The Use of Magnetic Resonance Imaging in the National Cancer Institute Clinical Cooperative Group Trials Program

TJ FitzGerald MD, Maryann Bishop Jodoin, Krishna Kandarpa MD, Nathan Hall MD, Michael Knopp MD PhD

Departments of Radiation Oncology and Radiology, University of Massachusetts Medical School, Worcester, Ma; Department of Radiology, Ohio State University, Columbus, Ohio; Quality Assurance Review Center, Providence RI.

Introduction:

The role of diagnostic imaging is rapidly expanding throughout current protocols in cooperative group clinical trials medicine. Clinical trials require response assessment to demonstrate therapeutic efficacy and imaging has become the preferred vehicle to validate response to anti-tumor therapy and to identify disease progression. It is also the infrastructure to validate compliance to study and credential institutions for participation on clinical trials. Therefore, the role of imaging is a vital and important vehicle in the infrastructure and development of clinical trials. With the rapidly expanding utility of targeted and small molecule therapies being vetted in clinical trials, the active participation of diagnostic radiologists in clinical protocols with real time response assessment imbedded into the matrix of many clinical trials is now crucial to study outcome. Magnetic resonance imaging currently plays a critical role in nearly every disease site and anatomical compartment in the management of cooperative group clinical trials medicine. The goal of this presentation is to review the current status of magnetic resonance imaging in clinical trials and identify future opportunities for magnetic resonance clinical trial objectives with image based clinical study endpoints.

Current Status:

The Children's Oncology Group has the largest number of protocols using magnetic resonance imaging with many requiring or permitting the use of MR and 40 protocols in development with imaging imbedded into the study. Many studies are written for image acquisition for definition of radiation therapy treatment fields and tumor target delineation. The protocols for treatment of tumors to the central nervous system are the studies that require the majority of MR imaging. Protocol ACNS0226 is a phase two study evaluating the role of R115777 (Zarnestra) in children with recurrent or progressive high-grade glioma, medulloblastoma/PNET or brainstem glioma. Zarnestra is an agent that inhibits farnesyl transferase. To document the degree of residual tumor, MRI scan with and without contrast must be done prior to starting therapy with subsequent studies to assess response. Post-operative MR must be obtained with 48 hours of surgery prior to the onset of edema or hemorrhage. The following images are required for submission on study: sagittal T1 localizer, axial T2 and FLAIR (T2), FLAIR or axial proton density/T2 if FLAIR is not available, post gadolinium axial T1, and post gadolinium coronal/sagittal (at least one, both preferable). Optional for study are axial T1, and sagittal/coronal T2 depending on tumor configuration and orientation. For this study MR of the spine with

and without contrast is also required for patients with medulloblastoma and PNET as well as situations where it appears clinically indicated for glioma. The objective response should be confirmed by repeating these studies 4-6 weeks after the response is documented. The spine MR is obtained after course 4,6,9, 12, and every third cycle for all patients under evaluation. The entire spine must be imaged with contrast and must be performed in two planes. If there is significant motion artifact, the scan may not be evaluated for study and must be repeated for the patient to remain eligible for study. For submission, the protocol requires T1 whole spine images with 3 mm spacing. For a 26 cm field of view the investigator should use a 256 by 256 matrix. Anterior saturation pulses are used to minimize motion artifact from the chest and abdomen are strongly encouraged. Two separate sagittal saturations may be required to optimize placement of the presaturation pulse close to the anterior margin of the spinal column. Axial T1 images through the lumbar spine and suspicious regions of the cervical and thoracic spine are required. If a radiologist does not directly monitor the study, whole spine axial T1 images are required with 5 mm thickness and 2 mm gap. The study objective is to assess response to experimental therapy with MR as the vehicle for validation of response to treatment and identify progression when it occurs.

Similar recommendations are used for the ACNS0331 standard risk medulloblastoma clinical trial that evaluates the role of chemotherapy and radiation therapy for standard risk patients with surgically resected medulloblastoma. Standard risk on this study is defined as having residual tumor measuring less than 1.5 cm on post-operative MR imaging and no radiographic or cytological evidence of subarachnoid metastasis. One study objective is to randomize younger children (age 3-7) to receive less dose radiation therapy (1800 cGy vs. 2340 cGy) to the cranial spinal component of their care. This study asks an interesting radiation oncology question as a point of study randomization imbedded into this study. The final phase of management (boost) is randomized between the traditional posterior fossa anatomic based field coverage and an image guided boost target based on a fusion strategy between the pre-operative MR and the postoperative surgical cavity also defined by MR. Thus half of the patients on this study are not treated to the anatomic margins established for the posterior fossa. The strategy is to see if a target volume limited to the image guided surgical volume with margin can be used for treatment of the final phase with the intent of sparing normal tissue including pituitary, cochlea, and temporal lobe when possible. The outcome of this protocol may change the radiation therapy treatment strategy for this disease with respect to the final volume of management and further promote the use of image-guided strategies for radiation therapy treatment planning. If validated through this trial, radiation oncologists will treat smaller volumes in the final phase of management with opportunity to spare more normal tissue when the surgical target does not coincide with normal tissue in close proximity to the cavity. Similar strategy for MR has been established for the intracanial germinoma protocol currently under development in COG.

There is a low-grade glioma protocol now active in the COG (ACNS0221). This protocol requires both contrast enhanced T1 and T2 weighted images for target volume definition with a limited target volume (5 mm) for margin beyond disease defined on post-operative imaging. This limited target volume has been vetted through previous clinical trials and

investigators have found few treatment failures at or beyond the margin of the field. For this study the imaging criteria to submit for central review at the time of study entry include MR with axial imaging with and without contrast, T2 and FLAIR images, as well as coronal studies of the same images. Due to location these tumors are often not fully resected, therefore the radiation therapy target volume to be treated will be determined by the extent of tumor defined on gadolinium T1 performed prior to the start of radiation therapy plus any non-enhancing abnormality seen on T2 or FLAIR identified during the same study. For patients with diffuse tumors, the gross tumor volume will be defined from the T2 or FLAIR study abnormality identified at that time. This is an important protocol in the COG as this disease grade has not been studied with radiation therapy for several years, and the use of MR in the definition of the target volume is being introduced in this disease as part of the study. Response and disease progression will also be determined by MR submission required on this protocol. Modern radiation therapy will be used on this study including image based treatment platforms with intensity modulation when appropriate.

MR is playing a crucial role in defining target volumes in pediatric sarcoma and retroperitoneal sarcoma in the adult population. Both COG and the American College of Surgeons Oncology Group has studies of sarcoma including soft tissue sarcoma, Ewing's sarcoma, and rhabdomyosarcoma. These protocols include the use MR to define to radiation therapy target volume of interest. In these studies the MR must include images in at least two planes with pre-contrast images with T1, fast spin echo T2 weighted with fat saturation, and short tau inversion recovery (STIR). Post contrast imaging includes T1 weighted pulse sequence with fat suppression. In cooperative group protocols that use chemotherapy as the first treatment sequence, response target volumes determined by MR imaging can be used for radiation therapy when the disease extends into a body cavity at presentation and responds to initial treatment. Response imaging is therefore very important in this disease as it helps define the target volume for treatment. For example, for Ewing's sarcoma arising in the ileum, often a soft tissue mass can extend into the true pelvis. If the tumor responds, often bowel can enter the region of the original target volume defined on pre-treatment imaging, therefore adjustments can be made in this section of the target if excessive normal tissue would be at risk if the original target is used to define the area of treatment. MR imaging often is superior in defining the extent of bony involvement in comparison to other imaging modalities, therefore is considered the imaging study of choice in these protocols.

MR is playing a crucial role in validating a point that has eluded radiation oncologists in their daily practice. Because most radiation oncology treatment planning strategies use computer tomography based platforms, pediatric patients are often not re-imaged during treatment to determine if there has been a change in the definition if the target volume. We have assumed for years that the target volume in the central nervous system is not subject to motion or changes in shape during treatment, therefore the target defined at planning often remains the target used for the entire treatment course. Investigators at St. Jude Medical Center have a planning system which is MR based as this institution treats many pediatric patients with cancers in the central nervous system. The MR has been extremely helpful and has provided interesting and novel information. They have

repeated MR images during treatment, often on a weekly basis, to validate position of the target. This practice has led to an unanticipated and unique observation. Cystic lesions such as craniopharyngiomas, are capable of having measureable changes in their volume during treatment and can extend beyond the confines of the target volume defined at the time of initial planning. Whether this explains, in part, treatment failure remains to be determined, however it may become more commonplace that radiation oncologists need to co-register MR studies during treatment in order to insure appropriate coverage of the target volume of interest. The use of proton MR spectroscopy, coupled with routine MR and functional MR techniques, will support future strategies in defining tumor target volumes for patient care.

Future Strategies:

There are many opportunities for the use of MR in future clinical trials. MR is improving our understanding of target volume, thus will be instrumental in developing clinical trials in radiation therapy and validating response to new targeted therapies deemed promising for cancer care.

Prostate cancer clinical trials will be significantly influenced by MR with the likely addition of MR spectroscopy to define the target volume of treatment. Radiation oncologists have difficulty drawing exact prostate anatomy and CT volumes drawn tend to be larger than the actual gland. MR depicts the posterior wall and nerve bundles very well, however its greatest strength will be in defining extension of tumor outside of the prostate capsule and defining dominant lesions within the gland that can be treated to higher radiation doses using intensity modulation with and without brachytherapy. These issues will be included into iterations of future clinical trials. There is active interest in the fusion of MR into ultrasound in prostate cancer planning in order to validate target volume definition for prostate brachytherapy and make real time adjustments in radioactive seed placement based on MR guided anatomy and tumor definition.

Cooperative groups are now in discussion concerning a prostate brachytherapy protocol to treat patients with locally recurrent disease with implant therapy. There is active interest in defining the target volume of interest with MR and MR spectroscopy. Because these patients would have received previous external radiotherapy, it would be advantageous to place radiation dose gradients across normal tissues (rectum and bladder) in order to limit risks of normal tissue injury with re-treatment. Using primary MR or MR/ultrasound fusion may facilitate target volume definition and limit radiation dose to normal tissue.

Breast cancer provides exciting opportunity for clinical research with MR strategies. MR is proving to be an outstanding vehicle for tumor definition, both within the breast and in metastatic foci. For patients presenting with more locally advanced disease or inflammatory histology, neo-adjuvant chemotherapy is often the initial treatment strategy after the diagnosis is established and staging is complete. Many small molecule therapies including angiogenesis inhibitors are having a positive impact on patients with metastatic disease; therefore there is considerable interest in moving forward in bringing these

therapies into an adjuvant and neo-adjuvant setting. MR will prove to be an important point to validate response in this select group of patients.

Head and neck cancer is an important area for clinical trials. Many targeted therapies and treatments directed to hypoxia are currently under clinical investigation for validation. Investigators from many countries participate in clinical trials in this disease site. Imaging provides a common platform for staging and an excellent vehicle to validate tumor response or progression. MR plays a very important role in defining tumor extent at presentation as well as response to management during therapy. Lesions in the oral cavity and base of tongue are often difficult to completely visualize on computer tomography and the extent of disease is often best seen on MR imaging. This is an area of significant research for molecular imaging as ras amplification at surgical resection margins may be a prognostic indicator of local tumor relapse in spite of surgically negative margins. Fusion of strategies between nuclear medicine (SPECT and PET), MR, and ultrasound will be of critical importance in the development of future molecular image strategies for both diagnosis and treatment.

Expanding the role of MR in clinical trials will influence gynecologic oncology protocols. Cervix cancer is now treated with chemoradiotherapy when not treated by surgery. Many targeted therapies including vaccines are now being evaluated in the management of this disease. Data from the Ohio State University suggests that response to chemoradiotherapy defined by MR is a predictive indicator of outcome. This is exciting data and will provide a vehicle to test targeted therapies in this disease. MR is proving extremely valuable in demonstrating the depth of myometrial invasion in patients with primary adenocarcinoma of the endometrium and will be incorporated into future staging trials for patients affected by this disease.

Many signaling pathway (EGFR) and cell adhesion targeted therapies are showing promise in gastro-intestinal malignancies. MR has proven to be the best vehicle to document hepatic metastasis and it is proving very effective in documenting the target volume in the pancreas and peri-portal region. MR angiography is proving invaluable in documenting response to anti-angiogenesis therapies in multiple disease sites including the central nervous system. Pioneer efforts in the Pediatric Brain Tumor Consortium (PBTC) under the leadership of Dr. Kun have demonstrated tumor vessels and their response to treatment with this mechanism. Future studies in this area for adult malignancies will include renal tumors and their metastasis, as these appear to demonstrate significant response to these specific therapeutic interventions. The American College of Surgeons and COG have an open protocol evaluating the role of radiation therapy in retroperitoneal sarcoma with MR obtained on a pre and post-operative basis in order to define tumor extent and site of radiation therapy treatment planning fields.

Credentialing institutions for clinical trials is an important function of quality assurance. The newly opened low-grade glioma trial in COG will require institutions to co-register a MR scan with a CT study for entering patients on this study. Nearly all treatment planning systems used for radiation oncology are based on computer tomography

platforms with MR fusion capability written into most programs to permit target definition as needed with this tool. This has been very important in treating patients with malignancies in the centrals nervous system and is rapidly expanding into other anatomical compartments as well. The strategies are most commonly used for radiosurgery, however this protocol is expanding this concept into daily treatment into other body regions. The credentialing vehicle (benchmark) is a patient image with a single CNS lesion that is only visible on MR. However; the radiation therapy planning is determined from computer tomography coordinates. Institutions download the images from the Quality Assurance Review Center website and co-register them within their treatment planning system. Institutions report placement of the abnormality based from rod fiducias supplied on the study. With a limited data set (6 institutions with 6 planning systems) to date, median displacement has been 3.3 mm. More data is needed to validate this point, as the results of the fusion study will influence the geometry and extension of the target volume to be used on this and future studies in the central nervous system. Other MR based benchmark strategies are in development including a benchmark for dynamic contrast MR.

These and other studies are reviewed centrally at the Quality Assurance Review Center in order to validate response to therapy, review best response, and evaluate time to progression. Radiation therapy objects are reviewed pre-treatment in order to make certain the treatment strategy is compliant to study. Dicom format is the preferred format for transmission of data to QARC as well as the core-imaging center for the CALGB at Ohio State directed by Dr. Knopp. QARC is able to accept electronic imaging data in lieu of hard copy when digital data is in a Dicom format. The digital images can be burned to a CD and mailed to QARC and to Ohio State. Alternatively, when permitted by institutional information systems, images can be e-mailed to QARC at COG@QARC,org. Institutions with PACS systems can contact QARC regarding the installation of the COG Dicommunicator software. QARC and Ohio State currently use webex interactions to resolve controversies of patient staging and eligibility with web based tools for these interactions in development. The imaging center at Ohio State is the imaging core facility for the CALGB and has been extremely valuable to QARC in advanced technology imaging trials including MR and PET. There is active exchange between this group and QARC in order to share data and not duplicate service for institutions participating in cooperative group clinical trials. Images can be forwarded to Ohio State or QARC with facile exchange between the facilities for data transfer and image archive. The long-term goal is to establish a real time web based vehicle for review of imaging objects for both radiologists and investigators requiring data for clinical research. In the next iteration of these interactions, the implementation aspect of these strategies will need to be compliant to the cancer bioinformatics project currently in development.

Thus MR currently plays a very important role in the cooperative group and industry clinical trials program. It has growing influence in the definition of tumor targets and is an important vehicle for validating response to treatment in many anatomical locations. It is an extremely valuable tool for imaging and radiation oncology clinical trials and will become an integral component to the national cancer institute clinical trials program.

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