

What is the relevance of determining EGFR-variant-III status in glioblastomas?

Original article Pelloski CE *et al.* (2007) Epidermal growth factor receptor variant III status defines clinically distinct subtypes of glioblastoma. *J Clin Oncol* 25: 2288–2294

SYNOPSIS

KEYWORDS epidermal, glioblastoma, growth factor receptor, molecular marker, prognostic

BACKGROUND

The prognostic value of EGFR-variant-III (EGFRvIII) expression in glioblastomas has not been determined. Furthermore, the relationship between EGFRvIII expression and other molecular markers is currently unclear.

OBJECTIVE

To assess the clinical significance of EGFRvIII expression in glioblastoma subtypes.

DESIGN AND INTERVENTION

This study enrolled 649 patients with newly diagnosed glioblastoma treated during the period 1992–2003 and for whom paraffin-embedded tumor tissue was available. The study population was divided into two groups, an initial cohort ($n=268$) and a validation cohort ($n=381$). For clinical risk stratification, the revised Radiation Therapy Oncology Group recursive partitioning analysis (RTOG-RPA) classification system for glioblastomas was used. The expression of chitinase-3-like protein 1 (YKL-40), phosphorylated mitogen-activated protein kinase (MAPK), phosphorylated protein kinase B (p-AKT), phosphorylated mammalian target of rapamycin (mTOR), ribosomal protein S6 kinase beta-1 (p-p70S6K) and EGFRvIII in the tumor tissue was analyzed using immunohistochemistry.

OUTCOME MEASURE

The primary outcome was survival, measured from the time of diagnosis to last follow-up or death.

RESULTS

The median ages of patients in the initial and validation groups were 59 years and 55 years,

respectively, and the respective median survival times were 50 weeks and 56 weeks. Among the initial group of 268 patients, 84 patients had tumors that expressed EGFRvIII; the panel of markers expressed in this group also included panEGFR and p-EGFR, YKL-40 and phosphorylated intermediates of AKT and MAPK. In the initial cohort, worse RTOG-RPA class was associated with decreased overall survival ($P<0.021$). Further analyses of the initial cohort demonstrated that RTOG-RPA was highly predictive of survival in those patients with tumors negative for EGFRvIII ($P<0.001$), but not in those with EGFRvIII-positive tumors ($P=0.810$). Among the 381 patients in the validation cohort, EGFRvIII expression was observed in 93 patients. RTOG-RPA class was significantly associated with decreased overall survival ($P<0.002$) in this cohort. When the entire population of 649 patients was analyzed, the researchers found that the RTOG-RPA system was a robust risk stratification tool in the 472 patients with EGFRvIII-negative tumors, but not in the 177 patients with EGFRvIII-positive tumors. RTOG-RPA class was a highly significant predictor of survival in both YKL-40-positive and YKL-40-negative patient subsets ($P<0.001$). Within both cohorts, age, Karnofsky Performance Status (KPS), EGFRvIII, YKL-40 and EGFRvIII/YKL-40 interaction were independent prognostic factors, while the other molecular markers examined were not. Patients with tumors negative for both EGFRvIII and YKL-40 had significantly longer survival times than did patients with other protein-marker combinations. Classification regression tree analysis of the EGFRvIII-negative patients revealed age and YKL-40 status as the most important risk factors, but no risk factors could be identified in the EGFRvIII-positive group.

CONCLUSION

The expression of EGFRvIII is not a strong prognostic factor in glioblastoma. Tumors negative for both EGFRvIII and YKL-40 were less aggressive than tumors positive for one or both markers.

COMMENTARY

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The initial enthusiasm aroused by anti-EGFR strategies in gliomas has been curbed by the disappointing results of the first clinical trials of EGFR-tyrosine-kinase inhibitors, which found no, or very few responses in unselected patients with recurrent glioblastoma.¹ A correlative study linked to such trials has, however, suggested that tumors co-expressing EGFRvIII and phosphatase and tensin homolog (PTEN) are more likely to respond to these drugs.² Such findings have prompted efforts to better understand the significance of EGFRvIII expression in these tumors and to reappraise the relevance of EGFR as a therapeutic target in this disease. To address these issues, Pelloski *et al.* sought to define the prognostic impact of EGFRvIII expression and other molecular abnormalities on the outcome of patients with glioblastoma.

Previously reported retrospective studies examining the prognostic relevance of EGFRvIII in gliomas have found conflicting results.^{3,4} Such discrepancies have been explained by the relatively small sample sizes, varying techniques for determining EGFRvIII expression, incomplete clinical data, and inconsistent information on the status of other molecular abnormalities. Building on the results of their previous study,⁵ Pelloski *et al.* sought to overcome such limitations through evaluation of a large cohort of patients, and inclusion of comprehensive clinical data and information on the status of several other molecular abnormalities in the multivariate analyses. Overall, this study provides a simple explanation for the discrepancies found in the literature: analysis of EGFRvIII expression by immunohistochemistry, alone, is a weak predictor of survival in glioblastoma. Conversely, the study highlighted the prognostic value of YKL-40 expression, and the interaction between EGFRvIII and YKL-40 in this disease. Patients who were negative for both markers did significantly better than the rest of the population, as exemplified by the 2-year overall survival of 43% for this subgroup, compared with 12% for the rest of the patients. Moreover, multivariate analysis revealed that other molecular markers such as components of the RAS and PI3K pathways were no longer independent prognostic

factors when EGFRvIII and YKL-40 were included among the variables, highlighting the importance of including comprehensive molecular data in this type of study. While data on EGFRvIII-negative tumors confirmed the value of patient age and YKL-40 expression as robust prognostic factors, patients with EGFRvIII-positive tumors seemed to behave differently—traditional prognostic factors (i.e. age, KPS, extent of resection, RTOG-RPA class) did not seem applicable in this group of patients.

This study must be appraised in the light of the adequate methodology and extensive inter-institutional collaboration. It provides important information on the prevalence of several molecular abnormalities evaluable in paraffin-embedded tissue that can be used in future studies as historical controls and for estimation of feasibility of molecularly tailored trials. In addition, this study highlights the fact that future trials need to include molecular information for multivariate analyses of prognostic factors; the suggested classification generated by the classification and regression tree analysis might turn out to be useful for interpretation of results and stratification of patients. Results suggest that EGFRvIII-positive tumors may have a different biological behavior, and that absence of both EGFRvIII and YKL-40 increases the chance of achieving long-term survival. From a routine clinical practice standpoint, however, information on EGFRvIII status does not provide treatment guidance at the present time, and it will become relevant only if ongoing studies on anti-EGFR strategies confirm EGFRvIII as a robust marker of response to new treatments.

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Competing interests

The author declared no competing interests.

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PRACTICE POINT

EGFRvIII expression is not a strong predictor of survival in glioblastomas, but absence of both EGFRvIII and YKL-40 expression is associated with a better prognosis; traditional prognostic factors do not seem to apply in EGFRvIII-expressing tumors