CASE COMPREHENSIVE CANCER CENTER

STUDY NUMBER:	CASE 4314
STUDY TITLE:	Optimal Timing of Postoperative Magnetic Resonance Imaging (MRI) in Patients with Extradural Spinal Tumors - a Pilot Study
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1.0 BACKGROUND AND RATIONALE

Currently there is no evidence supporting the optimal timing for the post-op MRI imaging in patients with extradural spine tumors. The goal of that imaging is to get the optimal image quality for the evaluation of the degree of resection of spine tumors, in order to guide further therapy as indicated. The current practice is based on brain tumor literature and involves MRI within 72 hours after surgery {Albert, 1994 #9}. The drawbacks of this practice are potentially suboptimal image quality, presence of peri-operative changes that resolve over time and do not represent neoplastic disease, patient discomfort associated with early postoperative pain and need to be positioned in the scanner for a certain time, difficulties arranging the scans within the time constraints.

Hypothesis:

The working hypothesis is that MR imaging 2 to 3 weeks after surgery is no worse in quality and utility than immediately postoperatively (within 72 hours).

Background and significance:

The current standard of care in the management of the extradural spinal tumors is a multidisciplinary approach involving medical, surgical and radiation oncology teams.

In case of extradural spinal tumors, the goals of surgery are either extensive local disease debulking, decompression of neurological elements and/or creation of a tumor-free zone between the spinal cord and tumor (separation surgery) to allow subsequent stereotactic radiosurgery (SRS).

Stereotactic radiosurgery is a relatively new and rapidly developing method that allows curative as well as long term palliative control of primary and metastatic tumors. It is a form of radiotherapy which can be highly effective not only in radiosensitive tumors, like breast cancer, but also in tumors resistant to conventional radiotherapy, like renal cell carcinoma{Balagamwala, 2012 #12;Gerszten, 2007 #14;Gerszten, 2005 #13}. SRS is typically scheduled two-to-four weeks after the surgical procedure.

Planning phase of SRS includes imaging of the surgical bed in the form of MRI so as to delineate the precise area to be radiated. This is required in order to give maximum radiation to the tumor tissue and at the same time minimizing normal tissue irradiation (spinal cord and nerves), which can have debilitating side effects. MRI allows to distinguish normal from pathologic tissue, but the MRI picture in the post-operative period is confounded due to the presence of surgical perturbation leading to edema, blood and serum collection in the early phase and neovascularization later. Optimal timing for postoperative MRI that allows best quality images is currently unknown. Current protocol utilized by our multidisciplinary spine tumor team is based on the earlier reports from brain. According to it, MRI is obtained within 48 – 72 hours postoperatively.

Several studies have been done to find an optimal timing of imaging, especially MRI in the last 2 decades, which have shown that the imaging in the first 72 hours is essential to collect information in order to plan postoperative radiotherapy {Albert, 1994 #9}. These findings have been formulated as Canadian recommendations in the treatment of glioblastoma multiforme {Mason, 2007 #3}. However a recent study on tumor bed dynamics in brain metastasis has supported obtaining MRI as close to SRS as possible {Jarvis, 2012 #10}. There is no literature to support timing for MRI in spinal column tumors.

2.0 OBJECTIVES

Study Design:

This is a prospective diagnostic study for which no standard of care currently exists.

Primary aim:

Assess if Magnetic Resonance Imaging (MRI) at 2 to 3 weeks after surgery (aka: later imaging) leads to the same clinical decisions and has the same probability of being chosen by a physician for guiding the subsequent management of the patient, compared with immediately postoperative MRI (within 72 hours, aka: early imaging).

Secondary aims:

Investigate the differences between early and late MRI by comparing:
Size of tumor in three dimensions;
Extent of edema;
Presence and extent of fluid collection;
Spine Oncology Study Group score;
Involvement of adjacent levels;
Progression of tumor;
Patient's preference/performance scale right after each image had taken: level of discomfort (measured by visual analog scale) at around the time (within 48 hours) each MRI was performed.

Sample:

Patients admitted to Cleveland Clinic for surgical management of metastatic extradural spinal tumors will be considered for the study. We anticipate the initial enrollment of 8 patients, which is a number chosen arbitrary for the pilot study. Based on results of this study we will perform power analysis and determine the number of subjects needed to get statistically significant results. Inclusion will not depend in any way on age, gender, ethnicity, or any other personal characteristics other than clinical relevance. We expect the study population to be similar to the spine surgery population seen at the Cleveland Clinic for neoplastic pathologies.

3.0 PATIENT/SAMPLE SELECTION

Inclusion criteria:

Patients meeting the following criteria will be included to the study:

- Age > 18 yrs;
- Metastatic or primary malignant tumor involving spinal column, with or without extension into the epidural space
- Operated for debulking, decompression or separation surgery;
- An MRI performed within 72 hours after surgery is needed;
- Image quality acceptable for comparison with later MRI as read by a neuroradiologist;
- Karnofsky score of 60 or higher;
- Able to consent for the study.

Exclusion criteria:

- Any patient who previously underwent spinal surgery at these levels will be excluded to eliminate late postoperative changes.
- Intradural extension of the tumor.
- Patients, whose MRI at post operative 48-72 hours are not readable due to artifacts or disease process shall not be included in the study.
- Patient not able to tolerate MRI scan due to claustrophobia or severe pain or allergic reaction to contrast.
- Patients with a eGFR < or = to 30 will be excluded to avoid issues related to contrast administration in such patients. This GFR threshold cutoff level is chosen per institutional policy, because below that level other measures would be required (hydration or no contrast administration). In order to keep the imaging information as uniform as possible in such a small study group, patients with a low GFR will not be enrolled in the study.

4.0 REGISTRATION PROCEDURES

Since this is a non-therapeutic trial, summary information for monthly accrual will be entered into the Oncore database.

5.0 RESEARCH PLAN

Imaging protocol:

We will identify the patients meeting the above criteria and consent them for the study. Another MRI will be obtained 2-3 weeks postoperatively. The routine spine MRI protocol will be utilized, which includes the following sequences: haste localizer, sagittal T1, T2, and STIR, axial T2 for lumbar spine or axial gradient echo for cervical and thoracic spine, axial T1, post contrast sagittal and axial T1. All scans will be obtained using a 1.5 Tesla magnet. When indicated, sedation or anxiolysis and IV hydration for low glomerular filtration rate will be administered by radiology per protocol.

Image analysis:

The image acquisition dates will be blinded and the images independently reviewed by two neuroradiologists, a radiation oncologist, and a spine surgeon. Each of them will compare and choose a better-quality image. These results will be compared and inter-observer variability will be established.

Radiology (2 independent neuro-radiologists) will be blinded to all quantitative data (including the date of post-op MRI) and they will be asked to evaluate the following parameters:

a. Level(s) of surgery = number ie L3, L4
b. Presence of hardware = Y or N
c. Does hardware obscure canal = Y or N
d. Nature of surgery = 0 separation surgery/decompression only, 1 corpectomy, 2 combination of 0+1
e. Fluid collection = AP*Lateral*CC in CM
f. Epidural disease pre op = SOSG grading system AND max thickness at N level
g. Epidural disease post op = SOSG grading system AND max thickness at N level
h. Nature of marrow replacement (preop and residual on post op) = 1-4 for 25%, 50%, 75%, and 100% replaced respectively
i. Compression fracture pre and post = Y or N
j. Adjacent level involvement pre and post = Y or N

Spine surgeon and radiation oncologist will be blinded to date and use a scale of

a. 0 = not confident,
b. 1 = confident
c. 2 = very confident

in terms of confidence in contouring/tumor targeting using a particular image set

6.0 STUDY PARAMETERS

Parameters	Baseline (Pre-Op)	72 Hrs Post-Op	2-3 Weeks Post-Op
MRI	X	X	X

7.0 CORRELATIVE STUDIES (if applicable)

This is not a correlative study.

8.0 STATISTICAL CONSIDERATIONS

Power analysis was not performed for this pilot study, since magnitude of differences is unknown. Obtained data will be used for designing a larger study. Kappa statistics will be calculated to evaluate the inter-rater reliability for the primary aim. For the secondary aims, descriptive statistics will be used.

9.0 RECORDS/DATA TO BE KEPT

The data will be stored in a password protected computer in the spine fellow's room, which is a locked room. Paper documents will also be stored in a locked closet in the same room. Alternative location to store data and documents is the PI's office (locked closet and password protected computer). The neuroradiologists may also store data in password protected computers in their reading room.

10.0 REFERENCES

References are sited within Background & Rationale