

A prospective study using implanted fiducial markers to assess treatment accuracy and esophageal toxicity in spinal stereotactic body radiation therapy

Protocol Body

1.0 Objectives

- 1.1 Assess the use of implanted fiducial markers in the treatment planning and delivery workflow for frame-based spinal stereotactic body radiation therapy (spinal SBRT).
- 1.2 Characterize the six-dimensional set-up accuracy of the ExacTrac patient positioning system as applied to spinal SBRT for lesions of the thoracic and lumbar spine.
- 1.3 Establish whether the addition of implanted gold seed fiducials enhances the ability of the ExacTrac system to detect and correct patient position relative to image fusion based solely on bony anatomy.
- 1.4 Characterize the radiation dose delivered to organs at risk (OARs) when accounting for intrafraction OAR motion through the use of 4 dimensional CT simulation for treatment planning.
- 1.5 Characterize the radiation tolerance of the normal esophagus to large-fraction radiation treatment through dose constraint relaxation.

2.0 Background

Spinal metastases represent a common site of metastasis, representing up to 70% of all bony metastases (1). In addition to pain caused by bone destruction or pathologic fracture, metastases to the vertebral column pose the additional threat of progressive neurological morbidity from epidural cord compression; 8-20% of patients with spinal metastases will

develop symptomatic cord compression. Radiation therapy has a well-established role in the management of spinal metastases, but the efficacy of conventional radiation therapy is ultimately limited by the tolerance of the spinal cord. Stereotactic radiation techniques for spinal metastases circumvent this limitation, using a combination of stereotactic localization and intensity modulation to precisely deliver highly conformal treatments.

Spinal SBRT is a non-invasive treatment for spinal metastases which achieves a high probability of local tumor control by conformal administration of hypofractionated radiation with submillimeter precision. This approach carries several advantages, including greater efficacy for radioresistant histologies (e.g., renal cell carcinoma or melanoma (2-4) and the ability to offer a short course of treatment (typically 1-3 fractions) in the palliative setting. First clinically applied to 5 patients using a skeletally fixed stereotactic frame in 1995 (5), the clinical literature now describes some 700 patients, with over 900 lesions treated with stereotactic radiotherapy (6). With growing clinical experience, it has become clear that the outcomes from spinal SBRT are excellent: ~80-90% actuarial 1 year local control (7-9) and successful palliation in 85-90% of patients (7, 10, 11). The hypothesis that spinal SBRT can provide superior pain control is currently under formal investigation in RTOG 06-31 (12), which randomizes patients to SBRT (16 Gy in 1 fraction) vs. 8 Gy in 1 fraction.

While spinal SBRT is an emerging modality with maturing follow-up data, its widespread clinical adoption is still relatively recent, and, as such, there are still a multitude of questions as to best practices for use of this modality. A chief limitation of spinal SBRT is the technical expertise required to safely and effectively administer the treatment. Treatment delivery systems employ stereotactic immobilization with image guidance, and require extreme accuracy and meticulous attention to detail – several groups have published the technical details

of their approaches (13-15). A commonality among these approaches is the use of two-dimensional patient alignment techniques, followed by three dimensional imaging to assess patient set-up at the time of treatment (e.g. cone-beam CT, CT-on-rails), as defined by 3D-3D matching of the CT simulation dataset to the daily verification imaging . However, with the advent and adoption of advanced patient positioning systems, e.g. ExacTrac (BrainLab), it remains unclear whether new alignment technologies obviate the need for the latter step of 3D-3D verification. Furthermore, the extent to which these systems can account for rotational set-up error is not completely understood.

We have thus designed this protocol to address these gaps in current clinical knowledge. Broadly, our protocol first seeks to combine implanted gold fiducials, four-dimensional treatment planning, and CT-on-rails capability at the time of treatment delivery to establish a platform for obtaining very precise measurements of patient position and dose delivered. With this tool in hand, we next seek to obtain high quality data on the radiation tolerance of esophageal tissues to large fractions of radiation, through gradual constraint relaxation and prospective toxicity monitoring.

2.1 Characterizing geometric uncertainty in treatment delivery

For spinal SBRT, accuracy in patient positioning is the cornerstone of providing safe and high quality treatment. Previous work from our institution underscored the importance of precise patient set-up, permuting delivered treatment plans to account for potential setup error, and demonstrating that a 2mm translational error can lead to >5% loss of tumor coverage, and greater than 25% increase in the maximal dose to the organs at risk (16).

Our current practice employs the Brain Lab ExacTrac targeting system (17, 18) which uses floor-mounted kV imagers to acquire a pair of orthogonal oblique films, which are used

(sometimes in conjunction with external locator devices) by the system software to compare the patient's position relative to the treatment planning dataset on the basis of bony anatomy. Based on this software fusion, the system calculates the required couch shifts to achieve optimal patient alignment, which are executed through a robotic couch system. Next, the coordinates of the final isocenter are verified using a CT-on-rails system to acquire a three-dimensional dataset. In-house software (19) is used to perform a 3D-3D fusion of the datasets, which then allows computation of the deviation from the planning CT, with tolerances for translation and rotational error of 1 mm and 2 degrees, respectively. Our current practice thus uses the ExacTrac system software to calculate the necessary couch corrections based on algorithmic alignment of bony anatomy alone. However, the ExacTrac software also has the capability calculate patient position based on implanted fiducial markers, provided that the markers are present at the time of CT simulation. Based on our extensive experience with the ExacTrac system, we observe that the bony fusion based calculations excel at detecting translational set-up errors, but can yield discrepancies in assessing rotational error (roll, pitch, yaw). We hypothesize that the addition of implanted fiducials will improve setup accuracy, particularly with regard to rotational error.

The incorporation of implanted fiducials would thus allow us to address two important questions. Firstly, by having the ExacTrac software calculate the required couch corrections with and without consideration of the fiducial markers, we will be able to assess whether the use of implanted fiducials enhances the accuracy of the ExacTrac fusion as compared to fusion based on bony anatomy alone, verified by CT-on-rails. Secondly, the presence of fiducial markers will allow a more accurate comparison of the verification CT dataset with the planning CT, thus allowing us to assess whether our current practice of final 3D-3D verification is necessary.

The use of implanted fiducial markers has been well established in other radiation therapy platforms, including use in image guided radiation therapy for prostate cancer (20) or SBRT for liver disease (21). With respect to spinal SBRT, the Cyberknife platform for stereotactic treatment delivery uses implanted fiducial markers as part of a frameless treatment delivery system (10, 22).

While implanted gold seeds are commonly and safely used for multiple indications, and frequently utilized in clinical spinal SBRT practice, the use of implanted fiducials for patient setup analysis in frame-based spinal SBRT has not been well reported in the clinical literature. A pilot study at the University of Arizona investigated their use in three patients treated with the Novalis Body system, finding the use of implanted fiducials provided superior set-up as compared to bony fusion alone (23). A limitation to this study was the lack of final 3D verification of the type that our CT-on-rails system can provide – thus, the comparisons between bony fusion and marker fusion ultimately derived from ExacTrac software based calculation of true fiducial position – not an independent verification scan.

Thus, the most basic goal of this protocol is to incorporate a well-established practice (implanted gold fiducials) into our treatment delivery platform for spinal SBRT, allowing us to validate the robustness of our system, and, with increased confidence in the accuracy of treatment delivery, enhance clinical decision making.

2.2 Normal organ tolerance to hypofractionated radiation

The use of SBRT has increased dramatically within the past decade (24) – in addition to emerging as a standard of care option for non-resectable Stage I/II non-small cell lung cancer (NSCLC, (25), SBRT has been applied to malignant disease at multiple body sites, including liver (26), prostate (27), adrenal (28), and spine. As a relatively young technology, robust

clinical data is not yet available on the tolerance of normal tissues to large dose hypofractionated radiation (e.g. 60 Gy in three fractions for NSCLC). Indeed, the normal tissue tolerance used on current prospective protocols are derived from a consensus of expert opinion (29), and not on rigorously acquired clinical data.

This paucity of data is particularly acute for the esophagus, which has not been a focus of analysis in prior single or multi-institutional trials. A review of the literature (Table 1) underscores this point, as multiple single institutional experiences do not specify their esophageal dose constraints, nor elaborate on the details of toxicity. While there are several ongoing multicenter trials of SBRT for lung and spine, the esophageal constraints are quite variable across trials (Table 2).

Table 1. Reported esophageal constraints and toxicities from single institution reports of SBRT. NS = not specified

Study	Target	Fractions	<5cc	Dmax	Esophageal toxicity
Yamada 2008 (15)	Spine	1	NS	NS	1 TE fistula
Fakiris 2009 (30)	Lung	3	NS	NS	None reported
McGarry 2005 (31)	Lung	3	NS	NS	None reported
Baumann 2009 (32)	Lung	3	NS	NS	4% G1-G2 esophagitis
Grills 2010 (33)	Lung	4-5	NS	NS	None reported
Chang 2007 (8)	Spine	3-5	15 Gy	21 Gy	1 case G3 dysphagia
Onishi 2007 (34)	Lung	1-22	Not constrained	Not constrained	1% G3 esophagitis

Table 2. Reported esophageal constraints and toxicities from multicenter trials using SBRT.

Study	Target	Fractions	<1cc	Dmax	Esophageal toxicity
RTOG 0236 (35)	Lung	3	NS	27 Gy	1/55 G3 GI, no esophageal tox.
RTOG 0618 (36)	Lung	3	NS	27 Gy	Results pending
RTOG 0631(12)	Spine	1	11.9 Gy	16 Gy	Results pending
RTOG 0813 (37)	Lung	5	NS	52.5 Gy	Results pending
ROSEL (38)	Lung	3	24 Gy	NS	Results pending

Overall, the current state of the clinical literature highlights the need for high quality data for esophageal toxicity in the setting of large dose hypofractionated radiation therapy. Taken together, these reports indicate that, in current practice, SBRT is exceptionally well-tolerated with respect to the esophagus, and suggest that current practice may reflect overly conservative esophageal dose constraints. In the setting of spinal SBRT, while primarily driven by the spinal cord tolerance, esophageal dose constraints can be another significant factor forcing clinicians to compromise CTV coverage for fear of inducing esophageal toxicity.

Interestingly, while a significant portion of SBRT data come from respiratory gated four dimensional (4D) CT based treatment of lung tumors, the question of how organ motion should be incorporated into setting dose constraints for normal tissues has been largely ignored. A prior

study of esophageal motion in 29 patients using 4D CT demonstrated a substantial degree of esophageal motion, noting that 9 mm and 8 mm margins respectively would have been necessary to incorporate all movement of the distal esophagus in the medio-lateral and dorso-ventral directions (39).

Given that the current state of SBRT practice thus relies on esophageal constraint parameters which a) may unnecessarily force compromise of CTV coverage through overly strict constraints and b) do not account for organ motion, the second major goal of this protocol is to employ our fiducial-enhanced, 4DCT based, treatment platform to prospectively collect high-quality data on esophageal dose tolerance through careful constraint relaxation.

2.3 Incorporation of lessons learned to date

As of this revision (Version 8), we have accrued 7 patients into Stage 1 of the protocol (five in group 1, and two in group 2). In reviewing our data to date, we conclude that the residual alignment error as calculated using either the bony fusion algorithm or implanted fiducial methods are in good agreement, with no significant difference between the methods (Figure 1).

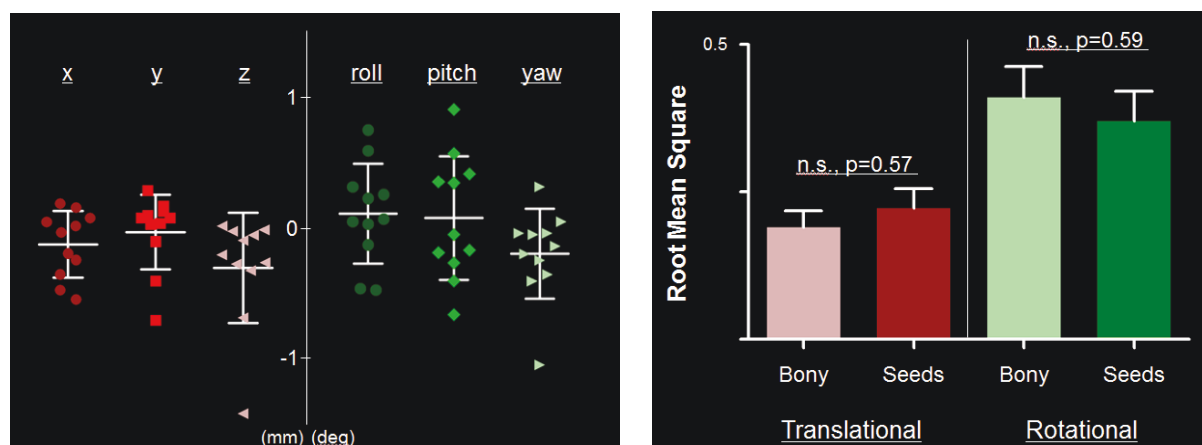


Figure 1: Left panel - Examining the differences in the calculated error in each dimension using both fusion and fiducials reveals good agreement (average difference near zero). Right panel - RMS analysis demonstrates no statistical or clinically meaningful difference.

Extending our analysis, we have performed offline 6D fusions of the CT-on-rails-datasets with the simulation data sets, and conclude that fiducials are no better than the bony fusion algorithm for correcting rotational error (Figure 2).

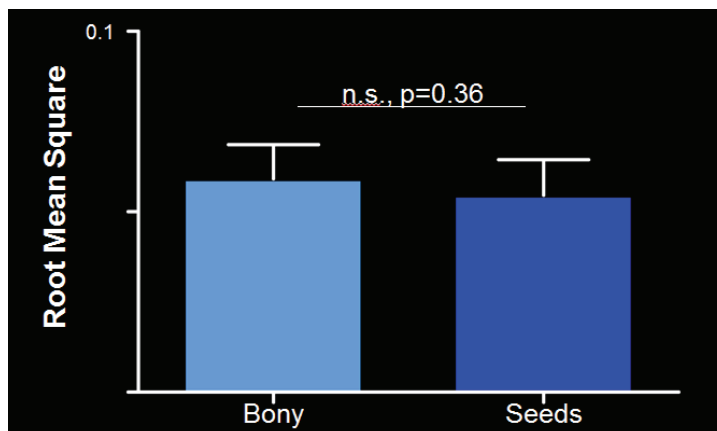


Figure 2: Using offline 6 dimensional fusion, an accurate assessment of residual rotational error can be performed. RMS analysis demonstrates no significant difference in performance between the two approaches.

An additional development has been the migration of our spinal SBRT treatments to a new linear accelerator, with upgraded capabilities (e.g. 6D robotic couch correction, cone-beam CT, and improved fusion algorithm). These new capabilities will further improve the overall accuracy of patient setup with respect to rotational error. As we have demonstrated that any difference between the fusion approach and the fiducial approach has thus far been too small to detect, we believe that the improved platform would further close the hypothetical gap between the approaches, and that we will not be able to observe it.

Thus, going forward, we will:

- Remove the fiducial component from the protocol

- Prospectively enroll additional patients (without the need for fiducials) to characterize the accuracy of the new treatment platform, including a group of patients with tumors in the cervicothoracic junction (who were not originally included because of challenges with fiducial placement)
- Perform a retrospective study of setup accuracy in patients with cervicothoracic junction tumors as historical controls

3.0 Patient Eligibility

3.1 Inclusion Criteria

Stage 1:

- 1) Greater than or equal to 18 years of age
- 2) Pathologically confirmed diagnosis of cancer, including, but not limited to non-small cell lung cancer, breast, prostate, renal cell, melanoma, gastrointestinal, sarcoma, thyroid, head and neck primary, and carcinoma of unknown primary
- 3) Signed informed consent

Stage 2:

- 1-3 above, and
- 4) Patients undergoing single fraction spinal SBRT

3.2 Exclusion Criteria

Stage 1:

- 1) Patient with radiosensitive histologies (lymphoma, multiple myeloma, small cell carcinomas, germ cell tumors)
- 2) Extensive (> 50%) height loss of the involved vertebral body

3) Inability to tolerate lying flat on treatment table for greater than 30 minutes

4) Pregnancy

3.3 Additional exclusion criteria, Stage 2

1) Prior irradiation of the spine site and level to be treated

2) Patients with primary disease arising in the posterior elements of the VB in question

3) History of Barrett's esophagus, esophageal webbing, stricture, or fistula

4) Prior radiation to the esophagus

4.0 Pretreatment evaluation

1) Patients will undergo a thorough history and physical.

2) Patient cases will be reviewed at a multidisciplinary stereotactic spine conference to discuss dose, fractionation and radiosurgical target.

3) An MRI of the spine must be performed within 4 weeks of registration.

5.0 Treatment Plan

5.1 Summary of study design

Our overall study plan consists of two stages. In the first stage, we will seek to characterize the accuracy of our new treatment platform and perform analysis of the ExacTrac positioning system.. Four dimensional CT datasets are recommended for simulation will also allow us to use data from this portion of the protocol to characterize the degree to which organ at risk (OAR) motion is relevant at each spinal level. In this stage, we will now close accrual to

Groups 1 (T4-T12 with fiducials) and 2 (L1-L5 with fiducials) and begin enrollment in three new groups of 10 patients each:

Group 5: tumors from C5-T3

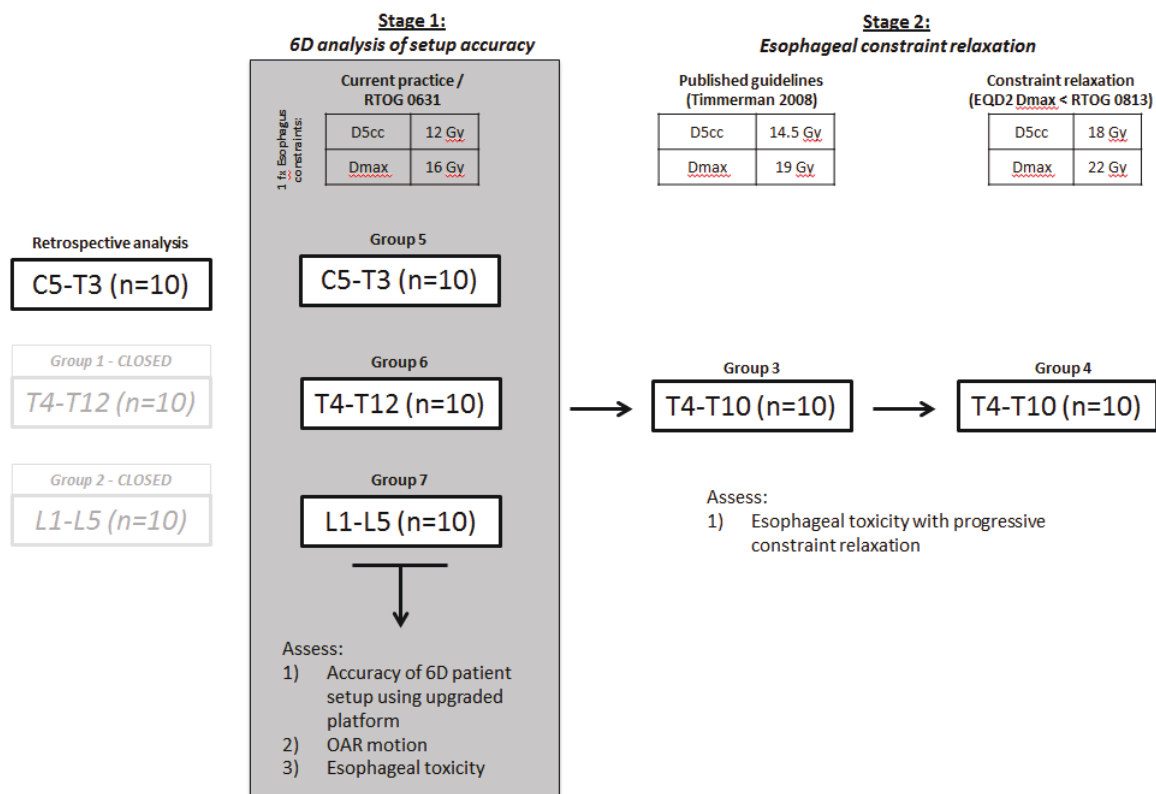
Group 6: T4-T12

Group 7: L1-L5

Patients in groups 5-7 will not undergo gold fiducial placement. In this stage of the study patients will be treated with the standard dose constraints to normal tissues.

In the second stage, we will seek to characterize the tolerance of the esophagus to hypofractionated radiation doses through prospective constraint relaxation and toxicity monitoring. In this stage, we will seek to accrue 20 additional patients in two groups of 10, to be filled sequentially with progressive constraint relaxation (Group 3: T4-T10 / constraint level 2, Group 4: T4-T10 / constraint level 3). The data collected from Group 1 in the first stage of the protocol will give us data on the dose delivered to the esophagus under our current practice guidelines (which are commensurate with the guidelines of the multicenter RTOG 06-31 trial (12), and will serve to verify the safety of our current practice. The second stage of the protocol will accrue in parallel with stage 1. Once Group 3 has completed accrual, patients will be prospectively monitored for a period of 3 months for signs of adverse esophageal toxicity before Group 4 opens. The dose constraints that will be used for Groups 3 allow higher dose than is used in our practice at MD Anderson, but comply with published guidelines for SBRT treatment (29). The dose constraints for Group 4 represent a modest increase of esophageal dose maximums from these guidelines, but the maximum esophageal dose falls well under the maximum allowed on the current RTOG 0813 trial (37). Detailed dose constraint parameters are

enumerated in Section 5.6.2, below. In total, the study seeks to accrue 40 patients. The overall trial schema is summarized below.



5.2 Treatment summary

All patients will receive CT-guided spinal SBRT using intensity modulated radiation therapy to maximize the conformality of the treatment plan to the target volume, while sparing normal structures.

5.3 Simulation

For simulation and treatment, we will employ our previously described SBRT setup (14), using a stereotactic BodyFix cradle. At the time of simulation, patients may be administered barium sulfate oral contrast (40) to aid in delineation of the esophagus on axial imaging. A CT dataset will be acquired for treatment planning – a four dimensional CT using optical respiratory monitoring is recommended.

5.4 Organ at risk delineation

For treatment planning purposes, contouring of normal structures will be performed on the “average” CT dataset. For assessment of OAR motion, the data analysis will involve re-contouring at each phase of the respiratory cycle.

5.4.1 Esophagus

The full thickness of the esophagus will be contoured using oral contrast media (Esophocat) in conjunction with mediastinal windowing on CT. Sagittal and coronal reconstructions will be used to verify the 3-dimensional coherence of the esophageal volume. The esophageal volume should (at minimum) include the esophagus from the top of the VB one level above the target and continuing on every CT slice to the bottom of the VB one level below the target. For treatment planning, oral contrast in the esophagus will be assigned the density of soft tissue to minimize any alteration of the calculated dose distribution. For additional analysis (but not for dose constraint purposes) the contrast media will be used to create regions of interest corresponding to the lumen (contrast media) and organ wall (esophagus volume – lumen)

5.4.2 Other organs at risk

Other organs at risk that may be contoured include: spinal cord, lungs, liver, kidneys, larynx/pharynx, trachea, and skin. These structures will be contoured as per the guidelines established in RTOG 0631 (12).

5.5 Dose constraints

5.5.1 Esophageal dose constraints

The esophageal dose constraints for the protocol are summarized in Table 3. In stage 1, focusing on use of the fiducial system, patients dispositioned to undergo single and multi-fraction treatments will be enrolled, using our current practice guidelines for esophageal dose

constraints. For single fraction treatments, 5 cc of the esophageal volume must receive less than 12 Gy and the maximum dose (defined as that delivered to less than 0.01 cc of the esophageal volume) must not exceed 16 Gy. For 3 fraction treatments, 5 cc of the esophageal volume must receive less than 15 Gy and the maximum dose received must not exceed 21 Gy. The dose to 1cc of esophageal volume will be recommended, but not required, to be under 14 and 17 Gy respectively.

In stage 2 of the protocol, only patients receiving single fraction treatment will be eligible. Group 3 patients will be planned with constraints of 14.5 and 19 Gy to 5cc and 0.01 cc's respectively, with a recommended dose of 17 Gy as a 1 cc constraint. These dose constraints represent published guidelines issued by other groups with expertise in stereotactic radiation treatment, and will be prospectively validated in our system. Once Group 3 accrual and monitoring has been completed, we will enroll patients to Group 4, with 5 cc and 0.01 cc constraints of 18 Gy and 22 Gy and a recommended 1cc limitation to 20 Gy. The maximum esophageal dose in this group compares favorably to the maximum dose allowed on RTOG 0813 (when converted to 2 Gy fraction equivalents using the linear-quadratic model, the Group 4 Dmax is 80% of the dose allowed on this multicenter protocol).

The doses constraints chosen for Group 4 have clinical relevance for patients undergoing spine SBRT for metastatic renal cell carcinoma – these tumors are prescribed to receive a single fraction dose of 24 Gy, yet, for lesions adjacent to the esophagus, tumor coverage must sometimes be compromised to respect our current esophageal maximum of 16 Gy. Thus, prospective validation of higher esophageal tolerances would allow improved tumor coverage, with expected improvement in tumor control.

Table 3. Esophageal Dose Constraints for single fraction treatments (Gy).

* = recommended, but not mandated.

Stage	Patient Group	< 5cc	<1cc*	<0.01 cc
Stage 1	Group 1	12	14	16
	Group 2	12	14	16
Stage 2	Group 3	14.5	17	19
	Group 4	18	20	22

5.5.2 Non-esophageal dose constraints

With the exception of esophageal dose, treatment planning will be based on our group's current standards for organ-at-risk (OAR) dose constraints; however the final target volume and treatment plan will be at the discretion of the attending physician. Treatment planning will be carried out using the "average" image stack if a 4D CT data set is used.

5.6 Set-up verification

On the day of treatment, patients will first be set up on the treatment table as per our standard practice. Once the patient has been positioned by the treatment team, the ExacTrac software will calculate couch correction based on bony fusion of kV images with the treatment planning CT scan. These couch corrections will be transmitted to the patient couch, and the ExacTrac software will re-verify. Next, the cone beam CT will be used to perform a verification scan. In-house 3D-3D matching software will be used to verify the position of the final treatment isocenter. This procedure represents our current clinical practice, and is unchanged for this protocol. The cone beam CT dataset will also provide independent, 6-dimensional information on the accuracy of the calculated couch correction.

6.0 Evaluation During Study

Following treatment, patients will be evaluated in follow-up visits at months, 3 (+/- 2 weeks), 6 (+/- 4 weeks), 9 (+/- 4 weeks), 12 (+/- 8 weeks), 18 (+/- 8 weeks) 24 (+/- 8 weeks), and annually thereafter. Additional follow-up visits may be scheduled as needed in the judgment of the attending physician.

Toxicity will be monitored and recorded as per the NCI Common Terminology Criteria for Adverse Events (CTACE) version 4.0. Specific esophageal toxicity endpoints to be monitored include: dyspepsia, dysphagia, fistula, hemorrhage, necrosis, obstruction, pain, perforation, stenosis, ulcer, varices and esophagitis. Additional workup of esophageal symptoms (e.g., endoscopy, swallowing evaluation) will be at the discretion of the treating physician. Additional systemic agents or subsequent radiation therapy to the esophagus in the course of treatment will be recorded at each follow-up.

While acute esophagitis is not the primary parameter to be monitored, this protocol will also assess transient effects of spinal SBRT. Patients will complete MD Anderson Symptom Inventory (MDASI), with inclusion of the MDASI lung module, which has been previously used to assess acute esophagitis during thoracic chemoradiation therapy (41), at baseline and then weekly for four weeks following treatment. The MDASI spine module will also be incorporated into the questionnaire. Patients in Groups 1, 3, and 4 will also be asked to score use of antacids or anti-reflux medications at baseline and weekly for four weeks following treatment. Changes in patient medications (e.g. prescription of corticosteroids) at the time of spinal radiation therapy will be recorded.

7.0 Criteria for Response

Radiographic Treatment Failures

Primarily, this protocol is one of technology verification and toxicity monitoring. As such, tumor response will not be a primary data point. However, patients will be monitored at each follow-up visit, with MRI of the spine performed at each follow-up time point during the first year. Treated lesions will be classified as progressive (defined as $> 25\%$ increased volume), stable (defined as radiographically unchanged), or smaller, and spinal tumor progression-free survival (PFS) will be calculated.

Pre-Specified Dosimetric Analysis

Assessment of dose delivered to esophagus will include analysis of several dosimetric parameters, including:

- 1) Maximum dose (Dmax) = the highest dose received by 0.01 cc volume of esophagus
- 2) Dose to 5 cc (D5cc) = the highest dose received by a 5 cc volume of esophagus
- 3) Central lumen dose = the dose delivered to the centroid of the esophageal contour as calculated on a given axial slice.
- 4) Full thickness dose = dose delivered to the full thickness of the esophageal wall as calculated on a given axial slice

Any adverse esophageal events will be correlated with these parameters to determine the most appropriate definition of esophageal dose constraints.

8.0 Statistical Considerations

Study Plan

We expect to enroll one to three patients per month. The first stage of this trial adds a minor interventional radiology procedure and enhanced simulation technique to our current

standard practice – as such, we anticipate minimal added risk, and rapid accrual of appropriate patients. The second stage of this trial is more restrictive in the vertebral bodies that will be eligible, and as such, may accrue more slowly.

Safety

In a recent analysis of esophagitis symptoms in 652 patients receiving radiation treatment for lung cancer at MD Anderson, 11% developed Grade 3+ esophageal toxicity (Gr3 n = 70, Gr4 n= 4; Gomez et al., *in preparation*). Based on our previous prospective data (8) and the low incidence of spine SBRT induced esophagitis reported in the literature (Table 1), we expect the incidence of Grade 3+ esophageal toxicity to be well below this number. However, it is instructive to note that of these Grade 3+ toxicities, greater than 95% occurred within the first 90 days from the start of radiation treatment. Additionally, previously published work (42) has shown that, while the frequency of significant late radiation-induced esophageal toxicity is low, late esophageal toxicity is presaged by acute toxicities. Taken together, these data suggest that a 3 month monitoring period will be safe and appropriate to detect increases in esophageal toxicity.

The dose constraint relaxation stage (stage 2) of the trial will begin with accrual to Group 3 (using esophageal doses higher than our current practice, but used in clinical practice at other specialized centers). Given the low probability of increased complication in this moderate constraint relaxation, we will plan to enroll patients to this group in 2 cohorts of 5, following the first 5 patients for 3 months before enrolling the next. Any Grade 3 or higher esophageal toxicity will terminate accrual to patient Group 3.

Once Group 3 has completed accrual and all patients have been followed for 12 weeks from the end of radiation treatment, Group 4 will open for accrual, enrolling patients in cohorts

of 3, 3, and 4, with each cohort followed for 3 months before enrolling the next cohort. Any Grade 3 or higher esophageal toxicity will terminate accrual to patient Groups 3 and 4. Accrual to patient Group 2 (lumbar spine, standard esophageal constraints) may continue during Stage 2 if this arm has not yet reached its accrual goals.

Analysis

We will use descriptive statistics to summarize the demographic and clinical characteristics of patients enrolled in this study. We will similarly summarize Dmax, D5cc, central lumen dose, and full thickness dose for each patient group (defined above).

We will use the methods of Bland and Altman (43) to compare the positioning of the isocenter with respect to 6 directional orientations (superior-inferior, anterior-posterior, lateral-medial, pitch, roll, and yaw) using the implanted fiducial markers and using our standard practice for each patient group. We will similarly compare the 3-dimensional distance from the isocenter as calculated using the implanted fiducial markers and using our standard practice. We will also estimate these paired differences (fiducial – standard practice) with 95% confidence intervals, and we will estimate with 95% confidence intervals the correlation between the measures made using the fiducial markers and those made using standard practice. We will similarly analyze Dmax, D5cc, central lumen dose, and full thickness dose for each patient group.

We will tabulate adverse events by grade for each patient group.

Sample Size

We will test whether the paired difference (fiducial – standard practice) in 3-dimensional distance from the isocenter is significantly different from 0. A sample size of 10 patients in each patient group will give us 80% power to detect an effect size of 1 standard deviation with a 2-sided significance level of 0.05. A sample size of 10 patients will also give us 82% power to

detect a correlation between the 2 methods of estimating the position of the isocenter of at least 0.80 using a 2-sided significance level of 0.05. These sample size calculations were performed with nQuery Advisor ® 7.0 (Copyright © 1995-2007, Statistical Solutions, Saugus, MA).

9.0 Reporting Requirements

Adverse events will be reported to the IRB including serious adverse events classified as NCI Grade 3 and 4 toxicity, as well as hospital admissions related to treatment occurring within one month of treatment.

The adverse events will be graded according to NCI CTC version 4. Only grade 2 and above toxicity that is directly related to therapy will be required to be documented.

Pretreatment symptoms should not be considered as toxicity related to the treatment and are not required to be documented unless the symptoms worsen as a result of therapy.

10.0 References

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