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OTEH-2. High-dimensional analysis of spatial immune cell heterogeneity in glioblastoma reveals differences between contrast-enhancing and non-contrast-enhancing tumor rims

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OMRT-15. MULTIDISCIPLINARY MANAGEMENT OF NON-SMALL CELL LUNG CANCER PATIENTS WITH LEPTOMENINGEAL METASTASIS IN THE TKI ERA

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BACKGROUND: leptomeningeal metastasis (LM) is a devastating scenario in patients with non-small cell lung cancer (NSCLC), with an estimated median overall survival (OS) of 4–6 months from diagnosis. Several studies have clarified the prognosis of treatment modalities after LM. However, just a few studies have clarified the prognosis of LM patterns. We evaluate the prognosis based on various patterns of LM under multidisciplinary treatment (MDT). METHOD: This retrospective study evaluated NSCLC patients treated at National Taiwan University Hospital between 2007–2019 with brain metastases (BM) and LM. LM was classified into LM only, LM concurrent with BM, and LM after BM. Treatments including systemic therapy, whole-brain radiotherapy (WBRT), stereotactic radiosurgery (SRS), and intrathecal chemotherapy with Methotrexate (IT MTX) were recorded. BM excision was done by a neurosurgeon using minimally invasive neurosurgery. The MDT was done according to patients' clinical situations. Kaplan-Meier methodology was used to describe overall survival OS. Multivariate Cox regression model was used to access prognostic factors. RESULT: One hunderd patients with NSCLC CNS metastasis was included in this study. Median OS in patients with single, oligo and multiple BM was 42.0 months (95% CI= 0.12–83.89), 58.1 months (95% CI= 13.00–103.26), and 21.3 months (95% CI= 16.93–25.73), respectively. The median OS of all LM patients was 9.8 months. The median OS of LM after BM, concurrent BMLM, and LM only was 8 months (95% CI= 2.58–13.56), 41.5 months (95% CI= 0.00–94.36), and 18.5 months (95% CI=3.68–33.32), respectively. Multivariate Cox regression analysis showed only IT MTX (p= 0.010, HR= 0.392, 95%CI= 0.19–0.80) was associated with survival. CONCLUSION: MDT in the TKI era has led to a dramatic improvement of OS in patients with LM (4–6 months vs. 9.8 months). NSCLC patients with LM only and concurrent BM LM has a better prognosis and longer survival, and thus are worth receiving intensive MDT care.

FINAL CATEGORY: OMICS OF TUMOR EVOLUTION AND HETEROGENEITY

OTEH-1. ALTERNATIVE RNA SPLICING MODULATES COMPOSITION OF RIBOSOMES AND DETERMINES SPATIAL PHENOTYPE OF GLIOBLASTOMA CELLS

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Glioblastoma (GBM) is an extremely heterogeneous tumor and its different regions are populated with phenotypically distinct types of cancer cells. However, it is still unclear how multiple GBM populations arise from the originally homogenous group of tumor precursor cells. Here we showed that GBM cells from the core and edge of the tumor have different composition of ribosomes due to the alternative RNA splicing of multiple ribosomal genes with highest differences observed for RPL22L1. We found that cells at the edge of the tumor express classical isoform of RPL22L1 (RPL22L1a) while core cells have a novel RPL22L1b isoform. RPL22L1b appears due to low pH condition at the core of the tumor. It allows cells to survive during acidosis, promotes more aggressive phenotype in vivo and correlate with worse patient outcome. Mechanistically, RPL22L1b binds to lncRNA MALAT1 in the nucleus and induces its degradation enhancing stemness of GBM cells. On the other hand, RPL22L1a interacts with ribosomes in cytoplasm and upregulates p53 translation favoring less aggressive edge phenotype of GBM. The splicing switch between RPL22L1 isoforms is regulated by SRSF4 proteins. We identified a small molecule compound that inhibits SRSF4 and impairs splicing of RPL22L1, inducing apoptosis of GBM cells and decreasing tumor growth in vivo. Altogether, our data unraveled the mechanism by which less aggressive edge-like GBM cells acquire more malignant core-like phenotype during tumor growth. It may also explain discrepancies between proteome and transcriptome of GBM cell populations. Targeting this pathway may help to decrease tumor heterogeneity and eliminate therapy resistant cells at the tumor core.

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OTEH-2. HIGH-DIMENSIONAL ANALYSIS OF SPATIAL IMMUNE CELL HETEROGENEITY IN GLIOBLASTOMA REVEALS DIFFERENCES BETWEEN CONTRAST-ENHANCING AND NON-CONTRAST-ENHANCING TUMOR RIMS

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BACKGROUND: Glioblastoma (GBM) is the most common primary malignant brain tumor in adults. GBM remains an incurable disease, with a median survival ~20 months. Complex intercellular interactions within the tumor microenvironment and spatial heterogeneity have challenged and impeded therapeutic efficacy. The non-contrast-enhancing (by T1-weighted MRI) rim of GBM is not always safely resectable and represents a major source of recurrence. We hypothesized that differential immune infiltration is an underlying factor of spatial heterogeneity in GBM, particularly in the non-contrast-enhancing tumor rim. METHODS: Five patients with newly diagnosed GBM (ages 53–84) were recruited to a device feasibility study (NCT04545177) utilizing an intraoperative high-resolution MRI-based navigation system coupled with the NICO Myriad (a non-ablative semi-automated resection tool) and a coupled automated biological Tissue Preservation System (NICO APS) to sample spatially mapped regions of tumors in a reproducible and minimally destructive manner. We obtained brain tumor tissue from: (a) tumor core, (b) contrast-enhancing tumor rim and (c) non-contrast-enhancing tumor rim. Downstream processing consisted of digestion of tumor tissue (Miltenyi human tumor digestion kit) for subsequent single-cell isolation, viability assessment and immediate staining for multiparametric flow cytometry for immune profiling. RESULTS: Viability varied across sampled regions (median 85%, range 52–100%). With the exception of 1 sample, viability was >70% in all specimens. High-dimensional analysis with 26 marker flow cytometry revealed spatial heterogeneity in the frequency of myeloid-derived suppressor cell subsets, regulatory T cells, CD8+ T cells, as well as expression of T cell activation and exhaustion markers. CONCLUSIONS: Semi-automated, spatially mapped intraoperative sampling of GBM with high viability of specimens is feasible and reproducible with the NICO Myriad and APS devices. High-dimensional analysis of immune cells in the GBM microenvironment captured the spatial heterogeneity of GBM. Future studies will expand on these observations by analyzing more patient specimens in combination with multiple omics assays.

OTEH-3. TARGETED GENE-EXPRESSION ANALYSIS DURING MALIGNANT TRANSFORMATION IN PRIMARY AND SECONDARY MALIGNANT MENINGIOMA

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BACKGROUND: Malignant meningiomas comprise 2–5% of all meningiomas. The process of malignant transformation when benign meningiomas (WHO grade I-II) become malignant (WHO grade III) has not previously been investigated in sequential tumour surgeries. Upregulation of FOXM1 expression and DREAM-complex repression have shown phenotypical subgroups correlating with WHO grade and aggressiveness. We investigated the RNA expression of 30 genes central to meningioma biology and 770 genes involved in neuroinflammatory pathways in primary and secondary malignant meningioma patients who underwent one to several operations. METHODS: We identified a cohort of consecutive malignant meningioma patients treated at Rigshospitalet, Copenhagen from 2000–2020 (n=51) and gathered their malignant tumours and previous WHO grade I/II tumours. The malignant cohort (MC) was counter matched with a benign cohort (BC) where patients had no recurrences during follow-up. RNA expression signatures from 140 samples from the MC and 51 samples from the BC were analysed with the Nanostring Neuroinflammation panel customized with 30 genes known to be relevant in meningioma phenotypes. RESULTS: 49% of MC patients had a previous grade I/II meningioma making them secondary malignant meningioma patients. Progression-free survival calculated from first malignant surgery to first recurrence or death showed no significant difference in the