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PROGNOSTIC EVALUATION IN SUPRATENTORIAL ASTROCYTIC TUMORS USING P53, EPIDERMAL GROWTH FACTOR RECEPTOR, C-ERB B-2 IMMUNOSTAINING

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Molecular pathology may play an important role in predicting the tumor prognosis, particularly p53, epidermal growth factor receptor (EGFR), and c-erbB-2. We investigated six variables (age, sex, histopathological grade, p53, EGFR, and c-erbB-2) to identify the role of such factors in predicting the outcome of patients with supratentorial astrocytic tumors. Thirty-seven tumors were studied including 9 well-differentiated astrocytomas (WHO grade 2), 19 anaplastic astrocytomas (WHO grade 3), and 9 glioblastomas multiforme (WHO grade 4). In univariate analysis, no statistical significance was found for the prognostic value of the sex (p=0.2188), age (p=0.5530), *p53* immunostain (p=0.2194), and *c-erbB-2* immunostain (p=0.4203). A significant correlation with the prognosis was found with respect to the histopathological grade (p=0.0049) and EGFR expression (p=0.0284). In multivariate analysis, the histopathological grade was shown to be significant independent variable (p=0.0152). In WHO grade 2 and 3 astrocytomas, expression of p53 or EGFR was associated with poorer patient outcome. In glioblastomas, expression of p53 was also associated with poorer prognosis. Our studies suggested that conventional histological assessment of supratentorial astrocytic tumors remains the best guide to prognosis. Although no statistical significance was found between the immunostains and survival in variant grades of astrocytomas, there was a trend between p53 or EGFR proteins expression and the decrease of survival time.

Key words: astrocytoma, histopathology, prognosis

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It is important to know the factors affecting prognosis and to use a reliable method evaluating prognosis for individual patients with specific tumors. Much effort in cancer research is, therefore, directed at finding a potentially marker for tumor prognosis. Several prognostic factors proposed in astrocytic tumors include patient age[1], histopathological grade[2,3], sex[1], tumor extent[1], and preoperative mental status[1]. Nowadays, there is increasing evidence that molecular pathology may play an important role in predicting the tumor prognosis[4-7], particularly p53, epidermal growth factor receptor (EGFR), and c-erbB-2. In the studies of breast cancer, p53, EGFR, and c-erbB-2 have been shown to be adverse prognostic factors[4-6,8,9], although some authors reported no significant association of such proteins expression and patient outcome[7]. The relationship between patient prognosis and expression of p53, EGFR, and c-erbB-2 in astrocytic tumor remains controversial. In Taiwan, the studies of prognostic analysis in astrocytic

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tumors are rare[10, 11]. The aim of this study was particularly to identify some prognostic factors in molecular neuropathology that could predict the outcome in the patients with supratentorial astrocytic tumors. We investigated six variables: age, sex, histopathological grade, p53, EGFR, and c-erbB-2.

MATERIALS AND METHODS

The study population for this series consisted of 50 patients with supratentorial astrocytic tumors. A complete clinical and histopathological follow-up evaluation was obtained in 37 patients. The follow-up periods ranged from 2 months to 125 months. Incomplete follow-up was found in eight and insufficiency of tissue block in five. Six prognostic factors were investigated in this study: age of patient, sex, histopathological grade, p53, EGFR, and c-erbB-2.

The ages of patients at the time of their first operation ranged from 13 to 69 years (mean, 45 years). Three age groups were made: less than 40 years, between 40 and 60 years, and more than 60 years. Twenty-four patients were male (64.9 %) and 13 were female (35.1 %). These 37 supratentorial astrocytic tumors corresponded to cerebral infiltrating astrocytomas. All tumors were studied by pathologists according to the World Health Organization (WHO) classification[12]. These included 9 well-differentiated astrocytomas (WHO grade 2), 19 anaplastic astrocytomas (WHO grade 3), and 9 glioblastomas multiforme (WHO grade 4).

The immunohistochemical staining was performed using 5μm formalin-fixed and paraffin-embedded tissue sections. The slides were deparaffinized and hydrated. For the p53 immunostain, antigen retrieval was done with a microwave oven in 10 mM citrate buffer for a total of 20 minutes (two 10-minute cycles). Then, the slides were treated with 3% hydrogen peroxide in methanol to block endogenous peroxidase activity. For the EGFR and c-erbB-2 immunostain, the slides were incubated with 0.1% pepsin in 0.01N HCl (pH2.25) 37℃ for 30 minutes. After washing with phosphate-buffered saline (PBS), pH7.4, the slides were incubated with primary monoclonal antibody (anti-EGFR, Clone: E30, 1:20; anti-c-erbB-2, Clone: CB11, 1:20; PAb 1801, 1:20) (Bio Genex, USA) for 30 minutes at room temperature. Then, they were washed with PBS and incubated with biotinylated link antibody (DAKO, Denmark) for 30 minutes. The specimens were washed with PBS again and then incubated with peroxidase-labeled streptavidin (DAKO, Denmark) for another 30 minutes. The visualization was achieved by incubation with diaminobenzidine (DAB) and counterstained with Mayer's hematoxylin. Dehydration and clearing were achieved in graded alcohol and xylene respectively. Finally, the slides were mounted with Entellan (MERCK, Germany). A specimen from breast carcinoma was used for a positive control. Negative controls were performed by the replacement of primary antibody with non-immune mouse serum (DAKO, Denmark).

The immunohistochemical staining was graded as negative when there was complete absence of membranous and cytoplasmic staining (EGFR or c-erbB-2) or nuclear staining (p53). For the EGFR or c-erbB-2 immunostain, the immunopositive tumor samples were graded as "+", "++", and "+++" according to the degree of staining of cells in all areas of the specimens examined. Thus, a positive immunoreaction in single cells was graded as "+" (less than 5% of the total cell population), in numerous cells or foci of positive cells as "++" (5 to 50%), and in large areas as "+++" (more than 50% of the total cell population).

Three patterns of p53 immunoreactivity were evident, i.e., negativity, local scattering, and diffuse clustering. In the locally scattered pattern, singly scattered immunopositive cells or sparse collections of positive cells comprised less than 10% of the total cell population, surrounded by fields of entirely immunonegative cells. The diffusely clustered pattern consisted of a majority of positive cells with intervening negatively stained cells or of a prominent positive cell clusters separated from completely negative cells. The immunopositive cells in diffusely clustered patterns accounted for 10-100% of the total cell population. The end point of this study was the survival time. Cumulative survival time was calculated by the Kaplan-Meier method. A P value less than 0.05 was considered statistically significant. Variables that achieved statistical significance in those univariate analyses were subsequently included in Cox's multivariate analysis. These prognostic variables analyses were computed

using the SPSS window system.

RESULTS

Table 1 shows the results of the univariate analysis of prognostic factors. No statistical significance was found for the prognostic value of the sex variable (p= 0.2188), age at the time of diagnosis (p= 0.5530), *p53* immunostain (p= 0.2194), and *c-erbB-2* immunostain (p= 0.4203). A high level of statistical significance was obtained with respect to the histopathological grade prognostic value (p= 0.0049). The EGFR protein expression also had a significant correlation with the prognosis (p=0.0284). Although the medium survival months were 28 and 15 in the patients under the age of 40 and those over 60 years, respectively, there was no statistical significance (p=0.1321). The Cox's multivariate analysis was then used to examine the independent contribution of important related variables (i.e., histopathological grade and EGFR protein expression). The histopathological grade was shown to be significant independent variable (p=0.0152), but the EGFR protein expression variable did not reach the statistical significance (p=0.1405). Table 2 reveals the relationship between p53, EGFR, and c-erbB-2 immunostains and mean survival months in variant grades of astrocytic tumors. Although no statistical significance was found between them, there was a trend between p53 or EGFR proteins expression and decreased mean survival time. In well-differentiated astrocytoma group, expression of p53, EGFR, or c-erbB-2 was apparently associated with poorer patient outcome. In anaplastic astrocytoma group, patients with lack of p53 or EGFR expression had better prognoses than those with such proteins expression. In the glioblastoma group, expression of p53 was associated with a slightly poorer prognosis. In this study, all the glioblastoma patients, had stronger EGFR expression and we cannot make any conclusion about the effect of EGFR variable on prognosis.

DISCUSSION

The prognosis of patients with astrocytic tumors remains poor. Although considerable variation exists within these patients with respect to postoperative survival, the main reason for poor outcome is the aggressive behavior of the tumor or high recurrence rate. Much evidence has demonstrated that biological aggressiveness is associated with genetic alterations. The present study was designed to evaluate the clinical relevance of sex, age of patient, tumor grade, and p53, EGFR and c-erbB-2 immunohistochemistry.

The relationship between sex and overall survival in the patients with astrocytic tumors is a controversial one. The majority of studies demonstrated no relationship [11, 13] but one study reported a better outcome in male patients[14]. Our study showed no significant difference between survival times related to sex. Patient age was as a strong prognostic factor for survival [13, 15]. There is a significant association between younger age and longer survival time [16, 17]. For patients under the age of 40 with malignant gliomas, the 18-month survival rate was 64% compared to 8% for those over the age of 60 years [16]. In our study, the median survival months were 28 and 15, respectively, in the patients under 40 and those over 60 years, but it was not statistically significant (p=0.1321). This may be due to the relatively small patient numbers of our study series. There is a significant correlation between astrocytoma grade and survival [18, 19]. Montine *et al.* [20] reported that histological grade was a powerful prognostic variable, with median survival of 88, 18, and 9 months for astrocytoma, anaplastic astrocytoma, and glioblastoma patients,respectively. Our study showed that conventional histological assessment of astrocytic tumors remains the best guide to prognosis (p=0.0049). This finding is in accordance with reports by other groups[18, 19].

The EGFR gene is the most commonly affected oncogene abnormality in astrocytic. tumors[21]. The proliferative ability of astrocytoma cells determined by Ki-67 was positively influenced by expression of EGFR protein, which suggested that EGFR might be involved in controlling tumor proliferation[22]. EGFR gene amplification also was reported to stimulate progression of malignant grade[23-26]. Schlegel *et al.*[27] observed more rapid tumor regrowth kinetics as indicated by MRI examination in 31 glioblastomas with amplified EGFR gene. Although the frequency of EGFR gene alterations increases with the malignance grade of astrocyto-

Table 1. The univariarte analysis of prognostic factors

	Case no.	Mean survivial (months)	Median survival (months)	Significance (p value)
Sex				
Male	24	45.63	16	P=0.2188
Female	13	23.00	18	
Age(years)				
<40	16	38.63	28	P=0.5530
40-60	13	33.00	16	
>60	8	21.38	15	
Histopathology				
Astrocytoma	9	92.44	56	P=0.0049
Anaplastic astrocytoma	19	21.63	16	
Glioblastoma multiforme	9	16.78	16	
P53 immunostain				
(-)	17	43.76	29	P=0.2194
Focal scatter	16	31.06	16	
Diffuse	4	11.00	6	
EGFR immunostain				
(-)	6	80.50	42	P=0.0284
(++)	7	17.57	10	
(+++)	24	26.17	16	
c-erbB-2 immunostain				
(-)	18	41.78	18	P=0.4203
(+)	9	36.22	29	
(++)	6	23.83	14	
(+++)	4	17.75	9	

Table 2. The relationship between immunostain and survival in variant grades of astrocytic tumors

Immunostain	Astrocytoma		Anaplastic astrocytoma		Glioblastoma multiforme		Significance (p value)
	Cases	Mean survival months	Cases	Mean survival months	Cases	mean survival months	
p53							
Positive	5	54.8	8	19.13	7	16.29	p=0.6761
Negative	4	101.25	11	23.45	2	18.5	
EGFR							
Positive	6	56.00	16	16.50	9	16.78	
Negative	3	97.33	3	49.00	0		
c-erbB-2							
Positive	3	59.33	11	23.45	5	20.8	p=0.3065
Negative	6	92	8	19.13	4	11.75	

mas, the EGFR gene alterations and their expression and patient prognosis remain controversial. Bigner *et al.*[28], Hawkins *et al.*[29], and Diedrich *et al.*[30] found no significant correlation between either EGFR gene amplification or protein expression and patient survival. In glioblastomas the occurrence of EGFR gene mutations was not associated with a worse prognosis[30], while Hurtt *et al.*[15] reported a statistically significant relationship between EGFR gene amplication and shortened survival in such patients.

Schober *et al.*[31] reported that the degree of EGFR gene amplification revealed a positive correlation with the grade of immunohistochemical protein expression, both in regard to the fraction of positive cells and to the overall staining intensity. They also found a negative relationship between the survival time and the degree of EGFR gene amplification. Using immunohistochemical staining, Zhu *et al.*[32] observed that EGFR positivity was a significant and independent prognostic indicator for overall survival and recurrence-free survival for irradiated patients with astrocytic tumors. Our study showed that EGFR positivity was related to survival in patients with well-differentiated astrocytomas and anaplastic astrocytomas.

Mutations of the p53 gene are currently the most frequent genetic abnormalities found in human tumors[33], and produce inactive proteins that fail to bind DNA[34]. This permits the replication of damaged DNA which may then act to promote the mutational activation of protooncogenes. In normal cells, the p53 protein is present in minute quantities that are undetectable by immunohistochemistry. Mutation of the p53 gene or stabilization of the wild type protein by various mechanisms increases the half life of the protein and produces immunohistochemically detectable levels[35]. P53 positive astrocytomas have a higher growth fraction than p53 negative tumors, as assessed by immunolabelling with an antibody against PCNA[36] or Ki-67[22]. Although a positive correlation between accumulation of p53 and indices of cell proliferation has been proposed for astrocytic tumors[36,37], the significance of prognostic evaluation by p53 is controversial.

For tumors of all grades, Jaros *et al.*[22] found reduced survival for p53-positive versus negative astrocytomas, although several laboratories[18-20] reported no difference between these two groups. However, an apparent trend for better survival was found in the p53-negative astrocytomas[19]. This trend was in concordance with our study. Therefore, separate analysis of low or high grade astrocytomas should be done. For survival of patients with p53-positive versus negative high grade astrocytoma (anaplastic astrocytomas and glioblastomas), no statistically significant difference (or even trend for difference) was found[19,38,39]. In contrast, the presence of p53 overexpression in well-differentiated astocytomas seemed from survival curves to indicate shorter survival compared with patients who had no p53 immunoreactivity[38]. However, this variable did not quite reach statistical significance ($p=0.08$) as an independent predictive variable in multivariate analysis. This may be attributed to the relatively small population of patients with such tumors that were studied ($n=24$). In previous studies of p53 immunohistochemistry in astrocytic tumors reported by Chozick *et al.*[40], Ellison *et al.*[41], and Howng *et al.*[42], different distribution patterns of immunopositive cells were noted in variant grades of astrocytic tumors. Therefore, the correlation of survial time and *p53* immunostaining patterns was examined but no statistical significance was found ($p=0.2194$). Iuzzolino *et al.*[43] subdivided WHO grade 2 astrocytomas in three groups: negative, low positive with p53 label index between 1-10%, and highly positive with p53 label index >10%. The survival curve showed a trend towards a more aggressive course in p53-positive patients 3-4 years after surgery. Five years after diagnosis the survival estimate with the Kaplan-Meier method was 21.2% for patients with p53-positive tumors and 45.9% for patients with p53-negative tumors. The trend could be related to the time needed by the p53-positive clone to outgrow the rest of the p53-negative neoplastic cell population.

The human c-erbB-2, also called HER-2 or neu, encodes a 185-kD transmembrane glycoprotein that is homologous but not identical to epidermal growth factor receptor-encoding erbB oncogene. The frequency of c-erbB-2 immunoreactions showed a tendency to increase with the grade of malignancy between WHO grade 2 and 4 astrocytomas[44, 45]. However, information between c-erbB-2 expression and prognosis in astrocytic tu-

mors has been limited. Schwechheimer *et al.* [44] reported that the overexpression of c-erbB-2 was not correlated with the postoperative relapse-free interval or with the overall length of survival. In our study, no statistically significant difference or trend for difference was found between the prognosis and c-erbB-2 expression.

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以 p53、上皮生長因子受器及 c-erbB-2 免疫染色評估天幕上區星狀細胞瘤患者的預後

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分子病理學對於預測腫瘤患者預後扮演著重要的角色，其中以 p53、上皮生長因子受器（epidermal growth factor receptor）和 c-erbB-2 的研究較爲廣泛。本研究分析六個預後因子（年齡、性別、組織惡性度分級、p53、上皮生長因子受器、c-erbB-2）對於天幕上區星狀細胞瘤患者預後的影響。本研究收集 37 例星狀細胞瘤，包括 9 例分化良好星狀細胞瘤（WHO 第 2 級），19 例分化不良星狀細胞瘤（WHO 第 3 級），和 9 例最惡性的多形性神經膠母細胞瘤（WHO 第 4 級）。在單變項分析中，對預後無統計學意義者包括：性別（p=0.2188），年齡（p=0.5530），p53 免疫染色（p=0.2194），和 c-erbB-2 蛋白免疫染色（p=0.4203）；而組織惡性度分級（p=0.0049）與上皮生長因子受器免疫染色（p=0.0284）對預後評估有統計學上的意義。在多變項分析中，只有組織惡性度分級表現出有意義的獨立變項（p=0.0152）。在 WHO 第 2 級和第 3 級星狀細胞瘤中，p53 或上皮生長因子受器的表現和預後不好有關。在多形性神經膠母細胞瘤中，p53 和預後不好有關。本研究顯示，組織惡性度分級是天幕上區星狀細胞瘤預後預測最好的指標。p53 或上皮生長因子受器和預後有關，但無統計學的意義。

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