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Phase III randomised trial

SPACE – A randomized study of SBRT vs conventional fractionated radiotherapy in medically inoperable stage I NSCLC

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ABSTRACT

Background: Stereotactic body radiotherapy (SBRT) has been introduced for small lung tumors due to excellent local control and few side effects, even though there are no comparative studies. SPACE (Stereotactic Precision And Conventional radiotherapy Evaluation) is the first randomized phase II trial comparing SBRT and conventional fractionated radiotherapy (3DCRT).

Methods: Patients with stage I medically inoperable NSCLC were randomized to receive SBRT to 66 Gy in 3 fractions (one week) or 3DCRT to 70 Gy (7 weeks). Patients were followed to assess efficacy, toxicity and HRQL.

Findings: Between 2007 and 2011, 102 patients were randomized. Mean age 74 (57–86), 60% women, the vast majority (92%) had COPD or cardiovascular comorbidity. The SBRT arm included more patients with T2-tumors ($p = 0.02$) and male gender ($p = 0.35$). The median follow-up was 37 months with a 1-, 2- and 3-year PFS of: SBRT: 76%, 53%, 42% and 3DCRT: 87%, 54% 42%, HR = 0.85 (95% CI 0.52–1.36) with no difference between the groups and no difference in OS (HR = 0.75, 95% CI 0.43–1.30). At the end of the study 70% of SBRT patients had not progressed compared to 59% (3DCRT, $p = 0.26$). Toxicity was low with no grade 5 events. Pneumonitis of any grade was observed in 19% (SBRT) and 34% (3DCRT, $p = 0.26$), and esophagitis in 8% and 30% respectively ($p = 0.006$).

Findings: HRQL was evaluated with the EORTC QLQ 30 and LC14 module and patients treated with 3DCRT experienced worse dyspnea ($p = 0.01$), chest pain ($p = 0.02$) and cough (>10 points difference).

Interpretation: There was no difference in PFS and OS between SBRT and conventionally treated patients despite an imbalance of prognostic factors. We observed a tendency of an improved disease control rate in the SBRT group and they experienced better HRQL and less toxicity. SBRT is convenient for patients and should be considered standard treatment for patients with inoperable stage I NSCLC.

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Surgery is the standard treatment for stage I non-small cell lung cancer (NSCLC). However, a substantial proportion of patients are medically inoperable, mainly due to poor lung function or comorbidity, such as cardiovascular disease. Traditionally, these patients have received radiotherapy, conventionally fractionated to total doses around 60 Gy. Several retrospective reports have been published with diverging results. In a review of the literature, Qiao et al. [1] found a mean overall survival of 34% at three years and a low rate of local control.

A method for stereotactic body radiotherapy of extracranial targets (SBRT, synonymous with stereotactic ablative radiotherapy – SABR) was developed at the Karolinska University Hospital in the early nineties which included a body frame for set-up and fixation, soft-tissue imaging and hypofractionation with generally three fractions [2]. Since then, the interest in this treatment technique for small lung tumors has grown exponentially. There is an extensive amount of literature describing excellent results in terms of local control and low toxicity for SBRT in stage I NSCLC [3–19]. However, no randomized study has been performed; the data consist of retrospective series or rather small prospective studies. The Scandinavian SBRT study group aimed to compare SBRT in a randomized way with conventional fractionated radiotherapy delivered in a modern setting using relevant doses and embarked on the SPACE-study (Stereotactic Precision And Conventional radiotherapy Evaluation). The study was designed as a multicenter randomized phase II trial with progression-free survival as the primary endpoint.

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Methods

The inclusion criteria were patients in WHO performance status zero to two with stage I (T_{1-2}N0M0, AJCC 6th edition) non-small cell lung cancer who were medically inoperable or refused surgery. The tumors should be morphologically verified. If that was impossible due to peripheral lesion and poor lung function (intolerance for pneumothorax), there had to be an increasing tumor size in repeated CT-scans and a positive PET-scan. The main exclusion criteria were central tumor growth adjacent to trachea, main bronchus or esophagus, maximal tumor diameter >6 cm, patients with prior malignancy in the last five years and if previous radiotherapy had been delivered to the thorax. There were no restrictions with regard to lung function.

The diagnostic work-up consisted of a CT-scan of the chest and upper abdomen, a PET-scan (optional), dynamic spirometry and a CO-diffusion test, blood tests, WHO performance status and baseline assessment of quality of life (EORTC QLQ 30 and LC 14 formula). Patients who after oral and written information accepted participation were randomized 1:1 to the two treatment arms with no stratification. Neoadjuvant or adjuvant chemotherapy or targeted drugs were not used in this study.

Study arm A: Stereotactic radiotherapy

A stereotactic body frame with vacuum-pillow was used for set-up and fixation, respectively, with lasers being set to skin marks. If tumor movements were larger than 10 mm during fluoroscopy, abdominal pressure was applied to reduce movements. The tumor tissue visible on CT constituted the gross tumor volume (GTV) and clinical target volume (CTV) comprised the GTV including diffuse margins at the tumor border. Planning target volume (PTV) was defined as the CTV with a 5 mm margin in the transversal plane and 10 mm in the longitudinal direction. A dose plan was created normally with 5–7 static coplanar or non-coplanar fields with 6 MV photons. In addition to the CT used for dose planning, a second CT was performed before the first treatment to verify tumor reproducibility with predefined tolerance limits. CBCT (cone beam CT) and 4DCT was allowed but only available at a few sites. A heterogeneous dose distribution within the PTV was used. The prescribed dose was 22 Gy times three at the isocenter during one week (15 Gy at the periphery of PTV, corresponding to the 68% isodose).

Study arm B: Conventional fractionated radiotherapy

A vacuum-pillow was used for fixation and set-up, with lasers being set to skin marks. GTV and CTV were delineated in the same way as in arm A and the PTV was defined as the CTV with a 20 mm margin in all directions. Three to four coplanar fields with 6 MV photons were used with a homogeneous dose distribution. The prescribed dose was 70 Gy with 2.0 Gy per fraction, five days a week for seven weeks. The 95% isodose was required to cover 95% of the PTV. Portal imaging with bone and soft tissue matching was used for set-up verification with 5 mm deviation as the action level.

Dose constrains were set for the spinal cord with 21 Gy in arm A and 48 Gy in arm B, no other constraints were used but doses to organs at risk were registered.

Endpoints

The primary endpoint was progression free survival at three years. Secondary endpoints were overall survival, local control, acute toxicity, late toxicity and quality of life.

Follow-up

The same schedule was used for both study groups consisting of CT-scans at 7 weeks, 3, 6, 12, 18, 24 and 36 months. WHO-criteria were used for response assessment. Toxicity was scored at the same time-points using CTC version 3.0 by the investigators. A dynamic spirometry was repeated at 12 months and quality of life questionnaires EORTC QLQ 30 and LC 14 were sent out by mail at 7 weeks, 6, and 12 months after treatment.

Ethical approval was received from the regional ethics board in Gothenburg, Sweden. Additional approvals were obtained from the University of Trondheim and Arhus for Norway and Denmark. The trial was registered at www.clinicaltrial.gov with the number NTC01920789. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines as defined by the International Conference on Harmonization. Written informed consent was collected from all the patients before enrollment.

Statistics

The study was originally planned as a phase III trial with an estimated survival difference at three years of 50% (SBRT) vs. 30% (3DCRT). With 80% power, a two-sided alpha significant level of 95% and an inclusion rate of 40 patients per year, the study population would be 91 patients per arm. Taking into account a drop-out rate of 10%, the total number would add up to 200 patients. However, the 30% survival rate at three years for conventional radiotherapy was considered very uncertain due to lack of data on the survival of stage I patients after modern staging and up to date radiotherapy techniques. Therefore the study was scaled down to a phase II approach with 50 patients in each arm decreasing the power to 67% while changing the primary endpoint to PFS.

PFS was defined as the date of randomization to progression or death, and PFS and OS were analyzed with the Kaplan–Meier method. Possible differences between the SBRT and 3DCRT groups were analyzed with the log-rank test and potential impact of prognostic factors (i.e. gender, stage, performance status, histology) were analyzed independently.

HRQL was analyzed with EORTC QLQ30 and LC 14, where aggregated scale scores were calculated according to the EORTC guide-

Table 1
Patient demographics.

	A: SBRT $n = 49$	B: 3DCRT $n = 53$	p-Value
Age mean (range)	73 (57–86)	75 (62–85)	0.04
Gender			
Male	22 (45%)	19 (36%)	0.35
Female	27 (55%)	34 (64%)	
Cardiovascular disease	28 (57%)	28 (53%)	0.66
COPD	35 (71%)	34 (64%)	0.43
FEV1 mean	1.3L (0.5–3.2)	1.6L (0.6–2.9)	
% (of predicted)	53% (25–110%)	61% (22–130%)	0.48
CO diffusion capacity % (of predicted)	57% (22–96%)	52% (22–109%)	0.29
Histology			
Adenocarcinoma	16 (33%)	17 (32%)	
SCC	9 (18%)	15 (28%)	
NSCLC NOS	5 (10%)	2 (4%)	
Not performed	18 (37%)	19 (36%)	
Missing	1 (2%)		0.46
ECOG performance status			
0	11 (22.5%)	5 (9.5%)	0.19
1	27 (55%)	33 (62%)	
2	10 (20.5%)	14 (26.5%)	
Missing	1 (2%)	1 (2%)	
Tumor stage			
T1	26 (53%)	40 (75%)	0.02
T2	23 (47%)	13 (25%)	
Diagnostic PET-CT	30 (61%)	36 (68%)	0.48

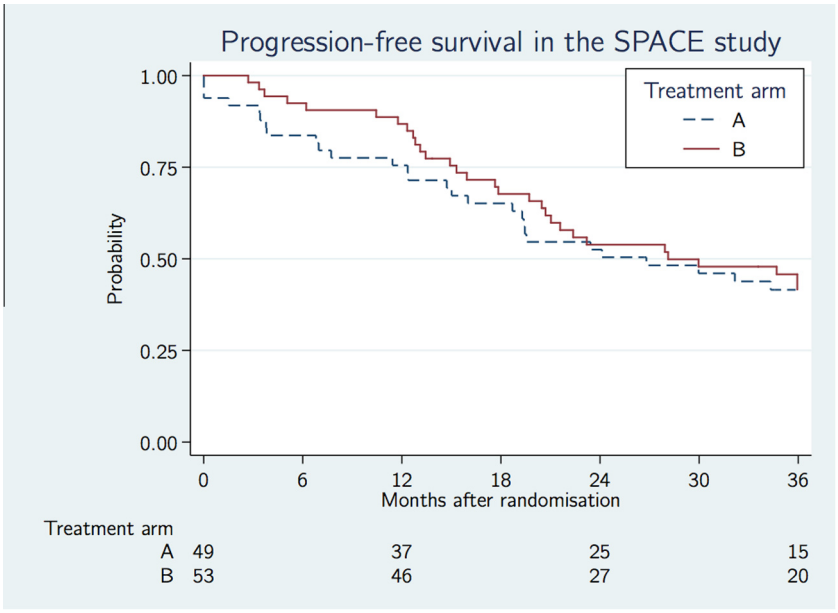

Fig. 1. Progression free survival by treatment arm (A = SBRT, B = 3DCRT), ITT analysis. HR = 0.85, 95% CI: 0.52–1.36.

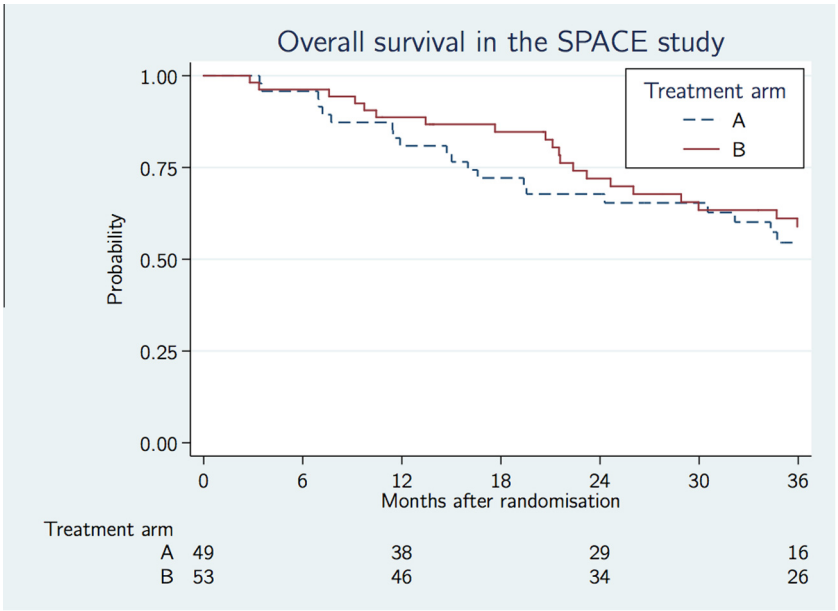

Fig. 2. Overall survival by treatment arm (A = SBRT, B = 3DCRT), ITT analysis. HR = 0.75, 95% CI: 0.43–1.30.

lines. For analysis of HRQL changes over time, repeated measures ANOVA was used with a p-value of < 0.05 being significant. A difference of more than 10 points was also considered clinically significant [20].

Role of the funding source

The funders of the study had no role in the study design, data collection or data analysis. The corresponding author had full access to all of the data in the study and had the final responsibility for the decision to submit for publication.

Results

Between January 2007 and July 2011, 102 patients were randomized in nine Scandinavian centers to receive either SBRT to 66 Gy in three fractions during one week ($n = 49$, arm A) or conventionally fractionated 3DCRT to 70 Gy in 35 fractions during seven weeks ($n = 53$, arm B). The mean age was 74 years (range 57–86) and the population was 60% women. Significant comorbidity, COPD and/or cardiovascular disease, was seen in 92% of the patients. With regard to lung function, the mean FEV1 was 1.4L (range 0.5–3.2) and mean diffusion capacity was 55% (range 22–109). Sixty-four percent had a histopathological diagnosis where the majority was adenocarcinomas. T1 tumors were seen in 65% and T2 in 35%. The two treatment arms differed somewhat in terms of tumor size and gender where the SBRT arm included more patients with T2 tumors (47% and 25% respectively, $p = 0.02$) and male gender (45% vs 36%, $p = 0.35$), both negative prognostic factors. In contrast arm A had more patients with a WHO performance status of zero (22.5% vs. 9.5%, $p = 0.19$). See Table 1 for details. Three patients did not receive the planned treatment; they were

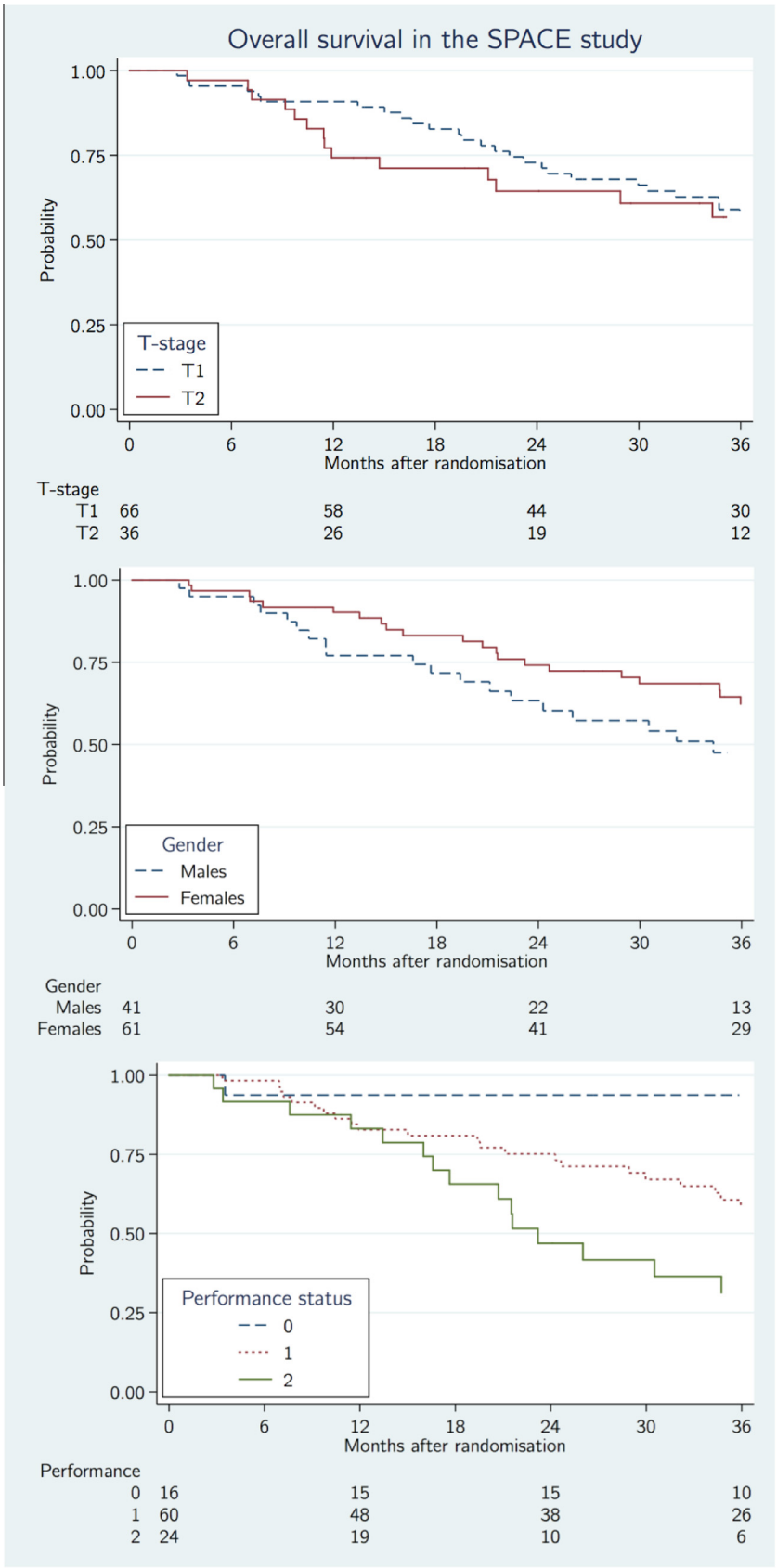

Fig. 3. Overall survival by tumor stage ($p = 0.32$), gender ($p = 0.13$) and performance status ($p = 0.0003$).

Table 2
Response at end of study. CR = complete remission, PR = partial remission, SD = stable disease, PD = progressive disease.

	A: SBRT $n = 49$	B: 3DCRT $n = 53$
CR	6 (12%)	7 (13%)
PR	12 (24%)	7 (13%)
SD	13 (27%)	15 (28%)
PD	13 (27%)	20 (38%)
Missing	5 (10%)	4 (8%)

all randomized to SBRT but received 3DCRT due to wrong inclusion with more advanced growth ($n = 2$) or withdrawal of consent ($n = 1$). Those patients are included in the intention-to-treat analysis.

The gross tumor volumes (GTV) were larger in arm A, 15.5 cm^3 (mean, range 1–67), compared to arm B, 8.9 cm^3 (mean, range 1–32, $p = 0.02$). Due to the treatment technique, the PTV's were larger in arm B, 180 cm^3 (mean, range 40–430) compared to arm A, 74 cm^3 (mean, range 22–210, $p < 0.001$). The means (range) of the maximal physical doses to organs at risk in arm A and B were as follows (not corrected for fractionation differences); for esophagus 13 Gy (0.5–36.5) versus 19 Gy (0.5–45.0), for spinal cord 12 Gy (1.1–23.4) versus 18 Gy (0.9–47.8) and the percentages of lung volumes receiving more than 20 Gy (V_{20}) were 6% (1.5–23.6) and 16% (6.7–33.5), respectively.

The median follow-up was 37 months and the 1-, 2- and 3-year progression free survival (PFS) was 76%, 53% and 42% in arm A and 87%, 54% and 42% in arm B, respectively. The hazard ratio was 0.85 (95% CI 0.52–1.36) with no statistical difference (Fig. 1).There was no difference between the groups when analyzed per protocol.

The overall survival (OS) at 1-, 2- and 3 years was 81%, 68% and 54% for arm A and 89%, 72% and 59%, for arm B, respectively, with a hazard ratio of 0.75, (95% CI 0.43–1.30) also no significant difference (Fig. 2), and no difference when analyzed per protocol. We did not observe any survival difference between patients with and without a histopathological diagnosis (data not shown), but there was a significant survival difference with regard to performance status ($p < 0.001$) and trends for gender and T-stage (Fig. 3).

Response was measured by CT-scan during the follow-up period. Response at the end of study at 36 months is shown in Table 2. Seventy percent of the patients in arm A did not have any progression at the end of the study, compared to 59% in arm B. The relapse pattern showed local progression in six patients in arm A and seven patients in arm B, rendering a local control of 86.4% in arm A and 85.7% in arm B. Regional recurrence was observed in 7% in arm A and 8% in arm B, and distant metastases were found in 24% and 23%, respectively. In total, seven patients had combined recurrences.

Eighteen patients died during follow up in arm A, five of them from lung cancer (10%). In arm B, 21 patients died, eight from lung cancer (15%). Other causes of death were cardiovascular disease ($n = 6$), COPD ($n = 4$), infections ($n = 3$), other malignancy ($n = 2$), dementia ($n = 2$) and miscellaneous ($n = 11$).

Toxicity was generally mild in both treatment arms. We did not see any grade five toxicities and only one grade four occasion which was thrombocytopenia in arm B, most likely not related to radiotherapy. However, there were numerically more toxicities reported in arm B in most variables except for rib fractures which were more common in arm A. Toxicity is presented in Table 3. Esophagitis was significantly worse in the conventional arm ($p = 0.006$) and pneumonitis and dyspnea borderline significant.

Quality of life: HRQL was evaluated with EORTC QLQ30 and LC 14 at baseline, and at seven weeks, six and 12 months follow-up. The compliance rates were 98% and 94% for questionnaire No. one in the SBRT and 3DCRT group respectively, which decreased to 92% and 77% at 12 months (questionnaire No. four). The repeated measures ANOVA, to compare the treatment arms over time, was performed on the patients that submitted all four formulas (70%). Patients treated with 3DCRT experienced worse dyspnea ($p = 0.01$), chest pain ($p = 0.02$) and cough ($p = 0.4$ but > 10 points difference) compared to the SBRT patients, a decrease that also lasted over time (Fig. 4). Other variables did not display clinically significant differences.

Discussion

SBRT has become the recommended standard of care for medically inoperable patients with stage I NSCLC, for example in the ESMO guidelines [21], even though there is no randomized evidence for superiority over conventional therapy. However, favorable results in terms of local control (74–100%), low rate of grade three to five toxicities, and a stable quality of life post-treatment, have been reported for peripheral tumors in an extensive body of literature [3–19].

SPACE is, to our knowledge, the first randomized study comparing SBRT and external beam radiotherapy (EBRT) in stage I NSCLC patients. We did not observe any significant difference between the treatments in terms of progression free survival, overall survival or local control. The ability to detect such a difference is of course hampered by the phase two design with a relatively low power. Toxicity was mild (mostly grade 1–2) in both treatment arms, but less toxicity was observed with SBRT in terms of esophagitis and trends for less pneumonitis and dyspnea. Differences in toxicity are probably explained by the smaller treatment volumes in SBRT. Quality of life was significantly better in the SBRT arm for dyspnea, cough and chest pain, and it is obviously more convenient with three treatment visits compared to 35, both for the patients and the health care providers. The results of the SBRT arm are consistent with previous studies from our group [4,11,16], but we were partly surprised by the comparatively good results for EBRT regarding local control and a three-year survival of nearly 60% with low toxicity. Most of the poorer EBRT results in the literature are 10–20 years old with inferior staging procedures and treatment techniques according to today's standard [1].

There are two other ongoing studies with similar concepts as the SPACE trial. In Australia, the CHISEL study has recruited 101

Table 3
Maximal toxicity CTC-AE v. 3.0, grade 1–3, by treatment arm.

Toxicity	A: SBRT $n = 48$, grade:			B: 3DCRT $n = 53$, grade:			p-Value for difference between arms
	1	2	3	1	2	3	
Esophagitis	4 (8%)	0	0	15 (28%)	1 (2%)	0	0.006
Pneumonitis	7 (15%)	2 (4%)	0	13 (24%)	4 (8%)	1 (2%)	0.085
Dyspnea	19 (40%)	8 (17%)	5 (10%)	22 (42%)	16 (30%)	5 (9%)	0.097
Fibrosis	20 (42%)	4 (8%)	0	24 (45%)	2 (4%)	1 (2%)	0.925
Cough	19 (40%)	5 (10%)	1 (2%)	31 (58%)	3 (6%)	0	0.22
Skin reactions	13 (27%)	2 (4%)	1 (2%)	17 (32%)	5 (10%)	0	0.40
Rib fractures	6 (13%)	2 (4%)	0	5 (9%)	1 (2%)	0	0.44

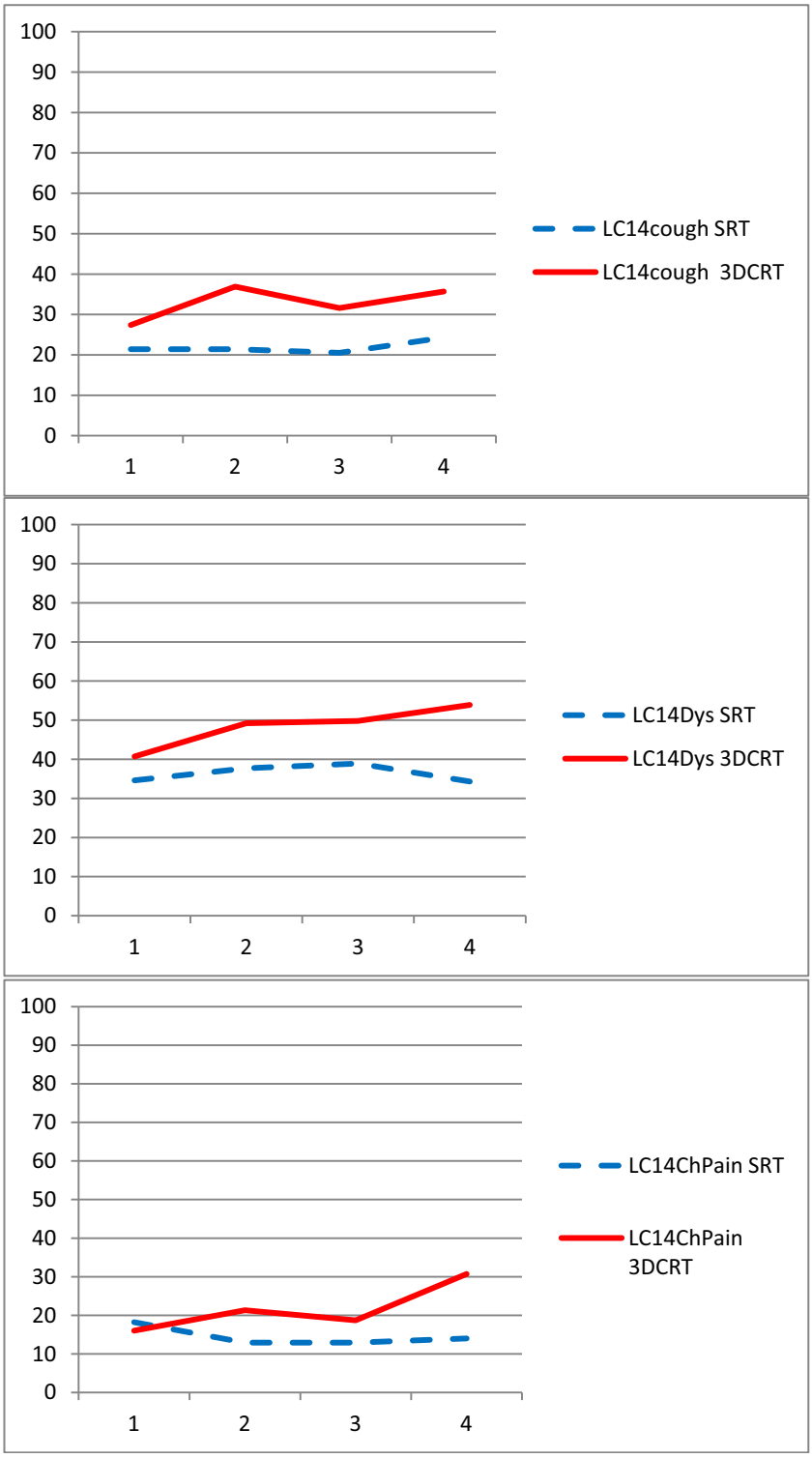

Fig. 4. Health Related Quality of Life by treatment arm. LC14cough = cough according to the EORTC lung cancer specific module LC 14, Dys = Dyspnea, ChPain = chest pain. 1 = at baseline, 2 = at seven weeks, 3 = at six months, 4 = at twelve months.

patients and is closed for inclusion (NCT01014130 at ClinicalTrials.gov). SBRT (18 Gy ×3 or 12 Gy ×4) is compared to EBRT to 66 Gy in 33 fractions or 50 Gy in 20. The first analysis is planned for 2017. The LUSTRE trial is ongoing in Canada (NCT01968941) and has included approximately 10% of its planned 324 patients. SBRT (12 Gy ×4 or 7.5 Gy ×8 for central tumors) will be compared to a hypofractionated EBRT, 60 Gy in 15 fractions. Both of these trials are also investigating quality of life.

There are at least four retrospective series and one meta-analysis comparing SBRT and EBRT that have been published [22–26]. They all have shortcomings e.g. EBRT cohorts being treated at earlier time periods and there are differences between

patients groups. Jeppesen et al. [22] compared 100 medically inoperable patients treated with two different fractionation schedules of SBRT in 2005–2012 with a cohort of 32 patients treated with EBRT to 80 Gy in 35–40 fractions in 1998–2011. They found a superior median overall survival for the SBRT group, 36.1 vs. 24.4, but no difference in local control. Widder et al. [23] investigated the results of 202 medically inoperable patients treated with SBRT with two different fractionation schedules in 2006–2009 and a group of 27 patients treated with 70 Gy in 35 fractions in 1994–1996. Overall survival and local control were significantly better for the SBRT group and quality of life was stable, whereas it decreased for the EBRT group. Shirvani et al. [24] compared the effect of five different treatment strategies for patients 67 years or older with stage I NSCLC from a national database in 2001–2007 including 124 patients treated with SBRT and 1613 with EBRT. In a matched pair analysis of 124 patients the overall survival was significantly better for the SBRT group compared to EBRT patients, but not for lung-cancer specific survival. Chiang et al. [25] matched 57 patients treated with SBRT 48–52 Gy in 4–5 fractions with an earlier cohort of 57 patients treated with EBRT 48–60 Gy in 12–15 fractions. Local control and OS were statistically improved for the SBRT group; however staging was different between the groups. Grutters et al. [26] performed a meta-analysis including 11 observational studies of SBRT in 2001–2008 (895 patients) and another 11 studies of EBRT (1326 patients). Two- and five-year OS and LCSS were significantly better for the SBRT studies.

A shortcoming in our study is that approximately one third of the patients (36%) did not have a histological verification of the tumor. This was mainly due to poor lung function and a risk for serious complications if a pneumothorax occurred when the tumor was biopsied. To include these patients, there had to be a growing tumor on repeated CT scans and a positive PET scan. We observed identical survival and local control for patients with and without histological confirmation implying similarity but because the majority died of other causes than lung cancer the interpretation must be cautious. PET-positive lesions without a histopathological confirmation have been studied by a Dutch group where they did not find any difference in results in 591 patients with or without histology. Using FDG PET scans, the probability of malignancy using a clinical diagnosis (absence of pathology) was 92.5% [27].

There were some imbalances according to known prognostic factors between the two treatment arms. There were 47% T2 tumors in the stereotactic arm compared to 25% in the EBRT arm. There was also a male predominance (45% vs 36%), both negative factors. In contrast, more patients with ECOG performance status 0 were included in the stereotactic arm, 23% vs 10%. The impacts of these factors on survival for the entire study population are shown in Fig. 3.

There has been a substantial technical development of SBRT since this study was planned which most likely influences the results. CBCT (cone beam computer tomography) for patient positioning in the treatment room was introduced during the study and for approximately the latter half of the patients this technique was used. 4DCT was only used at one center for a few patients at the end of the study.

There is no clear consensus on how to prescribe and report doses with SBRT, especially with a heterogeneous dose-distribution, which makes it difficult to compare different studies. We have used a hypofractionated schedule of 22 Gy $\times 3$ to the isocenter where the 68% isodose (i.e. 15 Gy) should encompass the PTV [4]. If the LQ model is used and α/β values of 10 for tumor and 3 for normal tissue effects are applied and converted to standard fractions of 2 Gy (EQD_2), this would be equivalent to a dose of 94 Gy ($\alpha/\beta = 10$) and 162 Gy ($\alpha/\beta = 3$) at the periphery of PTV and 176 Gy ($\alpha/\beta = 10$) and 330 Gy ($\alpha/\beta = 3$) at the isocenter (and 70 Gy for the EBRT arm). If BED calculations are applied and an α/β of 10, BED = 112.5 Gy for SBRT at the periphery and 84 Gy for EBRT. The high BED for the SBRT group may be "overkill" as proposed by van Baardwijk et al. [28].

With improved local therapy distant metastases may be a growing problem, which almost a quarter of the patients in this trial experienced (24%), most of them with local control. The figures are similar to surgically treated groups of patients [29], where adjuvant chemotherapy has become a standard for patients with stage IB or higher. Adjuvant chemotherapy was not used in this study and most patients were not fit for chemotherapy due to severe comorbidity. A theoretically attractive alternative could be adjuvant immunotherapy with a superior toxicity profile. In addition a so called abscopal effect has been demonstrated with tumor regression outside the irradiated area due to an induced immunogenic response [30,31]. Studies with this concept are in progress.

To summarize, this is the first randomized study on SBRT and EBRT for stage I NSCLC and it did not show any difference in terms of progression free survival, overall survival or local control between arms. However, quality of life was significantly better for the parameters dyspnea, cough and chest pain with SBRT, and less radiotherapy related CTC-scored toxicities were observed. A recent editorial highlighted unresolved issues with SBRT [19] and this trial adds information about survival, toxicity and HRQL in an elderly and comorbid population in a randomized and prospective manner. Reduced treatment costs have been demonstrated for SBRT compared with EBRT in a previous study [32], and together with the convenience of three fractions instead of thirty-five, SBRT is in our opinion justified as the standard treatment for peripheral stage I NSCLC.

Contributors

JN, RL and IL were involved in the study design. JN, AH, JÅL, OTB, PB, and SF ran the trial. BB was responsible for the quality of life analyses and EH for the statistics. All of the authors were responsible for data interpretation and analysis. JN and AH wrote the initial manuscript, with review and revisions made available to all of the authors.

Conflicts of interest

None of the authors have any relevant conflicts of interest to disclose.

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