中国抗癌协会神经肿瘤专业委员会第二次学术会议暨

神经系统肿瘤基础研究及临床诊治进展学习班

论

文

集

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中国抗癌协会神经肿瘤专业委员会主办

四川大学华西医院神经外科承办

2005.11.11-14 成都

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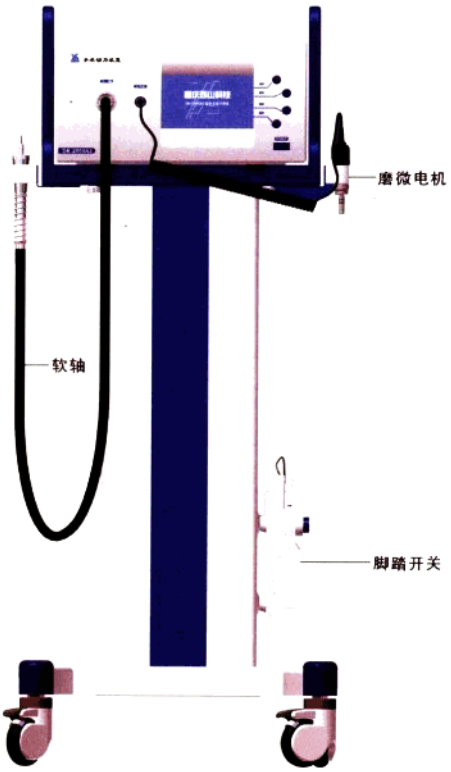

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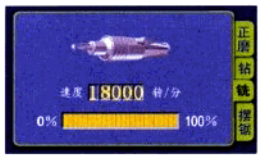

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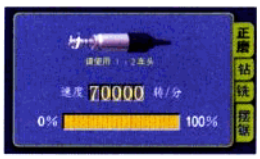

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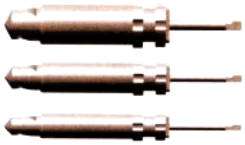

颅骨钻头

- 钻穿即停机构
- 设计钻孔深度：13mm
- 设计耐用次数：300孔

骨钻头

- 钻头长度：65mm
- 直径：Φ2.5、Φ2.7、Φ3.0、Φ3.2、Φ3.5、Φ4.0
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铣手机

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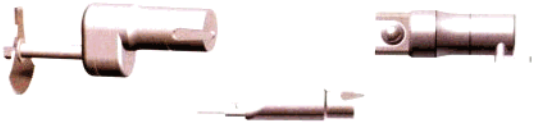

锯手机（垂直摆锯、平摆锯、往复锯）

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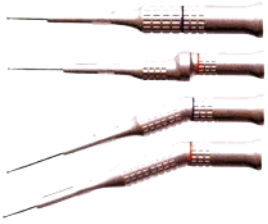

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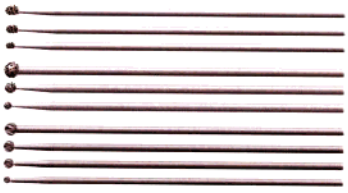

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软轴

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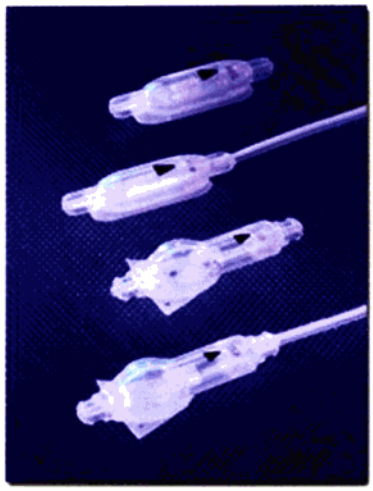

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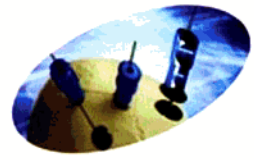

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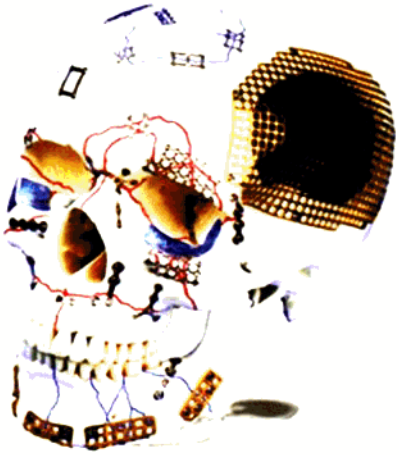

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基础

My Concept for Human Glioma Treatment

Yoshihiko Yoshii, M.D.

Department of Neurosurgery, University of the Ryukyus, Okinawa.

Primary malignant glioma is a devastating disease by a low cure rate and short survival. Especially the outcome of glioblastoma is still disappointing.

Glioma is a very smart brain tumor, therefore we need a theoretical strategy for glioma treatment.

There are still many unknown issues in the pathological and/or biological behavior of glioma, However, in the present studies we have some concepts of pathobiology, neuroimages and therapy selection in human glioma.

In my lecture, I would like to mention about concept of glioma therapy based on an analysis studied at our department and some literatures. There are four categones in my lecture.

Firstly, in addition to the wellknown pathobiological concepts for glioma, our study about the relationship between the expression of detoxifying enzymes after radio-chemotherapy and the cellular heterogeneity showed that the immunoreactivity of bcl-2 and GST-pi in malignant gliomas might be very important factors in radio-and chemo-sensitivity, and showed that GST-pi was induced by radiation and anti-cancer drugs.

Secondly, in glioma surgery we have essential aims that the patient's neurological state must be kept more than 70% KPS and can expect to prolong his survival time by cytoreduction of large volume after modern enbloc total resection using neuronavigation. Thereafter we have treated the patients with malignant glioma by radiotherapy combined with hyperbaric oxygen therapy and PAV-chemotherapy. Thereafter, the patients have received the early and late maintenance therapy for 2 on 5 years after operation. I suggest that the patient with modern enbloc and grossly total tumor resection survived longer than the patient with subtotal resection of tumor by Kaplan Meier's method.

Thirdly, in the differentiation of recurrent glioma from other neuroimages mimicking the viable tumor, we have usually used 201Tl-SPECT or MRI. However, we have to know that 201 Tl-SPECT illustrates a diagnostic pitfall for distinguishing radionecrosis from recurrent glioma.

Fourthly, in the cognitive function we also have to know that the patient with malignant and low grade glioma located in dominant hemisphere shows the poor cognitive function before and/or after treatment.

Recent evaluation of malignancy in glioma

Keiji Kawamoto

Department of Neurosurgery, Kansai Medical University, Japan

Malignancy of astrocytoma is usually used by WHO classification, and pathological grading was

classified into I-IV grade, but biological characteristics and cell kinetics have been disclosed by immunohistochemical, molecular biological and genetic approaches in glioma.

Our department is studying for the malignancy and biological characteristics with use of flow cytometry(FCM), laser scanning cytomery (LSC), FISH and PCR in surgical cases of glioma.
Preoperative evaluation; neuroimaging, immunological activities

Intraoperative evaluation: rapid diagnosis from frozen specimen, LSC

Postoperative evaluation: proliferation index, DNA-index, suppressor gene expression, Cyclin D1&B1 expression.

These studies would be useful for the information of prognosis and therapies in glioma.

Treating Patients at M D Anderson with High-Grade Gliomas: Clinical perspectives and Translational Research

Charles Conrad, MD, Associate Professor, Medical Director,

Brain and Spine Center, M.D. Anderson Cancer Center, Houston, TX 77030 USA

The Brain and Spine Center at M D Anderson Cancer Center encompasses over 15,000 patient visits per year and evaluates approximately 800 patients with newly diagnosed brain tumors. Treatment practices vary among the 11 neuro-Oncologists and the 10 neurosurgeons, however commonly patients with high-grade gliomas are routinely aggressively treated. Most patients are placed on treatment protocols after evidence of progressive disease. Some examples are provided of in-house protocols that were given to patients in an up-front fashion and have demonstrated significant improvement in median survival in comparison to historical and study controls. Multi-modal treatment consisting of aggressive surgery, typically focal conformal radiation therapy and adjuvant chemotherapy is commonly given. Patients with recurrent disease are typically placed on clinical trials.
Chemotherapy Trends

At M. D. Anderson Cancer Center, the use of PCV is typically restrictive to patients with oligodendrogliomas that have demonstrated loss of chromosomal arms 1p and 19q. Although there is a trend, even in these patients, to use Temozolomide initially and then switch to PCV if a good response to Temozolomide is not seen within a 2-4 cycles. This practice, however, is somewhat controversial since there are no studies at this point directly comparing Temozolomide and PCV in patients with oligodendroglioma. The replacement of Temozolomide for PCV in anaplastic astrocytoma is largely due to the significant myelosuppression that is commonly seen with BCNU and CCNU-containing regimens. This degree of toxicity is not seen typically with Temozolomide. More recently, a large multi-institutional study demonstrated a benefit of the concurrent use of Temozolomide with radiation therapy followed by 6 courses of adjuvant Temozolomide in patients with glioblastoma multiforme. This large study performed by the European Organization for Research on the Treatment of Cancer (EORTC) and the National Cancer Institute of Canada (NCIC), investigated the use of 75 mg/ m2 on a continuous daily basis during the six-week course of radiation therapy and followed by 6 courses of adjuvant Temozolomide at 200/ m2, demonstrated a significant improvement in a percentage of patients who survived two years or longer (10% versus

26%). Also an improvement in the median survival was seen with this large consortium trial (12.1 months versus 14.6 months). Because of this study Temozolomide used concurrently with radiation therapy and then followed with between 6 months to 2 years of adjuvant Temozolomide is currently considered the standard of care for patients with glioblastoma multiforme. In addition, we have experience with "dose intensified" Temozolomide using a week "on" week "off" schedule. This schedule will be the basis for the largest phase III clinical trial for patients with Glioblastoma in the world (Mark Gilbert as P.I.) In terms of cytotoxic chemotherapy, other drugs are used occasionally in a salvage setting. In addition to nitrosourea agents such as Irinotecan, carboplatin, and more recently, Xeloda, have found some limited antidotal support with use of these agents in a salvage setting.

Potential Targets in Gliomas and Translational Research

Malignant gliomas, like other malignant solid tumors have a number of dysregulated or mutated gene products to enable the cancer cell to grow. Tumor cells need to have features of unlimited replication, avoidance of apoptotic signals, become independent of external growth factors, obtain the ability to invade surrounding normal tissue, stimulate angiogenesis and avoid immune surveillance. These features are provided by dysgegulated genetic pathways, which can be used to target these tumors. In the case of malignant gliomas, a number of common pathways tend to be exploited. For instance, gliomas tend to have dysregulated Rb/p16/E2F pathway members driving unchecked cell cycle, p53/mdm2 dysfunction creating a failure of apoptosis, growth factor amplification or mutations in genes coding for epidermal growth factor receptor (EGFR), Platelet derived growth factor receptor (PDGF-r) and insulin-like growth factor receptor (IGF-r) to list a few. Survival, invasion and stimulated angiogenesis seem to be commonly driven by the PI3-kinase/PTEN/AKT/mTOR pathways as well as activated STAT3 pathways. Because these dysfunctional pathways exist in a large proportion of high-grade gliomas, opportunity exists to target these pathways with novel approaches. It is felt that cytotoxic chemotherapy is often ineffective predominantly due to intrinsic resistance of glioma cells to these agents. This resistance is mediated through induction of cell survival and anti-apoptotic signals. The major pathways that mediate these survival signals include the PI3K/AKT axis, the Jak/STAT and Ras/MEK/ERK pathways. Another novel area that may preferentially be advantageous in the treatment of high-grade gliomas is to target the glycolytic phenotype of these tumors with specific inhibitors to Glycolysis. Examples of treatment strategies targeting some of these areas will be presented.

A number of mechanisms are being explored to improve the treatment possibilities with patients at M. D. Anderson Cancer Center and we believe that combination studies using multiple signal transduction inhibitors potentially with toxic chemotherapy may offer advantages to these patients that were clearly not available previously. Our continued philosophy is to actively enroll patients who have failed standard forms of therapy.

Recent Management of Functioning Pituitary Adenomas

Akira Teramoto, M.D., D.M.Sc., F.J.C.N.S.

Department of Neurosurgery, Nippon Medical School,

We have experienced 1,610 transsphenoidal surgeries (TSSs) until the end of last year. Among them, non-functioning, GH secreting, PRL secreting, ACTH secreting and TSH secreting adenomas

occupied 36.6, 26.5, 16.5, 7.8 and 1.6 %, respectively. Most of the others (11.1%) were pituitary cystic diseases, such as Rathke cleft cysts. Based on these surgical results, our recent management for functioning pituitary adenomas will be introduced.

GH secreting adenoma (acromegaly): The first choice of treatment is TSS. According to the recent strict criteria (Cortina consensus), the postoperative cure ratio was usually 50-60 %. However, if we look at the microadenoma group, it increased to 80-90 %. The patients without remission are treated with bromocriptine (BC) and/or octreotide (OCT) LAR.

New pharmacotherapies, such as pegvisomant, somatostatin receptor selective analogs will be available soon. For those who are resistant to medical treatments, the stereotactic irradiation, such as gamma knife, will be given.

PRL secreting adenoma (prolactinoma): Although BC and related medicines are very useful, they must be administered for a long time. If we focus on the enclosed (non-invasive) microadenomas which can be identified by MRI, the postoperative cure ratio is very high (more than 90%). For invasive and/or large adenomas, medical treatments are selected according to the sensitivity of each drug.

ACTH secreting adenoma (Cushing disease): The differential diagnosis of ACTH-dependent Cushing disease can be made by the cavernous sinus sampling, since it is sometimes very difficult only from conventional endocrine tests. High quality MRI can detect a tiny microadenoma in about 90 %. After the definite diagnosis, the treatment choice must be TSS. The success rate is generally 80-90%. Patients without remission or those with recurrence are treated with radiosurgery and/or cortisol synthesis blockers.

Treatment against Human Malignant Glioma in relation to Comprehensive Gene Expression Analysis by cDNA microarray

Hiroshi Takahashi, M.D., Ph.D.

Department of Neurosurgery, Nippon Medical School Dai-ni Hospital, Kanagawa, JAPAN

The treatments of malignant gliomas are still extremely difficult and these tumors almost invariably recur and often progress rapidly despite aggressive various therapy. Treatment options are usually classified into surgery, radiation therapy, or chemotherapy, but there are many indistinct points in molecular mechanism participating in growth and development of malignant brain tumors. Thus, we tried to extract related genes by comparing gene expression profile of malignant glioma according to malignancy grade, and apply such results to a clinical treatment.

Radical resections of contrast-enhancing tumor in patients with malignant gliomas may be pertinent for survival, so some novel methods like neuronavigator or fluorescence-guided surgery, awake craniotomy and brain mapping are being examined which aim at enhancing resections.

On the other hand, we extracted mRNA from 22 surgical specimens which were 8 diffuse astrocytomas (grade 2), 6 anaplastic astrocytomas (grade 3), 8 glioblastomas (grade 4) by conventional method, and the microarray analysis of complementary DNA (cDNA) using commercial human brain total RNA (Clontech company) as control was done. The interferon (IFN) effect prediction tip on which 777 genes were selected (MBC company) were used for analysis of

human malignant glioma by taking advantage of building up future therapeutic strategy.

As the result of this study, manifest changes were recognized by 32 genes when having compared grade 4 with grade 2, and significant variations were recognized by 12 out of 32 genes. There was restraint tendency of gene expression level in grade 4 generally, and in particular expression of interferon reference genes were restrained. These results were extremely interesting when we consider about the correlation with malignancy and therapeutic effects of gliomas.

In conclusion, this gene expression analysis study by cDNA microarray revealed that appropriate therapeutic strategy like an interferon combined chemotherapy against glioblastomas which are very difficult to be treated is enabled.

Analysis of six cytokines in cystic fluids associated with cystic brain tumors measured by cytometric bead array

Qiang Li[1], Takashi Ryu[1], Keiichi Azuma[1], Hideyuki Ohshige[1],

Tomoyuki Murakami[2], Yoshiharu Numa[1] ,Yasuo Yamanouchi[1],
Zhongping Chen[3], Shiguang Zhao[4], Keiji Kawamoto[1]

[1)]Department of Neurosurgery, Kansai Medical University. Moriguchi, Japan, [2)]Department of Respiratory Medicine, National Sanyo Hospital, Respiratory Disease Center, Ube, Japan, [3)]Department of Neurosurgery, Cancer center, Sun Yat-sen University, Guangzhou, China, [4)]Department of Neurosurgery, Harbin Medical University, Harbin, China.

PURPOSE: Cystic lesions are frequently found in malignant or nonmalignant brain tumors. Pathogenesis of the cyst formation is considered following with central necrosis and cellular secretion as two main factors, but molecular determinants of cystic lesions are still under investigation. A cross-talk among a variety of cytokines in local lesion is suspected to play a significant role in the development and healing of the lesions, including stroke, pneumonia, asthma, pleural effusion and so on. Little is known, however, about possible interactions between individual cytokines in terms of regulation of their relative abundance in cystic brain tumors. A new flow cytometric technique, cytometric beads array (CBA), is a tool to simultaneously measure not only absolute abundance of various cytokines but also their relative abundance in a small amount of liquid sample. With this information as a background, we studied 28 samples of cystic fluids from patients with cystic brain tumors

MATERIALS AND METHODS: In this study, cystic fluids were collected from 28 patients with cystic brain tumors. The breakdown was as follows: 7 cases of metastatic brain tumors, 12 cases of glioma (4 cases of astrocytoma (grade I-II), 4 cases of anaplastic astrocytoma (grade III) and 4 cases of gliomablastoma (grade IV)), 2 cases of craniophcarnyngioma, 2 cases of hemangioblastoma, and 3 cases of the others. Cystic fluids concentrations of IL-2, IL-4, IL-5, IL-10, TNF-alpha, and INF-gamma were simultaneously measured by cytometric bead array (CBA) using a Human Th1/Th2 Cytokines----Cytmetric Bead Array KitTM (BD) on FACSCalibur. We also detected the expression of IL-5, IL-10 receptors in specimens from the IL-5 and IL-10 CBA-positive cases by immunohistochemistry.

RESULTS: Positive expression rates of 6 Cytokines in 28 cases were IL-5 (20/28cases) = IL-10

(20/28cases) >IL-2 (10/28cases) > INF-gamma (8/28cases) > TNF-alpha (4/28cases) > IL-4 (2/28cases). IL-10 positive was found in all of metastatic brain tumors (7/7cases) and the positive rates of 6 cytokines were the highest in metastatic brain tumors than in other tumors. The percentage of IL-5 positive and the percentage of IL-10 positive were high in gliomas, but TNF-alpha and INF-gamma was not detected in any case of gliomas. In 2 craniopharnyngiomas, we detected INF-gamma, IL-10, IL-5, TNF- alpha. In the cases of IL-5 positive, cells of tumor block specimens expressed IL-5 receptors, and IL-10 receptors were detected in the IL-10 positive cases by immunohistochemistry.

CONCLUSION: We confirmed that cystic fluids contain particular cytokines which may play important roles in pathogenesis of the cyst formation associated with cystic brain tumors. The CBA methodology provides a convenient tool to simultaneously measure abundance of these cytokines even in a small amount of cystic fluid sample. Although, In current study of 28 cases, no significant difference was observed between any sort of tumors, it is proposed that we maybe need more cases to detect.

KEYWORDS: cystic brain tumor, cytometric beads array (CBA), cytokine.

Microarray and Biochemical Analysis of Lovastatin-induced Apoptosis in Human Glioblasto ma Cell Lines: its synergistic effect with a tumour necrosis factor

Wai POON, David CHAN, George CHEN

Division of Neurosurgery, Prince of Wales Hospital, The Chinese University of Hong Kong

Lovastatin, an HMG-CoA reductase blocks the synthesis of mevalonate resulting in reduction of cho lesterol synthesis, antiproliferation and proapoptosis. It is also known that statin can induce mitocho ndrial stress (the intrinsic pathway) leading to cell apoptosis. Tumour Necrosis Factor-related Apopt osis-incucing Ligand (TRAIL), a member of the tumour necrosis factor alpha family, can induce can cer cell death thorugh death domain containing receptors (extrinsic pathway). We hypothesize that tr iggering both the intrinsic and extrinsic pathways could amplify apoptotic cell death in glioma. We have test this hypothesis with three human glioblastoma cell lines (A172, M059J and M059K). Syne rgistic effects were demonstrated. The mechanism of this favourable effect was partially delineated by microarray and biochemical analysis.

从分子水平认识和治疗胶质瘤

陈忠平

（中山大学肿瘤医院神经外科/神经肿瘤科，广州 510060）

胶质瘤是神经系统最常见的原发性肿瘤，临床上预后还不乐观。但我们注意到即使是相同病理类型和级别的胶质瘤，治疗效果存在很大差异。如低级别的胶质瘤（WHO I-II 级），多数病人治疗效果良好，但有部分病人易于恶变、复发；此外，同样是胶质母细胞瘤，多数病人生存时间不超过一年，但也有部分病人可以达到 5 年以上生存。这种差异的原因是什么？治疗上的差异无疑是重要影响因素，但肿瘤内在的生物学特性，特别是分子水平的差异应该是关键所在(1-3)。因此，在胶质瘤的临床治疗实践中，如何根据肿瘤的分子病理特征和病人的具体情况，进行个体化的治疗，是提高疗效的一个有效措施，也是神经肿瘤医师面对的现实问题。

1 胶质瘤的分子病因

胶质瘤的确切病因是什么目前还没有明确答案。一般认为与环境、遗传和机体免疫功能失调等综合因素有关。近年胶质瘤的分子生物学研究表明，胶质瘤是一种基因病(4)，体内外各种因素使抑癌基因的失活/原癌基因的活化是胶质瘤发生/发展的关键。研究发现，血管内皮生长因子受体（vascular endothelial growth factor receptor，VEGFR）、血小板源生长因子受体(platelet-derived growth factor receptor, PDGFR) 和 p53，它们作为转录因子，对细胞周期、DNA 修复、遗传稳定性和细胞凋亡起重要调节作用。磷酸酯酶及张力蛋白同源物(phopsphatase and tensin homology deleted on chromosome ten，PTEN/ mutated in multiple advanced cancers，MMAC)，恶性脑肿瘤删除基因 1（gene deleted in malignant brain tumor 1, DMBT1)，鼠类双微粒体 2(murine double minute 2, MDM2)，结直肠癌删除基因(gene deleted in colorectal cancer, DCC)，细胞周期依赖激酶 2（cyclin-depend kinase 2, CDK2)，视网膜母细胞瘤基因（retina blastoma,RB1）等与多形胶质母细胞瘤的发生密切相关（5）。此外，有研究发现纤维母细胞生长因子 2 及其受体（fibroblast growth factor2/recepter, FGF2/FGF2R)，胰岛素样生长因子 1 及其受体（insulin-like growth factor1/recepter, IGF1/IGF1R)，C-erB-2,增殖细胞核抗原（proliferative cell nucle antigen, PCNA)，肝细胞生长因子等与胶质瘤侵袭和恶性变相关（6）。众多癌相关基因的相互作用，使细胞生长调节异常、细胞之间缺乏接触抑制和细胞的遗传特性不稳定，最终影响细胞周期控制、凋亡、血管生成、细胞黏附、跨膜信号转导和 DNA 修复，导致了肿瘤的发生和发展。然而，胶质瘤发生、发展的细节还远不清楚。以往对胶质瘤的研究主要集中在对单基因变化的考察，这些基因可能参与了胶质细胞的恶性转化。显然，胶质瘤的发生不是单基因改变的结果，而是由于众多原癌基因和抑癌基因复杂相互作用的结果。因此，全面、系统认识这些原癌基因和抑癌基因，大规模地比较它们的表达模式和下游基因产物的差异，才有希望提供治疗胶质瘤有效的新靶向和新策略。晚近，胶质瘤干细胞概念的提出，以及与神经干细胞和正常胶质细胞三者间能否转化的探索为胶质瘤分子病因的研究提供了新思路（7）。

2 胶质瘤的分子病理

近来发现，按常规组织病理学分类属于同一类型和级别的胶质瘤，其分子遗传学背景可以是不同的，而正是这种差异使组织学类型相同的胶质瘤在同样的治疗干予下其临床预后明显不同。因此，深入研究胶质瘤的分子遗传学变异，制定胶质瘤分子病理分类标准，将对合理的个体化治疗及评估患者预后均具有重要的理论意义和实用价值（8)。

在少突胶质细胞瘤，1p 及 19q 丢失的发生率较高，现已初步证实 1p 和 19q 丢失与少突胶质细胞瘤发生、发展密切相关。有 1p 和（或）19q 丢失的少突胶质细胞瘤对放射治疗和 PCV 方案化疗敏感，已得到众多研究的证实，此类患者的临床预后相对较好(9)。而增殖标记物 Ki-S1 的标记指数（labeling index，LI） > 10%，p27 LI < 20%提示可能恶性变。在室管膜瘤的 Ki-S1 LI >5%，细胞间粘附抑制因子（Tenascin)，VEGF 和 VEGFR 阳性是恶性的表现。胶质瘤的 PCNA 阳性，p53 突变和端粒酶活性升高也多提示肿瘤有恶性变的倾向(10)。部分低级别星形细胞瘤具有恶性胶质瘤的遗传学异常改变，如 9p21 和 10q23-25 的杂合性丢失（11)。

现已公认，胶质母细胞瘤可分为原发性（de novo）和继发性两类。原发胶质母细胞瘤多有 EGFR 过表达、肿瘤抑制基因 PTEN(MMAC1)突变、p16 (也称周期依赖性激酶 2A（cyclin-dependent kinase inhibitor 2A，CDKN2A)）丢失，还可见 MDM2 基因扩增；而继发性胶质母细胞瘤常见 p53 突变，端粒酶活性阳性者占 90%。晚近， Liang 等发现，在发展迅速的胶质母细胞瘤中有大约 70 个基因表达上调，通过 105 例病例对比研究证实其中一