



FOCUS ON
HEALTH

Radiography and Clinical Technology

Self-study CPD activity

Activity Reference Number:

A26(25) 2029

Topic

Lung cancer

Article(s)

Stereotactic body radiation therapy (SBRT) of centrally located medically inoperable early-stage non-small cell lung cancer (T1-T3N0M0) _A subgroup analysis of the expanded HILUS study

Speciality

Radiation

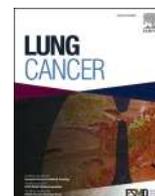
Oncology

Profession(s)

Radiographer

Radiologist

This activity is approved for **THREE (3) Clinical** Continuing Education Units (CEU's)



Research Paper

Stereotactic body radiation therapy (SBRT) of centrally located medically inoperable early-stage non-small cell lung cancer (T1-T3N0M0) – A subgroup analysis of the expanded HILUS study

Sara Lindberg^{a,b,*}, Vitali Grozman^{c,d}, Kristin Karlsson^{a,e}, Eva Onjukka^{a,e}, Elias Lindbäck^{a,e}, Joanna Östling Palme^b, Karam Al Jirf^b, Ingmar Lax^{a,b}, Peter Wersäll^{a,f}, Gitte Fredberg Persson^{g,h,i}, Mirjana Josipovic^{g,i}, Azza Ahmed Khalil^{j,k}, Ditte Sloth Møller^{j,k}, Lone Hoffmann^{j,k}, Marianne Marquard Knap^j, Jan Nyman^{l,m}, Ninni Druggeⁿ, Per Bergström^o, Jörgen Olofsson^o, Lotte Victoria Rogg^p, Tina Traa^p, Rebecca Knoph Hagen^p, Anne-Sofie Frøland^p, Christina Ramberg^q, Charlotte Kristiansen^r, Stefan Starup Jeppesen^{s,t}, Tine Bjørn Nielsen^u, Britta Löden^v, Hans-Olov Rosenbrand^v, Silke Engelholm^w, André Ånghede Haraldsson^w, Charlotte Billiet^x, Rolf Lewensohn^{a,b}, Karin Lindberg^{a,b}

^a Department of Oncology and Pathology, Karolinska Institutet, Stockholm, Sweden

^b Theme Cancer, Department of Head, Neck, Lung and Skin Tumors, Karolinska University Hospital, Stockholm, Sweden

^c Section of Thoracic Radiology, Department of Imaging and Physiology, Karolinska University Hospital, Stockholm, Sweden

^d Department of Molecular Medicine and Surgery, Karolinska Institutet, Stockholm, Sweden

^e Section of Radiotherapy Physics and Engineering, Department of Medical Radiation Physics and Nuclear Medicine, Karolinska University Hospital, Stockholm, Sweden

^f Section of Radiotherapy, Department of Cancer, Karolinska University Hospital, Stockholm, Sweden

^g Section of Radiotherapy, Department of Oncology, Rigshospitalet, Copenhagen, Denmark

^h Department of Oncology, Herlev-Gentofte Hospital, Herlev, Denmark

ⁱ Department of Clinical Medicine, Copenhagen University Hospital, Copenhagen, Denmark

^j Department of Clinical Medicine, Faculty of Health Sciences, Aarhus University Hospital, Denmark

^k Department of Oncology, Aarhus University Hospital, Aarhus, Denmark

^l Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden

^m Department of Oncology, Sahlgrenska University Hospital, Gothenburg, Sweden

ⁿ Department of Therapeutic Radiation Physics, Sahlgrenska University Hospital, Gothenburg, Sweden

^o Department of Oncology, Northern Sweden University Hospital, Umeå, Sweden

^p Department of Oncology, Oslo University Hospital, Oslo, Norway

^q Department of Medical Physics, Oslo University Hospital, Oslo, Norway

^r Department of Oncology, Vejle Hospital, University Hospital of Southern Denmark, Vejle, Denmark

^s Department of Oncology, Odense University Hospital, Odense C, Denmark

^t Institute of Clinical Research, University of Southern Denmark, Odense C, Denmark

^u Laboratory of Radiation Physics, Odense University Hospital, Odense C, Denmark

^v Oncology department, Central Hospital in Karlstad, Karlstad, Sweden

^w Department of Hematology, Oncology and Radiation Physics, Skåne University Hospital, Lund, Sweden

^x Department of Radiation Oncology, Iridium Network, Wilrijk, University of Antwerp, Belgium

ARTICLE INFO

SBRT of inoperable central early stage non-small cell lung cancer (ES NSCLC)

Keywords:

Stereotactic body radiotherapy

SBRT

Lung tumors

ABSTRACT

Introduction: Centrally located early-stage non-small cell lung cancer (ES NSCLC) with tumors close to the bronchi is potentially curable with stereotactic body radiation therapy (SBRT). To evaluate the clinical benefit of the treatment, both the risk of high-grade toxicity as well as the treatment efficacy need to be assessed.

Material and methods: From the expanded HILUS cohorts, 72 patients with T1-T3N0M0 NSCLC were included in the current analysis. All patients had been treated with SBRT in 8 fractions to 56 Gy for a tumor located within 2 cm from the tracheobronchial tree. Primary endpoint was progression free survival (PFS) and secondary

* Corresponding author at: Eugeniavägen 3, A4:01 NKS, 171 64 Solna, Stockholm, Sweden.

E-mail address: sara.lindberg@ki.se (S. Lindberg).

<https://doi.org/10.1016/j.lungcan.2025.108527>

Received 19 December 2024; Received in revised form 26 March 2025; Accepted 29 March 2025

Available online 31 March 2025

0169-5002/© 2025 The Author(s). Published by Elsevier B.V. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

endpoints included pattern of failure, local control (LC), lung cancer-specific survival (LCSS), overall survival (OS) and toxicity. The Kaplan-Meier method and Cox regression analysis were used.

Results: The median age of the cohort was 73 years and all patients suffered from comorbidities prior to SBRT. T2-T3 tumors were seen in 65 % of the patients. Seventeen patients relapsed after SBRT and distant recurrence was the most common form of relapse. Three-year PFS was 31 % (95 % CI 22–44) and largely explained by the short overall survival (38 % (95 % CI 22–44) at 3 years). Three-year rates of LC and LCSS were 97 % (95 % CI 92–100) and 76 % (95 % CI 65–89), respectively. Twelve patients (17 %) suffered from grade 5 toxicity, of which 9 were bronchopulmonary bleedings.

Conclusion: The severe toxic profile limits the clinical benefit using SBRT with the investigated approach for patients with centrally located ES NSCLC.

1. Introduction

Centrally and ultra-centrally located early-stage non-small cell lung cancer (ES NSCLC) are complex to treat, due to the tumor location near vital organs at risk (OAR), and additionally, comorbidities often need to be considered. In such cases, surgery may be technically challenging with a resultant risk of a non-radicality [1], and conventionally fractionated radiotherapy (CFRT), using large radiation fields, may not always allow to deliver ablative tumor doses in frail patients with poor pulmonary function [2]. While stereotactic body radiation therapy (SBRT) is an attractive alternative, it has been associated with high risk of treatment-related toxicity for central tumor lesions of all histologies [3–6]. Additional complexity follows from the greater risk of regional lymph node metastases and metastases to distant organs associated with centrally located ES NSCLC compared to peripherally located ES NSCLC [7–11]. We have previously reported on the outcome of a risk-adapted SBRT fractionation schedule using 7 Gy x 8 for centrally located tumors in the lung of different histologies [12]. In that analysis we showed that a high maximum dose to the mainstem bronchi or the intermedium bronchus was associated with high risk of fatal toxic events (predominantly bronchopulmonary bleedings), which was further augmented in the presence of tracheobronchial tumor compression.

In the current analysis, we specifically evaluate patients with ES NSCLC included in the HILUS cohorts. The overall aim was to examine whether the used regimen is suitable for this potentially curable patient group, given the few, and suboptimal, treatment options available. The primary endpoint was progression free survival (PFS), and secondary endpoints included pattern of failure, type of first failure, prognostic factors for recurrence, overall survival (OS), lung cancer-specific survival (LCSS) and toxicity. The study has received ethical approval (2011/676-31/3, 2019-06046).

2. Materials and methods

2.1. Study cohort

The current study is a sub analysis of patients with ES NSCLC included in the expanded HILUS study [12]. The expanded HILUS study is a pooled cohort of patients from the Nordic countries (Sweden, Denmark, Norway) constituting both patients from the prospective phase II HILUS trial (n = 65, treated per protocol) [6] and a retrospective expansion cohort (n = 165, treated outside HILUS-protocol). In the expanded HILUS study, all tumors (primary lung cancer or metastasis of any histology) were located within 2 cm from the tracheobronchial tree (i.e. the trachea, the mainstem bronchi, the intermedium bronchus and the lobar bronchi) and treated with SBRT in 8 fractions to 56 Gy, between 2010 and 2018.

From the expanded HILUS cohort, patients with ES NSCLC, T1-T3N0M0, were extracted and included in the current sub analysis. At the time of diagnosis, the patients were classified according to the AJCC 7th edition [13] which defines a T2 tumor as up to 7 cm in diameter. Hence, at the reclassification to the AJCC 8th edition [14] performed for the study, 10 of these tumors were instead considered T3 tumors, but since these patients had been treated as ES NSCLC, we still included

them in the analysis.

2.2. Clinical and dosimetric data

Clinical and dosimetric data collected for the expanded HILUS cohort [12] were used for the current analysis. Additional data which were relevant for the current sub analysis were collected retrospectively from each participating center. These comprised additional patient- (smoking status and comorbidities relevant to Charlson age-adjusted comorbidity index (ACCI) and tumor characteristics (diagnostics, TNM stage and local-, regional- or distant recurrences). Data on toxic events and survival were updated accordingly. Toxicity was graded according to the Common Toxicity Criteria for Adverse Events v.4.0 [15] and tumor response was evaluated according to the RECIST v.1.1 criteria [16].

The diagnosis of ES NSCLC (T1-T3N0M0) was confirmed by histology or cytology, and subclassified as squamous cell carcinoma (SCC) or adenocarcinoma (ADCA) when possible. Alternatively, the diagnosis of ESNSCLC was based on a positive uptake on an ¹⁸F-fluorodeoxyglucose-positron-emission tomography/computed tomography (¹⁸F-FDG-PET-CT) in combination with tumor growth in at least two CT scans. Diagnostic endobronchial ultrasound (EBUS) of central lymph nodes was analyzed when possible.

Dose-volume data for target volumes and OAR, collected for the expanded HILUS cohort [12], were used for the current analysis. The included variables were PTV volume, PTV minimum dose (PTV D_{min}), mean dose to the gross tumor volume (GTV D_{mean}) and maximum dose (dose to 0.001 cm³) to the mainstem bronchi and/or the intermedium bronchus. All doses were converted to equivalent doses in 2 Gy fractions (EQD₂), using $\alpha/\beta = 10$ Gy for tumor tissue and $\alpha/\beta = 3$ Gy for normal tissue [17,18].

2.3. SBRT

The methodology and technology of SBRT have been described in detail in our previous publication [12]. In summary, the stereotactic body frame, vacuum mould and the abdominal compression were common devices for immobilization. Abdominal compression was generally applied if the tumor motion exceeded 5–10 mm in any direction as assessed by 4-dimensional-CT (4D-CT). Included were two different approaches for PTV definition, depending on local protocols: a GTV/CTV-PTV protocol and an ITV-PTV protocol, respectively. In the GTV/CTV-PTV approach, the PTV margin consisted of a 5 mm expansion in the transversal direction and a 10 mm expansion in the longitudinal direction of the CTV/GTV. When the PTV margin was not sufficient, it was increased to account for the full amplitude of the tumor motion as measured in the 4D-CT scan (applying abdominal compression when used). In the ITV-PTV approach, the PTV margin consisted of a 4–5 mm expansion in all directions from the ITV. The ITV was delineated to correspond to the GTV position throughout the breathing cycle as it appeared on a pre-treatment 4D-CT scan. Increased margins were used for 2 patients (GTV/CTV-PTV approach) in the longitudinal direction (up to 12 mm).

A treatment-planning CT with 2–5 mm slice separation was either performed in a random respiratory phase or chosen from the 4D-CT

study. For daily image guidance a cone-beam CT image was acquired. The treatment, 56 Gy in 8 fractions, was prescribed to the isodose encompassing the periphery of the PTV, with a median maximum dose of 150 % (103 %-174 %) of the prescribed dose at the center of the target. The dose distribution was generally planned to be inhomogeneous.

The organs at risk were delineated on the treatment-planning CT according to local protocols at each center. The bronchial structures (the trachea, the mainstem bronchi and lobar bronchi) were retrospectively re-delineated for all patients according to the HILUS-protocol (supervised by a thoracic radiologist). The shortest distance between the treated tumor (GTV) and the outer contour of the wall of the tracheo-bronchial tree was measured consistently using sagittal, coronal and axial views. Tracheobronchial tumor compression was defined as a tumor-induced compression and narrowing of the internal lumen of the tracheobronchial structures in the treatment-planning CT. Dose constraints were applied according to the HILUS-protocol [6] (prospective cohort), but were tailored individually for some patients (retrospective expansion cohort). The treatment planning was generally performed using 6 MV photons and all centers used a type B dose calculation algorithm (AAA, CC).

In addition to the treatment of the centrally located tumors, other radiotherapy treatments (SBRT, CFRT) occurring before and after SBRT for the HILUS-related target were included in the dosimetric analyzes, in cases where the estimated maximum dose exceeded 2 Gy to the mainstem bronchi ($n = 1$ prior and $n = 3$ post SBRT). A detailed description of the dose summation procedure can be found in our previous publication [12].

2.4. Statistical methods

Progression-free survival (PFS) was calculated from the start date of SBRT to the date of first radiological recurrence or death. Similarly, time to relapse (TTR) was calculated from the start date of SBRT to the date of first radiological proven recurrence. Local failure was defined as a recurrence inside or at the edge of the PTV. Regional failure was defined as a relapse outside the PTV, in the ipsilateral lung or ipsilateral lymph node. A failure not defined as a local- or regional failure was considered a distant failure. Distant failures were further classified into disseminated- (more than 3 metastases) or oligometastatic (less or equal to 3 metastases) recurrence. Point of time, type of first recurrence (local, regional or distant) and whether the first recurrence after SBRT was treated with curative intent or not, were analyzed. Overall survival (OS) (death due to any cause) and lung cancer-specific survival (LCSS) (death due to lung cancer) were evaluated. Patients who did not experience the event of interest within the study period, or were lost to follow-up, were censored at their last known follow-up time.

The probabilities for the study endpoints (PFS, OS, LCSS, LC) were estimated using the Kaplan-Meier method. Risk factors for PFS and TTR were evaluated with univariable Cox regression (UVA) and for PFS with multivariable (MVA) Cox regression. Variables for MVA (histology, tumor stage, GTV D_{mean}) were selected based on clinical relevance in combination with results obtained from UVA. A maximum of three predictors were considered, given the limited number of events. Medical comorbidity was represented by ACCI [19] with subgrouping based on data distribution. The ACCI referred to the time of the SBRT treatment (age dependent), excluding previously curatively treated malignancy. All statistical analyses were two sided, with p values of 0.05 or less considered statistically significant. The statistical analyses were performed using R version 4.3.3 [20].

3. Results

3.1. Study cohort

An overview of the study cohort is presented in Table 1. In total, 72

Table 1
Study cohort characteristics.

	Number	Percentage/(range)
Patients	72	100
Sex: men/women	35/37	49/51
Age: median, years	73	(60–87)
Performance status: 0–1/ 2/ 3	59/5/8	82/7/11
ACCI: 2–4 / 5 / 6–9	27/17/28	37/24/39
FEV1 (baseline), median, l*	1.2	(0.5–3)
Staging with PET/CT: Yes	69	96
EBUS: Yes	35	49
Tumors: NSCLC, LC**	49/23	68/32
specify: ADCA/ SCC/ LC**	22/27/23	30/38/32
TNM ^{8th} : T1 a/b/c NOM0	2/7/16	3/10/22
T2 a/b NOM0	20/17	28/23
T3 NOM0	10	14
Tumor size, largest diameter, median, mm	36	(10–69)
Bronchial tumor compression: yes	6	8
Shortest distance tumor – mainstem/lobar bronchi: ≤ 0–5 / 6–10 / >10 mm	36/18/18	50/25/25
PTV volume, median, cc	65	(16–202)
GTV D_{mean} , median, Gy ₁₀ , EQD ₂	78	(56–85)
PTV D_{min} , median, Gy ₁₀ , EQD ₂	46	(12–55)

Abbreviations: FEV1: Forced expiratory volume in 1 s (L of expected).

* 50 % of cohort ($n = 36$), ACCI: Age-adjusted Charlson comorbidity index, PET/CT: Positron emission tomography/computed tomography, EBUS: Endobronchial ultrasound, NSCLC: Non-small cell lung cancer.

** LC: Lung cancer (radiologically diagnosed early stage NSCLC), ADCA: Adenocarcinoma, SCC: Squamous cell carcinoma, PTV: Planning target volume, GTV: Gross tumor volume. EQD₂: Equivalent dose in 2 Gy fractions using $\alpha/\beta = 10$ Gy (Gy₁₀).

patients were eligible for the analysis. The median age of the patient cohort was 73 years [21–28] and the majority of the patients had a PS of 0–1 (82 %). Baseline ¹⁸F-FDG-PET-CT was performed in 96 % ($n = 69$) and diagnostic EBUS in 49 % ($n = 35$) of the patients. The diagnosis of ES NSCLC ($n = 72$) was verified by histology or cytology in 72 % ($n = 49$) of the patients. Twenty-seven tumors were subclassified as SCC (55 % of those proven by biopsy). In the investigated cohort, the majority of the treated tumors were large, and T2- (37 tumors) and T3 tumors (10 tumors) represented 65 % ($n = 47$) of treated tumors. The largest tumor diameter was 0–2 cm in 9 tumors (12 %), 2–3 cm in 16 tumors (22 %), 3–4 cm in 20 tumors (28 %), 4–5 cm in 17 tumors (24 %) and 5–7 cm in 10 tumors (14 %). The median maximum tumor diameter and median PTV volume were 36 (10–69) mm and 64 (16–202) cm³, respectively.

Of all the treated tumors, 50 % ($n = 36$) were located within 0–5 mm, 25 % ($n = 18$) between 5–10 mm and 25 % ($n = 18$) more than 10 mm from the tracheobronchial tree. At the time of SBRT, all patients suffered from additional comorbidities (other than lung cancer), with a median ACCI of 5 [19]. Chronic obstructive pulmonary disease was recorded in 65 % of the patients. A complete pulmonary function test, before and after SBRT, was performed in 50 % ($n = 36$) of the patients.

3.2. First recurrences

After a median follow-up of 22 (2–121) months after SBRT, 17 patients (24 %) had relapsed, out of which 13 patients had undergone diagnostic EBUS. Among the patients who relapsed, first failure was distributed as follows: distant only ($n = 8$), distant + regional ($n = 3$), regional only ($n = 4$), regional + local ($n = 1$) and local only ($n = 1$) (Fig. 1). The median time to first recurrence (any) was 13 (2–47) months, to local failure 10 (7–13) months, to regional failure 17 (3–47) months and to distant failure 13 (2–47) months. Among the distant failures, 6 patients had oligometastatic recurrence and 5 had disseminated recurrence. Two of the patients were curatively treated for the first relapse after SBRT (1 patient with radiosurgery for a solitary brain metastasis and 1 patient with radio-chemotherapy for a locoregional

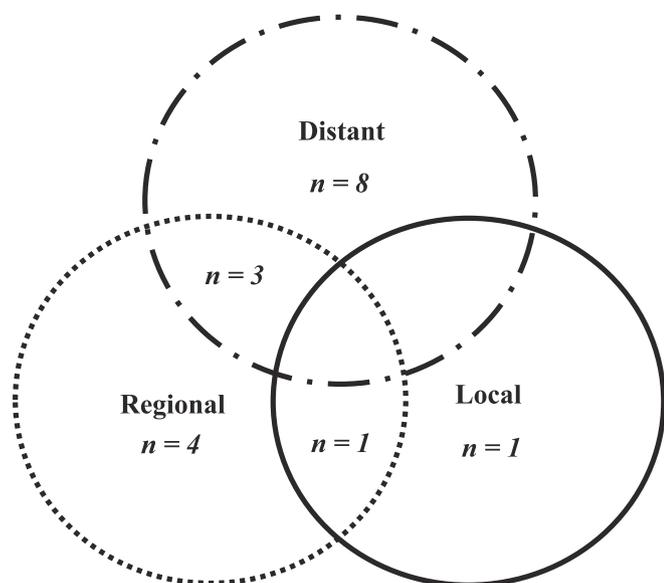


Fig. 1. First failure after SBRT.

failure). The patient treated with radio-chemotherapy for a locoregional recurrence after SBRT, had no sign of recurrence at last radiological follow up 2 years later. Details of first failures are summarized in [ES Table I](#).

3.3. Kaplan-Meier analysis

Kaplan-Meier analyses of PFS, LC, LCSS, OS are presented in [Fig. 2](#). PFS at 1-, 3- and 5-years were 76 % (95 % CI 67–87), 31 % (95 % CI 22–44) and 22 % (95 % CI 14–34). We noted excellent LC at 1-, 3- and 5-years (98 % (95 % CI 95–100), 97 % (95 % CI 92–100), and 97 % (95 % CI 92–100)) and promising LCSS (94 % (95 % CI 88–100), 76 % (95 % CI 65–89), and 66 % (95 % CI 52–83) at the same time points. However, the OS of the investigated cohort was generally poor (82 % (95 % CI 73–91), 38 % (95 % CI 28–51), and 24 % (95 % CI 16–37) at 1-, 3- and 5-years, respectively).

3.4. Predictors for PFS

In UVA, significant predictors of better PFS and TTR after SBRT were: radiologically diagnosed ES NSCLC; maximum dose ≥ 70 Gy in EQD₂ ($\alpha/\beta = 3$ Gy) to the mainstem bronchus and intermedius bronchus; and PTV-overlap of the bronchi. In MVA, the only significant predictor of PFS after SBRT was radiologically diagnosed ES NSCLC. Results of UVA and MVA are presented in [Table 2](#) and [Table 3](#), respectively.

a) Overall survival (OS)

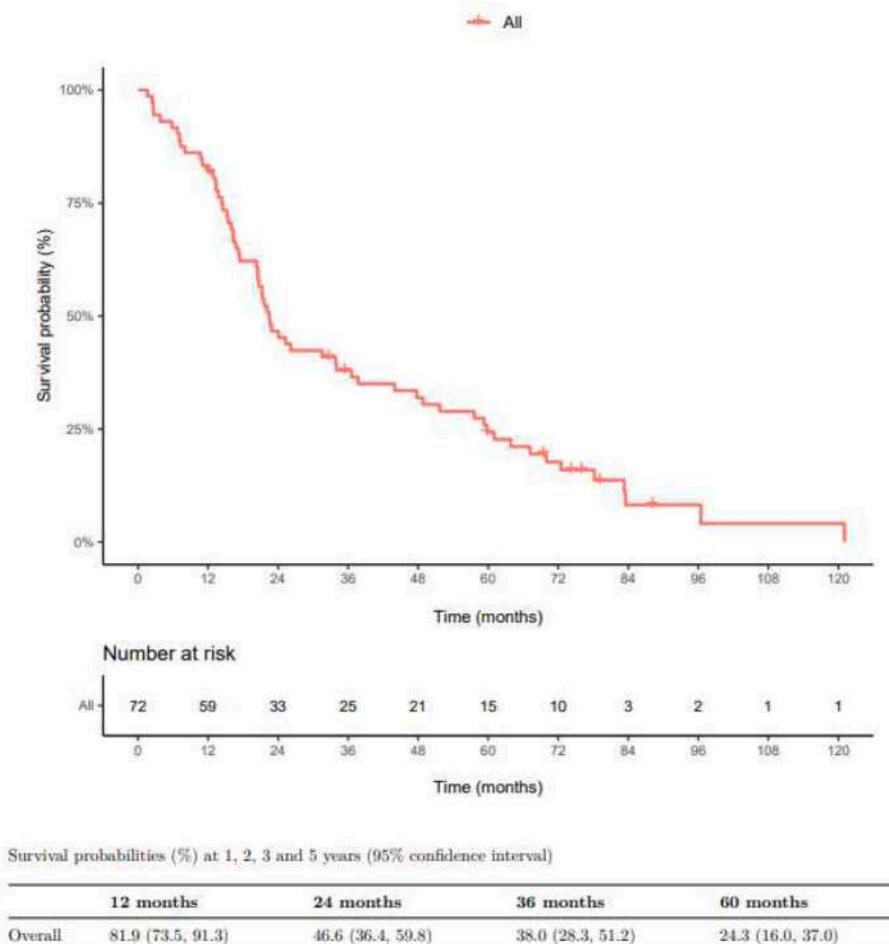


Fig. 2. Kaplan-Meier analysis of a) Overall survival (OS), b) Progression-free survival (PFS), c) Lung cancer-specific survival (LCSS), d) Local control (LC).

b) Progression-free survival (PFS)

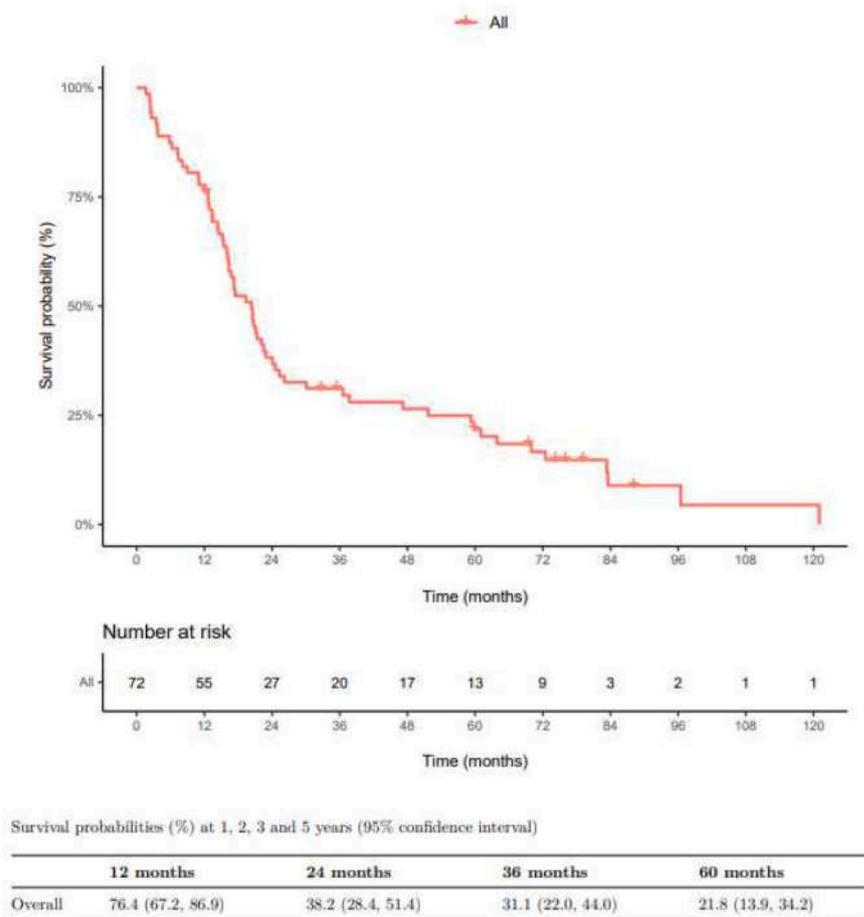


Fig. 2. (continued).

3.5. Toxicity

Twelve patients (17 %) suffered from grade 5 toxicity after SBRT. The most common grade 5 toxic event was bronchopulmonary bleeding (n = 9) which presented after a median of 13 (3–83) months post treatment. In the current analysis, one new event of grade 5 bronchopulmonary bleeding was identified (not being analyzed in our previously reported expanded HILUS-analysis), presenting 15 months after SBRT. One patient developed both a distant recurrence (isolated brain metastasis presenting 9 months after SBRT) and a grade 5 bronchopulmonary bleeding (presenting 21 months after SBRT). Two additional patients with grade 5 toxicity (n = 1 with respiratory failure, n = 1 with bronchopulmonary bleeding) died before first radiological examination after SBRT (2.6 months and 1.7 months, respectively). [ES Table II](#) summarizes all grade 5 toxic events, and [Table 4](#) the most severe recorded toxicity per patient.

3.6. Survival

Ten (14 %) patients were alive at last follow up. Death from lung cancer was reported for 24 % (n = 17) of the patients, and death from other causes than lung cancer in 62 % (n = 16 deaths from comorbidity, n = 12 deaths from grade 5 toxicity, n = 16 deaths not-specified, n = 1 death following hepatocellular carcinoma).

4. Discussion

In the current study, we report on 72 patients treated for a centrally located ES NSCLC (T1-T3N0M0) with an 8-fraction SBRT regimen. Despite excellent local tumor control and favorable cancer-specific survival, PFS was limited and largely explained by the short survival of the cohort and a high rate of serious toxic events.

We observed a 3-year PFS of 31 % which is lower than the 3-year PFS of 40–70 % reported after SBRT of inoperable central ES NSCLC [29–33] and 50–90 % after SBRT of medically inoperable peripheral ES NSCLC [29,34–38]. The limited PFS could at least partially be explained by the high incidence of fatal toxic events (n = 12) and severe comorbidities of the patients. However, the overall recurrence rate of 24 % as well as the most common failure pattern being distant recurrence, followed by regional-, and lastly, local failure, are in line with other reports evaluating SBRT of central and peripheral ES NSCLC [29,31,32,34–41]. The high rate of local tumor control (97 % at 3-year) is also consistent with other studies evaluating SBRT of central ES NSCLC [29,31,32,38,42], reflecting SBRT as a highly effective local treatment.

Centrally located ES NSCLC in general, and especially cases of large tumors, represent a subgroup of tumors with a higher incidence of malignant intrathoracic lymph nodes compared to small peripheral ES NSCLC [7–9,43,44]. Occurrence of occult nodal spread, already present at diagnosis, has been associated with risk of out-of-field recurrences after local primary curative treatment in central lung tumors [10,45].

c) Lung cancer-specific survival (LCSS)

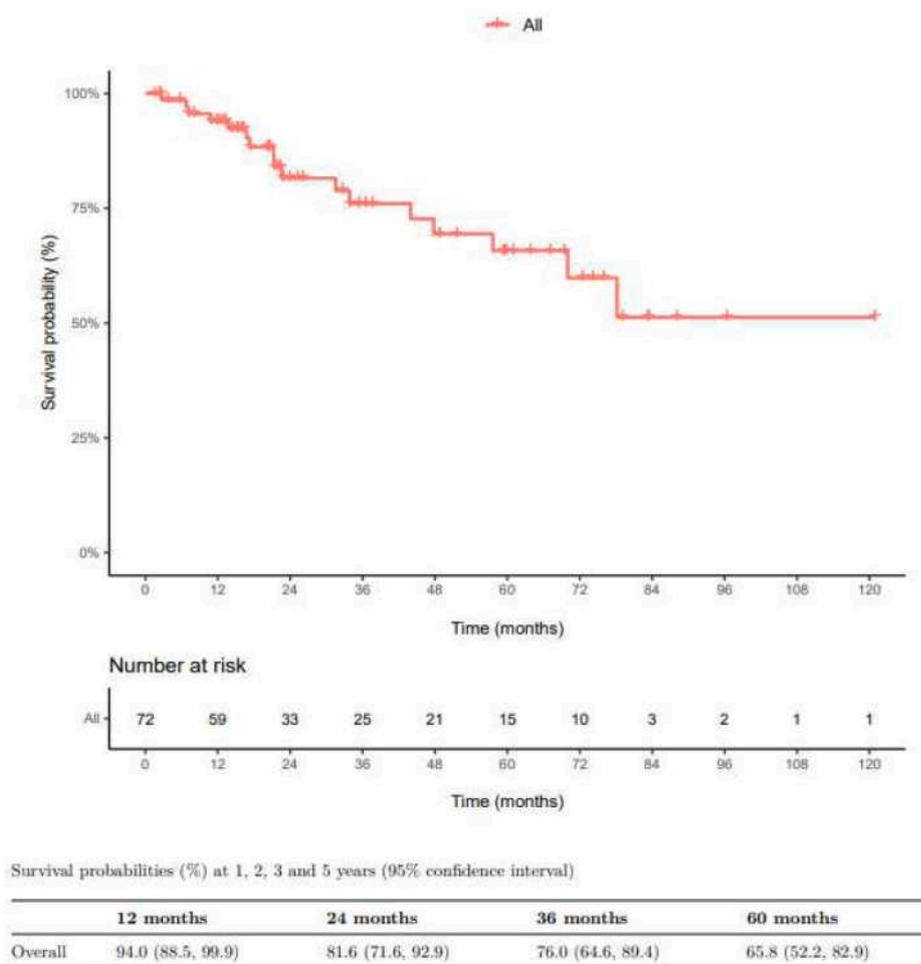


Fig. 2. (continued).

For this reason, endobronchial ultrasound (EBUS) with transbronchial needle aspiration (TBNA) of the mediastinal and intrathoracic nodes are recommended as part of the staging procedure in centrally located NSCLC [46], which was performed for 49 % of our cohort. However, the majority of patients referred to SBRT due to ES NSCLC are old, frail and suffer from medical comorbidities, meaning that invasive staging of the lymph nodes through EBUS-TBNA may thus not always be feasible [38,47,48]. There is also a procedure-related risk of complications such as bleedings, infections, bronchial perforation, pneumothorax and pneumomediastinum [49]. For many of the patients undergoing SBRT, nodal staging will thus be limited to radiology only, through ^{18}F -FDG-PET-CT, which provides information on metabolism and aids the diagnostic accuracy [50–54]. However, the risk of false positive findings must be considered when using PET-CT, and invasive diagnostics is often desirable in case of a positive lymph node uptake on a PET-CT [46,54]. False negative results are also a clinical problem which is illustrated by the finding that 18 % of T1-T2N0M0 NSCLC staged with ^{18}F -FDG-PET-CT were reported to have occult lymph node metastases, predominantly in nodes in N1 position [55]. Interestingly, despite the more detailed assessment of mediastinal and hilar lymph nodes in patients undergoing surgery for ES NSCLC, a similar rate of nodal failures was reported in a systematic review evaluating SBRT and surgery of ES NSCLC (10 % in mean) [45], which is in line the findings of the current analysis.

The pathological confirmation of NSCLC in our cohort was limited to 68 % of the treated tumors, due to the fragility of the patients and the

unfavorable tumor location. Patients without pathological confirmation had significantly better PFS and TTR, which may be a chance finding given the small cohort and relatively few events. As demonstrated by Van Tinteren et al., the risk of treating a benign lesion based on a positive PET-CT and tumor growth is less than 5 % [56].

In addition to central- and ultra-central tumor location [11], histological subtype SCC [57–59] and primary tumor size of more than 40–50 mm are known risk factors for recurrence [29,40,60–62]. However, we could not confirm any of these as predictors in our analysis. Unexpectedly, maximum dose to the mainstem bronchi and intermedium bronchus (≥ 70 Gy in EQD₂ using $\alpha/\beta = 3$ Gy) and PTV overlap of the mainstem bronchus were predictors of PFS and TTR in UVA. A possible explanation is that these variables act as surrogates for treating the tumors aggressively. However, the potential gain from an aggressive treatment needs to be balanced against the risk for increased high-grade toxicity when exposing the bronchi to high doses. The absorbed dose to the tumor and bronchi after SBRT will be better characterized in an ongoing sub analysis of the expanded HILUS study, evaluating the cumulative delivered dose to the target and bronchi, considering geometrical uncertainties.

The observed 3-year OS of 38 % reported in current analysis is lower than the 50–72 % reported after SBRT of inoperable central ES NSCLC [29–33,63] and the 60–78 % after SBRT of inoperable peripheral ES NSCLC [29,34–38]. As previously reported, the OS after SBRT in the current type of cohort is limited by relapses which are often not possible

d) Local control (LC)

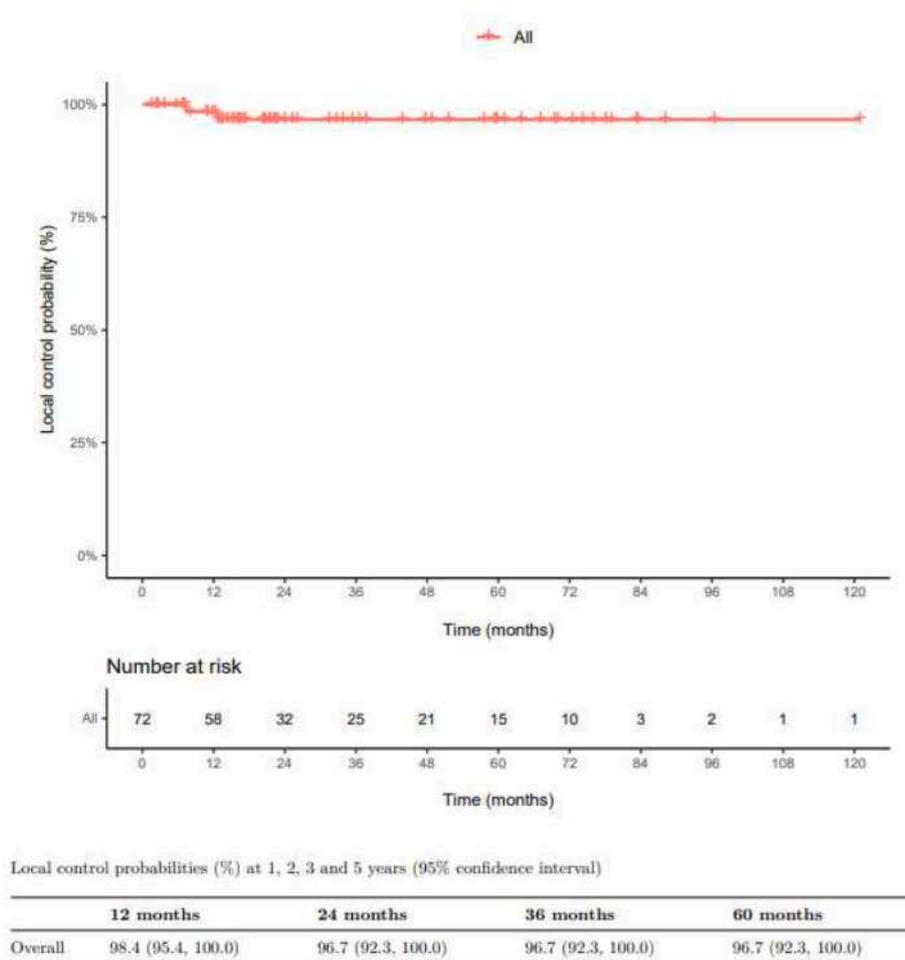


Fig. 2. (continued).

to treat curatively [29,38,39], by age and by comorbidities [64,65]. Comorbidities are represented by ACCI which has been reported as a predictor for OS after SBRT of ES NSCLC [66]. In the current analysis, the median ACCI was 5, in line with a study by DeWees et al evaluating SBRT of ES NSCLC [66]. Patients with an ACCI above 6 have been reported to have an increased risk of death post SBRT of ES NSCLC [65,66]. Given that 39 % of the patients in our cohort had an ACCI of 6 or more, it is likely that the comorbidities contributed to the short survival after SBRT in our cohort. However, the lung cancer-specific survival of 76 % at 3 years is more favorable, and comparable to the previously published 85 % at 3 years after SBRT of inoperable peripheral ES NSCLC [35,41].

Our current results highlight the clinical challenges when treating central- and ultra-central ES NSCLC. The expected benefit of high-risk SBRT needs to be weighed not only against the risk of tumor recurrence, but also against the limited expected overall survival due to pre-existing comorbidities. Clinical outcome data to guide the selection of dose constraints for the bronchi are scarce, but the ongoing STRICT and STAR Lung trials using MR-guided plan adaptation (ultra-central tumors) [67] and strict dose constraints to central structures will contribute to the understanding of bronchial tolerance. A novel and interesting approach for this patient group could also be the combination of novel systemic therapies with SBRT while using strict or conservative dose constraints to central structures. Immunotherapy, with a less toxic profile than traditional chemotherapy [21], has in

combination with SBRT of advanced stage NSCLC shown promising results [22] and is reported to be safe and effective for medically inoperable ES NSCLC [23]. The possible use of immunotherapy in conjunction with SBRT of medically inoperable ES NSCLC is being further explored in ongoing clinical trials [24–27].

The high incidence of grade 5 toxicities (17 %) reported in the current analysis, compared to results from the SUNSET and RTOG 0813-trial, may be explained by the consistently short distance between tumors and the tracheobronchial tree, resulting in high bronchial doses in our study [28,33]. Furthermore, we cannot determine whether a natural cause of uncontrolled tumor growth in absence of SBRT would have affected the incidence of the observed bronchopulmonary bleedings. The dose to adjacent OAR, as well as clinical risk factors, must be carefully considered before treating such patients with SBRT, in order to minimize the risk of treatment-related side effects.

4.1. Strengths and limitations

Clear strengths of the current material are the consistent dose prescription, the staging with PET/CT and the regular follow-up. However, the study has several limitations, including a small cohort with few events, retrospective study design with incomplete data on pathological tumor subtype and lack of lymph node staging. Similarly, the patients' multiple medical comorbidities may also have influenced the interpretation of adverse events, with a potential overestimation of the

Table 2
Univariable analysis of PFS and TTR.

Variable	n	PFS			TTR		
		HR	95 % CI	p-value	HR	95 % CI	p-value
Age (median, years)							
< 73	36	1.00			1.00		
≥ 73	36	1.00	0.39, 2.60	> 0.9	1.16	0.45, 3.03	0.8
Gender							
Female	37	1.00			1.00		
Male	35	0.54	0.20, 1.46	0.2	0.51	0.19, 1.37	0.2
ACCI							
2-4	27	1.00			1.00		
5	17	0.61	0.19, 1.98	0.4	0.60	0.21, 2.25	0.5
6-9	28	0.47	0.15, 1.54	0.2	0.54	0.17, 1.75	0.3
Performance status							
0-1	45	1.00			1.00		
2	27	0.65	0.21, 2.01	0.5	0.75	0.24, 2.34	0.6
COPD							
No	25	1.00			1.00		
Yes	47	2.68	0.77, 9.33	0.12	2.21	0.63, 7.72	0.2
Histology							
ADCA	22	1.00			1.00		
LC	23	0.26	0.07, 0.99	0.048	0.24	0.06, 0.90	0.034
SCC	27	0.45	0.15, 1.31	0.14	0.39	0.13, 1.14	0.085
TNM^{8th}							
T1-T2	62	1.00			1.00		
T3	10	1.33	0.38, 4.64	0.7	1.06	0.41, 5.00	0.6
Target size (median, mm)							
≤ 36	37	1.00			1.00		
> 36	35	0.86	0.33, 2.26	0.8	0.87	0.33, 2.27	0.8
Tumor distance from the mainstem or lobar bronchi (mm)							
≤ 5	35	1.00			1.00		
6-10	19	2.59	0.86, 7.75	0.09	2.43	0.81, 7.29	0.11
> 10	18	1.96	0.55, 7.00	0.3	2.24	0.62, 8.04	0.2
Endobronchial tumor growth (mainstem or lobar bronchi)							
No	66	1.00			1.00		
Yes	6	0.90	0.12, 6.85	> 0.9	1.25	0.16, 10.1	0.8
Maximum dose to the mainstem or intermedium bronchus (median, Gy₃, EQD₂)							
< 70	36	1.00			1.00		
≥ 70	36	0.31	0.10, 0.96	0.043	0.33	0.11, 1.00	0.05
Maximum dose to the mainstem or intermedium bronchus (median, Gy₃, EQD₂)							
< 92	42	1.00			1.00		
≥ 92	30	0.32	0.09, 1.13	0.077	0.34	0.10, 1.17	0.087

Table 2 (continued)

Variable	n	PFS			TTR		
		HR	95 % CI	p-value	HR	95 % CI	p-value
PTV-overlap of the mainstem, intermedium or lobar bronchi							
No	25	1.00			1.00		
Yes	46	0.32	0.11, 0.91	0.032	0.31	0.11, 0.88	0.028
PTV volume (median, cc)							
≤ 65	36	1.00			1.00		
> 65	36	1.26	0.48, 3.27	0.6	1.32	0.51, 3.44	0.6
GTV D_{mean} (median, Gy₁₀, EQD₂)							
≤ 78	39	1.00			1.00		
> 78	33	1.41	0.54, 3.68	0.5	1.45	0.56, 3.78	0.4
PTV D_{min} (median, Gy₁₀, EQD₂)							
≤ 46	38	1.00			1.00		
> 46	34	0.79	0.29, 2.15	0.6	0.80	0.29, 2.18	0.7

Abbreviations: PFS: Progression-free survival, TTR: Time-to-relapse. ACCI: Age-adjusted Charlson comorbidity index, COPD: Chronic obstructive pulmonary disease, ADCA: Adenocarcinoma, LC: Lung cancer (radiologically diagnosed early stage non-small cell lung cancer), SCC: Squamous cell carcinoma, EQD₂: Equivalent dose in 2 Gy fractions using $\alpha/\beta = 3$ Gy (Gy₃) or $\alpha/\beta = 10$ Gy (Gy₁₀), Maximum dose: Dose to 0.001 cc, PTV: Planning target volume, GTV: Gross tumor volume.

Table 3
Multivariable analysis of PFS.

Variable	n	HR	95 % CI	p-value
Histology				
ADCA	22	1.00		
LC	23	0.24	0.06, 0.95	0.041
SCC	27	0.44	0.15, 1.30	0.14
TNM 8th				
T1-T2	62	1.00		
T3	10	1.26	0.36, 4.45	0.7
GTV D_{mean} (median, Gy₁₀, EQD₂)				
≤ 78	39	1.00		
> 78	33	1.58	0.60, 4.17	0.4

Abbreviations: PFS: Progression-free survival. ADCA: Adenocarcinoma, LC: Lung cancer (radiologically diagnosed early-stage non-small cell lung cancer), SCC: Squamous cell carcinoma, GTV: Gross tumor volume EQD₂: Equivalent dose in 2 Gy fractions using $\alpha/\beta = 10$ Gy (Gy₁₀).

treatment-related toxicity.

5. Conclusions

The benefits of using SBRT with the investigated approach for central ES NSCLC are outweighed by the high rate of severe toxicity. In each individual case, risk factors for high-grade toxicity after SBRT, and the dose to central thoracic structures, need to be considered and compared to other treatment options.

Responsible for statistical analysis

Hanna Vikman and Anders Berglund (Epistat AB Uppsala, Sweden).

CRedit authorship contribution statement

Sara Lindberg: Writing – review & editing, Writing – original draft,

Table 4
Worst grade recorded treatment related toxicity (n = 72 patients)*.

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Side-effect	<i>n</i>	<i>n</i>	<i>n</i>	<i>n</i>	<i>n</i>
Atelectasis	6	6			
Bronchial occlusion/ stricture		4			
Cardiac failure			1	1	1
Chest pain	6	2	1		
COPD			2		1
Cough	2	9			
Dyspnea			1		
Esophagitis	1				
Fatigue		1	3		
Fever		2			
Hemoptysis	2	1			9**
Pneumonia		6	1	1	1**
Pneumonitis	5	3	1		
Pleural effusion	3	1			
Pulmonary fibrosis	5	3			
Respiratory failure				1	1
Skin rash		1			
Swallow pain	1	2			

Abbreviation: COPD: Chronic obstructive pulmonary disease.

* Per symptom according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

** One patient developed 2 grade 5 toxicities (bleeding and pneumonia), only the grade 5 bleeding was included in the analysis.

Conceptualization. **Vitali Grozman**: Writing – review & editing, Conceptualization. **Kristin Karlsson**: Writing – review & editing, Conceptualization. **Eva Onjukka**: Writing – review & editing, Conceptualization. **Elias Lindbäck**: Writing – review & editing, Conceptualization. **Joanna Östling Palme**: Writing – review & editing, Conceptualization. **Karam Al Jirf**: Writing – review & editing, Conceptualization. **Ingmar Lax**: Writing – review & editing, Conceptualization. **Peter Wersäll**: Writing – review & editing, Conceptualization. **Gitte Fredberg Persson**: Writing – review & editing, Conceptualization. **Mirjana Josipovic**: Writing – review & editing, Conceptualization. **Azza Ahmed Khalil**: Writing – review & editing, Conceptualization. **Ditte Sloth Møller**: Writing – review & editing, Conceptualization. **Lone Hoffmann**: Writing – review & editing, Conceptualization. **Marianne Marquard Knap**: Writing – review & editing, Conceptualization. **Jan Nyman**: Writing – review & editing, Conceptualization. **Ninni Drugge**: Writing – review & editing, Conceptualization. **Per Bergström**: Writing – review & editing, Conceptualization. **Jörgen Olofsson**: Writing – review & editing, Conceptualization. **Lotte Victoria Rogg**: Writing – review & editing, Conceptualization. **Tina Traa**: Writing – review & editing, Conceptualization. **Rebecca Knoph Hagen**: Writing – review & editing, Conceptualization. **Anne-Sofie Frøland**: Writing – review & editing, Conceptualization. **Christina Ramberg**: Writing – review & editing, Conceptualization. **Charlotte Kristiansen**: Writing – review & editing, Conceptualization. **Stefan Starup Jeppesen**: Writing – review & editing, Conceptualization. **Tine Bjørn Nielsen**: Writing – review & editing, Conceptualization. **Britta Löden**: Writing – review & editing, Conceptualization. **Hans-Olov Rosenbrand**: Writing – review & editing, Conceptualization. **Silke Engelholm**: Writing – review & editing, Conceptualization. **André Ånghede Haraldsson**: Writing – review & editing, Conceptualization. **Charlotte Billiet**: Writing – review & editing, Conceptualization. **Rolf Lewensohn**: Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Conceptualization. **Karin Lindberg**: Writing – review & editing, Writing – original draft, Visualization, Supervision, Investigation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement

This study was supported by grants from the Stockholm Cancer Society (#221212), Swedish Cancer Society (CAN2021/1469 and CF 23 2948 FK), the Stockholm County Council (#909121#), the ALF-funds (FoUI-987045) and the Nordic Trial alliance.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.lungcan.2025.108527>.

REFERENCES

Available on request

QUESTIONNAIRE

A26(25)

Stereotactic Body Radiation Therapy to the Foot for Bone Metastasis

INSTRUCTIONS

- Read through the article and answer the multiple-choice questions provided below.
- **Some questions may have more than one correct answer;** in which case you must mark **all** the correct answers.

Question 1: Stereotactic body radiation therapy (SBRT):

- A:** Delivers high radiation doses in a precise and highly conformed manner
- B:** Represents a new treatment paradigm in oncological care to oligometastatic lesions

Question 2: Is it **TRUE** that SBRT is generally safe and well-tolerated?

- A:** YES
- B:** NO

Question 3: Metastasis - directed therapy has been studied for specific cancer types and heterogeneous results were reported. In which cancer types did this approach improve progression-free survival?

- A:** Hepatocellular carcinoma (HCC)
- B:** Prostate cancer
- C:** Breast cancer
- D:** Lung cancer

Question 4: Which of the following is **NOT TRUE** about the technical considerations in delivering a high radiation dose to a distal extremity?

- A:** Distal extremities are known to have poor radiation tolerance
- B:** They are in close proximity of complex neurovascular elements
- C:** There is no potential risk of functional and cosmetic complications

Question 5: The following was **TRUE** about the patient in this study, except for:

- A:** He was an 83-year-old man with a history of hepatitis B cirrhosis.
- B:** He was diagnosed with HCC, which was not treated previously
- C:** The pathology report showed a 4-cm moderately differentiated HCC with clear margins
- D:** The disease was in remission until November 2019
- E:** The patient experienced right foot pain and an elevated alpha-fetoprotein (AFP) level (14ng/mL)

Radiation therapy technique

Question 6: The gross tumor volume was outlined with reference to the clinical finding, CT, and MRI images. The planning target volume was?

- A:** 47.4cm³
- B:** 120.4cm³
- C:** 77.8cm³

Follow-up

Question 7: A mildly painful skin ulcer (RTOG grade4⁸) with serous discharge developed after RT. The ulcer was treated with a course of antibiotics, regular debridement, and dressing and slowly dried up at weeks after RT.

- A:** 40 weeks
- B:** 80 weeks
- C:** 8 weeks
- D:** 2 weeks

Question 8: Which of the following is **NOT** a **TRUE** result of the physical examination?

- A:** Neurovascular compromise was shown
- B:** The range of motion was maintained
- C:** The patient remained ambulatory with minimal assistance from a walking stick
- D:** He could walk unaided 1 year after treatment
- E:** Limb preservation was attained

Discussion

Question 9: What of the following was concluded from the case report?

- A:** SBRT to the cuboid bone metastasis showed excellent local control
- B:** Oncologists need to be cautious about acute and chronic skin toxic effects

Question 10: Because the tumor was very close to the skin, the skin was contoured as a rind.

- A:** 2.5-mm rind
- B:** 3 to 5-mm rind

Question 11: Despite the adherence to the constraints of the UK SABR Consortium Guidance, and Task Group TG101 of the American Association of Physicists in Medicine (AAPM), which of the following were found?

- A: The patient still experienced significant skin toxicities
- B: A prolonged period of wound care was necessitated

Question 12: Is it **TRUE** that to deliver an effective and safe treatment, oncologists should balance the risk and benefit of giving a higher dose?

- A: YES
- B: NO

Question 13: Is it **TRUE** or **FALSE** that the occurrence of radiation dermatitis depends only on treatment-related factors?

- A: TRUE
- B: FALSE

Question 14: Which of the the following is a high-risk feature that should be taken into account In the future, when a more stringent dose constraint may be advisable in treating sites?

- A: Excellent blood supply
- B: A tendency for infection
- C: Venous sufficiency

Conclusion

Question 15: In this study the **positive** outcome was which of the following?

- A: A more stringent skin constraint may be warranted to treat high-risk sites
- B: SBRT to the foot resulted in excellent local control
- C: SBRT to the foot resulted in grade 4 chronic dermatitis

THE END



MEMBER INFO

(Complete sections marked with an asterisk *)

***FOH number**

***HPCSA number**

ID number

Personal detail changes

I hereby declare that the completion of this document is my own effort without any assistance.

SIGNED:

DATE:

This activity is accredited for **THREE (3) CLINICAL CEU'S**. You have to achieve **70%** to pass this activity.

ANSWER SHEET

A26(25)

Stereotactic body radiation therapy (SBRT) of centrally located medically inoperable early-stage non-small cell lung cancer (T1-T3N0M0) _A subgroup analysis of the expanded HILUS study

	*Time spent on activity						hour					min				
	A	B	C	D	E		A	B	C	D	E	A	B	C	D	E
1						9										
2						10										
3						11										
4						12										
5						13										
6						14										
7						15										
8																

How relevant was the content of this activity to your scope of practice?			
			
Not at all	Somewhat	Mostly	Extremely

RETURN ANSWER SHEET TO

Online members, complete your answer sheet online

CPD PORTAL: <http://foh-cpd.co.za/cpd-online/cpd-user> (Username: FOH number & Password: ID)
(Results are available immediately)

Email or hard copy members, complete your answer sheet online or return it to:

WHATSAPP: 074 230 3874 **EMAIL:** info@foh-cpd.co.za
(Results will be sent via email)

You will receive a confirmation of receipt SMS within 12-24hours, if not received please send again.

Have a suggestion or comment?

Send it to us on **EMAIL** or **WHATSAPP**