Prognostic and predictive value of MGMT evaluated by immunohistochemistry in a series of glioblastoma multiforme

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Background

- The presence of the repair enzyme MGMT (O^6-methylguanine-DNA methyltransferase) in glioblastoma multiforme (GBM) cells has been correlated negatively to prognosis and response to chemotherapy[2].
- The value of immunohistochemistry (IHC) in assessing MGMT status has been questioned and methylation specific polymerase chain reaction (PCR) has shown greater accuracy and consistency[1].
- PCR is relatively complicated, time-consuming and has practical disadvantages.
- GBM's are heterogeneous tumors and may harbor focal areas of MGMT positivity, rendering tissue micro array (TMA) analysis insufficient.

Aim

To examine the value of MGMT immunohistochemistry of *whole tumor slides* as a prognostic and predictive factor in a retrospective series of GBM

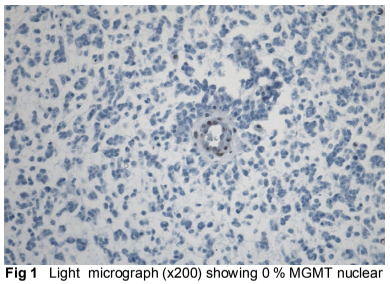


Fig 1 Light micrograph (x200) showing 0 % MGMT nuclear staining in GBM cells. Note the staining endothelial cells which serve as positive controls.

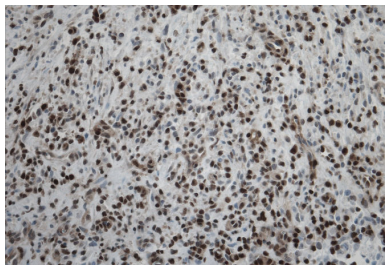


Fig. 2 Light micrograph (x200) showing >50 % MGMT staining in GBM cells.

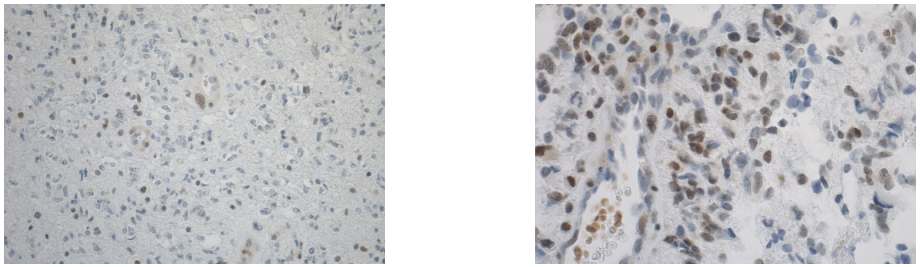


Fig. 3 Light micrographs (x 200/400) of the same tumor specimen showing areas of no or little MGMT staining (left picture) and **focal** areas of high MGMT staining (right picture).

Materials and Methods

Patients

- 96 consecutive patients with GBM treated at Copenhagen University Hospital between march 2005 and may 2008.
- All patients received standard chemoradiation and adjuvant temozolomide (Stupp/EORTC-NCIC regimen)[3]

Baseline characteristics

	n = 96
Age	
median (range)	58 (31-75)
ECOG performance status (%)	
0	63
1	26
2	11
Extent of surgery (%)	
Biopsy	16
Partial resection	53
Complete resection	31

Immunohistochemistry of GBM whole tumor slides

- Paraffin embedded histological tumor slides were stained using the Chemicon monoclonal mouse anti-MGMT, Clone 1:200 (MAB 16200) antibody.
- Presence of MGMT was evaluated semiquantitatively and divided into four groups, but also dichotomized as negative or positive as follows:
  - 0% cells staining
  - 0-10 % cells staining — negative
  - 10-50 % cells staining
  - >50 % cells staining — positive
- In heterogeneous tumors, focal areas of positivity translated into overall positivity.

Pathology review

- All slides were evaluated by two examiners. In case of disagreement, final answer was reached by consensus.

Statistics

All statistics were calculated using SPSS 15.0 software.

Ethics

The study was approved by the local ethics comitee of Region Hovedstaden (journal nr. H-C-2008-095)

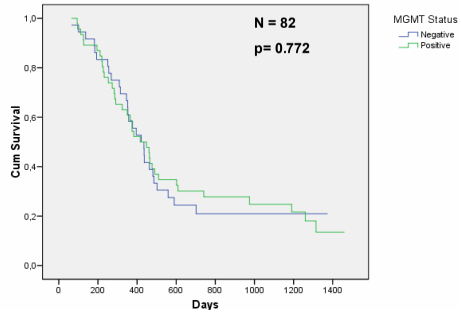
Results of MGMT immunostaining

Total number of patients:	96	
tumor slides available for MGMT analysis	89	
Positive controls	82	
0% cells staining	2.4%	Negative = 43.9 %
0-10 % cells staining	41.5%	
10-50 % cells staining	43.9%	Positive = 56.1 %
>50 % cells staining	12.2 %	

Multivariate analysis by Cox Regression

Variable	Exp(B) – Hazard rate	Significance
Age (>/< median 58 years)	1.828	0.058
WHO performance status	1.347	0.199
Extent of surgery	0.933	0.765
MGMT positive or negative	0.789	0.456

Overall survival by MGMT status



Results

- Expression of MGMT evaluated by IHC on whole tumor slides was heterogeneous. Focal areas of positivity could be identified in several cases.
- MGMT immunostaining was negative in 43.9 % and positive in 56.1 % of tumors. Interobserver agreement was acceptable at approximately 80 % of cases.
- Positive MGMT immunostaining was not correlated to either prognosis or response to standard treatment with radiotherapy and temozolomide.
- Survival analysis of all 96 patients shows a significant number of patients surviving beyond 3 years. Age seems to be the single most important prognostic factor.

Conclusions

The value of MGMT immunohistochemistry as a prognostic and/or predictive factor seems limited.
Longer term survival with GBM is probably becoming increasingly frequent, especially in younger patients.

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References:

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