



MEMORIAL SLOAN-KETTERING CANCER CENTER
IRB PROTOCOL #: 12-260 A(4)

A Pilot Study of Image-Guided Navigation for High Dose Rate Temporary Interstitial Brachytherapy in the Palliative Management of Previously Treated Tumors of the Spine and Pelvis

PROTOCOL FACE PAGE FOR
MSKCC THERAPEUTIC/DIAGNOSTIC PROTOCOL

Principal Investigator/Department:	Yoshiya Yamada, MD	Radiation Oncology
Co-Principal Investigator(s)/Department:	Mark H. Bilsky, MD	Neurosurgery
Investigator(s)/Department:	Iya Laufer, MD Eric Lis, MD George Krol, MD Joan M. Zatcky, NP Gil'ad N. Cohen, MS Marco Zaider, PhD Laszlo Voros, MS Patrick Boland, MD Zhigang Zhang, PhD	Neurosurgery Radiology Radiology Radiation Oncology Medical Physics Medical Physics Medical Physics Surgery Epidemiology & Biostatistics
Consenting Professional(s)/Department:	Yoshiya Yamada, MD Mark Bilsky, MD Iya Laufer, MD Eric Lis, MD George Krol, MD Joan M. Zatcky, NP	Radiation Oncology Neurosurgery Neurosurgery Radiology Radiology Radiation Oncology

Please Note : A Consenting Professional must have completed the mandatory Human Subjects Education and Certification Program.

Memorial Sloan-Kettering Cancer Center
1275 York Avenue
New York, New York 10065

Table of Contents

1.0	PROTOCOL SUMMARY AND/OR SCHEMA	3
2.0	OBJECTIVES AND SCIENTIFIC AIMS	3
3.0	BACKGROUND AND RATIONALE	4
4.0	OVERVIEW OF STUDY DESIGN/INTERVENTION	7
4.1	Design	7
4.2	Intervention	7
5.0	THERAPEUTIC/DIAGNOSTIC AGENTS	8
6.0	CRITERIA FOR SUBJECT ELIGIBILITY	8
6.1	Subject Inclusion Criteria	8
6.2	Subject Exclusion Criteria	9
7.0	RECRUITMENT PLAN with limited waiver of authorization	9
8.0	PRETREATMENT EVALUATION	10
9.0	TREATMENT/INTERVENTION PLAN	10
10.0	EVALUATION DURING TREATMENT/INTERVENTION	12
11.0	TOXICITIES/SIDE EFFECTS	13
12.0	CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT	14
13.0	CRITERIA FOR REMOVAL FROM STUDY	15
14.0	BIOSTATISTICS	16
15.0	RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES	16
15.1	Research Participant Registration	16
16.0	DATA MANAGEMENT ISSUES	17
16.1	Quality Assurance	17
16.2	Data and Safety Monitoring	17
17.0	PROTECTION OF HUMAN SUBJECTS	18
17.1	Privacy	18
17.2	Serious Adverse Event (SAE) Reporting	18
18.0	INFORMED CONSENT PROCEDURES	19
19.0	REFERENCES	20
20.0	APPENDICES	21

1.0 PROTOCOL SUMMARY AND/OR SCHEMA

This pilot study is an investigation into the use of Ir-192 high dose rate (HDR) afterloader-based brachytherapy with catheter placement using image-guided surgical navigation techniques for patients with painful/symptomatic metastatic or recurrent lesions in the spine and/or pelvis that have been maximally treated with external beam radiation therapy. This study will assess the feasibility of this approach in terms of appropriate dosimetric coverage of the target volume with sparing of tissues/organs at risk from excessive radiation dose.

Patients enrolled on this study will undergo HDR brachytherapy using the same equipment, techniques and treatment planning aspects as currently practiced at MSKCC, with the exception of the incorporation of image-guided surgical navigation equipment into the HDR catheter placement procedure.

Patients will be followed at 2 months (+/- 2 weeks) post-treatment and then approximately every 3 months (+/- 2 weeks) until approximately 11 months of follow up. They will be evaluated for pain referable to the treated site, clinical and radiographic evidence of local progression, and treatment related toxicity. Thereafter, patients will be followed as clinically indicated.

Twenty patients will be entered into this protocol which is expected to take 4 years to complete.

2.0 OBJECTIVES AND SCIENTIFIC AIMS

The objective of this study is to validate methods of delivering adequate conformal dose to spinal and pelvic targets with HDR catheters using image-guided navigational techniques.

The Specific Aims of this study are to:

1. Verify feasibility of HDR treatment of spinal and/or pelvic lesions using catheters placed under image-guided navigational techniques, to provide improved dosimetric coverage of lesions such that
 - a. Gross Target Volume (GTV) D90 \geq 80%
 - b. Cord/Cauda max dose (Cord/Cauda Dmax) of < 8 Gy

Secondary objectives:

1. Demonstrate safety of HDR brachytherapy for previously irradiated lesions of the spine and/or pelvis, defined as an acceptable level of severe toxicity (both acute and late effects) in the setting of HDR brachytherapy treatment. Severe toxicity will be defined as \geq grade 3 NCI CTCAE v 4.0 toxicity that is at least possibly related to treatment (see Appendix 2).
2. Assess patient pain scores referable to the treatment site using the standardized 11-point pain scale.
3. Assess patients for duration of in-field progression-free survival at the treatment site.

3.0 BACKGROUND AND RATIONALE

Current treatment regimens at MSKCC for metastatic and primary lesions in the spine and paraspinal lesions of the pelvis include a range of external beam fractionation schedules, ranging from conventional low-dose-per-fraction (high total dose) treatments extending over many weeks to high dose single-fraction treatments delivered in a single day. Conventional external beam therapy has been shown to achieve local control rates range less than 50%. [Greenberg 1980, Maranzano 1998, Klekamp 1998] In contrast, advances in stereotactic external beam radiation therapy have improved local control of lesions in the spine to >90% using high-dose single fraction treatments as initial therapy. [Yamada 2008, Moulding 2010] For the subset of patients who progress locally after optimal treatment, local control may be difficult or impossible to salvage with additional external beam radiation therapy due to limits of normal tissue tolerance to radiation, particularly that of the spinal cord.

The generally accepted dose limit for the spinal cord is 45 Gy at 1.8-2.0 Gy/fraction (Schultheiss 1995); 50 Gy is observed in otherwise healthy patients treated with curative intent where the tumor location prohibits limiting the cord to a lower dose, with an attendant 5% risk of myelopathy at 5 years. [Emami 1991, Schultheiss 1995] For patients undergoing high-dose spinal cord radiosurgical procedures, spinal cord tolerance is defined as a cord maximal dose of 14 Gy, or less than 10 Gy to 10% volume of the spinal cord per level. [Ryu 2007, Yamada 2008] In the event of failure, these limitations may preclude or impair the ability of radiation oncologists to offer effective salvage therapy with external beam techniques. Toxicity resulting from repeat irradiation is a subject of open investigation, with thresholds of 100-135 BED Gy equivalent proposed for late complications due to repeat irradiation of the spinal cord. [Rades 2005, Nieder 2005, Sahgal 2012] (BED Gy equivalent is determined by the biological equivalent dose (BED) calculation; $BED = nd(1 + d/\alpha/\beta)$, where n = number of fractions and d = dose per fraction; α/β is the constant for spinal cord late effect and equals 2.)

Intraoperative and percutaneous high-dose rate brachytherapy techniques may address this issue to improve local control, pain control, and prevent progressive neurological deficit. At our institution, 5 patients have undergone placement of high-dose-rate brachytherapy catheters; 2 patients using intraoperative techniques and 3 patients using percutaneous techniques; treatment delivery has not yet been standardized and we have not determined the optimal techniques for placement of HDR catheters.

As proposed, we will use HDR brachytherapy (Ir-192) to provide tumoricidal doses of radiation directly to lesions in the vertebral bodies and paraspinal tissues through brachytherapy catheters placed using advanced image-guided surgical navigation techniques. The penetration characteristics of Ir-192 are well suited to delivering a conformal therapeutic dose of radiation to the region of catheter placement and sparing critical nearby structures including the spinal cord, cauda, bowel, etc. This makes it possible to give an extremely high dose of radiation to the spine lesion and a margin of surrounding tissues over a short period of time as an outpatient procedure, with the source placed temporarily into the target vertebral body and/or paravertebral tissues. However, to achieve this type of dose distribution, proper catheter placement is essential. Use of image-guided surgical navigation will allow pre-planned catheter trajectories to be optimized as well as reproducibly executed, providing improved delivery of radiation dose. Patients will be treated

in a shielded treatment room by passing an Ir-192 source through the transcutaneous catheters which have been placed directly into the vertebral body and/or paravertebral tissues.

3.1 Advantages of brachytherapy over external beam radiotherapy

Brachytherapy techniques provide a superior means of delivering high doses of radiation to localized targets than external beam radiation. Dose delivery from radiation is dependent upon the inverse square law, which states that the radiation delivered to a point is proportional to the inverse square of the distance between the point and the source of radiation. By taking advantage of this law, when brachytherapy sources are placed within lesions in the spine and pelvis, very high doses of radiation are absorbed by malignant tissue physically near the source while doses to normal tissues outside the target receive doses of radiation much lower relative to that within the target. The converse is true of external beam radiotherapy; because the difference in the distance between the source and the lesion vs. surrounding normal tissues is not significantly different, the dose of radiation absorbed by the target lesion and nearby normal tissue may be nearly the same. External radiation beams must therefore be specifically shaped and meticulously planned and placed in order to minimize the dose to critical normal structures. However, since patient motion and setup uncertainties exist between the target lesion and the radiation beam, and since many photon beams will have some degree exit dose through the spine lesion, there will always be a significant dose of radiation absorbed by any structure in the path of the exiting megavoltage photon beam. Although the same is true of radiation from brachytherapy sources, the dose of radiation absorbed by nearby critical structures is significantly less, and minimizing treatment uncertainty permits precise dose localization and delivery of a more radiobiologically effective treatment in a single fraction. Coupled with computer optimized inverse treatment planning algorithms, brachytherapy is well suited to deliver high doses of radiation to the spine lesion while limiting doses to nearby sensitive normal structures such as the spinal cord, cauda equina, bowel, and other nearby tissues.

3.2 Use of image-guided surgical navigation systems

Our current experience with HDR brachytherapy for lesions of the spine and pelvis requires placement of the catheters under either direct visualization or fluoroscopic guidance, and has not been optimized to ensure that the catheter placement provides the best possible coverage of the target lesion while sparing critical dose-limiting structures. Using a pre-implant CT would allow us to determine the optimal configuration of brachytherapy catheter placement in prior to surgery, improving target coverage and reducing procedure time; image-guided surgical navigation systems would then allow us to precisely track their surgical instruments in relation to patient anatomy and place the brachytherapy catheters along the pre-planned trajectories.

The Medtronic O-arm surgical imaging system and STEALTH® surgical navigation system (Medtronic Inc., Minneapolis MN USA) has been proposed as the platform for image-guided navigation of brachytherapy catheters along these pre-planned trajectories. This system is a multi-dimensional surgical imaging platform that is designed for use in spine, orthopaedic, and trauma-related surgeries and approved for clinical use for applications such as pedicle preparation and screw placement; it provides real-time, intra-operative imaging of a patient's

anatomy with high quality images and a large field-of-view in both two and three dimensions. Integration of this platform into our procedures may improve catheter placement accuracy, reduce the total time for treatment, improve target coverage and help meet dose constraints for critical structures such as the spinal cord/cauda equina.

3.3 Published Outcomes with HDR brachytherapy for spine lesions

HDR brachytherapy for spine lesions is a novel technique developed at Memorial Sloan-Kettering Cancer Center; previous techniques have used either electron cone applicators requiring an invasive open procedure with poor conformality (Seichi 1999); the INTRABEAM electron applicator (XRS 4, Carl Zeiss Surgical Oberkochen, Germany) which delivers a non-conformal dose via a percutaneous technique (Schnieder 2011), and injection of samarium-153 during kyphoplasty, again with limited conformality (Cardoso 2009).

We have presented on our own limited experience in HDR brachytherapy for palliation of previously treated lesions in the spine at the World Congress of Brachytherapy in May of 2012. [Yamada 2012] In our experience, 5 patients were identified with progressive disease at multiply irradiated sites in the spine; 2 patients subsequently received HDR brachytherapy using catheters placed intraoperatively in the vertebral bodies during surgery and 3 patients have been treated using percutaneously implanted catheters with the assistance of interventional radiology. All treatments were performed using a two-stage interstitial catheter system (Mick Radionuclear, Mt. Vernon NY) and GammaMed Plus HDR afterloaders (Varian Medical Systems). In all cases treatment was successfully delivered with no brachytherapy-related complications. At a median followup of 4.8 months, there has been no local progression of disease. Median dose delivered was 14 Gy (range 12-18 Gy) with a median GTV V90 of 77% (range 40-89%) and median GTV D90 of 75% (range 31-94%). (Appendix 3, figures 1 and 2 show a representative plan). In all cases the spinal cord/cauda maximum dose constraints were met. No significant difference was noted between the intraoperative or percutaneous approach. 3 patients (60.0%) had pain relief 1-4 weeks following treatment. It was noted that patients with lower D90 coverage had suboptimal HDR brachytherapy catheter placement, and coverage improved rapidly with experience.

3.4 Expected Toxicity from HDR brachytherapy for spine and pelvic lesions

Expected toxicities are limited to tissues within close proximity to the treated spine or pelvic lesions, where the highest doses of radiation are absorbed. We would expect that the toxicities resulting from treatment would be similar to those experienced with any percutaneous procedure (biopsy or kyphoplasty), including standard risks of anesthesia, bleeding, and infection. Mild fatigue and irritation at the sites of catheter insertion are also likely. For patients who have received previous treatment to the spine using external beam treatment techniques, they will be at increased risk of neurologic injury (due to repeat radiation exposure to the spinal cord and/or cauda equina and exiting peripheral nerves) and musculoskeletal injury (due to treatment effect on paraspinal musculature and the vertebral bodies themselves). Based on the experience of Seichi et al [Seichi 1999], where 37 patients received intraoperative radiation therapy to the spine (22 of 37 had additional radiation therapy), only 1 patient (2.7%) developed radiation myelopathy of the spine. In our own limited series, there have been no treatment related complications and no late effects.

observed. As such, we would expect that the likelihood of neurological toxicity would be on the order of 5%.

3.5 Benefits to Patients

While high-dose single fraction radiosurgical techniques have reduced the risk of local failure to less than 10%, for patients who have local progression after maximal external beam radiation for lesions in the spine and pelvis, the only options are aggressive surgical intervention, protracted courses of steroid therapy, or systemic chemotherapy; unfortunately these alternatives come at the price of high morbidity, and often these patients are poor surgical candidates or have already failed multiple lines of chemotherapy and as such have no further systemic options available. This protocol will allow for the possibility of retreatment in the setting of multiply irradiated lesions of the spine and pelvis, with the potential of improved local control, prevention of progressive neurological benefit, and alleviation of symptoms.

4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.1 Design

The objective of this study is to validate methods of delivering adequate conformal dose to previously treated spinal and pelvic targets with HDR catheters using image-guided navigational techniques

Patients enrolled on this study will undergo HDR brachytherapy using the same equipment, techniques and treatment planning aspects as currently practiced at MSKCC, with the exception of the incorporation of image-guided surgical navigation equipment into the HDR catheter placement procedure. The prescribed dose of radiation will be 14 Gy in a single fraction.

Patients will be followed at 2 months post-treatment and then approximately every 3 months until approximately 11 months of follow up. They will be evaluated for pain referable to the treated site, clinical and radiographic evidence of local progression, and treatment related toxicity. Thereafter, patients will be followed as clinically indicated.

Any severe toxicities (defined as \geq NCI CTCAE v4.0 grade 3) will be carefully evaluated (see Section 11) case by case. Further accrual will be stopped if the level of toxicity is higher than expected (grade 3 toxicity $\geq 10\%$). The protocol may then be terminated or modifications submitted to the IRB for review, as determined by the principal investigator.

Patients with previously treated malignant lesions of the spine and/or pelvis will be eligible for this study (see section on Patient Eligibility).

4.2 Intervention

The Spine Tumor service at MSKCC has extensive experience with all aspects of HDR brachytherapy. The treatment will be performed utilizing the same equipment and software currently used in standard HDR treatments for sarcoma, prostate, and other malignancies, with the exception of the incorporation of Medtronic STEALTH® applications for guided placement of brachytherapy catheters. Otherwise, all other aspects of the treatment are as currently practiced.

MEMORIAL SLOAN-KETTERING CANCER CENTER IRB PROTOCOL #: 12-260 A(4)

All procedural aspects of HDR brachytherapy will be performed as currently practiced by the brachytherapy service at MSKCC. The technical aspects of intraoperative HDR treatment planning (equipment used, acquiring images, computer optimized treatment planning, treatment delivery) will otherwise be no different than those currently employed. As part of the intervention, patients will undergo a minimum of 2 cone-beam CT scans, with an effective dose of 10 mSv per scan. Operator doses will be monitored as per institutional standards and will be carefully controlled during catheter placement.

All other aspects of treatment followup will be no different from the current standard of care for stereotactic external beam radiation therapy for spinal lesions. The patient will be followed at two months and then approximately every three months thereafter with clinical examination and spinal imaging (preferably MRI unless otherwise contraindicated), as per routine until approximately 11 months of follow up. After 1 year, patients will be followed as per standard clinical practice.

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

The major components required for this study are the HDR catheters and remote afterloader, the off-line treatment planning software, and the Medtronic O-arm imaging / STEALTH surgical navigation systems.

All treatments will be performed using a two-stage interstitial catheter system (Mick Radionuclear, Mt. Vernon NY) and GammaMed Plus HDR afterloaders (Varian Medical Systems, Palo Alto CA).

The Medtronic STEALTH® surgical navigation system (Medtronic Inc., Minneapolis MN USA) integrates an O-arm cone-beam CT scan taken in the operative room to a set of optically tracked tools (drills and probes); the system is in regular use by our orthopedic and neurosurgical services at MSKCC. The STEALTH® system is FDA approved for procedures in the spine, including surgery, biopsy, and the placement of hardware or other devices in or near the spinal column. While this is not an investigational device, its application in this protocol is off label will be used to assist in the guidance of brachytherapy catheters into pre-planned positions within the vertebral body and/or paravertebral tissues in which the lesion of concern is located; while this system is not marketed for use in placement of HDR brachytherapy catheters, it is approved for use in spine applications including placement of hardware such as pedicle screws into the vertebral pedicles and bodies. We would also investigate integration of the Medtronic Synergy Cranial application to improve workflow in an off-label use to assist in automated image fusion of the pre-planning CT scan and intraoperative imaging, a process that is currently performed manually in our treatment planning system. Synergy Cranial is a software package used to register and fuse CNS CT and/or MRI images; while it has additional functionality for interventional use, we would only plan to take advantage of the image fusion capability. Image fusion in our treatment planning system may take several minutes, while automated image fusion is practically instantaneous; all fused images would still be reviewed by the clinician to ensure adequacy.

6.0 CRITERIA FOR SUBJECT ELIGIBILITY

6.1 Subject Inclusion Criteria

- Patients must have histologic proof of a malignancy suitable for radiation therapy.
- Patients must have received prior external beam radiation therapy to the region proposed for HDR brachytherapy treatment; evaluation of doses previously delivered to spinal cord/cauda equina, pelvis, and other critical structures (bowel, kidneys, rectum) will be taken into consideration.

MEMORIAL SLOAN-KETTERING CANCER CENTER

IRB PROTOCOL #: 12-260 A(4)

- If repeat irradiation would exceed any normal tissue constraint set by MSKCC Radiation Oncology Department dose constraint criteria, the patient will potentially be eligible.
- If the total prior radiation dose to the cord or pelvis exceeds 100 Gy BED equivalent, the patient will be potentially eligible, where a total of 100 BED Gy equivalent is determined by the biological equivalent dose (BED) calculation; $BED = nd(1 + d/\alpha/\beta)$, where n = number of fractions and d = dose per fraction; α/β is the constant for spinal cord late effect and equals 2. [Rades 2005, Neder 2005, Sahgal 2012]
- KPS \geq 60 (See Appendix 1).
- Age \geq 18 years old

6.2 Subject Exclusion Criteria

- Patients who may receive therapeutically effective doses via an external beam approach to the lesion of interest as specified by MSKCC Radiation Oncology Department dose constraint criteria.
- Patients with kyphoplasty cement or hardware that would preclude effective catheter placement
- Patients with paraspinal extension of disease with visceral involvement.
- Abnormal complete blood count. Any of the following:
 - Platelet count $<$ 75,000/ml
 - Hb level $<$ 9gm/dl
 - WBC $<$ 3.5/ml
- Abnormal coagulation profile: INR $>$ 2.5 and/or PTT $>$ 80
 - Patients who are on anticoagulation medication that may not be safely held for the procedure (\geq 5 days for antiplatelet agents and warfarin; \geq 24 hours for low-molecular weight heparin formulations) will be excluded.
- Contraindications to general anesthesia

7.0 RECRUITMENT PLAN with limited waiver of authorization

We have taken notice of NIH/ADAMHA policies concerning the inclusion of women and minorities in clinical research populations. We expect that the study population will be fully representative of the range of patients seen at MSKCC without exclusion to age ($>$ 18 years), or ethnic background. Given the limited number of subjects to be entered onto the study, no specific outreach efforts are planned.

Potential research subjects will be identified by a member of the patient's treatment team, the protocol investigator, or research team at Memorial Sloan-Kettering Cancer Center (MSKCC). If the investigator is a member of the treatment team, s/he will screen their patient's medical records for suitable research study participants and discuss the study and their potential for enrolling in the research study. Potential subjects contacted by their treating physician will be referred to the investigator/research staff of the study.

The principal investigator may also screen the medical records of patients with whom they do not have a treatment relationship for the limited purpose of identifying patients who would be eligible to enroll in the study and to record appropriate contact information in order to approach these patients regarding the possibility of enrolling in the study. Those patients who are screened will be recorded on the protocol screening log.

MEMORIAL SLOAN-KETTERING CANCER CENTER IRB PROTOCOL #: 12-260 A(4)

During the initial conversation between the investigator/research staff and the patient, the patient may be asked to provide certain health information that is necessary to the recruitment and enrollment process. The investigator/research staff may also review portions of their medical records at MSKCC in order to further assess eligibility. They will use the information provided by the patient and/or medical record to confirm that the patient is eligible and to contact the patient regarding study enrollment. If the patient turns out to be ineligible for the research study, the research staff will destroy all information collected on the patient during the initial conversation and medical records review, except for any information that must be maintained for screening log purposes.

In most cases, the initial contact with the prospective subject will be conducted either by the treatment team, investigator or the research staff working in consultation with the treatment team. The recruitment process outlined presents no more than minimal risk to the privacy of the patients who are screened and minimal PHI will be maintained as part of a screening log. For these reason, we seek a limited waiver of authorization for the purposes of (1) reviewing relevant to the enrollment process; (2) conversing with patients regarding possible enrollment; (3) handling of PHI contained within those records and provided by the potential subjects; and (4) maintaining information in a screening log of patients approached (if applicable).

8.0 PRETREATMENT EVALUATION

Any time prior to treatment start

- Review of all prior external beam radiation therapy (dose volume histograms, beam arrangement, and port films required)
- MSKCC pathology review

Within 3 months prior to treatment start

- History and physical
- KPS
- Baseline pain assessment
- Assessment of baseline comorbidities
- Conmed review

Within 30 days prior to treatment start

- CBC, Comprehensive Serum Chemistry, INR/PTT
- MRI if not otherwise contraindicated
- CT scan without contrast in the prone position (optional if supine CT already performed)
- Standard preoperative workup

Within 2 weeks prior to treatment start

- Pregnancy test for women of childbearing potential

9.0 TREATMENT/INTERVENTION PLAN

All eligible patients will be approached for enrollment. Patients enrolled on the protocol will be scheduled for brachytherapy as per routine, including all necessary laboratory tests for preadmission testing as currently practiced.

Prior to procedure :

1. Patient radiographic scans (CT and/or MRI) will be reviewed by the physicians prior to the HDR catheter placement procedure to determine the optimal catheter placement trajectories.

HDR Catheter Placement using image-guided navigation:

The procedure is as currently performed with the addition of the optical fiducial placement and registration to the Medtronic STEALTH® system; fiducial placement, image acquisition, and image registration is expected to add 10-20 minutes to the procedure.

1. The patient will be intubated following induction of anesthesia.
2. The patient will be positioned in the prone position and prepped.
3. An optical fiducial will be placed in the patient for registration with the Medtronic STEALTH system (either mounted on a spinous process near the treatment site or on a post fixed to the iliac crest through a stab incision).
4. A fine-slice (~1mm thick slices with 1mm spacing) cone-beam/O-arm CT scan will be obtained and registered to the Medtronic STEALTH® system.
5. Catheters will be placed under Medtronic STEALTH® guidance, either into the vertebral bodies/ paravertebral tissues or pelvic tissues. Placement will be based upon size and location of the lesion, proximity to critical structures, and hardware already present in the patient (i.e.: post-surgical fixation and stabilization). Where possible, it is preferred to keep the catheters at least 5mm apart. Catheters will be placed such that they will extend to the anterior portion of the vertebral body where applicable; spatial information of all catheters will be used to avoid overlap and/or collision during placement.
6. Depth of placement will be verified with fluoroscopic images and a repeat O-arm CT scan will be taken.
 - a. As with the pre-placement CT scan, image slices should be ~1mm thick with 1mm spacing.
 - b. Field of view of the CT scan must encompass the tips of each catheter as well as the buttons used to secure the catheters to the skin; Teflon filaments will be left in the brachytherapy catheters during the scan.
 - c. Each catheter filament will be marked and labeled with depth of insertion into the catheter.
 - d. Final setup picture with catheters in place will be taken and placed in the patient's treatment chart.

Treatment planning: as currently performed without new devices or techniques.

1. Intraoperative CT scans will be transferred to our treatment planning system (Brachyvision) with the assistance of Brachytherapy Physics:
 - a. Catheter positions will be digitized for planning by Brachytherapy Physics.
 - b. The vertebral body/paraspinal tissue and/or pelvic lesion will be contoured to provide the gross target volume (GTV), as well as a clinical target volume (CTV) to encompass potential microscopic disease; in some cases the GTV = CTV, at the discretion of the planning radiation oncologist.
 - c. Associated critical structures that have received significant prior radiation dose such as esophagus, bowel, kidneys, and rectum will be contoured and appropriate dose constraints will be applied as per standard practice. In all cases the spinal canal, cord and/or cauda will be contoured.
2. The final treatment plan will be generated by Brachytherapy physics based on the post-placement images utilizing computer optimized three dimensional treatment planning.

MEMORIAL SLOAN-KETTERING CANCER CENTER IRB PROTOCOL #: 12-260 A(4)

- a. The following dose constraints will be used for treatment planning:
 - i. Prescribed dose is 14 Gy to the periphery of the GTV.
 - ii. GTV coverage by the prescription dose will at least be 80% (D90 \geq 80%).
 - iii. Maximum cord dose (cord Dmax) will be 8 Gy.
 - iv. For lesions in close proximity (<5cm) to visceral organs, the relevant constraints will be applied:
 1. Esophagus max dose (esophagus Dmax) will be 9 Gy.
 2. Kidney max dose (kidney Dmax) will be 11 Gy.
 3. Bowel/Rectum max dose (bowel/rectum Dmax) will be a BED Gy equivalent of 85 Gy in 2 Gy fractions (accounting for all prior treatment).
3. Plan will be reviewed and approved by the radiation oncologist.
 - i. If the target dose of 14 Gy to the GTV cannot be met without exceeding dose constraints to the cord and other organs-at-risk, the highest achievable dose will be delivered that does not exceed dose constraints to organs at risk (spinal cord/cauda, esophagus, kidney, or bowel).
4. The treatment plan will undergo quality assurance procedures as per routine.

Treatment delivery and completion of care: as currently performed without new devices or techniques.

1. The HDR unit is attached to the brachytherapy catheters and catheter positioning is verified using a combination of KV fluoroscopic images as well as checking individual catheter depths with marked filaments.
2. HDR brachytherapy is delivered in the HDR procedure room as per routine.
3. After completion of treatment, all HDR catheters will be removed with the assistance of Neurosurgery and bandages will be applied.
4. Patient will be monitored for a minimum of 1 hour after catheter removal and then discharged home if appropriate.
5. Patients will undergo deep venous prophylaxis and pain management throughout the course of treatment as per routine.

10.0 EVALUATION DURING TREATMENT/INTERVENTION

Dosimetric planning will be performed on pre-implantation planning CT and then merged with post-implant CT images obtained following catheter placement. Specific dosimetric parameters will include GTV V90, V100, V150, V200, D90, and cord/cauda dose volume histograms. Treatment complications will be monitored in terms of radiation related toxicity during post-procedure recovery and during followup visits; all patients treated on this protocol will be evaluated regardless of whether dosimetric goals were met.

Regular follow up visits will be scheduled at 2 months (+/- 2 weeks) and then at 3 month (+/- 2 weeks) intervals until approximately 11 months of follow up. During these follow up visits, standard evaluations currently performed on all spine and/or pelvic radiation therapy patients (physical examination and imaging) will be performed. Thus, no activities that are not currently billed will be necessary. Follow up after 1 year will be performed as per standard clinical practice with no further protocol obligations.

If after the 2 month follow up a patient is not available to come in for a follow up visit, a telephone follow up by a clinical investigator will be allowed for up to two of the remaining follow up visits. If a phone call follow up is used, the physical exam will be foregone. Outside imaging studies are also allowed but must be reviewed at MSKCC.

	Screening	Treatment	Follow up (2 months post-treatment, then every 3 months until approximately 11 months of follow up)
Review of pathology	X		
Review of prior treatment	X		
Medical history	X		
Physical Exam, including neurological assessment and ambulation assessment	X		X
KPS	X		
CBC	X		
Comprehensive Serum Chemistry	X		
INR/PTT	X		
CT spine or pelvis ¹ (without contrast)	X ²	X	X ³
MRI spine or pelvis ¹ (unless contraindicated)	X		X
Pre-operative workup	X		
AE assessment	Baseline comorbidities		X
Pain assessment	X		X
Review of Commeds	X		
Pregnancy test	X		
HDR		X	

1 Imaging location will be dependent on the lesion site of interest

2 CT scan in prone position is required unless a supine CT has already been performed within 30 days of planned treatment

3 Optional if MRI is performed

11.0 TOXICITIES/SIDE EFFECTS

For non-serious adverse events, we will only be capturing the toxicities that are possibly related to protocol treatment. The National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be used as an instrument to evaluate toxicities, discussed in section 12.

The toxicities associated with radiation therapy to the spine or pelvis can be classified as either early (occurring within 90 days of the treatment) or late toxicities (after 90 days to 1 year). Mild acute toxicities that are expected from treatment include Grade 1-2 fatigue and irritation at the sites of catheter insertion, as well as a generally transient pain flare in the treated bone site. Less likely (<5% of the time) would be infection or bleeding at the sites of catheter insertion. Rare but serious (<1%) acute toxicities could include complications such

MEMORIAL SLOAN-KETTERING CANCER CENTER IRB PROTOCOL #: 12-260 A(4)

as perforation of a visceral organ during catheter placement (lung, bowel, or kidney) or fractures in the bones of the spine.

There are two types of toxicity which will be considered as potentially serious adverse events from the brachytherapy treatment: neurologic and musculoskeletal. These generally occur late and include myelitis or pathologic fractures of the bones of the spine and/or pelvis. Neurologic and musculoskeletal toxicities will be evaluated with the National Cancer Institute (NCI) Common Toxicity Criteria v4.0 (discussed in section 12, also see Appendix 2 for specifics). The probability of severe (\geq grade 3) neurologic and musculoskeletal toxicity is expected to be less than 10%, which is below the currently observed rate of severe toxicity reported by patients who undergo standard radiation therapy for lesions of the spine at MSKCC.

DEFINITIONS

1. Definition of an Adverse Event (AE)
 - a. An Adverse Event is defined by the GCP (Guide to Good Clinical Practice) as any undesirable experience occurring to a subject during a clinical trial, whether or not it is considered related to the investigational product(s). In this trial we will only document those AEs that are at least possibly related to protocol therapy.
2. Definition of a Serious Adverse Event (SAE)
 - a. A Serious Adverse Event is an adverse experience that:
 - i. is fatal or life-threatening
 - ii. is disabling
 - iii. results in hospitalization or prolongation of hospitalization, with the exception of an overnight admission following the procedure.
 - iv. results in a congenital anomaly or occurrence of malignancy
 - b. Any neurologic and musculoskeletal toxicity that is grade 3 or higher will be considered a serious adverse event.
3. Definition of an Unexpected Adverse Event
 - a. An Unexpected AE is an experience not previously reported (in nature, severity, or incidence) in the current Investigator's Brochure or general investigational plan.

Evaluation of SAE:

Review of the patient record including the treatment dosimetry will be undertaken by the principal investigator with the assistance of the co-principal investigator and at least one investigator from both Medical Physics and Radiology. The principal investigator may decide to continue the protocol without modification, discontinue the study altogether, or to modify the protocol prior to enrolling more patients pending the results of the review.

12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

Review of dosimetric characteristics of the patients' treatment plans will be performed to determine if the treatments were able to adequately meet determined parameters.

The primary objective of the study is to validate the feasibility of HDR treatment of spine and pelvic lesions using catheters placed under image-guided navigational techniques:

1. This will be accomplished by the following criteria: We consider a D90 of $\geq 80\%$ for the lesion GTV with cord and/or cauda equina maximum doses ≤ 8 Gy as acceptable dosimetric endpoints. Dosimetry will be evaluated following implantation of

MEMORIAL SLOAN-KETTERING CANCER CENTER IRB PROTOCOL #: 12-260 A(4)

brachytherapy catheters and prior to patient treatment.

The secondary objectives concern toxicity and clinical outcomes, and will be evaluated regardless of whether the primary objective was met:

1. Demonstration of the safety of HDR brachytherapy for previously irradiated lesions of the spine and pelvis.
 - a. Both acute and late (1 year post-treatment) toxicity will be evaluated. Neurological evaluation and ambulation assessment will be carried out prior to treatment to serve as a baseline. During each subsequent follow up visit, patients will be asked to provide evaluations of their symptoms. The primary expected toxicities are musculoskeletal and neurological. Grade 2 toxicity is almost always self limiting and by definition manageable with medications, not requiring invasive procedures. Thus grade 2 toxicities will not be considered as serious adverse events.
2. Efficacy of HDR brachytherapy for relief of pain
 - a. Patients will be assessed prior to treatment and at each followup visit using the standardized 11-point (0-10) Numeric Rating Scale (NRS-11). Descriptive statistics regarding time to, degree of, and duration of relief from pain (if any) will be reported in summary form.
3. Disease-free progression at the treatment site.
 - a. Imaging studies and clinical assessment performed at each followup date will be used to assess degree of response; tumor control will be defined for this study as the lack of tumor progression at the treated site, where progression may consist of an increase in maximal dimension of the tumor by $\geq 20\%$, compromise of the spinal cord/cauda equina and/or exiting spinal nerves (assessed clinically or radiographically), or both.

The following instruments will be used in the evaluation of toxicities:

NCI Common Toxicity Criteria. The NCI scales are simple to complete and provide a means for assessing patient symptoms. For the purposes of this study, the musculoskeletal panel of questions will be limited to those pertaining to back pain and myositis (see Appendix 2). To evaluate neurological toxicities, the categories will be limited to cerebrospinal fluid leak and myelitis (see Appendix 2). Only the CTCAE v4.0 will be used in toxicity grading.

Numeric Rating Scale (NRS-11). The NRS-11 numeric rating scale is a validated tool for discriminating pain level, in which patients rank their "pain score" on a scale of 0 to 10, where 0 is equivalent to "no pain," and 10 is "unbearable pain." [Downie 1978, Paice 1997]

13.0 CRITERIA FOR REMOVAL FROM STUDY

The study subject will be removed from the study for any of the following after review by the primary investigator:

1. If a change in the patient's medical status unrelated to HDR brachytherapy results in the patient being unable to comply with the protocol.
2. Patient is unable to comply with the follow up requirements of the protocol.
3. Patient request. Patients will be able to withdraw at any time without cause or reason.

4. If the attending radiation oncologist believes that the patient will be adversely affected by any aspect of the treatment.

14. BIOSTATISTICS

This is a pilot interventional study to evaluate the feasibility of high dose rate (HDR) brachytherapy using image-guided navigational techniques as salvage therapy for previously treated lesions of the spine. The primary outcome that we wish to assess is the reproducibility of the treatment plan parameters; secondary outcomes include toxicity, relief of pain, and local disease progression.

In terms of technical feasibility, a patient is regarded as being successfully treated if the target D90 is $\geq 80\%$ AND the cord/cauda max dose is 8 Gy. To this end we will enroll 20 patients and declare the procedure feasible if at least 15 patients can be successfully treated. For this decision rule we have the following probability table:

True feasibility rate	55%	60%	65%	70%	75%	80%	85%	90%
Probability of declaring feasible	0.055	0.126	0.245	0.416	0.617	0.804	0.933	0.989

We believe this procedure will be quite safe for patients; a previous study from Japan [Seichi 1999] showed serious toxicity rates of approximately 3%, and we anticipate ours will be even lower. Among the 20 patients we expect to see less than 2 adverse events. In the event that a second serious adverse event (\geq Grade 3, or as otherwise defined above in Section 11.0) occurs, this protocol will be immediately halted and the investigator will carefully examine the cases with the assistance of the co-principal investigator and at least one investigator from both Medical Physics and Radiology and review the protocol (to be either terminated or modified in order to proceed further). Self-reported pain scores will be recorded and descriptive statistics regarding time to, degree of, and duration of relief from pain (if any) will be summarized numerically and/or graphically. In-field progression-free probability will be estimated using Kaplan-Meier estimation.

15.0 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.1 Research Participant Registration

Confirm eligibility as defined in the section entitled Criteria for Patient/Subject Eligibility.

Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures.

During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist.

All participants must be registered through the Protocol Participant Registration (PPR) Office at Memorial Sloan-Kettering Cancer Center. PPR is available Monday through Friday from 8:30am – 5:30pm at 646-735-8000. Registrations must be submitted via the PPR Electronic Registration System(<http://ppr/>). The completed signature page of the written consent/RA or verbal script/RA, a completed Eligibility Checklist and other relevant documents must be

uploaded via the PPR Electronic Registration System.

16.0 DATA MANAGEMENT ISSUES

A Research Study Assistant (RSA) will be assigned to the study. The responsibilities of the RSA include protocol compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordinate the activities of the protocol study team.

Research material from this study will be handled with the same confidentiality as patients' other medical data. The data collected for this study will be entered into a secure database. Source documentation will be available to support the computerized patient record.

16.1 Quality Assurance

Eligibility of patients will be verified with the principal investigator. Only the designated investigators will obtain informed consent. An assigned RSA will work with the principal investigators to ensure proper adherence to the protocol, eligibility verification, informed consent and data accuracy.

Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and accuracy of evaluations and follow-up will be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action.

16.2 Data and Safety Monitoring

With the help of the RSA, the principal investigators will review each case at the time of enrollment to verify eligibility. The RSA will work with the principal investigators to ensure that the protocol is followed carefully.

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan-Kettering Cancer Center were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the document entitled "Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials" which can be found at: <http://cancertrials.nci.nih.gov/researchers/dsm/index.html>. The DSM Plans at MSKCC were established and are monitored by the Office of Clinical Research. The MSKCC Data and Safety Monitoring Plans can be found on the MSKCC Intranet at: <http://mskweb2.mskcc.org/irb/index.htm>.

There are several different mechanisms by which clinical trials are monitored for data, safety and quality. There are institutional processes in place for quality assurance (e.g., protocol monitoring, compliance and data verification audits, therapeutic response, and staff education on clinical research QA and departmental procedures for quality control, plus there are two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The committees: Data and Safety Monitoring Committee (DSMC) for Phase I and II clinical trials, and the Data and Safety Monitoring Board (DSMB) Institutional Review Board.

During the protocol development and review process, each protocol will be assessed for its level of risk and degree of monitoring required. Every type of protocol (e.g., NIH sponsored, in-house sponsored, industrial sponsored, NCI cooperative group, etc.) will be addressed and the monitoring procedures will be established at the time of protocol activation.

17.0 PROTECTION OF HUMAN SUBJECTS

There are no foreseen additional risks to the patients from this study. Every effort will be made to protect the rights of human subjects as per institutional policy. A full discussion of risk, benefits, expected toxicities/side effects, alternatives/options for treatment will be undertaken. No additional financial costs or burdens will result as a consequence of joining this study. Informed consent is a prerequisite to enrollment on the study.

In accordance with institutional policy, privacy and confidentiality of medical records will be strictly observed. All data pertaining to the study will also be likewise protected. The study is entirely voluntary. Patients who do not wish to participate in the study will be offered all treatment options including but not limited to those considered to be the standard of care.

17.1 Privacy

MSKCC's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board (IRB/PB).

17.2 Serious Adverse Event (SAE) Reporting

Any SAE must be reported to the IRB/PB as soon as possible but no later than 5 calendar days. The IRB/PB requires a Clinical Research Database (CRDB) SAE report be submitted electronically to the SAE Office at sae@mskcc.org. The report should contain the following information:

Fields populated from CRDB:

- Subject's name (generate the report with only initials if it will be sent outside of MSKCC)
- Medical record number
- Disease/histology (if applicable)
- Protocol number and title

Data needing to be entered:

- The date the adverse event occurred
- The adverse event
- Relationship of the adverse event to the treatment (drug, device, or intervention)
- If the AE was expected
- The severity of the AE
- The intervention
- Detailed text that includes the following
 - A explanation of how the AE was handled
 - A description of the subject's condition
 - Indication if the subject remains on the study
 - If an amendment will need to be made to the protocol and/or consent form.



MEMORIAL SLOAN-KETTERING CANCER CENTER IRB PROTOCOL #: 12-260 A(4)

The PI's signature and the date it was signed are required on the completed report.

18.0 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants' consent should be obtained prior to treatment planning being completed. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

19.0 REFERENCES

1. Klekamp J, Samii H. Surgical results for spinal metastases. *Acta Neurochir (Wien)* 1998;140:957-967.
2. Greenberg HS, Kim JH, Posner JB. Epidural spinal cord compression from metastatic tumor: results with a new treatment protocol. *Ann Neurol* 1980;8:361-366.
3. Maranzano E, Latini P. Effectiveness of radiation therapy without surgery in metastatic spinal cord compression: final results from a prospective trial. *Int J Radiat Oncol Biol Phys* 1995;32:959-967.
4. Moulding HD, Elder JB, Lis E, et al. Local disease control after decompressive surgery and adjuvant high-dose single-fraction radiosurgery for spine metastases. *J Neurosurg Spine* 2010;13:87-93.
5. Yamada Y, Bilsky MH, Lovelock DM, et al. High-dose, single-fraction image-guided intensity-modulated radiotherapy for metastatic spinal lesions. *Int J Radiat Oncol Biol Phys* 2008;71:484-490.
6. Seichi A, Kondoh T, Hozumi, T, Karasawa, K. Intraoperative Radiation Therapy for Metastatic Spinal Tumors. *Spine* 24(5):470-473 (1999).
7. Schneider F, Greineck F, Clausen S, Mai S, Obertacke U, Reis T, Wenz F. Development of a novel method for intraoperative radiotherapy during kyphoplasty for spinal metastases (KYPHO-IORT). *Int. J. Radiation Oncobgy Biol. Phys.*, 81(4):1114-1119 (2011).
8. Cardoso ER, Ashamalla H, Weng L, Bahaa Mokhtar B, Ali S, Macedon M, Adel Guirguis A. Percutaneous tumor curettage and interstitial delivery of samarium-153 coupled with kyphoplasty for treatment of vertebral metastases. *J Neurosurg Spine* 10:336-342 (2009).
9. Emami B, Lyman J, Brown A, et al. Tolerance of normal tissue to therapeutic irradiation. *Int J Radiat Oncol Biol Phys* 21:109-122 (1991).
10. Schultheiss TE, Kun LE, Ang KK, et al. Radiation response of the central nervous system. *Int J Radiat Oncol Biol Phys* 131:1093-1112 (1995).
11. Yamada Y, Bilsky MH, Lovelock DM, et al. High-dose, single-fraction image-guided intensity-modulated radiotherapy for metastatic spinal lesions. *Int J Radiat Oncol Biol Phys* 2008;71:484-490.
12. Ryu S, Jin JY, Jin R, et al. Partial volume tolerance of the spinal cord and complications of single-dose radiosurgery. *Cancer* 2007;109:628-636.
13. Nieder C, Grosu AL, Andratschke NH, Molls M, "Proposal of human spinal cord reirradiation dose based on collection of data from 40 patients," *Int. J. Radiation Oncology Biol. Phys.*, 61(3):851-855 (2005).
14. Rades D, Stalpers LJ, Veninga T, Hoskin PJ, "Spinal reirradiation after short-course RT for metastatic spinal cord compression," *Int J Radiat Oncol Biol Phys* 63(3):872-5 (2005).
15. Sahgal A, Ma L, Weinberg V, Gibbs IC, Chao S, Chang UK, Werner-Wasik M, Angelov L, Chang EL, Sohn MJ, Soltys SG, Létourneau D, Ryu S, Gerszten PC, Fowler J, Wong CS, Larson DA, "Reirradiation human spinal cord tolerance for stereotactic body radiotherapy," *Int J Radiat Oncol Biol Phys* 82(1):107-16 (2012).
16. Downie WW, Leatham PA, Rhind VM, Wright V, Branco JA, Anderson JA, "Studies with pain rating scales," *Ann Rheum Dis* 37:378-381 (1978).
17. Paice JA, Cohen FL, "Validity of a verbally administered numeric rating scale to measure cancer pain intensity," *Cancer Nurs* 20(2):88-93 (1997).

18. Soderberg M, Abul-Kasim K, Ohlin A, Gunnarsson M, Medical Imaging 2012: Physics of Medical Imaging. Edited by Pelc N, Samei E, Nishikawa R, Proceedings of the SPIE, Volume 7961, pp. 79613G-6 (2011).

20.0 APPENDICES

1. Karnofsky Performance Status
2. National Cancer Institute Common Terminology Criteria for Adverse Events v4.0
3. HDR Treatment planning