

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



(<http://www.csno.cn>)

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

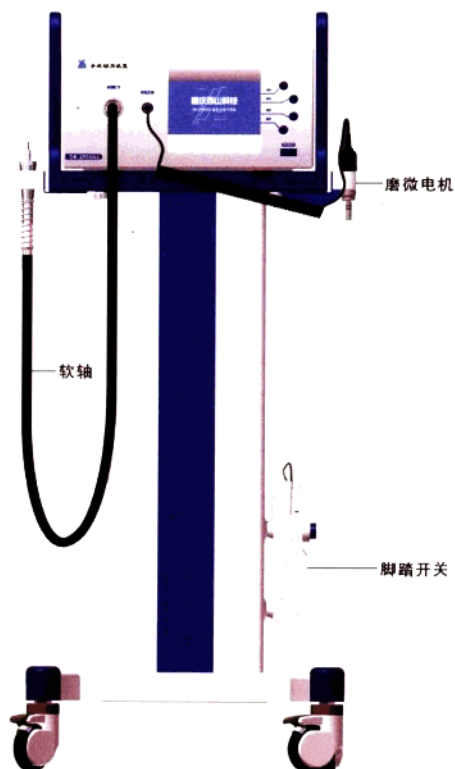
2005.11.11-14 成都

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- ◆ 国家发改委《医疗器械国产化专项项目》
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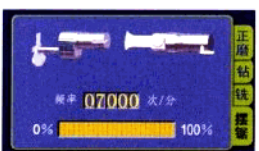
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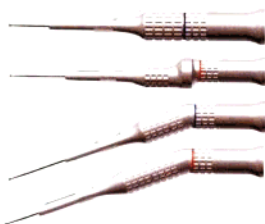
铣手机

- 快速接口设计，铣刀装卸快捷方便
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锯手机(垂直摆锯、平摆锯、往复锯)

- 发热小，噪音低，运动平稳
- 刀片装卸快捷方便



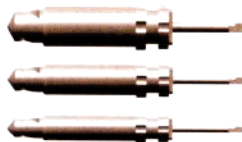
磨钻手柄

- 直手柄长度：70mm、95mm、125mm
- 弯手柄长度：70mm、95mm、125mm
- 磨转速：0-35000r/min；0-70000r/min



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- 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
- 设计耐用次数：200孔



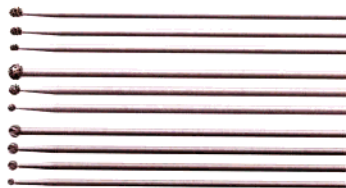
铣刀

- 直刃、螺旋刃
- 铣刀设计耐用次数：20例(20cm/例)
- 铣刀缝宽：1.5~2.0mm
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骨锯片

- 360°内10个角度方向可调
- 摆锯摆动角度7°，往复锯位移量5mm，锯缝隙宽1.5mm内



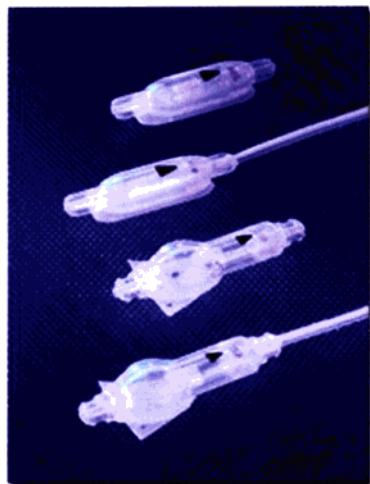
磨头

- 金刚砂、切削刃
- 长度：70mm、95mm、125mm，柄径Φ2.35mm
- 金刚砂头部直径：Φ1.0、Φ2.0、Φ3.0
- 切削刃头部直径：Φ3.0、Φ4.0、Φ5.0



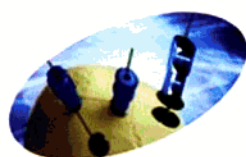
软轴

- 长度1800mm，2000mm，2200mm
- 最小弯曲半径<150mm

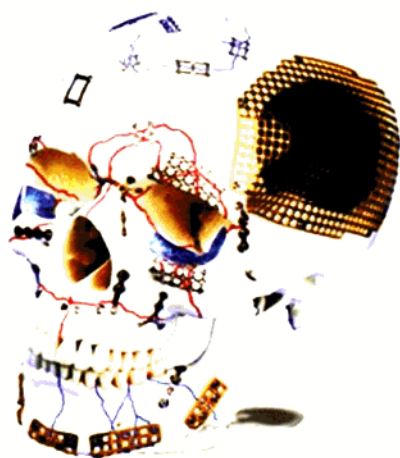


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目录

基础

My Concept for Human Glioma Treatment	Yoshihiko Yoshii (1)
Recent evaluation of malignancy in glioma	Keiji Kawamoto (1)
Treating Patients at MD Anderson with High-Grade Gliomas: Clinical perspectives and Translational Research	Charles Conrad (2)
Recent Management of Functioning Pituitary Adenomas	Akira Teramoto (3)
Treatment against Human Malignant Glioma in relation to Comprehensive Gene Expression Analysis by cDNA microarray	Hiroshi Takahashi (4)
Analysis of six cytokines in cystic fluids associated with cystic brain tumors measured by cytometric bead array	Qiang Li, et al. (5)
Microarray and Biochemical Analysis of Lovastatin-induced Apoptosis in Human Glioblastoma Cell Lines: its synergistic effect with a tumour necrosis factor	Wai POON, et al. (6)
从分子水平认识和治疗胶质瘤	陈忠平 (7)
胶质瘤分子病因研究	黄强 (10)
脑血管母细胞瘤蛋白质组学研究	陈露萍 (10)
垂体瘤基础与临床研究进展	雷霆 (10)
荧光引导鼠脑胶质瘤切除的实验研究	赵世光, 陈雷, 赵洪波, 等 (13)
颅咽管瘤动物模型的建立及肿瘤生物学特性的研究	游潮, 徐建国 (14)
内、外源性光敏剂PDT治疗大鼠脑内C6胶质瘤的实验研究	李明, 冯华, 李飞, 等 (15)
MVD及VEGF在颅咽管瘤中的表达及其与预后的关系	徐建国, 游潮, 王晓洁, 等 (15)
细胞缝隙连接通讯在肿瘤自杀基因“旁观者效应”中的作用及机制探讨	苑玉清, 游潮 (15)
大鼠脑外伤后血脑屏障、超微结构变化及VEGF表达的研究	杨咏波, 游潮 (17)
颅内动脉瘤动物模型建立及发病机制的研究	郭予大, 游潮 (17)
组蛋白去乙酰化酶抑制剂诱导胶质瘤细胞凋亡机制的研究	张豫滨, 叶远柱, 刘赞, 等 (19)
人脑胶质瘤为血管内皮细胞的分离培养及体外生物学特性观察	卢佳友, 蒋雪峰, 冯华, 等 (19)
Photodynamic Effect of 5-Aminolevulinic Acid on U251 human glioma cells	DING Lian-shu, et al. (19)
胶质瘤促血管生存素2基因表达与血管生成的关系	石松生, 罗望池, 杨卫忠, 等 (20)
连接蛋白43联合自杀基因治疗胶质瘤的研究	强, 浦佩玉, 夏之柏, 等 (20)

LRIG 基因家族在星形细胞瘤中的表达——郭东生, 席桂发, Hedman Håkan, 等(23)

胶质瘤组织中 DNA 修复基因 MGMT 启动子区过甲基化研究——王之敏, 高薇, 朱凤清, 等(23)

DNA 修复基因 MGMT 启动子区过甲基化与脑胶质瘤——高薇, 许期年, 左剑玲, 等(24)

PTTG、bFGF 和 MMP-9 mRNA 的表达与垂体腺瘤侵袭性的关系——赵建农, 王宇田(24)

靶向 Survivin 基因的短发卡 RNA 在体内对 U251 细胞移植瘤的影响——甄海宁, 章翔, 师长宏, 等(24)

胶质瘤细胞株中 ERCC1、ERCC2 基因启动子区 CpG 岛的甲基化分析——陈华云, 张俊英, 陈忠平, 等(25)

p53 基因联合自杀基因治疗恶性胶质瘤的研究——黄强, 浦佩玉, 夏之柏, 等(25)

短发卡 RNA 对 Survivin 基因在人脑胶质母细胞瘤 U251 细胞中表达的影响——甄海宁, 章翔, 杨彤涛, 等(26)

骨桥蛋白在胶质瘤细胞中的表达及其信号传导途径——俞文华, 车志豪, 张祖勇, 等(26)

胶质瘤 DNA-PK 活性与化疗药物耐药关系研究——邵翠杰, 夏云飞, 史泓洙, 等(27)

反义 GFAP 对人恶性胶质瘤细胞系 CHG-5 和 SHG-44 增殖及分化的影响——卢佳友, 赵雯, 冯华, 等(27)

胶质瘤细胞中 RNA 编辑酶 ADAR2、ADAR3 mRNA 表达——田宇, 潘玉琢, 高宇飞, 等(27)

雷公藤红素对荷 SHG44 胶质瘤裸鼠的抑瘤试验——周幽心, 姜华, 陈学彬, 等(28)

大剂量间歇 X 线照射诱导人胶质瘤细胞株 MGR2 放射和化疗抗拒性的产生——胡震, 程金建, 史泓洙, 等(28)

水通道蛋白、血管内皮生长因子在人脑胶质瘤中的表达及意义——焦保华, 王志强(29)

Silenced EGFR expression by antisense or small interference RNA inhibite glioma cell growth in vitro and in vivo——Chun-Sheng Kang, et al. (29)

脑胶质瘤中富亮氨酸胶质瘤失活基因 1 突变的初步研究——王金环, 宋振国, 徐新女, 等(30)

人 IFN-β 基因脂质体对胶质瘤及其血管生成的抑制作用——林伟, 章翔, 王占祥, 等(31)

人脑胶质瘤中 14-3-3 蛋白的表达——曹卫东, 章翔, 张剑宁, 等(31)

人脑胶质瘤中 MAGE-A1 的表达及意义——程光, 章翔, 张赟, 等(31)

三氧化二砷对人胶质瘤细胞系 U87MG、T98G 细胞程序性死亡及细胞周期调控相关基因表达的影响——张健, 张豫滨, 刘耀华, 等(32)

神经干细胞对胶质瘤趋向性研究——姬西团, 章翔, 费舟, 等(32)

整合素 β1 和局灶粘附激酶在垂体瘤侵袭行为中的作用和意义——万锋, 雷霆, 舒凯, 等(32)

星形细胞瘤中突变型 P53、O6-甲基鸟嘌呤 DNA 转移酶表达及其与亚硝胺耐药的关系——李剑敏, 黄卡特(33)

自体特异性免疫效应细胞(CTL)体外能够诱导胶质瘤细胞分化吗?——史泓洙, 陈忠平(33)

树突状细胞疫苗免疫治疗策略的实验研究——王煜, 牛洪泉, 董芳永, 等(34)

特异性 siRNA 对人脑胶质瘤细胞 Survivin 基因表达的抑制作用——叶明(34)

- CD44s、CD44V6 与 VEGF 在颅内转移瘤与胶质母细胞瘤中的表达研究——熊正文, 范水平, 冯骥良, 等(35)
- Celecoxib 诱导胶质瘤细胞凋亡作用机制初探——杨武双, 林清国, 杨 修, 等(35)
- 脑胶质瘤原代细胞药敏与 MGMT 表达的相关性研究——许洪升, 张俊英, 岳伟英, 等(35)

手术

- Surgical treatment and long term follow-up on pediatric craniopharyngiomas——Zhang YQ, et al. (36)
- 颈静脉孔区肿瘤的治疗体会——徐启武(36)
- 斜坡肿瘤的手术治疗——张俊廷(37)
- 内镜下经鼻蝶治疗鞍区病变——张亚卓, 王忠诚, 刘丕楠, 等(37)
- 手术根除胶质瘤的可能与策略——漆松涛, 刘承勇, 俞方毅, 等(38)
- 脑胶质瘤手术策略与相关技术——王伟民(38)
- 肿瘤医院神经外科治疗脑肿瘤病人: 五年工作体会——陈忠平, 牟永告, 张湘衡, 等(39)
- 颅底肿瘤显微手术进展——于春江(40)
- 经单鼻孔-蝶窦摘除垂体腺瘤的微创技术——章 翔, 费 舟, 张剑宁, 等(44)
- 海绵窦肿瘤的显微手术治疗——章 翔, 张剑宁, 费 舟, 等(44)
- 颅眶沟通性肿瘤的显微手术探讨——杜长生, 肖利华, 李钟路, 等(45)
- 手术切除颅咽管瘤 278 例报告——石祥恩, 吴 斌, 周忠清, 等(46)
- 椎管内肿瘤的外科治疗——附 696 例临床资料总结——王贵怀, 杨 俊, 王忠诚, 等(46)
- 51 例听神经瘤的显微外科治疗——于春江, 任 铭(49)
- 儿童三脑室前、中、后部肿瘤的手术治疗——邢 俭, 周 强, 马振宇, 等(49)
- 垂体微腺瘤的诊断和治疗(附 45 例报告)——张宏伟, 于春河, 闰长祥, 等(49)
- 翼点入路切除鞍结节脑膜瘤的手术技巧——孙 炜, 于春江, 寸恩浩, 等(50)
- 颈髓髓内血管网质细胞瘤的诊断及显微外科治疗——惠旭辉, 蔡博文, 游 潮(52)
- fMRI 影像导航结合术中运动诱发电位监护在脑皮质运动区病变手术中的应用——赵建农, 刘小丘, 吴硕琳, 等(53)
- 锁孔微创入路切除三脑室肿瘤——兰 青(53)
- 前纵裂入路切除鞍区巨大多部位肿瘤——迟广明, 陈 刚, 郑 勇, 等(53)
- BAEP、EMG 在桥小脑角肿瘤术中的应用——吴国材, 朱 刚, 林江凯, 等(54)
- 垂体瘤切除术后近期并发症的分析——王文伟, 崔高宇, 冯 华, 等(54)
- 垂体微腺瘤的治疗决策体会——陈明振, 胡裕全(54)
- 非典型和恶性脑膜瘤 20 例临床回顾分析——周建军, 施益民, 官 卫, 等(55)
- 颅底脑膜瘤的手术治疗——157 例报告——冯 华, 李 飞, 朱 刚, 等(56)

复发性脑胶质瘤的临床研究	高伯元, 卢佳友, 冯 华, 等(56)
功能区影像导航辅助下显微手术切除大脑皮层运动区附近病变	吴 南, 冯 华, 朱 刚, 等(56)
显微手术切除颅底部肿瘤(附 21 例报告)	韩 富, 龙新兵, 于春江, 等(57)
基底节区生殖细胞瘤的诊断和治疗	罗代伟, 冯 华, 陈 志, 等(57)
脊髓髓内病灶的处理	林江凯, 冯 华, 艾 松, 等(57)
经蝶垂体腺瘤切除术后头痛原因分析及对策	张永琴, 蔡艳丽, 郭丝锦, 等(58)
巨大蝶骨嵴内侧型脑膜瘤的手术治疗	付洛安, 章 翔, 费 舟, 等(58)
巨大脊髓髓内肿瘤的显微手术	张剑宁, 章 翔, 高大宽, 等(59)
两种手术方法治疗海绵窦海绵状血管瘤的临床体会	李立新, 胡卫星, 傅 震, 等(59)
颅底肿瘤术中运动颅神经组合监测和预后探讨	赵建农, 王宇田, 王鹏程, 等(59)
颅-眶沟通瘤的微创手术	章 翔, 费 舟, 付洛安, 等(60)
颅眶额部沟通肿瘤的显微外科治疗:22 例体会	周旺宁, 陈忠平, 伍国号, 等(60)
颅内胆脂瘤临床诊治的分析	陈红林, 高伯元, 冯 华, 等(61)
颅内胆脂瘤的显微手术治疗	王静波, 史益民(61)
颅内生殖细胞性肿瘤显微手术治疗	蒋晓帆, 章 翔, 费 舟, 等(62)
中颅窝囊性面神经鞘瘤—1 例报道及文献复习	赛 克, 周旺宁, 牟永告, 等(62)
内镜辅助改良翼点“锁孔”入路结合术中眼球运动神经监护在中脑病变手术中的应用	赵建农, 刘小丘, 梁 元, 等(62)
脑转移瘤手术治疗的回顾性分析	李 鹏, 李文良, 王晓光, 等(63)
前、中颅凹颅内外沟通瘤显微外科手术治疗	费 舟, 章 翔, 蒋晓帆, 等(63)
神经导航治疗辅助颅内病变	王彦刚, 章 翔, 刘卫平, 等(63)
神经内镜控制下经鼻-经蝶手术入路切除垂体腺瘤	孟 辉, 冯 华, 王宪荣, 等(64)
神经内镜镜下经单鼻孔-蝶窦切除垂体瘤配合 98 例	王西玲, 于 玲, 邓 琪, 等(64)
实时 B 超在神经外科手术中的应用	赵 明, 徐 欣(64)
矢状窦旁和大脑镰旁脑膜瘤的手术治疗	邓聪颖, 朱 刚, 林江凯, 等(65)
VEP 监测下鞍区肿瘤切除的临床研究	吴国材, 林江凯, 朱 刚, 等(65)
手术治疗天幕脑膜瘤	刘卫平, 章 翔, 费 舟, 等(65)
松果体区肿瘤的手术治疗	张剑宁, 章 翔, 高大宽, 等(66)
幕下小脑上入路切除松果体区肿瘤的显微手术体会	陈建良, 吴耀晨, 赵永阳, 等(66)
锁孔开颅显微手术处理颅内病变 124 例报告	王国良, 白红民, 蒋晓星, 等(66)

脑干占位病变治疗及相关问题探讨	王向宇, 柯以铨, 王清华, 等	(66)
下丘脑神经元错构瘤的显微外科治疗(附一例病例)	郭 睿, 李 牧, 肖福顺	(67)
显微手术治疗颅咽管瘤 46 例报道	刘 智, 王宪荣, 高伯元, 等	(68)
显微外科手术切除矢状窦旁脑膜瘤	贺晓生, 章 翔, 费 舟, 等	(69)
显微外科治疗颅咽管瘤	贺晓生, 章 翔, 费 舟, 等	(69)
嗅沟脑膜瘤外科治疗 38 例	张 川, 吴 南, 王俊伟, 等	(70)
翼点入路切除鞍区肿瘤的临床研究(附 150 例报告)	邵 彤, 陈德勤, 聂振明, 等	(70)
原发性中枢神经系统恶性淋巴瘤临床分析	邱 骥, 崔高宇, 冯 华, 等	(71)
小儿椎管内肠源性囊肿	吕海欣	(71)
听神经瘤的显微外科手术治疗: 17 例体会	朱从付, 孟宪团	(71)

放疗

立体定向放射性粒子 ^{125}I 组织间种植治疗脑肿瘤	许建平	(72)
Synchronous Solitary Brain Metastases in Patients with Non-Small-Cell Lung Cancer: A retrospective study	Chao-su Hu, et al.	(73)
15 例脑胶质瘤的 X 刀分次立体定向放射治疗	肖建平, 姜雪松, 徐国镇	(74)
儿童脑干胶质瘤的放射治疗	夏云飞	(74)
脑高分级胶质瘤生物调强放射治疗剂量提升 I/II 期临床研究	吴少雄, 邓美玲, 赵 充, 等	(78)
389 例脑胶质瘤立体定向放射治疗效果评价	牛道立, 何 中, 胡慧玲	(78)
颅内肿瘤伽玛刀治疗后再开颅切除原因分析	许自强, 赵普学, 安 全	(79)
脑胶质瘤 OUR-XGD 伽玛刀和显微外科手术疗效临床探讨	罗光华, 唐启信, 陈显钊	(79)
手术高风险区颅内病变的伽玛刀治疗	罗光华	(80)

化疗

脑恶性肿瘤的预见性、个体化化疗	张俊平, 陈忠平	(80)
ACNU 和 DDP 联合连续灌注化疗治疗脑胶质母细胞瘤	李文良, 刘 群, 朴颖哲, 等	(82)
体外药敏试验指导的恶性脑胶质瘤预见性化疗	陈建文, 张俊平, 程金建, 等	(82)
As_2O_3 在脑胶质瘤化疗中应用及疗效观察	甄云波, 滕 雷, 刘耀华, 等	(83)
MGMT 指导下的恶性脑胶质瘤预见性化疗近期疗效分析	张俊平, 魏大年, 徐红超, 等	(83)
短期快速化疗药物交叉治疗脑胶质瘤 8 例报告	黄大成, 翁 明	(84)

病理

胶质瘤染色体 DNA 失衡研究的意义及进展	于士柱, 赵文娟	(85)
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与难治性癫痫相关的脑肿瘤的临床病理学——陈 莉, 卢德宏(86)

脑多形性黄色星形细胞瘤的临床与病理——李南云, 周婧, 周航波, 等(89)

AFM 观察海人酸作用下星形胶质细胞形态结构变化——储卫华, 冯华, 徐如祥, 等(89)

脑膜瘤质地与细胞增殖及复发关系的研究——赛 克, 牟永告, 张湘衡, 等(89)

小儿颅内肿瘤 100 例临床病理分析——朱国玲, 王 伟(90)

影像

脑肿瘤的 fMRI——黄 力, 凌雪英(90)

胶质瘤的分子影像学研究进展——廖丹玲, 梁碧玲(91)

脑磁图临床应用——孙吉林(95)

分子影像学在神经胶质瘤的诊断与治疗中的应用——芮春朵, 沈海林(95)

鸣谢——(97)

基础

My Concept for Human Glioma Treatment

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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 categories 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 201TI-SPECT or MRI. However, we have to know that 201 TI-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

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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 cytometry (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

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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 dysregulated 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

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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

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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

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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 glioblastoma (grade IV)), 2 cases of craniopharyngioma, 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 craniopharyngiomas, 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 Glioblastoma Cell Lines: its synergistic effect with a tumour necrosis factor

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Lovastatin, an HMG-CoA reductase blocks the synthesis of mevalonate resulting in reduction of cholesterol synthesis, antiproliferation and proapoptosis. It is also known that statin can induce mitochondrial stress (the intrinsic pathway) leading to cell apoptosis. Tumour Necrosis Factor-related Apoptosis-inducing Ligand (TRAIL), a member of the tumour necrosis factor alpha family, can induce cancer cell death through death domain containing receptors (extrinsic pathway). We hypothesize that triggering 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). Synergistic 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

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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(phosphatase 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/receptor, FGF2/FGF2R), 胰岛素样生长因子 1 及其受体(insulin-like growth factor1/receptor, IGF1/IGF1R), C-erbB-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预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