Integrating machine learning and immunology: a path to predicting and engineering glioblastoma outcomes

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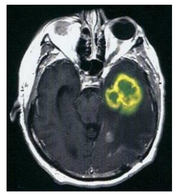
Glioblastoma (GBM): an invasive, challenging to treat cancer

- IDH-wild, WHO grade 4 astrocytoma with diffusive infiltrative growth[1]
- Median progression-free survival: 9-10 months, median overall survival ~15 months, and low 5 year survival[1,2]
- Treated by Stupp protocol: surgery, chemoradiation, maintenance chemotherapy[2]
- At recurrence, patients are eligible for clinical trials

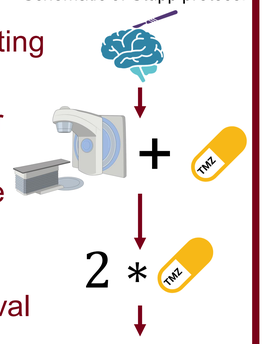


MRI image (contrast enhanced T1-weighted) of GBM. From /www.aboutcancer.com/mri_gbm.htm

GBM immune effects and treatments

- Tumor microenvironment enriched in myeloid-derived suppressor cells modulating cytotoxic T-cell behavior[3,4]
- Surgery and corticosteroids further impair immunity while radiotherapy and temozolomide deplete circulating immune cells counts[5,6]
- White blood cell (WBC) counts have prognostic links to progression-free survival and overall survival[7]
- Serial WBC counts may capture dynamic effects of tumor progression and treatment, providing signals for decision support and modeling evaluation/endpoints[8]

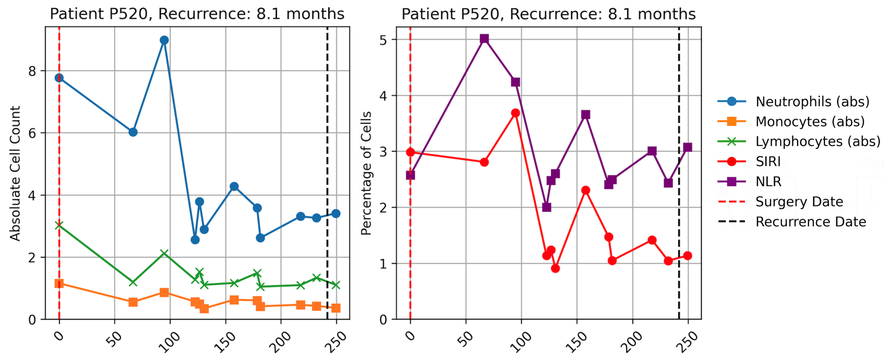
Schematic of Stupp protocol



Objective: GBM recurrence biomarker for clinical application and model assessment

- *Original objective*: Mechanistic systems model of MDSC, T-cell, and tumor interactions to optimize radiotherapy
- *Revised objective*: Pivoted to data-driven survival modeling using routine WBC cell counts for its immediate clinical applicability and form a foundation for upcoming translational dynamic modeling
- Aim: Generate a dynamic, clinically accessible risk score to drive earlier clinical trial entry and support model-informed treatment planning and design

Method: Determining recurrence indicators

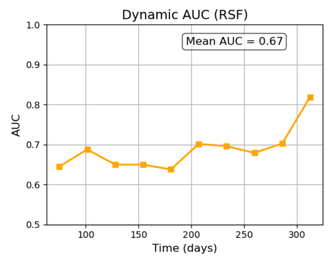


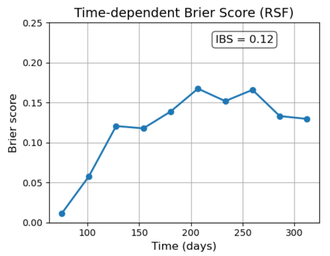
Example patient time course. Left: WBC subpopulations. Right: SIRI and NLR

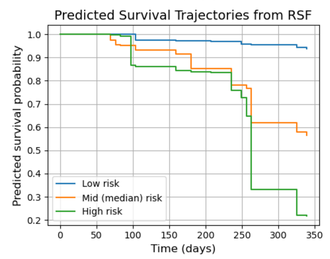
- Retrospective cohort (n=39) of Cleveland Clinic patients; 663 peripheral WBC counts with differential (subpopulation counts)
- Time frame: peri-operative through chemoradiation and maintenance phase to recurrence
- Data: neutrophil, lymphocyte, and monocyte counts with derived static (max/min/range/etc) and time-varying features: neutrophil to lymphocyte ratio (NLR), (neutrophil*monocyte)/lymphocyte (SIRI)
- Model with Cox proportional hazard random survival forest

Results

- Used cluster-based prescreening and elastic net for feature selection in Cox model
- Model (both static and time-varying) struggled due to noisy data and small data set, lacking significant C-index
- Preliminary discrete-event random survival forest used dynamic features and landmarking to approximate recurrence risk
- Best predictors were SIRI, monocytes, and NLR (via permutation analysis)
- Yielded concordance score nearing significance (C-index = 0.622; 95% CI: 0.502-0.751)
- Additional metrics reinforce the presence of predictive signal: AUC_t, time-dependent Brier scores and rank ordering of predicted survival curves from low to high risk







Discussion

- Preliminary modeling of peripheral WBC features show modest prognostic value
- Random survival forest model captured a signal (C-index 0.622) from time series monocytes, NLR and SIRI
- Static and time-varying Cox proportional hazard models failed to capture signal, likely due to noise in data and small cohort size, highlighting the need for models that can handle nonlinear relationships
- Presence of predictive signal in routine clinical data suggest feasibility of integrating statistical model metrics into clinical decision tools

Outlook

- Expand features to include time-derivates, weighting of time points near recurrence, and additional clinical covariates (e.g. steroid use)
- Develop and integrate a mechanistic WBC count model and tumor-immune (including MDSCs) microenvironment
- Use survival model to assess mechanistic model outputs to optimize treatments (radiotherapy hypofractionation vs. SOC) and test agents such as ibudilast via *in silico* virtual clinical trials[9,10]
- Advance refined WBC count biomarker to the clinic in collaboration with partners and offer clinically testable treatment regimens to community

Mechanistic TIME and treatment model

References

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