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脳腫瘍の診断と治療

—最新の研究動向—

III. 脳腫瘍の病理　分類/小児脳腫瘍

小児神経膠腫

西川　亮

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小児神経膠腫

Pediatric gliomas

西川　亮

Key words　脳幹部神経膠腫，膠芽腫，pilocytic astrocytoma，congenital brain tumors

はじめに

小児神経膠腫という疾患単位は存在しないが，小児期にみられる神経膠腫には成人とは異なった疾患分布や病態が認められる．本稿では．小児神経膠腫の中でも特徴的な疾患群である毛様細胞性星状細胞腫，脳幹部神経膠腫，および乳児あるいは新生児の神経膠腫を取り上げて概説する．

1. 毛様細胞性星状細胞腫(pilocytic astrocytoma)

a. 概　念

細長い毛様の突起をもつ双極性紡錘形の細胞から構成される星状細胞腫の亜型である．微小嚢胞変性(microcystic degeneration)に富み細胞密度が低い水腫様部分と，双極性の細胞が束状に増殖する充実性部分とが，様々な割合で混在することを組織像の特徴とし，小児に好発すること，小脳，脳幹，視神経・視交叉・視床下部に好発すること，一般に良性の経過をたどることを臨床像の特徴とする．

b. 分　類

星状細胞腫の亜型に分類され，WHO grade 1である[1]．

c. 病　因

神経線維腫症1型(neurofibromatosis type 1: NF1)に合併する視神経毛様細胞性星状細胞腫がよく知られている．欧米ではNF1の約15％にみられるといわれ，しばしば両側性である[2]．しかし，孤発例の毛様細胞性星状細胞腫の成因としてはNF1遺伝子の関与は否定的である[2]．また星状細胞腫においてはTP53遺伝子の異常が高い頻度で認められることが知られているが，本腫瘍では結論は出ていない[2]．

d. 症　候

本腫瘍は脳腫瘍の6％を占め，そのうち80％は小脳に発生し，これは小脳神経膠腫全体の約2/3にあたる．小児神経膠腫の30％が毛様細胞性星状細胞腫である[3]．発生年齢のピークは10歳前後である．通常の星状細胞腫に比べて好発部位はやや正中線上あるいはその近くの構造に偏っていて，大脳半球には少ない．すなわち，小脳，脳幹，視神経・視交叉・視床下部，視床を好発部位とする．

e. 診　断

1) 画像診断

一般に腫瘍の境界は明瞭で，しばしば嚢胞を形成する．実質部分はCTでもMRIでも造影剤によって増強されることが多い．視神経・視交叉・視床下部に発生した場合は，腫瘍占拠部位の腫大所見を認める．

2) 組織診断

微小嚢胞変性に富み細胞密度が低い水腫様の

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表1 小児脳幹部神経膠腫の臨床的分類(文献[10]改変)

	diffuse intrinsic gliomas びまん性神経膠腫	focal glioma 限局性神経膠腫	
		posterior exophytic/cervicomedullary gliomas 後方突出型・頸髄延髄部神経膠腫	focal tectal gliomas 被蓋神経膠腫
頻 度	80%	10-15%	5%
部 位	橋	第四脳室底または頸髄延髄	中脳被蓋
MRI	びまん性の橋の腫大	限局性の後方へ突出する病変または限局性	限局性
組 織	星状細胞腫	毛様細胞性星状細胞腫	びまん性星細胞腫
治 療	放射線照射が主体	手術+放射線照射	シャント，経過観察
生存期間中央値	1年以下	5年以上	7年以上

部分と，双極性の細胞が束状に増殖する充実性部分とが，様々な割合で混在する二相性組織像(biphasic pattern)を示す若年型(juvenile type)と，後者の充実性部分のみからなる成人型(adult type)に分類される．充実性部分の腫瘍細胞突起内に強い好酸性を示す棍棒状あるいはソーセージ状の構造物(Rosenthal fiber)が認められることがある．このRosenthal fiberは本腫瘍においてよく知られている所見であり，しばしば認められるが，しかし本腫瘍に特異的な構造物というわけではないので注意が必要である[2,4]．むしろ，細胞室内に出現する微細な硝子滴の集合(eosinophilic granular body)が診断上重要な所見で，毛様細胞性星状細胞腫，神経節細胞腫瘍などのWHO grade 1の腫瘍と，pleomorphic xanthoastrocytomaに特徴的であるといわれている[2]．CTスキャンやMRIで増強効果を示すことからも想像されるように，本腫瘍は血管に富んだ腫瘍であり，ときには膠芽腫にみられるような血管内皮の増殖が認められることもある．またクロマチンに富んだ奇妙な形をした核をみることなどもあるが，これらの所見は分裂像の増加を伴っていなければ悪性所見とは考えない[1,2]．免疫染色ではGFAP陽性である．

f. 治療と予後

本腫瘍は視神経・視交叉に発生したもの以外は通常境界明瞭であり，それが解剖学的に可能でさえあれば全摘することができる．全摘された場合，予後良好であると考えられている．20年生存率がおよそ80%と報告されている[5]．また，臨床的に腫瘍の増殖が次第に停止し，ときには退縮の方向に向かうような症例も存在する[2]．bromodeoxyuridine labeling indexを検討した結果，本腫瘍の増殖は20歳までの間にしだいに遅くなっていって頭打ちとなるという報告がある[6]．しかし一方，再発し悪性転化する症例の存在も報告されている[5,7]．手術後残存腫瘍がある場合，放射線照射の有効性を認める報告も多いが，放射線照射の適応についてはいまだ完全には意見の一致を見ていない[7,8]．化学療法についても有効であるとの報告もあるが，今後の課題である[9]．

2. 脳幹部神経膠腫

a. 概念，分類

脳幹部神経膠腫は症候と画像から診断され，組織診断が行われないことが多い．臨床的には**表1**に示したような3つのカテゴリーに分類して理解するとわかりやすい[10]．

b. 病態，症候，診断

1) びまん性脳幹部神経膠腫

5-10歳に好発し，症状の進行は比較的急速である．小脳失調，long tract sign，脳神経麻痺を3主徴とする．橋に発生することが多いため，脳神経麻痺としては外転神経麻痺と顔面神経麻痺が高頻度である．MRIでは橋の腫大を示し，初期にはガドリニウムによる増強効果はみられないことも多く，みられたとしても不均一なことが多い．橋病変の場合，延髄との境界が鮮明に認められることが特徴とされ，これは脳幹を横断する橋小脳路が障壁となるためとされる(**図1**)[11]．一方，この障壁の少ない中脳や小脳

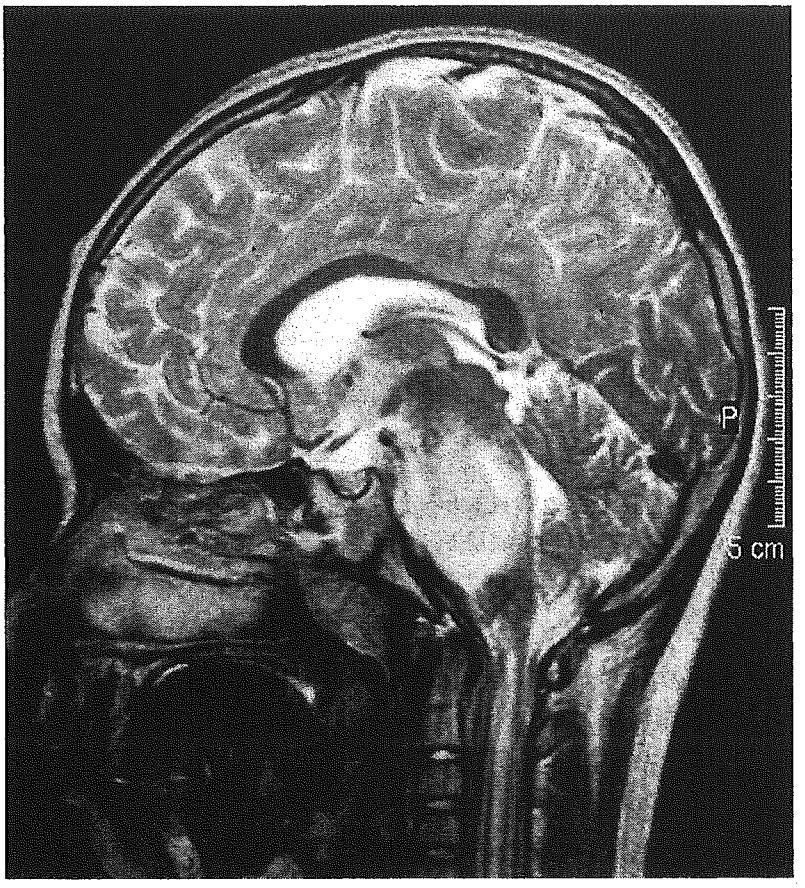


図1 びまん性脳幹部神経膠腫のMRI T2強調画像
延髄との境界がnatural barrierの存在により明瞭に描出されている.

脚方向には初期から浸潤性の伸展がみられることが多い.

2) 限局性脳幹部神経膠腫

脳幹部神経膠腫の中で,発症からの経過が長く,組織型が高分化で,手術が可能であり,比較的長期生存する症例群である.脳幹部神経膠腫の15%を占めるが,後方突出型の腫瘍と頸髄延髄部腫瘍が主体である[10].合併する水頭症からの頭痛や嘔吐を主症状とすることが多いが,腫瘍が延髄に存在すれば下位脳神経麻痺やlong tract signを示す.MRI所見はまさにその名のとおり限局性で,組織型も毛様細胞性星状細胞腫であることが多い[12].

3) 被蓋神経膠腫

中脳被蓋に限局した神経膠腫であるが極めて緩徐な経過をたどることが知られている.組織が取られている症例では大半がびまん性星細胞腫である.合併する水頭症による症状を呈するので脳室腹腔短絡手術や第三脳室開窓術が行われ,腫瘍に対しては増大傾向を示さないかぎり積極的な治療は不要なことが多い[10].

c. 治療と予後

1) びまん性脳幹部神経膠腫

放射線照射もいかなる化学療法も,一時的な症状の改善はみられても有意な生存期間の延長をもたらすまでには至っていない[13].hyperfractionated radiotherapyの効果も否定された[14].

2) 限局性脳幹部神経膠腫

手術による摘出が可能であれば,症状の改善をみることが多く,また組織型が毛様細胞性星状細胞腫であれば長期生存が期待され得る[10].

3. 乳児あるいは新生児の神経膠腫

一般に乳児の脳腫瘍は年長児に比べて,①テント上腫瘍の比率が高く(**図2**),②頻度の高い組織型は星状細胞腫ならびに髄芽腫であるが,

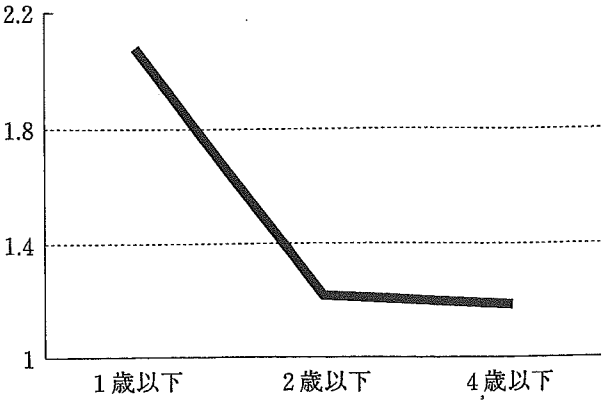
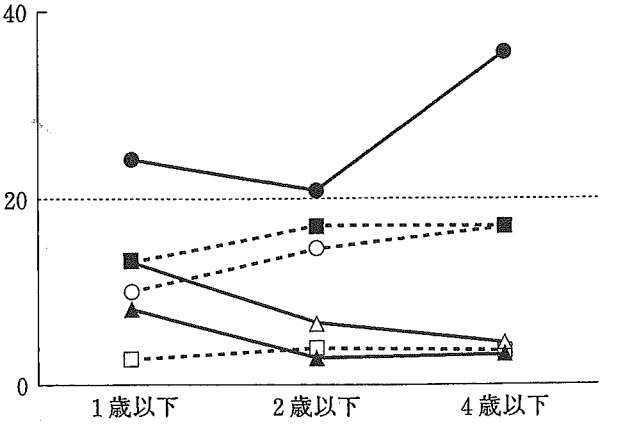


図2 乳幼児脳腫瘍のテント上/テント下局在の比率（文献[16]から作成）
文献から渉猟したデータであるために，2歳以下とは1-2歳の間ではなく，1歳以下も含んでの2歳以下である．4歳以下も同様．



	1歳以下	2歳以下	4歳以下
星状細胞腫	24.1	20.7	35.5
髄芽腫	13.3	16.9	16.9
上衣腫	9.8	14.5	16.7
脈絡叢乳頭腫	13.1	6.6	4.3
PNET	2.6	3.9	3.5
奇形腫	7.9	2.8	3.1

図3 乳幼児脳腫瘍の組織別頻度（文献[16]から作成）
文献から渉猟したデータであるために，2歳以下とは1-2歳の間ではなく，1歳以下も含んでの2歳以下である．4歳以下も同様．表の数値および縦軸は%．
PNET: primitive neuroectodermal tumor.

③脈絡叢乳頭腫と奇形腫の頻度が2歳以降に比べて高く（**図3**），④予後が悪いと報告されている[15,16]．若年者ほど奇形腫が多い傾向は特にいわゆるcongenital tumorで顕著であり，生後2カ月以内に発症した新生児脳腫瘍に限ってみれば，その37%は奇形腫である[17]．

新生児における神経膠腫の内訳は星細胞腫が29%，脈絡叢乳頭腫が23%，上衣腫が21%，膠芽腫が11%となっていて，成人症例に比べて脈絡叢乳頭腫と上衣腫が多く，膠芽腫が少ない[17]．新生児における膠芽腫の性質は基本的には成人の膠芽腫と同様であるが，①一部に境界の明瞭な腫瘍が存在することや，②予後良好な腫瘍が存在することが報告されている[18]．24例を渉猟した報告によれば，治療を行った（行い得た）症例5例の生存期間中央値は2年以上で，5年生存者が2人あったとのことである[18]．米国のthe Pediatric Oncology Groupは'Baby POG'と呼ばれる悪性脳腫瘍を対象とした化学療法先行の臨床試験の結果を報告している[15]．悪性神経膠腫としては，3歳未満の18例の膠芽腫または退形成性星細胞腫が登録された．cyclophosphamideとvincristineによる化学治療の結果，評価可能10症例のうち6例がPRで，更に3-4歳を越えてから照射も行って，5年生存率50%であったとのことである．以上のように，新生児あるいは乳児神経膠腫の中には，成人の腫瘍と違う形質を示し，治療感受性の高い症例が含まれている可能性が示されているが，更に検討が必要であろう．

文　献

1) Kleihues P, et al: Histological Typing of Tumours of the Central Nervous System, 2nd ed, p14-15, Springer-Verlag, Berlin Heidelberg, 1993.
2) Burger PC, et al: Pilocytic astrocytoma. In: Pathology and Genetics of Tumours of the Nervous System (ed by Kleihues P, Cavenee WK), p29-33, International Agency for Research on Cancer, Lyon, 1997.
3) Zuelch KJ: Brain Tumors—Their Biology and Pathology, 3rd ed, p221-232, Springer-Verlag, New York, 1986.

4) Russell DS, Rubinstein LJ: Pathology of Tumours of the Nervous System, 5th ed, p105-111, Edward Arnold, London, 1989.
5) McLendon RE, et al: Tumors of central neuroepithelial origin. In: Russell and Rubinstein's Pathology of Tumors of the Nervous System, 6th ed(ed by Bigner DD, et al), p342-352, Edward Arnold, London, 1998.
6) Ito S, et al: Proliferative characteristics of juvenile pilocytic astrocytomas determined by bromodeoxyuridine labeling. Neurosurgery **31**: 413-418, 1992.
7) 松谷雅生：脳腫瘍，第2版，p74-88，篠原出版，1996.
8) National Cancer Institute: Childhood cerebellar astrocytoma(PDQ®). Health Professional Version. http://www.cancer.gov/cancertopics/pdq/treatment/child-cerebellar-astrocytoma/healthprofessional/
9) National Cancer Institute: Childhood visual pathway and hypothalamic glioma(PDQ®): Treatment. Health Professional Version. http://www.cancer.gov/cancertopics/pdq/treatment/child-visual-pathway/healthprofessional/
10) Guillamo JS, et al: Brain stem gliomas. Curr Opin Neurol **14**: 711-715, 2001.
11) 松谷雅生：脳腫瘍，第2版，p90-98，篠原出版，1996.
12) Fisher PG, et al: A clinicopathologic reappraisal of brain stem tumor classification. Identification of pilocytic astrocytoma and fibrillary astrocytoma as distinct entities. Cancer **89**: 1569-1576, 2000.
13) National Cancer Institute: Childhood brain stem glioma(PDQ®): Treatment. Health Professional Version. http://www.cancer.gov/cancertopics/pdq/treatment/child-brain-stem-glioma/healthprofessional/
14) Mandell LR, et al: There is no role for hyperfractionated radiotherapy in the management of children with newly diagnosed diffuse intrinsic brainstem tumors: results of a Pediatric Oncology Group phase III trial comparing conventional vs. hyperfractionated radiotherapy. Int J Radiat Oncol Biol Phys **43**: 959-964, 1999.
15) Duffner PK, et al: The treatment of malignant brain tumors in infants and very young children: An update of the Pediatric Oncology Group experience. Neurooncol **1**: 152-161, 1999.
16) Rickert CH, et al: Primary intracranial neoplasms of infancy and early childhood. Childs Nerv Syst **13**: 507-513, 1997.
17) Wakai S, et al: Congenital brain tumors. Surg Neurol **21**: 597-609, 1984.
18) Winters JL, et al: Congenital glioblastoma multiforme: a report of three cases and a review of the literature. J Neurol Sci **188**: 13-19, 2001.

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外科治療　1
脳神経外科領域

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● はじめに

脳神経外科領域における代表的な悪性腫瘍としては，神経膠腫，中枢神経悪性リンパ腫，転移性脳腫瘍の3疾患をあげることができる。とくに神経膠腫と中枢神経悪性リンパ腫はきわめて浸潤性の高い腫瘍である。たとえば代表的な神経膠腫である膠芽腫の細胞は，神経線維の走行に沿って浸潤し，反対側の大脳に至ることもしばしば経験される（**図1**）[1]。中枢神経悪性リンパ腫も，その高い浸潤性のゆえにあたかも多発性病変のように見えることも珍しくない（**図2**）。したがってこれらの腫瘍においては，全摘出は通常不可能であり，手術は原則として断端陽性の絶対非治癒切除である。転移性脳腫瘍は周囲脳との境界が比較的鮮明であることが知られているが，やはり手術のみでは高率に局所再発が認められ，放射線照射を必要とする[2]。

したがって，悪性脳腫瘍においては手術に加えて放射線照射や化学療法をも駆使した，いわゆる集学的治療が不可欠である。治療成績を向上させるためには，手術，放射線照射，化学療法のそれぞれにおいて最大限の努力が必要である。手術においても可能な限りに摘出率を向上させて，治療成績を少しでも向上させるために，

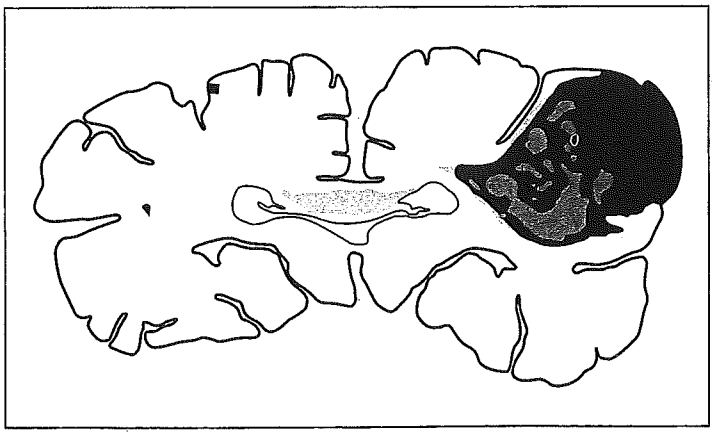

図1　剖検脳における未治療膠芽腫の進展範囲
図の濃く塗った部分は腫瘍中心部，その内部の色の薄い方は壊死の部分。腫瘍周囲および脳梁の淡く塗った部分は顕微鏡下に観察された腫瘍浸潤部である。膠芽腫においては，しばしばこのように脳梁線維を辿っての対側脳への浸潤が観察される（文献1改変）。

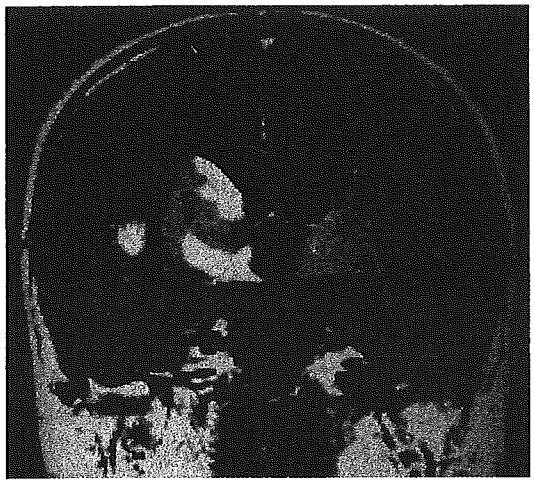

図2　中枢神経悪性リンパ腫症例のMRI（ガドリニウム造影T1強調画像冠状断）
右基底核にあたかも三つの腫瘍が発生したように見えるが，あくまで一つの腫瘍が浸潤性に発育した像と考えられる。

表 1　神経膠腫における手術摘出率と生存期間
（脳腫瘍全国集計調査報告[3]から改変。膠芽腫は p.56，星細胞腫は p.62 の表を改変した）

	手術摘出率*	症例数	1 年生存率	2 年生存率	3 年生存率	5 年生存率
膠芽腫	生検・部分摘出	794	41.8	15.7	9.7	5.6
	50%摘出	478	47.0	15.8	6.8	4.0
	75%摘出	1016	54.5	20.7	12.2	7.1
	95%摘出	732	65.9	29.4	20.2	10.2
	100%摘出	235	73.0	36.6	25.8	17.5
テント上星細胞腫	生検・部分摘出	923	82.7	68.6	62.8	55.5
	50%摘出	276	85.2	76.3	68.6	58.0
	75%摘出	505	86.5	75.8	66.9	56.9
	95%摘出	474	93.4	83.8	79.8	69.8
	100%摘出	269	96.9	91.1	87.5	84.2

*膠芽腫においては 75%摘出と 50%摘出以下，95%摘出と 75%摘出以下，100%摘出と 95%摘出以下の間で Mantel Chi-square test による有意の（$p<0.01$）生存期間の差を認めている。テント上星細胞腫においては 95%摘出と 75%摘出以下，100%摘出と 95%摘出以下の間で同様に有意の差を認めている。

図 3　基底核 germinoma 症例の tractography
右の基底核のやや白っぽく丸く見える部分に腫瘍が存在し，そのために錐体路が外側にシフトしているのがわかる。実際には 3 次元的に解析を行い，この症例では腫瘍の前方やや内側寄りから定位的生検を行った。

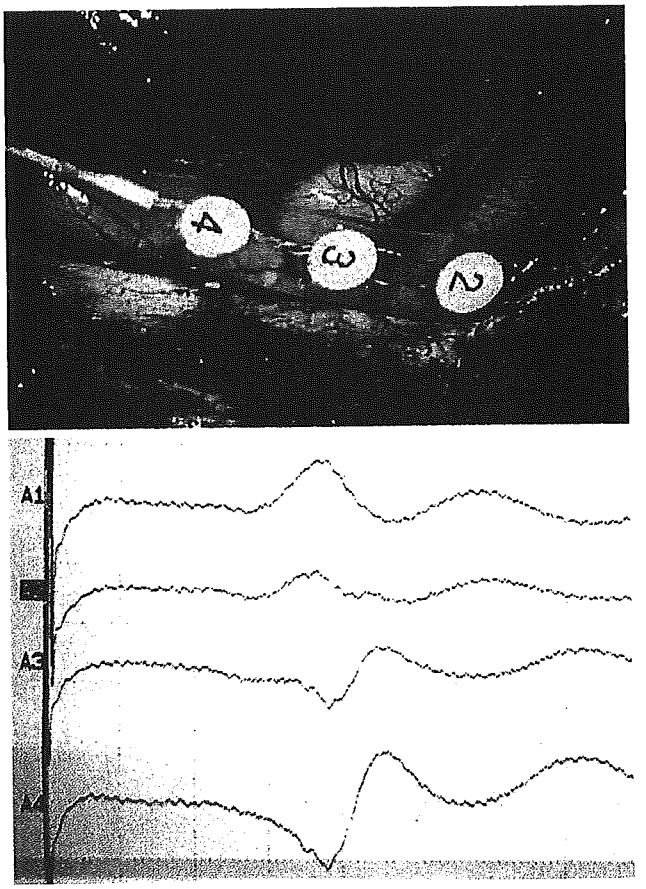

図 4　脳表に置いた電極による SEP の実際
中ほどの波が 1 と 2 では上向きであるのに対して 3 と 4 では下向きである。したがって電極 2 と 3 の間に中心溝が存在すると判断される。

さまざまな工夫が行われている。本稿では悪性脳腫瘍，とくに神経膠腫における手術療法の意義と最近の進歩について概説する。

● 神経膠腫における手術の意義

わが国の脳腫瘍全国集計調査の調査項目には，手術における摘出度が含まれている（**表 1**）[3]。代表的な神経膠腫である膠芽腫では，摘出率が 75%から 95%，95%から 100%と向上す

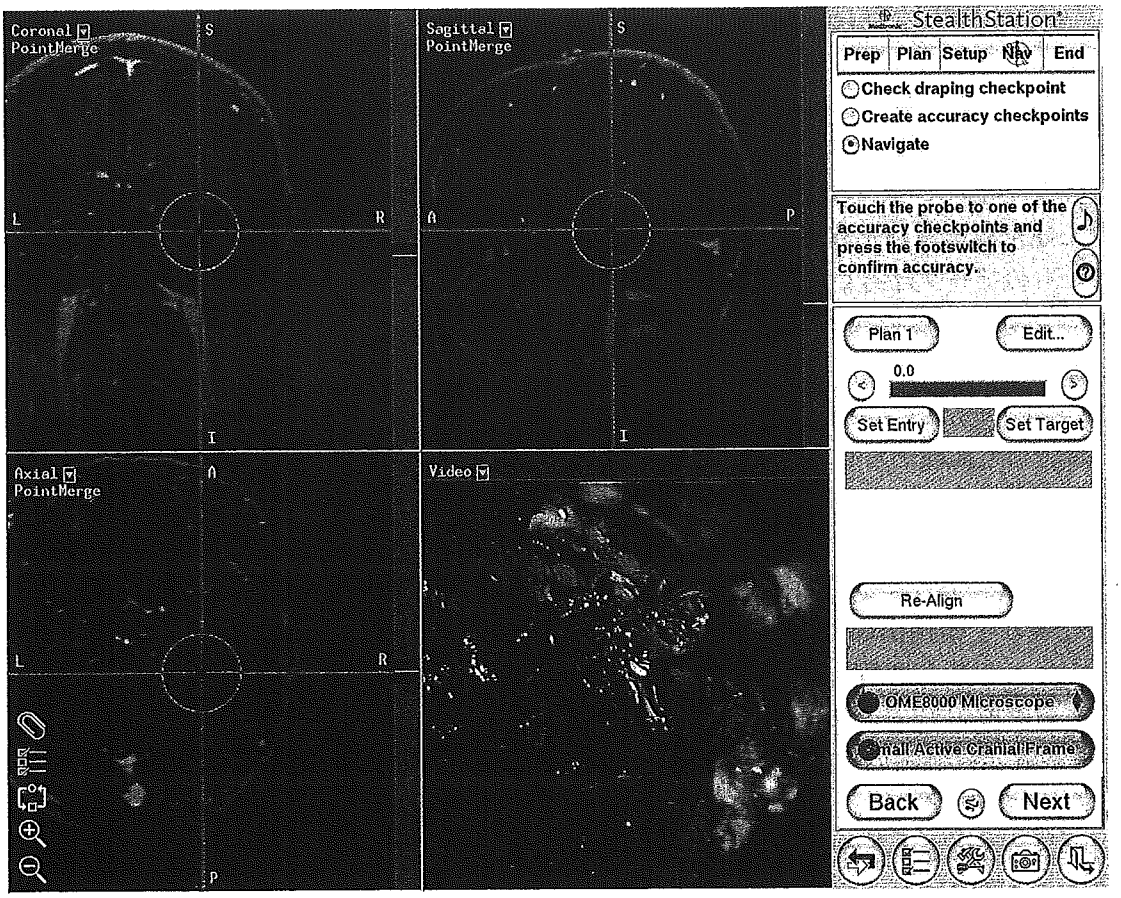

図 5　側頭葉内側の神経膠腫の術中ナビゲーションの様子

図の緑の十字の中心部が，現在操作している手術用顕微鏡の視野の中心を示している。右下の手術ビデオにおいてピンセットで示している腫瘍が，腫瘍の中心部よりやや後方に相当することが左下と右上の MRI からわかる。

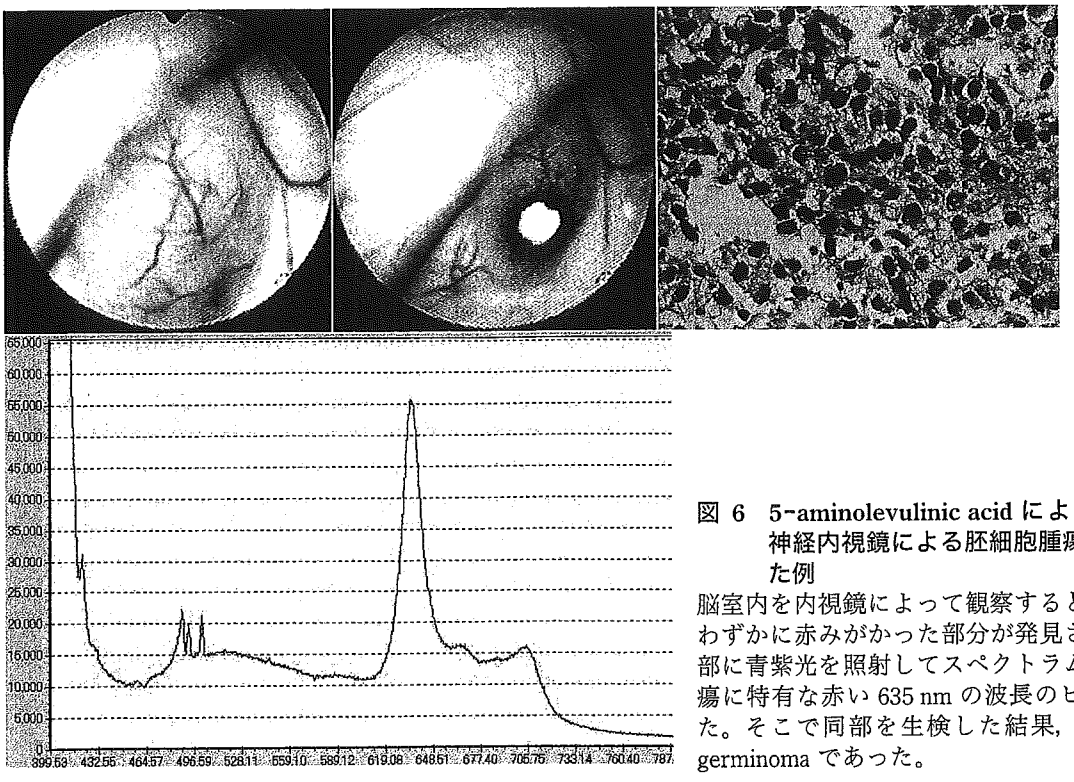

図 6　5-aminolevulinic acid による腫瘍の発光を神経内視鏡による胚細胞腫瘍の生検に応用した例

脳室内を内視鏡によって観察すると上段左のようにわずかに赤みがかった部分が発見された。そこで同部に青紫光を照射してスペクトラムを測定すると腫瘍に特有な赤い 635 nm の波長のピークが観察された。そこで同部を生検した結果，上段右のようにgerminoma であった。

るにつれて生存期間が延長することが示されている。また，やや悪性度の低いテント上星細胞腫においても，95%以上の摘出率を達成した症例は生存期間が延長している。最近のアメリカからの報告においても，膠芽腫では98%以上摘出し得た症例は有意に生存期間が長い[4]。もちろんこれらのデータはあくまで，広範に摘出できる安全な部位に腫瘍が存在した場合において，広範な摘出が可能であった結果をみているに過ぎない。したがって腫瘍が危険な場所にあった場合にも危険を冒してまで摘出率を上げることを正当化するものではない。

● 悪性脳腫瘍における手術の最近の試み

可能な限り手術摘出率を上げようという場合，現実にぶつかる問題症例は運動野や言語野などのいわゆるeloquent area近傍腫瘍である。eloquent area近傍腫瘍の手術に際しては，どこまでは安全に摘出できて，どこは手を付けてはいけないかを判断する必要がある。正常解剖の知識だけでは腫瘍によって偏位している実際の症例に対応できない。

近年の電気生理学や放射線診断学を含むさまざまな技術の進歩によってeloquent area近傍腫瘍の手術は目覚ましく進歩した。たとえば術前にfunctional MRIやMEGによって実際に運動野や言語野を同定し，腫瘍との位置関係を把握することが可能となった。これらは大脳皮質における機能局在を同定するものであるが，腫瘍摘出においては深部白質の情報も重要であり，これも近年開発された神経線維tractographyによって可能となった（**図3**）。手術中にはsomatosensory evoked potential（SEP）やmotor evoked potential（MEP）といった電気生理学的なモニターによって実際の運動野の位置を同定し（**図4**），手術操作によってMEPが変化するかどうかによって運動野や運動線維への侵襲の程度をリアルタイムに把握することが可能となった。言語野のモニターは覚醒下手術の導入によって可能となった。

以上は腫瘍を取り囲む脳の側からの情報であり，どこからは傷をつけてはいけないかという情報であるが，逆の側からの情報，どこまでが腫瘍かという情報も不可欠である。手術による摘出範囲を決めるために，従来は肉眼的に腫瘍を見極めて摘出していたが，これも近年はナビゲーションの導入によって，実際に操作している部位がMRI上のどこに当たるのか，腫瘍として描出されている範囲を操作しているのかどうかを術中に判断することが可能となった（**図5**）。また5-aminolevulinic acid（5ALA）を内服させ，術野に青紫光を当てると腫瘍が赤く発光することを利用して，赤く光っている腫瘍のみを摘出する試みもいくつかの施設で行われている（**図6**）。究極的には手術室にMRIが導入されている施設もあり，摘出範囲を正確に評価することができるようになりつつある。

これらの技術の進歩によって悪性脳腫瘍の生存期間はどの程度延びているのであろうか。これから次々と成果が発表されてくるものと期待されている。

文献

1) Berger PC, Heinz ER, Shimata T, Kleihues P. J Neurosurg 1988；68：698-704.
2) Patchell RA, Tibbs PA, Regine WF, Dempsey RJ, Mohiuddin M, Kryscio RJ, et al. JAMA 1998；280：1485-9.
3) The Committee of Brain Tumor Registry of Japan. Report of brain tumor registry of Japan (1969-1993), 10th edition. Neurologia Medico-chirurgica 2000；40 (Suppl).
4) Lacroix M, Abi-Said D, Fourney DR, Gokaslan ZL, Shi W, DeMonte F, et al. N Neurosurg 2001；95：190-8.

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REVIEW ARTICLE

Takamitsu Fujimaki

Surgical treatment of brain metastasis

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Abstract Treatment modalities for brain metastasis or metastatic brain tumor include surgery, conventional irradiation, stereotactic radiosurgery (SRS), chemotherapy, and supportive care with corticosteroid. In most cases, these treatments are used in combination. For a single metastasis, surgery followed by whole-brain radiation therapy (WBRT) has been the standard treatment. SRS has become increasingly popular and challenges the standard procedure, but there are still insufficient data for the outcomes of combinations including SRS. For the treatment of multiple metastases, WBRT is the standard procedure. For tumors larger than 3 cm, and in life-threatening situations such as a large metastasis to the cerebellum, surgery is the only feasible approach. Histological examination is sometimes useful for characterizing metastatic tumors from unknown primary sites. Thus, although brain metastasis invariably indicates a stage 4 cancer, some patients can benefit from surgery.

Key words Brain metastasis · Surgery · Radiation therapy · Chemotherapy · Stereotactic radiosurgery · Corticosteroid

Introduction

Decision-making for the surgical treatment of brain metastasis or metastatic brain tumor is a complicated issue, because the development of brain metastasis itself means that the patient has a stage 4 cancer. Surgery is generally not indicated for stage 4 cancers and can be undertaken only for palliative purposes in most patients. However, surgical treatment is often performed for brain metastasis, and is justifiable for many reasons. Strategic treatments can often relieve symptoms, improve the quality of life, and offer long-term survival in some patients (Fig. 1).

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Treatment of brain metastasis includes multiple, modalities, such as surgery, radiation, or chemotherapy, or a combination of them. Therefore, surgery for brain metastasis cannot be discussed without considering other forms of treatment. In this review, each of these treatment modalities is briefly summarized and then their use in combination is discussed.

Frequency of brain metastasis

At autopsy, one-fourth of cancer patients are found to have brain metastases.[1] Among the more than 500000 cancer patients dying in the United States every year, 130000 harbor brain metastases.[2] In Japan, approximately 850 patients with brain metastases were registered in the Japanese Brain Tumor Registry each year between 1991 and 1993, and this number accounted for one-fifth of all primary brain tumors.[3] Although this register is assumed to cover one-third of all brain tumors in Japan, the approximate number of 2500 patients (850 × 3) is clearly too low. The patients registered are mainly those treated in neurosurgical units, and thus the numbers registered do not include those who are not referred for neurosurgery. Many internists and general surgeons would consider that metastasis to the brain is a final stage of cancer, and this probably explains why many such patients are not referred to neurosurgeons.

Treatment modalities for brain metastasis

There are five modalities of treatment for brain metastasis: surgery, conventional irradiation, stereotactic radiosurgery (SRS), chemotherapy, and supportive care. Often these are used in combination. However, not all patients with brain metastasis are candidates for intensive treatment. For example, patients with multiple systemic metastases can be treated only by supportive care, such as administration of corticosteroid. However, patients with slowly progressive

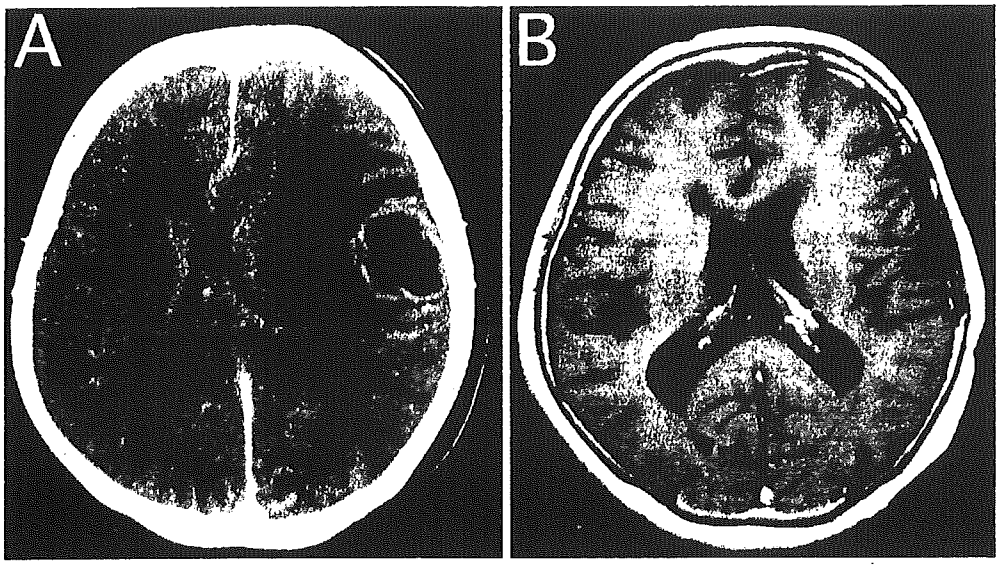

Fig. 1A, B. Magnetic resonance imaging (MRI) scans of a 56-year-old woman who was found to have a metastasis in the left frontal lobe. After resection of the metastasis, her lung cancer was also surgically resected. After whole-brain irradiation, MRI showed complete disappearance of the lesion. She had been doing well without evidence of disease for 5 years up to the time the author moved to another hospital

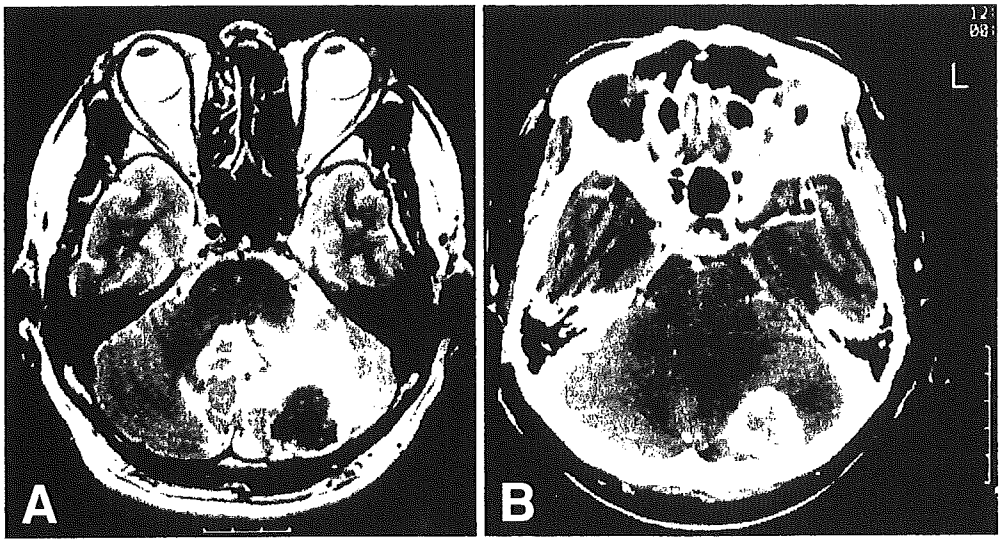

Fig. 2A,B. Imaging scans in a 53-year-old man who developed cerebellar metastasis 5 years after resection of colorectal cancer. A T2-weighted MRI scan (**A**) showed marked perifocal edema, although the tumor itself was only 2.2 cm in diameter. Nine days later, a computed tomography (CT) scan (**B**) revealed that the tumor had grown to 2.5 cm, and the patient developed markedly increased intracranial hypertension despite the administration of corticosteroid. The tumor was removed by emergency surgery, followed by whole-brain radiation therapy. The patient returned to his job for another 8 months until he was admitted for chemotherapy for lung metastasis

systemic disease or stable systemic metastases are the exception, and can be considered as candidates for intensive treatment. Thus, decision-making about suitable treatment modalities is often very difficult, because many factors need to be considered.

Surgery

Because most brain metastases occur at the border of the cortex and the white matter,[4,5] these tumors are located close to the surface of the brain, and thus a surgical approach is generally not difficult. Even multiple lesions can be handled in a single operation[6] if they are located in the same hemisphere and are close to each other. However, if there are multiple metastases, i.e., three to four or more not in the same hemisphere, they cannot be handled in one operation and may require another type of treatment, such as whole-brain irradiation. Deeply seated lesions or metastases located in functionally eloquent areas, such as motor or verbal areas, are also difficult to handle by surgery and require other modalities, such as SRS. On the other hand, a large metastasis to the cerebellum (Fig. 2), which is a life-threatening condition because of brainstem compression or acute hydrocephalus due to interference with the cerebrospinal fluid (CSF) pathway, can be treated only by surgery. Although brain metastases appear well demarcated macroscopically or by observation with an operative

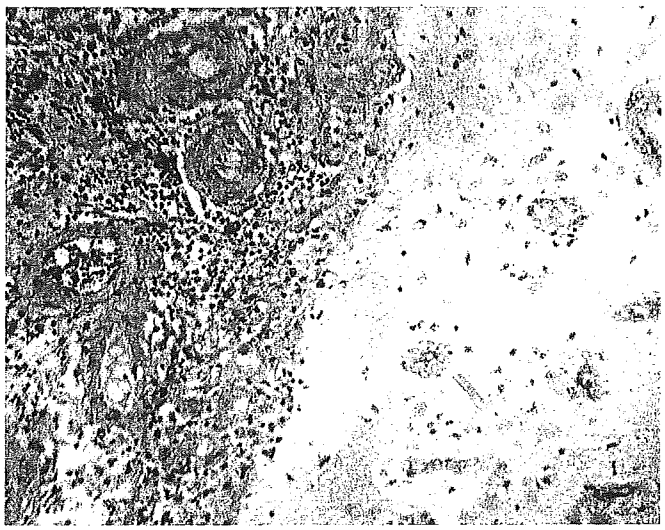

Fig. 3. Histological examination of the border between a metastasis and the brain. The tumor (*left side*) is relatively well circumscribed, but there are invasive tumor cells in the brain tissue (*right side*). HE, ×20

microscope, they are found to be invasive on histological examination (Fig. 3). Mostly, postoperative irradiation is performed to eradicate any theoretically residual invasive tumor cells, but the role of irradiation after surgery is still controversial. Advances in neurosurgery, including functional mapping with magnetic resonance imaging (MRI) or neuronavigation, have made the situation more complicated.[7] Recently it has become possible to resect deeply seated metastases or lesions in functionally important areas to some extent with the aid of these advanced techniques.

Conventional irradiation

Conventional irradiation, which in most situations is used as a palliative treatment, can prolong the survival of patients with brain metastasis. Ninety percent of lesions less than 2 cm in diameter can be controlled by conventional irradiation,[8] except for some cancers that are radioresistant. Thus, a standard treatment for brain metastasis has been whole-brain radiation therapy (WBRT) of 30 Gy in 3-Gy fractions or 40–45 Gy in 2- to 2.5-Gy fractions. WBRT may be effective against developing lesions that have not become evident on computed tomography (CT) or MRI, but it has not yet been determined whether WBRT can prevent such "future" metastasis. One of the disadvantages of WBRT is brain atrophy or impairment of cognitive function in some cases.[9,10] Therefore local irradiation is recommended by some authors, who have reported that it is rather advantageous in terms of recurrence rate or survival.[11] Recently, as SRS has become increasingly popular and can be used to treat even multiple lesions, the role of WBRT should be re-evaluated in the near future.

Stereotactic radiosurgery (SRS)

The Gamma knife (Elekta Instrument AB, Stockholm, Sweden), linear accelerator-based stereotactic radiosurgery (X-knife) and the Cyberknife (Accuray, Sunnyvale, CA, USA) have become widely used for SRS recently. SRS can provide good control of both surface-localized and deeply seated lesions without the need for performing open surgery. Multiple lesions, usually up to three or four, can be treated in one day, and in fact there is one report of more than ten lesions being treated simultaneously.[12] SRS is superior to surgery in terms of noninvasiveness and its ability to handle multiple lesions, but there are also some drawbacks. SRS can handle only small lesions up to 2 or 3 cm in diameter, and the larger a tumor is, the lower the possibility of tumor control becomes. Another disadvantage is the time required until SRS begins to have a positive effect against a tumor. Moreover, not all tumor cells become necrotic after SRS, some becoming quiescent for a while and regaining their proliferative activity later.

Chemotherapy

Apart from a few reports on brain metastases from small-cell lung cancer,[13,14] the effect of chemotherapy alone on brain metastasis appears to be very limited. It is widely accepted that this is, to some extent, due to the presence of the blood-brain barrier (BBB), which prevents the penetration of drugs in circulating blood into brain tissue. In the center of a tumor, the BBB is disrupted, and an experimental study has confirmed this.[15] However, the amount of drug delivered to invasive cells is considered to be insufficient. Recently, a new drug, temozolomide, which can pass through the BBB, has been developed and has been shown to be effective against gliomas. This new drug is also effective against extracranial malignancies, especially melanomas. However, its effectiveness is not outstanding against brain metastases, even those from melanoma.[16] Thus, chemotherapy alone has not proved to be effective against brain metastasis, except that from small-cell lung cancer.

Supportive care

Corticosteroid administration, which is not a substantial treatment, can alleviate the symptoms of brain metastasis.[17] Most brain metastases have accompanying perifocal edema, and the symptoms caused by the mass effect of brain metastases are due to a combination of this edema and the metastases themselves. Corticosteroid administration lessens the perifocal edema and alleviates the symptoms in most cases. However, corticosteroid is an immunosuppressant and thus might impair the effectiveness of a patient's immune system against systemic cancer. Furthermore, it cannot suppress the progression of brain metastasis. Despite its potential drawbacks, the temporary alleviation of symptoms and improvement of quality of life resulting from corticosteroid administration may be remarkable, and for

this reason, most clinicians eventually choose to prescribe it for patients with brain metastases.

Decision-making about treatment for brain metastasis, with special emphasis on the role of surgery

Single brain metastasis

Although the factors to be considered in a patient with a single brain metastasis are less complicated than those for multiple brain metastases, decision-making about treatment is often not easy.

When there is a single brain metastasis, it should be decided whether only this local lesion should be treated, whether local treatment followed by WBRT should be employed, or whether WBRT should be done from the beginning. In 1990, a prospective randomized trial showed that surgery and postoperative radiation therapy achieved a better survival outcome than WBRT alone.[18] Several prospective and retrospective studies[19,20] subsequently confirmed this result, except for one report[21] (Table 1). In regard to postoperative radiation therapy, surgery alone showed poorer results than surgery followed by postoperative irradiation, probably due to the presence of invasive residual tumor cells,[22] although other reports denied this.[23,24] Thus, surgery plus postoperative irradiation seems to be the best choice for a single brain metastasis, although the necessity for postoperative irradiation is not fully proven. This should be confirmed using a prospective and multi-institutional approach, like that about to be undertaken in Germany (G Schackert, personal communication). As for the methods employed for postoperative irradiation, the necessity for WBRT is not yet clear. As most reported studies of postoperative irradiation have involved WBRT, the outcomes of focal therapy have not been well documented. Although several studies have employed local irradiation,[25,26] only one study has reported that postoperative local irradiation gave better results than postoperative WBRT.[11]

Thus, until recently, surgery plus postoperative irradiation has been the standard procedure for the treatment of a single brain metastasis. However, this situation is changing because of the emergence of SRS procedures. As a focal therapy, SRS instead of surgery has become widely employed recently. No randomized trial has compared the difference in outcome between surgery and SRS, but one retrospective survey showed that SRS was as effective as surgery plus postoperative WBRT.[27] A case-control study by Schoggl et al.[28] showed equality between SRS plus WBRT and surgery plus WBRT. Another study showed that SRS was superior to WBRT for treating a single brain metastasis.[29] Also, the effectiveness of an SRS boost after WBRT was confirmed by a randomized trial.[30] Most of the results obtained with SRS alone or in combination with other modalities have shown an approximate median survival time of 9 months or more,[29,31,32] which is comparable with, or superior to, that of WBRT or surgery followed by radiation treatment. Because SRS seems to be less invasive, it tends to be used rather than open surgery if the tumor size is less than 3 cm.

In conclusion, patients with a single lesion larger than 3 cm receive the best benefit from open surgery. Surgery is also indicated for patients with a life-threatening mass and those requiring immediate decompression. Patients with metastasis from an unconfirmed primary cancer can also be considered for surgery in order to obtain tissue for histological diagnosis, because sometimes gliomas or other lesions are misdiagnosed as metastases by neuroimaging.[18,19]

Multiple metastases

If multiple intracranial metastases are found, the possible presence of more metastases that are still undetectable should always be considered. WBRT is the standard procedure in this situation, although it cannot control large lesions effectively. Even if lesions stop growing or shrink after irradiation, they will not disappear completely, and will resume their growth after a certain period. Metastases from small-lung cell cancer, which respond well to radiation therapy, are the exception and may be well controlled by external conventional irradiation. Thus, WBRT for multiple brain metastases other than small-cell lung cancer is a palliative, rather than a curative approach. However, most patients with multiple brain metastases usually have multiple systemic metastases and their life expectancy is limited. Thus, if the neurological symptoms can be controlled for a certain period, such treatment would be beneficial.

The situation has also been changing as a result of the spread of SRS. As mentioned before, it has been assumed that if multiple metastases are present, then additional lesions are likely, and WBRT is the only approach that can treat both visible and nonvisible multiple metastases. Recently, however, a study has shown that multiple metastases can also be treated by SRS. Sneed et al.[33] compared the results of treatment of multiple metastases (up to four lesions) with SRS with and without WBRT. Although there was a difference in the recurrence rate, the survival time were almost the same. A recent randomized trial in Japan comparing SRS and SRS plus WBRT[34] showed that the tumor control rate was better for SRS plus WBRT, although the overall survival rates were almost the same. Another report described that patients with more than ten metastases treated with SRS showed a median survival of 10 months, and no patient died due to brain metastasis-related symptoms. Thus, with the emerging role of SRS, it has become difficult to standardize the treatment for multiple metastases. The results of treatment for multiple metastases are summarized in Table 2.[6,31,35–39] Although WBRT or SRS plays a major role in the treatment of multiple metastases, in this situation also, neither approach can handle large metastatic lesions. If a patient has multiple lesions that

Table 1. Results of treatment for single brain metastasis

Treatment modality A/B	Median survival after A (months)	Median survival after B (months)	Statistics	References trial	Prospective randomized	Remarks
Surgery vs WBRT	–	–		No study		
Surgery vs Surgery + WBRT	14.4	20	B is better	De Angelis, 1989[22]		
	10.8	12	NS	Patchell, 1998[23]	Yes	B is better for local control
	8	13	NS	Schackert, 2001[24]		Better in radiated patients (NS)
Surgery + WBRT vs WBRT	10	4	A is better	Patchell, 1990[18]	Yes	
	12	7	A is better	Vecht, 1993[19]	Yes	
	6.3	5.6	NS	Mintz, 1996[21]	Yes	Background different instead of randomized trial
	8	4	A is better	Broadbent, 2004[20]		Part of the report
Surgery + WBRT vs SRS	15.9	8.2	NS	Muacevic, 1999[27]		
Surgery + WBRT vs SRS + WBRT	9	12	NS	Schoggl, 2000[28]		
SRS vs WBRT	9.3	5.6	A is better	Li, 2000[29]		
SRS vs SRS + WBRT	9.3	10.6	NS	Li, 2000[29]		
	10.7	13.2	NS	Pirzkall, 1998[31]		
	8.3	8.4	NS	Sneed, 2002[32]		Part of the report
SRS + WBRT vs WBRT	10.6	5.6	A is better	Li, 2000[29]		
WBRT + SRS vs WBRT	6.5	4.9	A is better	Andrews, 2004[30]	Yes	Part of the report
Surgery + WBRT vs surgery + local R	7.7	20.7	B is better	Ueki, 1996[11]		Lung cancer only
Surgery + local R	7.2			Coucke, 1998[25]		Extra field recurrence rate is high
Surgery + WBRT + local R	15			Rodrigus, 2001[26]		Lung cancer only

WBRT, whole-brain radiation therapy; SRS, stereotactic radiosurgery; NS, not significant

Table 2. Treatment results for multiple metastases

References	Number of metastases	Randomized trial	Treatment modality	Median survival (months)	Remarks
Bindal[6] 1993	Single or multiple		Surgery w/wo WBRT	14	
			Surgery w/wo WBRT	14	
			Surgery residual disease w/wo WBRT	6	
Bindal[35] 1996	Multiple		SRS w/wo WBRT	7.5	
			Surgery w/wo WBRT	16.4	
Pirzkall[31] 1998	1–3		SRS (20 Gy)	8.3[a]	
			SRS (15 Gy) + WBRT	15.4[a]	
Sneed[33] 1999	Single or multple		SRS	11.3	
			SRS + WBRT	11.1	
Kondziolka[37] 1999	2–4	Yes	SRS + WBRT	11	Study terminated because SRS group did better
			WBRT	7.5	
Sperduto[39] 2000	2–3	Yes	SRS + WBRT	5.3	In-field recurrence, 21% (abstract/preliminary result)
			WBRT	6.7	In-field recurrence, 37%
Suzuki[12] 2000	≧10		SRS	3.3	
Grob[36] 1998	Single or multiple		SRS Single	22	Melanoma
			SRS Single+systemic metastasis	7.5	
			SRS Multiple	4	
Amendola[38] 2000	Single or multiple		SRS	8	Renal cell carcinoma, 82%; multiple, 50% Recurrence after WBRT

w/wo, with or without; SRS, stereotactic radiosurgery
[a] Patients without active extracranial disease

include one large (>3 cm) metastasis together with smaller lesions, the only effective therapy is to resect the large lesion, regardless of the treatment modalities used for the other lesions.

Role of surgery in the treatment of brain metastasis

The adoption of an aggressive approach for the treatment of patients with stage 4 cancer might be regarded as a somewhat controversial issue. With regard to brain metastasis, the issue is complicated, because many factors need to be considered and there is a paucity of clinical data. As criteria for treatment in many studies have tended to exclude patients with poor performance status, there is currently a lack of reliable criteria for decision-making about treatment for such patients. Moreover, most previous controlled studies were done before the SRS era, thus making the situation more complicated. However, the fact that some patients can survive for a long period after aggressive treatment, including surgery, prompted us to treat brain metastasis. Surgery plays an important role in this context. Emergency decompression for patients with impending herniation, or for patients with a large cerebellar metastasis and acute hydrocephalus, cannot be done by other methods. A large metastasis more than 3 cm in size cannot be handled with SRS. Surgery for these patients certainly improves their clinical condition. Also, patients with metastasis from an unknown primary tumor might benefit from surgery in order to verify the histology. However, whether such patients genuinely benefit from surgery is difficult to decide, because other systemic metastases or their general condition might worsen as a result of anesthesia or the surgery itself. In patients whose tumors are small and can be handled with SRS, the role of surgery is more difficult to determine, because SRS can control tumor cells for a certain period but cannot control all the tumor cells permanently, whereas surgery cannot control invasive tumor cells without postoperative radiation therapy in most patients.

Conclusion

Surgery has a certain role to play in the treatment of brain metastasis, especially in patients with a large single metastasis or in those with a life-threatening mass effect. However, the role of surgery in other situations should be determined in future by more detailed analysis. Moreover, most previous studies have been based on survival, and few have addressed the quality of life, length of hospitalization, or cost of the treatment. It is therefore an urgent priority to carry out some well-planned clinical studies to establish the optimal treatment strategies, including the role of surgery, considering not only the survival of patients, but also their quality of life, the cost of the treatment, and other factors.

References

1. Takakura K, Sano K, Hojo S (1982) Metastatic tumors of the central nervous system. Igaku-shoin, Tokyo
2. Johnson JD, Young B (1996) Demographics of brain metastasis. Neurosurg Clin N Am 7:337–344
3. The Committee of the Brain Tumor Registry of Japan (1993) Report of Brain Tumor Registry of Japan (1969–1993), 10th edn. Neurol Med Chir 40 (Suppl):1–106
4. Patchell RA (2003) The management of brain metastases. Cancer Treat Rev 29:533–540
5. Nonaka H, Akima M, Hatori T, et al. (2003) The microvasculature of the cerebral white matter: arteries of the subcortical white matter. J Neuropathol Exp Neurol 62:154–161
6. Bindal RK, Sawaya R, Leavens ME, et al. (1993) Surgical treatment of multiple brain metastases. J Neurosurg 79:210–216
7. Kondziolka D, Lunsford LD (1996) Intraoperative navigation during resection of brain metastases. Neurosurg Clin N Am 7:267–277
8. Matsutani M, Nakamura O (1995) Treatment of brain metastasis from lung cancer. Jpn J Cancer Clin 41:1504–1510
9. DeAngelis LM, Delattre JY, Posner JB (1989) Radiation-induced dementia in patients cured of brain metastases. Neurology 39:789–796
10. Asai A, Matsutani M, Kohno T, et al. (1989) Subacute brain atrophy after radiation therapy for malignant brain tumor. Cancer 63:1962–1974
11. Ueki K, Matsutani M, Nakamura O, et al. (1996) Comparison of whole brain radiation therapy and locally limited radiation therapy in the treatment of solitary brain metastases from non-small cell lung cancer. Neurol Med Chir (Tokyo) 36:364–369
12. Suzuki S, Omagari J, Nishio S, et al. (2000) Gamma knife radiosurgery for simultaneous multiple metastatic brain tumors. J Neurosurg 93 (Suppl 3):30–31
13. Lee JS, Murphy WK, Glission BS et al. (1989) Primary chemotherapy of brain metastasis in small-cell lung cancer. J Clin Oncol 7:916–922
14. Tanaka H, Takifuji N, Masuda N, et al. (1993) Systemic chemotherapy for brain metastasis from small cell lung cancer (in Japanese). Nihon Kyobu Shikkan Gakkai Zasshi (Jpn J Thorac Dis) 31:492–497
15. Zhang RD, Price JE, Fujimaki T, et al. (1992) Differential permeability of the blood-brain barrier in experimental brain metastases produced by human neoplasms implanted into nude mice. Am J Pathol 141:1115–1124
16. Agarwala SS, Kirkwood JM, Gore M, et al. (2004) Temozolomide for the treatment of brain metastases associated with metastatic melanoma: a phase II study. J Clin Oncol 22:2101–2107
17. Black P (1979) Brain metastasis: current status and recommended guidelines for management. Neurosurgery 5:617–631
18. Patchell RA, Tibbs PA, Walsh JW, et al. (1990) A randomized trial of surgery in the treatment of single metastases to the brain. N Engl J Med 322:494–500
19. Vecht CJ, Haaxma-Reiche H, Noordijk EM, et al. (1993) Treatment of single brain metastasis: radiotherapy alone or combined with neurosurgery? Ann Neurol 33:583–590
20. Broadbent AM, Hruby G, Tin MM, et al. (2004) Survival following whole brain radiation treatment for cerebral metastases: an audit of 474 patients. Radiother Oncol 71:259–265
21. Mintz AH, Kestle J, Rathbone MP, et al. (1996) A randomized trial to assess the efficacy of surgery in addition to radiotherapy in patients with a single cerebral metastasis. Cancer 78:1470–1476
22. DeAngelis LM, Mandell LR, Thaler HT, et al. (1989) The role of postoperative radiotherapy after resection of single brain metastases. Neurosurgery 24:798–805
23. Patchell RA, Tibbs PA, Regine WF, et al. (1998) Postoperative radiotherapy in the treatment of single metastases to the brain: a randomized trial. JAMA 280:1485–1489
24. Schackert G, Steinmetz A, Meier U, et al. (2001) Surgical management of single and multiple brain metastases: results of a retrospective study. Onkologie 24:246–255
25. Coucke PA, Zouhair A, Ozsahin M, et al. (1998) Focalized external radiotherapy for resected solitary brain metastasis: does the dogma stand? Radiother Oncol 47:99–101
26. Rodrigus P, de Brouwer P, Raaymakers E (2001) Brain metastases and non-small cell lung cancer. Prognostic factors and correlation with survival after irradiation. Lung Cancer 32:129–136
27. Muacevic A, Kreth FW, Horstmann GA, et al. (1999) Surgery and radiotherapy compared with gamma knife radiosurgery in the treatment of solitary cerebral metastases of small diameter. J Neurosurg 91:35–43
28. Schoggl A, Kitz K, Reddy M, et al. (2000) Defining the role of stereotactic radiosurgery versus microsurgery in the treatment of single brain metastases. Acta Neurochir 142:621–626
29. Li B, Yu J, Suntharalingam M, et al. (2000) Comparison of three treatment options for single brain metastasis from lung cancer. Int J Cancer 90:37–45
30. Andrews DW, Scott CB, Sperduto PW, et al. (2004) Whole brain radiation therapy with or without stereotactic radiosurgery boost for patients with one to three brain metastases: phase III results of the RTOG 9508 randomised trial. Lancet 363:1665–1672
31. Pirzkall A, Debus J, Lohr F, et al. (1998) Radiosurgery alone or in combination with whole-brain radiotherapy for brain metastases. J Clin Oncol 16:3563–3569
32. Sneed PK, Suh JH, Goetsch SJ, et al. (2002) A multi-institutional review of radiosurgery alone vs radiosurgery with whole brain radiotherapy as the initial management of brain metastases. Int J Radiat Oncol Biol Phys 53:519–526
33. Sneed PK, Lamborn KR, Forstner JM, et al. (1999) Radiosurgery for brain metastases: is whole brain radiotherapy necessary? Int J Radiat Oncol Biol Phys 43:549–558
34. Aoyama H, Shirato K, Nakagawa K, et al. (2004) Interim report of the JROSG99-1 multi-institutional randomized trial, comparing radiosurgery alone vs radiosurgery plus whole brain irradiation for one to four brain metastases. J Clin Oncol, 2004 ASCO Annual Meeting Proceedings (Post-Meeting Edition) 22(14S):1506
35. Bindal AK, Bindal RK, Hess KR, et al. (1996) Surgery versus radiosurgery in the treatment of brain metastasis. J Neurosurg 84:748–754
36. Grob JJ, Regis J, Laurans R, et al. (1998) Radiosurgery without whole brain radiotherapy in melanoma brain metastases. Club de Cancerologie Cutanee. Eur J Cancer 34:1187–1192
37. Kondziolka D, Patel A, Lunsford LD, et al. (1999) Stereotactic radiosurgery plus whole brain radiotherapy versus radiotherapy alone for patients with multiple brain metastases. Int J Radiat Oncol Biol Phys 45:427–434
38. Amendola BE, Wolf Al, Coy SR, et al. (2000) Brain metastases in renal cell carcinoma: management with gamma knife radiosurgery. Cancer J 6:372–376
39. Sperduto PW, Scott C, Andrews D, et al. (2000) Preliminary report of RTOG 9508: a phase III trial comparing whole brain irradiation alone versus whole brain irradiation plus stereotactic radiosurgery for patients with two or three unresected brain metastases (abstract). Int J Radiat Oncol Biol Phys 48:113

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脳腫瘍の診断と治療

—最新の研究動向—

VIII. 転移性脳腫瘍

癌脳転移（転移性脳腫瘍）：概論

藤巻高光

VIII. 転移性脳腫瘍

癌脳転移(転移性脳腫瘍):概論

Brain metastases, incidence, etiology and treatment modalities: review

藤巻高光

Key words brain metastasis, radiation, stereotactic radiosurgery, surgery, chemotherapy

1. 癌脳転移の疫学

癌の脳転移の患者数の正確な統計は存在しない．米国のやや古い統計によると，Takakuraらは，癌患者の剖検症例の25.6%に脳実質転移を認め，28.7%に頭蓋内転移を認めたという[1]．またJohnsonらは，脳転移に関する総説において剖検からの推計として1年間に13,300人が脳腫瘍で死亡し，一方，他の癌で死亡する547,000人のうち131,280人が脳および頭蓋内に転移巣を有しているであろうとしている[2]．

日本のほぼ全剖検例が登録されていると思われる日本病理剖検輯報第44輯[3](2002年)では，全剖検例26,056件中，悪性腫瘍が15,123件，うち脳，髄膜，神経系への転移を有する例が686件である．悪性腫瘍剖検例の4.5%に脳，神経系への転移が生じていることとなる．日本人口動態統計[4]では，年間約30万人が悪性腫瘍で死亡しており，これから推計すると年間約13,500人の癌患者が脳に転移を有して死亡しているという計算になる．人口動態統計による同年の原発性脳腫瘍による死亡は1,616人であり，原発性脳腫瘍で死亡する患者の8倍以上の癌患者が死亡時に脳，神経系への転移を有しているということになる．

しかし，臨床の場では，これらの脳転移例すべてが積極的治療の対象となっているわけではない．主として脳外科医からの登録によっている日本脳腫瘍統計[5]によると，1993年に登録された癌脳転移症例は879例であり原発性脳腫瘍(4,197例)の1/4以下にすぎない(なお，本統計は，全国の原発脳腫瘍症例の約1/3が登録されていると考えられる)．これは，脳転移が存在すること自体が癌の病期としては既にステージ4であり，外科あるいは内科から脳外科へ紹介されない，あるいは，紹介されても治療の対象外とされているためではないか，と推定される．一方，最近のガンマナイフの統計によると，2004年には1年間で延べ8,000例近い症例が，ガンマナイフ治療を受けており，ガンマナイフの登場が，今まで治療されていなかった脳転移の治療の需要を掘り起こした可能性が考えられる．

2. 脳転移の原発巣

それぞれの統計の年度が若干異なるが，日本脳腫瘍統計，日本病理剖検輯報での中枢神経系への転移および厚生労働省班研究(津熊班)[6]による悪性腫瘍の罹患率の比較を**表1**に示す．脳腫瘍統計および剖検輯報の中枢神経系転移の頻度の傾向はほぼ同一である．すなわち脳腫瘍統計では癌脳転移例の約半分が肺癌からであり，

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