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Glioblastoma treatment, end-of-life resource utilization, and outcomes in Ontario

Y Ellenbogen (Toronto) S Taslimi (Kingston) R Alkins (Kingston)*

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Background: The end-of-life (EoL) phase of care is pivotal for glioblastoma (GBM) patients. While early integration of palliative care has shown benefits in various cancer types, its role in GBM care remains underexplored. This study aims to characterize EoL care patterns in GBM patients, assessing their temporal evolution, regional disparities, and socioeconomic influences. Methods: This is retrospective study of all patients with GBM treated in Ontario between 1994 and 2018 using the ICES data repository. Variables analyzed included patient demographics, comorbidities, palliative care utilization, and aggressive/supportive care components. Results: We identified 9,013 GBM patients within the study period. There was a gradual increase in palliative care utilization over time, accompanied by a decrease in in-hospital deaths. However, the proportion of patients receiving chemotherapy in the last 14 days of life increased. Multivariate logistic regression found socioeconomic status influenced palliative care access and rural patients also had a higher rate of in-hospital deaths, possibly due to limitations in outpatient palliative care services. Conclusions: The findings in this study clarify the status of EoL care for GBM patients within Ontario, and demonstrates key areas for future research, underscoring the need for standardized EoL care practices to enhance the quality of care for GBM patients.

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Transfer RNA fragments in patient plasma extracellular vesicles as biomarkers of high grade glioma

T Phinney (Halifax) A Alwadei (Halifax) J Han (Halifax) K Attwood (Halifax) M MacNeil (Halifax) G Wajnberg (Moncton) J Roy (Moncton) A Weeks (Halifax)*

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Background: High-grade gliomas (HGG) present challenges with short post-surgery survival and high progression rates. Extracellular vesicles (EVs) in the tumor microenvironment (TME) contribute to a pro-tumorigenic setting. Investigating Transfer RNA fragments (TfRNA) in HGG patient plasma EVs reveals potential biomarkers and therapeutic targets, shedding light on the molecular landscape for enhanced diagnostic and therapeutic strategies. This study examines TfRNA in 10 HGG patients at diagnosis, offering insights into the molecular landscape for improved management strategies. Methods: The study involved the collection of plasma samples from HGG patients and controls. EVs were isolated from these samples and subsequently analyzed for tfRNA. Results: Analysis of plasma EVs highlighted distinct differences in TfRNA fragments between High-Grade Glioma (HGG) and control samples. HGG EVs showed a global reduction in tRNA content, higher 5' tfRNA proportions, and increased nuclear tfrna compared to controls. A notable biological marker, elevated in HGG, holds potential as a diagnostic indicator. Conclusions: Our study concludes that High-Grade Gliomas (HGG) demonstrate a global reduction in tfRNA content in plasma extracellular vesicles compared to non-cancer controls, echoing findings in other cancers. Despite this, specific tfRNA molecules in HGG show significant differential expression or sorting into EVs, indicating their potential as future biomarkers or therapeutic targets.

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Plasma extracellular vesicle sampling from high grade gliomas demonstrates a small RNA signature indicative of disease and identifies lncRNA RPPH1 as a novel biomarker

J Han (Halifax) K Attwood (Halifax) J Roy (Moncton) A Weeks (Halifax)*

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Background: High grade gliomas (HGGs) and cells of the tumour microenvironment secrete extracellular vesicles (EVs) into the plasma that contain genetic and protein cargo which function in paracrine signalling. Isolation of these EVs and their cargo could lead to an important tool that can inform on diagnosis and disease-course of HGGs. Methods: EVs were isolated using Vn96 capture from plasma obtained longitudinally from HGG patients. sRNA was enriched from the EVs, followed by next-generation sequencing, multidimensional scaling, differential expression, and *in silico* functional enrichment analyses. Results: Over 750 differentially expressed sRNA were identified between HGG and controls. Pathway analysis revealed miRNA highly enriched in both EV and HGG pathways demonstrating the validity of results in capturing a signal from HGG. Other sRNA included several novel HGG plasma-EV biomarkers including lncRNA *RPPH1*, *RNY4,* and *RNY5*. Furthermore, in paired longitudinal patient sampling, *RPPH1* informed on surgical resection (decreased on resection) and importantly increased again with clinically defined progression. TCGA analysis demonstrated increased expression of *RPPH1* in HGG tissue and additionally, higher expression of *RPPH1* was associated with a worse disease-specific prognosis. Conclusions: The present study supports the role of plasma-EV sRNA sampling (and particularly *RPPH1*) as part of a multi-pronged approach to HGG disease course surveillance.

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Integration of Ultrasensitive electroluminescent immunoassay and cell-free DNA methylation analysis for the non-invasive discrimination of adult diffuse gliomas

A Ajisebutu (Winnipeg) M Chatanaka (Toronto) V Patil (Toronto) I Prassas (Toronto) D Eleftherios (Toronto) G Zadeh (Toronto)*

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Background: Gliomas are highly aggressive brain tumors with nearly universal recurrence rate. Despite this, the ability to accurately predict tumor recurrence relies solely on serial MRI imaging, highlighting the need for prognostic biomarkers. Due to

the low accuracies of individual serum markers, we have proposed the use of an integrated, multi-platform approach to biomarker discovery. Methods: A cohort of 107 glioma plasma samples, including 30 pairs, underwent plasma proteomic, consisting of a panel of serum proteins (FABP4, GFAP, NFL, Tau and MMP3,4 &7) quantified through ultrasensitive electrochemiluminescence multiplexed immunoassays, and plasma DNA methylation analysis, captured through cell-free methylated DNA immunoprecipitation and high-throughput sequencing. Results: Unsupervised hierarchal clustering revealed robust separation of primary and recurrent tumors through plasma proteomics, associated with a distinct plasma methylation signature. NFL, Tau and MMP3 levels differed between primary and recurrent samples; pair-wise analysis revealed increased in NFL and Tau concentrations upon recurrence. Tau levels predicted outcome independent of WHO Grade and IDH status. A predictive model created through the integration of the proteomic and methylation signatures revealed an AUC of 0.83. Conclusions: The combination of DNA methylation and plasma proteomics showcases that an integrative approach may improve the ability of these techniques for the serial monitoring of gliomas patients.

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Automated pituitary adenoma segmentation for radiosurgery with deep learning-based model

N Balasubramaniam (Laval) M Cerny (Praha) J May (Praha) L Hamackova (Praha) J Novotnyml (Prague) D Barucic (Prague) J Kybic (Prague) M Majovsky (Praha) H Hallak (Riyadh) R Liscak (Prague) D Netuka (Praha)*

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Background: Pituitary adenomas are treated with endoscopic surgery, while stereotactic radiosurgery addresses complex cases. Our study highlights AI's role in accurate segmentation, improving treatment planning workflow efficiency Methods: In a retrospective study at Na Homolce Hospital (January 2010 to October 2022), SRS for pituitary adenomas was analyzed. Data were split 80:20 for training and validation. Using nnU-net, a medical image segmentation tool, a model predicted precise tumor, optic nerve, and pituitary gland segmentation. Accuracy was evaluated quantitatively with Dice similarity coefficient and qualitatively by human experts. The study explored the impact of tumor volume and hormonal activity status on segmentation accuracy. Results: The study comprised 582 and 146 patients in training and validation sets, respectively. The model achieved Dice similarity coefficients of 83.1% (tumor), 62.9% (normal gland), and 78.0% (optic nerve). Expert assessments deemed 41% directly applicable, 31.5% needing minor adjustments, and 27.4% unsuitable for clinical use. Larger tumor volume and non-functioning adenomas correlated with higher accuracy. Including T2 weighted scans improved DSC for optic nerve and normal gland. Conclusions: The study showcases deep learning's potential in automating pituitary adenoma segmentation from MRI data, particularly excelling in large, hormonally inactive macroadenomas. Encourages collaborative use with clinicians for improved neurosurgical patient care.

Neurocritical Care

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Prognostic value of NIRS regional oxygen saturation based cerebrovascular reactivity in TBI: a Canadian high resolution traumatic brain injury (CAHR-TBI) cohort study

A Gomez (Winnipeg) L Froese (Winnipeg) D Griesdale (Vancouver) EP Thelin (Stockholm) R Raj (Helsinki) L van Iperenburg (Maastricht) J Tas (Maastricht) M Aries (Maastricht) KY Stein (Winnipeg) C Gallagher (Calgary) F Bernard (Montreal) AH Kramer (Calgary) FA Zeiler (Winnipeg)*

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Background: Near-infrared spectroscopy regional cerebral oxygen saturation (rSO_2) has gained interest as a raw parameter and as a basis for measuring cerebrovascular reactivity (CVR). This study aimed to identify threshold values of rSO_2 and rSO_2 based CVR at which outcomes worsened following traumatic brain injury (TBI). Methods: A retrospective multi-institutional cohort study was performed. The cerebral oxygen indices, COx (using rSO_2 and cerebral perfusion pressure) as well as COx_a (using rSO_2 and arterial blood pressure) were calculated for each patient. 2x2 tables were created grouping patients by alive/dead and favorable/unfavorable outcomes at various thresholds of COx and COx_a as well as rSO_2 itself. Chi-square values were calculated to identify the most discriminative significant threshold. Results: In the cohort of 129 patients rSO_2 did not have any statistically significant threshold value. For COx and COx_a, an optimal threshold value of 0.2 was identified for both survival and favorable outcomes with values above this associated with worse outcomes. Conclusions: In this study, raw $rSO_2$was found to contain no significant prognostic information. However, rSO_2 based indices of CVR, were found to have a uniform threshold of 0.2, above which clinical outcomes worsened. This study lays the groundwork to transition to less invasive means of continuously measuring CVR.

Neuroimaging

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Corpus callosum changes in children affected by infantile hydrocephalus

D Adil (London) E Duerden (London) R Eagleson (London) S de Ribaupierre (London)*

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Background: Infantile hydrocephalus is characterized by an atypical accumulation of cerebrospinal fluid in the brain, diagnosed and treated before the age of 2 years. Hydrocephalus development is linked to thinning of the corpus callosum (CC), mainly due to the expansion of lateral ventricles, causing upward