Articles

Stereotactic ablative radiotherapy versus standard radiotherapy in stage 1 non-small-cell lung cancer (TROG 09.02 CHISEL): a phase 3, open-label, randomised controlled trial

David Ball, G Tao Mai, Shalini Vinod, Scott Babington, Jeremy Ruben, Tomas Kron, Brent Chesson, Alan Herschtal, Marijana Vanevski, Angela Rezo, Christine Elder, Marketa Skala, Andrew Wirth, Greg Wheeler, Adeline Lim, Mark Shaw, Penelope Schofield, Louis Irving, Benjamin Solomon, on behalf of the TROG 09.02 CHISEL investigators

Centre for Biostatistics and Clinical Trials (A Herschtal PhD, M Vanevski MSc),
Peter MacCallum Cancer Centre (Prof D Ball MD, Prof T Kron PhD, B Chesson BApplSc, A Wirth MD, G Wheeler MBBS, M Shaw MBChB, Prof P Schofield PhD, Prof B Solomon MBBS), **Melbourne, VIC, Australia; Sir Peter MacCallum Department of Oncology, University of Melbourne, Melbourne, VIC, Australia** (Prof D Ball, Prof T Kron, Prof B Solomon); **Princess Alexandra Hospital and University of Queensland, Brisbane, QLD, Australia** (G T Mai PhD); **Liverpool Hospital and University of New South Wales, Sydney, NSW, Australia** (Prof S Vinod MD); **Christchurch Hospital, Christchurch, New Zealand** (S Babington MBChB); **Alfred Hospital and Monash University, Melbourne, Victoria, Australia** (J Ruben MD); **Canberra Hospital, Canberra, ACT, Australia** (A Rezo MBBS); **Auckland City Hospital, Auckland, New Zealand** (C Elder MBChB); **Royal Hobart Hospital, Tasmania, Australia** (M Skala MBBS); **Austin Hospital, Melbourne, VIC, Australia** (A Lim MBBS); **Swinburne University, Melbourne, VIC, Australia** (Prof P Schofield); **and Royal Melbourne Hospital and University of Melbourne, Melbourne, Victoria, Australia** (L Irving MBBS)

Summary

Background Stereotactic ablative body radiotherapy (SABR) is widely used to treat inoperable stage 1 non-small-cell lung cancer (NSCLC), despite the absence of prospective evidence that this type of treatment improves local control or prolongs overall survival compared with standard radiotherapy. We aimed to compare the two treatment techniques.

Methods We did this multicentre, phase 3, randomised, controlled trial in 11 hospitals in Australia and three hospitals in New Zealand. Patients were eligible if they were aged 18 years or older, had biopsy-confirmed stage 1 (T1–T2aN0M0) NSCLC diagnosed on the basis of ^{18}F-fluorodeoxyglucose PET, and were medically inoperable or had refused surgery. Patients had to have an Eastern Cooperative Oncology Group performance status of 0 or 1, and the tumour had to be peripherally located. Patients were randomly assigned after stratification for T stage and operability in a 2:1 ratio to SABR (54 Gy in three 18 Gy fractions, or 48 Gy in four 12 Gy fractions if the tumour was <2 cm from the chest wall) or standard radiotherapy (66 Gy in 33 daily 2 Gy fractions or 50 Gy in 20 daily 2·5 Gy fractions, depending on institutional preference) using minimisation, so no sequence was pre-generated. Clinicians, patients, and data managers had no previous knowledge of the treatment group to which patients would be assigned; however, the treatment assignment was subsequently open label (because of the nature of the interventions). The primary endpoint was time to local treatment failure (assessed according to Response Evaluation Criteria in Solid Tumors version 1.0), with the hypothesis that SABR would result in superior local control compared with standard radiotherapy. All efficacy analyses were based on the intention-to-treat analysis. Safety analyses were done on a per-protocol basis, according to treatment that the patients actually received. The trial is registered with ClinicalTrials.gov (NCT01014130) and the Australia and New Zealand Clinical Trials Registry (ACTRN12610000479000). The trial is closed to new participants.

Findings Between Dec 31, 2009, and June 22, 2015, 101 eligible patients were enrolled and randomly assigned to receive SABR (n=66) or standard radiotherapy (n=35). Five (7·6%) patients in the SABR group and two (6·5%) in the standard radiotherapy group did not receive treatment, and a further four in each group withdrew before study end. As of data cutoff (July 31, 2017), median follow-up for local treatment failure was 2·1 years (IQR 1·2–3·6) for patients randomly assigned to standard radiotherapy and 2·6 years (IQR 1·6–3·6) for patients assigned to SABR. 20 (20%) of 101 patients had progressed locally: nine (14%) of 66 patients in the SABR group and 11 (31%) of 35 patients in the standard radiotherapy group, and freedom from local treatment failure was improved in the SABR group compared with the standard radiotherapy group (hazard ratio 0·32, 95% CI 0·13–0·77, p=0·0077). Median time to local treatment failure was not reached in either group. In patients treated with SABR, there was one grade 4 adverse event (dyspnoea) and seven grade 3 adverse events (two cough, one hypoxia, one lung infection, one weight loss, one dyspnoea, and one fatigue) related to treatment compared with two grade 3 events (chest pain) in the standard treatment group.

Interpretation In patients with inoperable peripherally located stage 1 NSCLC, compared with standard radiotherapy, SABR resulted in superior local control of the primary disease without an increase in major toxicity. The findings of this trial suggest that SABR should be the treatment of choice for this patient group.

Funding The Radiation and Optometry Section of the Australian Government Department of Health with the assistance of Cancer Australia, and the Cancer Society of New Zealand and the Cancer Research Trust New Zealand (formerly Genesis Oncology Trust).

Correspondence to:
Prof David Ball, Peter MacCallum
Cancer Centre, Melbourne,
VIC 8006, Australia
david.ball@petermac.org

Research in context

Evidence before this study

Using the search terms "review", "lung cancer", "hypofractionation", "radiosurgery", and "stereotactic radiotherapy" to search for English systematic reviews published from 2000 to 2008, we identified a previously published systematic review (upon which the design of our trial was based) of hypofractionated small-volume or stereotactic radiotherapy for early-stage non-small-cell lung cancer. The systematic review was based on a MEDLINE search from January, 2001, to April, 2007, using the search terms "hypofractionation", "stereotactic body radiotherapy (SBRT)", "external beam radiotherapy (EBRT)", "lung", "non-small cell lung cancer (NSCLC)", and "radiotherapy". In that systematic review (published in 2008), the authors found good local progression-free survival with stereotactic radiotherapy, with a pooled estimate of 89% at 2 years, which was consistent across studies. Actuarial 2 year pooled overall survival was lower, at 65%, which intuitively seemed superior to the 53% 2-year overall survival reported after conventional radiotherapy, but the two treatments had not been directly compared. In particular, the authors of the systematic review found no data from a phase 3 randomised trial. Therefore, whether or not local control was superior following stereotactic radiotherapy or was associated with either a survival benefit or excessive toxicity compared with more conventional standard radiotherapy techniques or schedules, was unknown.

Added value of this study

To our knowledge, this was the first randomised trial to compare stereotactic ablative body radiotherapy (SABR) with standard radiotherapy in patients who had pathologically proven non-small cell lung cancer at stage T1–T2aN0M0, as determined by ^{18}F-fluorodeoxyglucose (FDG)-PET scanning. This was also, to our knowledge, the first trial in which all radiotherapy plans took into account tumour motion, either with 4D CT (for patients randomly assigned to SABR) or FDG-PET scanning (for patients randomly assigned to standard radiotherapy).

Implications of all the available evidence

Our study indicated high local control of NSCLC and supports the findings of the SPACE randomised trial, which also compared SABR with conventional radiotherapy. Toxicity was mild in both studies. Although there were no differences in overall survival in the SPACE study, the convenience, safety, and efficacy, including an overall survival benefit with SABR seen in our study, and the available evidence indicates that SABR should be the treatment of choice for patients with inoperable peripherally located stage T1-T2aN0M0 NSCLC.

Introduction

The standard of care for stage 1 non-small-cell lung cancer (NSCLC) is surgical resection, but many patients have smoking-related cardiac or respiratory comorbidities that make them unfit for an operation. For these patients, radiotherapy represents a safer and potentially curative option. Historically, a course of curative radiotherapy is given as 20 or more fractions delivered over a period of 4–6 weeks. Fractionating the treatment improves the therapeutic ratio by enabling escalation of the dose to tumouricidal amounts while allowing interfraction recovery of the incidentally irradiated dose-limiting normal tissues. Advances in radiotherapy technology, including image guidance and tumour motion management, have led to more precise conformal dose delivery to the tumour and substantially less dose delivery to the surrounding healthy tissues. As a result, safe delivery of extremely high (ablative) doses to smaller tumours without the need for protracted fractionation is possible. This technique, typically given as a hypofractionated course of one to five treatments over 1–2 weeks, is termed stereotactic ablative body radiotherapy (SABR), and its use for treating medically inoperable stage 1 NSCLC has increased rapidly since 2001.[1]

Single-arm studies have consistently shown high local control with the use of SABR. For example, in one prospective trial[2] of SABR for inoperable early-stage NSCLC (RTOG 0236), the 3-year primary tumour control was 90%—far superior to the 30–40% control observed historically using fully fractionated techniques. Despite the high local control achieved, overall survival in RTOG 0236 was only 55·8% at 3 years, and no randomised trials have indicated that the high local control translates into improved overall survival compared with standard radiotherapy. The Scandinavian SPACE trial[3] randomly assigned patients with medically inoperable non-central stage 1 NSCLC to SABR or standard fractionated radiotherapy. No significant differences in overall survival between the treatment groups were recorded, but any potential benefits of the SABR approach might have been masked by the inclusion of patients either with poor performance status, no pathological diagnosis, or incomplete staging due to omission of ^{18}F-fluoro-deoxyglucose (FDG)-PET in a substantial proportion of patients. We therefore did a randomised trial of SABR versus standard fractionated radiotherapy in patients with biopsy-confirmed FDG-PET stage 1 NSCLC that was either inoperable or the patient refused surgery to prospectively assess the effect of radiotherapy technique on local control, overall survival, toxicity, and quality of life.

Methods

Study design and participants

In this multicentre, phase 3, randomised controlled trial (Trans Tasman Radiation Oncology Group [TROG] 09.02, Australasian Lung Cancer Trials Group [ALTG] 09.05, acronym CHISEL), patients were recruited under the auspices of the TROG and ALTG from 14 participating

hospitals, 11 in Australia and three in New Zealand (appendix pp 14). Eligible patients had cytologically or histologically proven stage T1N0M0 or T2aN0M0 NSCLC according to the seventh edition of the Union for International Cancer Control TNM staging manual.[4] Several primary cancer types were eligible, including squamous cell carcinoma, adenocarcinoma, large cell carcinoma, bronchioloalveolar cell carcinoma, large cell neuroendocrine carcinoma, and non-small-cell carcinoma not otherwise specified. All patients had their cancer stage established on the basis of a whole-body FDG-PET scan done within 6 weeks before randomisation. Patients were aged 18 years or older and had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. The tumour had to be non-central, defined as at least 1 cm from the mediastinum and 2 cm from the bifurcation of the lobar bronchi.[5] To be eligible, the patient's tumour had to be assessed as medically inoperable by a multidisciplinary team including thoracic surgeons and respiratory physicians, or the patient had to have refused surgery. Patients were ineligible if they had had previous chemotherapy or radiotherapy for the index cancer, or had multiple synchronous primary tumours requiring radiotherapy. Comorbidities were recorded using the Simplified Comorbidity Score.[6] To be eligible, patients needed to have a life expectancy of 2 years or more. Female patients of childbearing age and male patients had to agree to use adequate contraception throughout the treatment phase of the study.

All patients provided written informed consent and the study was approved by the ethics committees of all participating institutions. The trial was designed and overseen by a trial management committee consisting of lead investigators and biostatisticians of the TROG and ALTG. Quality assurance procedures were overseen by staff at the TROG Central Office in Newcastle, NSW, Australia. The conduct of the trial was monitored by an independent data and safety monitoring committee appointed by TROG.

Randomisation and masking

Patients were randomly assigned to SABR or standard radiotherapy in a 2:1 ratio in favour of the SABR group. The shorter SABR course was expected to be more attractive to patients because of convenience, so we hoped that the 2:1 randomisation ratio might improve recruitment. Allocation to treatment group was done by fax from the participating site to the Centre for Biostatistics and Clinical Trials at the Peter MacCallum Cancer Centre (Melbourne, VIC, Australia). Eligibility was checked by the central study coordinator (MV) and patients were stratified at randomisation by T stage (T1 vs T2a) and according to whether they were medically operable (but refused surgery) or inoperable. Treatment was allocated by a computer application that used the minimisation method. Minimisation was dynamic and included a random

element, so there was no pre-generated sequence. Clinicians, patients, and data managers had no previous knowledge of the treatment group to which patients would be assigned; however, after treatment allocation the study was open labelled due to the nature of the interventions. Cancellation of any randomisation was not permitted.

Procedures

Before participation in the trial, all sites were independently provided with credentials to deliver SABR. This required a site visit with a lung phantom that reproduced the anatomy of a moving lung tumour to measure the delivered dose to ensure it matched the prescribed dose.[7]

Treatment was planned to commence ideally within 4 weeks but no later than 6 weeks after randomisation. Treatment in the SABR group consisted of three fractions of 18 Gy each (total 54 Gy), or if the tumour was less than 2 cm from the chest wall, four fractions of 12 Gy each (total 48 Gy). Treatment was prescribed such that 100% of the planning target volume received at least 95% of the prescription dose. The internal target volume was delineated on the basis of a four-dimensional CT planning scan to take account of tumour motion. The internal target volume was expanded 5 mm in the axial plane and 10 mm in the cranio-caudal plane to create the planning target volume. All contours and plans were independently reviewed and approved before any treatment could be delivered. Treatments were administered at a rate of two fractions per week using either arcs or a minimum of eight fixed beams. Image guidance with cone beam CT or implanted fiducial markers was used to confirm the position of the tumour immediately before each treatment.

Treatment in the standard radiotherapy group consisted of 66 Gy in 33 daily 2 Gy fractions over 6·5 weeks or 50 Gy in 20 daily 2·5 Gy fractions over 4 weeks according to institutional preference. The schedule, once chosen, remained consistent within each institution. The dose was prescribed according to International Commission on Radiation Units and Measurements Report Number 50 guidelines.[8] The technique that was used was three-dimensional conformal with a minimum of three beams. Motion had to be accounted for using either four-dimensional CT or planning FDG-PET CT in the treatment position. The planning target volume was created using an isotropic 10 mm expansion on the internal target volume (consisting of the gross tumour volume and its position throughout the ventilatory cycle plus a 5 mm expansion for subclinical extension of disease). Dose constraints for organs at risk can be found in the trial protocol (appendix pp 23). Trial data were collected at each trial site. Data cleaning and analysis were done by staff (AH and MV) at the Centre for Biostatistics and Clinical Trials, Peter MacCallum Cancer Centre.

Patients were followed up for a minimum of 2 years after accrual of the last patient. All patients had a physical examination and a CT scan of the thorax 1 month after

completion of treatment, and then every 3 months for 24 months, and then every 6 months thereafter. Because the dense fibrosis induced by SABR can mimic tumour progression, the primary endpoint of local treatment failure had to be confirmed by either biopsy, FDG-PET scan, or in cases where these types of confirmation were not possible, by independent masked expert radiology review. The primary endpoint was not centrally reviewed. Adverse events were recorded using the Common Terminology Criteria for Adverse Events version 4.0 (CTCAE 4.0) and were recorded every week during treatment, at 1 month after completion of treatment, at 1-month intervals for 24 months, and then every 6 months thereafter. Quality of life was measured according to the European Organisation for Research and Treatment for Cancer (EORTC) core quality-of-life instrument (EORTC QLQ-C30) and the lung cancer quality-of-life module (EORTC QLQ-LC13)[9] before treatment then at 1 month and 3 months after treatment, then at 3-month intervals for 2 years, and then at 6-month intervals until 5 years after treatment. The EORTC QLQ-C30 quality-of-life instrument contains five functional subscales, nine symptom subscales, and an overall global scale. A high score on a functional scale represents high functioning (ie, better quality of life), but on the symptom scales, a high score indicates a high number of symptoms (ie, worse quality of life).

Outcomes

The primary endpoint, local treatment failure, was defined using the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0, in which local treatment failure is specified as at least a 20% increase in the longest diameter relative to the previous smallest longest diameter recorded since (and including) the baseline longest diameter equal to an absolute increase of at least 5 mm, or the presence of any new disease (ie, a new separate lesion) within 1·5 cm of the internal target volume. The secondary endpoints were overall survival, lung cancer-specific survival, treatment-related toxicity, and quality of life. All survival events were measured from time of randomisation. Freedom from local treatment failure was measured from the time of randomisation until documented local treatment failure. Patient withdrawal, death, regional treatment failure, distant metastasis, and loss to follow-up were all censoring events for local treatment failure. Overall survival was measured from the time of randomisation until death from any cause. Lung cancer-specific survival was measured from the time of randomisation until death due to lung cancer. Patient withdrawal, loss to follow-up, and death from a cause other than lung cancer were censoring events for lung cancer-specific survival.

Statistical analysis

The hypothesis to be tested was that SABR for peripherally located inoperable T1 and T2a NSCLC treated using a dose of 54 Gy in three fractions or 48 Gy in four fractions would result in superior control of disease at the primary site compared with standard care consisting of standard radiotherapy using a dose according to local institutional practice (66 Gy in 33 fractions or 50 Gy in 20 fractions). Assuming constant hazard within each group, a two-sided type 1 error of 5%, a 4 year accrual period consisting of accrual of 36 patients over the first 2·5 years and 64 patients over the remaining 1·5 years, a 2-year follow-up period after accrual of the last patient, a competing event rate of 20%, a 2:1 allocation ratio (SABR vs standard radiotherapy), and a true underlying hazard ratio (HR) corresponding to freedom from local treatment failure of 90% in the SABR group and 70% in the standard radiotherapy group at 2 years, the study had 80% power to detect a difference between the groups. The estimates of freedom of local treatment failure at 2 years were based on published reports of local control following SABR[10] and standard radiotherapy.[11] Freedom from local treatment failure, overall survival, and lung cancer-specific survival were compared between groups using Cox proportional hazards regression to estimate the HR and its 95% CI. A log-rank test was used to calculate the p value for the hypothesis test with a null hypothesis of no difference in hazard between the groups. The assumption of proportionality of hazards was assessed and no evidence was found to reject it (p=0·82). The intention-to-treat principle, by which patients were analysed according to the treatment group to which they were randomly assigned, was used for all efficacy analyses. Aside from the main analysis of the primary objective in which no covariates were considered, the primary objective was also investigated using two sensitivity analyses. In the first of these analyses, the primary objective was addressed using randomisation stratification factors, namely reason for no surgery (medically inoperable vs refused surgery) and T stage, as covariates, rather than the Colinet Simplified Comorbidity Score and the lung lesion longest diameter. In an additional sensitivity analysis, the primary objective was investigated using competing risks regression. Missing data were not imputed and patients with missing data required for a specific endpoint were omitted from the analysis for that endpoint. Patient withdrawal and loss to follow-up were the only censoring events for overall survival.

Toxicities were tabulated per group, in which the worst toxicity grade per patient per toxicity type was recorded. Only toxicities deemed to be possibly, probably, or definitely related to treatment were considered. To avoid bias due to potentially inconsistent follow-up for toxicity between treatment groups, all toxicities that occurred after local treatment failure or after censoring for local treatment failure were omitted from the analysis. Analysis of toxicities was done according to the treatment that patients actually received (per protocol), regardless of the treatment group to which they were originally randomly assigned.
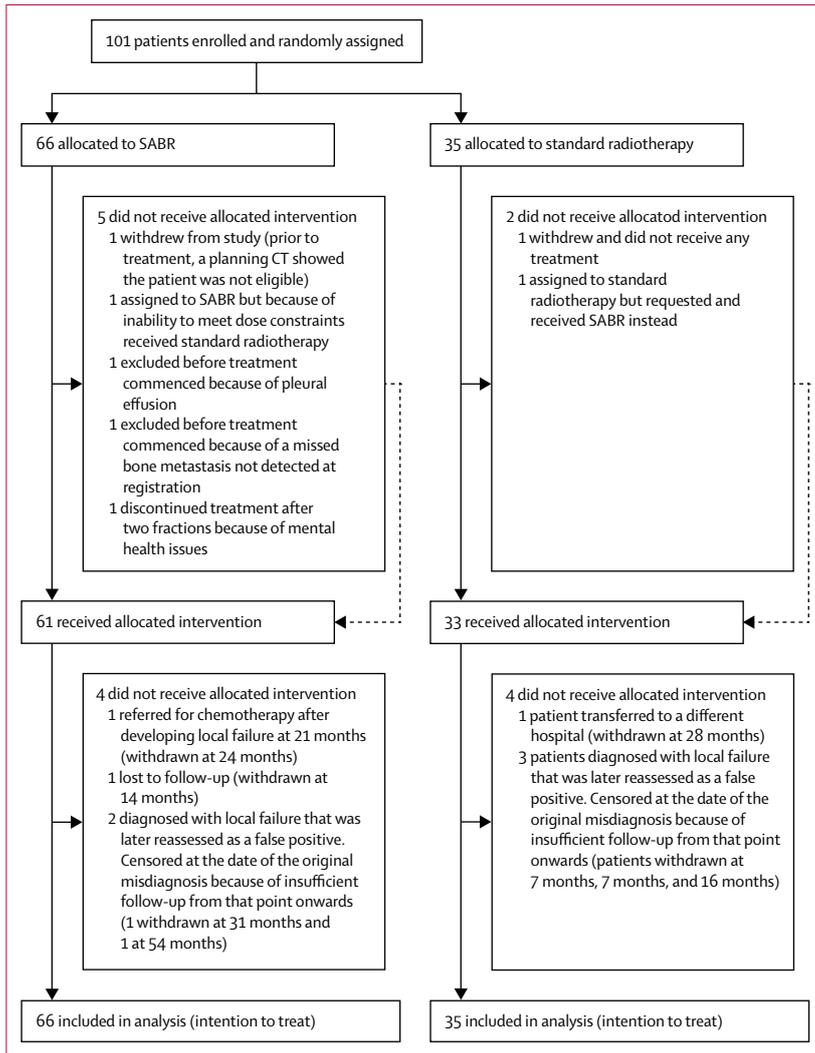
Figure 1: Trial profile
SABR=stereotactic ablative body radiotherapy.

	SABR group (n=66)	Standard radiotherapy group (n=35)
Sex		
Male	36 (55%)	20 (57%)
Female	30 (45%)	15 (43%)
Age, years		
Mean (SD)	74 (8)	75 (7)
Median (IQR)	73·2 (68·9–78·6)	77·0 (69·6–81·2)
ECOG performance status		
0	18 (28%)	10 (29%)
1	47 (72%)	25 (71%)
Missing	1 (1%)	0
		(Table 1 continues on next page)

For the quality-of-life analysis, the area under the quality-of-life time curve (AUC) until 3·5 years was estimated for each group and differences between groups was calculated using a linear mixed-effects model with the appropriate linear contrast applied. Scores were standardised to be on a scale from 0 to 100. The analysis procedure followed for the QLQ-C30 subscales was repeated for the LC13 subscales. Quality of life was analysed using intention to treat (ie, by treatment assigned not treatment received). Adverse events were analysed according to treatment received rather than treatment assigned.

Cox proportional hazards regression was used in a post-hoc analysis to compare the ten patients in the standard radiotherapy group treated with 50 Gy with the 23 patients treated with 66 Gy, to estimate the HR and its 95% CI. The log rank test was used to calculate the p value for the comparison.

The trial was monitored by an independent data-monitoring committee. All analyses were done using the R platform for statistical programming, version 3.4.2.

The trial is registered with ClinicalTrials.gov (NCT01014130) and the Australia and New Zealand Clinical Trials Registry (ACTRN12610000479000).

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

Results
Between Dec 31, 2009, and June 22, 2015, 101 patients were enrolled and randomly assigned to either standard radiotherapy (35 patients) or SABR (66 patients; figure 1). Details of patients who withdrew, were removed from study or crossed over, and the reasons why are shown in figure 1. Delays in installation and provision of credentials for advanced technologies required for the experimental group of the trial at numerous sites resulted in a longer accrual period than planned. The accrual target was reached on June 22, 2015, and a study-wide closeout date for the final analysis was set 2 years after the last patient completed treatment. The baseline characteristics were well balanced, with no differences between treatment groups (table 1). Notably, of the 66 patients randomly assigned to SABR, 28 (43%) had a previous history of cancer compared with 12 (34%) of the 35 patients randomly assigned to standard radiotherapy.

Of the patients randomly assigned to SABR, one patient's plan could not meet the brachial plexus constraints and he was treated with standard radiotherapy instead but analysed for the efficacy outcomes according to the original randomisation. Three (5%) of the 66 patients assigned to SABR were withdrawn from the trial before

treatment (one because of bone metastasis, one because of pleural effusion, and one because of local disease progression), and another patient withdrew before completing treatment because of mental health issues (figure 1). Thus, 61 (92%) of 66 patients in the SABR group were treated according to protocol. For the three patients randomly assigned to SABR who withdrew before treatment, the number of fractions used for treatment was not available. Of the remaining 63 patients in the SABR group, eight (13%) of 63 were treated with 54 Gy in three fractions and 55 (87%) of 63 were treated with 48 Gy in four fractions because of tumour proximity to the chest wall. Of the patients randomly assigned to standard radiotherapy, one chose to have SABR instead, but was analysed according to randomisation for the efficacy analyses, and another withdrew from the study (figure 1). Thus 33 (94%) of 35 patients in the standard radiotherapy group were treated according to protocol.

The median follow-up per group for local treatment failure was 2·1 years (IQR 1·2–3·6) for patients randomly assigned to standard radiotherapy and 2·6 years (1·6–3·6) for patients assigned to SABR. As of July 31, 2017, the data cutoff date, 20 (20%) of 101 patients had progressed locally (nine [14%] of 66 patients in the SABR group and 11 [31%] of 35 patients in the standard radiotherapy group) and 48 (48%) of 101 patients had died (26 [39%] of 66 patients in the SABR group and 22 [62%] of 35 patients in the standard radiotherapy group). Local treatment failure was established by biopsy in three (15%) of 20 patients (one [9%] of 11 patients in the standard radiotherapy group and two [22%] of nine patients in the SABR group), by FDG-PET and CT in 13 (65%) of 20 patients (five [45%] of 11 patients in the standard radiotherapy group and six [66%] of nine in the SABR group), and by CT alone in four (20%) of 20 patients (three [27%] of 11 patients in the standard radiotherapy group and one [11%] of nine in the SABR group).

Freedom from local treatment failure was improved in the SABR group compared with the standard radiotherapy group (HR of 0·32 [95% CI 0·13–0·77], p=0·008; figure 2). The median freedom from local treatment failure was not estimable in either treatment group because the Kaplan-Meier curve never reached 50% for this endpoint in either group. Local control at 2 years for patients randomly assigned to SABR was 89% (95% CI 81–98) compared with 65% (49–87) in patients randomly assigned to standard radiotherapy. The 2-year cumulative incidence of local treatment failure was 10% (95% CI 4–19) for patients receiving SABR and 26% (13–42) for those receiving standard radiotherapy. Patterns of the first sites of treatment failure are listed by treatment group in table 2.

Similarly, the overall survival for patients assigned to SABR was longer than with standard radiotherapy. Median overall survival was 5 years (95% CI 3·4 to not estimable) in the SABR group and 3 years (1·9 to not

	SABR group (n=66)	Standard radiotherapy group (n=35)
(Continued from previous page)		
Reason for no surgery		
Medically inoperable	58 (88%)	31 (89%)
Refused surgery	8 (12%)	4 (11%)
Current smoker		
No	45 (69%)	21 (60%)
Yes	20 (31%)	14 (40%)
Missing	1 (1%)	0
Current or previous smoker		
No	2 (3%)	0
Yes	63 (97%)	35 (100%)
Missing	1 (1%)	0
Smoker pack-years		
Mean (SD)	51 (30)	48 (28)
Median (IQR)	42 (33–60)	45 (30–58)
Missing	1 (1%)	0
Previous cancer		
No	37 (57%)	23 (66%)
Yes	28 (43%)	12 (34%)
Missing	1 (1%)	0
T stage		
1	47 (71%)	24 (69%)
2a	19 (29%)	11 (31%)
Colinet Simplified Comorbidity score		
Mean (SD)	10 (3)	10 (3)
Median (IQR)	9 (8–11)	9 (9–13·5)
Missing	1 (1%)	0
Lung lesion longest diameter, mm		
Mean (SD)	25 (9)	28 (9)
Median (IQR)	22·5 (19–31)	27 (20·5–32)
Missing	2 (3%)	0
Synchronous primary lung tumour count		
0	64 (97%)	33 (94%)
1	1 (2%)	2 (6%)
2	1 (2%)	0
Histological subtype		
Adenocarcinoma	32 (48%)	14 (40%)
Large cell carcinoma	1 (2%)	1 (3%)
Mixed	2 (3%)	0
Non-small-cell carcinoma (not otherwise specified)	9 (14%)	4 (11%)
Squamous cell carcinoma	22 (33%)	16 (46%)

Data are n (%) unless otherwise stated. Note that not all percentages add up to 100% because of rounding of the values. SABR=stereotactic ablative body radiotherapy. ECOG=Eastern Cooperative Oncology Group.

Table 1: Baseline characteristics

estimable) in the standard radiotherapy group (HR 0·53 [95% CI 0·30–0·94], p=0·027; figure 3). Overall survival at 2 years was 77% (95% CI 67–88) for those in the SABR
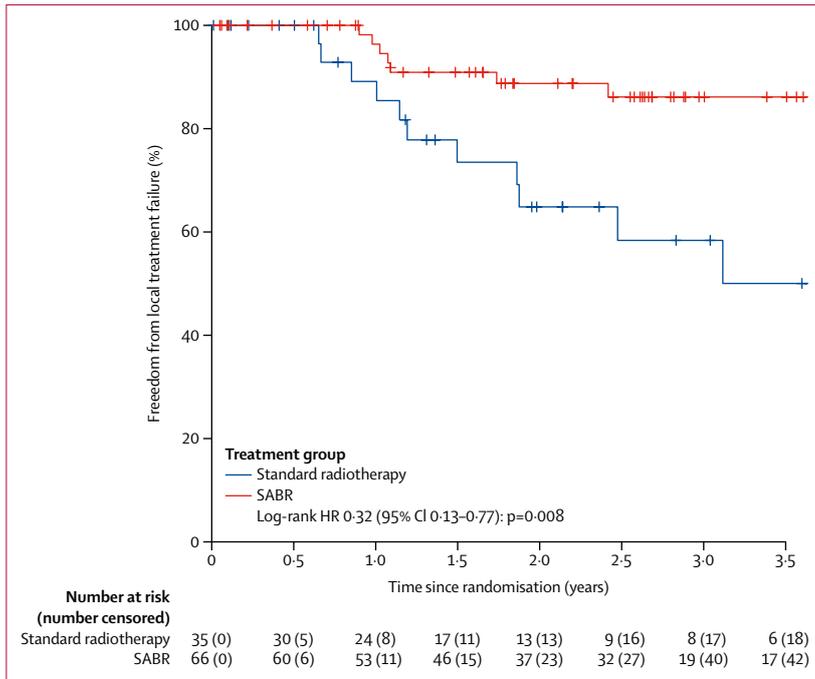
Figure 2: Freedom from local treatment failure
Tick marks represent censored patients (patients were censored for regional failure and distant metastasis, as well as for withdrawal, death, and loss to follow-up). SABR=stereotactic ablative body radiotherapy.

	SABR group (n=66)	Standard radiotherapy group (n=35)
Censored	31 (47%)	10 (29%)
Death	15 (23%)	8 (23%)
Distant treatment failure only	9 (14%)	2 (6%)
Local treatment failure	9 (14%)	11 (31%)
Regional and distant treatment failure	1 (2%)	2 (6%)
Regional treatment failure only	1 (2%)	2 (6%)

Data are n (%). SABR=stereotactic ablative body radiotherapy.

Table 2: Type of first treatment failure event

group and 59% (44–78) for those in the standard radiotherapy group.

Lung cancer-specific survival was also improved in patients randomly assigned to SABR compared with those assigned to standard radiotherapy (HR 0·49 [95% CI 0·21–1·14]; p=0·092). The median lung cancer-specific survival was not estimable in either treatment group because the Kaplan-Meier curve did not reach 50% for this endpoint for either group.

As a sensitivity analysis, we did a competing risks regression for the primary objective (with local treatment failure as the event of interest). The resulting HR was 0·39 (95% CI 0·16–0·93, p=0·033). In another sensitivity analysis, the analyses for freedom from local treatment failure, overall survival, and lung cancer-specific survival

were repeated using the randomisation stratification factors (T stage and medical operability) as covariates. When this analysis was done, the HRs were 0·34 (95% CI 0·14–0·84, p=0·020) for freedom from local treatment failure, 0·55 (0·31–0·98, p=0·055) for overall survival, and 0·52 (0·22–1·22, p=0·24) for lung cancer-specific survival.

At data cutoff, 26 patients in the SABR group and 22 patients in the standard radiotherapy group had died. The causes of death were lung cancer (seven in the SABR group *vs* ten in the standard radiotherapy group), lung cancer and other causes (four *vs* none), other causes (13 *vs* 11), other malignancy (two *vs* one) and unknown (one *vs* none). The specific reasons for the deaths listed as other causes are in the appendix (p 103).

Of the patients randomly assigned to standard radiotherapy, ten (29%) of 35 were treated with 50 Gy and 23 (66%) of 35 with 66 Gy. One patient randomly assigned to SABR was treated with 66 Gy standard radiotherapy. In a post-hoc analysis based on treatment received, local control and overall survival were compared for the two schedules. The HR for freedom from local treatment failure for patients treated with 66 Gy compared with 50 Gy was 0·78 (95% CI 0·17–3·68, p=0·76), and for overall survival the HR was 0·49 (0·20–1·20, p=0·12; data not shown).

Treatment was generally well tolerated in both groups. No treatment-related deaths occurred, and only one grade 4 adverse event, a patient treated with SABR who developed dyspnoea, was recorded. Seven instances of grade 3 adverse events related to treatment were recorded in patients treated with SABR, and two grade 3 adverse events were recorded in patients treated with standard radiotherapy (table 3). When comparing the toxicities between groups, the fact that the cumulative time at risk over all patients for adverse events differed between the groups is important to note. This cumulative time at risk was 153 years for the SABR group and 66 years for the standard radiotherapy group.

For global health status measured with the QLQ-C30, the difference in the mean AUC subtracting the standard group from the SABR group was 5·19 (95% CI –3·9 to 14). No significant differences in functional or symptom scales, including fatigue (mean AUC difference 1·29, 95% CI –7·6 to 10), pain (–3·14, –13 to 6·7), or dyspnoea (–6·15, –17 to 4·5) were noted. For all quality-of-life analyses, see appendix (pp 101–102). A comparison of quality of life between the groups at specific timepoints (3 months and 6 months after treatment) yielded no significant differences in any of the scales (appendix p 101).

Discussion

In this multicentre, randomised, controlled, phase 3 trial, we have shown that use of SABR with a dose of 48 Gy or 54 Gy results in better local control of peripherally located stage 1 (T1–T2aN0) NSCLC than standard radiotherapy

with a dose of 50 Gy or 66 Gy. This finding was associated with an overall survival benefit for patients randomly assigned to SABR. To the best of our knowledge, this study is the first to make a direct comparison that indicates that SABR is associated with improved survival. At the time that this trial was conceived in 2008, a systematic review of the literature on SABR published between 2001 and 2007 found no phase 3 randomised data.[12] The rapid and widespread adoption of SABR in clinical practice had been driven by convenience, tolerability, and high primary tumour control. Despite excellent local control, there was no direct evidence that SABR improved overall survival. A beneficial effect of local control on overall survival can be difficult to detect because of competing risks for death, such as development of metastatic disease, serious comorbidities that are commonly found in patients with inoperable NSCLC, and a theoretical possibility that high doses of SABR might be responsible for unidentified fatal toxicities. In this trial, we minimised these competing risks through accurate staging using FDG-PET to exclude metastatic disease, excluding patients with serious comorbidities by limiting eligibility to ECOG performance status 0–1, and strict quality control and safety of the SABR with a rigorous credentialing and review process.

In the only other randomised trial to compare the two treatment techniques, the SPACE trial,[3] no evidence of a statistically significant difference in either local control or overall survival was found. There are important differences between the SPACE[3] and CHISEL trials that might explain why the CHISEL trial obtained a significant result and the SPACE trial did not. All patients in the CHISEL trial had an FDG-PET staging scan as opposed to 65% of patients in the SPACE trial. None of the patients in the CHISEL trial had an ECOG performance status of more than 1, whereas in the SPACE trial 24% of patients had a performance status of 2. Four-dimensional CT planning and cone-beam CT were available and mandatory for motion management and image guidance at all sites in the CHISEL study, but only at a few sites in the SPACE trial. The prescribed dose in the SABR group of the SPACE trial was 45 Gy in three fractions at the periphery of the planning target volume, compared with 54 Gy in three fractions or a lower biologically effective dose of 48 Gy in four fractions in our trial if the gross tumour volume was within 2 cm of the chest wall. Only a few patients were treated with 54 Gy, indicating that most of the tumours were close to the chest wall. The eligibility of all tumours, including location and dose, was reviewed independently before treatment to ensure compliance with the protocol, so there was no clinician preference for the lower dose. At the start of the CHISEL trial, concerns were raised that the high-dose option for tumours close to the chest wall would result in unacceptably high chest wall pain, so we were particularly conservative in choosing 2 cm as the threshold distance for excluding the higher dose
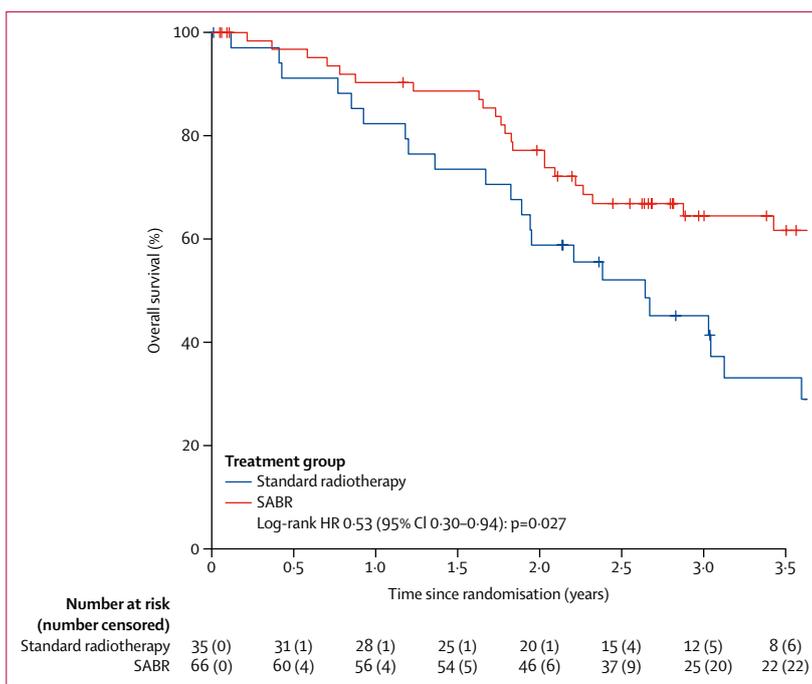

Figure 3: Overall survival
Tick marks represent censored patients (patient withdrawal and loss to follow-up were the only censoring events). SABR=stereotactic ablative body radiotherapy.

	SABR group (n=66)			Standard radiotherapy group (n=35)	
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3
Dyspnoea	22 (39%)	1 (2%)	1 (2%)	18 (58%)	0
Cough	33 (59%)	2 (4%)	0	15 (48%)	0
Fatigue	32 (57%)	1 (2%)	0	21 (68%)	0
Chest wall pain	21 (38%)	0	0	4 (13%)	1 (3%)
Lung infection	3 (5%)	1 (2%)	0	0	0
Pain	2 (4%)	0	0	0	1 (3%)
Cataract	0	1 (2%)	0	0	0
Hypoxia	0	1 (2%)	0	0	0
Weight loss	0	1 (2%)	0	0	0
Pulmonary fibrosis	22 (39%)	0	0	9 (29%)	0
Dermatitis radiation	6 (11%)	0	0	17 (55%)	0
Nausea	9 (16%)	0	0	5 (16%)	0
Atelectasis	9 (16%)	0	0	4 (13%)	0
Pneumonitis	10 (18%)	0	0	1 (3%)	0
Pleural effusion	7 (12%)	0	0	1 (3%)	0
Fracture	5 (9%)	0	0	1 (3%)	0
Anorexia	0	0	0	4 (13%)	0
Dysphagia	3 (5%)	0	0	1 (3%)	0
Bronchopulmonary haemorrhage	2 (4%)	0	0	1 (3%)	0
Dizziness	0	0	0	3 (10%)	0
Dry mouth	1 (2%)	0	0	2 (6%)	0
				(Table 3 continues on next page)	

	SABR group (n=66)			Standard radiotherapy group (n=35)	
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3
(Continued from previous page)					
Infections and infestations	1 (2%)	0	0	2 (6%)	0
Superficial soft tissue fibrosis	2 (4%)	0	0	1 (3%)	0
Back pain	1 (2%)	0	0	1 (3%)	0
Diarrhoea	1 (2%)	0	0	1 (3%)	0
Non-cardiac chest pain	1 (2%)	0	0	1 (3%)	0
Pericardial effusion	1 (2%)	0	0	1 (3%)	0
Respiratory, thoracic, and mediastinal disorders	1 (2%)	0	0	1 (3%)	0
Skin and subcutaneous tissue disorders	0	0	0	2 (6%)	0
Vomiting	0	0	0	2 (6%)	0
Abdominal distension	1 (2%)	0	0	0	0
Abdominal pain	1 (2%)	0	0	0	0
Anxiety	0	0	0	1 (3%)	0
Constipation	0	0	0	1 (3%)	0
Dehydration	0	0	0	1 (3%)	0
Dry skin	0	0	0	1 (3%)	0
Dysgeusia	0	0	0	1 (3%)	0
Erythema multiforme	0	0	0	1 (3%)	0
Esophagitis	1 (2%)	0	0	0	0
Gastro-oesophageal reflux disease	0	0	0	1 (3%)	0
Laryngeal inflammation	0	0	0	1 (3%)	0
Mucosal infection	0	0	0	1 (3%)	0
Musculoskeletal and connective tissue disorder	0	0	0	1 (3%)	0
Myalgia	1 (2%)	0	0	0	0
Oral haemorrhage	0	0	0	1 (3%)	0
Toothache	0	0	0	1 (3%)	0
Upper respiratory infection	0	0	0	1 (3%)	0
Urinary tract infection	0	0	0	1 (3%)	0

Data are n (%). There were no grade 4 events in the standard radiotherapy group. SABR=stereotactic ablative body radiotherapy.

Table 3: Adverse events

prescription. We had previously shown that for a 2 cm spherical tumour, for example, a 1 cm chest wall exclusion zone would render only 20–30% of peripheral tumours eligible for the high-dose prescription.[13]

Since we completed our trial, two large retrospective non-randomised studies[14,15] and one systematic review[16] have reported a survival benefit associated with SABR compared with standard radiotherapy, consistent with our results.

An important limitation of our trial is the choice of time to local treatment failure as the primary endpoint. Initially we planned to use the widely accepted RECIST criteria to record local treatment failure, with confirmation by biopsy or FDG-PET imaging. As the trial progressed, after SABR

many patients developed dense fibrosis within the irradiated volume that would erroneously satisfy the criteria for progressive disease using the RECIST criteria. Huang and colleagues[17] identified numerous radiological features that were associated with a higher risk of biopsy-proven recurrence. A list of these features was provided to the independent radiology review panel to assist them with their reports. We note that treatment-related changes are more likely to be mistaken for progressive disease in patients treated with SABR than in patients treated with a standard schedule, so any bias thus induced should be conservative, favouring the control group. The freedom from local treatment failure following SABR in our trial was consistent with other prospective studies.[2,18] Finally, we believe that the secondary but more reliable endpoint, overall survival, supports the local progression interpretations.

Another possible limitation of our trial is the inclusion of a large proportion of patients who had a previous cancer. Arguably, many of the patients enrolled could have had metastatic disease, and the survival difference between the groups could be due to a greater proportion of previous cancers in one group compared with the other. In fact, there were a higher proportion of patients with previous cancers in the SABR group than in the standard radiotherapy group, but despite this, their survival was longer. A further limitation is the choice of dose and fractionation in the standard radiotherapy group that was allowed in the protocol. One of the options, 50 Gy in 20 fractions, is numerically lower than the other option of 66 Gy in 33 fractions, and on theoretical grounds is biologically less effective. The benefit observed with SABR could arguably be a result of a suboptimal dose allowed in the control group. However, the 50 Gy was given in a much shorter overall time of 4 weeks instead of 6 weeks, which might compensate for the lower dose. The schedule of 50 Gy in 20 fractions is often used as a conventional curative fractionation schedule,[19] and thus reflects real-world practice.

The toxicity of treatment in both groups was low, with only one grade 4 adverse event that occurred in the SABR group. Toxicities that occurred after local treatment failure were not recorded consistently and hence needed to be omitted, which is a potential limitation. However, there was no suggestion of an excess of sudden deaths due to unidentified toxicities (eg, exsanguination outside the hospital) in the SABR group. We observed no significant differences in quality of life between the groups. Because the duration of treatment in the standard-of-care group was longer than that for the SABR group, alignment of quality-of-life assessments with end of treatment resulted in some misalignment of the timing of assessments taken after treatment relative to the baseline assessment. As a result, dyspnoea due to pneumonitis, which typically occurs 6–12 weeks after completion of treatment, might have occurred earlier in the patients treated with SABR than in those treated with

standard therapy, but there was no evidence of a difference between the groups at any timepoint.

In conclusion, the improvement of both local control and overall survival with SABR shown in this prospective randomised trial provides, to our knowledge for the first time, evidence supporting stereotactic ablative radiotherapy as the standard of care for the treatment of inoperable peripherally located stage 1 (T1N0M0 and T2aN0M0) NSCLC.

References
1 Palma D, Visser O, Lagerwaard FJ, Belderbos J, Slotman BJ, Senan S. Impact of introducing stereotactic lung radiotherapy for elderly patients with stage I non-small cell lung cancer: a population-based time-trend analysis. *J Clin Oncol* 2010; **28:** 5153–59

2 Timmerman R, Paulus R, Galvin J, et al. Stereotactic body radiation therapy for inoperable early stage lung cancer. *JAMA* 2010; **303:** 1070–76.

3 Nyman J, Hallqvist A, Lund JA, et al. SPACE–a randomized study of SBRT *vs* conventional fractionated radiotherapy in medically inoperable stage I NSCLC. *Radiother Oncol* 2016; **121:** 1–8.

4 International Union Against Cancer. TNM classification of malignant tumours, 7th ed. Geneva: John Wiley and Sons, 2009.

5 Timmerman R, McGarry R, Yiannoutsos C, et al. Excessive toxicity when treating central tumors in a phase II study of stereotactic body radiation therapy for medically inoperable early-stage lung cancer. *J Clin Oncol* 2006; **24:** 4833–39.

6 Colinet B, Jacot W, Bertrand D. A new simplified comorbidity score as a prognostic factor in non-small cell lung cancer patients: description and comparison with the Charlson's index. *Br J Cancer* 2005; **93:** 1098–105.

7 Kron T, Chesson B, Hardcastle N, et al. Credentialling of radiotherapy centres in Australasia for TROG 09.02 (CHISEL), a phase III trial on stereotactic body radiotherapy of early stage lung cancer. *Br J Radiol* 2018; **91:** 20170737.

8 International Commission on Radiation Units and Measurements. Prescribing, recording and reporting photon beam therapy. Report number 50. Bethesday: International Commission on Radiation Units and Measurements, 1993.

9 Hjermstad Mj, Fossa SD, Bjordal K, Kaasa S. Test/retest study of the European Organisation for Research and Treatment of Cancer core quality-of-life questionnaire. *J Clin Oncol* 1995; **13:** 1249–54.

10 Onishi H, Shirato H, Nagata Y, et al. Hypofractionated stereotactic radiotherapy (HypoFXSRT) for stage I non-small cell lung cancer: updated results of 257 patients in a Japanese multi-institutional study. *J Thorac Oncol* 2007; **2** (suppl 3): S94–100.

11 Campeau MP, Herschtal A, Wheeler G, et al. Local control and survival following concomitant chemoradiotherapy in inoperable stage I non-small cell lung cancer. *Int J Rad Oncol Biol Phys* 2009; **74:** 1371–75.

12 Brock, J, Ashley S, Bedford J, Nioutsikou E, Partridge M, Brada M. Review of hypofractionated small volume radiotherapy for early-stage non-small cell lung cancer. *Clin Oncol* 2008; **20:** 666–76.

13 Siva S, Shaw M, Chesson B, Gill S, Ball D. Analysis of the impact of chest wall constraints on eligibility for a randomized trial of stereotactic body radiotherapy of peripheral stage I non-small cell lung cancer. *J Med Imaging Radiat Oncol* 2012; **56:** 654–60.

14 von Reibnitz D, Shaikh F, Wu AJ, et al. Stereotactic body radiation therapy (SBRT) improves local control and overall survival compared to conventionally fractionated radiation for stage I non-small cell lung cancer (NSCLC). *Acta Oncol* 2018; **57:** 1567–73.

15 Haque W, Verma V, Polamraju P, Farach A, Butler EB, Teh BS. Stereotactic body radiation therapy versus conventionally fractionated radiation therapy for early stage non-small cell lung cancer. *Radiother Oncol* 2018; **129:** 264–69.

16 Hegi F, D'Souza M, Azzi M, De Ruysscher D. Comparing the outcomes of stereotactic ablative radiotherapy and non-stereotactic ablative radiotherapy definitive radiotherapy approaches to thoracic malignancy: a systematic review and meta-analysis. *Clin Lung Cancer* 2018; **19:** 199–212.

17 Huang K, Senthi S, Palma DA, et al. High-risk CT features for detection of local recurrence after stereotactic ablative radiotherapy for lung cancer. *Radiother Oncol* 2013; **109:** 51–57.

18 Chang JY, Senan S, Paul MA, et al. Stereotactic ablative radiotherapy versus lobectomy for operable stage I non-small-cell lung cancer: a pooled analysis of two randomised trials. *Lancet Oncol* 2015; **16:** 630–37.

19 Smith SL, Palma D, Parhar T, Alexander CS, Wai ES. Inoperable early stage non-small cell lung cancer: comorbidity, patterns of care and survival. *Lung Cancer* 2011; **72:** 39–44.