1 Correlation Analyses of Clinicopathological Factors With Recurrence

	Frequency (%)	Overall Cases	Group A	Group B	Group C	Group B+C
Mitoses (+)	7%	<0.0001				
Simpson Grades		<0.0001	<0.0001	NS	NS	NS
Simpson I or II	78	<0.0001	<0.0001	NS	NS	NS
Perifocal edema on MR images (+)	46	NS	0.009	NS	NS	NS
Hard tumors	48	NS	NS	NS	NS	NS
Arachnoid penetration (+)	26	NS	NS	NS	NS	NS
Well-demarcated tumors	96	0.01	0.006	NS	NE	NS
Tumor stain on angiograms (+)	75	NS	0.03	NS	NS	NS
Feeding from pial arteries on angiogram	28	NS	NS	NS	NE	NS
Tumor locations		0.03	0.0002	NS	NS	NS
Tumors located on skull base	48	0.01	<0.0001	NS	NS	NS

Frequency is calculated in overall cases.
Cases with no mitoses, those with 1–4 mitoses per 10HPF, and 4 or more mitoses per 10 HPF are present in each of the 3 groups.
NS = not significant, NE = not examined because of insufficient numbers of cases.

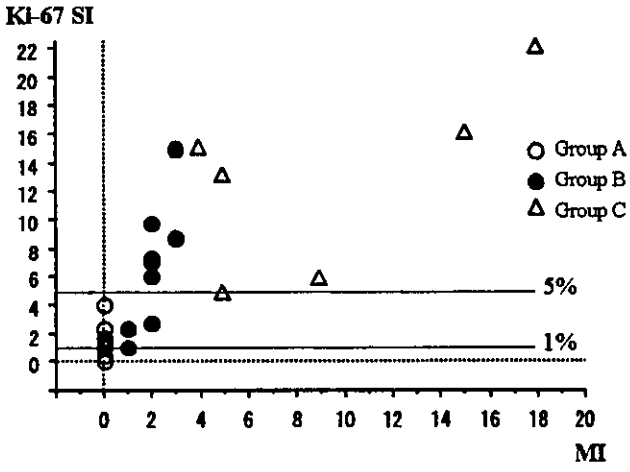
B and C combined, $p < 0.0001$). Group B and C did not significantly differ with respect to PFS ($p = 0.3945$).

The frequencies of radiologic, operative, and pathologic findings and their univariate associations are summarized in Table 1. In the analysis of overall cases and of Group A patients, parameters such as the Simpson grade, tumor demarcation, and tumor location contributed to variability in the Kaplan-Meier PFS curves assessed by the log-rank test. In contrast, none of the variables examined significantly affected the PFS curves of Group B and C, nor of Groups B and C combined.

Figure 1B shows the Kaplan-Meier PFS curves for all 326 Group A patients classified according to the Simpson resection grades. The estimated 5-year PFS rates for Simpson Grades I, II, III, and IV were 100%, 97%, 81%, and 77%, respectively; the 10-year PFS rates were 95%, 93%, 76%, and 38%; and the mean PFS was 121, 150, 132, and 85 months. According to the log-rank test, in Group A, the Simpson grade had a significant effect on PFS: the greater the extent of resection, the longer was the PFS and the lower the progression ratio ($p < 0.0001$). On the other hand, in Groups B and C, the extent of resection had no significant impact on PFS ($p = 0.71$) (Figure 1C). The estimated 2-year PFS rates for the 23 patients in Groups B and C who had undergone Grade I, II, III, or IV resection were 42%, 50%, 57%, and 75%, respectively; the median PFS was 19, 18, 49, and 6 months. In Group B alone and Group C alone, there was also no significant association of the Simpson's grade with PFS ($p = 0.97$ and $p = 0.58$, respectively).

KI-67 SI AND MI

In 29 of the 42 patients with recurrence we determined the Ki-67 SI in tumor samples from the initial surgery. The mean Ki-67 SI values ± SD were 1.5 ± 1.2 in Group A ($n = 14$), 6.7 ± 4.3 in Group B ($n = 9$), and 12.8 ± 6.5 in Group C ($n = 6$). Based on the Pearson correlation coefficient, there was a significant correlation between the MI and the Ki-67 SI ($r = 0.81$, $p < 0.0001$). Figure 2 shows that all cases with a Ki-67 SI below 1% were from Group A. An SI exceeding 5% was indicative of the presence of mitoses (Groups B and C). Patients from all groups could be found in the 1 to 5% SI range.



2 Correlation of mitotic index with Ki-67 staining index. Open circles, Group A (no mitotic figures); closed circles, Group B (more than 0 and fewer than 4 mitotic figures per 10HPF); open triangles, Group C (more than 4 mitotic figures per 10HPF).

COMPARISON BETWEEN THE MI AND PATHOLOGIC DIAGNOSIS

The 331 patients with a pathologic diagnosis of benign meningioma manifested an estimated 5-year PFS rate of 91% with a mean PFS of 144 months. On the other hand, in the 18 patients with atypical or anaplastic meningiomas, the estimated 5-year PFS rate was 32% with a median PFS of 52 months. Kaplan-Meier analysis showed that the difference in PFS between benign and atypical/anaplastic meningiomas was significant ($p < 0.0001$). The Simpson grade had a significant effect on PFS only in the 331 patients with benign meningiomas ($p < 0.001$); the estimated 5-year PFS rates for Grades I, II, III, and IV were 97%, 95%, 95%, and 90%, respectively; the 10-year rates were 76%, 70%, 80%, and 35%; and the mean PFS was 117, 148, 126, and 82 months.

In Group A, none of the 4 meningiomas designated atypical according to WHO criteria (MI = 0) recurred during a mean follow-up of 61 months. On the other hand, all 9 benign meningiomas in Group B recurred after a mean of only 38 months (range 18–64 months), a shorter interval than we expected for ordinary benign meningiomas.

DISCUSSION

Although meningiomas are generally benign, slow-growing tumors with apparent demarcation, they have a tendency to recur after a period of more than 10 years [14,28]. Putative prognostic factors are age, attachment to intracranial structures (location), the extent of resection [7,8,28], grade of malignancy [9,25], and proliferation indices [6,10–15,17,18,20,21]. The pathologic grade of malignancy has been proposed as the most relevant overall predictor of recurrence [14]. However, there are patients whose tumors are not pathologically identifiable as benign or atypical because the grade of malignancy cannot be unequivocally determined. The WHO classification proposes primarily qualitative criteria for defining grades of malignancy; except for the MI, it does not provide more precise quantitative indicators that could be assessed according to numerical scoring systems. For the purpose of diagnosing atypical meningiomas, the WHO criteria define increased mitotic activity as the presence of 4 or more mitoses per 10 HPF. However, with respect to assigning a malignant grade to meningiomas, the WHO classification system does not consider a finding of fewer than 4 mitoses of importance [14].

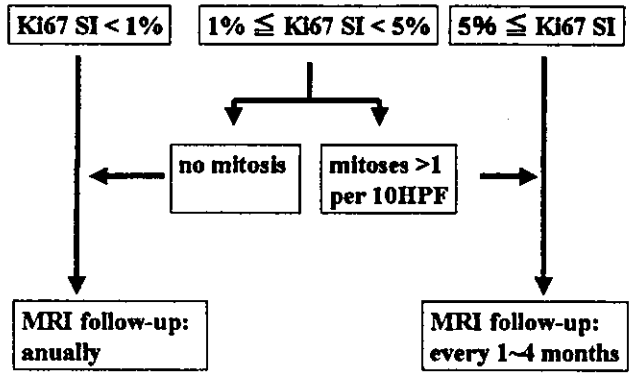
Proliferation indices such as the Ki-67 SI are useful for predicting tumor recurrence and survival. While previous studies documented that the Ki-67 SI significantly correlates with the pathologic grade of meningiomas, there is considerable variation in the Ki-67 SI values reported in different studies and by different institutions. In fact, the reported mean values for benign-, atypical-, and anaplastic meningiomas range widely between 0.7 and 3.8%, 2.1 and 7.1%, and 10.9 and 14.7%, respectively [1,10,14,15,21,26,27]. Moreover, some reports suggested significant overlapping of Ki-67 values among various pathologic grades of malignancy [1,6,12,13]. Perry et al [25] who performed statistical analyses of 62 meningioma cases, suggested that a Ki-67 SI of 4.2% represented a threshold and that an SI in excess of 4.2% was indicative of high tumor proliferation activity. Although we agree that values markedly above or below this threshold may signal unfavorable and favorable outcomes respectively, in view of the wide range of reported Ki-67 SI values, we favor the establishment of stricter SI criteria to predict clinical outcomes.

In efforts to develop a system whereby quantitative indicators can be used to predict the PFS of meningioma patients, we performed the current retrospective study. We assessed whether the combination of an MI that confirms the presence of even fewer than 4 mitoses per 10 HPF and the KI-67 SI is of prognostic significance. Surgically removed meningioma tissues in 326 of 349 patients (93.4%) exhibited no evidence of mitosis. In most of the remaining 23 tissue samples the MI was around 4 per 10 HPF; none of the patients had an MI of more than 20. We found that compared to the other 2 groups, in patients with no mitoses (Group A), the 5-year incidence of tumor progression was lower (7%) and the mean PFS longer (148 months), and that the Simpson grade had a significant effect on PFS. Group B (more than 0 and fewer than 4 mitoses) and Group C patients (MI of 4 or more) had higher 5-year recurrence rates at 90% and 87%, respectively, and shorter PFS (median 43 and 16 months, respectively). A Ki-67 SI of less than 1% corresponded with the absence of mitoses in the tumor samples (Group A), while an SI exceeding 5% reflected the presence of mitotic figures (Groups B and C). Therefore, we propose that SI values of 1% and 5% be used as threshold values for predicting favorable and unfavorable outcomes, respectively, in meningioma patients. Patients from all 3 groups were found in the SI value range from 1 to 5%, therefore, a Ki-67 SI in this range is not a reliable, independent predictive indicator of the outcome. Assessment of the Ki-67 SI is relatively easy com-

pared to the calculation of a low MI whose determination is complex. Although the Ki-67 SI alone is generally used for predicting the outcome in meningioma patients, we stress the need for determining the MI, especially in patients whose Ki-67 SI is in the 1 to 5% range.

Patients with atypical and anaplastic meningiomas diagnosed according to the current WHO criteria had higher recurrence rates and shorter PFS than did patients with benign tumors. This finding coincides with the difference we observed in the MI of Group A patients and the MI in Groups B and C. It is important to note that none of the 4 atypical meningiomas in Group A manifested recurrence during a mean follow-up period of 61 months whereas all 9 benign meningiomas in Group B recurred after a mean of only 38 months (range 18–64 months). The time to recurrence of these benign tumors was shorter than we would have expected. In some of our patients the clinical outcome was at variance with the expected outcome based on the malignancy grade determined by WHO criteria. We found that in such patients, the MI reflected the likelihood of short-term recurrence much better than did the malignant grade. In addition, although an MI of 4 or more per 10 HPF is the consensus criterion for atypical meningiomas, our results suggest that a small number of mitoses, even fewer than 4 per 10 HPF, is also an important indicator for predicting the short-term progression of meningiomas.

Atypical and anaplastic meningiomas tend to recur within a short period even after gross total removal. Patients with these meningioma types require repeated operations and some have been treated with postoperative extrabeam radiation therapy (EBRT) although high-grade meningiomas are usually refractory to EBRT [2–4,19,23]. In these meningiomas, stereotactic radiosurgery (SRS) as a boost to EBRT, as salvage therapy after EBRT, or instead of EBRT, has yielded disappointing results. In atypical meningiomas the 5-year local control and 5-year overall survival rates were 32 to 48% and 83 to 95%, respectively; in anaplastic meningiomas they were 0 to 34% and 21.5 to 60% [5,22,23]. As the tumor control rate following SRS was better in patients with small (< 8 cm^3) malignant meningiomas [22], we stress that early diagnosis and immediate treatment of small recurrent tumors is imperative for improving the outcomes of patients with atypical and anaplastic meningiomas. We need a method that allows us to predict the PFS in all meningioma patients so that postoperative therapy can be selected on a case-by-case basis.



3 Proposal schedule of postoperative follow-up MRI based on MI and Ki-67 SI.

Conclusion

Our retrospective study of 349 patients with surgically treated meningiomas revealed that numerical scoring systems, i.e., the Ki-67 SI and the MI, determined at the time of the initial operation, make possible the prediction of long or short PFS. Based on our results, we propose that tumors with a Ki-67 SI of less than 1% be followed as benign meningiomas and subjected to annual MRI study (Figure 3). On the other hand, surgical specimens with a Ki-67 SI greater than 5% should be monitored as atypical or anaplastic meningiomas and undergo follow-up MRI study at intervals of a few months. In cases where the Ki-67 SI is between 1 and 5%, we suggest that the MI of tumor tissue samples be carefully determined. If there is no evidence of mitoses, annual MRI study should be performed. However, patients with even a few mitotic figures should be followed by MRI at shorter intervals.

Our retrospective analysis of 349 surgically treated meningioma patients revealed that the presence of mitotic figures in tumor tissues obtained at the first operation correlated with shorter PFS when compared to patients whose specimens contained no mitotic figures. We also determined that the threshold for predicting favorable and unfavorable treatment outcomes with the Ki-67 SI are 1% and 5%, respectively. In meningiomas with a Ki-67 SI between 1% and 5%, the presence of mitoses, even less than 4 in 10 HPF, is indicative of an increased risk for recurrence. The combination of the Ki-67 SI and the MI represents a convenient and quantitative tool for predicting PFS. We posit that in cases where a diagnosis of malignant meningioma is based on current WHO criteria, these combined assays make possible a more precise prediction of the prognosis.

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専門医に求められる最新の知識

脳腫瘍

EBMに基づく悪性神経膠腫の化学療法

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Ⅰ. はじめに

Evidence-based medicine (EBM) とは科学的証拠に基づいた医療であり，その疾患に対し現在考えられる最適の医療といえよう．EBMの基礎となるのは信頼のおける臨床的データであり，そのデータは科学的手法による臨床試験を行うことによって初めてもたらされる．過去に行われた信頼すべき臨床試験結果を基につくられてきた標準治療と，安全性の確認できた新治療との間で比較試験を行い，統計的解析を行って有意に治療効果が勝っているものが新たに標準治療として確立されていく．

以下，悪性神経膠腫に対してエビデンスとなった過去の臨床試験が今日の標準治療を構築してきた過程を述べ，今後の臨床研究の進め方について概説する．

Ⅱ. 現在までの化学療法のエビデンス

悪性神経膠腫は，手術のみによっては治癒不可能な疾患である．腫瘍細胞はGadolinium-DTPAを用いたMRI T1強調画像で描出される部分のみでなく，さらに数cm離れた領域にまで認められ，少なくともT2強調画像での高輝度領域までを治療の対象としなければならないと考えられている．また，この疾患は腫瘍周辺に広範な脳浮腫を伴うため，T2高輝度領域をすべて手術により摘出することは不可能であり，腫瘍塊の一部あるいは浸潤部は残存することになる．

一方，最も悪性度の高い膠芽腫でさえも広汎に腫瘍を切除することによって予後が改善することが知られており，悪性神経膠腫の初期治療としては切除可能な範囲で開頭により最大限に切除することが望ましいと考えられている[13,17]．

しかしながら，実際には悪性神経膠腫を手術により全摘することは困難であり，画像上全摘されたと考えられる場合でも腫瘍細胞が残存していることは周知されているため，ほぼ全例に対して術後補助療法が行われることになる．

術後補助療法では米国を中心として放射線療法と化学療法を用いた集学的治療の開発が行われ，現時点において米国ではnitrosourea系のアルキル化剤であるBCNU (carmustine) と局所照射60Gyを用いた化学放射線療法が標準治療として行われている．

Andersonはglioblastoma 108例に対して術後の放射線の有無での比較試験を行い，手術単独では1年生存率が0％であったものが，45Gyの照射で19％に上昇したと報告した[1]．さらに，Walkerらは悪性神経膠腫467例に対する術後補助療法として「BCNU＋全脳照射60Gy」，「MeCCNU (semustine) ＋全脳照射60Gy」，「放射線治療（全脳照射60Gy）単独」，

「MeCCNU単独」の4群での比較試験を行い，化学療法単独に対してほかの放射線照射を含む3レジメンが生存にて有意に勝っていることを報告した[15]．そのほか，Changら，Greenらの報告でも「BCNU＋全脳照射60Gy」群が生存で最も勝っており，これらの結果からBCNU＋同時併用放射線照射が米国での標準治療レジメンとされるようになった[3, 6]．

放射線の総線量に関しては，Walkerらの比較試験で照射線量を45Gy，50Gy，55Gy，60Gyと増量するにつれて，生存期間中央値が13.5週，28週，36週，42週と延長し，前述のAndersonの45Gy照射群での28週と比較しても明らかに延長しているため，60Gyが術後放射線照射の標準線量と考えられている[1, 16]．

また，照射野についてはWalkerらをはじめとする米国での試験においては全脳照射が行われているが，現在は通常，局所照射が行われている．局所照射と全脳照射の比較試験は行われていないが，Hochbergらの報告によればglioblastomaでの再発は原発巣から2cm以内の局所再発が90％を占め，実際に悪性神経膠腫では局所再発がほとんどであることから，全脳照射を行う意味が少ないと考えられている[8]．

また，全脳照射を行うことによって記銘力障害や見当識障害など高次脳機能の低下が高頻度に出現し，さらに照射部位の放射線壊死の可能性が高くなることなどからも，局所照射による治療が広く行われている．

これに対しわが国では米国において標準的に用いられているBCNUが併用化学療法剤として認可されていないため，国内で開発されたACNU (nimustine hydrochloride) が用いられている．ACNUはBCNUと同じnitrosourea系薬剤で，化学式もBCNUとほぼ同様の構造であり，効果についてもほぼ同様であると考えられている．Glioma Meta-analysis Trialists (GMT) Groupによるmeta-analysisによる結果も悪性神経膠腫に対してnitrosourea系化学療法剤の併用が生存率の向上に寄与していることを示していることから，ACNUの選択は妥当であると考えられる[4]．

ACNUを用いた第III相臨床試験として，高倉らはanaplastic astrocytomaおよびglioblastomaに対し術後局所照射50～60Gyと，1～2回のACNU 100mg/m^{2}同時併用の有無の比較試験を行った[12]．その結果，奏効率（CT上の計測にて腫瘍が50％以上縮小した割合）が前者では13.5％であったのに対し後者は47.5％と有意に向上したが，生存に関しては各群40例程度の症例の集積ということもあり，ACNU併用群におけるanaplastic astrocytomaおよびglioblastomaの3年生存率は59.0％，16.3％と，放射線単独群の3年生存率48.9％，0％と比べ有意な差は得られなかった．

しかし，ACNU併用群が生存で上回っていること，同様の薬剤であるBCNUが米国での標準となっていることなどから，現在，わが国においては局所照射60Gy＋ACNU同時併用療法が悪性神経膠腫に対する標準治療と見なされるようになった．

このような結果を踏まえ，野村らは局所照射＋ACNU同時併用を行った後に2年間のACNUの維持化学療法の有無の比較試験を行った[9]．高倉らの試験において血液毒性が強く出現したため，この試験においてはACNUを80mg/m^{2}に減量して行われた．その結果，登録症例数は77例と少数での結果であるが，維持化学療法群にて再発までの期間が6.1ヵ月から9.2ヵ月へと延長し，統計学的に有意であったと報告された．

高倉らおよび野村らの報告はいずれも少数

例での比較試験の結果であり，比較試験として最も客観的事実として評価される生存率の差の有意な向上が認められないため，本来の意味では放射線単独に比べACNU併用群が勝っている，あるいは維持化学療法を行った群が勝っているとはいえないが，現時点では国内における悪性神経膠腫に対する標準治療は開頭手術後にACNUを併用した60Gyの放射線局所照射およびACNUによる維持化学療法であるとするのがevidence basedという点では妥当と考えられる．

Ⅲ．エビデンスレベル

どのような臨床試験により得られた結果であるのかによりエビデンスの信頼性は異なる．大規模な無作為化比較試験と単なる症例報告とはその信頼性，普遍性から判断してまったく質の異なったものである．

米国臨床腫瘍学会（American Society of Clinical Oncology：ASCO）ではエビデンスのレベルを5段階で提示している[7]．すなわち，最もエビデンスレベルの高いレベルⅠは良質比較試験のメタアナリシス（大規模無作為化比較試験），レベルⅡは複数個の良質研究（小規模無作為化比較試験），レベルⅢは準実験的研究（コホート，症例対照），レベルⅣは良いデザインの観察研究，レベルⅤは症例報告である．さらにそれを基にした推奨グレードとして，Grade A：レベルⅠまたは複数のレベルⅡ，Ⅲ，Ⅳの結果が一致，Grade B：レベルⅡ，Ⅲ，Ⅳの結果が一致，Grade C：レベルⅡ，Ⅲ，Ⅳの結果が不一致，Grade D：エビデンスなし，としている．

最もエビデンスレベルの高いものは大規模無作為化試験であり，通常，第Ⅲ相臨床試験として行われる．その際，対照となるのはその疾患に対する現時点での標準治療であり，新治療がこれと比較され，統計的解析が行われ，新しいエビデンスとなり得る．

Ⅳ．多施設共同試験

悪性神経膠腫のような希少疾患に対し単一施設で大規模無作為化試験を行うことは不可能である．

原発性脳腫瘍の発生頻度は10万人に対し年間11～12人程度とされており，単純計算によれば国内では年間13,000～14,000人の脳腫瘍が発生することになる[2]．これは脳外科専門医1人あたり1年間に2人程度ということになる．

また，脳腫瘍全国集計調査報告には国内300施設から年間約5,000人の脳腫瘍患者の登録があり，そのうち神経膠腫の占める割合は28％であるため，たかだか1,400人であり，平均すると1施設あたり4人，悪性神経膠腫に限れば2～3人程度となってしまう[13]．標準治療と比較して10％程度の優位性を証明するためには各群100例を超える登録が必要であることからも，同程度の治療設備が整った施設群での多施設共同試験が必須であることがわかる[14]（表1）．

Ⅴ．プロトコール作成

多施設共同試験では異なった施設で異なった担当医が統一された判断をもとに同様の治療を行わなければならない．そのためには，症例の選択，治療の割り付け，治療方法，評価方法などを網羅したプロトコールが必要である．悪性腫瘍に対する有効な治療法を開発し，これを適正な臨床試験により評価し，最善の治療法や標準的治療法を確立することを目的に，1990年に厚生省がん研究助成金指定研究「がんの集学的治療の研究」班（主任研究者：木外恵一）が結成され，それより発展設立された日本臨床腫瘍グループJapan Clinical Oncology Group

表1　臨床試験において統計学的に有意な結果を得るために必要なサンプルサイズ[14]

〔One-sided test:対立仮説：(P2>P1)〕

小さい割合	大きい割合—小さい割合 (P2-P1)						
(P1)	0.10	0.20	0.30	0.40	0.50	0.60	0.70
0.10	155	47	30	19	13	11	8
	390	120	60	41	28	20	16
0.20	230	63	36	23	15	10	8
	590	160	76	44	30	22	16
0.30	280	73	37	23	15	10	—
	720	185	85	47	32	20	—
0.40	310	76	37	23	13	—	—
	780	195	84	44	28	—	—
0.50	310	73	36	19	—	—	—
	780	185	76	39	—	—	—

上段の数字は $\alpha=0.05$, $\beta=0.20$ (検出力 Power＝0.80)
下段の数字は $\alpha=0.01$, $\beta=0.05$ (検出力 Power＝0.95)

(JCOG) ではプロトコールの標準化を図るため以下のような章構成を提案している[5, 11].

0) 概要
1) 目的 Objectives
2) 背景 Background
3) 診断基準 Staging criteria
4) 症例選択基準 Patient selection criteria
5) 登録・割付 Registration／randomization
6) 治療計画 Treatment plan
7) 予想される有害反応と変更基準
Expected adverse reaction and treatment modification
8) 評価項目・臨床検査・評価スケジュール
Required clinical evaluation, laboratory tests and schedule
9) データ収集 Data collection
10) 有害事象の報告 Adverse event reporting
11) 効果判定とエンドポイントの定義
Response evaluation criteria and endpoint definition
12) 倫理的事項 Ethical consideration
13) 統計的事項 Statistical consideration
14) モニターリングと監査
Monitoring and quality assurance audit
15) 特記事項
Discipline review and special instruction
16) 研究組織 Administration responsibilities
17) 研究結果の発表 Publication policy
18) 参考文献 References
19) 付表 Appendix

Ⅵ. データ管理および解析

作成されたプロトコールを用いて，被験者の不利益にならず，エビデンスとなり得る客観的なデータを集積するためには，その運用がきわめて重要である．常に蓄積されたデータを監視し，プロトコールからの逸脱がないようにしなければならない．そして何よりも有害事象をいち早く察知し，被験者の安全性が守られなければならない．また蓄積された

データを必要に応じて中間解析を行い，その結果によってはその臨床試験の中断あるいは中止も考慮する必要がある．

これらの判断の裏づけとして客観的な統計解析は必須であり，専門の生物統計家の介入が望ましい．治療担当医の判断は主観が入りがちとなるため，このようなデータ管理は第三者機関が行う必要がある．

欧米では多施設共同試験グループとしてEuropean Organization for Research and Treatment of Cancer (EORTC)，Radiation Therapy Oncology Group (RTOG)，Southwest Oncology Group (SWOG) などがあるが，国内では前述のJCOGがこれに相当する．平成14年には脳腫瘍研究グループがJCOG内に設立され，現在13の臓器グループが互いに監視しながら臨床試験を実施している．

その運営委員会のもとには臨床試験審査委員会，効果安全性評価委員会，監査委員会，放射線治療委員会，病理委員会などの各種委員会が設けられ，定期的な会合をもって，データセンターからの報告を受け，データの管理評価を行っていくとともにプロトコール自体の見直しを行っている．

Ⅶ. おわりに

悪性脳腫瘍の治療領域でのエビデンスは，きわめて少ないといえる．特に国内では標準治療といえる治療法も確立しておらず，各施設でまちまちな治療が行われているのが現状である．

従来，脳腫瘍治療領域においてはJCOGなどを利用した臨床試験が行われていなかったが，平成14年度に厚生労働科学研究費の助成を受けJCOG脳腫瘍研究グループが編成され，国内でも本格的な多施設共同試験が開始された悪性神経膠腫に対しては「悪性脳腫瘍の標準的治療法の確立に関する研究」という研究課題のもと，渋井らにより「星細胞腫Grade 3・4に対する放射線化学療法としてのACNU単独療法とProcarbazine＋ACNU併用療法とのランダム化第Ⅱ／Ⅲ相試験」の登録が開始された．

さらに，平成15年度からは「転移性脳腫瘍に対する標準的治療法の確立に関する研究」（嘉山班）が加わり，国内での脳腫瘍治療における本格的な多施設共同臨床試験の第一歩が踏み出されたことになる[10]．

悪性神経膠腫のような希少疾患では単一施設でエビデンスとなり得るデータを取得するのは不可能といえるため，同じ目的意識をもつ多数の施設での共同試験をしっかりとしたデータ管理機構のなかで行っていくことが必要である．JCOGでの試みを足がかりとして，今後，全国レベルでの臨床試験が行われていくことが望まれる．

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MRI and CT findings of neurohypophyseal germinoma

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Abstract

Objective: Magnetic resonance (MR) imaging and computed tomography (CT) findings of neurohypophyseal germinoma have not previously been described in detail. The purpose of the present study was to establish the spectrum of MR imaging and CT findings in neurohypophyseal germinomas. *Materials and methods:* MR and CT images of 13 consecutive patients (seven males, six females; mean age: 15 years; range: 6–31 years) with neurohypophyseal germinoma were retrospectively analyzed. The diagnosis had been made either histologically ($n = 8$) or clinically according to established criteria ($n = 5$). All patients had been examined using MR imaging and CT before treatment. *Results:* On MR imaging, infundibular thickening (up to 16 mm) was observed in all 13 cases. Hyperintensity of the posterior pituitary on T1-weighted image was absent in all 13 cases (100%) and 12 of the 13 displayed central diabetes insipidus. Ten germinomas (77%) were isointense to cerebral cortex on T1-weighted image, but variable intensities were exhibited on T2-weighted image. MR images revealed intratumoral cysts in six cases (46%), most of which demonstrated intra-third ventricular extension. Eleven of the 13 cases (85%) revealed hyperdense solid components on unenhanced CT. Calcification was absent in all cases (100%). *Conclusion:* Infundibular thickening, absence of the posterior pituitary high signal on T1-weighted image, lack of calcification and hyperdensity on unenhanced CT are common imaging features of neurohypophyseal germinoma.

Keywords: Germ cell neoplasm; Magnetic resonance imaging; Computed tomography; Neurohypophysis

1. Introduction

Germ cell tumors are relatively rare in Western countries, and constitute only 0.3–0.5% of all primary intracranial tumors [1–3]. However, these tumors are far more common in Northeast Asia, accounting for ≈3.0% of all primary intracranial tumors [4]. Approximately 90% of germ cell tumors occur in patients under 20-years-old. The pineal gland is the most common site of origin (≈50%), followed by the suprasellar region (20–30%). Other sites include the basal ganglia, thalamus, brainstem and spinal cord [1–3,5–7]. Germ cell tumors can be divided into germinomatous and non-germinomatous germ cell tumors. The former type is further classified into pure germinoma and germinoma with syncytiotrophoblastic giant cells (STGC), while the latter comprises teratoma, embryonal carcinoma, yolk sac tumor and choriocarcinoma [8].

According to pathological examination of autopsy cases, germinomas of the suprasellar region (suprasellar germinomas) involve the hypothalamo–neurohypophyseal axis (hypothalamus, infundibulum and posterior lobe of the pituitary gland), which is related to the development of diabetes insipidus [2,9]. MR findings also suggest that suprasellar germinomas primarily arise from the posterior pituitary to the infundibulum [10,11]. On the basis of these pathological and imaging findings, suprasellar germinoma is also called neurohypophyseal germinoma [10,12].

Although germinomas are fatal if untreated, they differ from other suprasellar neoplasms in that the tumors are highly susceptible to irradiation and chemotherapy and

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are potentially curable. If the possibility of germinoma can be determined prior to surgical intervention, biopsy and histopathological diagnosis would allow the avoidance of dissemination or hematogenous metastasis of tumor due to aggressive surgery [13]. Knowledge of the full spectrum of MR imaging and computed tomography (CT) findings of neurohypophyseal germinoma is therefore vital.

To the best of our knowledge, detailed evaluation of both MR imaging and CT findings of neurohypophyseal germinoma has yet to be reported. The purpose of the present study was to establish the spectrum of MR imaging and CT findings of neurohypophyseal germinoma correlating with clinical information, particularly central diabetes insipidus.

2. Materials and methods

Thirteen consecutive patients with neurohypophyseal germinoma hospitalized in the neurosurgical department of our institution from January 1987 to December 2002 were retrospectively enrolled in this study. Patients included seven males and six females with a mean age of 15 (range: 6–31 years). Diagnosis of neurohypophyseal germinoma was made histologically in eight cases. In the remaining five cases, diagnosis was made on the basis of clinical features including age, serum and/or cerebrospinal fluid (CSF) tumor markers and rapid tumor response to irradiation or chemotherapy, according to established criteria [14].

Cases diagnosed histologically as non-germinomatous germ cell tumor, cases positive for α-fetoprotein (AFP) and cases with markedly elevated serum and/or CSF concentrations of human chorionic gonadotropin (HCG) (>2000 mIU/ml) were excluded from the study. Elevated AFP is generally restricted to yolk sac tumors and some special types of teratoma [15]. Marked increases in serum or CSF HCG above 2000 mIU/ml are characteristic of choriocarcinoma, while moderate increases in serum or CSF HCG can be associated with germinoma containing HCG-producing STGCs (germinoma with STGC) with no definite evidence of choriocarcinoma [7]. The majority of germinomas with STGC can be clinically diagnosed when serum HCG concentration is elevated but below 2000 mIU/ml [16]. Seven of the 13 cases in the present study met this criterion, displaying moderately elevated concentrations of HCG suggestive of germinoma with STGC.

All patients had been examined using CT and MR imaging before treatment. Axial or coronal unenhanced CT scans were obtained with slice thicknesses of 5–10 mm. MR imaging studies were performed using a 1.5-T superconducting magnet. Both sagittal and coronal T1-weighted images (spin-echo; repetition time/echo time/excitations: 400-630/8-35/1-2) and axial and coronal T2-weighted images (spin-echo or fast spin-echo; 2000-7800/80-126/1-2) were obtained. Additional MR imaging parameters included 3–5 mm slice thickness, 20–24 cm field of view and a 192–256 × 256 matrix. Sagittal, in addition to axial or coronal contrast-enhanced T1-weighted images, were obtained in 11 patients (85%) after intravenous injection of either gadodiamide (Gd-DTPA-BMA) or gadopentetate dimeglumine (Gd-DTPA) at a dose of 0.1 mmol/kg bodyweight.

The results of MR imaging and CT were reviewed in a non-blinded manner by three experienced neuroradiologists. Tumor location, CT density, MR signal intensity and enhancement patterns were evaluated, as was the presence of calcification, infundibular thickening, posterior lobe hyperintensity and cystic components.

Tumor location was evaluated regarding the following four regions: (1) intrasellar; (2) infundibulum; (3) third ventricle; and (4) basal ganglia or lateral ventricles. Intrasellar involvement was determined by anterior displacement of the anterior pituitary or enlargement of the sella turcica. Infundibular involvement was defined when the maximum diameter of the infundibulum was equal to or >4 mm [17]. Intra-third ventricular extension was defined as protrusion of the tumor into the third ventricle.

According to medical charts, central diabetes insipidus was present in 12 of the 13 patients (92%). These 12 patients required desmopressin acetate (DDAVP) to control urinary volume. In the remaining case, clinical evaluation for diabetes insipidus was not possible due to the presence of bladder disturbance.

3. Results

MR imaging and CT findings are summarized in Table 1.

3.1. MRI findings

Infundibular thickening (up to 16 mm) was observed in all cases (Fig. 1c, Fig. 3b, Fig. 4b). Six of the 13 cases (46%) also displayed an intrasellar component (Fig. 1c). Intra-third ventricular extension was identified in five cases (38%) (Fig. 2b). Three tumors (23%) had infiltrated the basal ganglia, one of which had invaded the wall of the lateral ventricle (Fig. 4a). Four of the six cases displaying an intrasellar component revealed anterior pituitaries that were compressed anterior to the tumor (Fig. 1c). Three cases displayed enlargement of the sella turcica.

Hyperintensity of the posterior pituitary on T1-weighted images was absent in all cases (100%) (Fig. 1a, Fig. 3a).

On T1-weighted images, signal intensity of the solid portion was slightly hyperintense to cerebral cortex in two cases (15%), isointense in ten (77%) (Fig. 1a) and hypointense in one (8%). Five cases showed inhomogeneous signal intensity on the T2-weighted images. On T2-weighted images, signal intensity of the dominant solid portion was hyperintense to cerebral cortex in three cases (23%), isointense in eight (62%) (Fig. 1b) and hypointense in two (15%).

Contrast-enhanced T1-weighted imaging was performed for 11 patients. All tumors displayed significant contrast

Table 1
Clinical and radiological features of the 13 cases of neurohypophyseal germinoma

Case No.	Age	Sex	Diagnosis	Tumor marker (HCG)	Diabetes insipidus	CT density	Calcification	Location of the tumor	Infundibular thickening (Maximum diameter)	HIS at posterior pituitary	T1WI	T2WI	Contrast enhancement	Cyst formation	Remote lesion
1	31	M	HP	N/A	N/A	Hyperdense	–	IS-IT	+ (7 mm)	–	Slightly hyper	Hetero/hyper	N/A	–	Pineal, spinal cord
2	25	F	CD	+	+	N/E	–	IT-TV-B	+ (5 mm)	–	Iso	Hetero/iso	N/A	+	–
3	8	F	HP	+	+	Hyperdense	–	IS-IT-TV	+ (16 mm)	–	Iso	Hetero/iso	+ (hetero)	+	–
4	19	M	CD	+	+	Hyperdense	–	IT-B	+ (5 mm)	–	Iso	Homo/iso	+ (homo)	–	–
5	6	M	HP	+	+	N/E	–	IT	+ (5 mm)	–	Iso	Homo/hypo	+ (homo)	–	–
6	15	M	HP	–	+	Hyperdense	–	IT	+ (4 mm)	–	Iso	Homo/iso	+ (homo)	–	–
7	16	F	HP	+	+	Hyperdense	–	IT-TV-BV	+ (10 mm)	–	Hypo	Hetero/hyper	+ (hetero)	+	Pineal, lateral ventricle
8	11	F	HP	–	+	Hyperdense	–	IS-IT	+ (7 mm)	–	Iso	Homo/iso	+ (hetero)	–	–
9	15	M	CD	–	+	Hyperdense	–	IT	+ (6 mm)	–	Iso	Homo/hyper	+ (homo)	–	–
10	7	F	HP	–	+	Hyperdense	–	IS-IT	+ (4 mm)	–	Iso	Homo/iso	+ (homo)	–	–
11	9	F	CD	+	+	Hyperdense	–	IS-IT-TV	+ (7 mm)	–	Iso	Hetero/iso	+ (hetero)	+	Pineal
12	26	M	HP	–	+	Hyperdense	–	IS-IT-TV	+ (10 mm)	–	Iso	Homo/iso	+ (hetero)	+	–
13	17	M	CD	+	+	Hyperdense	–	IT	+ (6 mm)	–	Slightly hyper	Homo/hypo	+ (homo)	+	Pineal, lateral ventricle

HP, histologically proven; CD, clinically diagnosed by the established criteria [14]; HCG, human chorionic gonadotropin; N/A, not available; N/E, could not be evaluated; HIS, high intensity signal; IS, intrasellar; IT, infundibular thickening; TV, intra-third ventricular extension; B, BV, infiltration to the basal ganglia (B) and/or the wall of the lateral ventricle (V); T1WI, T1-weighted image; T2WI, T2-weighted image: The signal intensities on both sequences were compared with cerebral cortex. Homo, homogeneous; hetero, heterogeneous; hypo, hypointense; iso, isointense; hyper, hyperintense.

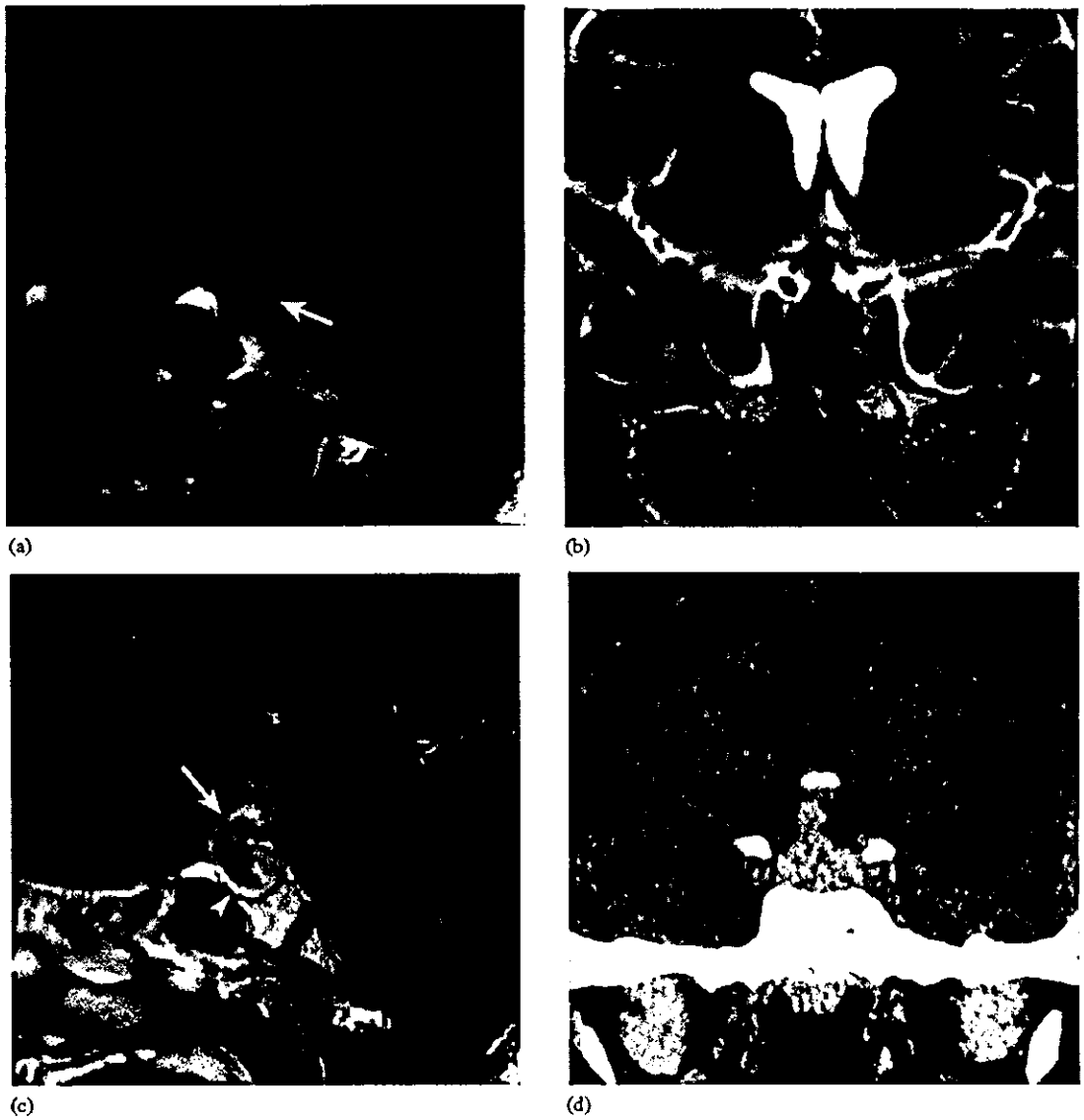


Fig. 1. Case 8. Neurohypophyseal germinoma in an 11-year-old girl. Intra- and suprasellar tumor components are homogeneous and isointense to cerebral cortex on both T1-weighted (SE 400/15) (a) and T2-weighted (FSE 5000/130) MR images (b). Sagittal T1-weighted MR image (SE 400/15) (a) shows absence of normal signal hyperintensity in the posterior pituitary (arrow). Sagittal post-gadolinium T1-weighted MR image (SE 400/15) (c) shows heterogeneously enhancing tumor involving the intrasellar region and infundibulum. Thickened infundibulum is observed (arrow). The anterior pituitary is compressed anteroinferiorly (arrowhead) [10,18,25]. The tumor is less enhancing than the anterior pituitary. Unenhanced CT reveals a hyperdense tumor with no calcification (d).

enhancement: six (55%) revealed homogeneous enhancement (Fig. 3b) and five (45%) showed heterogeneous enhancement (Fig. 1c, Fig. 2b, Fig. 4a). Four of the five cases with heterogeneous enhancement demonstrated involvement of the third ventricular floor or infiltration to the basal ganglia, while only one of the six cases with homogeneous enhancement displayed intra-third ventricular extension or infiltration to the basal ganglia.

Intratumoral cysts were seen in six of the 13 cases (46%), and five of these displayed intra-third ventricular extension (Fig. 2a, Fig. 4a). None of the remaining seven tumors without intratumoral cysts demonstrated intra-third ventricular extension.

Multifocal lesions were observed in four of the 13 cases (31%) and pineal lesions were observed in all four cases. In addition to the pineal lesions, two cases demonstrated ventricular wall dissemination and one displayed a spinal cord lesion.

3.2. CT findings

In 11 of the 13 cases (85%), the solid portion of the tumor was hyperdense to cerebral cortex on unenhanced CT (Fig. 1d, Fig. 2c). In the remaining two cases (15%), CT density could not be evaluated due to the small size of the lesion. Calcification was absent in all cases (100%).

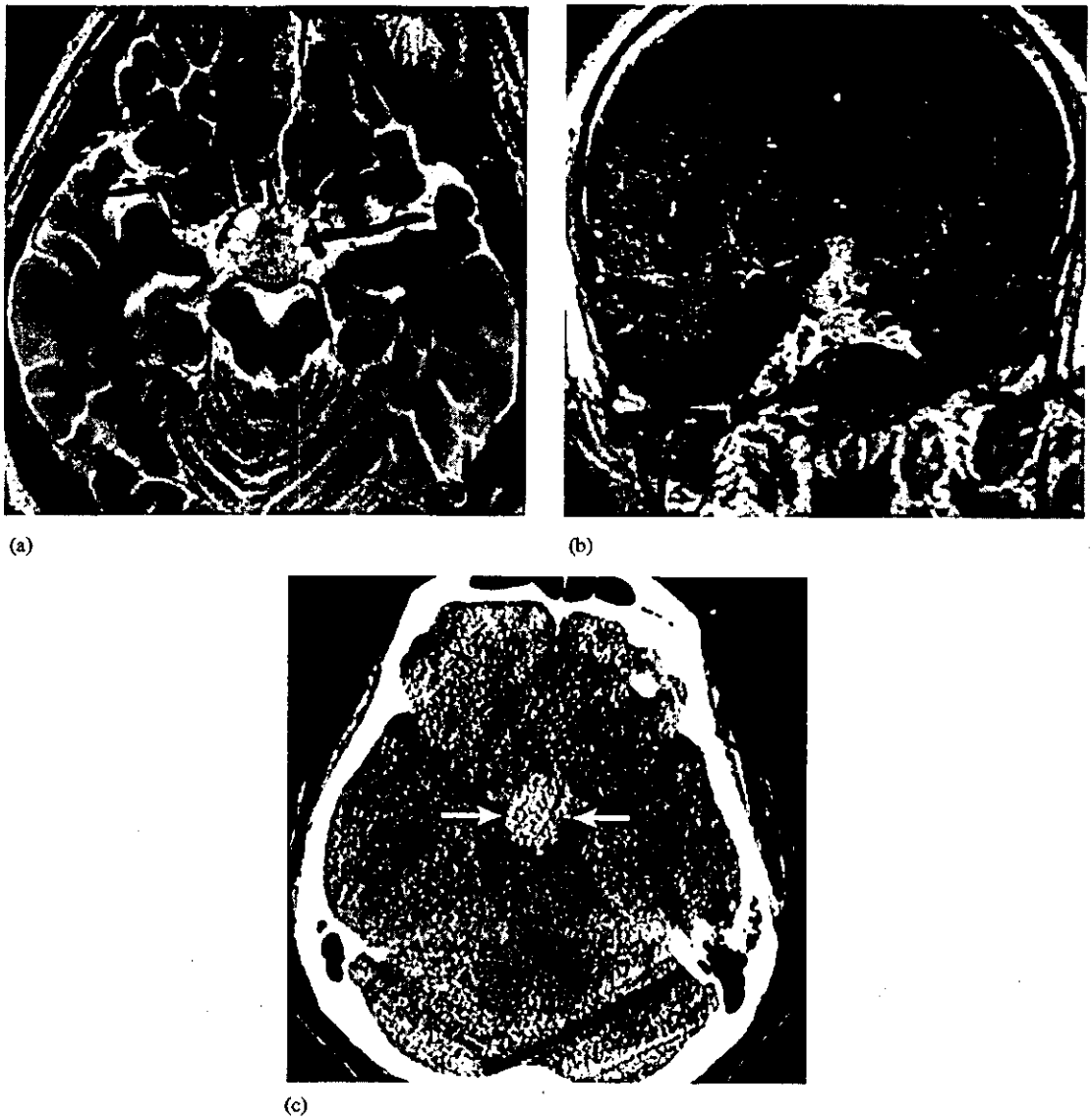


Fig. 2. Case 12. Neurohypophyseal germinoma in a 26-year-old man. Axial T2-weighted MR image (FSE 4100/80) displays multiple intratumoral cysts (arrowheads) (a). Coronal post-gadolinium T1-weighted MR image (SE 400/14) shows tumor protruding into the third ventricle (b). Tumor is hyperdense to cerebral cortex on unenhanced CT (arrows) (c).

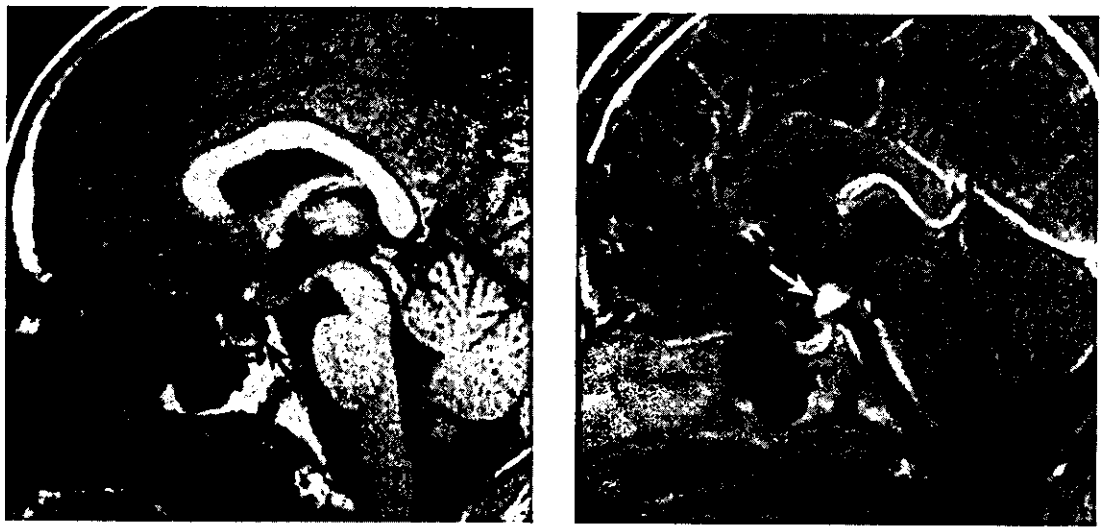
4. Discussion

To the best of our knowledge, few papers have evaluated infundibular thickening of neurohypophyseal germinoma [10,18]. All 13 cases in the present study displayed infundibular thickening. Fujisawa et al. [10] reported that six of their seven cases showed infundibular thickening and Liang et al. [18] described thickening of the infundibulum as the only abnormal imaging finding for small tumors. This high frequency of infundibular thickening is not unexpected given the predominant localization of neurohypophyseal germinoma in the hypothalamo–neurohypophyseal axis [10,11]. We consider infundibular thickening as a typical finding for neurohypophyseal germinoma.

The hyperintense signal of the posterior pituitary was absent in all 13 cases (100%) in our series, confirming the results of previous reports [10,19,20]. This absence of normal hyperintensity in the posterior pituitary is closely related to the loss of hypothalamo-hypophyseal function, particularly diabetes insipidus [21–23]. In the present series, 12 of the 13 patients (92%) showed evidence of diabetes insipidus.

MR signal intensity of the solid portion is non-specific on both T1- and T2-weighted images. Ten of the 13 germinomas (77%) were isointense to cerebral cortex on T1-weighted images, but intensities on T2-weighted images were variable. Typically, germinoma is iso- or slightly hypointense on T1-weighted images and iso- or hyperintense on T2-weighted images [18,24–26].

In our series, all 11 tumors examined under gadolinium administration revealed intense enhancement. Marked contrast enhancement is a common finding for neurohypophyseal germinoma [18,25]. Five of the 11 cases displayed



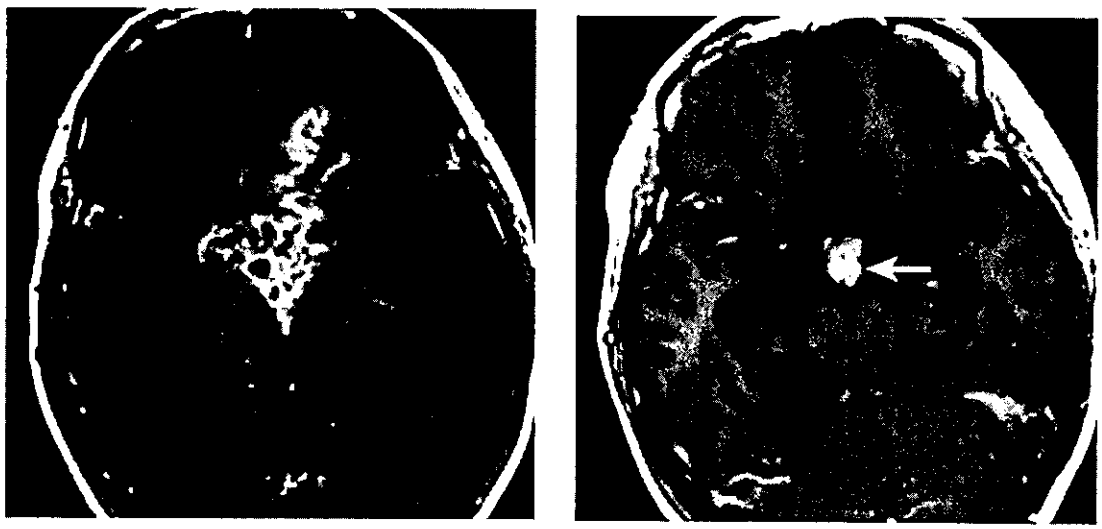
(a) (b)

Fig. 3. Case 9. Neurohypophyseal germinoma in a 15-year-old boy. Sagittal T1-weighted MR image (SE 400/20) (a) shows the absence of normal signal hyperintensity in the posterior pituitary (arrow). Sagittal post-gadolinium T1-weighted MR image (SE 400/20) (b) shows a small tumor involving the upper portion of the infundibulum (arrow).

heterogeneous enhancement. A recent study reported that heterogeneous enhancement is commonly seen in relatively large neurohypophyseal germinoma [18]. Large tumors tend to exhibit heterogeneous enhancement, probably due to inhomogeneous blood supply, microcyst formation or presence of necrosis [18].

To the best of our knowledge, frequency of intratumoral cysts in neurohypophyseal germinoma has not been evaluated. Intratumoral cysts were seen in six of our 13 cases (46%). Of these six cases, five displayed intra-third ventricular extension, while none of other seven cases without intratumoral cysts demonstrated either intra-third ventricular extension or infiltration to the basal ganglia. Germinomas arising from the basal ganglia or thalamus reportedly tend to contain multiple cysts of varying size [27–29]. Large tumor size and presence of brain parenchymal involvement could be related to intratumoral cyst formation also in neurohypophyseal germinoma.

Multifocal germ cell tumors usually involve the pineal and suprasellar compartments simultaneously or sequentially, and account for 6–13% of all intracranial germ cell tumors [1,3,30]. In our series, four of the 13 cases (31%) displayed a synchronous pineal lesion. If restricted to cases of neurohypophyseal germinoma, this rate is within the range



(a) (b)

Fig. 4. Case 7. Neurohypophyseal germinoma with STGC in a 16-year-old girl. Axial post-gadolinium T1-weighted MR image (SE 630/15) reveals a tumor with multiple intratumoral cysts extending into the third ventricle, basal ganglia and lateral ventricle (a). Another axial post-gadolinium image shows the thickened infundibulum (arrow) (b).

of those reported previously [18,25,31,32]. In general, synchronous mass lesions in these regions can be diagnosed as primary germ cell tumors. The origins of multifocal lesions as either metastatic spread from one location to another or as lesions of true multicentric origin remain controversial [30].

In our series, 11 of the 13 tumors (85%) were hyperdense to cerebral cortex on unenhanced CT. In the remaining two cases, CT density could not be evaluated due to the small size of the lesion. Hyperdensity on unenhanced CT is probably attributable to their hypercellularity [24,33,34]. No cases in the present study displayed calcification, again confirming the results of previous studies [24,34].

Infundibular thickening and absence of normal signal hyperintensity in the posterior pituitary on T1-weighted MR images and relative hyperdensity without calcification on unenhanced CT are characteristic but not specific for neurohypophyseal germinoma. Fifteen to 40% of patients with Langerhans cell histiocytosis (LCH) manifest with diabetes insipidus due to histiocytic infiltration of the neurohypophysis and may show pituitary stalk thickening in the absence of the posterior pituitary bright signal [35,36]. Diabetes insipidus may present as first manifestation in patients with LCH, but the majority of these patients develop diseases outside of the hypothalamo–neurohypophyseal axis during the follow-up course [37]. Lymphocytic infundibuloneurohypophysitis (LIN), an autoimmune-mediated inflammatory disorder which causes central diabetes insipidus, may also shows thickening of the pituitary stalk and absence of normal hyperintense signal of the posterior pituitary on T1-weighted images [38]. LIN can be differentiated from neurohypophyseal germinoma by the following: it usually occurs in adults; the natural course of this disorder is self-limited; and thickening of the pituitary stalk will disappear on follow-up course [23,38]. It might be difficult to differentiate lymphoma, leukemia and metastasis, which may localize in the neurohypophyseal region [39], from neurohypophyseal germinoma on the basis of radiological imaging alone. Many other clinical features of these diseases may aid in differentiating them from neurohypophyseal germinoma; lymphomas are predominantly seen in adults and their only involvement of the neurohypophysis is extremely rare [40], metastases are also common in adults and leukemias are usually seen with bone marrow lesions. Besides these, some other granulomatous diseases, such as tuberculosis, sarcoidosis, Wegener's granulomatosis and granulomatous hypophysitis may mimic neurohypophyseal germinomas [41–44]. Central nervous system (CNS) involvement of tuberculosis almost always occurs secondary to a non-CNS focus of infection and usually shows basal meningeal enhancement or enhancing nodules in the brain parenchyma [45]. Approximately 5% of patients with sarcoidosis may present with intracranial involvement and some may have infundibulo–neurohypophyseal axis involvement [46]. Most of patients with CNS sarcoidosis develop manifestations at non-CNS regions and demonstrate distinctive findings on chest X-ray, high titer of ACE, as well as the presence of uveitis [42].

5. Conclusion

Although MRI findings of neurohypophyseal germinomas except those involving the pineal gland are rather nonspecific, infundibular thickening and absence of normal signal hyperintensity in the posterior pituitary on T1-weighted MR images and relative hyperdensity without calcification on unenhanced CT represent common imaging features for neurohypophyseal germinomas.

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Randomized Controlled Trial on Malignant Brain Tumors

—Activities of the Japan Clinical Oncology Group-Brain Tumor Study Group—

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Abstract

The Japan Clinical Oncology Group (JCOG)-Brain Tumor Study Group was organized with the support of the Health and Labour Sciences Research Grants of the Ministry of Health, Labour and Welfare. The group is now preparing a multi-institutional randomized controlled phase II/III study of chemoradiotherapy using ACNU versus procarbazine and ACNU for astrocytoma grades 3 and 4. The overall survival and response rates will be compared between the patients treated with ACNU and those treated with ACNU plus procarbazine. This study, under the surveillance of the JCOG, aims to set a standard protocol for treating patients with malignant glioma. Moreover, the study will establish a proper methodology for performing randomized studies in the field of neuro-oncology.

Key words: Japan Clinical Oncology Group, randomized controlled trial, malignant glioma, ACNU, procarbazine, O^6-methylguanine deoxyribonucleic acid-methyltransferase

Introduction

The Japan Clinical Oncology Group (JCOG) is a multi-institutional cooperative oncology group conducting clinical research for cancer and related problems.[2] JCOG consists of 13 oncology groups as of 2003. The Brain Tumor Study Group (JCOG-BTSG) was organized in April 2002 with support from the Health and Labour Research Grants of the Ministry of Health, Labour and Welfare in order to establish a standard therapy for malignant brain tumors.

This study describes a randomized controlled phase II/III study of chemoradiotherapy using ACNU versus procarbazine and ACNU for astrocytoma grades 3 and 4.

Materials and Methods

Patients with newly diagnosed supratentorial astrocytoma grade 3 or 4 will be enrolled and randomly divided into two groups. Patients in Group A will be treated with ACNU (80 mg/m^2 iv) during the postoperative radiotherapy (60 Gy local), whereas patients in Group B with procarbazine (80 mg/m^2 for 10 days per os) preceding and in addition to the administration of ACNU. Each regimen will be repeated every 8 weeks for 2 years if tolerated by the patients. The primary endpoint is the overall survival rate and the secondary endpoints are the response rate on magnetic resonance imaging and the frequency of adverse events. This study starts as a randomized phase II trial and proceeds to the phase III study if the efficacy of the Group B regimen in phase II warrants a study continuation.

The study protocol was developed under guidance of the JCOG and approved by the institutional review board of the institution to which each JCOG-BTSG member belongs. The study will be performed under surveillance by the JCOG.

Results

This study starts at the beginning of 2004. The expected number of patient enrollments is 310 in 5 years. The collected data will be monitored and statistical analyses carried out by the JCOG Data Center. The results will be evaluated by the Steering Committee.

Discussion

A standard therapy for malignant gliomas has not been established and various trials have been carried out. In most neurosurgical institutes in Japan, nimustine hydrochloride (ACNU) is administered in conjunction with conventional radiotherapy after surgical removal of the tumor. However, this common treatment regimen has never been scientifically justified by a randomized controlled study, and so should be considered "community standard."

The efficacy of ACNU in malignant glioma patients was evaluated in a group who received postoperative administration of ACNU in conjunction with radiation therapy and another group was received only radiation therapy.[4] This controlled study revealed an improved response rate for the patients treated with ACNU, however, no significant difference in overall survival was observed between the two groups.

ACNU is one of the most effective chemotherapeutic agents to date for malignant gliomas. ACNU passes through the intact blood-brain barrier and alkylates deoxyribonucleic acid (DNA) causing the anti-tumor effect. Most malignant gliomas nevertheless recur after ACNU chemotherapy and radiotherapy. Malignant gliomas frequently express high activities of O^6-methylguanine DNA-methyltransferase (MGMT), a DNA repair enzyme, which is considered to be one of the causes of the chemoresistance to ACNU. Procarbazine is another alkylating agent that yields O^6-alkylguanine.[3] If procarbazine is administered prior to ACNU as in our current

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protocol, we expect the abundant O^6-alkylguanine to deprive MGMT, leading to increased efficacy of ANCU.[5] A similar treatment protocol was applied using BCNU, procarbazine, and vincristine to 58 patients with recurrent glioblastoma and reported a high response rate of 29% (complete response 10.3%, partial response 19%).[1]

In order to establish a standard therapy for a certain clinical entity, strict randomized controlled studies are essential. Few such studies in the neuro-oncological field have been carried out in Japan. Brain tumor is one of the so-called orphan diseases. Hence, multi-institutional cooperation is essential to accomplish randomized trials that require a large number of patient enrollment. JCOG is a group of oncologists that conduct cooperative studies on various cancers in Japan. The BTSG was newly organized in JCOG and is now preparing this randomized trial in an unprecedented organized manner. Upon completion, this study should provide a scientific basis for the standard therapy for malignant gliomas. Moreover, we hope to establish a proper methodology for performing randomized studies in the field of neuro-oncology.

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