BONY-M

Stereotactic ablative radiotherapy (SABR) of bony metastases in patients with oligometastatic disease - A phase II study

Study protocol

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1 Background

1.1 The oligometastatic state

Historically, patients with metastatic cancer are considered incurable and treated with palliative therapies. However, some of these patients have long disease-free survival when treated with ablative treatment strategies to all metastatic sites. The existence of an oligometastatic state between locoregional - and metastatic disease were first proposed by Hellman and Weichselbaum. They presented the idea of an oligometastatic state in 1995 describing a hypothetical intermediate state between localized and widespread metastatic disease [1]. They hypothesized that certain tumours have not fully developed their metastatic potential and show a slow natural history. Factors that favour a truly oligometastatic state include a long interval between the treatment of the primary tumour and the appearance of metastases, and a high ratio of the metastasis growth rate compared to that of the primary tumour. Withers and Lee summaries this idea as “The more micrometastatic doubling times elapsing between removal of the primary and the clinical detection of the 'leader' metastasis, the higher the probability of an oligometastatic distribution” [2].

The identification of patients with truly oligometastatic disease (OMD) is however difficult and a clear definition does not exist. It is likely cancer type dependent and best defined biologically [3]. Most studies have focused on up to five metastases, but some have included patients with up to eight metastases. These categories of OMD have been proposed:

- Patients with few metastases at diagnosis have *de novo OMD.*
- Patients with widespread disease that becomes oligometastatic after treatment have *induced OMD.*
- Patients in complete remission who develop oligometastatic *recurrence.*
- Patients with widespread disease receiving systemic therapy that progress in a limited number of sites have *oligo-progressive disease (OPD)*.

The introduction of targeted therapies and immune checkpoint inhibitors to control micro-metastatic disease together with advances in local therapy strategies, lead us to believe that a more aggressive approach to these patients may be meaningful.

Evidence is emerging, that definitive treatment of the oligometastatic categories is beneficial. A significantly prolonged survival in patients with oligometastatic disease compared with patients with more widely disseminated disease have been documented [4]. That statement has led some authors to conclude, that patients with oligometastatic disease will probably live long enough to benefit from the high rates of prolonged local control (LC) reported after an ablative strategy.

An oligometastatic treatment strategy has been established in respect to surgery and shown superior survival outcome [5-9] . Surgery has therefore become standard procedure in the treatment of patients and is increasingly used for oligometastatic lung-, colorectal- and kidney cancer. However, not all patients are eligible for surgery and not all metastases are resectable.

1.2 Stereotactic ablative body radiotherapy (SABR)

Radiotherapeutic challenges have historically been to deliver a truly ablative radiation dose without causing toxicity to the surrounding tissue. However, new technologies now allow delivery of radical ablative doses of radiation within 1-5 fractions and has made aggressive treatment of lesions close to sensible organs, such as the spinal cord and oesophagus possible, without violating dose constraints to these organs.

The American Society of Radiation Oncology defines stereotactic ablative radiotherapy (SABR) as external beam radiotherapy used to deliver a high dose of radiation very precisely to an extracranial target within the body, as a single dose or a small number of fractions [10]. SABR is also referred to as stereotactic body radiotherapy (SBRT). With new advances in radiotherapy we may be able to improve outcome for patients with oligometastatic disease.

A randomized, phase II study (OLIGOMEZ), presented at ASTRO 2018, have shown prolonged progression-free survival (PFS) when adding local consolidative treatment (SABR and/or surgery) to maintenance treatment after induction therapy for patients with lung cancer (Gomez et al., Oral Scientific Session, ASTRO 2018, data not yet published, see reference for protocol information [11]).

Palma, D.A has recently published data on the randomized, phase II, open-label study called SABR-COMET. The study recruited patients with a broad spectrum of different cancer subtypes and found improved PFS and overall survival (OS) when offering SABR to patients with OMD vs

palliative standard of care (SOC). Median OS was 28 months in the SOC group vs. 41 months in group offered SABR [12].

Ost et al. published in 2018 data on a multicenter phase II trial documenting the beneficial outcome of metastasis-directed therapy (MDT) (SABR and/or surgery) vs. surveillance alone for patients with oligo-recurrent prostate cancer. At a median follow-up time of 3 years, the median androgen deprivation therapy-free survival was 13 months for the surveillance group and 21 months for the MDT group [13].

Overall, these data suggest that local ablative therapy of metastases could improve the systemic control of disease.

1.3 Bone metastases and SABR

1.3.1 Bone metastases

Bone metastases are common in advanced cancer, with 70−85% of patients diagnosed with bone metastases at the time of autopsy [14]. Spine metastases occur in up to 70% of all involved osseous sites, leading to significant morbidity [15]. Bone metastases are complicated by skeletal-related events (SREs), which are local irreversible changes and include pathologic fracture, bone surgery, and spinal cord compression. Lage et al. showed that half of all patients with prostate cancer and bone metastases experienced 1 or more SREs [16]. Recently, a new endpoint termed symptomatic skeletal events (SSEs), defined as radiation to bone, symptomatic pathologic fracture, surgery to bone, or symptomatic spinal cord compression have been introduced in the literature [17-19]. In contrast with SREs, ascertainment of SSEs does not necessary include scheduled radiographic assessments and rate the symptomatology higher.

1.3.2 Local control rate

When SABR is used for treating spine bone metastases, the results are encouraging. Local control rates generally exceed 80% at 1 year, while high rates of pain control have been attained. Low rates of toxicity have been reported, assuming strict dose constraints are respected [20]. Most studies examining SABR of bone metastases have looked exclusively at spinal bone metastases, but studies documenting results in non-spine bone metastases have been published [21, 22]. Publications on

long-term follow-up following SABR are now emerging. Moussazadeh et al. reported in 2015 a median follow-up of 6.1 years where 91.6% of lesions remained stable [23]. These results suggest a durable response in long-term survivors.

In respect to spine bone metastases, a large proportion of the local failures can be attributed to poor tumour coverage limited by spinal cord constraints [24]. Previous reports have suggested that when an epidural tumour is within 2-5 mm of the spinal cord, target coverage is difficult to obtain [25]. Therefore, most studies exclude patients with epidural disease. Bishop et al. found, that minimum dose (D_{min}) to GTV ≤ 21 Gy in 3 fractions was an independent predictor for local recurrence [24] and argued that conservative spinal cord constraints increase the risk for marginal failures.

There is insufficient evidence to suggest superiority of either single or multiple fraction regimens with respect to local control and pain control [26]. However, there have been studies documenting that a single fraction treatment may have an increased frequency of toxicity, especially risk of fracture [27].

1.3.1 SABR versus palliative fractionation schemes

Palliative fractionation schemes have been proven to decrease pain and improve quality of life. However, no increase in overall survival has been reported [28, 29] in contrast to SABR. The crude local control (LC) rate is reported higher for SABR compared with palliative fractionation schemes, suggesting superiority of SABR [30, 31]. Approximately 8–42% of patients treated with palliative fractionation schemes need re-treatment due to pain progression [32], and this is more frequent compared to stereotactic higher doses according to Chow et al [29]. Radioresistant tumours like renal cell carcinoma or malignant melanoma shows LC rates after SABR, which are comparable to those obtained with SABR for radiosensitive tumours [33-38]. In contrast, for unfavourable histological types, large retrospective analyses of spinal metastases suggests, that the rate of relapse approaches 80% within 2 years after palliative fractionation schemes [39]. Recently, data from a prospective, randomized, single-institution, phase 2, non-inferiority trial have been published from the same author. The study assesses the relative efficacy of high-dose, single-fraction SBRT vs standard multifraction radiotherapy (MFRT). No differences were found in treatment-related toxic effects or quality-of-life scores after SABR vs MFRT. Local control rates at 1 and 2 years were higher

in patients receiving single-fraction SBRT. The authors conclude that SABR should be considered for patients expected to have relatively long survival [31] (*full article in print*).

1.3.2 Pain relief

Following low-dose palliative fractionation schemes, several randomized trials and meta-analyses have confirmed complete and overall pain response rates ranging from ~10% to 30% and 50% to 70%, respectively [29, 40]. There have been various studies showing that after treatment with palliative fractionation schemes, pain levels stabilize anywhere from four weeks to three months after treatment in a variety of tumours that have metastasized to the bone [41, 42]. SABR is expected to achieve higher rates of pain control than palliative fractionation schemes, because some retrospective analyses have shown that SABR offers an overall pain relief rate of 74.3–86%, regardless of the setting as either upfront or retreatment [43-46]. Nugyen et al. compared single-fraction SBRT vs MFRT for alleviation of pain in patients with mostly non-spine bone metastases. The author concludes that SABR has higher rates of pain response (complete response and partial response) than MFRT. At 2 weeks pain response was seen in 62% of patients treated with SABR versus 36% for patients treated with MFRT. The difference was significant, and the same tendency was seen at 3 and 9 months [31].

In addition, SABR may offer a quicker resolution of symptoms when compared to palliative fractionation schemes, due to the ability to limit dose to critical structures while enabling hypofractionation with higher fraction size to the disease.

Jhaveri et al. demonstrated that for patients treated with a BED greater than 85 Gy (α/β =7), pain relief was more consistent and quicker, as compared to patients treated with BED less than 85 Gy in patients with renal cell carcinomas (RCC). The average pain stabilization time was two weeks in the setting of RCC metastases, which are considered to be radioresistant when treated with palliative fractionation schemes [47].

1.4 SABR – what's left to explore

SABR to bone metastases is rapidly emerging into standard practice, however, it is still considered investigational and not without risk. Serious toxicities such as pneumonitis, radiation-induced myelopathy, esophageal toxic effects and fracture, including vertebral compression fracture (VCF),

have been reported. The literature is scarce in respect to the optimal dose fractionation scheme, and the optimal imaging work-up, is not yet clearly defined.

Prospective studies are needed to further evaluate efficacy, the optimal dose fractionation scheme and toxicity risk, before we can establish its role as a standard of care. Longer follow-up is warranted to accurately determine late effects. Furthermore, we need to explore the benefit of SABR over palliative fractionation schemes. A topic, that several studies are exploring [31, 48].

Besides treating OMD, SABR are being increasingly used to treat OPD with very little evidence to support superior outcome. A few small retrospective studies have addressed this topic and shown favourable survival outcome compared to historical data [38, 49-52].

2 Bony-M

The Bony-M trial evaluates the efficacy and safety of SABR to bone metastases in patients with OMD, when pragmatically introduced into a daily clinical setting. In this study all osseous oligometastases from all solid tumours can be treated regardless of location, if organ at risk (OAR) constraints can be met. The approach is pragmatic as all pre-treatment evaluations are done by the referring oncologist and the party that approve the SABR plan.

3 Endpoints

3.1 Primary endpoint

- Rate of local control (LC) 1-year post SABR

Aim: To evaluate the rate of LC at the radiated site 1- year post SABR

Hypothesis: The rate of LC is more than 75 % at 1-year post treatment.

How: Patients will have CT and clinical evaluation every 3-4 month after SABR according to the standard clinical follow-up program.

3.2 Secondary endpoints

- Rate of Symptomatic Skeletal Event (SSE) at the irradiated site(s)
- Progression-free survival (PFS)

- The rate of NCI CTCAE ≥ grade 3 toxicity
- Overall survival (OS)
- Time to progression (TTP) outside the radiation field
- LC rate two years post-SABR
- Pain reduction from baseline evaluated by "Numeric Pain Rating Scale (NPRS)" and analgesic consumption.
- Quality of life (QoL) measured with EQ-5D-5L.

Toxicity, NPRS, analgesic consumption /antineoplastic treatment and EQ-5D-5L will be registered at baseline and at each follow-up (see table 1).

3.3 Exploratory studies

- Delineation study (Difference in target volume definition of bone metastases: Dual energy CT versus conventional CT, MR versus CT, PET-MR versus CT and in intra/inter delineation).
- Subgroup analysis (outcome according to histological profile).
- Subgroup analysis (toxicity according to location of metastasis - spine metastasis versus non-spine metastasis).
- Description of the use of online treatment adaption to keep minimal doses to OAR.
- Frequency and extent of compromise in prescription dose and/or to target coverage (GTV/CTV/PTV) due to OAR constraints (6.2).

3.4 Definition of endpoint-related concepts

Only patients who receive the treatment are included for analysis.

- Local control rate is defined as the absence of progression within the treated area on imaging with CT -, MR -, or PET-CT - scan (radiologist interpretation, see section 5.5). Analysis is done at a lesion level, lesion by lesion. Patients are not censored from analysis in case of a new lesion outside the treated volume. Within the treated area is defined as, within or adjacent to the PTV.
- Symptomatic Skeletal Event (SSE) of the irradiated site is defined as a radiographically verification of fracture (vertebral or non-vertebral, pathological or non-pathological), within or adjacent to the PTV of the irradiated site. The fracture must co-exist with one of the

following symptoms/interventions: progression in pain (according to definition in section 3.5), development of neurological symptoms/ symptomatic spinal cord compression or a need for surgical intervention/ reirradiation. It should be concluded from the treating physician that the symptom/intervention is a result of the fracture. Vertebral fractures include end plate–only fractures. Analysis is done at a lesion level, lesion by lesion. Patients with a pathological fracture before the radiation therapy, will not be included for analysis.

- Progressive disease (PD) is noted if the radiologist has deemed clear progression, otherwise one or more consecutive imaging studies is needed (see section 5.5).
- Progression-free survival is defined as time from inclusion until disease progression or death.
- OS is defined as time from inclusion until death from any cause.
- Time to progression outside the radiation field is defined, as the time from inclusion until progression outside the radiation field, determined by a CT -, MR -, or PET-CT – scan (see section 5.5). Outside the radiation field is defined as outside and not adjacent to the PTV.
- Early toxicity is defined as toxicity occurring within three months of radiotherapy completion.
- Late toxicity is defined as toxicity occurring three months or longer after radiotherapy completion.
- Metastases are considered non-spine if they are located outside of the vertebral column or sacrum.
- Contiguous lesions treated within one volume represents one target.

3.5 Pain assessment and the Numeric pain rating scale (NPRS)

In the conventional radiation setting, the International Consensus Pain Response Endpoints (ICPRE) has been developed for clinical endpoints as pain for bone metastases [28]. There are currently no corresponding definitions for the use of SABR. A few studies have reported good pain control by SABR both in the upfront- and the retreatment setting, using the ICPRE guideline [46, 53, 54].

In this protocol, we will likewise use the ICPRE to evaluate pain response. Response categories is based on patient reported pain scores (NPRS) and analgesic consumption (convert to oral morphine-equivalent dose). The NPRS is a valid and reliable scale to measure pain intensity [59] [60]. The 11-

point NPRS ranges from '0' representing one pain extreme (e.g. “no pain”) to '10' representing the other pain extreme (e.g. “pain as bad as you can imagine” or “worst pain imaginable”). See Appendix F.

Registration of NPRS will be registered at baseline and each follow-up for all included patients. The patient will complete the baseline NPRS within one week prior the first day of treatment. Analysis of pain reduction will only include patients with NPRS ≥ 1 registered at baseline. We intend to report the best response during follow-up. If more than one lesion is treated with SABR, the index lesion will be used to assess the pain response. The index lesion is defined as the lesion with the highest pretreatment pain score. If a patient has two or more lesions with the same maximum pain score, the index lesion is defined as the most cranial located lesion.

- A complete pain response is defined as a pain score of 0 out of 10 at the treated site with no concomitant increase in analgesic intake
- A partial pain response is defined as a pain reduction of 2 or more at the treated site without analgesic increase, or an analgesic reduction of 25% with no increase in pain score or 1 point above baseline.
- Pain progression is defined as an increase in pain score of 2 or more above baseline with stable analgesic intake or an analgesic increase of 25% with stable pain score.
- An indeterminate response is any response not captured in the above definitions.

4 Study design, sample size calculation and timeframe

4.1 Study design

This is a prospective, investigator-initiated, phase II, multicentre-study, investigating the efficacy and toxicity of definitive SABR of osseous oligometastases, when pragmatically introduced into a daily clinical setting.

4.2 Sample size

At least 67 patients will be included in this study. Patients with de novo- and induced OMD, as well as patients with oligo-recurrence or oligo-progression disease can be included.

Following study closure, 12 months of follow-up after radiotherapy completion will be allowed for all patients, at which point data will be collected for primary end-point analysis. Further analysis will be performed 2 and 5 years after the last patient has completed radiotherapy. Analysis of data in respect to secondary endpoints and exploratory studies might be analysed at any point of time, at the discretion of the study group. Data will be kept in databases 10 years after the last patient is included.

Data will be filed and stored using electronical 'case report forms' (CRFs) in REDCap (Research Electronic Data).

4.3 Sample size calculation for primary endpoint

Simons two stage design is used for sample size calculation [55, 56]. Simons two stage design is used for sample size calculation [55, 56]. The null hypothesis that the true 1- year local control rate is 60% and will be tested against a one-sided alternative. The interim analysis will be performed after one-year follow up of the first 27 patients. Recruitment will continue after inclusion of these 27 patients and will not wait the results of the interim analysis. If there are 17 patients or fewer with local control at one year in these 27 patients at the interim analysis after one-year follow up, the study will be paused, and the trial committee will discuss cessation of the study or dose adjustment (see section 9.3). Otherwise, 40 additional patients will be included and treated for a total of 67 treated patients. The null hypothesis will be rejected if 47 or more out of 67 patients have local control, at the radiated site, at 1-year after treatment. This design yields a one-sided type I error rate of 5% and power of 80% if the true 1- year local control rate is 75%. The last reported CTCAE classification status and response assessment will be registered in cases where the patient is lost for follow-up (e.g. succumbs from a "not treatment related" grade 5 event) prior to the 1-year assessment. In other words, such patients will be recorded at one year according to the latest available toxicity and response assessment. A re-estimation of the required sample size will be made if more than 20% of patients fail to reach 1-year follow-up in the first stage of the trial in order to account for attrition and time-to-event analysis.

4.4 Timeframe

At least 67 patients will be enrolled within a timeframe of a maximum of three years. The study will close after three years regardless if the planned number of enrolled patients is reached or not.

5 Visits and follow-up procedure

5.1 Visits

Patients will be scheduled for visits/follow-up according to Table 1. Additional imaging or laboratory investigations are at the discretion of the treating oncologist.

Final assessment will be completed 52 weeks/12 months post radiotherapy and the participants will hereafter be registered through chart review and routine clinical appointments.

Registration will only be obtained from the patient's electronic records after they have signed informed consent. The clinical information registered will include age, sex, height, weight, smoking history, medical and surgery history, allergy, medicine, performance status, objective examination, type of disease, stage, disease localization, type of systemic treatment, details from the radiation treatment plan (e.g. prescription and delivered dose to target/organs at risk, size of targets, CTV and PTV margins and compromises), toxicity assessment, pain assessment, quality-of-life (QOL) questionnaires, time to disease progression, time to death, blood test results, pathology, and scan results.

The aim is to document long time follow-up in respect to local control rate, OS, PFS, rate of SSE, TTP outside the radiation field at 1-, 2- and 5-years and acute/ late toxicities.

5.2 Toxicity assessment.

Registration of toxicity will be assessed according to a prespecified selection of organ related adverse events defined by NCI-CTCAE version 5.0. See Appendix I and the following link: https://evs.nci.nih.gov/ftp1/CTCAE/About.html

The registration of the CTCAE will depend on the site of the target:

Thorax: Dermatitis Radiation, Esophagitis, Fistula, Fracture, Myelitis, Nausea, Pain, Perforation, Peripheral sensory/motor neuropathy, Pleuritis, Pneumothorax, Soft tissue necrosis, Ulcer.

Abdomen/pelvic: Acute kidney injury, Dermatitis Radiation, Diarrhoea, Fistula, Fractures, Gastro-intestinal obstruction, Haematuria, Haemorrhage, Myelitis, Nausea, Pain, Perforation, Peripheral sensory/Motor Neuropathy, Ulcer, Urinary tract obstruction.

Extremities: Dermatitis Radiation, Fractures, Joint range of motion decrease, Pain, Peripheral sensory/Motor Neuropathy, Soft tissue necrosis.

The scored toxicity is the highest toxicity in the period between the current and previous visit date.

5.3 Blood sampling

Blood samples are collected as part of the standard follow-up program and will be analysed immediately according to clinical practice. The test results will be registered in the electronical CRF. The standard panel registered is: haemoglobin, white blood cells, platelets, liver function tests; (alanine transaminase (ALT) or aspartate aminotransferase (AST), alkaline phosphatase (ALP), albumin, bilirubin, INR, APTT), kidney function test (creatinine, e-GFR) and relevant tumour markers depending on the underlying cancer (e.g. CEA, CA 19.9, CA-125, PSA).

Table 1 Schedule for registrations before radiation and at follow-up.

	Baseline	2 weeks post RT*	12 (11-13) weeks post RT	24 (22-26) weeks post RT	36 (34-38) weeks post RT	52 (50-52) weeks post RT
Signed consent	X					
Medical history	X					
Analgesic consumption /Antineoplastic treatment (see section 5.8)	X	X	X	X	X	X
Blood sample *2	X		X	X	X	X
(EuroQol EQ-5D-5L Index)	X		X	X	X	X
Symptom score (CTCAE 5.0) (including PS)	X	X	X	X	X	X
NPRS scoring	X	X	X	X	X	X
CT thorax/abdomen (within 28 days of inclusion, and according to standard Follow-up program)	X		X	X	X	X
MR columna totalis *3	(X)		(X)	(X)	(X)	(X)
Renography*4	(X)					

∗ Either consultation at the clinic or consultation by phone call.

∗2 Haemoglobin, white blood cells, platelets, liver function tests (alanine transaminase (ALT) or aspartate aminotransferase (AST), alkaline phosphatase (ALP), albumin, bilirubin, INR, APTT), kidney function test (creatinine, e-GFR), relevant tumour markers depending on underlying cancer (e.g. CEA, CA 19.9, CA-125, PSA).

∗3 Only mandatory before inclusion for vertebral or paraspinal targets, if epidural/intraspinal tumour growth cannot be precluded. For vertebral or paraspinal targets a simulation MR scan is mandatory.

∗4 Depending on the site of target and at the discretion of the treating physician.

Supplemental examinations i.e. test for lung function, blood sample or other examinations are prescribed before initiation of the SABR at the discretion of the treating physician.

5.4 Scanning procedure

All imaging at follow-up is considered standard and should minimally include a CT of thorax/abdomen. It is important to ensure that the irradiated treatment site is included in the scanning field. MR scan and/or PET-CT scan (with whatever relevant tracer) is recommended, if standard for that malignancy/site, or if the treating physician finds it relevant in respect to evaluating the target area(s).

5.5 Response evaluation

The application of the Response Evaluation Criteria in Solid Tumours (RECIST version 1.1) for bone metastases is limited, even though RECIST 1.1 was developed to include bone metastases as a measurable site to track [57]. It describes that lytic or mixed lesions are deemed to be measurable only if soft-tissue (e.g., paraspinal) extensions that are 10 mm or larger can be identified. Furthermore, blastic bone lesions are deemed non-measurable. There are currently no standardized criteria to classify bone lesions other than RECIST 1.1. The University of Texas MD Anderson Cancer Center (MDACC) has developed its own response criteria for bone metastases, which includes spinal bone metastases [58]. Conclusively, no validated criteria for response evaluation is eligible. Therefore, in our study we asses response evaluation based on the interpretation of a radiologist with oncological experienced and based on the below definitions, which are modifications from the MDACC response criteria's.

- A partial response (PR) is coded if there is unequivocal decrease in target lesions and/or development of a sclerotic rim or partial sclerotic fill for lytic lesions on CT.
- Progressive disease (PD) is based on increase in tumor size interpreted by a radiologist.
- A complete response (CR) is coded if there is complete disappearance of tracer activity on PET-CT, normalisation of signal intensity on an MR scan or bone density on CT or/and complete sclerotic fill for lytic lesions on CT.
- Stable disease (SD) is coded for any response other than CR, PR or PD.

In cases in which it is unclear whether changes within the bone is secondary to radiation or disease progression, one or more successive scanning evaluation showing enlarged dimensions is required, before the disease is classified as progressing. Due to risk of pseudo-progression and necrosis [59], confirmatory scans should be obtained if asymptomatic early tumor enlargement is seen. In some cases, biopsy might be needed to confirm diagnosis.

5.6 Supplemental treatment

Proton pump inhibitors (PPI) and other supportive medicine during treatment are prescribed at the discretion of the treating physician. Corticosteroid premedication can be mandated, at the discretion of the treating physician (in which case, its use needs to be reported on the appropriate CRF). Analgesic medication should be noted in the CRF at all visits. Paracetamol could be administered at day 1 after the last radiotherapy to avoid pain flare.

5.7 EuroQol EQ-5D-5L Index

To examine the participants' quality of life (QoL) during follow up, they will be asked to fill in a QoL questionnaire. The QoL questionnaire that will be used, is the EuroQol EQ-5D-5L Index, which is a standardized and validated instrument. The EQ-5D index is a relatively simple five-item questionnaire (measuring mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). It produces a composite score between 0 and 1 (multiplied by 100 to yield a result between 0-100).

5.8 Systemic therapy

Antineoplastic systemic therapy will be paused before, during and after radiation at the discretion of the physician, depending on the interaction with radiotherapy.

Hormonal therapy, bone antiresorptive therapy and immunotherapy are allowed throughout the treatment. The antineoplastic therapy (including bone antiresorptive medicine) should be noted in the CRF at all visits.

6 Participants

At least 67 patients will be included in the study.

Note that pain as a symptom is not required for inclusion in this protocol.

6.1 Inclusion criteria

- Histology or cytology proven non-haematological cancer.
- At least one lesion in the bones is required.
- ECOG performance status ≤ 2.
- ≥ 18 years old.
- Life expectancy > 6 months.
- GTV diameter ≤ 5 cm.
- In case of de novo OMD and OMD recurrence a maximum of 5 targets (including the primary tumour) in a maximum of 3 organ sites are allowed.
- In case of OPD * and induced OMD*[2] only 3 metastases (including the primary tumour) are allowed.
- The metastatic lesion(s) must be visible on a CT- or MR- scan and suitable for treatment with SABR.
- All metastatic sites are treated or planned for ablative therapy (including surgery) - for OPD only the sites in progression is required to fulfil this criterion.
- A baseline scan within 28 days of inclusion (CT or PET- CT).
- For spine/paraspinal targets, an MR scan is mandatory, if epidural growth cannot be precluded on the baseline CT scan.
- No curative intended treatment option available.
- An ablative strategy should be deemed clinically relevant and is at the discretion of the treating physician to decide.
- Ability to understand and the willingness to sign a written informed consent document.

6.2 Exclusion criteria

- Patient cannot tolerate physical set up required for SABR.
- Uncontrolled intercurrent illness.
- Pregnancy.
- Bilsky score ≥ 1b. If the patient is treated with surgery, a pre-operative Bilsky score ≥ 1b is an exclusion criterion as well. See appendix A for Bilsky score.
- Presence of myelopathy from the target area.
- Candidate for surgical treatment (determined by the institutions clinical oncologist, neurosurgeon or orthopaedic surgeon).
- For spine/paraspinal lesions where epidural growth cannot be precluded on the baseline CT scan: patients for whom an MR scan is contraindicated.
- Mechanical instability and/or fracture risk *[3].
- For spine disease, involvement of ≥ three contiguous vertebrae.
- Uncontrolled disease in respect to malignant pleural effusion, ascites, lymphangitic carcinomatosis, pleural carcinomatosis or peritoneal carcinomatosis.
- Patients with uncontrolled brain metastases.
- If the patient has received previous radiotherapy, the combined dose at the radiation site must not exceed the dose constraints according to Appendix B.

* OPD	Progression of a limited number of metastatic lesions, while remaining metastases are controlled with systemic therapy. A maximum of 3 progressing metastases. This includes both progressive enlargement of a known metastasis and the development of a new metastasis.
*[2] Induced OMD	widespread metastatic disease is mostly eradicated by systemic treatment, but drug resistant clones are left behind, or the metastasis is located at a site not accessed by systemic therapy: Maximum 3 metastases. Only pre-existing metastases are allowed. The development of new metastases is not allowed
*[3]	Clinicians should consult a neurosurgeon, orthopaedic surgeon or radiologist and evaluate patients for stabilization prior to SABR if the following risk factors are observed: baseline VCF, significant lytic tumour burden, spinal malalignment, a SINS[1] > 6 or if the physician, for any reason, suspect the lesion to be unstable.

[1] The Spine Instability Neoplastic Score (SINS) should be used in the risk assessment, but a modified SINS score, where evaluation of the radiographic spinal alignment in standing position is not necessarily required. (see Appendix G).

6.3 Enrolment

Bony-M is a national, multicentre study. The treating oncologists at the relevant Oncology Departments will be informed, when the study is ready to include patients. Potential participants will be informed about the trial, while attending a routine visit at the respective Oncology Departments, and after oral consent from the patient, be referred to the relevant unit. The local investigator will after the patient's referral, receive the relevant medical information from the referring physician. These information's will be used to evaluate possible treatments options and includes an assessment whether the patient is a candidate for this or other trials, which is a standard procedure for the clinics. Information searched includes diagnosis, previous treatment, latest scan and comorbidities.

If the patient is a relevant candidate for the study, he or she will be invited in for a detailed information by a physician of the project team. The patient should be provided with full and adequate verbal and written information about the objectives, the study outlines and possible risks and benefits of participating in the study. The information will be given under private conditions, and the patient will be encouraged to have a relative or friend attending. The subjects have the right to ask questions about the study and should be given adequate time, at least one day to make the decision to participate in the study or not. The subject should be clearly informed that the data collected in the study will not identify any subject taking part in the study, following the Law in Personal Data and the General Data Protection Regulation (GDPR) (EU) 2016/679.

The subjects should be informed that it is voluntary to participate and that they can withdraw from the study at any time without giving any reason. The subjects should further be informed that a decision not to participate in the study or to withdraw will not be questioned or effect their future medical care or treatment at the clinic.

Written Informed Consent must be obtained from all participating subjects before enrolment in the study. The Informed Consent form should also be signed, at the same occasion, by the investigator who gave the written and verbal information. No trial related procedures can take place unless a written informed consent is obtained.

The subjects will consent to participation in the study; regulatory authorities to gain full access to hospital records, to control the data collected in the study; recording, collecting and processing of

data and storing data in a database. Contact information for the oncologist responsible of the study will be provided.

If the patient chooses not to participate in the study, he or she will continue the standard treatment of care in the primary unit in charge of the oncology course.

6.4 Withdrawal from the study

A patient may be withdrawn from the study if any of the following events occur:

- If, in the opinion of the investigator, withdrawal is necessary for medical or technical reasons
- Major protocol violation
- Informed consent withdrawal

In case of a withdrawal before first treatment day, another patient will be enrolled (with a new patient number). The withdrawn patient will be accounted for in the statistical analysis. The reason for withdrawal should be clearly described. Relevant data should be obtained when possible, and all relevant assessments should be completed, preferably according to the schedule for the final assessment. The CRF should be completed.

7 Radiotherapy planning

7.1 Simulation

A CT scan with the patient immobilised in the treatment position is required for delineation. Slice separation ≤2 mm is mandatory. Use of intravenous contrast is at the discretion of referring physician.

A baseline MR scan (with axial T1-weighted and T2-weighted images) should preferably (but not mandatorily) be acquired with the patient in the treatment position. MR simulation should be used if available at the department. Additional requirements for spinal/paraspinal targets:

- Acquisition of the baseline MR scan with the patient in the treatment position is mandatory.
- MR slice separation should be ≤3 mm.

- MR and CT images must be co-registered prior to delineation and treatment planning, with focus on the treatment area.

If a PET-CT scan is available and acquired within 8 weeks prior to the current treatment it should be imported to the treatment planning system.

A variety of immobilization devices may be used. For cervical spine or cervicothoracic junctional areas, a rigid head and neck immobilization device is mandatory.

7.2 Dose prescription

Two dose fractionation schemes will be available

Table 2 dose prescribed to the GTV

Regime number	Total dose GTV (Gy)	Fractions	Dose per fraction GTV (Gy /%)	Dose per fraction PTV (Gy/%)	Prescribed dose GTV (BED 10)
1	37.5	3	12.5/100	8.375/67	84.4
2	30	3	10/100	6.7/67	60

Dose distribution within the target area should be non-homogenous, with steep dose gradients outside the gross tumour volume (GTV) according to the Nordic SABR practice [60-62]. Dose is prescribed to the GTV. GTV should be covered by 95% isodose (GTV D99% > 95%). Mean GTV dose ≥ 100%. CTV should be covered by 80% isodose (CTV D99% > 80%). The planning target volume (PTV) should be covered by the 67% isodose (PTV D99% > 67%).

Dose outside the GTV (Body- GTV) should preferably meet the constraint $D_{1cc} \leq 107\%$. Dose outside the PTV (Body-PTV) should be kept as low as possible and D_{1cc}, D_{2cc} and D_{5cc} for Body-PTV should be reported. The maximum allowed dose should fulfil $D_{0.1cc} \leq 140\%$. Hotspots at the edge of the GTV should be avoided.

The choice of dose regime depends on the proximity to OAR and the decision making should ideally follow the steps described here:

1. Dose regime one (12.5 Gy x 3 fractions) is recommended. Optimal GTV, CTV and PTV coverages, as described in this section, and constraints to OAR should be maintained.
2. If this is not possible due to OAR constraints, the target coverage can be compromised to parts of GTV, CTV and/or PTV. It is recommended that the mean dose to the GTV and PTV should be at least 80% of the prescribed dose, i.e. 30 Gy for the GTV and 20 Gy for the PTV.
3. If this also is not possible, dose regime two (10 Gy x 3 fraction) should be explored.
4. If this still is not possible due to OAR constraints, the target coverage can be compromised to parts of GTV, CTV and/or PTV. It is recommended that the mean dose to the GTV and PTV should be at least 80% of the prescribed dose, i.e. 24 Gy for the GTV and 16 Gy for the PTV.
5. If none of the above-mentioned requirements can be achieved, the patient should be withdrawn from the study.

7.3 Treatment delivery technique and position verification

SABR is delivered with external photon beam radiotherapy, utilizing energies in the range of 6-15 MV. Treatment is planned using Intensity modulated radiotherapy (IMRT) or volumetric modulated arc therapy (VMAT). The accuracy of target localization should be ≤ 2 mm from simulation through all steps and duration of treatment for spine/paraspinal targets. Strict dose constraint to the spinal cord will be applied. Daily adaption will be performed if available. Treatment using MR-linac can be used if available.

Daily image guidance is mandatory for position verification. The type and frequency of image guidance (e.g. Cone beam computed tomography (CBCT) or Exactrac) is at the discretion of the respective institutions. The anticipated setup uncertainty during treatment, the calculated treatment time and proximity to OAR must be considered.

Treatment interruptions should be kept to a minimum. Treatment can be given on the same day as simulation when feasible, but it is not required.

Patients are treated with conformal treatment plans. Modern dose calculation algorithms (Monte Carlo, Acuros, AAA, Collapsed Cone or similar) must be used to account for tissue inhomogeneities.

7.4 Quality assurance

To achieve similar dose planning strategies, all initially participating centres have performed dose planning for two representative patients and have reported set-up verification strategies. Centres joining the protocol will plan the same patients for comparison prior to first patient enrolment.

8 Target and organs at risk

8.1 Target definition

Target definition for bone metastases outside spine (outside C1-L5 and os sacrum):

Gross tumour volume (GTV) will be delineated as visible tumour.

GTV is defined as the area of disease seen on CT-scan and MR- scan. In addition, if the patient has a positron emission tomography (PET)/CT-scan recently done, the PET images should be fused with the simulation CT and PET avid areas contribute to GTV delineation.

CTV is defined by expanding the GTV with a margin of 5 mm and shaped to the bone (unless soft tissue involvement). Shaping to other anatomical boundaries is at the discretion of the treating oncologist and should be noted in the CRF.

The PTV margin follows the institutional practice and is registered in the CRF.

Target definition for bone metastases S1-S5:

For delineations of sacral targets, the GTV are delineated according to the International consensus recommendations for target volume delineation specific to sacral metastases and spinal stereotactic body radiation therapy (SBRT) (Dunne et al. 2020). See Appendix C. The PTV margin follows the institutional practice and is registered in the CRF.

Target definition for spinal bone metastases (from vertebrae C1-L5):

The clinical target volume (CTV) and gross tumor volume (GTV) are delineated according to

the International Consensus Guidelines by COX et al 2012 [63].

Gross tumor volume (GTV): Visible tumour on MR scan (T1 and T2 sequences), CT and/or PET-scan.

A paraspinal mass ≤ 5 cm in the greatest dimension contiguous with spine metastases is included.

Clinical target volume (CTV): GTV + involved sector according to Appendix D.
If the tumour is localized closer than 2 mm to a neighbouring sector, this sector should be included in the CTV as well. Circumferential CTVs encircling the cord should be used only when the vertebral body, bilateral pedicles or lamina and spinous process are all involved.

Planning target volume (PTV): CTV + 2 mm.

Instead of modifying the PTV at dural margin and adjacent critical structures to allow spacing, the PTV should be compromised to keep constraints to OAR.

8.2 Organ at risk (OAR) definition

8.2.1 OAR: none-spine

None-spine OAR are outlined as separate volumes as the outer contour of the organ, unless otherwise specified. For delineation we recommend following the contouring atlas at:
https://www.rtog.org/corelab/contouringatlases.aspx
It is for the treating physician to decide whether to contour the bowel bag or intestines.

8.2.2 OAR - Spine

Spinal cord constraints are defined according to the report of AAPM Task Group 101[66]. Spinal cord volume is defined as fusion with T2-weighted and T1-weighted MR scan and at contoured at least 10 cm above/below the superior/inferior extent. For spinal cord dose constraints see appendix B.

Spinal Cord is delineated encompassing medulla.

An OAR is only to be delineated if the organ is expected to receive a relevant radiation dose (at the discretion of the treating physician). See Appendix E.

Dose constraints to OAR are listed in Appendix B. Application of stricter constraints to OAR is at the discretion of the treating physician but should be noted in the CRF. Normal tissue constraints will be prioritized over target coverage and should not be compromised – this also apply within the PTV. However, for soft constraints (External (Skin) and the Thoracic Wall), the dose to OAR can be compromised in favour of covering the target if there is a strong clinical argument. The reason for this compromise should be noted in the CRF. See also section 7.2. The thoracic Wall is delineated as a 15 mm outer margin of the lung, including costae. Skin is delineated as an inner margin of 10 mm of BODY.

SpinalCord PRV is at the discretion of the respective institutions, but at least 1.5 mm margin is mandatory (not shaped to the bone). **Dose constraints for the spinal cord also apply to the spinal cord PRV**. For Stomach, Oesophagus, Duodenum, Small Intestines, Large Intestines, Rectum and the anal region a PRV margin of at least 5 mm is mandatory (shaped to the bone). Other margins are at the discretion of the institutional practice. Renography will be performed to evaluate kidney function before treatment in patients, where the kidneys can be expected to receive a relevant radiation dose (at the discretion of the treating physician). The renography is performed following the standard protocols of the individual departments.

8.3 Previous RT

If the patient has received previous radiotherapy, the combined dose must be considered, when evaluating if the dose constraints for the OAR are met.

9 Safety assessment

9.1 Adverse events (AE)

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject who has received SABR. This does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavourable and unintended symptom, (including an abnormal laboratory finding), or disease temporarily without any association with SABR. The AEs that will be reported are based upon organs at risks that most likely will be affected from SABR. This will depend on the site of treatment.

All adverse events will be graded according to the NCI-CTCAE v5.0 scale and will be reported on the appropriate CRF-form.

9.2 Serious adverse events (SAE)

A serious adverse event (SAE) in human trials is defined as any untoward medical occurrence that, at any dose, results in death or is life-threatening, is disabling, requires hospitalization (whether initial or prolonged and does not include planned hospitalization) or requires intervention to prevent permanent impairment/damage.

All SAEs must be registered by the local investigator on the appropriate CRF and must be followed until they are fully settled.

Progression or deteriorating of malignancy during the study (including new metastatic lesions or death due to progression), will be part of the efficacy assessment and should NOT be reported as an AE/SAE.

Symptoms clearly associated with malignancy during the study should NOT be reported as AE / SAE unless they are:

- Newly emerged (i.e. not present at baseline) and correlation with the underlying malignancy and old / new metastatic lesions are unclear.
- If there is any uncertainty as to whether an exacerbation of the subject's condition is due to the cancer disease or due to an AE, it must be reported as an AE or an SAE depending on the situation.

The local Investigator (together with the treating physician) must determine the relationship between the radiation treatment and the occurrence of a SAE as not suspected or suspected as defined below:

Not suspected:	A causal relationship of the radiation treatment is unlikely or remote, or other medications, therapeutic interventions, or underlying conditions provide enough explanation for the observed event.
Suspected:	There is a reasonable possibility that the radiation treatment caused the adverse event. 'Reasonable possibility' means there is evidence to suggest a causal relationship between the radiation treatment and the adverse event.

Furthermore, the local investigator (together with the treating physician) must determine whether a suspected serious adverse event is expected, or unexpected as defined below:

Expected:	If the treating physician/local investigator recognize the suspected SAE as an event reported in the literature and/or known from the clinical experience, this adverse event should be considered as expected.
Unexpected:	If the treating physician/local investigator do not recognize the suspected SAE as an event reported in the literature and/or known from the clinical experience, this event should be considered as unexpected.

The assessment of an SAE should be based upon organs at risks that most likely will be affected from the radiation.

Any suspected, unexpected SAE must be reported by the local investigator to the sponsor within one working day (after being aware of the incident). The sponsor can choose to change the registration of a suspected unexpected SAE to a suspected expected SAE after an audit of the case.

The Sponsor will inform the Ethical Committees of all relevant information about unexpected SAE, suspected to be related to the radiation treatment, that are fatal or life-threatening as soon as possible, and in any case no later than seven days after knowledge of such a case. Relevant follow-up information for these cases will subsequently be submitted within an additional eight days.

Once a year throughout the clinical trial, the sponsor will provide an updated safety report highlighting SAE to the Ethics Committee.

For events not reported in the CTCAE version 5.0, the investigator will use the grade or adjectives reported in the following:

Grade 1 Mild does not interfere with patient's usual function

Grade 2 Moderate Interferes to some extent with patient's usual function

Grade 3 Severe, Interferes significantly with patient's usual function

Grade 4 Life-threatening, results in a threat to life or in an incapacitating disability

Grade 5 Death

9.3 Trial management committee

A trial management committee (TMC) is set up with the participation of representatives from the different centres. The TMC will meet annually after study initiation, and after 1-year follow-up of 27 patients, conduct the interim analysis (see section 4.3 on sample size calculation for primary endpoint). Recruitment will continue after inclusion of the first 27 patients and will not wait the interim analysis. All events (See primary endpoint), will be reviewed by the TMC and if the rate of local progression at one year is excessive defined by the sample size calculation, the TMC can, at its discretion, recommend cessation of the study or dose adjustment. Furthermore, all grade 4 and 5 toxicity deemed caused by the radiation treatment will be reviewed by the TMC.

10 Ethical aspects

10.1 Ethical considerations

Patients with OMD will have very different outcome depending on the histological profile. If a patient is diagnosed with a bone metastasis, surgery is seldom a recommended solution, and the oncologist will most often consider the strategy as a palliative course and start chemotherapy or other systemic treatment. When the disease is stable, the oncologist will often continue therapy since the alternative (pause of treatment) may expose the patient to risk of progression and possible onset of symptoms in the treatment-free period. By offering an oligometastatic radiotherapy

treatment strategy, the patient might gain a chemo-free period, without side effects from systemic treatment.

However, there is a risk of progression during the RT treatment period. The protocol offers a stereotactic radiation plan with the maximum treating period of 6 days. This will most often mean a treatment-free interval from systemic treatment for about 3 weeks (depending on the type of systemic treatment). The risk of significant progression, during that time must, in most patients, be considered low for our study population. However, some patients might experience flare of the disease during the treatment pause. The treating oncologist must balance the pros and cons and involve the patient in the decision-making.

When receiving the radiotherapy, the patient might experience toxicity (early or late) from the radiotherapy. If the patient experiences toxicity ≥ grade 3, this might postpone the reintroduction of systemic therapy and affect the QoL.

10.2 **Toxicity**

In general, SABR to bones are well tolerated. Grade ≥ 3 toxicity is rare [21, 22, 47, 68, 69]. Toxicity depend on the anatomic structures proximate to the radiation sites. Frequently reported toxicities grade 1 and 2 are dermatitis, dyspnoea, pain flare, muscle soreness, oedema, tissue induration, loser stools, stomach ache, fatigue, nausea, vomiting, dysphagia and anorexia [36, 70-75].

10.2.1 Risk of fracture

The use of SABR in the non-spine bone metastasis setting has proven relatively safe with a crude fracture rate of approximately 3- 8.5% [29, 68].

Data on the risk of developing vertebral compression fracture (VCF) after spine SABR are variable 5.7%-39% [76-78]. In a recent review from Chang et al. the crude risk of VCF was 13.7% and, of whom 45% were surgically salvaged. The median time to VCF was within months post-SBRT (median, 3.3 months) [79]. A dose complication relationship has been confirmed by Sahgal et al. [27]. They observed a 39% risk of VCF with high dose single fraction SBRT (>24 Gy). High risk of VCF after single fraction regimes has been confirmed by other studies [4, 23, 76]. The following factors has been found to be significant predictors of VCF: dose per fraction, pre-existing fracture, lytic tumour, location in the thoracolumbar or lumbar region and spinal misalignment (kyphosis/scoliosis and

subluxation/translation) [27, 76]. SINS (Appendix G) is an important tool to identify the patients at greater risk for SABR-induced VCF, and therefore used in this protocol to assess the risk of mechanical instability and fracture risk [27]

10.2.2 Risk of joint stiffness

Another concern when using SABR to treat bone metastases is joint stiffness, which is thought to result from a gradual decrease in vascularity, radiation fibrosis and atrophy of joint muscles [80]. Joint stiffness tends not to manifest until 2–3 years after radiation therapy and therefore this toxicity is often underreported both in prospective and retrospective studies [81]. Stinson et al. found that 20% of the 145 cases in their study of limb sparing radiation therapy for soft-tissue sarcoma had joint contracture and it was determined that inclusion of more than 50% of the joint in the radiation field increased this risk [73].

A newly published work from Wang et al. compares outcome and toxicity of postoperative IMRT with two-dimensional radiotherapy in patients with soft tissue sarcoma of extremities and trunk [82]. They report a risk of joint stiffness of ≥ grade 2 to be 3.9% in the IMRT arm versus 12.3% in the 2D-RT arm (median follow up 58.1 months).

10.2.3 Radiation Myelopathy (RM)

RM is a late toxicity secondary to overdosing the spinal cord and is very rare in the modern era of 3-dimensional palliative fractionation schemes. The risk of RM has re-emerged because of the introduction of SABR. The diagnosis of RM is a diagnosis of exclusion and defined as: "*neurologic signs and symptoms consistent with radiation damage in the form of necrosis to the segment of the spinal cord irradiated, without MR evidence of recurrent or progressive tumour affecting the spinal cord".* Prospective studies reveal rates of RM after SABR, between 0% and 3% [48, 83-85].

Sahgal et al. reported in 2013 the first logistic regression model yielding estimates for RM specific to SABR [83]. Dose-volume histogram (DVH) results for 9 cases of post SABR RM were reported and compared with a cohort of 66 spine SABR patients without RM. They recommend limiting thecal sac maximum point volume (P_{max}) doses to 12.4 Gy in 1 fraction, 17.0 Gy in 2 fractions, 20.3 Gy in 3 fractions, 23.0 Gy in 4 fractions, and 25 Gy in 5 fractions.

A more recent publication from 2016 by Grimm et al [86] reviewed the literature and found only a single manuscript, that provided dose-volume data and outcomes for each spinal cord (102 spinal metastases in 74 patients treated by spinal radiosurgery) [87]. In total, 3 patients developed RM. Estimation from this dataset, the maximum dose limits according to QUANTEC (13 Gy in a single fraction and 20 Gy in 3 fractions), had less than 1% risk of RM. In this study we use the QUANTEC recommendations for spinal cord constraints and the constraints apply for both Spinal Cord (encompassing the medulla) and Spinal Cord PRV.

10.2.4 Pain flare

Limited data is available with respect to acute reactions. Pain flare is a common adverse event after radiation. From experience with palliative fractionation schemes, there is reported up to a 33% chance of a pain flare [88, 89]. Data on the risk of pain flare after SABR are variable. Owen et al. reported 10% risk of pain flare [21]. Chiang et al observed pain flare in 68.3% of patients, most commonly on day 1 after SABR [90]

In this study the toxicity according to the Common Toxicity Criteria, version 5.0 at frequent visits will be registered.

10.3 **Imaging**

Patients participating in this study will follow the same control schedule every 3 months as is standard outside trials. Radiation dose from a standard CT-scan examination is about 3-5 millisievert (mSv) and corresponding to about two times the annual background radiation. In some cases, the treatment is delivered with CT-guidance (CBCT- guidance). Two CBCT scans equals the radiation dose from one standard CT- scan. A CBCT before each treatment is standard practice. Depending on the target area, clinical situation and positioning challenges, additional CBCT's might be necessary during treatment delivery to ensure the correct position of the patient. The precise delivery of SABR is crucial due to the high dose gradients and small treatment margins. This is especially important when treating spine metastases. In some settings, the treatment is delivered with other forms of image-guidance (e.g. ExactTrac) and in these cases the dose corresponds to < 0.1 mSv pr. acquisition. Overall, the risk is not considered to be significant given the illness of the participants.

MR images are performed without ionizing radiation, so patients are not exposed to the harmful effects of ionizing radiation. But while there are no known health hazards from temporary exposure

to the MR environment, the MR environment involves a strong, magnetic field. The strong magnetic field may displace or cause heating of magnetic objects within the body (pacemaker, artificial joints, cochlear implants or other medical implants). Careful screening of people and objects entering the MR environment is critical to ensure nothing enters the magnet area that may become a projectile. Some patients find the inside of the MR scanner to be uncomfortably small and may experience claustrophobia. The magnetic fields that change with time create loud knocking noises which may harm hearing if adequate ear protection is not used.

The number of MR images/sequences performed before and during each treatment will depend on the biology of the primary tumor, the location of the target and the set-up challenges for the individual patient.

10.4 **Contrast agents and blood tests**

Contrast agents are used to improve visualization of the inside of the body produced by CT and MR imaging. The use of contrast agents also carries some risk, including side effects such as allergic reactions to the contrast agent. Mild reactions do occur and include metallic taste in the mouth, nausea and vomiting, headache, itching, flushing, mild skin rash or hives. Severe reactions are very uncommon and include difficulty in breathing, swelling of the throat, dizziness and profound low blood pressure and treatment is necessary. Death due to allergic reactions to the contrast is extremely rare.

After a blood test or injection, there is a risk of a small bruised area on the skin where the needle went in. Rarely a larger area of bruising may appear.

10.5 **Pregnancy**

Women of childbearing potential must agree to use adequate contraception (hormonal or barrier method of birth control; or abstinence) during treatment. Female partners of childbearing potential of male subjects must also agree to use highly effective contraception during treatment. If the woman wishes to become pregnant in the future, this must be discussed prior to entering the study.

10.6 **Insurance**

Patients participating in the study are covered by national regulations.

11 Data management

Data will be filed and stored using electronical 'case report forms' (CRFs) in a REDCap database provided by The Capital Region. The informed consent will ensure the sponsor, the representatives appointed by the sponsor and regulatory authorities' access to the patient's electronic records and collect information (see section 5.1). The access is required in order to conduct and report the results from the study and to secure that all regulations are followed. This includes both self-regulations, quality control and monitoring, of which all are obliged to follow.

All treatment plans will be exported to the Danish national radiotherapy plan database (DcmCollab database), from where doses to target and OAR will be extracted for analysis.

The data management system ensures compliance with current legislation and regulations on data handling and data safety. The study will be conducted in accordance with the General Data Protection Regulation (GDPR). All information will be kept strictly confidential in a database affiliated with this research project and in accordance with the rules of the GDPR (EU) 2016/679. The trial will be registered at the Hospitals Knowledge Center for Data protection compliance (Region Hovedstadens Videnscenter for Dataanmeldelser).

12 Protocol handling and economy

This study will be performed according to the Helsinki Declaration (Seoul version, October 2008). Approval from the ethical committee will be obtained before inclusion is started. The study is investigator initiated and the principal investigator has the overall responsibility for the scientific and ethical protocols, progression of the trial and finishing of academic publications. Regardless of positive, negative or inconclusive results, the trial will be made publicly available through conferences and international, scientific journals. The study group will follow the Vancouver rules (http://www.icmje.org/). Every 6 month the primary investigator review with the local investigator's submitted forms and treatment plans to ensure they are collected in line with the protocol. The trial management committee and others that have substantially contributed, will be invited for authorship of the final manuscript according to the Vancouver declaration. The study will be part of a PhD study, and is supported by Varian Medical Systems with 2.000.000 DKK and by DCCC Radiotherapy - The Danish National Research Centre for Radiotherapy via the Danish Cancer Society

(grant no. R191-A11526) with 450.000 DKK. The donations will cover a Ph.D. study, and this trial is one of two planned trials of the Ph.D. The donations will be deposited to a prespecified research account at the Department of Oncology, Herlev and Gentofte Hospital, which is subject to official control and audit. None of the researchers has financial interests in the investigation or the Varian Medical System. No remuneration will be paid to patients for participation in the trial.

13 Feasibility

Data from this study is the property of the investigators. Use of data or results derived from study population is only allowed if approved jointly by all members of the study group. Before a decision is made to publish, a consensus among the investigators must have been reached on how to interpret study results. The TMC and others that have substantially contributed will be invited for authorship of the final manuscript according to the Vancouver declaration.

14 Perspectives

The Bony-M study will facilitate the implementation of SABR for osseous oligo metastases, including the very important training of physicians, physicists and technologists in the practical manoeuvres in the online adaptation process. SABR represents a major undertaking for radiotherapy departments and is associated with risks of severe toxicity. We will gain knowledge on the effect of local definitive treatment of OMD.

We foresee that the demand for these treatments will increase significantly in near future. Exploring the exquisite technological solutions for precise delivery, will add to a broad catalogue of treatment options supporting the need for individualized treatment options.

The trial will be performed in close collaboration between different radiotherapy centres. This will support future collaborations between the centres. This collaboration will facilitate improved professional competences and a larger patient cohort, compared to a single centre study.

Appendix A Bilsky score

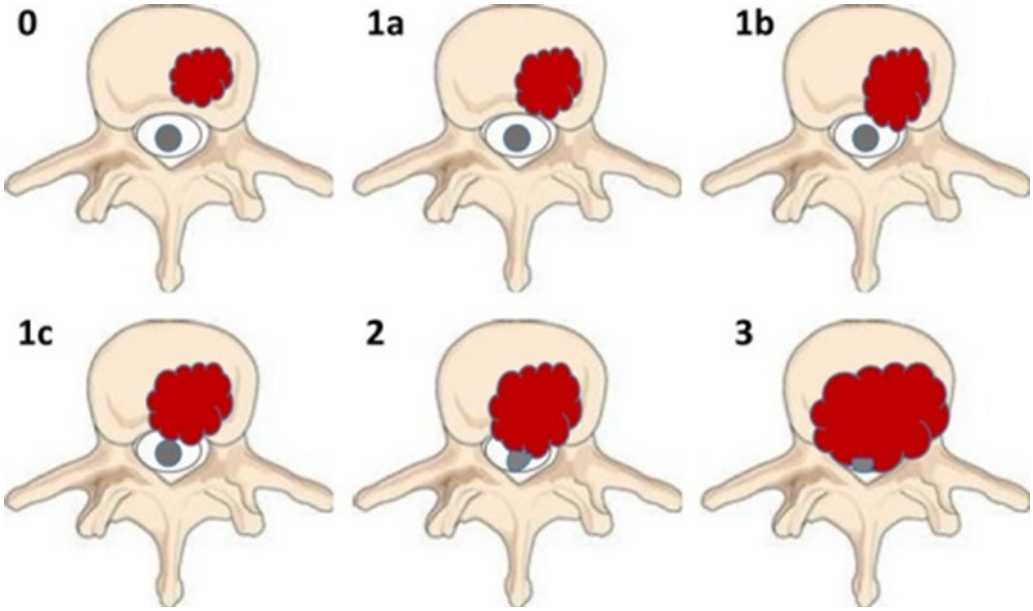

Figure of the 6-point epidural spinal cord compression (ESCC) grading scale proposed by Bilsky et al. [91]. Figure adapted from Tseng et al. [92]

Grade	Anatomical Involvement
0	Denotes bone-only disease
1a	Epidural impingement, without deformation of the thecal sac
1b	Deformation of the thecal sac, without spinal cord abutment
1c	Deformation of the thecal sac with spinal cord abutment, but without cord compression
2	Spinal cord compression, but with CSF visible around the cord
3	Spinal cord compression, no CSF visible around the cord.

Appendix B Constraints

Hard constraints (Bold type) signifies:	Planning objectives which should not be compromised.
Soft constraints (Italics) signifies:	Planning objectives which can be compromised in favor of covering the target if there is a strong clinical argument.
*D_{Max}	Defined as the near-point maximum dose, defined in this case as $D_{0.027\ cc}$

OAR	3 fractions	Endpoint
Hard constraints		
1 Esophagus	$D_{0.5cc}$ < 25,2 Gy[1]	Stenosis, fistula
2 Heart	$D_{0.035cc}$ < 30 Gy[2] D_{15cc} < 24 Gy [2]	Pericarditis
3 Trachea/MainBronchus (including the lobar bronchi)	$D_{0.5cc}$ < 32 Gy[1]	Stenosis, fistula, hemorrhage
4 Lung_R + Lung_L	V_{20Gy} < 10%[1]	Pneumonitis
5 GreatVessel (Aorta and V. cava)/Pulmonary vessels	$D_{0.5cc}$ < 45 Gy [1+2]	Aneurysm
6 Bladder	D_{15cc} < 16.8 Gy[1] $D_{0.5cc}$ < 28.2 Gy[1]	Cystitis fistula
7 Duodenum/Stomach	$D_{0.5cc}$ < 22,2 Gy [1] $D_{5,0cc}$ < 16,5 Gy [1]	Ulceration fistula obstruction Enteritis haemorrhage
8 SmallBowel	$D_{0.5cc}$ < 25,2 Gy [1] $D_{5,0cc}$ < 17,7 Gy [1]	Ulceration fistula obstruction Enteritis haemorrhage
9 LargeBowel/Rectum/AnalCanal	$D_{0.5cc}$ < 28,2 Gy [1]	Colitis
10 BowelCavity	D_{1cc} < 30Gy[3] D_{5cc} < 21 Gy[3]	Ulceration fistula obstruction Enteritis haemorrhage
11 Kidney	For each kidney: $V10_{Gy}$ ≤ 25%[4] For patients with one kidney or target close to the kidney: $V8.5_{Gy}$ < 10% to the residual healthy kidney[5]	Deterioration of kidney function
12 SpinalCord (encompassing medulla) + SpinalCord PRV **Both constraints should be fulfilled for both objectives (SpinalCord and SpinalCord PRV)**	$D_{max\ point}$ * < 21.9 Gy[2] $D_{0.35\ cc}$ < 18 Gy[2]	Myelitis
13 FemoralHead/HumeralHead	$D_{10\ cc}$ < 21,9 Gy [1]	Necrosis

14 Liver (minus GTV) **(healthy liver)**	Minimum 700 cm^3 below 15 Gy [3]	Liver function
Soft constraints		
15 External (Skin) ***Delineated as an inner margin of 10 mm of BODY.***	*D_{10cc} <30 Gy[2]*	*Ulceration*
16 Rib / ThoracicWall ***ThoracicWall is delineated as 15 mm outer margin of the lung, including costae.***	*$D_{0.5cc}$<37Gy[1]* *$D_{30\,cc}$ <30 Gy[1]*	*Fracture* *Soft tissue fibrosis*

1) Hanna, G.G., et al., UK Consensus on Normal Tissue Dose Constraints for Stereotactic Radiotherapy. Clin Oncol (R Coll Radiol), 2018. 30(1): p. 5-14 (35).

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3) DLGCG (Danish liver-gallbladder cancergroup): http://www.gicancer.dk/Content/Files/Dokumenter/DLGCG/Retningslinier_DLGCG%20Radioterapiudvalg.pdf

4) Personal communicater: Anna M.E.Bruynzeel, MD phD, VU University Medical Center Amsterdam.

5) Institutional practice.

Extra planning objectives

At the discretion of the treating physician to decide. Factors as the estimated life expectancy of the patient, risk of radiculopathy because of tumor growth and risk of radiation-induced radiculopathy must be balanced.

Constraints	3 fractions	Endpoint
SpinalNerve_ Roots	$D_{max\ point*}$ < 24 Gy[6] $V_{5\ cc}$ <20,4 [6]	Neuritis
CaudaEquina	$D_{max\ point*}$ < 24 Gy[6] $V_{5\ cc}$ <21,9[6]	Neuritis
SacralPlexus/BrachialPlexus	$D_{max\ point*}$ < 24 Gy[6] $V_{5\ cc}$ <22,5[6]	Neuritis
PeripheryNerve	$D_{max\ point*}$ ≤ 24.5 Gy[5]	Neuritis

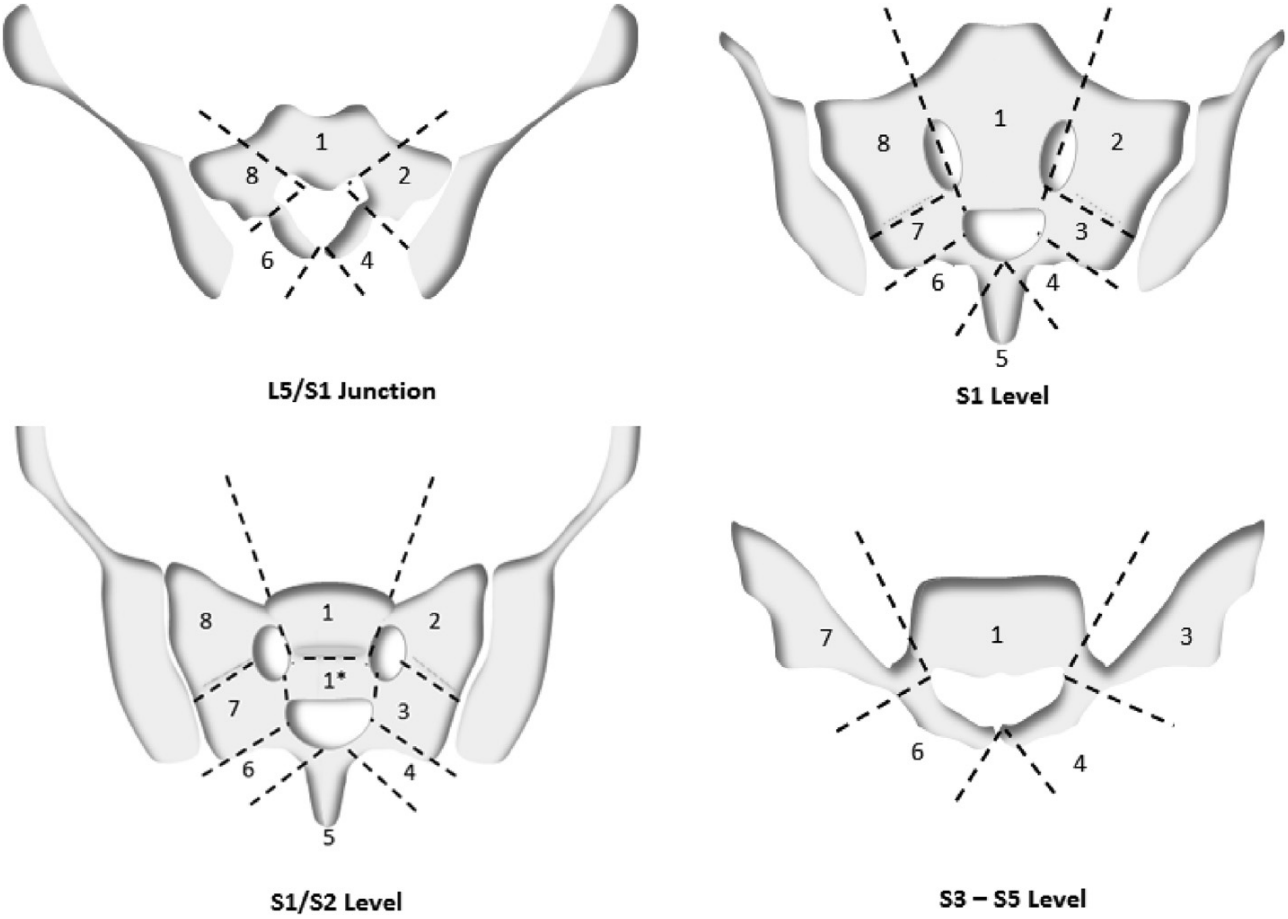
*D_{Max} The near-point maximum dose, defined in this case as D0.027 cc

5) Institutional practice.

6) Dr Luis Schiappacasse, Radiation Oncology Department UniversityHospitalLausanne (CHUV) Switzerland.

Appendix C Dunne - Target delineation in the sacrum

International consensus recommendations for target volume delineation specific to sacral metastases and spinal stereotactic body radiotherapy (SBRT) (Dunne 2020).



Stereotactic Radiosurgery Sacral Classification System. 1. vertebral body [1* represents the subsequent caudal vertebral body (S2 in this illustration)]; 2. left anterior ala; 3. left posterior ala; 4. left lamina; 5. spinous process; 6. right lamina; 7. right posterior ala; 8. right anterior ala.

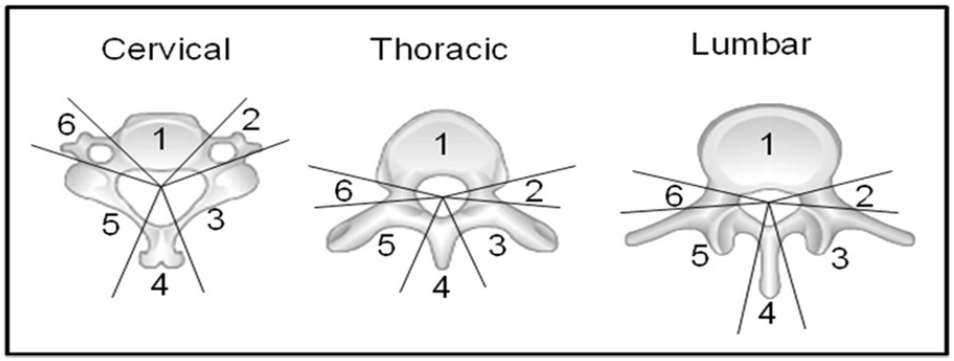
Recommendations for target volume definition of the sacrum in spinal stereotactic body radiation therapy/stereotactic radiosurgery (SBRT/SRS).

GTV involvement	Sacrum anatomic Map classification	Sacrum bony CTV recommendation	CTV description
Any portion of the VB	1	1	Entire VB
Lateralised within the VB (S1–S2)*	1	1, 2, 3	Entire VB and the ipsilateral ala. When contouring the ala, use the ossification line if visible to limit the extent of the CTV. The superior and inferior extent of the CTV is determined by the superior and inferior extent of the adjacent VB†
Lateralised within the VB (S3–S5)*	1	1, 3	Entire VB and the ipsilateral posterior ala. The superior and inferior extent of the CTV is determined by the superior and inferior extent of the adjacent VB
Diffusely involves the VB (S1–S2)*	1	1, 2, 3, 7, 8	Entire VB and bilateral alae. When contouring the ala, use the ossification line if visible to limit the extent of the CTV. The superior and inferior extent of the CTV is determined by the superior and inferior extent of the adjacent VB†
Diffusely involves the VB (S3–S5)*	1	1, 3, 7	Entire VB, bilateral posterior ala. The superior and inferior extent of the CTV is determined by the superior and inferior extent of the adjacent VB.
GTV involves VB and unilateral ala (S1–S2)*	1, 2, 3	1, 2, 3, 4	Entire VB, ipsilateral ala and ipsilateral lamina. The superior and inferior extent of the CTV is determined by the superior and inferior extent of the adjacent VB†
GTV involves VB and unilateral ala (S3–S5)*	1, 3	1, 3, 4	Entire VB, ipsilateral posterior ala and ipsilateral lamina. The superior and inferior extent of the CTV is determined by the superior and inferior extent of the adjacent VB.
GTV involves VB and bilateral ala (S1–S2)*	1, 2, 3, 7, 8	1, 2, 3, 4, 6, 7, 8	Entire VB, bilateral alae and bilateral laminae. The superior and inferior extent of the CTV is determined by the superior and inferior extent of the adjacent VB†
GTV involves VB and bilateral ala (S3–S5)*	1, 3, 7	1, 3, 4, 6, 7	Entire VB, bilateral posterior alae and bilateral laminae. The superior and inferior extent of the CTV is determined by the superior and inferior extent of the adjacent VB.
GTV involves the unilateral ala (S1–S2)*	2, 3	2, 3, ±1	Entire ipsilateral ala ± the entire adjacent VB. The superior and inferior extent of the CTV is determined by the superior and inferior extent of the adjacent VB†
GTV involves unilateral lamina	4	4, 5, ±1	Ipsilateral lamina, spinous process ± VB
GTV involves bilateral laminae	4, 6	4, 5, 6, ±1	Bilateral laminae, spinous process ± VB
GTV involves spinous process	5	4, 5, 6	Spinous process and bilateral laminae

Abbreviations: GTV, gross tumour volume; CTV, clinical target volume, VB, vertebral body, S1–S2 denotes sacral vertebral levels 1 and 2, S3–S5 denotes sacral vertebral levels 3, 4 and 5.
*The sacrum is a variable bone and at the level of S3, the ala may only be identified as having one segment.
†The exception is if the GTV involves any part of the S1 ala. Please see text for further discussion.

Appendix D Cox - CTV delineation guidelines

International Spine Radiosurgery Consortium anatomic classification system for consensus target volumes for spine radiosurgery (Cox 2012).



Guidelines for spinal SRS bony CTV delineation (Cox 2012).

GTV involvement	ISRC GTV anatomic classification	ISRC bony CTV recommendation	CTV description
Any portion of the vertebral body	1	1	Include the entire vertebral body
Lateralized within the vertebral body	1	1, 2	Include the entire vertebral body and the ipsilateral pedicle/transverse process
Diffusely involves the vertebral body	1	1, 2, 6	Include the entire vertebral body and the bilateral pedicles/transverse processes
GTV involves vertebral body and unilateral pedicle	1, 2	1, 2, 3	Include entire vertebral body, pedicle, ipsilateral transverse process, and ipsilateral lamina
GTV involves vertebral body and bilateral pedicles/transverse processes	3	2, 3, 4	Include entire vertebral body, bilateral pedicles/transverse processes, and bilateral laminae
GTV involves unilateral pedicle	2	2, 3 ± 1	Include pedicle, ipsilateral transverse process, and ipsilateral lamina, ± vertebral body
GTV involves unilateral lamina	3	2, 3, 4	Include lamina, ipsilateral pedicle/transverse process, and spinous process
GTV involves spinous process	4	3, 4, 5	Include entire spinous process and bilateral laminae

Abbreviations: CTV = clinical target volume; GTV = gross tumor volume; ISRC = International Spine Radiosurgery Consortium.

Appendix E DcmCollab export

List of structures to be exported to the Danish national radiotherapy plan database (DcmCollab database) :

GTV, CTV, PTV, Body-GTV, Body-PTV, trigger_BONYM, AnalCanal, Aorta, Bladder, BowelCavity, BrachialPlexus, BrachialPlexus PRV, CaudaEquina and SacralPlexus, Duodenum, Duodenum_PRV, Esophagus, Esophagus_PRV, External (skin), Femur_R, Femur_L, GreatVesselHumerus_R, Humerus_L, Heart, Ileum, Jejunum, Kidney_R, Kidney_L, LargeBowel, Liver, Lung_R, Lung_L, MainBronchus, PeripheryNerve, PeripheryNerve PRV, Rectum, Rib, SmallBowel, SpinalCord, SpinalCord_PRV, SpinalNerve_Roots, SpinalNerve_Roots PRV, Stomach, Stomach_PRV, Trachea, Uterus, V_CavaInferior, Vagina, VB_Thoracic, VB_Lumbal, VB_Sacrum.

A structure set including all the above-mentioned structures should be created for all patients. This will support the export to the DcmCollab database. Only relevant structures are delineated (at the discretion of the treating physician). The structure nomenclature should ideally follow Santanam et al. 2012 [93]. The trigger (trigger_BonyM) should be left empty in order to have an easy import into the BonyM protocol in the DcmCollab database. However, the specific naming can be determined by the individual institutions, but the naming should be consistent within an institution. Name of the DcmCollab protocol: Bony-M

Appendix F Numeric Pain Rating Scale (NPRS)

Generelle [område]-smerter

Hvis du skal beskrive den værste smerter du har haft [gennem de seneste 3 dage], hvordan har du da haft det?

Afkryds kun ét felt.

Ingen smerter										Værst tænkelige smerter
0	1	2	3	4	5	6	7	8	9	10

Forklaring:

[område] erstattes med fx 'ryg-/ben', 'skulder', 'knæ' osv.

Appendix G Spine instability neoplastic score (SINS)

Table adapted from Fisher et al. [94].

The Spine Instability Neoplastic Score (SINS) should be used in the risk assessment**.**

However in this study a modified SINS score is used, where evaluation of the radiographic spinal alignment in standing position is not necessarily required.

Element of SINS	Score
Location	
Junctional (occiput-C2, C7–T2, T11–L1, L5–S1)	3
Mobile spine (C3–C6, L2–L4)	2
Semi-rigid (T3–T10)	1
Rigid (S2–S5)	0
Pain relief with recumbency and/or pain with movement/loading of the spine	
Yes	3
No (occasional pain but not mechanical)	1
Pain free lesion	0
Bone lesion	
Lytic	2
Mixed (lytic/blastic)	1
Blastic	0
Radiographic spinal alignment	
Subluxation/translation present	4
De novo deformity (kyphosis/scoliosis)	2
Normal alignment	0
Vertebral body collapse	
>50% collapse	3
<50% collapse	2
No collapse with >50% body involved	1
None of the above	0
Posterolateral involvement of the spinal elements (facet, pedicle or CV joint fracture or replacement with tumor)	
Bilateral	3
Unilateral	1
None of the above	0

Appendix H EQ-5D-5L

Helbredsspørgeskema

Dansk version for Danmark

(Danish version for Denmark)

Under hver overskrift bedes du sætte kryds i DEN kasse, der bedst beskriver dit helbred I DAG.

BEVÆGELIGHED

- Jeg har ingen problemer med at gå omkring ❑
- Jeg har lidt problemer med at gå omkring ❑
- Jeg har moderate problemer med at gå omkring ❑
- Jeg har store problemer med at gå omkring ❑
- Jeg kan ikke gå omkring ❑

PERSONLIG PLEJE

- Jeg har ingen problemer med at vaske mig eller klæde mig på ❑
- Jeg har lidt problemer med at vaske mig eller klæde mig på ❑
- Jeg har moderate problemer med at vaske mig eller klæde mig på ❑
- Jeg har store problemer med at vaske mig eller klæde mig på ❑
- Jeg kan ikke vaske mig eller klæde mig på ❑

SÆDVANLIGE AKTIVITETER *(fx. arbejde, studie, husarbejde, familie- eller fritidsaktiviteter)*

- Jeg har ingen problemer med at udføre mine sædvanlige aktiviteter ❑
- Jeg har lidt problemer med at udføre mine sædvanlige aktiviteter ❑
- Jeg har moderate problemer med at udføre mine sædvanlige aktiviteter ❑
- Jeg har store problemer med at udføre mine sædvanlige aktiviteter ❑
- Jeg kan ikke udføre mine sædvanlige aktiviteter ❑

SMERTER / UBEHAG

- Jeg har ingen smerter eller ubehag ❑
- Jeg har lidt smerter eller ubehag ❑
- Jeg har moderate smerter eller ubehag ❑
- Jeg har stærke smerter eller ubehag ❑
- Jeg har ekstreme smerter eller ubehag ❑

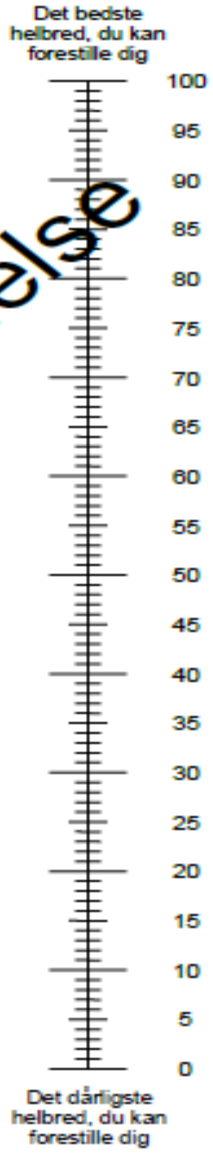
ANGST / DEPRESSION

- Jeg er ikke ængstelig eller deprimeret ❑
- Jeg er lidt ængstelig eller deprimeret ❑
- Jeg er moderat ængstelig eller deprimeret ❑
- Jeg er meget ængstelig eller deprimeret ❑
- Jeg er ekstremt ængstelig eller deprimeret ❑

2

- Vi vil gerne vide, hvor godt eller dårligt dit helbred er I DAG.
- Denne skala er nummereret fra 0 til 100.
- 100 svarer til det bedste helbred, du kan forestille dig.
  0 svarer til det dårligste helbred, du kan forestille dig.
- Sæt et X på det sted på skalaen, der viser, hvordan dit helbred er I DAG.
- Skriv derefter det tal, du har markeret på skalaen, ind i boksen nedenunder.

DIT HELBRED I DAG =



3

Appendix I CTCAE v. 5.0

MedDRA SOC	CTCAE Term	Definition	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Gastrointestinal disorders	Anal ulcer	A disorder characterized by a circumscribed, erosive lesion on the mucosal surface of the anal canal.	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; TPN indicated; elective invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Gastrointestinal disorders	Colonic obstruction	A disorder characterized by blockage of the normal flow of the intestinal contents in the colon.	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Hospitalization indicated; invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Gastrointestinal disorders	Colonic perforation	A disorder characterized by a rupture in the colonic wall.	-	Invasive intervention not indicated	Invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Gastrointestinal disorders	Colonic ulcer	A disorder characterized by a circumscribed, erosive lesion on the mucosal surface of the colon.	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; TPN indicated; elective invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Gastrointestinal disorders	Diarrhea	A disorder characterized by an increase in frequency and/or loose or watery bowel movements.	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline; limiting instrumental ADL	Increase of >=7 stools per day over baseline; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Gastrointestinal disorders	Esophageal perforation	A disorder characterized by a rupture in the wall of the esophagus.	-	Invasive intervention not indicated	Invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death

Gastrointestinal disorders	Esophagitis	A disorder characterized by inflammation of the esophageal wall.	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered eating/swallowing; oral supplements indicated	Severely altered eating/swallowing; tube feeding, TPN, or hospitalization indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Gastrointestinal disorders	Gastric perforation	A disorder characterized by a rupture in the stomach wall.	-	Invasive intervention not indicated	Invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Gastrointestinal disorders	Gastric ulcer	A disorder characterized by a circumscribed, erosive lesion on the mucosal surface of the stomach.	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; medical intervention indicated; limiting instrumental ADL	Severely altered GI function; TPN indicated; elective invasive intervention indicated; limiting self care ADL	Life-threatening consequences; urgent operative intervention indicated	Death
Gastrointestinal disorders	Gastrointestinal fistula	A disorder characterized by an abnormal communication between any part of the gastrointestinal system and another organ or anatomic site.	Asymptomatic	Symptomatic, invasive intervention not indicated	Invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Gastrointestinal disorders	Lower gastrointestinal hemorrhage	A disorder characterized by bleeding from the lower gastrointestinal tract (small intestine, large intestine, and anus).	Mild symptoms; intervention not indicated	Moderate symptoms; intervention indicated	Transfusion indicated; invasive intervention indicated; hospitalization	Life-threatening consequences; urgent intervention indicated	Death
Gastrointestinal disorders	Nausea	A disorder characterized by a queasy sensation and/or the urge to vomit.	Loss of appetite without alteration in eating habits	Oral intake decreased without significant weight loss, dehydration or malnutrition	Inadequate oral caloric or fluid intake; tube feeding, TPN, or hospitalization indicated	-	-
Gastrointestinal disorders	Obstruction gastric	A disorder characterized by blockage of the normal flow of the	Asymptomatic; clinical or diagnostic observations only;	Symptomatic; altered GI	Hospitalization indicated; invasive intervention	Life-threatening consequences; urgent operative	Death

		contents in the stomach.	intervention not indicated	function; limiting instrumental ADL	indicated; limiting self care ADL	intervention indicated	
Gastrointestinal disorders	Rectal obstruction	A disorder characterized by blockage of the normal flow of the intestinal contents in the rectum.	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; limiting instrumental ADL	Hospitalization indicated; invasive intervention indicated; limiting self care ADL	Life-threatening consequences; urgent operative intervention indicated	Death
Gastrointestinal disorders	Rectal perforation	A disorder characterized by a rupture in the rectal wall.	-	Invasive intervention not indicated	Invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Gastrointestinal disorders	Rectal ulcer	A disorder characterized by a circumscribed, erosive lesion on the mucosal surface of the rectum.	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function (e.g., altered dietary habits, vomiting, diarrhea)	Severely altered GI function; TPN indicated; elective invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Gastrointestinal disorders	Retroperitoneal hemorrhage	A disorder characterized by bleeding from the retroperitoneal area.	-	Self-limited; intervention indicated	Transfusion indicated; invasive intervention indicated; hospitalization	Life-threatening consequences; urgent intervention indicated	Death
Gastrointestinal disorders	Small intestinal obstruction	A disorder characterized by blockage of the normal flow of the intestinal contents of the small intestine.	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; limiting instrumental ADL	Hospitalization indicated; invasive intervention indicated; limiting self care ADL	Life-threatening consequences; urgent operative intervention indicated	Death
Gastrointestinal disorders	Small intestinal perforation	A disorder characterized by a rupture in the small intestine wall.	-	Invasive intervention not indicated	Invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Gastrointestinal disorders	Small intestine ulcer	A disorder characterized by a circumscribed, erosive lesion on the mucosal surface of the small intestine.	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; limiting instrumental ADL	Severely altered GI function; TPN indicated; elective invasive intervention indicated; limiting self care ADL	Life-threatening consequences; urgent operative intervention indicated	Death

Gastrointestinal disorders	Upper gastrointestinal hemorrhage	A disorder characterized by bleeding from the upper gastrointestinal tract (oral cavity, pharynx, esophagus, and stomach).	Mild symptoms; intervention not indicated	Moderate symptoms; intervention indicated	Transfusion indicated; invasive intervention indicated; hospitalization	Life-threatening consequences; urgent intervention indicated	Death
General disorders and administration site conditions	Pain	A disorder characterized by the sensation of marked discomfort, distress or agony.	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Infections and infestations	Myelitis	A disorder characterized by inflammation involving the spinal cord. Symptoms include weakness, paresthesia, sensory loss, marked discomfort and incontinence.	Asymptomatic; mild signs (e.g., Babinski's reflex or Lhermitte's sign)	Moderate weakness or sensory loss; limiting instrumental ADL	Severe weakness or sensory loss; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Musculoskeletal and connective tissue disorders	Joint range of motion decreased	A disorder characterized by a decrease in joint flexibility of any joint.	<=25% loss of ROM (range of motion); decreased ROM limiting athletic activity	>25 - 50% decrease in ROM; limiting instrumental ADL	>50% decrease in ROM; limiting self care ADL	-	-
Musculoskeletal and connective tissue disorders	Soft tissue necrosis	A disorder characterized by a necrotic process occurring in the soft tissues	-	Local wound care; medical intervention indicated (e.g., dressings or topical medications)	Operative debridement or other invasive intervention indicated (e.g., tissue reconstruction, flap, or grafting)	Life-threatening consequences; urgent intervention indicated	Death
Nervous system disorders	Peripheral motor neuropathy	A disorder characterized by damage or dysfunction of the peripheral motor nerves.	Asymptomatic; clinical or diagnostic observations only	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

Nervous system disorders	Peripheral sensory neuropathy	A disorder characterized by damage or dysfunction of the peripheral sensory nerves.	Asymptomatic	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	-
Renal and urinary disorders	Acute kidney injury	A disorder characterized by the acute loss of renal function (within 2 weeks) and is traditionally classified as pre-renal (low blood flow into kidney), renal (kidney damage) and post-renal causes (ureteral or bladder outflow obstruction).	-	-	Hospitalization indicated	Life-threatening consequences; dialysis indicated	Death
Renal and urinary disorders	Bladder perforation	A disorder characterized by a rupture in the bladder wall.	-	Invasive intervention not indicated	Invasive intervention indicated	Life-threatening consequences; organ failure; urgent operative intervention indicated	Death
Renal and urinary disorders	Hematuria	A disorder characterized by laboratory test results that indicate blood in the urine.	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; urinary catheter or bladder irrigation indicated; limiting instrumental ADL	Gross hematuria; transfusion, IV medications, or hospitalization indicated; elective invasive intervention indicated; limiting self care ADL	Life-threatening consequences; urgent invasive intervention indicated	Death
Renal and urinary disorders	Urinary fistula	A disorder characterized by an abnormal communication between any part of the urinary system and another organ or anatomic site.	-	Symptomatic, invasive intervention not indicated	Invasive intervention indicated	Life-threatening consequences; urgent invasive intervention indicated	Death

Renal and urinary disorders	Urinary tract obstruction	A disorder characterized by blockage of the normal flow of contents of the urinary tract.	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic but no hydronephrosis, sepsis, or renal dysfunction; urethral dilation, urinary or suprapubic catheter indicated	Altered organ function (e.g., hydronephrosis or renal dysfunction); invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Respiratory, thoracic and mediastinal disorders	Pleuritic pain	A disorder characterized by a sensation of marked discomfort in the pleura.	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Respiratory, thoracic and mediastinal disorders	Pneumothorax	A disorder characterized by abnormal presence of air in the pleural cavity resulting in the collapse of the lung.	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; intervention indicated	Sclerosis and/or operative intervention indicated; hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Injury, poisoning and procedural complications	Dermatitis radiation	A finding of cutaneous inflammatory reaction occurring as a result of exposure to biologically effective levels of ionizing radiation.	Faint erythema or dry desquamation	Moderate to brisk erythema; patchy moist desquamation, mostly confined to skin folds and creases; moderate edema	Moist desquamation in areas other than skin folds and creases; bleeding induced by minor trauma or abrasion	Life-threatening consequences; skin necrosis or ulceration of full thickness dermis; spontaneous bleeding from involved site; skin graft indicated	Death
Injury, poisoning and procedural complications	Fracture		Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic but non-displaced; immobilization indicated	Severe symptoms; displaced or open wound with bone exposure; limiting self care ADL; operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death

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