ESO-SPARE

Esophagus-sparing Radiotherapy for Thoracic and Cervical Metastatic Spinal Cord Compression- A randomized Phase III Trial

GLUC-DIAB

Glucocorticoid diabetes in patients with metastatic spinal cord Compression

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The trial management committee is responsible for maintaining protocol updates, quality assurance of the treatment plans collected in the data base and handle all serious adverse events (SAE) as reported from the participating centers.

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1 Background

1.1 Metastatic spinal cord compression

Metastatic spinal cord compression (MSCC) is a feared complication of metastases to the vertebra. Approximately 5-10 percent of patients with metastatic cancer experience MSCC, most commonly patients with lung-, breast-, prostate and renal cancer.[1] MSCC is a disabling condition that can lead to pain, disablement of sensory and motor function distal to the injury .[2] Early detection and onset of treatment is key to improve outcome results. Diagnosis is typically set through either CT or MRI scan; however, MRI is the preferred modality for diagnosing.[3] Symptoms are severe, unremitting pain, progressive discomfort, sensory symptoms, function deficits and bladder or bowel dysfunction[4]. Treatment is mainly high dose steroids to decrease edema and radiotherapy. Surgery is offered, when possible, to patients in good performance status and followed by radiotherapy[2]. Interventions mainly aim at pain relief and preserving motor functions. A small fraction of patients with highly chemo-sensitive tumors are offered chemotherapy.[4] The performance status at the time of diagnosis is the main determining factor of the post-treatment outcomes, with patients with lower-extremity function and sensation at the onset of treatment having a longer survival time[4]. When MSCC is diagnosed, life expectancy is typically short, with a 2-year survival of approximately 10% and a median survival of less than 6 months.[2,5] As treatment is palliative Quality of Life (QoL) is important, however, patients may experience early toxicity after radiotherapy, paradoxically causing reduced QoL.[5,6]

1.2 Radiotherapy treated MSCC and early gastro-esophageal toxicity

There are only few reports in the literature of gastro-esophageal toxicity after radiotherapy for MSCC. In the recent SCORAD trial, 694 patients were randomized to single or five fraction radiotherapy for MSCC [7]. It was a non-inferiority trial and the primary outcome was ambulatory at 8 weeks. Only half the patients were eligible for the intention to treat analysis that showed no difference between the groups. Almost half of the patients were in performance stage III-IV and 60% had metastases in the thoracic spine. The study reported grade I-II dysphagia in 7- 9%, grade I-II sore

throat in 4-10%, grade I-II nausea in 18% and grade I-II anorexia in 30% of the patients that reached the 8-week evaluation.[7] In a retrospective report on 1304 patients with MSCC and in another smaller study comparing radiotherapy techniques, Rades et al found no grade 2 or worse early esophageal toxicity and no late toxicity.[6,8] In a prospective study including 149 patients without spinal compression, treated stereotactically on the spine, Wang et al reported a single patient with grade 3 dysphagia [9]. In a phase III randomized trial comparing short course with split course radiotherapy in 276 patients with MSCC, Maranzano found grade 3 esophagitis or laryngitis in 1,5% of the patients. [10] However, in all these studies patient follow-ups occurred at varying times, typically months apart with no focus on the very early toxicity. In a small prospective study from Rigshospitalet by Gram et al, 30 patients with MSCC treated with 30 Gy in 10 fractions were included[11]. Patients were followed daily for 3 weeks and hereafter weekly for 4 weeks with telephone interviews and questionnaires. 14 patients were treated at Th8 or above. 11 of the patients treated at Th8 or above reported esophageal discomfort lasting for average 11 days (range 1-18 days). The toxicity mainly occurred within week 2 and 3 after radiotherapy start. Three other patients treated above Th8 reported no esophageal toxicity. There was a significant correlation between mean and maximum dose to the esophagus and reported toxicity. These results indicate that there is a high incidence of early esophageal toxicity, when irradiating vertebras above Th8. A dose-effect relationship assessment was attempted, see Figure 1.

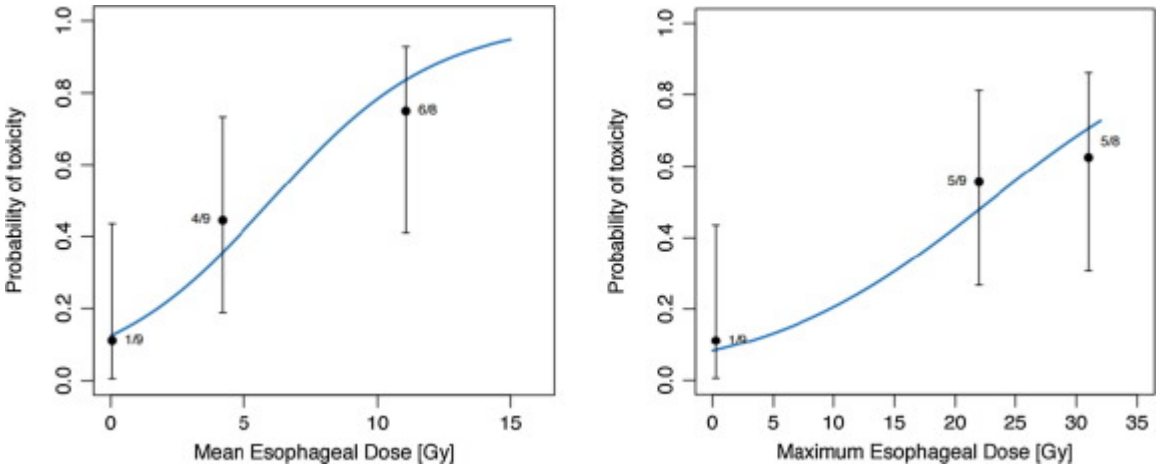


Figure 1 The risk of toxicity of the gastro-intestinal tract as a function of mean and maximum esophageal dose, as estimated using univariate logistic regression[11].

In most radiotherapy centers worldwide, simple radiotherapy techniques as one field or opposing fields are used to treat MSCC as this is the least resource craving techniques and treatment start is often the day as radiotherapy planning because of the urgent nature of MSCC. With these techniques sparing of the esophagus is not possible. Modern technology such as inversely modulated radiotherapy (IMRT) and volumetric arc therapy (VMAT) holds the potential for shaping the dose gradient smooth around the target and it is possible to prioritize avoidance of organs at risk. Furthermore, precise setup with Cone-Beam Computed Tomography (CBCT) enables the use of tighter safety margins for treatment.

Standard of care in our departments is VMAT and daily position verification with CBCT. Based on the dose response curves in Figure 1 we made VMAT dose plans that kept the maximum esophagus dose below 10 Gy when prescribing 30 Gy/10 fractions, see Figure 2.

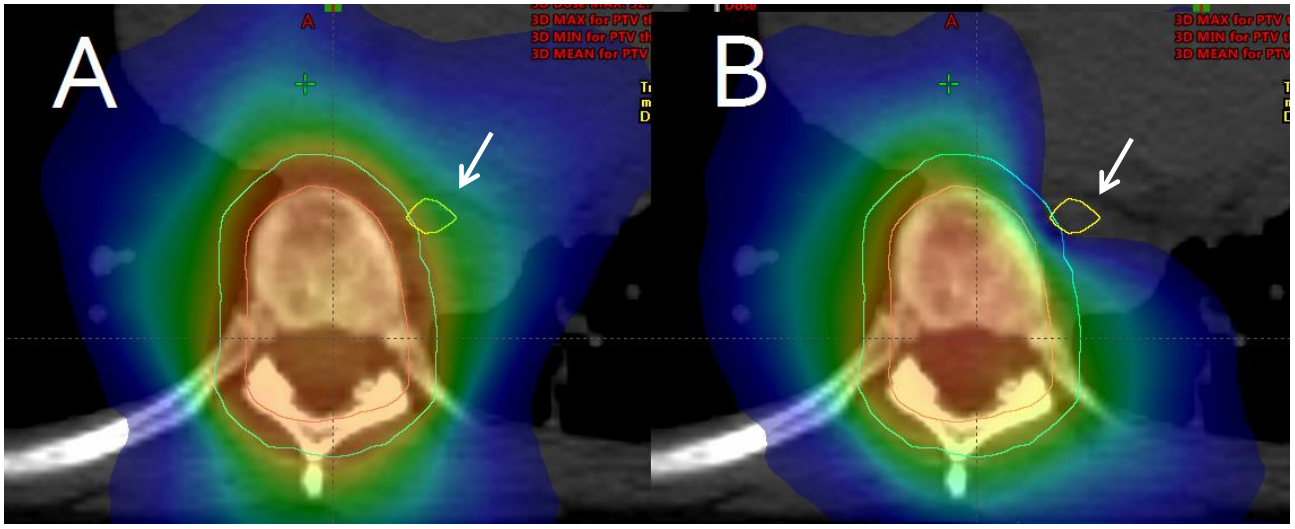


Figure 2. Axial cut of a vertebra with VMAT dose color wash and delineation of esophagus. Red area represents high-dose area. Blue area represents low-dose area. A: standard dose plan. B: esophagus sparing plan. The arrow points at the esophagus.

Sparing of the esophagus can only be achieved by compromising dose to the vertebra and/or increasing the dose from angles that do not pass the esophagus thereby increasing dose to other organs, e.g. the lungs. In the present proposal we want to examine the clinical effect of this compromise.

Esophagus sparing radiotherapy prerequisites thorough delineation of the esophagus and can delay treatment start. If esophagus sparing radiotherapy is to become standard and disseminated, the process should be automated. Preferably, leaving only delineation of the target as a manual task. Automatization of the planning process will reduce waiting time for treatment and treatment time, both of which are important for these fragile patients.

1.3 Glucocorticoid-induced diabetes

High dose glucocorticoid is used in MSCC to decrease inflammation and edema in the affected vertebra and neural tissue. In our clinic, patients are started on high-dose glucocorticoids (150 mg Prednisolone daily) when MCSS is suspected. During radiotherapy the dose is reduced to 75 mg daily. A minimum 5 days of treatment are mandatory, even for patients treated with single fraction. High-dose glucocorticoid treatment may be discontinued after 5 days or after end of radiotherapy treatment, whichever comes first. Depending on symptoms and duration of prior glucocorticoid treatment some patients may benefit from a gradual decrease. [12,13]

It is well established that glucocorticoid treatment can induce new-onset hyperglycemia and even glucocorticoid-induced diabetes mellitus (GIDM) in patients without a history of diabetes mellitus (DM) [14]. Hyperglycemia has been associated with complications such as longer hospital stays, delayed wound healing, increased infections and higher mortality rates. [14]

As of now there are only two studies describing glucocorticoid-induced diabetes in patients receiving treatment for MSCC.[15,16] Schultz et al performed a prospective study including 131 patients receiving high-dose glucocorticoids for MSCC. The patients were monitored with 1-3 finger prick glucose measurements for 12 days after treatment start. 43% of the patients presented plasma glucose values diagnostic of diabetes and 12% were treated with insulin[15]. A HbA_{1c}-value <39 mmol/mol was associated with a negative predictive value of 96% for not developing diabetes needing treatment with insulin.[15]

While insulin-treated diabetes was mainly diagnosed in the first week after treatment start, the incidence of non-insulin treated diabetes was rising through-out the study period[15]. There are no data describing glucose levels beyond the study period of 12 days.

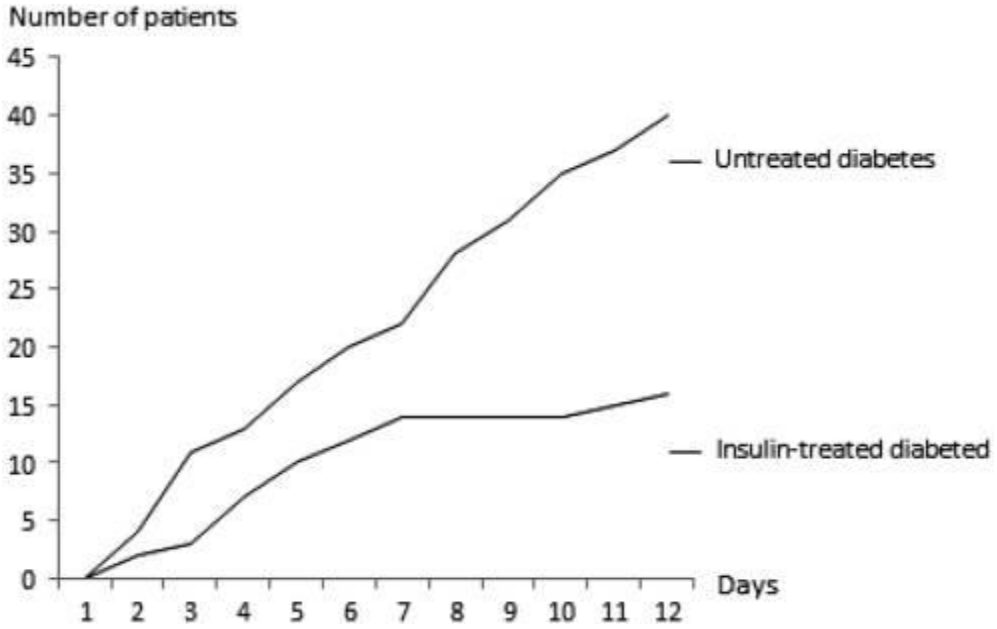


Figure 3 Time course of development of diabetes [15]

In patients that did not receive insulin, GIDM was left untreated.[16] Out of 16 patients treated with insulin, 14 had blood glucose measurements >15 mmol/l before insulin treatment was initiated, the last two patients had insulin after blood glucose measurements >14.0 and 14.4 mmol/l.[16] Development of insulin demanding diabetes was associated with reduced survival, suggesting either a metabolic effect of hyperglycemia on mortality or an underlying mechanism simultaneously promoting diabetes and mortality. [16]

The absence of international and national guidelines regarding treatment of glucocorticoid-induced hyperglycemia and diabetes in this patient cohort makes clinical treatment inhomogeneous as it mainly depends on the treating physician.

As an example, the local guidelines on management of glucocorticoid-induced hyperglycemia in the two centers participating in this study are different in their approach. The plasma-glucose threshold for considering treatment with insulin ranges from 11,1mmol/L-25 mmol/L in Herlev Hospital and Rigshospitalet respectively.[12,17] Only one center uses a HbA_{1c}-value of <39 mmol/mol to identify patients that do not need glucose monitoring.[12] See Table 5 and 6 for guideline summary.

Patients with MSCC constitute a unique population making treatment of glucocorticoid-induced hyperglycemia especially challenging. The patients are fragile with a short life expectancy and often already heavily medicated in relation to their cancer diagnosis. It is desirable not to burden these

patients with unnecessary hospital contacts, blood sampling and medical treatment. As most patients will not live to experience any late diabetic complications, it is reasonable that focus should be on managing symptomatic hyperglycemia and preventing acute hyperglycemic complications. If the hyperglycemia is transient and asymptomatic, it would be preferable to spare the patient from supplementary burdensome glucose monitoring and insulin administration.

As of now there are no studies describing the spontaneous course of plasma-glucose levels in patients treated with high-dose glucocorticoids for MSCC during and after treatment completion.

Flash glucose measurement technology has been available on the Danish market for approximately 5 years.[18] The FreeStyle Libre system uses a factory calibrated sensor placed on the upper arm. The sensor provides glucose measurements every 15 minutes, these can be read by swiping the sensor with a reading devise or a smartphone with a preinstalled app. Retrospective glucose data analysis can then be generated using the system software[19]. Because the sensor is factory calibrated, it can be worn for 14 days with no required intervention e.g. finger prick glucose measurements.

A blinded Flash sensor is available for professional use (FreeStyle Libre Pro™; Abbott Diabetes Care, Witney, UK).[20]

In this this study we wish to address two issues regarding glucocorticoid-induced diabetes.

Firstly, the dose and duration of glucocorticoid-treatment has been reduced significantly since 2014 where the study by Schultz et al was performed. The use of HbA1c < 39 mmol/mol as a cut-off to identify the patients at low risk of developing insulin demanding diabetes needs to be validated in this new setting.

Secondly, we wish to characterize the spontaneous course of plasma-glucose during and after high-dose glucocorticoid treatment using Flash patients with MSCC with no prior history of diabetes.

2 ESO-SPARE

We propose a phase III trial – ESO-SPARE, with randomization to esophagus sparring radiotherapy or standard of care radiotherapy for patients treated for MSCC in the thoracic and cervical spine. The primary aim of ESO-SPARE is to examine if advanced radiotherapy planning and delivery of radiotherapy with sparring of the esophagus can decrease patient reported esophageal toxicity.

Concurrently we want to conduct a observational study of clucocorticoid diabetes in patients with metastatic spinal cord compression (the GLUC-DIAB study). In this study we wish to characterize the spontaneous course of blood-glucose level during and after high-dose glucocorticoid treatment and validate the HbA_{1c} cut-off used in the clinic to identify patients in low risk of developing glucocorticoid-induced insulin-dependent DM.

We have the following research questions:

- Can esophagus sparring radiotherapy significantly decrease patient reported esophageal toxicity in patients with metastatic spinal cord compression without compromising their ambulatory function?
- Will esophagus sparing radiotherapy increase other toxicities compared to standard radiotherapy?
- What is the spontaneous course of blood-glucose level during and after high-dose glucocorticoid treatment for patients with MSCC?
- What is the incidence of glucocorticoid-induced diabetes in patients with MSCC?
- How many of the patients that develop glucocorticoid-induced diabetes, have normalized their plasma-glucose values on day 28 after start of glucocorticoid treatment?
- Can HbA1c be used as a negative predictive value for not developing insulin demanding diabetes?
- What is the incidence of hospital admissions due to new-onset diabetes?

2.1 Primary endpoint

- Early patient reported gastro-oesophageal toxicity measured as peak score within the first 5 weeks after treatment start measured by PRO-CTCAE, see Appendix A.

2.2 Co-primary endpoint

- Ambulatory function: Preserved ability to walk measured by EQ-5D-5L, see Appendix B.

2.3 Secondary endpoints

- Duration of gastro-oesophageal toxicity
- Reirradiation rate
- Preserved physical function measured by EORTC QLQ C30, see Appendix C.
- Changes in Quality of life (QoL) measured with EQ-5D-5L and EORTC QTQ C30
- Change in weight
- Pain reduction (MTS site) from baseline evaluated by “Numeric Pain Rating Scale (NPRS)”, see Appendix D.
- Change in analgesic consumption
- Overall survival (OS)
- Incidence of glucocorticoid induces diabetes
- Incidence of glucocorticoid induced diabetes treated with insulin
- Number of patients with normalized blood-glucose values on day 28 after start of treatment
- Incidence of hospital contacts requiring regulation of hyperglycemia
- Incidence of hospital admissions due to new-onset diabetes
- Time in range
- Time above range
- Time below range
- Mean glucose
- Standard deviation
- Coefficient of variation

2.4 Definition of endpoint related concepts

- The duration of patient reported gastric-oesophageal toxicity is measured as the time from an increase in gastro-oesophageal symptom score to a return to baseline
- Reirradiation rate is defined as fraction of patients getting reirradiation, where the same spine levels are included in the irradiated volume
- OS is defined as time from inclusion until death from any cause
- diabetes developed during glucocorticoid treatment will be defined as two random plasma glucose measurements ≥11,1 mmol/L.
- Time-in-range is defined as the percent of time glucose value is in normal range (3,9-10 mmol/L)
- Time above range is defined as the percent of time the glucose value is above normal range
- Time below range is defined as the percent of time the glucose value is below normal range
- Coefficient of variation for glucose is calculated as **(Standard Deviation / Mean) * 100**

2.5 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[21]. In this protocol, we will use the ICPRE to evaluate pain response. Response categories are based on patient reported pain scores (NPRS) and analgesic consumption (convert to oral morphine-equivalent dose).

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 C.

Registration of NPRS will be registered at baseline and subsequently according to Table 2. 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, 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.

2.6 HbA1c validation

Baseline HbA_{1c} is measured for all patients starting high glucocorticoid treatment for MSCC. Baseline values above 48 mol/mol are considered diagnostic for DM. For all other patients, diabetes developed during glucocorticoid treatment will be defined as two random plasma glucose measurements ≥11mmol/L. Based on baseline HbA_{1c} results and subsequent glucose measurements from the patients included in ESO-SPARE we will validate if the current HbA_{1c} cut off value (39 mmol/mol) can identify patients in low risk of developing glucocorticoid-induced insulin-dependent DM.

2.7 Exploratory studies

- Description of the dose-response relationship for the esophagus in the palliative dose spectrum.
- Atomization strategies: from delineation of risk organs to dose calculation.
- Adaptive esophagus sparing strategies.

3 Study design, sample size calculation and time frame

3.1 Study design

This is a prospective, investigator-initiated, phase III, multicenter-study, investigating if esophagus sparing radiotherapy for spinal cord compression can decrease patient reported gastro-esophageal toxicity without compromising their ambulatory function.

Concurrently we want to validate the HbA_{1c} cut-off value used in the clinic to identify patients in low risk of developing glucocorticoid-induced insulin-dependent DM and characterize the spontaneous course of plasma glucose levels during and after treatment with high-dose glucocorticoids.

3.2 Sample size

Esophagus-sparring radiotherapy: 200 patients will be included in this study. Accrual and compliance will be assessed after inclusion of the first 50 patients. If compliance falls below 50% in more than 1/4 of patients, accrual will be extended to 250 patients. If compliance falls below 50% in more than ½ of patients, accrual will be extended to 300. Following study closure, 9 weeks of follow up after start of treatment is completed, before data are collected for primary end-point analysis**.** OS analysis will be performed 6 month, 12 and 18 months after the last patient has completed radiotherapy.

Glucocorticoid-induced diabetes: 150 patients will be included in this study. If needed, inclusion may continue after closure of inclusion for esophagus-sparring radiotherapy.

Analysis of data in respect to secondary endpoints and exploratory studies may be analyzed 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.

3.3 Sample size calculation for primary endpoint

We assume that we can decrease maximum esophageal dose from 30 Gy to 10 Gy and that this will result in a 50% decrease in risk of early esophageal toxicity. [11] We want to conduct a phase III trial with 1:1 randomization between standard VMAT and experimental esophageal VMAT. Prior data

indicate that the rate of early esophageal toxicity with standard VMAT is 0.6. [11] If the true early esophageal toxicity rate in the esophagus sparing VMAT arm is 0.3, conventional power calculation indicates that we would need to include 62 patients in each arm, to be able to reject the null hypothesis that the toxicity rates for experimental and control arms are equal with a probability (power) of 0.9. The Type I error probability associated with the test of this null hypothesis is 0.05 and calculations are performed assuming Fisher's exact test. However, with this patient population we anticipate high rate of heterogeneity and we need to account for loss of follow-up due to patients dying early or being too frail. We increase the study size to 100 patients in each arm to account for these challenges. Patients will be stratified according to performance status and fractionation scheme.

3.4 Ambulatory function as a co-primary endpoint

We wish to demonstrate that the improvement in esophageal toxicity does not come at a price of reduced effect of the radiation. As a prioritized secondary endpoint, we choose ambulatory function (preserved ability to walk) measured on a 4-point scale. We assume that the conventional arm follows the distribution of the SCORAD trial and test our ability to detect a difference from an assumed inferior experimental arm in terms of ambulatory function, see Table 1.[7]

If the underlying "true" distribution on ambulatory grades is as depicted in the table and we assume 66 patients per arm are evaluable, we find that 84% of simulated trials would lead to statistically significant differences detected with a Wilcoxon rank sum test for comparing the trial arms. In other words, the power of the trial is enough to detect a deterioration according to the able, which would lead to rejection of the experimental treatment.

	Conventional arm	**Experimental arm**
Grade 1: Ambulatory without the use of walking aids	22	11
Grade 2: Ambulatory with walking aids	44	32
Grade 3: Unable to walk	26	37
Grade 4: Absence or flicker of motor power in any muscle group	8	20

Table 1: Distribution of ambulatory function. The conventional arm follows the SCORAD trial (7).

The power of ESO-SPARE is enough to detect a difference in ambulatory function as seen in Table 1.

3.5 Randomization

Patients will be randomized after signed informed consent. The randomization will be done in REDCap and be stratified for number of fractions and treating center. Patients will not be informed of randomization outcome. All patients can be included in validation of the HbA_{1c} cut-off after signed informed consent.

Patients from both arms can be included in validation of the HbA_{1c} cut-off after signed informed consent. Patients with prior history of diabetes and patients with HbA1c ≥ 48 mmol/mol will not be included. See **Figure 4** for patient distribution.

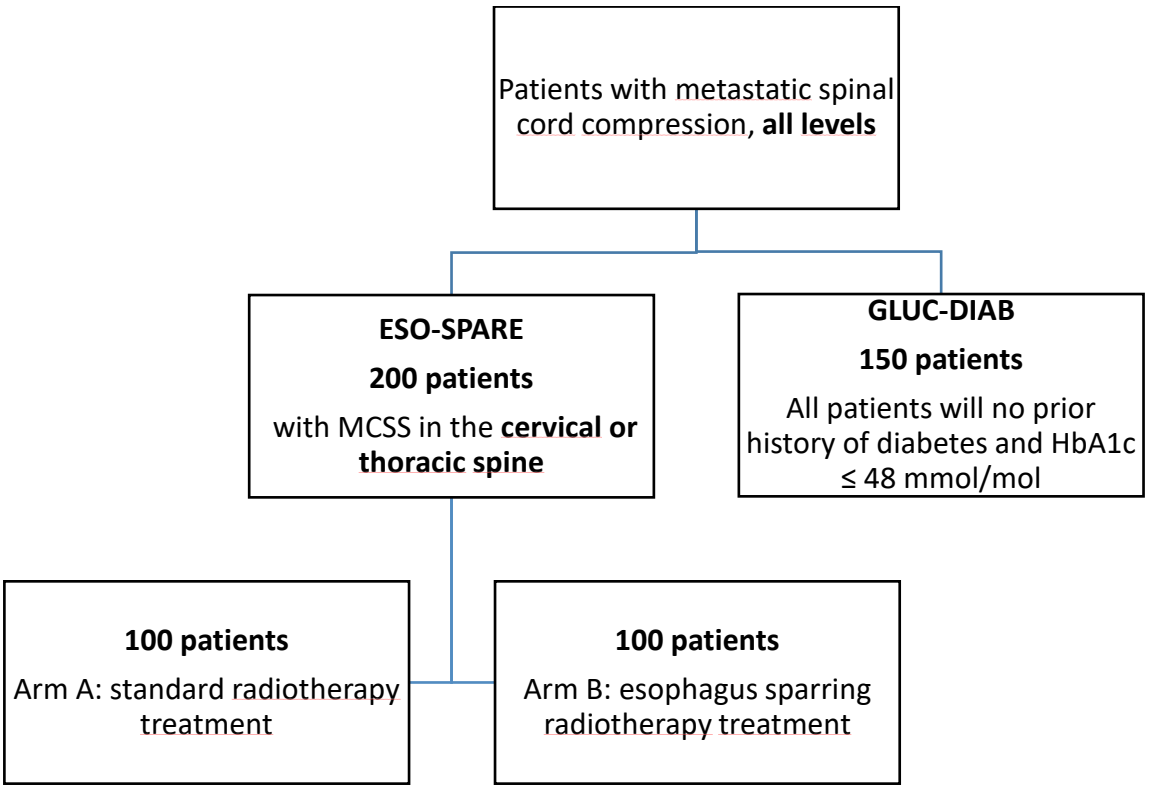


Figure 4. ESO-SPARE and GLUC-DIAB patient distribution.

3.6 Time frame

ESO-SPARE- Esophagus-sparring radiotherapy: 200 patients will be enrolled within a timeframe of maximum of three years. The study will close after three years regardless if the planned number of

enrolled patients is reached or not. Accrual and compliance will be assessed after inclusion of the first 50 patients. If compliance falls below 50% in more than 1/4 of patients, accrual will be extended to 250 patients. If compliance falls below 50% in more than ½ of patients, accrual will be extended to 300.

Compliance is defined as the patient's ability to answer at least half of the daily questionnaires within the first two weeks.

GLUC-DIAB - Glucocorticoid-diabetes: 150 patients will be enrolled within a timeframe of maximum of three years. The study will close after three years regardless if the planned number of enrolled patients is reached or not.

4 Visits and follow-up procedure

Patients will be scheduled for follow-up according to Table 2. Additional imaging or laboratory investigations are at the discretion of the treating oncologist. Inclusion of patients and recording of baseline data will take place when the patients come for the planning procedures for radiotherapy. Follow-up may be done electronically or using paper edition questionnaires. Paper edition questionnaires may be returned in relation to another hospital visit or by mail. Registration will 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 surgical history, all medicine, performance status, pathology, type of systemic treatment, scan results, radiotherapy dose and schedule, further irradiation including re-irradiation. Patients will be followed till death but will only actively be followed for 9 weeks.

	Baseline	EOT	Daily Week 1-4 after start of RT	Daily Week 1-5 after start of RT	Weekly Week 1-5 after start of RT	Weekly Week 6-9 after start of RT
Signed consent	x					
Performance status	x					
Weight*	x	x			x	x
Registrations of analgesic, steroids, antacids and antidiabetic medication	x	x			x	x
EuroQol EQ-5D-5L Index*	x				x	x
EORTC QLQ-C30*	x				x	x
PRO Gastro-oesophageal symptoms*	x			x		x
PRO pain incl. numeric pain rating scale*	x			x		x
HbA_{1c}	x					
Flash glucose measurements			x			

Table 2 Schedule for visits and follow-up procedure. *Electronic questionnaire or telephone questionnaire

Quality of life

The QoL questionnaires EuroQol EQ-5D-5L Index and EORTC QRQ C30, which are standardized and validated instruments, will be used to measure participants' quality of life (QoL) during follow up. 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).

The EORTC QRQ C30 is more detailed and will be used to calculate measures for physical function.

See appendix B and D.

4.1 HbA_{1C} and Flash glucose monitoring.

HbA_{1C} will be measured at baseline. The blinded Flash glucose monitoring system FreeStyle Libre Pro (FreeStyle Libre Pro™; Abbott Diabetes Care, Witney, UK) will be used to obtain continuous glucose measurements for 28 days from baseline.[19,20] The sensor must be changed after 14 days. This can be done in relation to another hospital appointment or by the patient at home with video assistance if necessary.

Data will only be extracted after the second sensor is dismantled. For quality assurance data will be extracted from the first sensor in the first 5 participants.

If the patients experience symptoms of hyperglycemia or hospitalized, glucose measurements will be at the discretion of the treating physician. See section 4.3 toxicity assessment.

4.2 Toxicity assessment

All toxicity assessment will be patient reported. If the patient cannot access the internet formula, the local investigator or a substitute will call them on the phone and record answers to the questions. QoL of Life schemes will be sent by mail. We will use the PRO symptom assessment that is found most suitable from an "pilot assessment" of different questions assessing oesophageal pain, difficulty swallowing, heart burn, nausea, pain from the irradiated volume and changes in pain medication. PRO symptoms will be daily assessed from start of radiotherapy and five weeks ahead,

from week 6-9 PRO symptoms will be assessed weekly. The participants will be reminded through a text message to their mobile phone or an email with a direct link to the eCRF in REDCap.

Patients participating in Flash glucose monitoring will be informed of symptoms of hyperglycaemia including needing to pee frequently, tiredness, recurrent infections and bad wound healing. See appendix E. Patients will be thoroughly instructed to contact the PI if symptoms of hyperglycaemia should occur**.** As many of the symptoms of hyperglycaemia overlap with symptoms related to end stage cancer, commencement of glucose measurements will be based on an individual assessment. If hospitalization is deemed necessary, glucose measurements will be at the discretion of the treating physician. If the patient is hospitalized for any reason, glucose measurements and treatment of hyperglycaemia if present, will be at the discretion of the treating physician.

The PRO questionnaire will contain a field where other symptoms not related to esophagitis can be recorded. See appendix A. If complete, this will appear as a pop-up message with the PI. Symptoms will then be assessed for symptoms of hyperglycaemia.

4.3 Imaging

No extra scans will be performed in the trial. The diagnostic magnetic resonance scan (MR), the planning computed tomography (CT) and the cone-beam CT scans used for set-up of the patient for treatment will be transferred to a research computer and used for training of an artificial intelligence (AI) software algorithm that automatically can outline the target area, the esophagus and stomach and compute an optimized radiotherapy plan. The computer is located behind the hospital firewall and meets all requirements for handling person-sensitive data.

4.4 Supplemental treatment

Analgesic drugs, corticosteroids, antacids and other supportive medicine during and after treatment are prescribed at the discretion of the referring physician. The use of these medications is reported in the electronic case report form (e-CRF)

4.5 Systemic therapy

Antineoplastic systemic therapy can be paused before, during and after radiation at the discretion of the physician, depending on the interaction with radiotherapy. The use of antineoplastic systemic therapy is reported in the e-CRF.

5 Participants

ESO-SPARE - Esophagus-sparring radiotherapy: 200 patients will be included in the study.

GLUC-DIAB - Glucocorticoid-induced diabetes: 150 patients will be included in the study.

5.1 Inclusion criteria

ESO-SPARE

- Histology or cytology proven cancer
- Referred for palliative radiotherapy of the **cervical or thoracic vertebra** for
    - epidural ingrowth
    - metastatic spinal cord compression
    - metastatic spinal nerve root compression
    - post-operative radiotherapy after decompressive surgery for spinal cord or nerve root compression
- Ability to understand and the willingness to sign a written informed consent document
- Ability to complete follow-up questionnaires, assessed by local investigator
- Referred for the following dose prescriptions 5 Gy x 5, 3 Gy x 10, 10 Gy x 1, 8 Gy x 1.
- ≥ 18 years old.

GLUC-DIAB

- Histology or cytology proven cancer
- Referred for palliative radiotherapy of **all spinal** levels for

- epidural ingrowth
- metastatic spinal cord compression
- metastatic spinal nerve root compression
- post-operative radiotherapy after decompressive surgery for spinal cord or nerve root compression

- Ability to understand and the willingness to sign a written informed consent document
- Ability to complete follow-up questionnaires, assessed by local investigator
- Referred for the following dose prescriptions 5 Gy x 5, 3 Gy x 10, 10 Gy x 1, 8 Gy x 1.
- ≥ 18 years old.
- No history of diabetes and HbA_{1C} < 48 mmol/mol, see **Figure 4.**

5.2 Exclusion criteria

- Age < 18 years
- Referred for > 10 fractions
- Exclusion criteria, HbA_{1C} validation and glucose monitoring (GLUC-DIAB): history of diabetes, HbA_{1C}>48 mmol/mol.

5.3 Enrolment

ESO-SPARE is a regional multi-center study recruiting patients referred for palliative radiotherapy of radiotherapy of the vertebra at Rigshospitalet or Herlev Hospital. The treatment is given sub-acutely and patients are often referred, planned and receiving their first treatment fraction within the same day. This means that the participants time for considering inclusion in the trial is short.

Potential participants (subjects) will be informed about the trial when they meet for treatment planning in the department's radiotherapy section. A member of the project team will provide verbal and written information on the trial and the subject will be provided with full and adequate information about the objectives, the study outlines and possible risks and benefits of participating in the trial. The information will be given under private conditions, and the subject will be encouraged to discuss participation with a relative or friend. If no relative or friend is present, the

subject is encouraged to call them on telephone and the project team member will give information to the friend or relative as well. The subjects have the right to ask questions about the study and should be given time, to make the decision to participate in the study or not. Because of the subacute treatment course only short time (1 hour) can be given for consideration.

The subjects should be clearly informed that the data collected in the study will not identify any subject taking part in the study, following the Data Protection Act 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 physician responsible of the study will be provided. If the subject chooses not to participate in the study, he or she will continue the standard treatment.

Patients may choose to participate in ESO-SPARE (esophagus sparring radiotherapy) or GLUC-DIAB (HbA_{1C} validation and glucose monitoring) only.

Participants will not be informed of randomization outcome.

Patients randomized to esophagus sparring radiotherapy needing reirradiation **(other target that primarily prescribed)** during the 9 weeks of FU, will receive esophagus sparring radiotherapy for the second target.

Participants will not receive remuneration.

5.4 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 eCRF should be completed.

5.5 End of study

Participants are active in the study until 9 weeks after radiotherapy or death whichever comes first. The participants are passively followed with registration of further courses of radiotherapy and OS.

6 Radiotherapy planning

6.1 Simulation

A CT scan with the patient immobilized in the treatment position is required for delineation. A CT slice thickness of minimum 2 mm is recommended. A variety of immobilization devices may be used. The use of intravenous contrast enhancement is optional.
An MRI of the spine with or without contrast enhancement is usually conducted by the radiology department as a part of the diagnostic process prior to referral. The MRI images available are used as an aid in treatment planning. A MRI is optional, for patients with contraindications for MRI.
The FreeStyle Libre censor will be applied outside the radiation field after the planning CT is performed.

6.2 Dose prescription

See Table 3 for dose prescriptions included in this study. The treatment is prescribed prior to inclusion at the discretion of the referring physician.

Fractionation (Dosis x Fraction)	**Total Physical Dosis (Gy)**	**Maximum delivery time (days)**
5 Gy x 5	25	14
3 Gy x 10	30	21
10 Gy x 1	10	1
8 Gy x 1	8	1

Table 3. Fractionation schedules included in ESO-SPARE

6.3 Target and organs at risk

Delineation of the CTV is conducted in accordance to local guidelines. [12]

- CTV includes the tumor affected vertebral body and adjacent soft tumor tissue (If any). CTV will often include the spinal canal, pediculus and arcus posterior. Processus transversi and spinosus will not be included in the CTV unless there is tumor infiltration here. Cranial/caudal delineation is limited by the upper and lower edge of the affected vertebrae. If the target area involves more than one vertebra, these may be included in the same CTV if they are separated by no more than 2 healthy vertebrae. If they are separated by 3 or more healthy vertebrae, two separate CTVs must be defined.
- The planning target volume (PTV) is computed by adding a 5 mm margin around the CTV.
- Esophagus and stomach are delineated for all patients
- Any other OAR is only to be delineated if the organ is expected to receive a relevant radiation dose (at the discretion of the treating physician).
- Local guidelines for dose constrains in palliative treatment will be followed .[22]

6.4 Esophagus sparing radiotherapy vs. standard treatment

For the patients in the standard arm, a standard radiotherapy plan computed using VMAT technique aiming at covering the PTV with at least 90 % of the prescribed dose and not taking the dose to the esophagus and/or stomach into account.

For the patients in the interventional arm, a plan using VMAT technique is computed aiming at keeping the maximum dose to the esophagus and/or stomach as described in Table 4. Even if it means compromising the dose to the PTV and CTV.

Patients randomized to esophagus sparring radiotherapy needing reirradiation **(other target that primarily prescribed)** during the 9 weeks of FU, will receive esophagus sparring radiotherapy for the second target.

	Maximum Physical Esophageal Dose ($D_{0,027cm3}$) (Gy)		**Max. Esophageal Dose in EQD2 ($D_{0,027cm3}$) (Gy), α/β = 3 Gy**	
Fractionation **(Dosis (Gy) x Fraction)**	**Standard arm**	**Esophagus sparring arm**	**Standard arm**	**Esophagus sparring arm**
5 Gy x 5	25	8,5	40	8
3 Gy x 10	30	10	36	8
10 Gy x 1	10	5	26	8
8 Gy x 1	8	5	17,6	8

Table 4. Maximum esophageal dose. Standard arm vs. esophagus sparring arm.

7 HbA_{1C} and Flash glucose monitoring

HbA_{1C} will be measured at baseline, which is standard procedure in one of the participating centers. [23] In order to obtain ambulatory glucose profiles for retrospective glucose data analysis we will use a blinded professional sensor-based Flash glucose monitoring system (FreeStyle Libre Pro™; Abbott Diabetes Care, Witney, UK).[19,20] The sensor is worn on the upper arm for 14 days. The sensor is factory calibrated which means that, after activating the sensor at baseline, no further intervention during the 14-day wear is required. As the sensor is blinded, data are not visible to participants or investigators during sensor wear. The sensor automatically captures and stores glucose data every 15 min (96 glucose readings/day). After 14 days the sensor is dismantled, and glucose data are wirelessly transferred to the pro-reader. Summary glucose reports are generated using the system software. Patients in our study will be followed for 28 days after start of radiotherapy treatment requiring one sensor change. This will include time without glucocorticoid treatment.

The patients participating in this part of the study will not be subject to standard glucose measurements; instead they will be thoroughly instructed to contact the PI if symptoms of hyperglycaemia should occur.

Patients not participating in Flash glucose measurements will follow local guidelines for glucose measurements. Current standard glucose measurements (for patients with no prior history of diabetes) in the two participating centers are summarized in Table 5 and 6.

Baseline HbA_{1C}	**Frequency of glucose measurements**
≤39 mmol/mol	No measurements
40–47 mmol/mol	Twice weekly
≥48 mmol/mol	Diagnostic for diabetes, glucose measurements minimum 4 times daily at the discretion of local diabetes team

Table 5 Standard glucose measurements Herlev Hospital. Frequency of glucose measurements is based on baseline HbA_{1C}. Patients presenting with 2 glucose values above 11 mmol/L are referred to the local diabetes team for further treatment planning. It is advised that severe hyperglycemia (BS>15-20 mmol/L) is avoided[23].

Plasma glucose	Frequency of glucose measurements
>15 mmol/L	Once daily
>20 mmol/L	A physician is consulted for further planning
>25 mmol/L	Insulin treatment should be initiated

Table 6 Standard glucose measurements Rigshospitalet. Glucose is measured twice weekly in all patients[17].

8 Safety assessment

8.1 Adverse events (AE)

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject who has received radiation therapy for MCSS. 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 radiation therapy for MCSS. The AEs that will be reported are based upon organs at risks that most likely will be affected from radiation therapy for MCSS.

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

8.2 Serious adverse events

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. In ESO-SPARE SAEs are only registered within the nine weeks study period unless the SAE started within the 9 weeks study period but is not settled after the expiration

of the nine-weeks study period. 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 or with concomitant or sequential systemic treatment, e.g. chemotherapy, 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 or systemic treatments 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

8.3 Trial management committee (TMC)

A trial management committee (TMC) is set up with the participation of representatives from the different centers and specialist (radiation oncologist and medical physicist). The TMC will meet annually after study initiation. All events (See primary endpoint), will be reviewed by the TMC and if the rate of reirradiation at one year is excessive defined by the sample size calculation, then 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.

9 Ethical aspects

9.1 Ethical considerations

The focus of this study is palliation with reduction of side effects from necessary radiation therapy for MSCC. The study participants are fragile with low life expectancy. [2,5] In order to minimize the time, spend in hospital, we designed the study with electronical/telephone follow-up only.

All toxicology data will be collected as patient reported outcomes (PRO). All though we will not act directly the collected PRO, the patients will be encouraged to contact the department with any problems there might occur.

In order to compute a radiation plan with sparring of the esophagus for patients in the experimental arm, it might be necessary to compromise the dose delivered to the anterior part of the vertebra close to the esophagus. While we do not expect the treatment in the experimental arm to be less effective, it is one of the objectives of this study to examine this. Reirradiation rates in the two arms will be assessed continuously. The TMC can recommend cessation of the study or dose adjustments if the reirradiation rate in the experimental arm is to excessive.

There will be no extra radiation from extra scans in this study.

In order to determine the natural course of plasma-glucose during and after high-dose glucocorticoid treatment, we wish to perform a real-life study with as little intervention as possible. Therefore, we intend to use blinded glucose measurements only. For study participants 1-2 fewer glucose measurements pr. week compared to current standard is expected. Patients participating in

the study by Schultz et al received 300 mg Prednisolone daily for 10 days, which was local standard at the time.[15] The guidelines have since been modified and currently recommended Prednisolone doses as well as duration of treatment is significantly lower.[13] Because of this, we expect the incidence of glucocorticoid induced hyperglycemia and diabetes to be lower in our study population.

All though we expect that hyperglycemia, in relation to high dose glucocorticoid treatments, is transient for most patients, it is one of the study objectives to examine this. To ensure that cases of symptomatic hyperglycemia are detected, all patients will be thoroughly informed to contact the PI in case any symptoms of hyperglycemia occur. In addition, daily PRO-CTC questionnaires will contain a section where any symptoms not related to esophageal toxicity or pain can be reported. These will be screened regularly for symptoms of hyperglycemia. Treatment of hyperglycemia in in-hospital patients will be at the discretion of the treating physician.

By using FreeStyle Libre system, we are able obtain extensive information about the patients' glucose values without burdening the patients with additional hospital visits or finger prick glucose monitoring.

9.2 Toxicity

Toxicity reports from palliative radiation for MSCC are scarce, as most studies focus on evaluating effectiveness of treatment.[6–8,10] Considering this, treatment is generally well tolerated.

In a retrospective review of 1304 patients evaluating prognostic factors for different radiation schedules, Rades et al found no relevant acute or late toxicity.[8] In another study of 324 patients by Rades et al acute radiation-related toxicity did not exceed grade 1 according to Common Terminology Criteria for Adverse Events version 3.0. No late toxicity was reported. [6]

In a randomized trial investigating the clinical outcome and toxicity of two different hypofractionated RT regimens Maranzano et al found grade 3 esophagitis in 1,5% of the patients and grade 3 vomiting or nausea in 6% of the patients. Grade 1-2 oral or esophagus dysphagia occurred in 14%. Late toxicity was never recorded.[10]

In the SCORAD trial Hoskin et al randomized 686 patient with MSCC between two RT regimens (8 Gy x 1 vs 4 Gy x 5).[7] Grade 1-2 adverse events occurred in 51,9%-56,9% of the patients. Most frequently

reported toxicities were fatigue, skin radiation reaction, anorexia, pain, nausea and diarrhea. Grade 3-4 events occurred in approximately 20,5% of the patients, dominated by fatigue, pain and respiratory symptoms. In contrast to other studies ESO-SPARE patients will be irradiated using VMAT technique only. [6–8,10] This enables us to shape the dose gradient more smoothly around target avoiding large radiation fields. ESO-SPARE only includes patients irradiated above Th12, therefore we do not expect any cases of treatment related diarrhea.

9.2.1 Radiation Myelopathy (RM)

RM is a feared late toxicity secondary to overdosing the spinal cord. It is rarely seen in the modern era of 3-dimensional palliative fractionation schemes. [6–8,10]

In this study we will use the QUANTEC recommendations for spinal cord constraints keeping the total dose below the tolerance dose of 50 Gy for patients radiated for the first time. Which associated with a 0.2% rate of myelopathy. [24] See Table 4.

Previously irradiated patients may be included in this study. Time from first treatment course and previous dose will be considered. We will aim at keeping the cumulative doses ≤60 Gy in 2-Gy equivalent doses according to QUANTEC recommendations. [24]

9.2.2 Pain Flare

Temporary worsening of pain in the treated site is a well-known phenomenon in patients receiving palliative radiotherapy for symptomatic bone metastases. It does not serve as a predictor for pain response. [25]

9.3 Cutaneous complications

Cutaneous complications from Flash glucose monitoring sensors have been reported. Most common cutaneous complications were wear-related erythema, itching, and induration. In a recent review the overall event rate reported from 19 trials was one event per eight weeks of sensor wear-time of which 1.5% were considered severe also most users experienced less pain or discomfort with CGM/FGM than capillary blood glucose testing.[26]

9.4 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.

9.5 Insurance

Patients participating in the study are covered by national regulations.

10 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. 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 local radiotherapy research databases 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).

11 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/). 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 two PhD studies, and is supported by Varian Medical Systems (2.480.000 DKK) and by the Danish Cancer Society (grant number R269-A15989) with 500.000 DKK. 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.

12 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. The results of this study will be published weather outcome is negative, positive or inconclusive.

13 Perspectives

The ESO-SPARE study will investigate the feasibility and outcome of esophagus sparing radiotherapy as compared to standard treatment. The results will indicate whether radiotherapy of vertebral metastases causing metastatic spinal cord compression can be treated while reducing early toxicity and improving QoL. The study will provide novel and important data that can lead to improved treatment strategies and will inform clinicians in the future. The principle of ESO-SPARE will be easily transferred to other treatment sites as sparring of the bowel rectum and bladder in

palliative lumbar and pelvic radiotherapy.

The trial will also provide knowledge on toxicity of modern era palliative radiotherapy. Not much is

known about toxicity as data are difficult to collect in societies where patients travel for

radiotherapy and are not followed up at the radiotherapy centers. We are leading on the use of technical advanced radiotherapy in the palliative setting and with this study we will increase treatment quality even further. The trial will be performed in close collaboration between different radiotherapy centers. This will support future collaborations between the centers. This collaboration will facilitate improved professional competences and a larger patient cohort, compared to a single center study.

There are no prior studies describing the spontaneous course of glucose levels using continuous glucose monitoring in relation to high dose glucocorticoid treatment I MSCC patients. Hopefully, the result of this study will provide information that will bring us closer to making more uniform evidence-based guidelines regarding treatment of glucocorticoid-induced glycaemia and diabetes in this patient cohort.

Appendix A

NCI-PRO-CTCAE® CUSTOM SURVEY

Item subset derived from PRO-CTCAE® Item Library Version 1.0
English
Form Created on 17-September-2020
https://healthcaredelivery.cancer.gov/pro-ctcae/builder.html

As individuals go through treatment for their cancer they sometimes experience different symptoms and side effects. For each question, please select the one response that best describes your experiences over the past 24 hours…

1a. In the last 24 hours, what was the SEVERITY of your DIFFICULTY SWALLOWING at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

2a. In the last 24 hours, how OFTEN did you have NAUSEA?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
2b. In the last 24 hours, what was the SEVERITY of your NAUSEA at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

3a. In the last 24 hours, how OFTEN did you have HEARTBURN?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
3b. In the last 24 hours, what was the SEVERITY of your HEARTBURN at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

4a. In the last 24 hours, how OFTEN did you have PAIN corresponding to the treatment site?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
4b. In the last 24 hours, what was the SEVERITY of your PAIN at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
4c. In the last 24 hours, how much did PAIN INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

OTHER SYMPTOMS	
Do you have any other symptoms that you wish to report?	
O Yes	O No

Please list any other symptoms:	
1.	In the last 24 hours, what was the SEVERITY of this symptom at its WORST? O None O Mild O Moderate O Severe O Very Severe
2.	In the last 24 hours, what was the SEVERITY of this symptom at its WORST? O None O Mild O Moderate O Severe O Very Severe
3.	In the last 24 hours, what was the SEVERITY of this symptom at its WORST? O None O Mild O Moderate O Severe O Very Severe
4.	In the last 24 hours, what was the SEVERITY of this symptom at its WORST? O None O Mild O Moderate O Severe O Very Severe
5.	In the last 24 hours, what was the SEVERITY of this symptom at its WORST? O None O Mild O Moderate O Severe O Very Severe

Appendix B

Health Questionnaire

English version for the UK

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

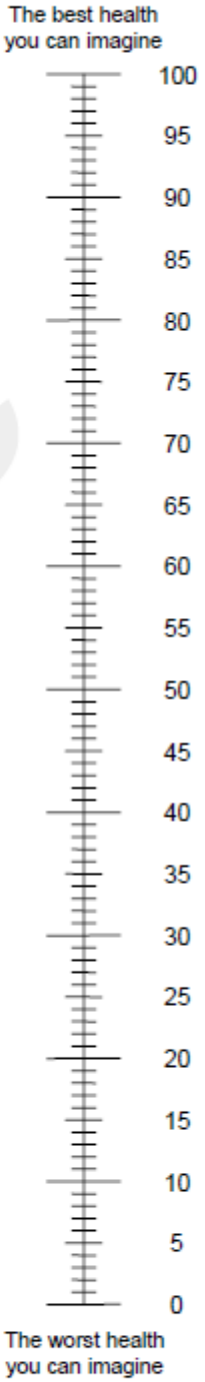
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Please mark an X on the scale to indicate how your health is TODAY.
- Now, write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



Appendix C

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ⌊_⌊_⌊_⌊_⌋

Your birthdate (Day, Month, Year): ⌊_⌊_⌋ ⌊_⌊_⌋ ⌊_⌊_⌊_⌊_⌋

Today's date (Day, Month, Year): 31 ⌊_⌊_⌋ ⌊_⌊_⌋ ⌊_⌊_⌊_⌊_⌋

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

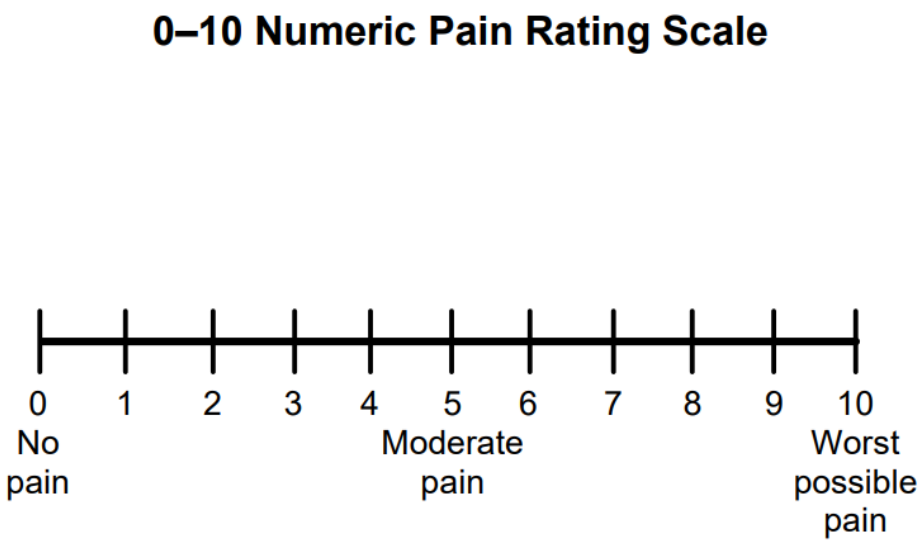
30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

Appendix D

Numeric pain rating scale.

On the scale below, please indicate the worst pain (treatment site) you have experienced in the last 24 hours.



Appendix E

Symptoms of hyperglycemia. Extract from patient information form.

As we will not measure you blood sugar during the trial, it is important that you are aware of the symptoms of high blood sugar. Because some symptoms of hyperglycemia resemble symptoms of other medical conditions including cancer, medical assessment may be needed.

If you experience one or more of the following symptoms, in a way that you feel concerned, you can contact PI MD Anna Mann Nielsen for further guidance.

Symptoms of high blood sugar:

- Feeling tired
- Frequent urination
- Thirst
- Frequent infections
- Slow wound healing

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