Clinical and molecular classification of glioblastoma patients

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Introduction

Glioblastoma (GBM) still carries a poor prognosis with an average survival of 12 to 15 months. However, survival is variable, ranging from a few months to several years, and difficult to predict. Prognostic classification trees exist, based on known clinical factors. These, however, were obtained with data collected beginning >30 years ago, when GBM treatment was heterogeneous. Applicability of these classifications to the current situation with standard treatments is thus limited. In addition, GBM is a biologically heterogeneous tumour and *clinically similar* patients may have fundamentally different survival outcome.

Aims of the project

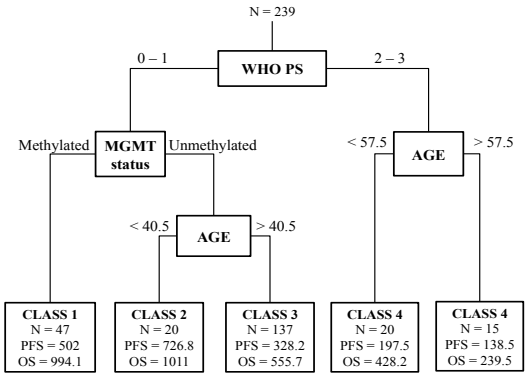
First, we will **update the clinical stratification of glioblastoma patients**, producing a prognostic model in a homogeneous population treated according to current standards of care. This will provide clinically more homogeneous prognostic patient groups.

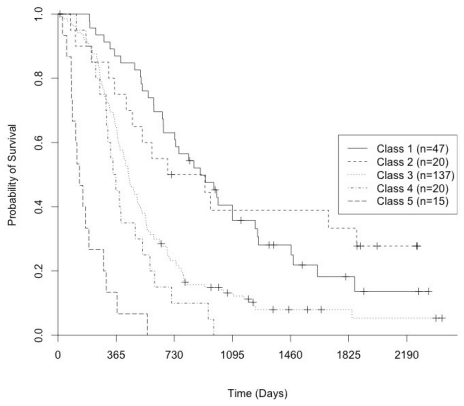
Second, based on this clinical analysis, **biological tumour markers** will be associated with survival differences *within* these prognostic groups.

Methods and Results

Sample: 239 patients from European Organization for Research and Treatment of Cancer (EORTC) treated according to the current gold standard (debulking surgery, radiotherapy plus concomitant and adjuvant temozolomide chemotherapy). We used recursive partitioning analysis to create a prognostic classification tree for GBM patients (left figure). PFS (progression-free survival) and OS (overall survival) are expressed in days.

Patients in Class 1, with good clinical performance (0 or 1) and MGMT promoter methylation, have a mean survival of nearly 3 years. Patients in Class 5, with low clinical performance and aged over 57.5 years, have a mean survival of 7 months. Survival difference between the groups are illustrated on Kaplan-Meier curves (right figure). This method of classification was then applied on two other patients samples from Liege University Hospital and TCGA (The Cancer Genome Atlas) and returned comparable results, with very similar age cut-offs.





Conclusions

In a first step, glioblastoma patients were stratified into prognostic groups with distinct survival. Patients with good clinical performance, a methylated MGMT promoter and younger age on average survive longer. These results **confirm** known clinical prognostic factors and **update** regression tree classification to populations treated according to the current treatment standard (Stupp protocol).

They also illustrate the **importance of stratification in clinical research,** which reduces potential misinterpretation of the treatment efficacy by significantly reducing confounding factors.

Perspectives

1. Further clinical study data is under request at the EORTC in order to increase patient numbers and significance of the obtained prognostic groups.
2. Since there still are short and long survivors in each prognostic group, **genetic factors** influencing survival will be assessed within these prognostic groups. The ultimate clinical goal is to refine prognostic predictions for individual patients to guide treatment strategies. Thus, prognostic signatures will be established, with the help of bioinformatic techniques, on the TCGA database. Existing molecular classifications (Verhaak, 2010) will be applied and new signatures defined within in the clinically homogenous groups (collaboration with Norlux Neuro-Oncology Laboratory and Genomics Research Unit, Luxembourg Institute of Health).
3. Prospective medical file data assembly and tissue collection are well under way in order to better anticipate tumour progression using these biological signatures.

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