Approaches to radiotherapy in metastatic spinal cord compression

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1. Suppli MH, Munck af Rosenschold P, Pappot P, Dahl B, Morgen SS, Vogelius I, Engelholm SA. *Stereotactic radiosurgery versus decompressive surgery followed by postoperative radiotherapy for metastatic spinal compression (STEREOCORD): Study protocol of a randomized non-inferiority trial.* Jour Radiosurgery SBRT 2016;4:S1–9.

2. Suppli MH, Munck af Rosenschold P, Dahl B, Berthelsen AK, Pappot H, Engelholm SA. *Premature termination of a randomized clinical trial on image-guided stereotactic body radiotherapy of metastatic spinal cord compression*. Submitted.

3. Suppli MH, Berthelsen AK, Munck af Rosenschold P, Hansen AE, Johannesen HH, Kjær A, Löfgren J, Paulus DH, Quick HH, Loft A, Andersen FL, Pappot H. *The potential use of PET/MRI in radiotherapy target definition of spinal metastases*. Submitted.

4. Suppli MH, Munck af Rosenschöld P, Pappot H, Engelholm SA. *Diabetes increases the risk of toxicity after re-irradiation of the spinal cord*. Manuscript in preparation

1. INTRODUCTION

Treatment of metastatic spinal cord compression (MSCC) is burdensome and survival is short. A common consequence of untreated MSCC is loss of gait function, which has serious implications for patient quality of life[1]. Therefore, MSCC diagnosis is considered an indication for urgent treatment even in a palliative care setting[2]. The randomized trial performed by Patchell et al. published in 2005 still defines surgery followed by radiotherapy as the standard of care and the median survival after MSCC has not changed substantially in recent years[3,4]. However, this approach is only available for a small selection of patients and the majority receives radiotherapy only[4,5]. Within this major group, short course radiotherapy is recommended but raises the risk of in-field progression of the irradiated tumor. Renewed treatment with overlapping fields within the spinal cord has the risk of radiation-induced myelopathy (RIM) and subsequent loss of gait. Radiation induced toxicity depends on the radiotherapy dose, dose per fraction, the irradiated organs and amount of tissue irradiated. All these factors are considered during the planning of radiotherapy in MSCC, and it is believed that a less invasive and shorter treatment of MSCC would be beneficial for patients. However, radiotherapy of MSCC should provide both efficient tumor control and acceptable compilations of normal tissue with a low risk of RIM.

2. OBJECTIVES AND OUTLINE

The studies in this thesis explore different approaches to treating metastatic spinal cord compression. The overall reason for embarking on these studies was to ameliorate patients from burdens of not only MSCC but also from potential adverse events and toxicity from the treatment.

The studies within this thesis is divided into four aims:

1. Design and initiate a randomized trial between SBRT and surgery plus fractionated radiotherapy in MSCC
2. Determine the feasibility of recruiting patients to be randomized between SBRT and surgery followed by fractionated radiotherapy
3. Investigate the feasibility of PET/MRI for target definition in radiotherapy of spinal metastases
4. Determine the rate of radiation-induced toxicity after re-irradiation of the spinal cord

3. FROM BONE METASTASES TO SPINAL CORD COMPRESSION

Bone metastasis is a common event across different types of primary cancers[6]. Morbidity due to skeletal metastasis during cancer progression has severe implications for the patient. Skeletal related events (SRE) as MSCC, pathologic fractures, radiation to the bone or bone surgery occurs in half of the patients with breast, lung or prostate cancer having bone metastasis[7]. These events affect the following disease course of patients with increased hospitalizations and higher mortality[8–13]. Bone metas-

tasis is frequently distributed to the spinal column leaving patients with risk of MSCC and vertebral fractures[6,14,15].

FORMATION OF BONE METASTASES

The selection of bone as a preferred site of metastasis has been known since Stephen Paget launched his "*Seed and Soil*" hypothesis in 1889[16]. Since the observation of a pattern of metastasis our understanding of this multistep process has increased[6]. The acquisition of features towards metastatic potential has been described and acknowledged as a key ability in cancer biology[17]. This has been termed the invasion-metastasis cascade and begins with local invasion followed by intravasation of cancer cells into the blood and lymphatic system. Through these vessels, cancer cells enter distant tissue and extravasate to form micrometastases[17]. These colonies of cancer cells grow to become metastatic tumors. This process requires specific changes in the cellular regulatory mechanisms and has been referred to as the epithelial-mesenchymal transition. As these steps in tumor progression are required, the bone microenvironment also plays a significant role in the formation of bone metastasis. Both cellular and structural features seems to be critical for preparing the "soil" before bone metastasis occurs. Adult bones are continuously remodeled by bone remodeling units (BMU)[6]. The formation of these units is regulated by the endocrine system. The availability of growth factors also regulate the number of BMU and thereby the rate of bone remodeling. The number of bone metastases is more dependent on bone remodeling than the number of cancer cells entering the system[18]. Clinical studies have shown a strong association between bone reabsorption and incidence of subsequent skeletal events in breast and prostate cancer[6]. The increased bone turnover also mediates preferential localization of metastasis[19]. Research have also hypothesized of the existence of a pre-metastatic niche in which a tumor prepares a distant site for metastasis[20]. In this concept, bone marrow derived hematopoietic cells are directed toward a future metastatic site to form fibronectin-rich patches prior to arrival of cancer cells. To enter the bone, cancer cells extravasate into bone marrow endothelium using the same physiological mechanism as used by hematopoietic stem cells homing to the bone[20].

INHIBITION OF BONE REMODELING

Bisphosphonates inhibit bone reabsorption thereby preventing and delaying SREs in patients with metastatic breast, prostate and lung cancer[10] . These drugs have also shown reduction in the development of new metastatic lesions in breast cancer. The antibody Denosumab against RANKL inhibit osteoclast modulation of bone and have shown superior effect on the incidence of SRE in breast cancer and prostate cancer[21]. Other bone targeting agents such as the alpha emitter Radium-223 also reduces the incidence of SRE in prostate cancer[22]. The use of these pharmaceuticals reduces the incidence of MSCC in the most heavily affected population of breast, lung and prostate cancer patients. A study by Coleman et al. showed no benefit in disease free survival when adding the bisphosphonate zoledronic acid as adjuvant treatment in early breast cancer. However a prespecified analysis of patients whom had undergone menopause for more than five years revealed a significant advantage of treatment with zoledronic acid[23]. The interplay between levels of estrogen and zoledronic acid is possibly affecting the microenvironment in bones creating a less hospitable sanctuary for cancers cells[24]. A meta- analysis showed significant reduction of local recurrence, distant recurrence, bone recurrence and death among patients with early breast cancer treated with adjuvant bisphosphonates[25]. A matched pair analysis also showed superior local control after radiotherapy of MSCC in patients treated with zoledronic acid[26]. Despite the amount of knowledge about the formation for spinal metastases, there exist no evidence of which metastases that will cause MSCC or any prognostic algorithms for the risk of developing MSCC[27].

4. METASTATIC SPINAL CORD COMPRESSION

CLINICAL PRESENTATION

Metastatic spread to the skeleton cause severe morbidity in cancer patients and results in a high frequency of SREs[7]. Spinal metastases can progress from a solitary uncomplicated lesion within the vertebral body to vertebral collapse or soft tissue expansion with compression of the spinal cord or the cauda equina[28]. The continuous compression and dislocation of the spinal cord will result in irreversible neurological injury. The progression to MSCC will lead to severe pain and loss of neurological function ending with paraplegia[27]. The natural history of development from spinal metastasis to MSCC is not fully studied. Numerous studies have revealed that early detection and treatment improve outcome in patients with MSCC[29–31].

Early diagnosis of MSCC before neurological deterioration is important for future preservation of motor function, as the loss of neurological function is often irreversible. Signs of epidural growth and symptoms therefore have to be acknowledged for diagnostic measures to be initiated. In a prospective study, the most common symptoms associated with MSCC were radicular pain followed by motor symptoms, sensory symptoms and bladder/bowel dysfunction. The distribution of symptoms was also associated to anatomical site of lesions. This is probably explained by the difference in the diameter of the spinal canal and difference in the length of nerve roots within the spinal canal that differs from the thoracic to lumbar spine [32]. Another study confirmed these symptoms with the finding of abnormal neurologic examination, stage IV cancer, known vertebral metastases and upper/middle back pain as independent predictors of MSCC diagnosis[33]. Pain is a non-specific symptom and very common in metastatic cancer patients and can therefore obscure the early acknowledgment of MSCC. Earlier papers divide the clinical picture of MSCC into a prodromal phase with local pain followed by a compression phase with development of more severe symptoms with radicular pain and subsequent neurological deficit progressing into paraplegia[34]. Uneven distribution of patient referral for radiotherapy in MSCC has been described and suggests a delay in diagnostic and referral procedures[35]. Delay in diagnosis and subsequent treatment will affect possible outcome and recovery of neurological deficits in MSCC. Therefore a low threshold for diagnostic MRI should be considered since pain often preludes neurological symptoms. In a Scottish study of delays in MSCC diagnosis, only 18% of patient were able to walk at the time of diagnosis but 94% of patients had progressive pain before neurological symptoms[28]. A similar pattern of MSCC diagnosis finds a preventable deterioration in neurological function during delays and better outcome in patients referred early to a designated center[36]. These delays remained a major problem in a study by Graham et al were patients had received insufficient doses of corticosteroids before referral to a tertiary center for treatment[37]. To reduce delays in MSCC several steps have to be considered from referral of patients under suspicion, initiation

of steroids, adequate capacity for urgent MRI, consultation with both surgeon and oncologist, so definitive treatment can start within short notice[38]. Despite majority of patients receiving radiotherapy only, a dedicated service for urgent surgical consultation should be provided for good prognosis patients. Lack of evaluation for surgery has been described within radiotherapy centers in the United Kingdom with only 41% of good prognosis patients being evaluated[5].

DIAGNOSIS

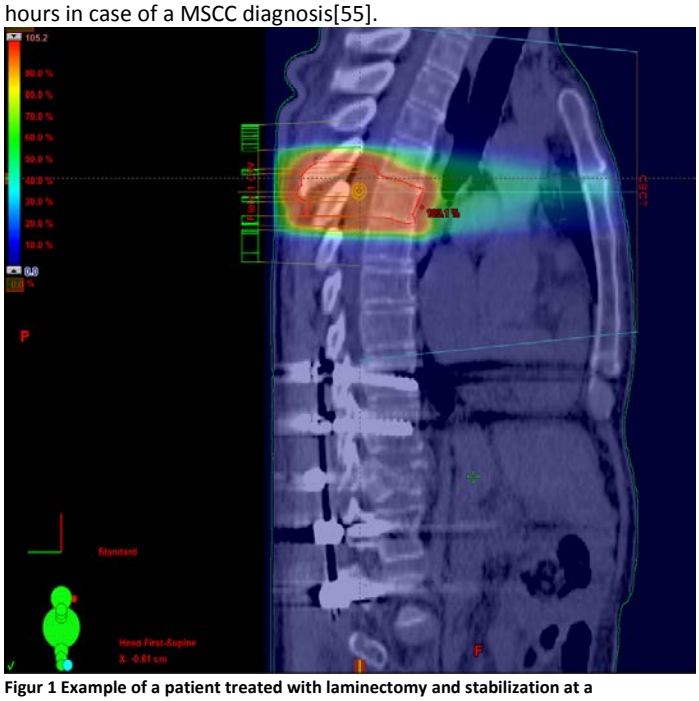
Appropriate imaging should follow the suspicion of MSCC. Today, the diagnostic features and availability of magnetic resonance imaging (MRI) has replaced the use of myelography. MRI has a higher sensitivity and specificity with the ability to differentiate between metastatic compression and vertebral fractures[39]. The use of MRI as a diagnostic imaging technique is recommended with both sagittal T1 and T2 weighted sequences with axial imaging of abnormal areas[40]. A disadvantage of MRI is the long scan time, which should be considered in patients with pain and neurological symptoms. Computer tomography is quick but less sensitive than MRI for detecting spinal metastases. In patients where MRI is contraindicated CT myelography remains the investigation of choice. Radiological MSCC is defined as "*the compressive indentation, displacement, or encasement of the thecal sac that surrounds the spinal cord or cauda equina by spinal epidural metastases or by locally advanced cancer*[2]".There exists no recommendation of routine MRI for the early detection of MSCC. One study found that 27% of patients with metastatic prostate cancer had non-symptomatic MSCC on MRI[41]. The use of screening MRI and pre-emptive treatment in castration resistant prostate cancer is currently studied in a randomized phase III trial (ISRCTN74112318). Patients with suspicion of MSCC should start corticosteroids to reduce edema and inhibit inflammatory response resulting in a delay of an irreversible injury to the spinal cord[2]. A randomized trial of high dose dexamethasone compared to none showed better neurological outcome[42]. The optimal dose has not been established as other studies failed to show a difference between high dose and low dose of corticosteroids[43]. Delays in patient referral and prior steroid use halted a full randomized comparison between 96 mg and 16 mg dexamethasone in an Australian setting[37]. In patients diagnosed with MSCC and no neurological deficits it may be safe to omit corticosteroids[44]. In patients undergoing palliative radiotherapy of bone metastases, dexamethasone reduces the incidence of pain flare[45]. The severity of MSCC is not uniformly described. Diagnostic imaging does not always correspond well to the neurological condition of the patient. As described above the existence of an occult compression without symptoms is detected in a MRI screened population[46]. The severity of compression may also differ from older studies using blockage of cerebrospinal fluid at a myelogram. In studies using MRI, the degree of spinal compression may also reflect differences in severity and outcome e.g. the randomized trial of surgical decompression required cord displacement instead of compression for trial inclusion[3]. A high discordance between level of pain, level of sensory disturbance and level of structural compression by MRI has been reported[28]. Since no definite consensus of MSCC severity exist the Epidural Spinal Cord Compression score (ESCC) has been developed and validated[47]. The inter- and intra-observer variation has been studied with substantial agreement of level of compression and grading on the ESCC score[48]. For clinical decision making Ryu et al. has criticized the lack of neurological status and suggested an dual grading consisting of radiographic and neurological grade[49].

These different grading systems have not been consistently used in existing trials and are not used in the presented studies within this thesis. However these differences in MSCC severity should be considered when interpreting literature. Diagnosis of subclinical MSCC defined as American Spinal Injury scale (ASIA) E with normal sensory and motor function has a favorable prognosis compared to ASIA A-D[50].

A more systemically use of grading is needed to describe patient characteristics within different trials. In a retrospective study of uncomplicated spinal metastases there was epidural involvement in more than 60% of patients[51].

5. DEFINITIVE TREATMENT OF METASTATIC SPINAL CORD COMPRESSION

The treatment strategy of MSCC is related on a number of patient related factors. The outcome after treatment relies heavily on functional status at the time of treatment. Long-term survival depends on primary tumor, anti-neoplastic treatment and functional outcome after treatment. There is consensus upon the immediate treatment of patients diagnosed with MSCC to preserve neurological function. Prolonged loss of motor function cannot be restored by either surgery or radiotherapy. The timeliness of treatment initiation influence the resulting outcomes in both radiotherapy and surgery with superior results if treatment starts within 48 hours of diagnosis[52–54]. The National Institute of Health and Clinical Excellence (NICE) in United Kingdom recommends MRI within 24 hours and definitive treatment within 24 hours in case of a MSCC diagnosis[55].



Figur 1 Example of a patient treated with laminectomy and stabilization at a lumbar lever of the spine. Renewed compression at a thoracic level and treated with RT only.

SURGERY FOLLOWED BY RADIOTHERAPY

A small study from 1980 randomized patients between surgery followed by radiotherapy or radiotherapy alone[56]. This showed no difference among 29 recruited patients. No proper powered

study of the role of surgical decompression in MSCC was therefore undertaken until 1992. To date only one properly conducted randomized clinical trial exists[3]. This trial compared surgical decompression plus radiotherapy with radiotherapy alone in surgical fit patients with a solitary lesion causing MSCC. Decompression and radiotherapy was superior to radiotherapy alone. Surgical approach was depended on localization and stabilization was done if spine instability was present. Radiotherapy was done with 30 Gy in 10 fractions. A higher post treatment ambulatory rate was achieved with surgery (84% vs. 57%) and patient retained ambulatory rate longer (median 122 days vs. 13 days). This study was closed early due to a predefined stopping rule. At the time of trial termination 101 patients were randomized from September 1st 1992 until December 31st 2002. The study has been criticized for having included the majority of patients from one center only with 70 of 101 patients enrolled at University of Kentucky. In the group randomized to radiotherapy only, 18 out of 51 patients had spine instability but as a result of the randomization they were excluded from surgical stabilization[57]. Radiotherapy may not relieve symptoms due to compression from bone fragments. The recruitment time of more than ten years and the criteria for eligibility have also been criticized for inducing selection bias[57,58]. Even though, this trial still defines the treatment for MSCC. Laminectomy may compromise spinal stability and therefore instrumentation and stabilization is usually performed in the same procedure[59].The role of postoperative radiation to preserve neurological function has been confirmed in a retrospective study[60].

FRACTIONATED RADIOTHERAPY

Fractionated radiotherapy is one of the most frequent used modalities for MSCC. Treatment with either single fraction or multiple fractionated RT has shown equivalent efficacy in both bone metastases and MSCC[61,62]. Single fraction RT is therefore preferred in majority of patients with limited expected lifespan and poor performance[63]. Local recurrences are more frequent after single fraction therapy so fractioned RT is often used in patients with favorable histology and in good performance[64]. Two Italian trials have reported the use of short course versus split course RT in MSCC. The first trial investigated the use of 16Gy in 2 fractions, split course with a six days break or short course of 30Gy in 6 fractions delivered in a split course of 15Gy/3 fractions with a four days break[61]. Patients had compression of the spinal cord, no indication for surgery and expected survival less than six months. 56% of patients experienced pain relief and 69.5% maintaining ambulatory function. None of seventeen paraplegics regained function. There was no difference between groups. One-year survival was 10.1% and 18.1% for short-course and split course regimens respectively (P=0.136). A following trial randomized patients with similar eligibility criteria to 16Gy/2 fractions, split course with a break or 8Gy/1 fraction[65]. Response with maintaining or improving motor function was achieved in 199 patients (66%; 95% CI, 60–71), 16GY/2F: 69% (95% CI, 61–76) and 8Gy/1F 62% (95% CI, 54–70). One of 26 paraplegics regained function.

A prospective non-randomized trial compared short course versus long course of RT[66]. Again there was no difference between short or long course treatment and neurological outcome. 111/131 patients (84%) treated with short course and 113/134 patients treated with long course maintained or improved neurological function. Local control rates were for the following regimens - 8Gy/1F: 59%; 20Gy/5F: 62%; 30Gy/10F: 83%; >30Gy: 76%. Short course RT was significantly associated with higher risk of local failure: risk ratio [RR] 2.27; 95% confidence interval [CI], 1.15–4.76; p = 0.018. A new randomized trial was undertaken by the same authors to randomize patients between 30Gy in 10 fractions and 20Gy in 5 fractions[62]. Patients recruited had poor or intermediate survival by a validated prognostic score[67]. All patients had motor deficits of the lower extremities and patients were not eligible for surgery. 203 patients were recruited and randomized to either short or long course RT. Primary endpoint was motor function defined as improvement or no further progression of deficits. At one month 88.4% of patients had improvement or maintained neurological function. By treatment this was 87.2%(68 of 78 patients) in short course RT and 89.6%(69 of 77 patients) after long course RT. (P = .73; X^2-test). Local progression free survival at six months was 81.8% after 30Gy/10F and 78.4 after 20Gy/5F(P=0.051; log-rank test). Median overall survival was 3.2 months. Two more randomized studies are awaiting publication. The ICORG 05-03 study comparing 10Gy/1F versus 20Gy/5F was presented at the American Society of Radiation Oncology Conference 2014 as a late breaking abstract but await full publication. The trial showed no difference in preserved mobility between 10Gy/1F versus 30Gy/5F[68]. The SCORAD trial has finished accrual and has randomized patients with MSCC between 8Gy/1F and 20Gy/5F (ISRCTN97108008).

STEREOTACTIC BODY RADIOTHERAPY

Stereotactic body radiotherapy (SBRT) is a recognized technique for delivery of radiation using spatial coordinates to irradiate the target[69]. Lars Leksell pioneered the technique of cranial SBRT with the development of the Gammaknife system in 1968 using of a stereotactic head frame and radioactive Cobolt-60 sources. The technique was then transferred to ekstracranial sites with the use of a stereotactic body frame[70]. This technique is now widely developed and used in a range of extra cranial sites. With this development of SBRT as modality, the use of spatial coordinates is not necessarily required and commonly referred as frame-less treatment. In current medical context, the term SBRT is therefore often used as a description of treatment with high radiotherapy doses with a highly accurate focus in one or few session. The purpose of delivering a high radiation dose is to increase efficacy in tumor response with a sparring of the normal tissue of a high dose of radiation due to accuracy of treatment but achieving a threshold to provide cure in early disease[71,72]. Stereotactic radiosurgery is used as the name for intracranial treatment and has also been applied to one session extracranial SBRT. As a precise definition is not agreed upon, the use of stereotactic ablative body radiotherapy (SABR) has also immersed as a name for SBRT/SRS modalities of radiation doses with curable intent[72]. SBRT has also been suggested as a method of overcoming intrinsic radioresistance as observed in different human cell lines[73]. The effect of radiotherapy has been described by the 5R's of radiobiology with the first four suggested by Withers and expanded with a fifth by Steel et al[73] .

1. Repair
2. Repopulation
3. Redistribution
4. Reoxygenation
5. Radiosensivity (Radioresistance)

SBRT is suggested an effective treatment modality in tumors believed to be less radiosensitive as renal cell carcinoma, sarcoma[74–76]. An additional effect of SBRT on tumor response to overcome intrinsic radioresistance due to vascular damage has been explored[77]. However current results suggest that the currently use of the linear quadratic model can explain clinically observed results in SBRT[71,78].

Since the first use of Spine SBRT in 1995 a number of reports have been published[69]. All these reports unfortunately lack a control group for direct comparison with fractionated RT to the spine. Numerous phase I/II trials, retrospective trials and consecutive single institutions series report different setups for treatment with different indications and different endpoint making comparisons very difficult[79–82,75,83,84]. Despite the lacking comparison with conventional techniques, spine SBRT has been widely adopted across the US and several European institutions[85,86]. Results from the RTOG0631 have been reported and show that spine SBRT is a feasible modality and treatment can be done with acceptable dose delivery, accuracy and target coverage[87]. A Phase III part of the RTOG0631 is currently recruiting. These studies are conducted with the aim of local tumor control and palliation but not for decompression of a threatened spinal cord compromise.

As spinal metastases progress and extent into the epidural space, the expansion will begin to compress the spinal cord. The development from localized spinal metastases to complete spinal cord compression must be considered a continuum. Trials of spinal metastases recruit patients allowing different degrees of epidural growth and compression. A framework for handling these discrepancies has been described in the NOMS framework from Memorial Sloan Kettering Cancer center[88].

There is strong agreement that metastatic spinal cord compression should be treated early to preserve neurological function. But retrospective analyses show that a large proportion of patients with spinal metastases from prostate cancer has radiological compression in the absence of clinical symptoms[46]. There is no consensus on the optimal timing of intervention of early treatment in asymptomatic patients since a very early treatment must be viewed as a preventive strategy[27]. To discriminate between vertebral metastases with epidural expansion and MSCC, trials of spine SBRT described above have in a number cases required a gap between target and spinal cord of two to five mm[89].

A single arm trial of SBRT treatment of MSCC has been published[90]. In the trial of 62 consecutive patients with 85 lesions were treated with SBRT. Patient had malignant disease with MRI consisted with canal compromise, thecal indentation or cord displacement. Patients had minor neurological deficits with muscle weakening. If patients had paralysis they were referred for surgery. Treatment was done within 48 hours with SBRT of multiple beams in a single fraction to a dose of 14Gy-20Gy prescribed to the 90% isodose line. This trial showed effect on MSCC with preserved neurological status in 85% (53/62 patients) with acceptable toxicity. A retrospective study of patients with MSCC due to myeloma has also been published[91]. Here 24 patients with 31 lesions were treated with SBRT to a dose of 10-18Gy. MRI confirmed MSCC diagnosis. Of the 24 patients, 3 patients were lost to follow up, one patient was referred to surgical decompression and remaining patients had preserved neurological status. The STEREOCORD trial described in this thesis was an effort to investigate this population in randomized trial comparing SBRT to current standard of treatment as described by Patchell et al[3].

POSTOPERATIVE STEREOTACTIC BODY RADIOTHERAPY

The rationale for the administration of SBRT postoperatively is to deliver a higher radiotherapy dose to the defined target. In selected patient with long time survival the incidence of in-field recurrence is high with conventional fractionated radiotherapy. Treatment dose escalation has been suggested to minimize the risk of relapse within the radiotherapy field and reduce the need for re-irradiation[92]. Postoperative SBRT gives the time for radiotherapy planning while the patient recovers from surgery. Special consideration has to be taken in postoperative SBRT due to instrumentation[92]. There are several reports of the application of postoperative SBRT after different surgical procedures of spinal metastases. One report of SBRT after kyphoplasty of malignant vertebral fractures shows local control in 24/26 patients (92%)[93]. In a report of different surgical approaches followed by SBRT, in patients with either neurological decline or epidural disease, 17/18 patients (94%) achieved local control [94]. For patients treated with SBRT after surgical decompression in radioresistant tumors, local control was reported in 18/21 patients. A larger series of patients receiving either stabilization and/or decompression with SBRT, local control was achieved in 59/80 patients (73%)[95]. To further dose escalate and spare the cord the term “separation” surgery as been deemed a way to allow this. In 186 patients who received decompressive surgery followed by high-dose radiotherapy, local control was achieved in 152/186 patients (82%)[96]. Another study reported local control of 74% of 69 treated tumors in 66 patients[97]. All of the mentioned studies are departmental series without comparative controls. Different eligibility criteria for treatment with SBRT exist with high number of tumors considered to be radio-resistant or previously treated with conventional radiotherapy. The reported rates of local control can therefore be a result of selection bias of patients with a different disease course. The degree of epidural disease is a risk factor for local failure after spine SBRT probably due epidural underdosing and spinal cord constraints[95]. Analyses of patterns of failures after postoperative spine SBRT highlight the need for throughout evaluation of preoperative imaging for epidural disease[98]. These findings have to be continuously incorporated into contouring guidelines and validated. Consensus on target definition in radiotherapy planning has been published to harmonize contouring guidelines for comparison between studies[99]. A decision tool to support the use of surgery in conjunction with SBRT exists with the NOMS decision framework[88]. Here surgery is indicated by either spinal instability or high-grade compression by ESCC scale. This decision tool also takes radioresistance of the tumor into consideration for the use of SBRT instead of conventional fractionated radiotherapy. A method to access spinal stability is the Spinal Instability Neoplastic Score (SINS)[100]. A high SINS score has been correlated with vertebral fractures after both fractionated radiotherapy and SBRT of spinal metastases[51,101].

6. IMAGING IN SPINAL METASTASES

RT of spinal metastases is planned from CT scanning images used to simulate patient setup and calculate radiation dose. Definition of the RT target is based on patients history, clinical examination and imaging. Historically the target included two vertebrae above and below the intended target[102]. In patients with metastatic

cancer and several metastatic lesions, there can be inconsistencies between patient history, clinical examination and imaging[28]. Furthermore, delivery of large fields of radiation can results in increased side effect from radiotherapy. Multiple lines of therapy using different modalities may also interfere with the concordance of findings during workup of patients referred for MSCC diagnostics. MRI is the preferred imaging modality in patients under evaluation for MSCC[40]. This modality provides the best soft tissue resolution to evaluate the compression of the spinal cord. This also provides the best sensibility of MSCC detection and can differentiate between malignancy and fractures[39]. The use of functional and molecular imaging modalities mimics intrinsic capabilities of tumors such as metabolism, hypoxia, proliferation and perfusion using techniques as positron emission tomography (PET), MRI and single-photon emission computed tomography (SPECT)[103]. PET allows visualizing the metabolism of specific injected radiotracers. The most common used tracer in cancer imaging is 18F-flouro-2-deoxy-D-glucose (FDG) that exploits the upregulation of glycolysis in cancer cells, known as the Warburg effect. FDG-PET/CT is a widely used imaging modality within cancer diagnostics and therapy. FDG-PET/CT is also common used for radiotherapy planning in target delineation e.g. Head and Neck, Gynecology malignancies etc. [104]. PET imaging can be used to detect bone metastases and evaluate treatment response[105]. PET imaging has better sensitivity and specificity than bone scintigraphy (99Tc-MDP). Specific tracers exist than can be used for bone metastases with better specificities than FDG. More bone specific tracer as 18F-NaF or 11C-choline is often used for diagnosis of bone metastases in breast- and prostate cancer. In more advanced disease stages, as when prostate cancer becomes castration resistant, FDG uptake is increased[106].The functional processes visualized can be used to guide radiotherapy by incorporating this into target definition and delineation. The quantitative metrics provides by PET has been considered especially valuable with the used of dose escalation and dose painting[107]. The purpose is to use this information to overcome intrinsic resistance to radiotherapy by escalating dose to hypoxic/hyperactive regions of the tumor[103]. The use of molecular imaging for the prescription of different dose levels within the radiotherapy target is called dose painting and not adopted for daily clinical practice. Another purpose of functional imaging could be to spare essential functioning organs from radiotherapy dose[108]. Functional imaging may also provide useful information for the planning and evaluation of palliative radiotherapy. A change in the maximum standardized uptake value (SUV_{max}) in 18F-FDG-PET is correlated with pain response in palliative radiotherapy of bone metastases[109]. The use of metabolic information in palliative RT of bone metastases has been evaluated in a phase II trial. Patients were randomized between three options of radiotherapy: 8Gy/1F, 8Gy dose painting by numbers/1F or SBRT 16Gy/1F. The results showed the best pain response after 8Gy dose painting by number. This approach is undergoing further evaluation in a randomized clinical phase III trial[110]. In spine SBRT the use of all available images is recommended incorporated into RT planning including the use of FDG-PET and functional MRI[111]. Particularly in instrumented postoperative patients, the metal distortion from spinal implants can affect target delineation and metabolic information may be useful[112]. Radiotherapy treatment of gliomas may result in pseudoprogression that accounts for the symptomatic and visually progression due to treatment effects instead of tumor progression. This has also been reported after spinal SBRT. Both PET and functional MRI has been suggested as an imaging modality to differentiate from true progression[113].

With the use of MRI modalities the superior soft tissue differentiation of the MRI can be applied to guide and monitor treatment with high-resolution soft tissue contrast. Newer imaging modalities have become available with the possibility of combining the anatomical images from MRI and functional imaging from PET. This is integrated in the hybrid PET/MR imaging. A PET/MRI system is installed at Rigshospitalet with numerous clinical investigations of clinical use[114]. This modality is believed to be of use to guide cancer treatment and monitor response especially were MRI is considered a preferred modality to CT.

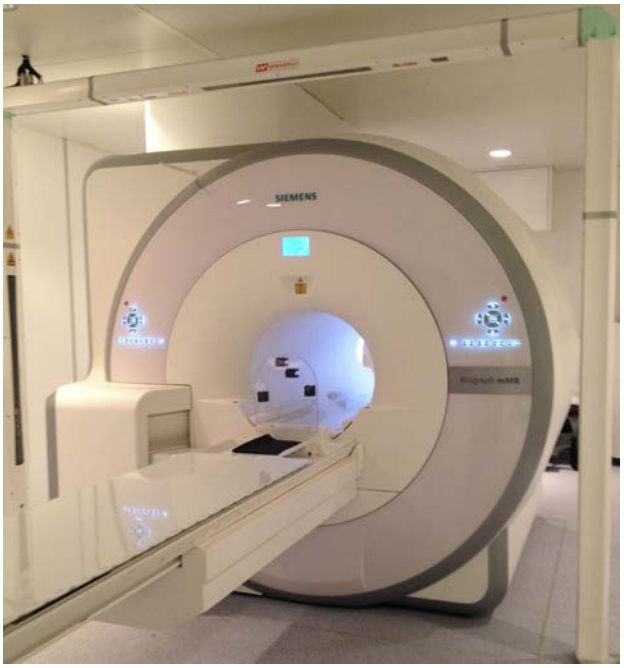


Figure 2 PET/MRI with the flat tabletop positioned on top of the conventional radiofrequency spine array coil and the systems patients table.

7. RE-IRRADIATION OF THE SPINAL CORD

Radiotherapy studies of different fractionations schedules show equal effect in neurological outcome. This is similar to the current recommendation for palliation of bone metastases with 8Gy/1F as the preferred schedule. In-field relapse is more common after shorter course of radiotherapy. Relapse will sub sequentially lead to symptomatic progression and a decision whether to re-irradiate the spinal cord at the same level. Radiation-induced myelopathy (RIM) is a risk following both primary irradiation and re-irradiation of the spinal cord. The consequences can be similar to that of MSCC with loss of neurological function and loss of gait. The risk has therefore to be considered before prescribing renewed radiotherapy within the spinal cord. However the consequences for a patient with developing MSCC left without treatment also needs to be considered in the risk assessment. Experimental animal model has shown a recovery from initial radiation within the first year after treatment[115]. The initial changes of RIM occurs within 4-6 months in animal models[116]. Due to the risk of myelopathy and paralysis, re-irradiation of the spinal cord has previously been considered an inacceptable option[117]. With the knowledge from animals models of partial

recovery re-irradiation begun to be prescribed. With the acceptance that the majority of patients are not alive long enough to experience myelopathy, patients with MSCC can be offered re-irradiation of the spinal cord[118]. Published cases of re-irradiation of the spinal cord report a low incidence of RIM[119,115,120–123]. Even second re-irradiation of the spinal cord has appeared to be effective and safe though the re-irradiation doses in second and third course was low (4Gy)[124]. Toxicity after re-irradiation of the spinal cord has been reviewed and updated with recommendation for risk assessment[125,126]. The risk of myelopathy is presumable low in the following conditions:

1. Cumulative dose is less 135.5 Gy_2
2. Interval between treatment is more than 6 months
3. No course exceeds the dose of 98Gy_2

$$Biological\ Effective\ Dose\ (BED) = nd\left(1 + \frac{d}{\alpha/\beta}\right)$$

According to Linear Quadratic model with n equals number of fractions, d equals dose pr. fraction α/β=2 Gy. Similar estimations have been done with re-irradiation of the spinal cord with SBRT using a normalized BED (nBED) to $Gy_{2/2}$[127,128]

Data on re-irradiation from the two Italian randomized clinical trials on fraction schedules have been published[129]. In field progression occurred in 24 patients with 12 patients receiving re-irradiation. No patients with RIM were recorded. In a retrospective analysis of re-irradiation of spinal metastases with intensity modulated radiotherapy (IMRT) there was no cases of RIM[130]. There were no toxicities in a similar study using IMRT to do relative sparring of the cord in 31 patients receiving re-irradiation of spinal metastases[131]. A number of studies have used spine SBRT techniques to escalate dose to the vertebrae with reduced spinal cord dose in the re-irradiation setting[132–136]. The dose escalation with spine SBRT does poses a risk for radiation-induced myelopathy due high dose to small volumes of spinal cord and dose-volume effect from radiation to partial/circumferential cord[137,138].

8. SUMMARY OF FINDINGS

STUDY I

Stereotactic radiosurgery versus decompressive surgery followed by postoperative radiotherapy for metastatic spinal compression (STEREOCORD): Study protocol of a randomized non-inferiority trial

This study presents the design of the randomized trial. The publication of trial protocols is encouraged to enhance the transparency of trial procedures and study end points. Registration in a trial register is also recommended. Since the investigational procedure in this study was not a standard treatment at the radiotherapy facility, a proper protocol of all steps of treatment was developed. During trial enrollment the procedure had to be done in a timely manner and all steps from the randomization to end of treatment had to be agreed upon by trial investigators. Some institutions fuse the images from the diagnostic MRI with the images from the simulation CT. The patients in this study had compression of the spinal cord and therefore potential progressive dislocation of the spinal cord with time. The accuracy of the spinal cord position has tremendous consequences for the dose planning in order to escalate the dose gradient towards the target[139,140]. Therefore this protocol demanded a repeated simulation MRI to be done on the same day of the simulation CT. The CT and MRI were then fused for delineation and dose planning.

Delineation was done as presented by the Spine Radiosurgery consortium but with allowance of epidural inclusion of the clinical target volume[141]. Target dose and normal tissue constraints were adapted from the RTOG0631[87]. The use of flattening filter free (FFF) beams were discussed but the trial refrained from this to ensure the timeliness of treatment delivery since only one linear accelerator with the possibility of flattening filter free beams is installed in our radiotherapy facility. The use of FFF beams has been suggested for the use in SBRT stadium I lung cancer and spine SBRT[142]. The advantage of this approach is to reduce dose to peripheral tissue from electronic scattering and thereby reducing normal tissue complications[143]. The removal of the flattening filter from the linear accelerator allows higher dose rate with dose being delivered faster. This could possibly reduce beam-on time with a reduction of intrafractional movement if the patient spends less time on the treatment table. Different modes of dose delivery are used among institutions. Intensity-modulated radiotherapy (IMRT) with steep and shoot is used at several institutions with usually several posterior beams used[80]. Volume-modulated arch therapy (VMAT) is another approach with the use of one or several arc[86]. IMRT with posterior beams is time consuming but allows multiple imaging during treatment. VMAT is more time efficient but leaves fewer options for image-guidance during treatment especially with the use of a single arc. Dosimetric studies shows better sparring of the spinal cord with IMRT compared to VMAT but multiple arc VMAT is comparable in respect to spinal cord dose[144]. There exist no international consensus on optimal treatment delivery and no clinically comparisons of techniques. Within the current trial three full arcs (180°) were used for treatment delivery. Different immobilization devices have been used for spine SBRT[145]. In this trial, a regular head mask including shoulder immobilization was used for upper thoracic and cervical lesions. No immobilization device was used for lower thoracic and lumbar lesions. Instead the trial relied heavily on online imaging and setup before and during treatment delivery with the use of cone beam CT and stereoscopic imaging (ExacTrac, Brainlab)[146].All procedures were controlled in a dry run before initiation of the trial. The trial was designed as a non-inferiority trial since the goal was not to prove superiority compared to surgical decompression and fractionated radiotherapy. In non-inferiority trials the chosen level of inferiority has an impact on the feasibility of the trial and on the subsequent interpretation of the trial. In this setting a very small level of inferiority would make the investigational procedure more attractive but require a high number of patients that would render the trial unfeasible. The level of inferiority was chosen to be a 15 % deterioration, which is comparable to similar trials in MSCC. The level of inferiority is debatable but the intervention should also be viewed in the context of the risk associated with standard procedure. The risk of non-neurological morbidity after a surgical intervention in published papers is on average 15 %[147] why it is could by acceptable with at rather high inferiority level of 15% if the investigational procedure is safer and tolerable for the patients. There is no consensus of the choice of study end points, which complicates comparison between clinical trials of neurological outcomes in patients [57]. In this trial a validated questionnaire was chosen with the reported ability to walk as the chosen end-point. Patients with MSCC are referred to our institu-

tion from other centers to receive treatment. Afterwards follow-up and additional cancer treatment will continue at the referring center. An end-point that required a minimal number of additional visits was preferred. Therefore the EQ-5D-5L questionnaire was used with the 5L version used to obtain more study power than if the 3L version was used. Global Spine Surgery Group recommends the use of this questionnaire due to its simplicity[148]. Other measures of outcome could have been used, such as physician accessed gait function. Questionnaires lack the ability to distinguish between causes for the functional decline. Patient-reported-outcomes have been used as end-point in other trials and have been used to assess pain, function and degree of symptom frustration after radiotherapy of bone metastasis[149]. In a previous study the use of EQ-5D-3L was shown to be feasible in a population with MSCC treated with either surgery or radiotherapy[150]. The answers in this cohort were used as a reference for the power calculation used in study I.

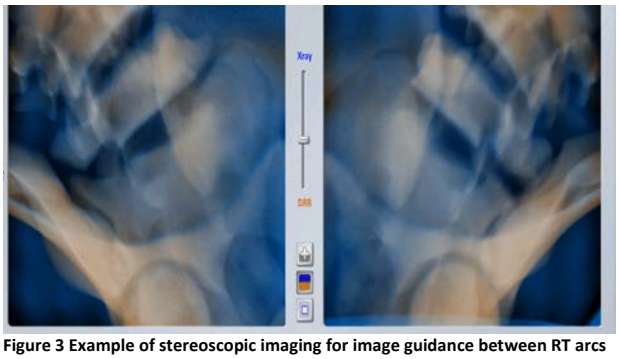


Figure 3 Example of stereoscopic imaging for image guidance between RT arcs (ExacTrac)

STUDY II

Premature termination of a randomized clinical trial on image-guided stereotactic body radiotherapy of metastatic spinal cord compression

Study II presents the results of the initiated randomized controlled trial to investigate the use of SBRT in patients with MSCC. Prior trials have been conducted in selected populations without comparison to conventional techniques. Spine SBRT has been widely adopted in American institutions but evidence supporting this adaptation is missing[69,85].

Due to the large number of patients referred for treatment of MSCC to our institution, we were confident that this trial was feasible[4]. Our institution has a single entry dedicated care path of patients with MSCC allowing multidisciplinary evaluation. However, the concluding review showed that only a limited number of patients were able to undergo surgery. The majority of patients operated did not undergo randomization due to the inclusion and exclusion criteria. The criteria used in this protocol were based on à priori knowledge of clinical presentation requiring surgical intervention, which precluded patients from entering the randomization. In the case of spinal instability, instrumentation is advised before radiotherapy, as vertebral fractures is a known adverse event after spine SBRT. Urgent treatment is required in acute onset of paresis to preserve neurologic function. The procedures in spine SBRT require a full day of planning before treating the patient and therefore it can take up to 48 hours from trial consent until treatment. In patients with complete motor paralysis, treatment is required within 48 hours to enhance chances of regaining neurological function[53]. Patients with complete motor paralyses were therefore not eligible for the trial. The eligibility criteria used in this research protocol are therefore agreed upon for the individual enrolled patient to fulfill the criteria for clinical equipoise and not being at risk of an inferior treatment[151].

The trial recruited ten patients in 23 months. The results showed that patients recruited could be planned and treated in a timely manner. The treatment was effective with preserved neurological function in three of four treated patients. The efficacy compared to surgical decompression followed by fractionated radiotherapy could not be provided due to premature termination of the trial. There is therefore sufficient scientific uncertainty of the clinical effect of SBRT to support continuous investigation of this modality in MSCC[151]. Two patients had a vertebral fracture as an adverse event. No other unexpected serious adverse events were registered during the study. Outcomes six weeks after treatment by the dimensions in the EQD5-5L are provided in supplementary. For the dimensions of mobility, self-care, usual activities, pain and depression/anxiety the results show either “No” or “Slight” problems after SBRT. Therefore in the patients randomly selected for SBRT, the procedure was safe, tolerable and feasible.

Age	Sex	Diagnosis	Intervention	Event	Spine level
68	Male	C. vesicae	Radiosurgery	Fracture	L4
72	Female	NSCLC	Radiosurgery	-	L4
66	Female	C. coli	Decompression	Palliative care	Th1
48	Male	C. oropharyngis	Decompression	-	Th2-Th3
55	Male	C. vesicae	Decompression	-	L4
77	Female	NSLC	Decompression	Reirradiation	L4
76	Male	hepatocellulært carcinoma	Decompression	-	L4
63	Male	Unknown primary	Radiosurgery	Neurological deterioration	Th6
80	Male	C. vesicae	Decompression	No postop RT / Palliative Care	L2
59	Male	C. renis	Radiosurgery	Fracture	Th4

Table 1: Characteristics of enrolled patients. Level of compression by vertebrae with thoracic (Th) and lumbar (L).

The randomized controlled trial (RCT) is considered the optimal way to collect data for evaluation of treatments. A well-performed RCT will provide the confidence in the effect of the treatment and the potential side effects associated with both the investigated treatment and comparator. A RCT is also the most effective way to avoid bias seen in uncontrolled trials where the believed benefit is not necessarily related to the treatment[152–

154]. Unfortunately, a RCT can be hard to complete. Numerous trial comparing radiotherapy and surgery has been terminated early due to accrual problems[154]. Even though trials have not recruited the intended number participants the data acquired should be provided by the investigators to secure maximum benefit of the invested time and discomfort for patients as well as provide essential information for future studies[155]. The results show that it can be very challenging to conduct a RCT in this setting with an acute event, rare eligible cases and a time consuming and laborious procedure. Even at our institution with a high number of patients and an acceptable number of cases offered decompression, a feasible recruitment rate was impossible. A number of precautions are necessary to offer patients the best treatment. Among the patients randomized, it was feasible to deliver SBRT in a timely manner with a positive effect on outcome. But unfortunately the current setup and limited amount of patients included was unable to establish non-inferiority of SBRT to surgical decompression with fractionated radiotherapy.
Vertebral compression remains a concern for the use of SBRT in MSCC. Due to the greater expansion of the tumor with involvement of the epidural space the concurrent risk of vertebral compression could be higher than in uncomplicated vertebral metastases. Treatment of solitary uncomplicated vertebral metastases without epidural involvement does not necessarily require surgical intervention and a randomized trial comparing surgical stabilization with SBRT in uncomplicated vertebral metastases would therefore not contain clinical equipoise[151].
The current study wanted to challenge the standard of care as defined by Patchell et al. Another option would be to conduct a trial that randomize patients between fractionated radiotherapy and SBRT in surgical unfit patients. This might be a more feasible trial but would not bring clarity of the considerable morbidity associated with surgery in this fragile patient population. The true benefit for the patient could therefore be minimal. Unfortunately termination of clinical trials is a major problem in medical research[156]. Poor accrual is the most significant obstacle to completing trials[156]. Factors associated with poor accrual have been identified as number of eligibility criteria, non-industry sponsorship, earlier trial phase, and fewer study centers[157]. Even though accrual is a practical problem it should also been seen an ethical problem. Patients included in clinical trials cannot be certain of a clinical benefit and are at risk for receiving a substandard treatment. If trial accrual is seriously haltered an early termination is recommended in order to maintain risk-benefit balance as perceived in the protocol. Continuing studies for a prolonged period of time with very low inclusion will change the risk-benefit standard to a lower proportion of benefit and a higher proportion of risk for a treatment without proven benefit[157]. Even though the included number of patients in the current trial was minimal the accumulated knowledge is valuable for future research and should therefore be published[157,158]. Evaluation of technical improvements has been challenging in medical research. In the case of robot-assisted surgery very little research has been conducted even though the technology has been widely adopted. A newly released randomized trial found no difference in clinical outcome between surgical modalities[159]. The adoption of SBRT has followed the same pattern with a widespread adoption without randomized evidence supporting the use[85]. The ROSEL and STARS trials are examples of randomization between surgery and SBRT in lung cancer. Both trials were closed early due to poor accrual[160]. A problem with introducing new technology within clinical trials is to make physicians believe in clinical equipoise between the modalities. Otherwise physicians may favor one treatment over another and be reluctant to enroll patients in the trial[151]. This was believed to be the problem with the MRC PR06 trial that randomized patients to radiotherapy and surgery in prostate cancer[154]. In the large PROTECT trial, specialist nurses were used to inform patients of trial complexities and successfully recruit patients thereby overcoming this physician inclusion bias[161,162]. The PROTECT trial also included a feasibility phase where the accrual rate (number of patients included in a specified length of time) was assessed – an approach to be used in the SABRTOOTH trial in lung cancer[163]. There are several explanations for the complexity of comparing inherently different modalities in a RCT such as the requirement of numerous patients to be enrolled, prolonged treatment time, different risk profiles of treatments etc. [154]. Randomization to either surgery or radiotherapy is shown to be associated with poor trial accrual in the American National Clinical Trials Network (NCTN). Suggestions to increasing the trial completion rate have been made to simplify trial design by reducing eligibility criteria, integrate trials into clinical practice, using cluster randomization and early consent provided by patients to enroll in experimental trials[164,165].

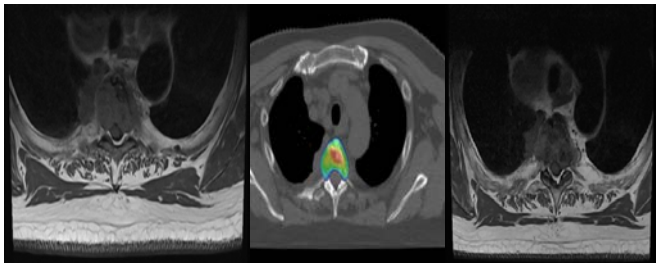


Figure 4 Imaging of a patient randomized to SBRT. Left: MRI pretreatment, Middle: Treatment dose plan on CT, Right: MRI evaluation 6 weeks after treatment

STUDY III

The potential use of PET/MRI in radiotherapy target definition of spinal metastases

We performed a study of PET/MRI for target definition in patients with MSCC. The PET/MRI was provided as an additional scan between simulation CT and radiotherapy. The investigation could only be performed when time slots at the PET/MRI scanner were available. Patients needed to be fasting before the administration of FDG due to proper interpretation of imaging. This left a very short time frame for the investigation to be performed. Initially the planned and performed imaging sequences made the investigational time too long to make the study feasible. Therefore the number of sequences was reduced. With this moderated imaging protocol the procedure was feasible. Comparison of target definition between MRI only and PET/MRI did not change the suggested target of radiotherapy. To perform the imaging procedure with the patients in the treatment position, a flat tabletop designated for radiotherapy was used in the enrolled patients. There are several limitations to this study. Due to the extra time used with four hours of fasting and an extra investigational procedure, only ten patients with MSCC were enrolled. The included patients were not representative of the population with a male predominance and a high number of esophageal cancers. Since the imaging was reviewed in a retrospective manner the findings had no influence on the subsequent treatment. Without any follow up included in the study, the clinical decision on target volume from

MRI only could not be validated. This could either have been done with follow up imaging or patient reported outcomes as in Study I and Study II.

No.	Age	Sex	Malignancy	Scan time (min)	Symptom	Target
1	75	Male	Prostate	80	Declining gait function	C7 to Th2
2	61	Male	Lung	25	Pain	Th2-4 & Th12
3	75	Female	Breast	44	Asymptomatic	L5
4	53	Male	Esophagus	25	Pain	L2
5	69	Male	Lung	30	Pain	Th2
6	67	Male	Esophagus	38	Pain	Th4
7	83	Male	Prostate	34	Pain	Th9 to Th11
8	44	Male	Esophagus	27	Pain	Sacral bone
9	76	Male	Unknown primary	29	Pain	L2
10	72	Male	Esophagus	33	Sensory loss	Sacral bone

Table 2: Characteristics of enrolled patients for PET/MRI. Level of compression by vertebrae cervical(C),thoracic (Th) and lumbar (L).

The inclusion of a flat table setup during the study distorted the original study focus from diagnostic decision on target volume to the possible fusion and alignment of MRI and CT. Since dose escalation and dose painting to spinal metastases was not the purpose this setup was unnecessary for study completion.
The study shows that PET/MRI imaging is possible in the group of patients with MSCC but investigational time has to be kept to a minimum. Therefore future studies has to focus on defining the purpose of the study to either:

1. Dose escalation and dose painting with increased tumor control probability (TCP)
2. Sparring of normal tissue with lower normal tissue complications probability (NTCP)

The use of multiple imaging platforms to identify tumor stage is extensively studied in current research. There is a renewed focus on oligometastases – a term first introduced in 1995[166]. The initial proposal was, that during the progression from a solitary lesion to widespread metastatic disease where a state with few (*oligo*) metastatic lesions. The current development in imaging techniques allows new modalities to visualize smaller metastatic lesions at an earlier time point. Technical innovations makes interventional procedures possible to be undertaken in order demolish these metastatic lesions. With the development of SBRT, a sufficient ablative dose of radiation can now safely be delivered to almost any organ[167]. Imaging of spinal metastases is therefore of special interest in cancers most commonly spreading to the bone such as prostate cancer. As the first key to success is to identify a truly oligometastatic stage, numerous combinations of imaging modalities of spinal metastases has been used to increase specificity and sensitivity of the investigational procedure with whole-body MRI, CT, scintigraphy and in combination with several different imaging isotopes/tracers[105]. In prostate cancer the tracer prostate specific membrane antigen (PSMA) PET in combination with either CT or MRI is promising as a modality to identify a oligometastatic state[168]. The hunt for metastatic lesions has resulted in an ironic commentary in European Urology "Pokemets – gotta catch them all" with a reference to the popular game "Pokemon Go" on the purpose of this chase[169]. Do physicians really need to catch them all (*the metastases*) and will metastasis directed therapy lead to a meaningful outcome for the treated patient? Despite the hype, there is still controversy of whether to treat with metastatic directed therapies[170]. Since most data is generated from observational studies other explanation exists for long term survival of selected patients as selection of biological phenotypes and immortal time bias[171]. New data from RCTs is emerging with promise of effect for carefully selected patients. In a phase II trial of metastatic lung cancer patients with three or fewer metastatic lesions, patients treated with local consolidation therapy had prolonged progression free survival[172].

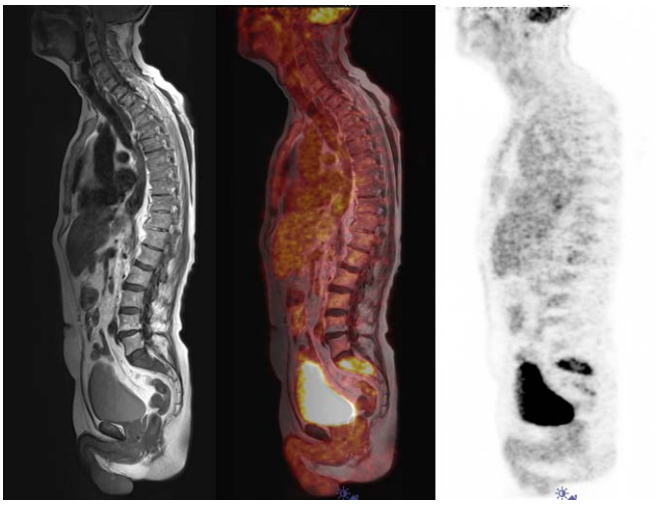


Figure 5 PET/MRI of a patient with esophageal cancer and metastasis to the sacral bone

STUDY IV

Diabetes increases the risk of toxicity after re-irradiation of the spinal cord

Current evidence supports the use of re-irradiation of the spinal cord in selected patient for palliative purposes of relieving pain and restoring neurological deficit in MSCC. A known risk after irradiation is myelopathy that increases with the accumulated dose of radiation. Myelopathy has been the major concern in performing re-irradiation. Therefore both irradiation and re-irradiation is delivered with focus on dose constraints on the spinal cord during treatment planning. We therefore sought to investigate the risk of myelopathy due to the use of re-irradiation in a retrospective consecutive cohort of cancer patients. We found that re-irradiation was a regular event with 220 patients of 2387 receiving radiotherapy with overlapping fields from prior

radiotherapy. The frequency of probable toxicity was found to be similar to previous reports of re-irradiation of the spinal cord. Toxicity in palliative patients after re-irradiation is dependent on patient survival. Our analysis shows an expected larger risk of toxicity over time. The majority of patients that experience toxicity after re-irradiation have vertebral fractures with neurological deficits due to compression by bone fragments. The major limitation of this study was the retrospective data collection. The data obtained can only be what was written in the charts. Therefore some patients that experience toxicity without being hospitalized is not registered. Risk factors may also be falsely registered or not registered at all. The vast majority of patients could be followed until death with only Greenlandic and Faroese patients being lost to follow-up. In a retrospective cohort the true incidence of vertebral fractures is unknown. In a cohort of cancer patients with many competing causes explaining back pain the clinical picture is blurred. This introduces a selection bias which leads to inclusion of a higher proportion of patient with vertebral fractures combined with neurological deficits into the study, which can explain the higher than expected frequency of this patient group in the study.

In uncomplicated vertebral metastases, only a part of the vertebrae with the corpus or the posterior elements may be affected. In a patient cohort with renewed MSCC and the clinical indication for re-irradiation, disease progression may have spread within the entire vertebrae and affected all vertebral elements. The cohort will therefore select patients with progression of a single lesion undermining the stability of the spine instead of patients dying from systemic progression. Therefore the risk of toxicity could be at least partially explained by the selection of certain tumor biology more likely present as disseminated disease rather than confined to a solitary lesion. The observed fracture rate is consistent with the rate of fractures seen resulting from dose escalation and is possibly correlated to a certain dose threshold. Future research should help define patients with the possibility of long-term survival and concurrent risk of vertebral fractures. This could help select patients for stabilization procedures in conjunction to radiotherapy.

The risk associated with vertebral fractures in cancer patients with diabetes should be confirmed in another cohort. International research shows that diabetes has a profound effect on bone metabolism[173]. Whether this is associated with a larger risk of bone fractures and spinal instability remains unknown. If the finding is replicated this should lead to consideration of the concurrent risk of toxicity after spinal irradiation. Given the low incidence of toxicity, patients with a need of therapy should receive it regardless of spinal cord overlap with consideration of prior dose distribution. In the case of re-irradiation of the same target, the current knowledge on optimal fractionation for re-irradiation is sparse. In a RCT of re-irradiation of bone metastases within different sites, patient were randomized to 8Gy in 1 fraction and 20 Gy in 5 fractions[174]. Patients received radiotherapy due to either insufficient pain response or renewed pain after initial therapy. Spinal or sacral metastases were treated in 237 of 850 of enrolled patients with a 116 patients of 425 in the group receiving 8Gy/1F and 121 patients of 425 in the group receiving 20Gy/5F. The pain response overall in the intention to treat group was low with a response in 28% in the 8Gy group and 32% in 20 Gy group. This result should be considered within the patient cohort eligible for the trial with either poor pain response or renewed pain after initially therapy thereby selecting patients with intractable pain. However these results has fueled the argument to use SBRT due to a better a pain response after re-irradiation[134]. Further studies in re-irradiation of spinal metastases and MSCC are required to determine dose, fractionation and delivery of therapy.

9. CONCLUSION AND PERSPECTIVES

Patients with MSCC have a tremendous risk of losing their gait function without urgent treatment. Their cancer is often incurable and patients remain fragile due to widespread disease. The studies included in this thesis focus on whether we can ameliorate patient from burdensome treatments or reduce risks of adverse events.

If spine SBRT could provide a similar clinical outcome compared to surgical decompression followed by fractionated radiotherapy this would be an attractive alternative. First of all, spine SBRT would be a safe alternative providing similar outcomes in regard to neurological function. Secondly, the treatment would be tolerable without any unexpected outcomes e.g. higher risk of myelopathy due to radiotherapy. Higher tolerability in patients treated with spine SBRT could also be due to the lack of morbidity normally associated with the surgical procedure. Finally, spine SBRT would be more tolerable due to a shorter treatment time with the planning and treatment executed in approximately two days. We designed a randomized clinical trial to investigate spine SBRT with the aim of providing this evidence. Unfortunately the trial had to close prematurely due to low accrual; however we found that the treatment approach was feasible, safe and tolerable.

The current evidence primarily supports the use of spine SBRT in spine metastases without cord compression. As described in the introduction we also lack the comparison of this modality with conventional treatments. But do we need the evidence from randomized controlled trial? The adaptation of other technical advances has not always been preceded by controlled trials. Proton and intensity modulated radiotherapy have been based on the biologically and physically properties of these techniques. Technical approaches in surgery with the use of robotic surgery are not based on knowledge gained by randomized controlled trials. In SBRT of stadium I lung cancer the evidence is collected in cohort studies and two failed RCTs. Current guidelines of the European Society of Medical Oncology now recommends SBRT as an alternative to surgery in patients unwilling to accept the risks associated with surgery[175]. The problem with the current observational studies is a highly selected group of patients and this precludes any conclusion on whether the outcomes observed is due to favorable biology or a true effect of the intervention. Both Study II and Study IV show a risk of vertebral fractures after dose escalation in both SBRT and re-irradiation. PET/MRI did not change target definition in conventional fractionated radiotherapy. However the imaging modality was feasible and could influence the target delineation in spinal radiotherapy and subsequent vertebral fracture. Therefore future studies of radiotherapy in MSCC have to consider this risk of spinal instability and how to address it. The studies in this thesis shows that it is feasible to dose escalate treatment toward the vertebrae in MSCC. The few patients randomized to SBRT showed a response with manageable toxicity. This is in concordance with published literature on the use of SBRT in cases with uncomplicated spinal metastases and in cases with MSCC. A future possibility is to use dose painting for dose escalation with PET/MRI. Future studies should focus

on showing true benefit for the patient comparing with a control group. Dose escalation might prove beneficial for several clinical indications. These can be divided into three distinctive groups:
Oligometastatic disease: Several studies are recruiting internationally with the intent to show a delay in disease progression and hopefully an increased overall survival[176,177].
Pain palliation: The high effect on pain as reported by the pain response rate among current studies has induced hope that better palliation of pain can be achieved with spine SBRT. One concern is an increase in vertebral fractures with induced mechanical pain. The study RTOG0631 is one example among others[87,178].
Preservation of neurological function: The current study within this thesis has shown that SBRT can preserve neurological function. Current studies on this indication are primarily done in surgical unfit patients[179].
We found that PET/MRI was feasible in the patient cohort with MSCC. The metabolic scan did not provide information that changed the radiotherapy target in an unselected population with MSCC. Future research of PET/MRI in spinal metastases should focus on a more selected patient group with prospectively evaluable end-points. The retrospective study on re-irradiation confirmed that with the known constraints on total spinal cord dose, myelopathy remains a rare event. This may be due to the time dependence of the event with death as a competing outcome. The risk of vertebral fractures with neurological deterioration was higher than expected. Radiotherapy dose, volume and time between treatments were not significant risk factors of toxicity. However, diabetes was shown to be an independent risk factor. Future research should focus on identifying patients with long-term survival after re-irradiation and therefore subsequent risk of toxicity. Our current prospective study will validate the risk of toxicity. The benefit of early stabilization of the spine should be explored in patients with long-term survival. The risk of toxicity in cancer patients with diabetes should be validated in another cohort of patients. MSCC still remains an important clinical risk for cancer patients. Further research is still needed to identify which patients who will benefit from escalated treatment intensity despite their incurable disease but at the same time ameliorate patients from treatments of which they will not benefit. For the future evaluation of trials, we have to refrain from calling trials *failed trials or negative trials*. Data from underpowered trials should be shared for future analysis to drive research for the benefit of the patients.

10. ABBREVIATIONS

MSCC – Metastatic spinal cord compression
RIM – Radiation induced myelopathy
PET – positron emission tomography
MRI – magnetic resonance imaging
SRE – skeletal related events
CT- computer tomography
LINAC - linear accelerator
Gy – Gray
XGy/XF – Total dose (X) in Gray delivered by number of fractions(X)
SBRT – Stereotactic Body Radiotherapy
SRS – Stereotactic Radiosurgery
SPECT - single-photon emission computed tomography
Et al – *et alii* in the meaning of "*and others"*
99Tc-MDP - Technetium (^{99m}Tc) medronic acid
FDG - 18F-flouro-2-deoxy-D-glucose
RCT – Randomized Controlled Trial
IMRT – intensity modulated radiotherapy
VMAT – volumetric modulated arc therapy
SINS – Spinal instability neoplastic score
RT- Radiotherapy
PSMA – prostate specific membrane antigen

11. SUMMARY

Metastatic spinal cord compression is caused by the progression of metastatic lesions within the vicinity of the spinal cord. The consequences are very severe with loss of neurological function and severe pain. The standard treatment is surgical intervention followed by radiotherapy or radiotherapy alone. However, the majority of patients are treated with radiotherapy only due to contraindications to surgery and technical inoperability. Stereotactic body radiotherapy is a technology to deliver higher radiation dose to the radiotherapy target with the use of spatial coordinates. This modality has shown positive results in treating lesions in brain and lungs. Hence, it could prove beneficial in metastatic spinal cord compression. We designed and planned a trial to investigate this method in patients with metastatic spinal cord compression. The method was usable but the trial was stopped prematurely due to low accrual that made comparison with surgery impossible. Low accrual is a known problem for trials evaluating new approaches in radiotherapy. Target definition in radiotherapy of metastatic spinal cord compression is defined by patient history, examination and imaging. Functional imaging could provide information to guide target definition with the sparring of normal tissue e.g. spinal cord and hematopoietic tissue of the bone marrow. In future trials this may be used for dose escalation of spinal metastases. The trial showed that PET/MRI was feasible in this group of patients but did not change the radiotherapy target in the included patients. Neurological outcome is similar irrespective of course length and therefore single fraction radiotherapy is recommended for the majority of patients. In-field recurrence is a risk factor of both short and long fractionation schemes and re-irradiation have the potential risk of radiation-induced myelopathy. In a retrospective study of re-irradiation, we investigated the incidence of radiation-induced myelopathy. In our study population, we found a higher number of patients experiencing vertebral fractures than the number of patient developing myelopathy. Patients with diabetes had an increased risk of toxicity compared to the remaining patients. Stereotactic body radiotherapy is effective in treating metastatic spinal cord compression but the efficacy cannot be determined due low accrual. The use of PET/MRI did not spare normal tissue in radiotherapy planning of spinal metastases. The incidence of toxicity after re-irradiation of the spine and spinal cord was low. For patients with in-field recurrence, re-irradiation is safe and has a low incidence of toxicity.

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