Conditional probability of survival in patients with glioblastoma multiforme in the temozolomide treatment era

by M. McNamara et al.

A pilot study correlating IDH-1/2 gene status with 2-Hydroxyglutarate concentration in plasma and urine from patients with glioma

by G. Lombardi et al.

Discussant

Wolfgang Wick, Dep. Neurooncology, Heidelberg, Germany

Disclosure slide

- Advisory Boards: Roche, MSD, Merck, Eli Lilly, Apogenix, Magforce
- Speakers Bureaus: Roche, MSD
- Grants: Apopgenix, Boehringer Ingelheim, MSD
- Patent: IDH1 R132 antibody

Prognostic and predictive markers

Who is likely to have a less aggressive course of the disease by nature or by tretaments? - **Prognosis**

Who should receive a certain therapy, RT, TMZ or Bevacizumab? - **Prediction**

What should I tell my patients? – **Day-to-Day Medicine**

Prognostic and predictive markers

Poster by E. Franceschi looking for a relation between the time off adjuvant TMZ and the interval of the second progression.

Outcome: Patients with a longer time from halting first intervention (TMZ) until 1. PD are more likely to have a longer time until 2. PD

Support: Perry et al. J Clin Oncol 2010 RESCUE

Introduction

- Conditional probability of survival is defined as the probability of surviving to some Y years after diagnosis given survival to some X years (X < Y).

- More relevant in the temozolomide treatment era as predictor of continued survival as long term survivorship is now being observed.

Study population

- **882 consecutive patients** (median age 62 [18-93] years), who presented to Princess Margaret Hospital, Toronto with a new diagnosis of glioblastoma multiforme from January 2004 – August 2010.

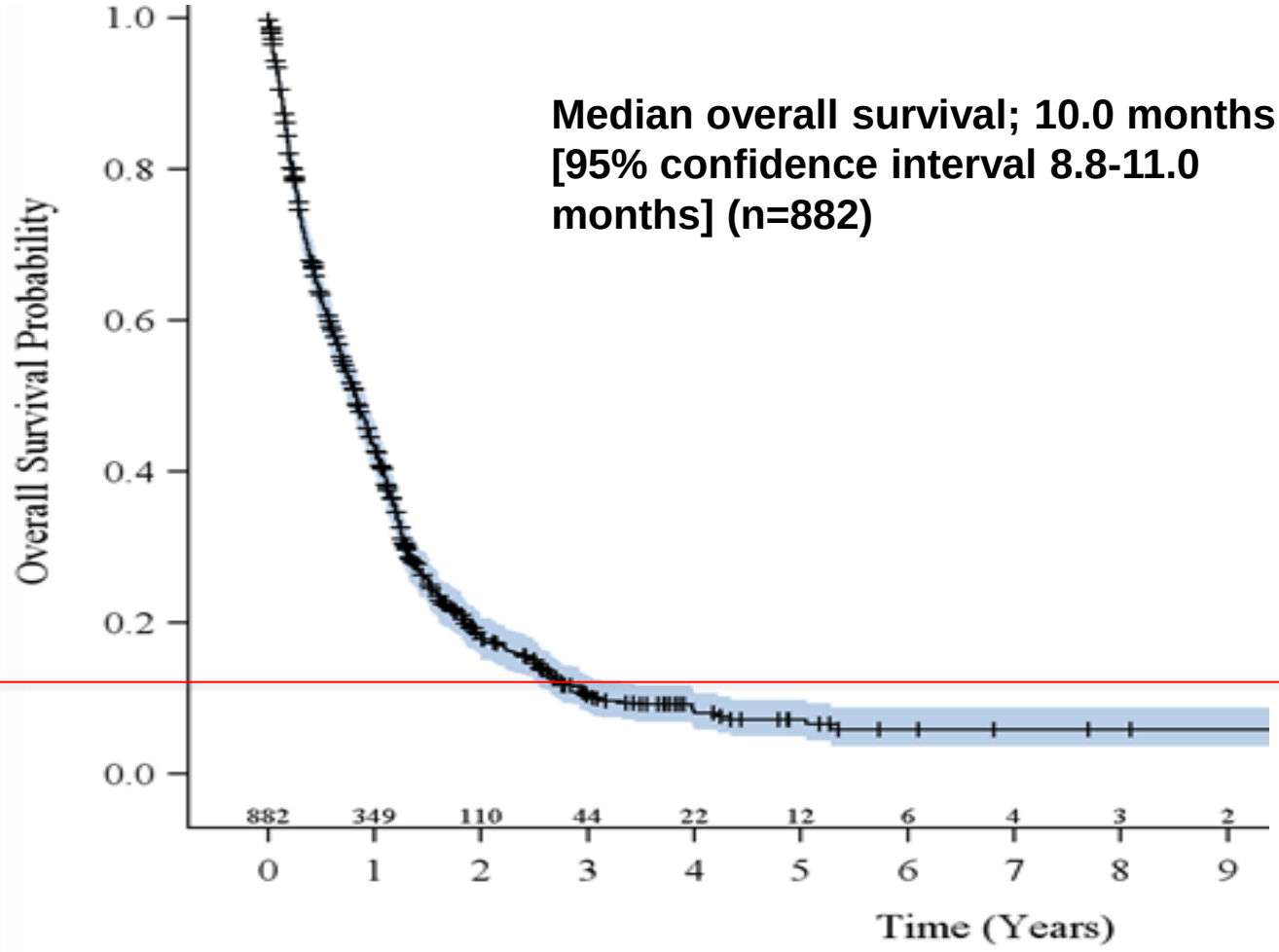
- Median follow up time of all patients was 8.8 months and for censored patients was 16.3 months.

Methods

- Conditional probability of surviving to 2 years, given survival to 1 year was calculated by dividing the 2 year survival rate by the 1 year survival rate.
- Conditional probabilities for other time intervals were calculated similarly.
- Confidence intervals were estimated using a variation of the “Greenwood’s formula” for unconditional survival.*

» *Davis *et al*., 1999, Cancer 85: 485-491

Overall survival curve



Median overall survival; 10.0 months [95% confidence interval 8.8-11.0 months] (n=882)

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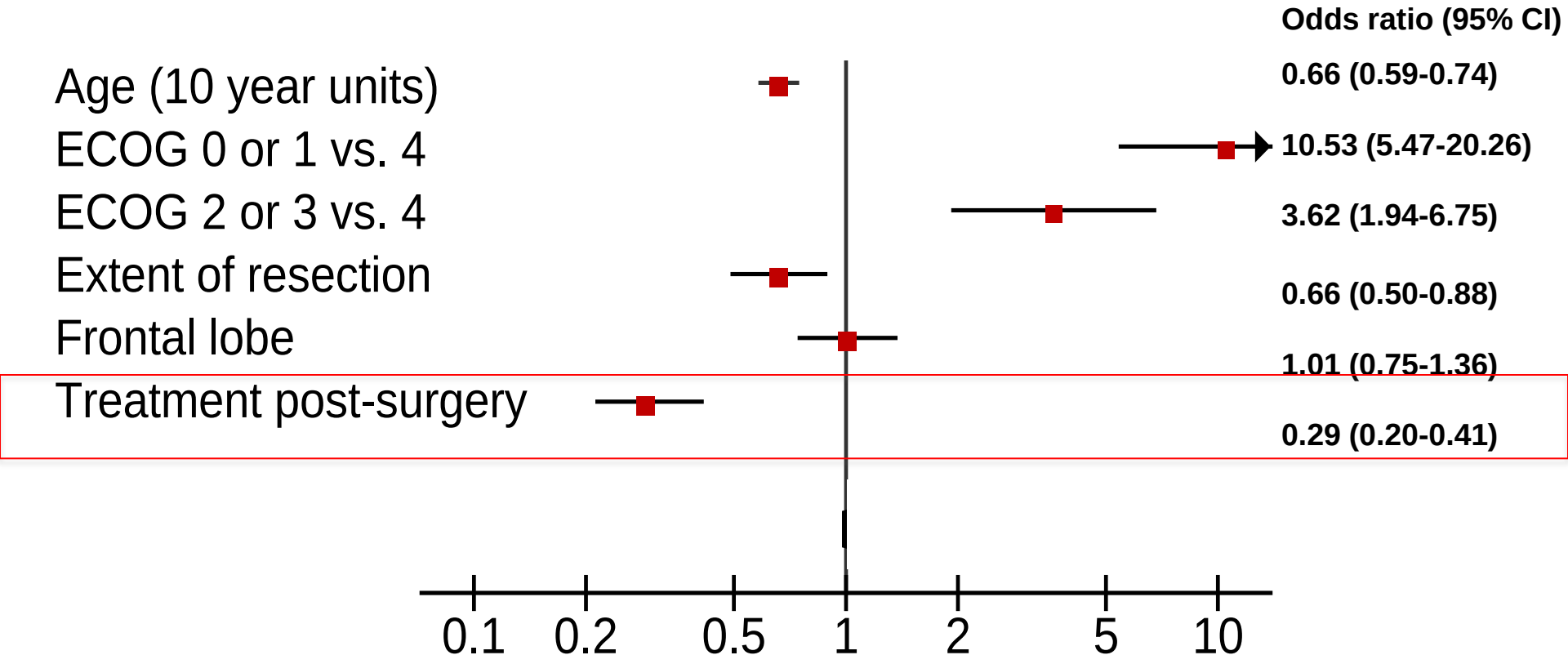
Characteristics of glioblastoma patients surviving > 60 months (n=12)

- 66% Male.
- Performance status 0-1.
- Age </= 58 years.
- 75% had partial/subtotal resection.
- 58% never relapsed following initial concurrent radiotherapy/temozolomide + adjuvant temozolomide.

Impact of clinical variables on overall survival (multivariable analysis)



ECOG; Eastern Cooperative Oncology Group performance status, CI; confidence interval. Log logistic model fits data better.

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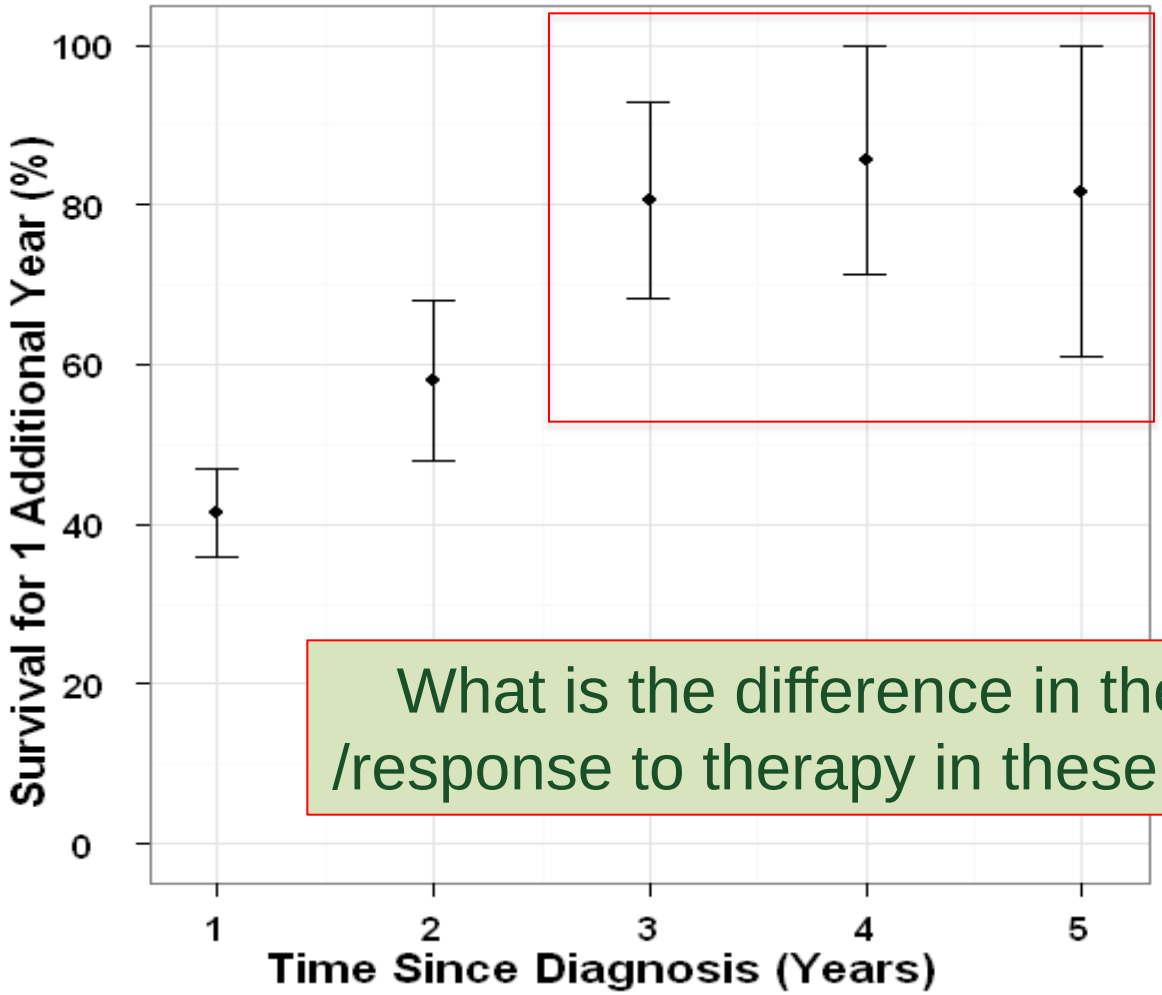
Conditional probability of surviving an additional year at various time points



What is the difference in the tumor /response to therapy in these patients?

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Nomograms from EORTC 26981/22981 NCIC CE.3 – newly diagnosed tumors

MGMT, age, performance status, extent of resection, and MMSE influence outcome and should be used as stratification factors

Nomograms can be used to predict an individual patient's prognosis, and they integrate pertinent molecular information that is consistent with a paradigm shift towards individualised patient management.

DISCUSSION: in reality patients use nomograms to calculate their survival chances

Gorlia et al. Lancet Oncol 2008

Prognostic factors from pooled EORTC trials– recurrent tumors

300 patients with recurrent glioblastoma recruited in eight phase I or II trials conducted by the EORTC Brain Tumour Group

Performance Status or > 1 lesion -> ↓ PFS and OS.

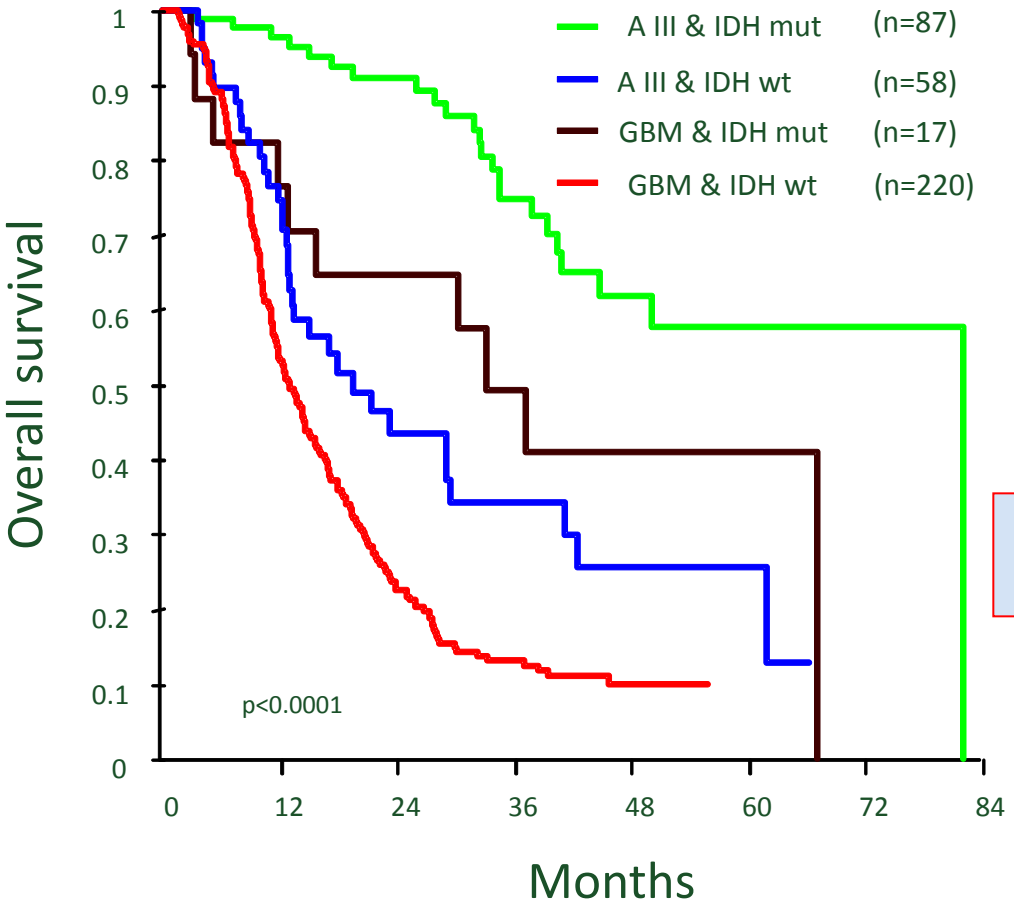
largest lesion (⩾42mm) and treated with steroids -> ↓ OS.

Frontal tumors (IDH?) -> ↑ OS

PS and multiplicity of lesions but not age influence PFS and OS

DISCUSSION: selected patients with non-resected tumors, heterogenous therapies and limited upper age

IDH in glioma



WHO-Grade

- Anapl. astrocytoma IDH1-mut
- GBM IDH1-mut
- Anapl. astrocytoma IDH1-wt
- GBM IDH1-wt

each

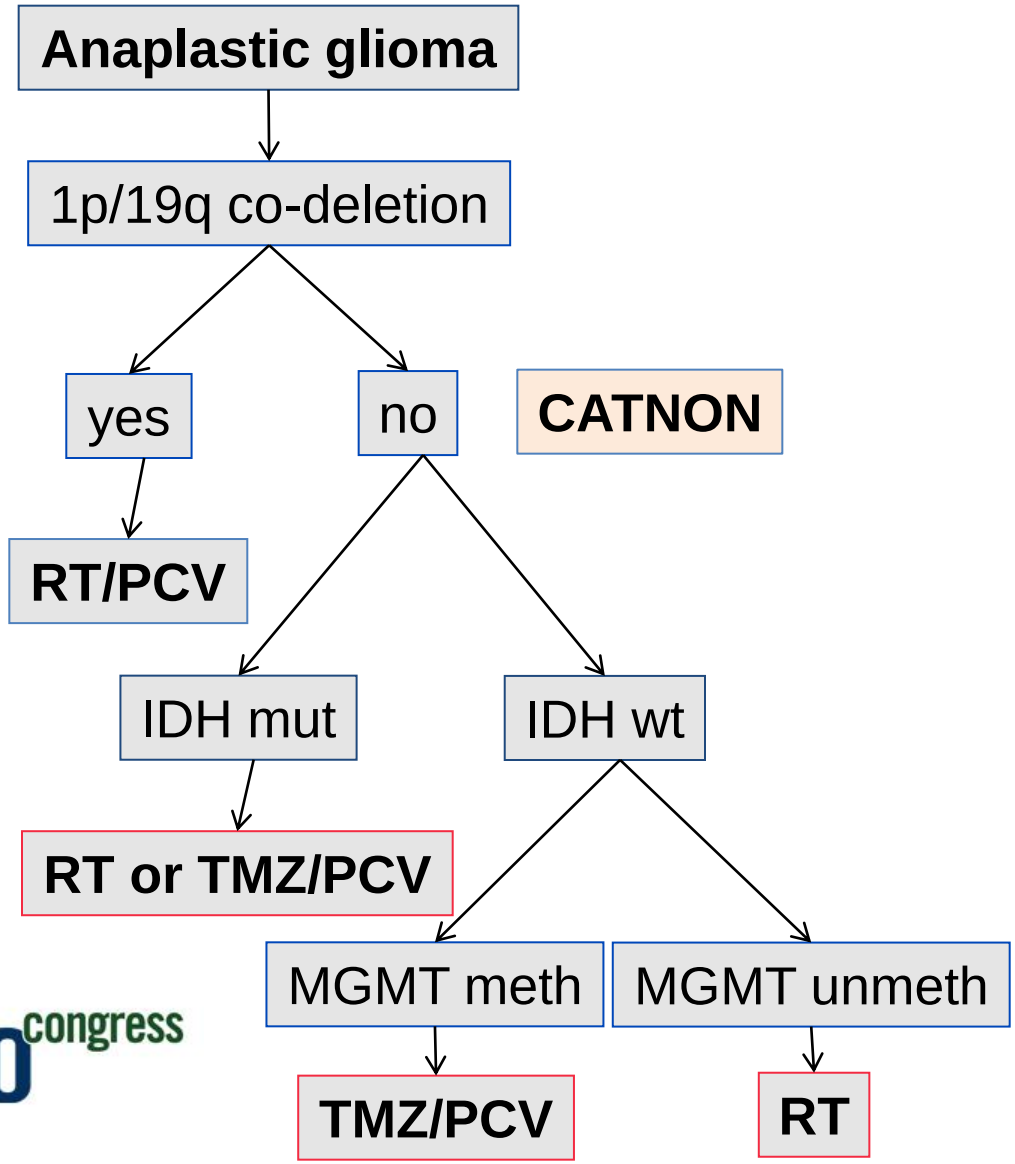
- MGMT meth.
- MGMT unmeth.

VIENNA 2012 ESMO congress

Hartmann et al. Acta NP 2010

Deutsches Gliomnetzwerk

IDH in glioma: the practical approach



IDH in glioma: can we detect mutant tumors by imaging?

NCT

- MR Spectroscopy to detect changes in the rheostat of 2-Hydroxyglurate and Ketoglutarate?

- Spectroscopy for further metabolites of the citrate cycle?

- Preferential frontal localization?

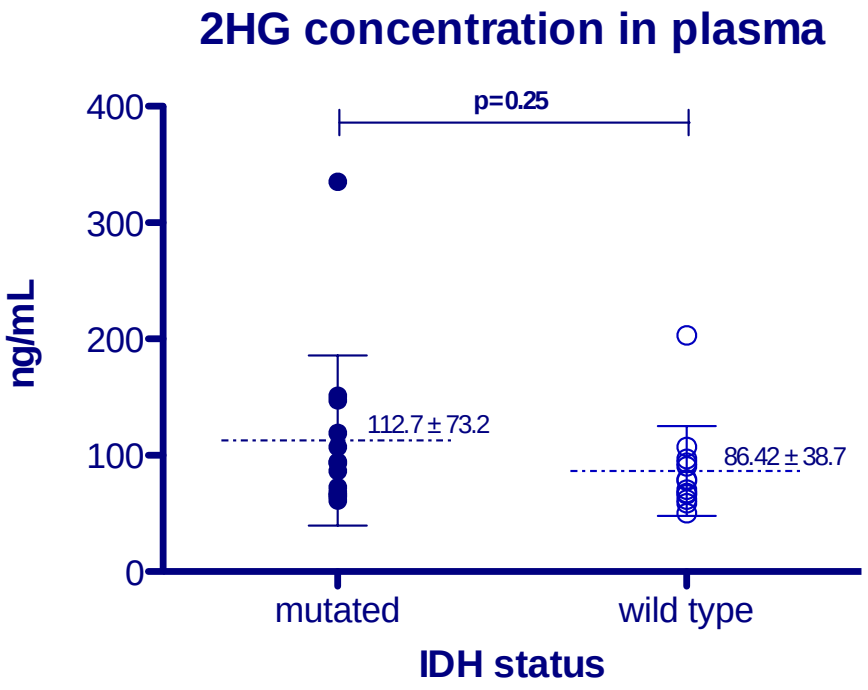
Aims of the Study

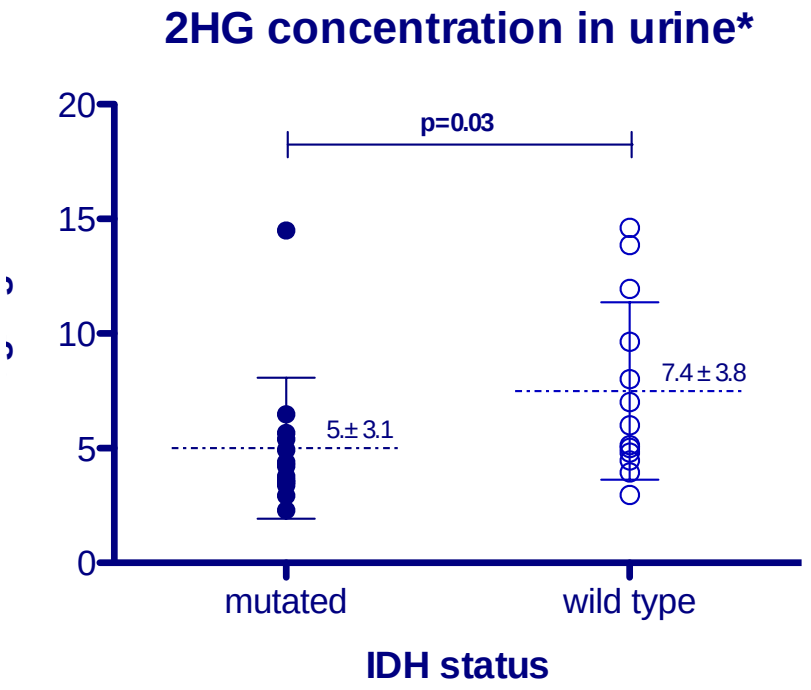
- Investigate the effect of mutant and wild-type IDH1/2 genes on **plasma and urinary 2HG** concentration in patients with glioma

- Investigate the correlation between **tumor volume/grade and 2HG concentration** in plasma and urine

- Investigate whether mutant IDH1/2 may influence the plasma and urinary concentrations of **other metabolites** involved in the citric acid cycle

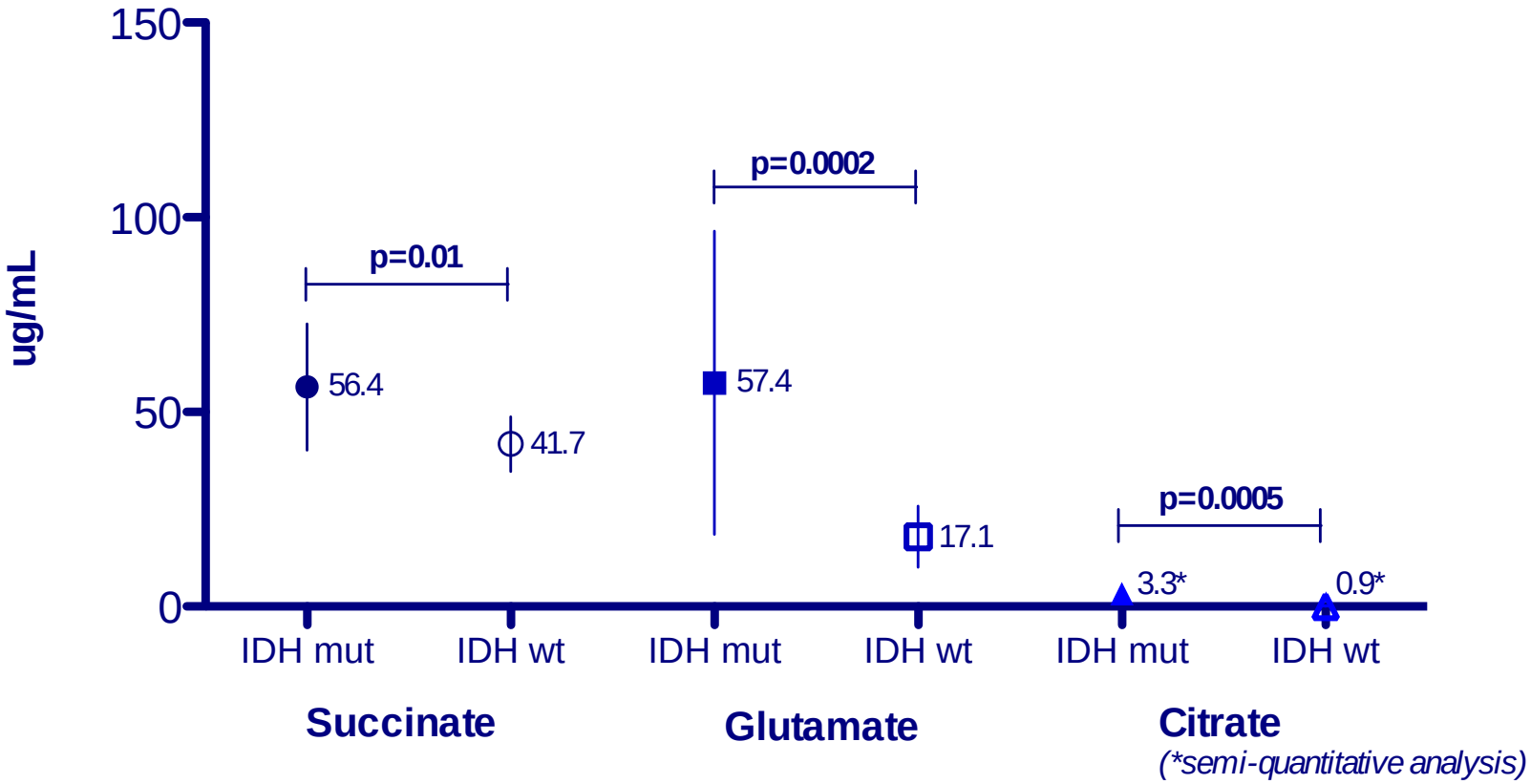
Differences in the sensitivity between plasma and urine analyses





*normalized by creatinine concentration

Concentrations of other metabolites in plasma



Statistically significant differences of succinate, glutamate and citrate concentrations between patients with mutant and wild-type IDH were detected *(Mann-Whitney test)*

Summary –basically negative

Urinary 2HG concentration in patients with mutant IDH was statistically lower than patients with wild-type IDH and there was a trend for a correlation with tumor size

No statistical difference in **plasma 2HG concentration** was observed between mutant and wild-type IDH and no association with tumor volume was found

In patients with mutant IDH **succinate, glutamate and citrate** had statistically higher plasma concentrations, but no associations with tumor volume were detected

Tumor grade did not correlate with plasma and urinary 2HG concentrations in mutant IDH gliomas

Conclusions

This is the first study analyzing the concentrations of citric acid cycle related metabolites in both plasma and urine from glioma patients with mutant IDH gene.

The aim to predict IDH mutations or monitor tumor growth or therapy response failed.

Unclear, whether this is due to insufficient technology, heterogeneity or inappropriate bioresources.

Attempts to do these analyses from microvesicles are awaited.