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# **Malignant glioma**

- the impact of treatment,  
sociodemographic factors and  
metabolomics on survival

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## **Academic dissertation**

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The thesis will be defended in Swedish.

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Malignant glioma - the impact of treatment, sociodemographic factors and metabolomics on survival

**Abstract****Background**

Gliomas constitute a large group of brain tumors. Glioblastoma, isocitrate dehydrogenase (IDH)-wildtype is the most common and most aggressive type of glioma. The initial treatment often includes surgery and postoperative radiotherapy and/or chemotherapy. Despite extensive treatment, the overall survival for patients with glioblastoma, IDH-wildtype is short, around 10 months in an unselected patient cohort. The prognosis is affected by several factors related to the patient (for example age, world health organization (WHO) performance status (PS) and comorbidities), the tumor (molecular biology/mutations) and the given treatment.

**Aims**

The aim of this thesis was to investigate prognostic and predictive clinical, sociodemographic and metabolic factors in glioma, especially glioblastoma, IDH-wildtype.

**Methods**

Survival was studied for all adult patients with glioma, WHO grade 4 in northern Sweden from 1995–2015. Tumor tissues from 244 patients undergoing surgery for glioblastoma, IDH-wildtype or astrocytoma, IDH-mutant, grade 4 from 2005–2015 were collected and stored in a biobank. Clinical data on prognostic factors and treatment were collected and analyzed for the patients with a tumor tissue sample in the biobank (the biobank cohort). Metabolite analyses were performed on tumor tissue samples through mass spectrometry-based methods and the metabolite data were evaluated in relation to overall survival and time to next intervention.

Survival in relation to sociodemographic factors was studied for patients with glioma, WHO grade 1–4 using the RISK North database. In RISK North, the National Quality Registry for Central Nervous System Tumors and sociodemographic registries were linked to study socioeconomic status, cohabitation status, travel time to the regional hospital and region of residence. Socioeconomic status was estimated through educational level.

**Results**

In Study I, an increased survival from 6.9–10.3 months was observed over time for all glioblastoma patients in northern Sweden diagnosed between 1995–2015. Clinical prognostic factors were studied in the biobank cohort. In the multivariable analysis, longer survival was associated with younger age at diagnosis, good WHO PS, extensive surgery, type of postoperative treatment and absence of metabolic disease/diabetes and inflammatory disease.

In Study II, an association was found between higher educational level and longer survival for patients with glioma, WHO grade 3–4. No differences in prognosis were observed when analyzing cohabitation status, travel time to the regional hospital or region of residence for glioma, WHO grade 1–4.

In Study III, different metabolites were associated with survival and time to next intervention. For survival, the analysis highlighted mainly metabolites related to amino acid, carbohydrate, and fatty acid metabolism, and for time to next intervention, amino acids and amino acid metabolites. Three predictive metabolic markers were found in the group treated with resective surgery and radiochemotherapy: indolelactate, 5,6-dihydrouracil and uridine 5'-diphospho-N-acetylglucosamine. Prognostic and predictive metabolites were merged into scores that were associated with survival or time to next intervention in multivariable analyses adjusted for other prognostic factors.

**Conclusion**

This thesis enhances the knowledge of the factors associated with survival and treatment response in glioma. The progress in treatment is studied in a clinical setting where earlier known prognostic factors are validated, and new data is presented on sociodemographic factors and on metabolic markers. Glioblastoma is a disease with, in many cases a short, expected survival and there is a substantial need for continued research with the main goal to improve the treatment for the patients.

**Keywords:** Glioma, prognosis, treatment, sociodemographic factors, metabolic markers

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