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# Optimizing Glioblastoma Trial Design: A Prognostic Model Harnessing Real-World Data and Genomic Alterations

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## Background

Glioblastoma (GBM) patients receiving standard therapy have a variable prognosis with a median overall survival (OS) of less than 18 months.

Prognostic modelling is needed for matching comparable patient groups for clinical trials.

## Methods

**Patients**

From a clinical database, all GBM IDHwt patients who received standard therapy in year 2016-21 at Copenhagen University Hospital - Rigshospitalet (Training cohort) and at Odense University Hospital (Validation cohort) were included.

**Candidate genomic biomarkers**

Tumor tissue was analyzed by WES, WGS or panel sequencing. (1)Pathogenic or likely-pathogenic SNVs, indels, and fusions; (2) amplifications; and (3) bi-allelic deletions. Gene alterations present in >5% of samples were selected as candidate factors.

**Statistics**

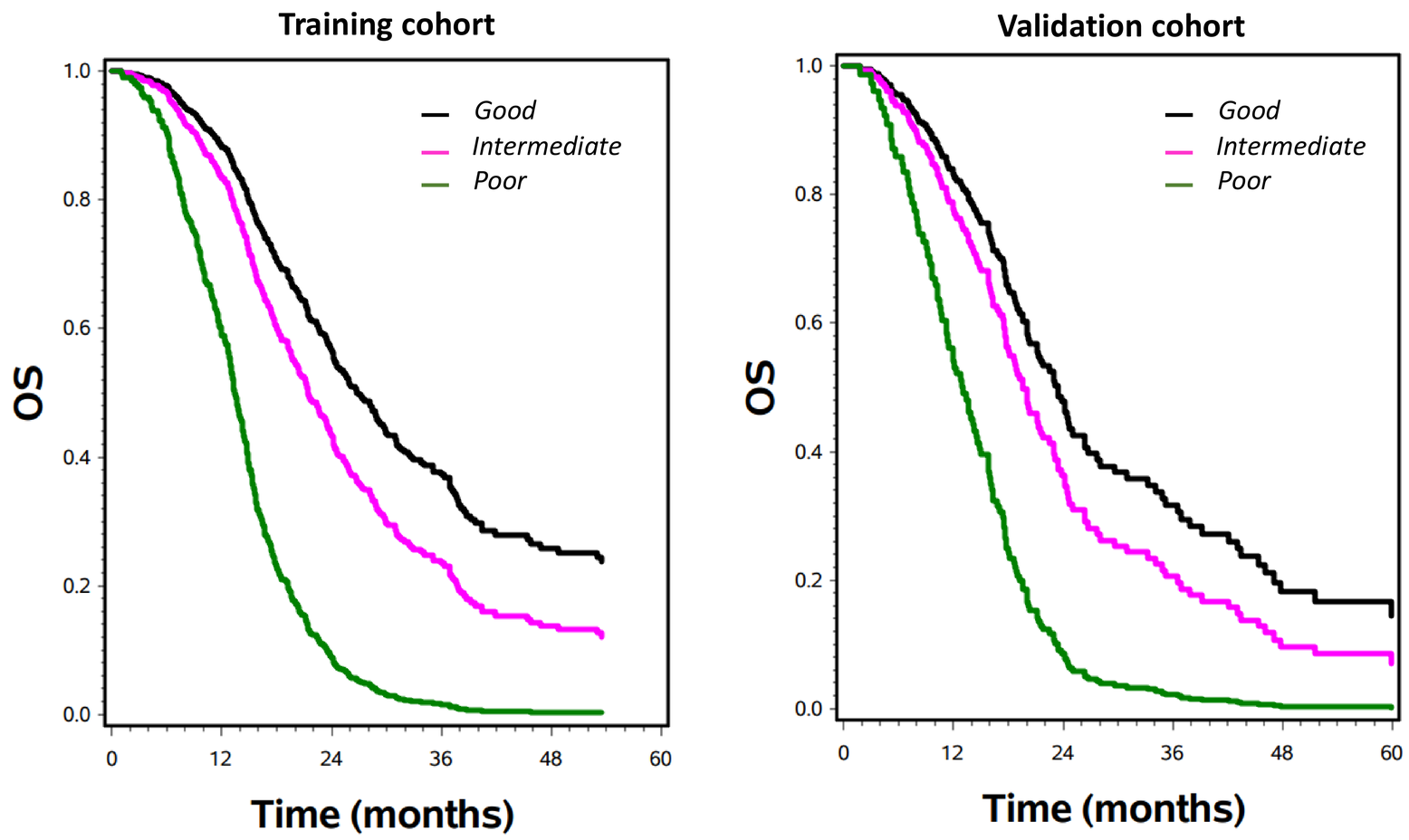
Cox-regression analysis was used for modelling OS and progression-free survival (PFS). A clinical prognostic model was established using multivariate analysis. Genes associated with survival ($p < 0.20$) were considered for inclusion in the clinical prognostic model.

## AIM: Establish and validate a prognostic model for GBM patients based on clinical factors and genomic alterations

## Results

| **Table 1. Patient characteristics** | Training *n = 370* | Validation *n = 160* |
|---|---|---|
| Median age, years (range) | 59 (17-78) | 64 (36-79) |
| Male gender, n (%) | 228 (61.6) | 98 (61) |
| ECOG PS 0-1, n (%) | 392 (94.3) | 135 (84) |
| Methylated *MGMT*, n (%) | 217 (58.6) | 80 (50) |
| Multifocal disease, n (%) | 59 (15.9) | 16 (10) |
| Resection, n (%) | 180 (89) | 134 (84) |
| MRI surgical extent, n ( %) | | |
| *Measurable* | 71 (19.2) | 44 (28) |
| *Non-measurable* | 93 (25.1) | 15 (9) |
| *No residual contrast* | 108 (29.2) | 73 (46) |
| *Biopsy* | 67 (18.1) | 26 (16) |
| Corticosteroid use, n (%) | 167 (45.1) | 54 (34) |
| Subependymal, n (%) | 150 (40.5) | No data |
| Median PFS (95% CI), months | 7.6 (6.8-8.3) | 8.9 (7.9-9.5) |
| Resection at relapse, n (%) | 127 (34.3) | 58 (36) |
| Second line therapy, n (%) | 258 (69.7) | 121 (76) |
| Median follow-up time, months (range) | 68.4 (30.0-95.6) | 65.8 (45.5-65.8) |
| Median OS (95% CI), months | 17.7 (16.3-19.4) | 17.7 (15.9-19.6) |

**Figure 1. Estimated survival based on prognostic groups**




**Three prognostic groups based on the final model**

| **Prognostic group** | **Good** | **Intermediate** | **Poor** |
|---|---|---|---|
| Resection | Yes | Yes | Yes |
| Methylated *MGMT* | Yes | Yes | No |
| Multifocal disease | No | No | Yes |
| ECOG PS | 0 | 1 | 1 |
| Cortocosteroid use | No | Yes | Yes |

**Table 2. Clinical factors associated with OS in multivariate analysis**

| | **HR (95%CI) *p*-value** |
|---|---|
| Age, 10-year increase | 1.09 (0.97-1.22) *p = 0.15* |
| Multifocal disease | 1.91 (1.40-2.62) **p < 0.01** |
| Resection | 0.92 (0.68-1.25) *p* = 0.60 |
| Unmethylated *MGMT* | 2.12 (1.66-2.70) **p < 0.01** |
| Corticosteroid use | 1.31 (1.03-1.66) **p = 0.03** |
| ECOG-PS 1 vs. 0 | 1.16 (0.90-1.48) *p* = 0.25 |
| ECOG-PS 2 vs. 0 | 1.88 (1.09-3.24) **p = 0.02** |

**Table 3. Multivariate analysis of genomic alterations added to the final prognostic model**

| | | **Training** | **Validation** |
|---|---|---|---|
| | | **HR (95%CI) *p*-value** | |
| ***NF1* alteration** | **OS** | 1.66 (1.05-2.61) **p = 0.03** | 1.24 (0.71-2.16) *p* = 0.46 |
| | **PFS** | *2.30 (1.45-3.56)* **p < 0.01** | 1.62 (0.94-2.82) *p* = 0.09 |
| ***RB1* alteration** | **OS** | 0.54 (0.35-0.85) **p < 0.01** | 0.38 (0.13-1.08) *p* = 0.07 |
| | **PFS** | 0.67 (0.44-1.02) *p* = 0.06 | 0.36 (0.14-0.88) **p = 0.03** |

## Conclusions

- A clinical prognostic model was established comprising 5 poor prognostic factors:
  - Unmethylated *MGMT*
  - Multifocal disease
  - Performance status
  - No tumor resection
  - Corticosteroid use
- Our clinical model was validated in an independent cohort with a concordance index of 0.65 ($p < 0.001$).
- *NF1* alteration was found to negatively impact prognosis
- *RB1* alteration was associated with a better prognosis

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