BRAIN TUMOUR PERFUSION IMAGING WITH 3T
A CANADIAN PERSPECTIVE

Department of Diagnostic Radiology
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Faculty: Omar Islam

Relationships with commercial interests: none

Potential for conflict(s) of interest: none

Mitigation of Potential Bias: none
PRESENTATION OBJECTIVES

- Review classification and pathophysiology of primary brain tumours
- Describe fundamentals of MR Perfusion imaging and protocols at 3T
- Apply MR perfusion in the assessment of tumour progression versus post-radiation change
**PRESENTATION PEARLS**

<table>
<thead>
<tr>
<th>In clinical practice, tumour grading important</th>
<th>Differentiation of tumour progression vs radiation change paramount</th>
<th>In clinical practice</th>
</tr>
</thead>
</table>
| • Conventional MRI  
  • Histopathology | • 3T MRI  
  • MR Perfusion  
  • Tumour Genetics | • Portion of most aggressive tumour (highest grade)  
• Features that suggest de-differentiation  
• Incorporate MR perfusion into routine primary brain tumour protocols |
BRAIN TUMOURS

• **Every day 27 Canadians are diagnosed with a brain tumour**
• **8 out of 100,000 people**
• **The most common type of primary malignant brain tumour is glioblastoma (WHO IV). Average survival, even with aggressive treatment, is less than 2 years.**
• **Brain tumours are located at the control centre for thought, emotion, and movement, they can dramatically affect an individual’s physical and cognitive abilities and quality of life.**
• **The average patient will make 52 visits to their health care team in the 1st year of diagnosis**
• **Data collection on brain tumours is incomplete. Accurate data is needed to better understand the disease and improve treatment**

1. Every day, 27 Canadians are diagnosed with a brain tumour.
2. Brain tumours affect people of all ages and backgrounds.
3. Brain tumours are the leading cause of cancer death in children under the age of 20.
4. There are over 120 different types of brain tumours, making treatment very complicated.
5. Brain tumours drastically affect physical and cognitive abilities and quality of life.
6. Although as many as 60% of children with brain tumours will survive, they are often left with long-term side effects.
7. Metastatic brain tumours occur at some point in 20-40% of people with cancer.
8. The average patient will make 52 visits to their health care team in the first year of diagnosis.
9. In Canada, data collection on brain tumours is incomplete. Accurate data is needed to better understand the disease and improve treatment.
10. An estimated 55,000 Canadians are living with a brain tumour.

www.braintumour.ca
1-800-265-5106
CONVENTIONAL IMAGING – 1.5/3T

Where not otherwise specified, images courtesy of Kingston Health Sciences Centre and Hamilton Health Sciences Centre.
CONVENTIONAL IMAGING

Butterfly Glioma
## WHO Tumour Grading System

<table>
<thead>
<tr>
<th>Grade</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade I</td>
<td>Slow-growing cells&lt;br&gt;Cells appear almost normal under microscope&lt;br&gt;Least malignant / aggressive&lt;br&gt;Usually associated with long-term survival</td>
</tr>
<tr>
<td>Grade II</td>
<td>Relatively slow-growing cells&lt;br&gt;Slightly abnormal cell appearance under microscope&lt;br&gt;Can invade nearby healthy tissue&lt;br&gt;Can recur as a higher grade tumour</td>
</tr>
<tr>
<td>Grade III</td>
<td>Actively reproducing abnormal cells&lt;br&gt;Cells appear abnormally under microscope&lt;br&gt;Affects nearby healthy tissue&lt;br&gt;Tumour tends to recur, often becoming a higher grade tumour</td>
</tr>
<tr>
<td>Grade IV</td>
<td>Abnormal cells that reproduce rapidly&lt;br&gt;Very abnormal cell appearance under microscope&lt;br&gt;Form new blood vessels to maintain rapid growth&lt;br&gt;Areas of dead cells in centre (necrosis)</td>
</tr>
</tbody>
</table>
GLIOBLASTOMA – WHO GRADE IV
MICROVASCULAR PROLIFERATION WITH ENDOTHELIAL HYPERPLASIA
HIGH PROLIFERATIVE INDEX
BRAIN TUMOURS

• CLASSIFICATION OF GLIOMAS WAS BASED PRIMARILY ON HISTOLOGY AND HOW FAST CELLS GREW AND HOW MUCH TUMOUR CELLS RESEMBLED OR WERE DIFFERENT FROM THE NON-CANCER CELLS OF ORIGIN (“GRADE”)

• FOR GLIOMAS, THE MAIN HISTOLOGICAL TYPES HAVE INCLUDED OLIGODENDROGLIOMA AND ASTROCYTOMA. THE GRADE OF THE TUMOUR RANGES FROM THE MOST BENIGN (GRADE I) TO THE MOST MALIGNANT (GRADE IV).

• WHO 2016 COMBINES NEW INFORMATION ABOUT MOLECULAR CHARACTERISTICS AND IMPORTANTLY, IT ALSO AFFECTS THE WAY ONCOLOGISTS TREAT THESE DISEASES

• EXAMPLES:
  • MUTATIONS IN A GENE CALLED ISOCITRATE DEHYDROGENASE (IDH1/2)
  • LOSS OF GENETIC MATERIAL ON CHROMOSOMES 1 AND 19 (1P/19 Q-COA-DELETION)
### WHO Tumour Grading System

<table>
<thead>
<tr>
<th>Grade</th>
<th>(Low-grade)</th>
<th></th>
<th>(High-grade)</th>
</tr>
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<td>• Slow-growing cells</td>
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**BRAIN TUMOURS**

- **Biomarkers**
  - IDH1 mutation
  - 1p 19q co-deletion
3T MR PERFUSION

Where not otherwise specified, images courtesy of Queen’s University
Perfusion MRI techniques can be used for quantitative assessment of specific pathophysiologic parameters. Perfusion assesses a highly specific indicator of malignancy: ANGIOGENESIS.
Tumour hypoxia is one of the initiating events

This leads to secretion of vasoactive substances by the tumour and host immune cells:
- VEGF
- IL-8, PDGF, EGFR

Induce expression of aquaporins (AQP4), which suppresses the expression of endothelial tight junction proteins, resulting in varying degrees of impairment of the BBB.

In GBM, formation of new dense beds of tortuous and abnormal neo-capillaries produces high local tissue blood volume*

To grow beyond a few mm in size, tumours must develop network of new vascular supply.

The new vessels formed are characteristically abnormal by virtue of having increased tortuosity, lack of maturity, and increased permeability due to the presence of large endothelial gaps.

This lack of maturity can be exploited by MR perfusion (PWI). The amount of perfusion signal is proportional to the number of vessels (capillaries) in the voxel. Capillary density, in turn, is a reflection of tumour aggressiveness.


Bottom line: Perfusion signal is proportional to tumour grade**.
HOW TO PERFORM MR PERFUSION
3T MRI PERFUSION PROTOCOL – QUEEN’S

- **Sequence name** - ep2d_fid
- **Sequence type** - Single Shot FID EPI, T2* weighted
- **Parameters:**
  - 2D acquisition in Axial plane
  - TR = 1860
  - TE = 30
  - **Slice thickness** = 4.5
  - **Resolution** = 128
  - **Matrix** = 1.8 x 1.8 x 4.5
  - **Acceleration Factor** = Grappa 2
  - **Bandwidth** = 1446

- **Number of slices** = 26 (whole head coverage)
- **Number of measurements** = 50
- **Scan time** = 1:39
- **Auto generates maps** - GBP, PBP, TTP, relCBV, relCBF, relMTT

**Injection setup:**
- **Double Gado dose** (0.1 ml/Kg x 2)
- 4 ml/sec bolus followed by 20 ml of saline at the same speed.
- Good IV access with 22 gauge cannula if possible in antecubital region.

**Running the sequence instructions:**
- Trigger the injection, wait 10 seconds then start the scan (to ensure an accurate baseline before Gado arrives).
3T MR PERFUSION – RAW DATA IMAGES

- Dynamic IV injection
  - ASL
- ~ 650-700 images
- Temporally and anatomically spaced
3T MR PERFUSION - KINETICS

Cha S et al. Radiology 2002;223:11-29
MR PERFUSION KINETICS

- **Negative Enhancement Integral**
- **Total Area ("Integral") Under the Signal Intensity Curve During First Pass of GD**
- **Total Amount of Contrast Transiting Through the Regional Vascular System and Is Roughly Proportional to Blood Volume**
- **Baseline Does Not Return to Normal at the End of the First Pass. An Arbitrary Decision Must Then Be to Make as to Define the Right Hand Limit of Integration**

MR PERFUSION APPLICATIONS

- Grading
  - Monitoring low-grade gliomas
  - Monitoring high-grade gliomas
- Mapping boundaries
  - Radiation necrosis versus tumour progression
  - Others: Metastases, Lymphoma, Meningioma, TDL
MR PERFUSION APPLICATIONS

Grading
Strong correlation between rCBV from perfusion MRI and glioma grade*

Bisdas et al. found that rCBV_{max} greater than 4.2 was predictive of recurrence and that rCBV_{max} of 3.8 or less was predictive of 1-year survival of astrocytoma**


CASE 1

ASYMMETRIC SNHL!

ACOUSTIC SCAN NEGATIVE, BUT ...
Low vs High Grade - CBV


Study involved 33 patients (22 high-grade and 11 low-grade glioma cases)

In high-grade gliomas, rCBV ratio was 6.50+/-.4.29

In low-grade gliomas, rCBV ratio was 1.69+/-.0.51

The rCBV ratios of the lesions were obtained by dividing the values obtained from the normal white matter of the contralateral hemisphere

Perfusion MRI is useful in the preoperative assessment of the histopathological grade of gliomas

Clin Radiol. 2005 Apr;60(4):493-502
MR PERFUSION - TUMOUR GRADE
CASE 3

R_CBV > 3.5
Monitoring low-grade gliomas
CASE 1 - 41 Y.O. MALE, 3 SEIZURE-LIKE EPISODES
Grade II astrocytoma, +Del chromosome
rCBV 1.58
CASE 2 - 36 Y.O. OLIGODENDROGLIOMA RESECTED IN 1996
CASE 3

33 YEAR OLD FEMALE
AM HEADACHES FOR 3 WEEKS
NAUSEA & VOMITING, VERTIGO
NO FOCAL NEUROLOGICAL DEFICITS
CASE 8
OLIGODENDROGLIOMA, WHO GRADE II
IDH1 R132H MUTANT
1P/19Q CO-DELETED
MR PERFUSION APPLICATIONS

Mapping boundaries
Biopsy of brain tumors is guided by either contrast-enhanced CT or MRI.

Sampling error is a major pitfall with this method because the most malignant portion of the tumor may not necessarily show contrast enhancement. 38% of anaplastic astrocytomas are not substantially enhancing; as many as 25% of brain tumors are likely undergraded as a result.

Relative CBV maps can be used to better select the highest-grade regions for biopsy targets of both enhancing and non-enhancing tumors.
CASE 1 – 79 YEAR-OLD MALE

BIOPSY GUIDANCE

Grade IV astrocytoma (GB); rCBV 7.5
Monitoring high-grade gliomas
New molecularly targeted anti-angiogenic drugs are being developed. PWI offers a method to monitor response to such chemotherapeutic agents.

Earlier detection of tumour progression:

In one study of 59 patients, progression was detected by CBV maps an average of 4.5 months earlier than by MRI in 32%, an average of 4.5 months earlier than by TI-SPECT in 63%, and an average of 6.0 months earlier than clinical assessment in 55%*.

CASE 1

59 YEAR-OLD WOMAN

RAPIDLY DETERIORATING LUE AND LEE POWER – 2 MONTHS

FREQUENT FOCAL SEIZURES AND SECONDARY GENERALIZATION
TUMOUR PROGRESSION VERSUS RADIATION NECROSIS

**CRITICAL:**

- **Vastly different management strategies:** Further surgery and chemotherapy/radiation therapy vs. steroids
- **Conventional contrast-enhanced MRI is not reliable for differentiating**
- **Relative CBV appears to be elevated in patients with recurrent tumour, likely reflective of the increased vascular proliferation and leaky capillaries of recurrent tumour**
- **Relative CBV is decreased in radiation necrosis due to composed of extensive fibrinoid necrosis, vascular dilatation, and endothelial injury**

TUMOUR PROGRESSION VERSUS RADIATION NECROSIS

- In a study of 20 patients after radiotherapy, an enhancing lesion with relative regional CBV ratios of higher than 2.6 indicates tumour recurrence, while ratios lower than 0.6 indicates therapy-related non-neoplastic contrast enhancement.

- Sensitivity 50%, specificity 90%
### TUMOUR PROGRESSION VERSUS RADIATION NECROSIS

#### Table 3:

Results of semiquantitative analysis of MET PET/CT and PWI parameters for the differentiation of recurrence from radiation injury in patients with HGGs

<table>
<thead>
<tr>
<th></th>
<th>Recurrence</th>
<th>Radiation Injury</th>
<th>( P \text{ Value} )</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SUV(_{\text{max}})</strong></td>
<td>5.10 ± 2.41</td>
<td>2.41 ± 1.67</td>
<td>.003</td>
</tr>
<tr>
<td><strong>SUV(_{\text{mean}})</strong></td>
<td>2.83 ± 1.27</td>
<td>1.39 ± 0.9</td>
<td>.003</td>
</tr>
<tr>
<td><strong>TBR(<em>{\text{SUV}(</em>{\text{max}})})</strong></td>
<td>3.48 ± 1.17</td>
<td>1.96 ± 0.96</td>
<td>.003</td>
</tr>
<tr>
<td><strong>r(<em>{\text{CBV}(</em>{\text{mean}})})</strong></td>
<td>2.68 ± 1.14</td>
<td>1.33 ± 0.77</td>
<td>.004</td>
</tr>
</tbody>
</table>

\( a \) All \( P \) values for discrimination between recurrence and radiation injury are significant.
CASE 1 - 23 YEAR-OLD, RIGHT HAND TREMOR

2009
Grade II oligo, -Del

May 2011
Radiation Necrosis
CASE 2 – 2 YEARS AFTER THERAPY: PROGRESSIVE HEADACHE, CONFUSION, BEHAVIORAL CHANGES
Pathology:

Typical features of coagulation necrosis with profound vascular changes, including fibrinoid necrosis and hyalinization of wall and occlusion of lumina by fibrin thrombi.
CASE 4

51 YEAR-OLD MALE

SEIZURE
GLIOBASTOMA – WITH EXTENSIVE RADIATION-TYPE NECROSIS
DECREASED TUMOUR CELL PROLIFERATION
VACUOLIZATION WITH CYSTIC CHANGE
Does MR Perfusion Imaging Impact Management Decisions for Patients with Brain Tumors? A Prospective Study

BACKGROUND AND PURPOSE: MR perfusion imaging can be used to help predict glioma tumor grade and disease progression. Our purpose was to evaluate whether perfusion imaging has a diagnostic or therapeutic impact on clinical management planning in patients with glioma.

MATERIALS AND METHODS: Standard MR imaging protocols were interpreted by a group of 3 NPs in consensus, with each case being interpreted twice: first, including routine sequences, and second, with the addition of perfusion imaging. A multidisciplinary team of treating physicians assessed tumor status and created hypothetic management plans, on the basis of clinical presentation and routine MR imaging and then routine MR imaging plus perfusion MR imaging. Physicians’ confidence in the tumor status assessment and management plan was measured by using Likert-type items.

RESULTS: Fifty-nine consecutive subjects with gliom tumors were evaluated; 56 had known pathologic diagnoses. NPs and the treatment team agreed on tumor status in 45/50 cases (X2 = 0.61). With the addition of perfusion, confidence in status assessment increased in 20/20 cases for NPs and in 20/20 cases for the treatment team. Of the 59 patient-care episodes, the addition of perfusion was associated with a change in management plan in 6 (8.5%) and an increase in the treatment team’s confidence in their management plan in 34 (57.6%). NPs and the treatment team found perfusion useful in most episodes of care and wanted perfusion included in future MR images for >60% of these subjects.

CONCLUSIONS: Perfusion imaging appears to have a significant impact on clinical decision-making and subspecialist physicians’ confidence in management plans for patients with brain tumor.

ABBREVIATIONS: ASL = arterial spin labeled; COE = Center of Excellence; DSC = dynamic susceptibility contrast; GBM = glioblastoma multiforme; NR = neurologist; PASL = pulsed arterial spin-labelling; ROC = receiver operating characteristic; SPGR = spoiled gradient-recalled

“Perfusion imaging appears to have a significant impact on clinical decision-making and subspecialist physicians' confidence in management plans for patients with brain tumor.”

Perfusion imaging appears to have a significant impact on clinical decision-making and subspecialist physicians' confidence in management plans for patients with brain tumor.
BRAIN TUMOUR DIAGNOSTIC ALGORITHM

Al-Okaili R N et al. Radiographics 2006;26:S173-S189
Working together to improve Ontario's cancer system
Breast Cancer Pathway Map

This pathway map provides an overview of the evidence-based best practices for the management of breast cancer patients in Ontario, across all phases...

Cervical Cancer Pathway Map

Lung Cancer Pathway Map

Thyroid Cancer Pathway Map

Colorectal Cancer Pathway Map

Ovarian Cancer Pathway Map

Prostate Cancer Pathway Map

Bladder Cancer Pathway Map
Oropharyngeal Squamous Cell Cancer Diagnosis
Pathway Map
Version 2019.09

Disclaimer
The pathway map is intended to be used for informational purposes only. The pathway map is not intended to constitute or be a substitute for medical advice and should not be relied upon in any such regard. Further, all pathway maps are subject to clinical judgment and actual practice patterns may not follow the proposed steps set out in the pathway map. In the situation where the reader is not a healthcare provider, the reader should always consult a healthcare provider if he/she has any questions regarding the information set out in the pathway map. The information in the pathway map does not create a physician-patient relationship between Cancer Care Ontario (CCO) and the reader.
Oropharyngeal Squamous Cell Carcinoma Diagnosis Pathway Map

Initial Presentation

Version 2019.09 Page 3 of 5

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Screen for psychosocial needs, and assessment and management of symptoms. Click here for more information about symptom assessment and management tools.

Consider the introduction of palliative care, early and across the cancer journey. Click here for more information about palliative care.

Patient presents with:
- Lump in neck or mouth
- Back of throat

Findings or symptoms suspicious of cancer:
- Persistent/Non-responding nodes
- Dysphagia
- Voice changes
- Ear pain
- Pharyngeal bleeding
- Throat pain

No

Symptomatic Treatment

Findings or symptoms resolve?

Yes

Return to Primary Care Provider

Patient presents with:
- Rapidly increasing neck mass
- Neck mass with skin involvement (i.e., retraction)
- Cranial Neuropathy (Secondary to head and neck disease, or as the primary disease)

Emergency Department

Imaging as appropriate

No

Oropharyngeal Cancer Suspected

Treatment for presenting symptoms

Yes

Urgent referral to Otolaryngologist?

Yes

Otolaryngologist

History (including smoking & alcohol)

Physical Exam including head and neck

Mirror and/or Fiberoptic Exam

Tissue Biopsy of Primary Site

Imaging should not delay referral to Otolaryngologist.

No

Otolaryngologist

Lobectomy Imaging: CT Head & Neck or MRI Nasopharynx and Oropharynx

CT Throat

Abdominal imaging (CT or US)

Other investigations as necessary

Pain management with or without biopsy

PET- PET Brain Scan

No, other or unknown primary mass

If not previously done:

Throat Biopsy of Primary Site

Surgical Oncologist

Yes, oropharyngeal primary mass?

Yes

As a primary oropharynx site detected (including panendoscopy assessed?)

No

Proceed to Page 4

Visit to Healthcare provider or Dental practitioners

1 Urgent referrals should be seen within 2 weeks of referral.

2 Unknown H&N Primary in histologically confirmed squamous cell carcinomas (neg. ENT exam, negative CT or MR of the neck), note a panendoscopy is not required prior to PET scan. Baseline staging node positive (prospective nodal stage N1-3) H&N Cancer where PET will impact radiation therapy.
Oropharyngeal Squamous Cell Carcinoma
Diagnosis Pathway Map

Screen for psychosocial needs, and assessment and management of symptoms. Click here for more information about symptom assessment and management tools.

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Note: EBS 95-5 is currently in review.

1 Unknown HN/N Primary in histologically confirmed squamous cell carcinoma (eg. ENT exam, negative CT or MRI of the neck), note a panendoscopy is not required prior to PET scan. Baseline staging node positive (presumptive nodal stage N1-3) HN/N Cancer where PET will impact radiation therapy.

2 The tumours of all adult patients presenting with oropharyngeal squamous cell carcinoma should be routinely tested for HPV status.

3 HPV positive status when the following criteria are met: cytological and nuclear staining, staining is moderate to strong and diffuse, staining is present in at least 50% of tumour cells (Refer to: EBS 8.5.9). Some centres may require staining in at least 70% of tumour cells.
Reviewed classification and pathophysiology of primary brain tumours

Reviewed fundamentals of MR Perfusion imaging using 3T

Applied MR perfusion in the assessment of tumour progression versus radiation necrosis

Future is Integration of MR in Cancer Imaging Protocols
THANK YOU