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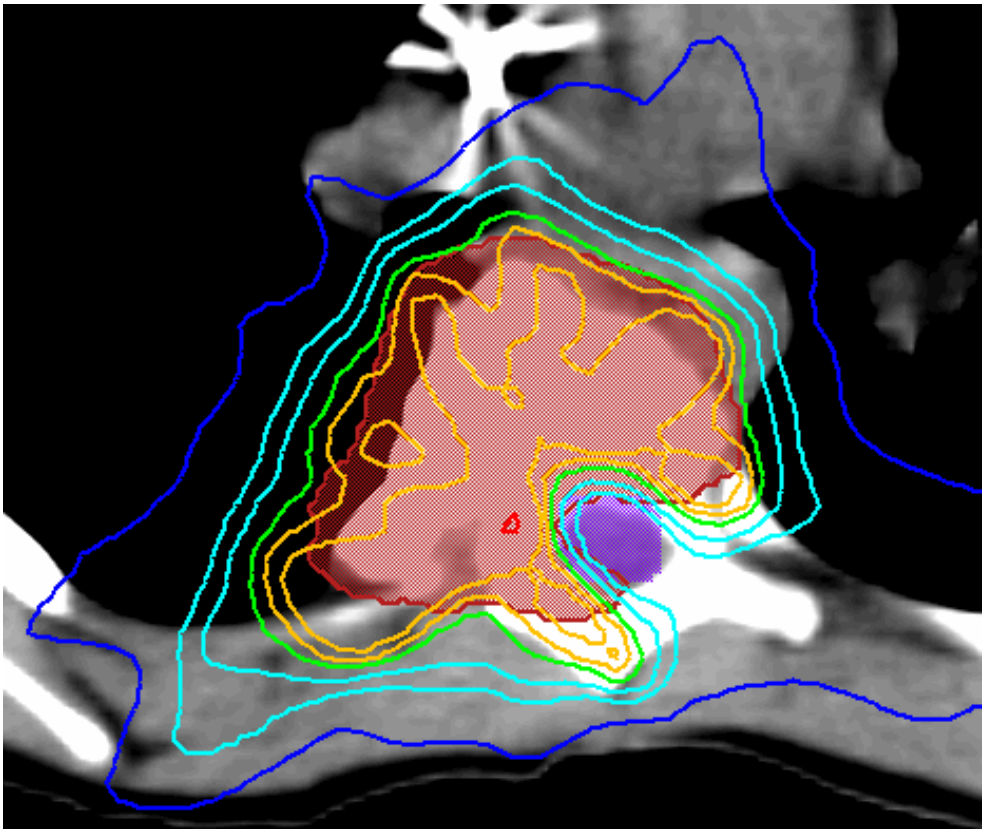

DOSE-INTENSIFIED IMAGE-GUIDED FRACTIONATED STEREOTACTIC BODY RADIATION THERAPY FOR PAINFUL SPINAL METASTASES (DOSIS) VERSUS CONVENTIONAL RADIATION THERAPY: A PHASE II RANDOMISED CONTROLLED TRIAL

-DOSIS RCT-

Dear colleagues,

As we presented on this year's SASRO and DEGRO meeting, we have initiated a multi-center randomised controlled phase II trial to compare long-term pain control after dose-intensified image-guided hypofractionated SBRT versus conventional radiation therapy for painful mass-type spinal metastases. This study will enroll total number of 146 patients randomized between the experimental and control arm. The study is open to all interested institutions:

We kindly ask you to participate in this initiative.

What is the background and rationale for this study?

Radiation therapy is an effective palliative treatment for painful spinal metastases. Because metastatic disease is considered incurable and uncontrollable, palliation - pain relief, stability of the vertebra and stabilization/improvement in neurological functions – is the primary treatment goal. Recent improvements in diagnosis, systemic and supportive treatments offer a chance to extend the life span of patients with spinal metastases beyond several months to several years. With longer survival the patients are at higher risk of metastatic tumor recurrence, especially patients with mass-type spinal metastases, a factor associated with poor local metastasis control. Thus, there is a need for a treatment that would ensure both durable pain control and metastatic tumor control in the patients with longer life expectancy, ensuring long-term palliation.

With the introduction of high dose stereotactic radiosurgery (SRS) and stereotactic body radiation therapy (SBRT) radiation doses become "curative" as compared to "palliative" low doses of conventional radiation therapy. The treatment goal is shifted from short-term symptom control to long-term local metastasis control and makes SRS and SBRT a candidate treatment for painful spinal metastases.

Despite its promising results, single-fraction SRS is associated with more recurrences in the epidural space and more frequent vertebral compression fracture (VCF). Hypofractionated SBRT may overcome the limitations of single-fraction SRS by redefining the target volumes and improving metastatic disease control while minimizing radiation-induced toxicity.

We hypothesize that hypofractionated SBRT employing simultaneous integrated boost (SIB) allows radiation dose escalation without increasing the risk of radiation-induced myelopathy and VCF. Radiotherapy dose escalation is expected to achieve long-term local metastasis control and thereby long-term pain control and long term palliation. Hence, a randomized phase II clinical trial with pain control at six months (primary end-point) and metastatic tumor control (secondary endpoint) in patients with painful mass-type spinal metastases and a long life expectancy was initiated.

What are the primary and secondary end-points of this study?

The primary end-point is pain response – improvement by ≥ 2 points on the pain Visual Analogue Scale at 6 months post-treatment at the treatment site. Secondary end-points are: local metastasis control, overall survival, Quality-of-life (Qol) and acute and late toxicity.

What are eligibility criteria for inclusion into this study?

Eligibility criteria for inclusion into this study are: Established histological diagnosis of a malignant primary or metastatic tumor; histologically, radiologically or scintigraphically proven spinal metastasis; pain in the affected spinal region or free of pain under pain medication; age ≥18 years old; Karnofsky performance status (KPS) ≥60%. For a more detailed list of eligibility criteria please refer to the study protocol.

What is the workload associated with this study?

Participating institutions must have a Quality Assurance (QA) for spine SBRT based on the site's SBRT method and equipment. The participating institutions will be credentialed, for which a facility questionnaire as well as a benchmark spinal metastasis case for static or rotational IMRT that they plan to use, must be completed. Unless the institution has been credentialed to participate in another EORTC or RTOG SBRT protocol, an Image-guided Radiation Therapy (IGRT) credentialing study is required. Before centers can be activated for the study, the protocol, the proposed patient information and consent form as well as other study-specific documents shall be submitted to a properly constituted Competent Ethics Committee (CEC) / foreign competent authority in agreement with local legal requirements, for formal approval. We will assist by providing background information and required documents.

All patients must be followed-up actively 2 years after treatment completion or until death. During active follow-up patients will be seen every 3 months. The following procedures will be done at every follow-up visit: physical and neurological examination; weight, vital signs, KPS; assessment of pre-specified protocol-specific adverse events applying the NCI CTCAE version 4.03 criteria; recording of all other adverse events; recording of pain and pain medications; recording of concomitant medications; radiology as clinically indicated for mass-type lesions, based on standard institutional protocol (CT and/or MR scans at 3, 6, 12, 18 and 24 months of follow-up); Health-related Quality-of-Life as measured by the EORTC QLQ-C15-PL, EORTC-BM22 and EQ-5D-5L patient reported questionnaires. Study data is entered into the Web-based data capture system SecuTrial®, Clinical Trials Center, University Hospital Zurich (USZ).

What is the timeline of this study?

This study has been open for recruitment since July 2016, and the first patient was recruited at USZ in September 2016. Last patient enrollment is expected for December 2018.

What can you expect from your participation?

According to the previous and successful practice of the working group, all participating centers will be co-authors on all publications. Results will be presented and discussed at the twice-annual working group meeting to ensure rapid distribution of new knowledge.

Patient fees as financial compensation for participating centers:

We will be able to provide a small financial compensation for data management.

We would like to ask you to confirm your interest in this study by responding to dosis@usz.ch and include the name of the contact person for your institution.

This study was presented at the Working Group Meeting in Zurich on December 10th. You will find detailed study information attached to this invitation.

Should you have any further questions, please to not hesitate to contact us..

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Publications:

1: Toussaint A, Richter A, Mantel F, Flickinger JC, Grills IS, Tyagi N, Sahgal A, Letourneau D, Sheehan JP, Schlesinger DJ, Gerszten PC, Guckenberger M. Variability in spine radiosurgery treatment planning - results of an international multi-institutional study. Radiat Oncol. 2016 Apr 18;11:57.

2: Thibault I, Chang EL, Sheehan J, Ahluwalia MS, Guckenberger M, Sohn MJ, Ryu S, Foote M, Lo SS, Muacevic A, Soltys SG, Chao S, Gerszten P, Lis E, Yu E, Bilsky M, Fisher C, Schiff D, Fehlings MG, Ma L, Chang S, Chow E, Parelukar WR, Vogelbaum MA, Sahgal A. Response assessment after stereotactic body radiotherapy for spinal metastasis: a report from the SPIne response assessment in Neuro-Oncology (SPINO) group. Lancet Oncol. 2015 Dec;16(16):e595-603.

3: Jawad MS, Fahim DK, Gerszten PC, Flickinger JC, Sahgal A, Grills IS, Sheehan J, Kersh R, Shin J, Oh K, Mantel F, Guckenberger M; on behalf of the Elekta Spine Radiosurgery Research Consortium.. Vertebral compression fractures after stereotactic body radiation therapy: a large, multi-institutional, multinational evaluation. J Neurosurg Spine. 2016 Jun;24(6):928-36.

4: Guckenberger M, Mantel F, Gerszten PC, Flickinger JC, Sahgal A, Létourneau D, Grills IS, Jawad M, Fahim DK, Shin JH, Winey B, Sheehan J, Kersh R. Safety and efficacy of stereotactic body radiotherapy as primary treatment for vertebral metastases: a multi-institutional analysis. Radiat Oncol. 2014 Oct 16;9:226.

5: Guckenberger M, Hawkins M, Flentje M, Sweeney RA. Fractionated radiosurgery for painful spinal metastases: DOSIS - a phase II trial. BMC Cancer. 2012 Nov 19;12:530.