ESO-SPARE: Esophagus-sparing radiotherapy for cervical and thoracic spinal cord compression. A randomized phase 3 trial.

Statistical Analysis Plan

Trial registration number:

Danish Ethical committee: H-20069184

Clinicaltrials.gov: NCT05109819

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Study Description

Summary

This study is a randomized, single blind, phase III clinical trial investigating if esophagus-sparing radiotherapy can reduce dysphagia in patients with cervical and thoracic Metastatic Spinal Cord Compression (MSCC), without hampering the patient's ambulatory function.
Co-primary endpoints are severity of patient reported dysphagia within five weeks after treatment start measured by PRO-CTC-AE and ability to walk at nine weeks measured by the mobility dimension in EQ-5D-5L.

Condition or disease

MSCC in the cervical and thoracic spine from any cancer type, treated with palliative radiotherapy of 1-10 fractions.

Intervention

Esophagus-sparing radiotherapy.

Purposes

1. To investigate if esophagus-sparing radiotherapy can decrease patient reported dysphagia without compromising the patient's ambulatory function.

2. To investigate if there is a difference in pain response, weight, primary treatment site re-irradiation, quality of life and overall survival in patients treated with esophagus-sparring radiotherapy compared to patients receiving standard treatment.

3. To describe the dose-response relationship for the esophagus in the palliative dose spectrum.

4. To investigate if esophagus-sparring radiotherapy will increase other toxicities compared to standard radiotherapy.

Primary endpoints

Co-primary endpoints are

a. Peak patient reported dysphagia (PRO-CTC-AE version 1) within the first five week after treatment start.
b. Ability to walk, measured by the mobility dimension of the EQ-5D-5L questionnaire.

Secondary endpoints

- Quality of life, measured by EORTC-QLQ-C30 and EQ-5D-5L
- Nausea and dyspepsia measured by PRO-CTC-AE Version 1.0
- Treatment site pain response measured by International Consensus Pain Response Endpoints (ICPRE)
- Patient reported toxicity reported in PRO-CTC-AE-Version 1.0 “Other symptoms” section
- CTC-AE* Version 5: Cough, dyspnea, dyspepsia, dysphagia, hoarseness, oropharyngeal pain
- Changes in weight
- Consumption of corticosteroids, antacids and antiemetics
- Treatment site re-irradiation rate
- Hospitalization rate
- Overall survival

*Registered from patient no. 107

Trial design

The trial is designed as a phase III, randomized, single-blind clinical trial, clinicaltrials.gov ID No. NCT051098**.**

The trial is performed in a public health care system including two academic cancer centers treating MSCC. The individual centers are started at different times due to logistics. Patients are randomized 1:1 to either esophagus-sparring treatment or standard treatment. Patients are followed actively for 9 weeks after treatment start. Dysphagia, nausea and dyspepsia from the NCI PRO-CTC-AE Version 1.0 library and treatment site pain (Numeric Pain Rating Scale) are reported daily for 5 weeks and subsequently weekly for 4 weeks. Quality of life (EQ-5D-5L and QLQ-C30), use of medication (glucocorticoid, antiemetic, analgesic) and weight are reported weekly for 9 weeks, **Table 1.**

Data are reported by the patient in a paper-edition trial diary, by electronic questionnaires or by telephone consultations. Survival data, re-irradiation, and hospitalization data are derived from patient's treatment records. After the results of an interim analysis revealing low compliance (1)), weekly CTC registrations were implemented for all patients in the first 5 weeks after treatment start (from patient No. 107).

Table 1. Follow-up schedule in the ESO-SPARE trial

	Treatment start	**Daily 1-5 weeks**	**Weekly 1-5 weeks**	**Weekly 1-9 weeks**
PRO-CTC-AE: Dysphagia, nausea, dyspepsia	**X**	**X**		
CTC-AE 5.0*	**X**		**X**	
EORTC-QLQ-C30 and EQ-5D-5L	**X**			**X**
Medication: Analgesics, corticosteroids, antiemetics	**X**			
Weight	**X**			**X**

*Starting from patient No. 107

Estimated Enrollment: 200 patients.

Allocation: Patients are randomized 1:1 to either esophagus-sparring treatment or standard treatment. Patients are stratified by center and fractionation. Randomization is performed in REDCap using random allocation with a block size of four and six.

Masking: Single-blind. Patients are blinded to randomization outcome.

Study Start Date: May 2021

Estimated Primary Completion Date: April 2024

Study Completion Date: The last patient will be included on April 30, 2024, or after the inclusion of 200 patients, whichever comes first.

Timing of final analysis

Following study closure, nine weeks of follow-up after radiotherapy start will be allowed for all patients, at which point data will be collected for primary end-point analysis. Analysis of data in respect to secondary endpoints and exploratory studies might be analyzed at any point of time, at the discretion of the study group.

Data

Data are captured in REDCap. Data will be kept in databases 10 years after the last patient is included.

Sample size

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. We want to conduct a phase III trial with 1:1 randomization between standard VMAT and experimental esophageal VMAT. Prior data (2) indicate that the rate of early esophageal toxicity with standard VMAT is 0.6. 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 fractionation scheme and treating center.

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 2.

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.

The power of ESO-SPARE is enough to detect a difference in ambulatory function as seen in Table 2

	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 2: Distribution of ambulatory function. The conventional arm follows the SCORAD trial (Hoskin et al., 2019).

Recruitment, withdrawal, and follow-up

Enrollment, intervention, allocation, follow-up, and data analysis will be summarized in a CONSORT diagram in accordance with CONSORT 2010 guidelines (4)

Statistical principles

Confidence intervals and P values

Level of significance: $p < 0.05$ with no adjustment for multiplicity. Confidence intervals are reported at 95 % limits (bound by zero) and calculated by the binominal distribution for rates and as per Kaplan-Meier method for time-to-event analyses.

Analysis

We will report our data in accordance with the CONSORT 2010 guidelines including the CONSORT Patient-Reported Outcome (PRO) extension (4,5) .

Analyses will be performed per-protocol for all patients who have received any study treatment.

Primary analysis of NCI-PRO-CTC-AE toxicity will only include weeks where ≥ 3 days questionnaires are completed.

Primary analysis of EQ-5D-5L and EORTC-QLQ-C30 will only include completed questionnaires.

All CTC-AE and PRO-CTC-AE grades will be reported.

Missing data will be described in detail, se missing data section.

A. **Co-primary endpoints**

1. **Peak dysphagia (difficulty swallowing) measured by NCI-PRO-CTC-AE within 5 weeks after start of radiotherapy (daily measurements).**
   PRO-CTC-AE responses are scored from 0 to 4, with 0 representing “None” and 4 representing “Very severe”. For each patient the peak value within 5 weeks after start of radiotherapy (daily measurements) will be included in the analysis. Difference in scores between treatment arms will be compared using Wilcoxon rank-sum test.

2. **Ambulatory function measured by EQ-5D-5L mobility dimension at 9 weeks after start of radiotherapy.**

EQ-5D-5L measures individual generic health status using 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 levels depending on the severity of symptoms, with 1 representing “No problems” and 5 representing “Extreme problems”. Difference in scores between mobility dimension treatment arms will be compared using Wilcoxon rank-sum test.

B. **Severity of dysphagia, nausea and dyspepsia measured by NCI-PRO-CTC-AE [Time Frame: Week 1-9 after start of radiotherapy (repeated measurement)].**
CTC-AE responses are scored from 0 to 4, with 0 representing “None” and 4 representing “Very severe”.
For each of the first five weeks, where daily measurements are recorded, the peak value will be used for analysis. Changes in severity score over time (repeated measurement) will be analyzed using Generalized Linear Mixed Models.

C. Duration of dysphagia, nausea and dyspepsia measured by NCI-PRO-CTC-AE [Time Frame: within five weeks after start of RT (daily measurements) and at 6, 7, 8, and 9 weeks].
Duration of toxicity will be presented graphically in separate figures.
For the first five weeks mean duration (days) in each group will be compared using Wilcoxon rank-sum test.

D. **Severity of cough, oropharyngeal pain, dyspnea, dysphagia, hoarseness, and dyspepsia measured by CTC-AE (weekly measurements) [Time Frame: Week 1-5 after start of radiotherapy (repeated measurement)].**
CTC-AE responses are scored from 0 to 4, with 0 representing “None” and 4 representing “Very severe”.
Changes in severity score over time (repeated measurement) will be analyzed using Generalized Linear Mixed Models.

E. **Duration of cough, oropharyngeal pain, dyspnea, dysphagia, hoarseness, and dyspepsia measured by CTC-AE (weekly measurements) [Time Frame: Week 1-5 after start of radiotherapy (repeated measurement)].**
Duration of toxicity will be presented graphically in separate figures. Mean duration (weeks) in each group will be compared using Wilcoxon rank-sum test.

F. **Demographics:** Subject demographics, baseline characteristics and medical history will be summarized descriptively. Generally, range, mean and standard deviation, or median and inter quartile range, will be reported for continuous variables. Frequencies and proportions will be reported for categorical variables.

G. **Treatment site pain response [Time frame: weekly, 1-9 weeks after start of RT]:**
Only patients with baseline pain will be included in the analysis.
Pain response will be measured by the ICPRE score (6). Possible responses are “Complete response”, “Partial response”, “Pain Progression” and “Intermediate response”.
For each of the first five weeks, where daily measurements are recorded, the worst response will be used for analysis. Changes in ICPRE score over time (repeated measurement) will be analyzed using Generalized Linear Mixed Models.

H. **Duration of treatment site pain response [Time Frame: Weekly week 1-9 after start of radiotherapy].**
Duration of pain response measured by the ICPRE score will be presented graphically in separate figures. For each of the first five weeks, where daily measurements are recorded, the worst response will be used for analysis.
Mean response duration in each group will be compared using Wilcoxon rank-sum test.

I. **Quality of life [Timeframe: weekly, 1-9 weeks after start of RT]:** measured by EORTC-QLQ-C30 and EQ-5D-5L will be scored per instruction of the instrument and summarized for each arm The scores will be presented graphically in separate figures. Changes in scores over time (repeated measurement) will be analyzed Generalized Linear Mixed Models.

J. **EORTC QLQ-C30, other domains [Timeframe: weekly, 1-9 weeks after start of RT]:** Descriptive statistics of QLQ-C30 domains will be performed. Changes over time (repeated measurement) will be analyzed using Generalized Linear Mixed Models.

K. **Weight [Timeframe: weekly week 1-9]:** Changes in weight from baseline (repeated measurement) will be analyzed using Generalized Linear Mixed Models

L. **Hospitalization:** Hospitalization rate will be calculated as days hospitalized of days alive during the 9-weeks follow-up and compared between treatment arms.

M. **Re-irradiation rate (primary treatment site):** The results will be reported for each treatment group using time-to-event analysis (Kaplan-Meier), and differences in curves will be tested using the Log-rank test.

N. **Overall survival** [Time Frame: Analysis will be made up to 2 years after study completion] is defined as time from inclusion until death from any cause. Overall survival will be reported off the Kaplan-Meier curves. Differences in survival curves will be tested by Log-rank test. If reached, the median survival time will be reported with a 95% confidence interval.

O. **Analysis of correlation** between target coverage and pain response, re-irradiation (primary treatment site) and ability to walk.

Reporting of the radiation details

The following radiation details will be reported and compared between the two arms using Wilcoxon rank-sum test.

1. Delivery: VMAT, IMRT or opposing fields

2. Target doses and volumes:
    - PTV V80, V90: the volume of the PTV (%) that is covered by the 80% and 90% isodose.
    - CTV V80, V90: the volume of the CTV (%) that is covered by the 80% and 90% isodose
    - Esophagus D0.027cm^3, D1cm^3, D2cm^3 and D5cm^3 (Gy)
    - Posterior pharyngeal wall D0.027cm^3, D1cm^3, D2cm^3 and D5cm^3 (Gy)
    - The volume of esophagus and posterior pharyngeal wall (% and cm^3) receiving more dose than the prescribed constraint
    - Selected OAR will be presented (e.g., Spinal Cord D0.027cm^3, D0.5cm^3, lung V20 and V5)

Double included patients

The ESO-SPARE protocol allowed participants to be included twice at the discretion of the treating oncologist. Double included participants were excluded at the second entry for time-to-event analyses (survival) and the quality-of-life analyses. For radiation details analyses, all lesions will be included.

Missing data

- We will report the numbers and proportions of missing data in each trial arm including:
  - Number of participants who have died.
  - Number of surviving participants with missing data.
  - The proportion of participants with partly completed questionnaires and the proportion of item-level missing data at each timepoint.
- Reasons for missing data will be collected for all randomized patients and reported for each trial arm.

- The assumed missing data mechanism will be reported for all primary and secondary outcome measures. For each outcome missing data will be categorized as.

  a. Missing completely at random – when missingness is nothing to do with the participant.

  b. Missing at random – when missingness is related to the participant and can be predicted from other information about them.

  c. Missing not at random – when missingness is specifically related to the data that are missing.

- We will provide a detailed comparison of the characteristics of those with observed and missing data before and after the interim analysis (1).

- In case of non-complete reporting of measurements, the follow assumptions are made:

  If the NPRS score is not given, but the patient is described without any pain and take no analgetic medication, the NPRS score is set to zero. All other cases, the NPRS is recorded as “not available”.

- Where missing data is present, secondary sensitivity analysis using multiple imputation and model-based methods assuming that data are missing not at random may be performed.

Statistical software

All statistic calculations will be performed using SPSS (SPSS Inc, Illinois, USA) and R statistics (RCRAN).

Analysis summary

Outcome	Instrument/Method/Unit	Timeframe	Data type	Statistical analysis
Primary **Peak dysphagia**	NCI-PRO-CTC-AE	Within five weeks after start of radiotherapy	Ordinal	Wilcoxon rank-sum test
Primary **Ambulatory function**	EQ-5D-5L mobility dimension	At nine weeks after start of radiotherapy	Ordinal	Wilcoxon rank-sum test
Severity of dysphagia, nausea, and dyspepsia	NCI-PRO-CTC-AE	Weekly, week 1-9 after start of radiotherapy	Ordinal, repeated measurement	Generalized Linear Mixed Models
Duration of dysphagia, nausea, and dyspepsia	NCI-PRO-CTC-AE	Within five weeks after start of RT (daily measurements) and at 6, 7, 8, and 9 weeks	Continuous, mean [range]	Descriptive graphical presentation and Wilcoxon rank-sum test for group comparison
Severity of cough, dyspnea, dyspepsia, dysphagia, hoarseness, oropharyngeal pain	NCI-CTC-AE	Weekly, week 1-5 after start of radiotherapy	Ordinal, repeated measurement	Generalized Linear Mixed Models
Duration of cough, dyspnea, dyspepsia, dysphagia, hoarseness, oropharyngeal pain	NCI-CTC-AE	Weekly, week 1-5 after start of radiotherapy	Continuous, mean [range]	Descriptive graphical presentation and Wilcoxon rank-sum test for group comparison
Pain response, severity	ICPRE score	Weekly, week 1-9 after start of radiotherapy	Ordinal, repeated measurement	Generalized Linear Mixed Models

Quality of life	EQ-5D-5L	Weekly, week 1-9 after start of radiotherapy	Categorical (index), and Visual analog scale (continuous)	As per described in EQ-5D-5L guidelines (7) Combined index is calculated using Denmark as reference. Changes in EQ-index value and VAS-score over time (repeated measurement) will be analyzed with Generalized Linear Mixed Models.
Quality of Life	EORTC-QLQ-C30	Weekly, week 1-9 after start of radiotherapy	Categorical (raw QLQ-C30 scores) and Continuous (the raw QLQ-C30 scores can be transformed to scores ranging from 0 to 100	As per described in EORTC-QLQ-C30 guidelines (8). Descriptive statistics of QLQ-C30 domains and analysis of changes over time with Generalized Linear Mixed Models
Weight	Change in kg from baseline	Weekly, week 1-9 after start of radiotherapy	Continuous, repeated measurement	Linear Mixed Effects Models
Hospitalization rate	Days hospitalized of days alive (absolute numbers and %)	Week 1-9	Continuous, mean [range]	Wilcoxon rank-sum test
Re-irradiation rate, primary site	Number of patients receiving re-irradiation in each arm (absolute numbers and %)	3, 6- and 12-months after inclusion	Continuous, mean [range]	Wilcoxon rank-sum test
Dosimetry parameters. See Radiation details section.	Absolute and relative numbers (Gy and %)	After treatment completion	Continuous, median [Inter quartile range]	Wilcoxon rank sum test

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