Folate Receptor Overexpression in Human and Canine Meningiomas – Immunohistochemistry and Case Report of Intraoperative Molecular Imaging

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Learning Objectives

By the conclusion of this session, participants should be able to:

1) Describe the importance of near-infrared imaging in potentially enhancing resection rates in intracranial tumors

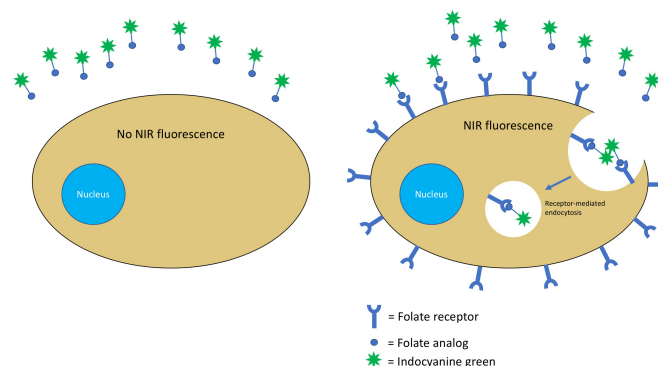2) Discuss the role of targeted molecular imaging in neurosurgery

Introduction

Meningiomas are well-encapsulated benign brain tumors and surgical resection is often curative, especially for the low-grade meningiomas. Nevertheless, this is not always possible due to the difficulty of identifying residual disease intraoperatively and recurrences are common. Intraoperative near-infrared imaging has demonstrated utility in real-time, highly sensitive detection of residual neoplasm. We hypothesized that meningiomas would overexpress folate-receptor-alpha (FRa), allowing targeted intraoperative molecular imaging with a folate-linked near-infrared dye. In this study, we sought to determine FRa expression in both human and canine meningioma specimens. We also present a case study of a meningioma resection with intraoperative near-infrared fluorescence imaging, as a proof-of-concept for this novel technique.
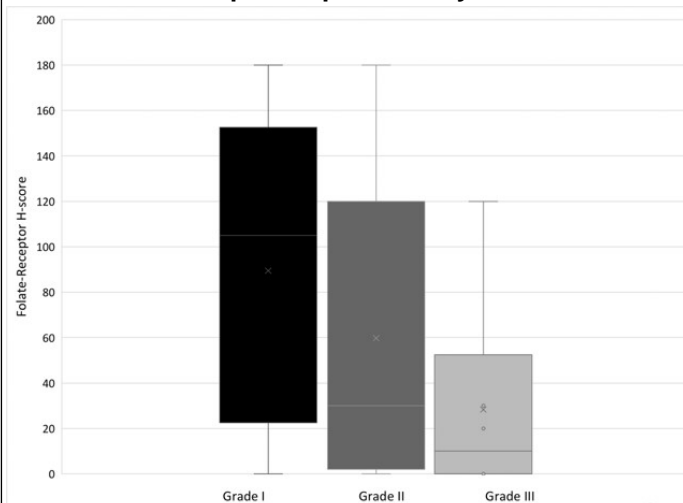
Methods

Tissue samples from 27 human meningioma and 7 canine meningioma were immunohistochemically stained for FRa, with normal dura, skeletal muscle, and kidney tissue serving as the controls. We then enrolled a patient with a concurrent pituitary adenoma and tuberculum-sella meningioma in a clinical trial, in which the patient received an infusion of folate-linked, near-infrared fluorescent dye prior to surgery.
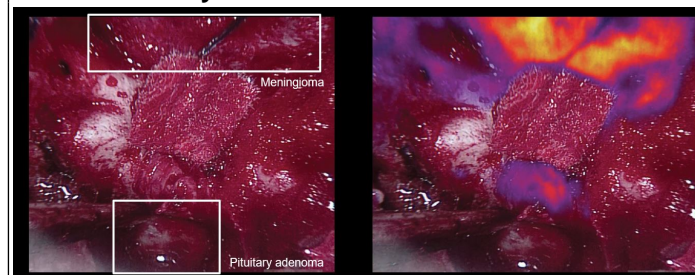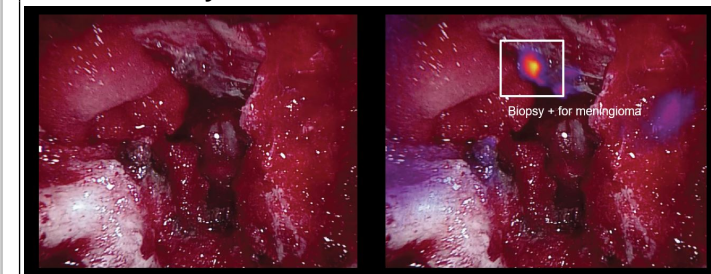
Folate Receptor Targeting Dye Mechanism

No NIR fluorescence

NIR fluorescence

Nucleus

Receptor-mediated endocytosis

Y = Folate receptor
● = Folate analog
✳ = Indocyanine green

Folate Receptor Expression by WHO Grade

Case Study - Pre-resection Near-Infrared View

Meningioma

Pituitary adenoma

Case Study - Post-resection Near-Infrared View

Biopsy + for meningioma

Results

In the cohort of human meningiomas, 9 WHO Grade I, 12 Grade II, and 6 Grade III tumors were identified. 89% of WHO Grade I, 67% of Grade II, and 50% of Grade III tumors overexpressed FRa. All 7 canine meningioma samples stained positively for FRa. Normal dura from both human and canine autopsy samples demonstrated no evidence of FRa overexpression. In the case study, the meningioma demonstrated a high near-infrared signal-to-background-ratio of 4.0 and demonstrated strong FRa immunohistochemistry staining. Near-infrared imaging detected an area of residual fluorescence, which had not been identified as abnormal without fluorescence. This area was biopsied and found to be tumor.

Conclusion

This study directly demonstrates FRa overexpression in both human and canine meningiomas. We also demonstrate superb intraoperative imaging of a meningioma using a FRa-targeting near-infrared dye. Thus, meningiomas are suitable for tumor-specific molecular imaging, which could improve resection rates and patient outcomes.