determine the differential diagnostic value of $^{201}$Tl Cl SPECT after GKS for metastatic brain tumors.

## Clinical Material and Methods

Among 701 patients with 6503 metastatic brain tumors 1404 were treated with GKS between 1998 and 2003. Of these 72 lesions in 70 patients in whom regrowth was demonstrated on follow-up MR imaging were studied with

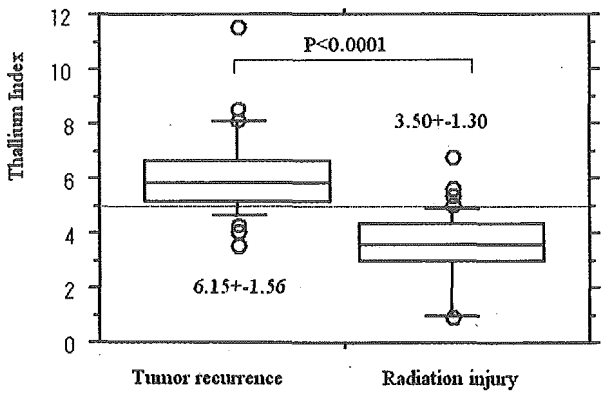


FIG. 1. Graph showing the distribution of Tl indices.

*Abbreviations used in this paper:* GKS = gamma knife surgery; MR = magnetic resonance; SPECT = single-photon emission computerized tomography.

TABLE 1
*Treatment summary of 72 lesions**

| Variable | Min | Max | Mean | SD | Median |
|---|---|---|---|---|---|
| tumor vol ($cm^3$) | 0.25 | 16.0 | 5.73 | 4.44 | 4.70 |
| peripheral (%) | 38.1 | 91.6 | 53.6 | 10.7 | 49.9 |
| peripheral dose (Gy) | 14.0 | 30.0 | 20.4 | 2.7 | 20.0 |
| max dose (Gy) | 24.8 | 59.8 | 28.9 | 6.9 | 40.1 |
| no. of isocenters | 1 | 24 | 8.2 | 5.8 | 6.5 |

* SD = standard deviation.

$^{201}$Tl SPECT and analyzed for this study. The mean patient age was 63.8 years (range 46–86 years). There were 37 men and 33 women. The primary cancer was from the lung in 57 (79.2%), gastrointestinal tract in 10 (13.9%), urinary tract in two (2.8%), breast in one (1.4%), and other in two (2.8%). The early Tl index was quantified using a triple-head gamma camera equipped with low-energy high-resolution fan beam collimators (GCA9300A/UI; Toshiba, Tokyo, Japan). The data were acquired in a 128 × 128 matrix over a 120° rotation at angular intervals of 4°. The energy was set at 75 keV for the main window and at 7% for the subwindow. Data were collected 20 minutes after intravenous administration of 111 MBq $^{201}$Tl. Scatter correction was performed by the triple-energy window method, but absorption correction was not used. The SPECT images were gathered after filtered-back projection with a Butterworth filter (cut-off frequency 0.34 cycles/cm). The region of interest was automatically drawn with a lower cut-off for the lesion at 80%, to minimize errors between radiation technicians. The control region, approximately 100 pixels, was the contralateral or distant normal brain.

When the Tl index was greater than 5, the lesion was diagnosed as tumor recurrence. If the index was less than 3 the lesion was diagnosed as radiation injury. In cases in which the Tl index was between 3 and 5, $^{201}$Tl SPECT was repeated once per month until the Tl index was either greater than 5 or less than 3. If the Tl index fluctuated between 3 and 5 for 2 months, the lesion was diagnosed as radiation injury. The final diagnosis was based on histological examination or clinical course. In patients whose lesions did not undergo histological examination, radiation injury was diagnosed when the enhanced lesion did not increase in size on subsequent MR imaging for 3 months or more. A paired Student t-test was used to compare the Tl indices of tumor recurrence with those of radiation injury. A probability value less than 0.05 was considered statistically significant.

## Results

The treatment data are summarized in Table 1. The mean tumor volume was 5.8 $cm^3$, and the mean radiation dose at the periphery was 20.5 Gy. The mean number of isocenters was 8.4. The mean interval from GKS to the first radioisotope diagnosis was 7.3 months (range 1.2–44.6 months). The equivalent mean interval to the last radioisotope diagnosis was 8.7 months (range 2.1–44.6 months). Thirty-one

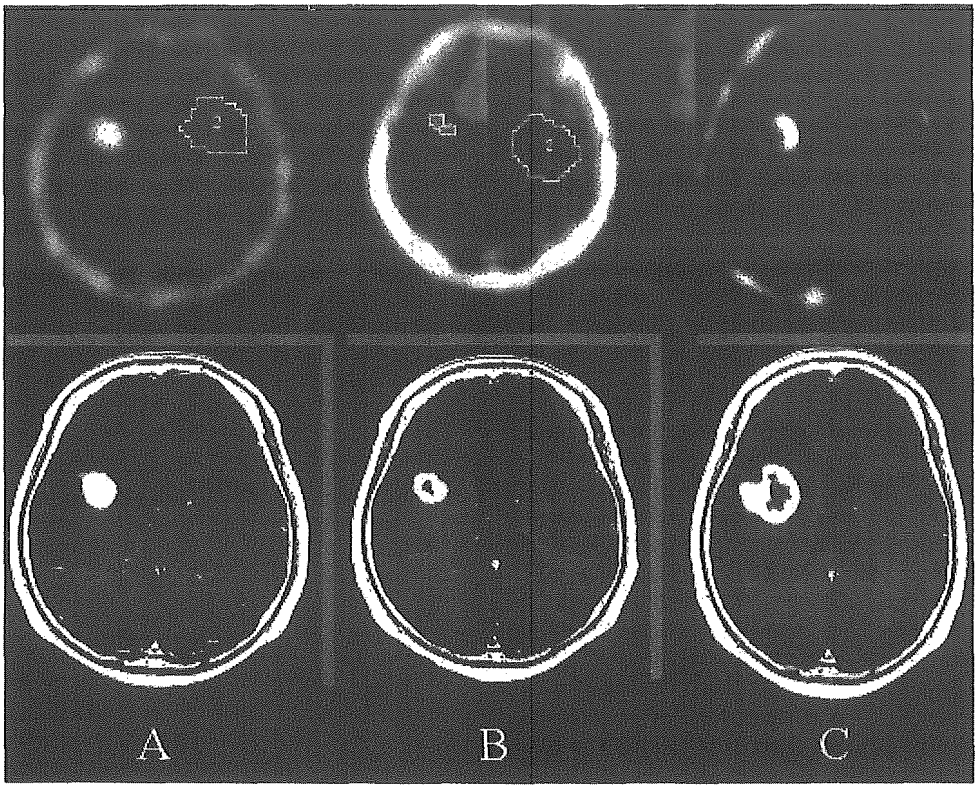


FIG. 2. Serial enhanced MR and $^{201}$Tl SPECT studies obtained in the patient in Case 1. A: Pre-GKS: a right frontal metastatic lesion from colon cancer. The Tl accumulation was intense (Tl index 11.43). B: Two months later: the tumor shows shrinkage and the Tl index has decreased to 2.75. C: Seven months later the tumor has increased in size and the Tl index has risen to 5.8. The radioisotope diagnosis was tumor recurrence. The tumor was resected.

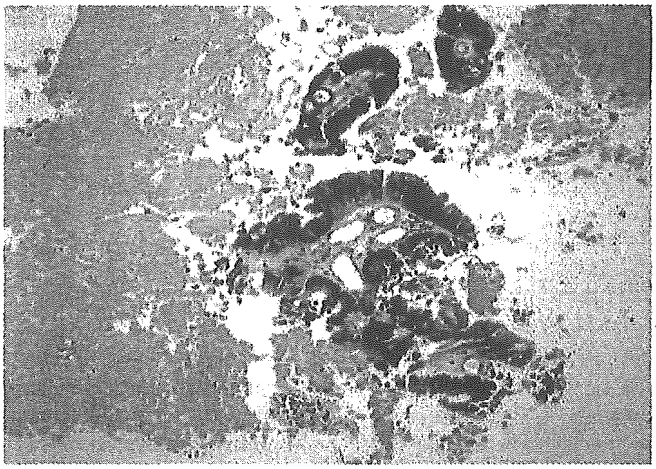

FIG. 3. Photomicrograph obtained in Case 1. Histopathological examination confirmed viable tumor cells. H & E.

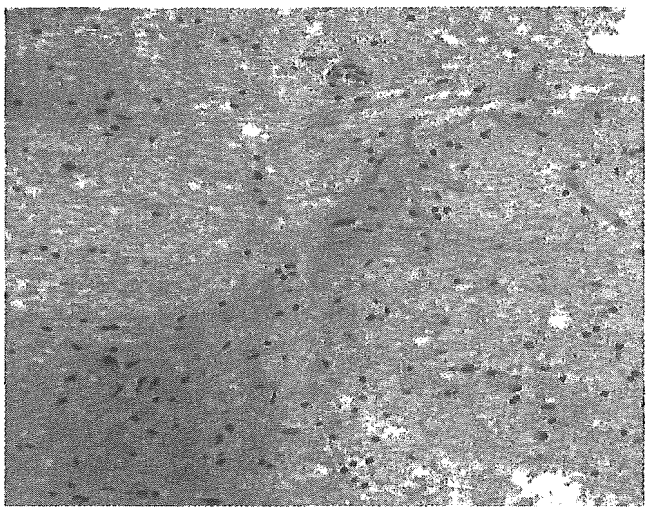

FIG. 5. Photomicrograph obtained in Case 2. This specimen was obtained by MR-guided stereotactic biopsy and shows no viable tumor cells

lesions (43.1%) were diagnosed based only on the first Tl index measurement, and 41 (56.9%) required serial Tl measurements. Distributions of the Tl index are shown in Fig. 1. The mean Tl indices of tumor recurrence and radiation injury were 6.15 and 3.5, respectively, a statistically significant difference ($p < 0.0001$). The final diagnosis was tumor recurrence in 30 and radiation injury in 42. Ten lesions (14.1%) were histopathologically examined. There were three false-positives and four false-negative results. For 65 lesions, the radioisotope and final diagnoses were compatible (accuracy 90.3%). Sensitivity was 90% and specificity was 90.5%.

*Case Presentation*

*Case 1. Tumor Recurrence.* This 62-year-old woman had a single 25-mm metastatic lesion in the frontal lobe from colon cancer (Fig. 2A). The pre-GKS Tl index was 11.43. The lesion was treated by GKS with 26 Gy to the 52% isodose line. Gadolinium-enhanced MR imaging obtained 2 months later revealed tumor shrinkage (Fig. 2B) and the Tl index had decreased to 2.75. Seven months later, however, MR imaging demonstrated tumor regrowth (Fig. 2C) and the Tl index had increased to 5.8. The radioisotope diagnosis was tumor recurrence. The tumor was surgically removed, and histopathological examination revealed viable tumor cells (Fig. 3).

*Case 2. Radiation Injury.* This 72-year-old man had multiple brain metastases from lung adenocarcinoma. A lesion in the caudate nucleus was irradiated with 22 Gy to the 50% isodose line (Fig. 4A). The pre-GKS Tl index was 4.63. Two months later MR imaging revealed marked tumor shrinkage (Fig. 4B), and there was no abnormal Tl accumulation. Six months later, MR imaging demonstrated tumor regrowth (Fig. 4C) and the Tl index was low but not

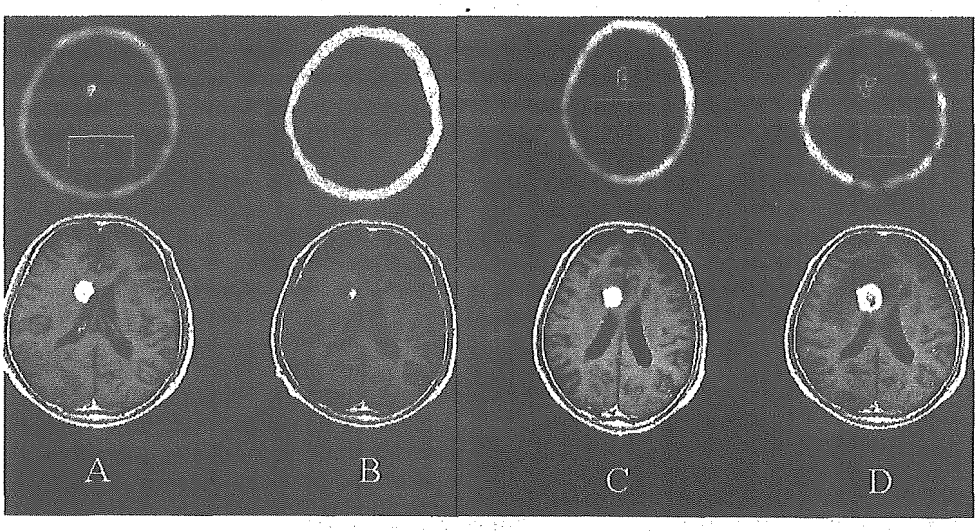


FIG. 4. Serial enhanced MR image and $^{201}$Tl SPECT studies obtained in the patient in Case 2. A: Pre-GKS: a metastatic lesion in the right caudate from lung adenocarcinoma. The pre-GKS Tl index was 4.63. B: Two months later the tumor shows marked shrinkage. There is no abnormal Tl accumulation. C: Six months later MR imaging demonstrated tumor regrowth, but the Tl index remains low (3.08), necessitating serial measurements. D: Eight months later the area of enhancement has again increased in size. The Tl index remains low (3.43). The radioisotope diagnosis was radiation injury.