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Original Article

Contact of a tumour with the pleura is not associated with regional recurrence following stereotactic ablative radiotherapy for early stage non-small cell lung cancer

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ABSTRACT

Background and purpose: The aim was to investigate the incidence of isolated regional failure following stereotactic ablative radiotherapy (SABR) and risk factors for recurrence.
Materials and methods: Early stage non-small cell lung cancer (NSCLC) patients treated with SABR were included in this retrospective cohort study, with isolated regional recurrence (IRR) as primary endpoint, distant recurrence (DR) and overall survival (OS) as secondary endpoints. Survival analyses were performed using the cumulative incidence function (IRR and DR) or the Kaplan–Meier method (OS) and Cox proportional hazards modelling for univariate and multivariate analyses. The prognostic effect of contact between the tumour and the pleura was investigated using the CT scans used for SABR planning.
Results: A total of 554 patients were included, of whom 494 could be analysed for IRR. The median follow-up for surviving patients was 48.1 months. Twenty-one patients developed an IRR (4%). The cumulative incidence of IRR and DR after 1-, 2-, and 5 years was 2%, 3%, 7% and 8%, 15% and 21%, respectively. Two year OS was 71%. The presence and type of pleural contact was not associated with any of the studied outcomes.
Conclusion: The presence, type and length of pleural contact as surrogate for visceral pleural invasion were not predictive for outcome. Further studies focussing on risk factors for occult nodal involvement, (I)RR, distant metastases and mortality in early stage NSCLC are warranted for the development of risk adapted diagnostic, treatment and follow-up strategies as more younger, operable and fitter patients receive SABR.
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Stereotactic ablative body radiotherapy (SABR) of early stage non-small cell lung cancer (NSCLC) has been shown to result in excellent local control rates of more than 90% [1]. The predominant site of failure is distant, with approximately 20% of the patients developing distant metastases within 3 years [1]. Regional lymph node recurrence (RR) following SABR occurs in approximately 10% of the patients and predominantly involves lymph node stations 4, 7 or 10 [2–5]. An isolated regional recurrence (IRR) can potentially be treated with curative-intent surgery or radiotherapy, possibly complemented with (concurrent) chemotherapy depending on disease stage [6–8]. The identification of patients at high risk of occult nodal disease and regional recurrence is desirable when defining the diagnostic work-up prior to SABR and risk-based follow-up regimens following SABR, especially as more younger and fitter patients are receiving SABR. These patients are more likely able to undergo adjuvant systemic treatment in case of a high disease recurrence risk and/or salvage treatment in case of an IRR compared to the traditionally elderly, inoperable SABR population.

In multiple studies, attempts have been made to identify risk factors for the development of a regional recurrence, as summarized in a recent systematic review [2]. Hampered by the predominantly retrospective nature of the studies, variable staging procedures, a low number of events and unclear definitions of nodal failure, a subgroup of patients at high risk for regional recurrence could not be defined. Anaemia, male gender and incidental dose to the regional lymph nodes were found to be relevant. The

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surgical literature has provided risk factors such as occult nodal involvement, lymphovascular space invasion (LVI), and visceral pleural invasion (VPI) [2]. A suggested route for lymph node metastases originating from a tumour with VPI is subpleural lymphatic drainage of tumour cells from the pleural cavity through the hilar lymph nodes and/or diaphragmatic lymphatics into the mediastinal lymph nodes [9,10]. As VPI and LVI are determined on resected specimens, they cannot hold predictive value for patients undergoing SABR. However, the presence of VPI can be predicted using thoracic CT images [11].

The aim of this large multi-institutional retrospective study was to describe patterns of nodal failure following SABR and to identify patient-, tumour- and treatment-related risk factors for IRR. The prognostic value of the relation of the tumour to the visceral pleura was investigated retrospectively using the CT scans for SABR planning.

Materials and methods

Patients and treatment

All patients included in this retrospective cohort study were treated with image-guided SABR between 2007 and 2015, in one of three international institutions: MAASTRO clinic (MC, the Netherlands), the Netherlands Cancer Institute (NKI, the Netherlands), or the University Hospital Carl Gustav Carus of the Technische Universität Dresden (UHCGC, Germany). Patients were staged with a total-body ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT). Mediastinal lymph node staging with endobronchial ultrasound (EBUS) or mediastinoscopy was performed at the discretion of the treating physician, depending on the (PET/)CT findings. A clinical diagnosis of (assumed) cT1-3, N0, M0 NSCLC based on serial CT imaging and/or PET/CT results was required for treatment. Histologic proof of malignancy was pursued whenever possible, but neither required for SABR (when fulfilling the aforementioned criteria) nor for inclusion in the current study. SABR was performed following the local practice guidelines for treatment planning and delivery at each institution, including daily image guidance. Various treatment planning techniques were used, including fixed-beam and arc-techniques based on forward- or inverse-planning. Follow-up imaging was performed in accordance with local and national guidelines, typically consisting of a CT scan within 6 weeks to 4 months after SABR and annually thereafter. If disease recurrence (local, regional or distant) was suspected, a PET/CT and/or biopsy were usually performed if clinically relevant.

The following exclusion criteria were applied: multiple lung tumours, non-NSCLC histology (small cell lung cancer, pulmonary metastases from other primary tumours), previous treatment with intrathoracic surgery or intrathoracic radiotherapy for cancer (with the exception of whole breast irradiation), treatment for any type of cancer (excluding basal cell carcinoma of the skin) less than two years prior to SABR, a maximum tumour diameter (MTD) >6 cm, and a Biologically Effective Dose (BED) <95 Gy.

Assessment of pleural contact

To avoid differences in outcome due to measuring inconsistencies, the MTD and presence and type of pleural contact were ascertained and measured by one researcher (KW) in all three institutions. For all measurements, the standard lung-window setting was used on the CT. For tumours abutting the pleura, the maximum pleural distance (MPD) constituted the maximum length of pleural contact in the axial, sagittal or coronal plane (Fig. 1). In case of multiple sites of pleural contact (for example the interlobar fissure and the pleura lining the thoracic wall), the maximum length of contact of each site added up to the cumulative MPD. Consequently, an MPD larger than the MTD was possible. Furthermore, three types of pleural tags were identified for tumours in contact with, but not abutting, the pleura: (1) a linear tag on lung window, (2) a tag on mediastinal window with a soft tissue component at the pleural end or (3) a cord-like tag on mediastinal window ([12]; Fig. 2).

Outcomes and statistical analyses

Isolated regional recurrence was considered our primary endpoint, distant recurrence (DR) and overall survival (OS) were secondary endpoints. IRR was defined as a new or growing lymph node on CT combined with FDG-PET avidity, and/or a biopsy confirmed regional recurrence and/or continuing lymph node enlargement on serial CT scans (lymph node $\geq$1 cm) [2]. Patients with an IRR had no evidence of distant metastases within 2 months after diagnosis of the nodal recurrence. As it is challenging to ascertain a local recurrence (LR) following SABR due to heterogeneous radiographic changes, the local disease status was not assessed. Therefore, patients with an IRR could have a simultaneous LR, still representing a potentially curable disease stage. Time to recurrence and survival were calculated from the first day of stereotactic radiotherapy. For IRR, patients were censored at the date of the last acquired (PET/)CT. For DR, patients were censored at the date of last contact with a physician. OS data was collected from a Dutch or German national database. The patients from UHCGC were included in the overall survival analyses only, since follow-up data on the course of the disease (occurrence of IRR and/or DR) were not retrievable from the referring centres.

Survival analyses were performed using the Kaplan–Meier method (OS) or the cumulative incidence function (IRR and DR). Cox proportional hazards modelling was used for univariate and multivariate analyses, to test the prognostic significance of several patient and tumour related variables, e.g. tumour size, patient age and performance status, the use of metformin at the time of SABR [13]. The following variables describing the relation of the tumour with the pleura were evaluated: the type of pleural contact (no contact, pleural tag or tumour abutting the pleura), the MPD (as continuous variable and dichotomized in two categories using the median distance) and the MPD/MTD ratio [11]. An overall chi-squared test was performed for categorical variables with more than two factors. Variables with significant correlation to outcome in univariate analysis were entered in multivariate models. A p-value <0.05 was considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics 24 (IBM Corporation, Armonk, NY).

Results

In total 554 patients met the inclusion criteria. Patient and treatment characteristics are given in Table 1. The median follow-up for all patients was 36.1 months (range 1.1–118.3 months) and 48.1 months (range 26.6–118.3 months) for surviving patients. For IRR, the median FU was 20.0 months (range 1.1–108.3 months). The median patient age was 74 years (range 42–91 years), 58% were male and 64% had a good general performance (WHO score 0 or 1). A total 545 patients (98%) were staged with a pre-treatment FDG-PET/CT. Sixty-eight percent of the patients (377/554) received SABR on a suspicion of malignancy without histological proof. The median prescribed dose was 54 Gy (range 45–75 Gy in 3–8 fractions). Most lung tumours were peripherally located and 66% were situated in one of the upper lobes (365/554). Seventy-nine percent (439/554) had some form of pleural contact (pleural tag or tumour abutting the pleura).

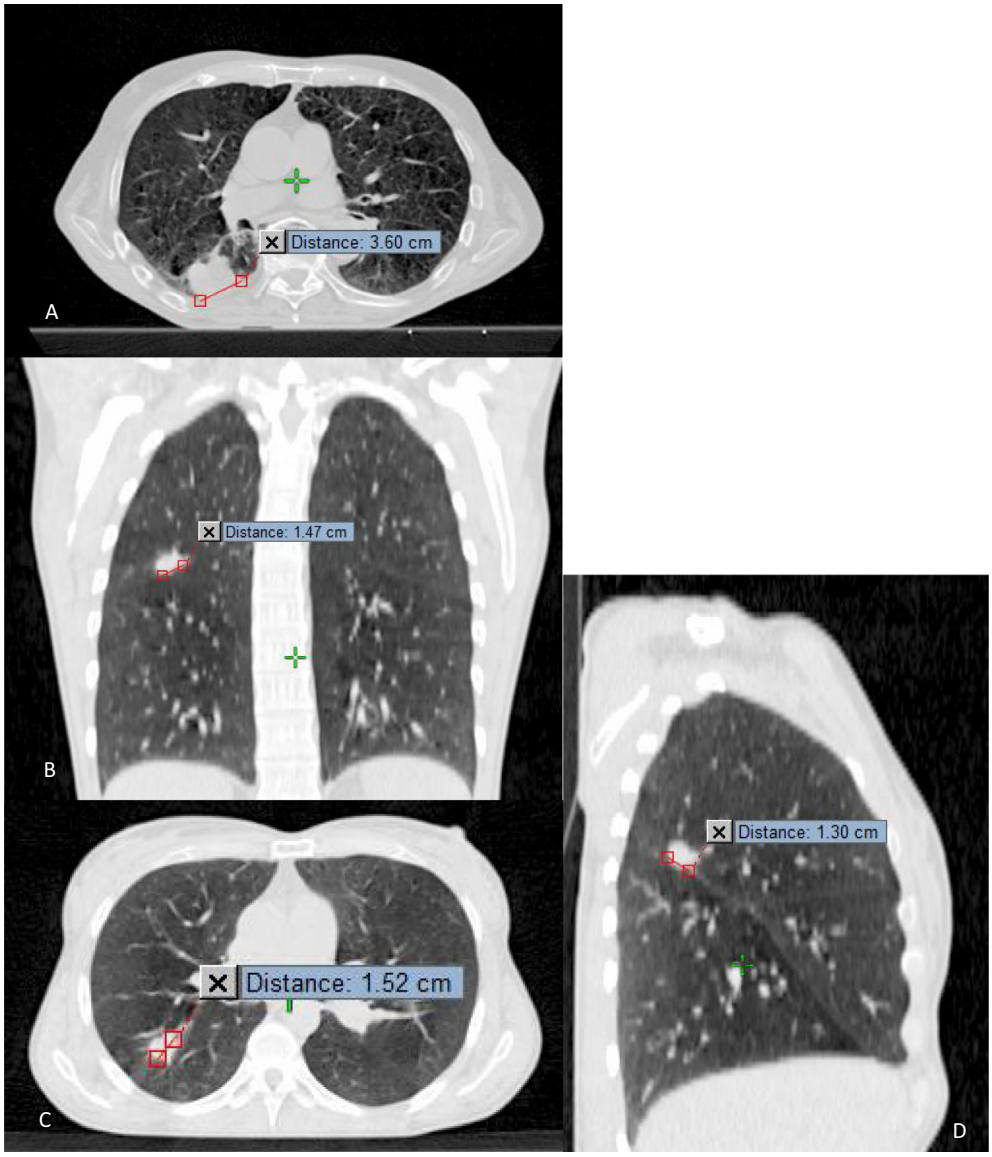

Fig. 1. The maximum pleural distance (MPD) was measured in three directions, of which the largest distance was used for the analyses. This figure shows examples of measurements for: (A) a tumour in contact with the thoracic wall (axial view) and (B–D) a tumour in contact with the interlobar fissure, in all three measuring directions (coronal, axial, sagittal).

Median MPD was 23 mm (range 6–79 mm), consisting of two measurements in 13 patients.

Clinical outcomes

A total 494/554 patients were analysed for incidence of IRR. A regional lymph node recurrence was diagnosed in 39 patients (8%) and distant metastases in 91 patients (18%). Of the 39 patients with a RR, 22 were also diagnosed with a DR (56%), of whom 18 prior or synchronous to the RR (46%). Therefore, the incidence of IRR was 4% (21/494). In 76% (16/21), the upper mediastinum was involved (lymph node stations 2–4), in 48% (10/21) the lower mediastinum (stations 5–8), in 19% (4/21) the ipsilateral hilar region, in 14% (3/21) the contralateral hilar region and in 5% (1/21) the supraclavicular region. The median time to both IRR and DR was not reached. The 1-, 2- and 5-year cumulative incidence of IRR and DR were 2%, 3%, 7% and 8%, 15% and 21%, respectively (Fig. 3A and B). The 2- and 5-year overall survival rates were 71% and 47%, respectively, and the median overall survival time following SABR was 54 months (a Kaplan–Meier plot is available as Online Supplementary Figure). Best supportive care was given to 43% of patients with an isolated nodal recurrence (9/21), 7 patients (33%) were radically treated with either radiotherapy alone or sequential or concurrent chemoradiotherapy, 2 patients (10%) received systemic therapy only and for 3 patients (14%) the treatment was unknown.

The results of the univariate and multivariate analyses for IRR and DR are presented in Tables 2 and 3 (OS results are available as Online Supplementary Material). The presence and extent of pleural contact were not associated with IRR or any of the other studied outcomes, including RR (data on RR not shown). While a younger age and a smaller GTV were significantly associated with less IRR in univariable analysis, their significance was lost in multivariable analysis. The cT-stage did correlate significantly with DR

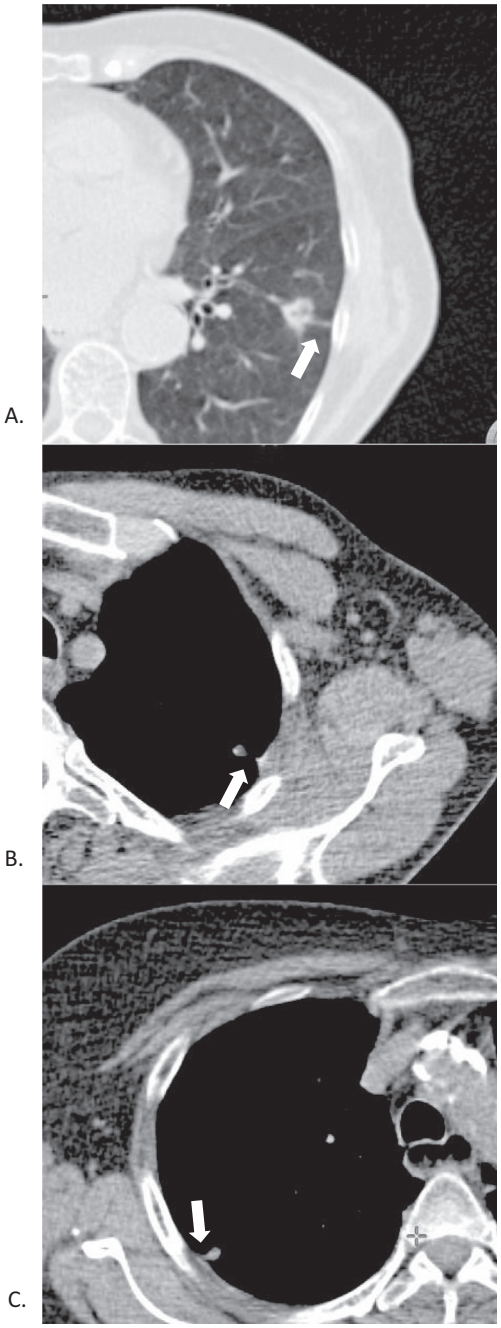

Fig. 2. Types of pleural tags: (A) linear pleural tag on lung window, (B) linear pleural tag with soft-tissue component at pleural end on mediastinal window, (C) cord-like pleural tag on mediastinal window.

(cT1 superior to cT2/cT3, $p < 0.001$). A total 66/554 patients were using metformin at the time of SABR. Metformin use did not result in improved outcomes following SABR.

Discussion

To the best of our knowledge, the current study is the largest to date analysing the incidence of isolated regional recurrence following SABR for NSCLC and the prognostic value of the type and extent of contact between the tumour and the pleura. The overall incidence of IRR as first recurrence was 4% and the overall RR rate was 8%, which is comparable to the IRR and RR rates reported in the literature [2,4,7].

Table 1
Patient characteristics.

Parameter	Number of patients (%)
Institution	102/60/392
MAASTRO clinic/UHCGC/NKI	(18.4/10.8/70.8)
Gender	320/234
male/female	(57.8/42.2)
Location	209/156/104/66/18
RUL/LUL/RLL/LLL/RML	(37.7/28.2/18.8/11.9/3.2)
Histology	66/66/28/3/14/377
ACC/SCC/LCC/AIS/NSCLC NOS/none	(11.9/11.9/5.1/0.5/2.5/68.1)
cT Stage	428/124/2
1/2/3	(77.2/22.4/0.4)
WHO PS	85/269/161/23/3/13
0/1/2/3/4/unknown	(15.3/48.6/29.1/4.2/0.5/2.3)
Metformin	462/66/26
no/yes/unknown	(83.4/11.9/4.7)
Pleural contact	79/244/195/36
no/pleural tag/tumour abuts pleura/unknown	(14.3/44.0/35.2/6.5)
Pleural tag type ($n = 244$)	65/84/92/3
Linear lung/linear mediastinal/cord-like mediastinal/undefined	(26.6/34.4/37.7/1.2)
Pleural distance ($n = 195$)	93/86/16
MPD $\leq$ 23 mm/MPD > 23 mm/unmeasurable	(47.7/44.1/8.2)
Parameter	**Median (range)**
Age (years)	74.0 (42.0–91.0)
BMI (kg/m^2)	24.6 (12.3–51.2)
GTV (ml)	6.0 (0.3–95.3)
EQD2 95% (Gy)	115.9 (81.3–200.4)
MPD (mm)	23.0 (6.0–79.0)

ACC = adenocarcinoma, AIS = adenocarcinoma in situ (former bronchoalveolar carcinoma), BMI = Body Mass Index, EQD2 95% = 95% of the prescribed dose as an equivalent dose of 2 Gy fractions, using an α/β ratio of 10 Gy for the tumour, GTV = gross tumour volume, LCC = large cell carcinoma, LLL = left lower lobe, LUL = left upper lobe, MPD = maximum pleural distance, NKI = National Cancer Institute, NSCLC NOS = non-small cell lung cancer not otherwise specified, RLL = right lower lobe, RML = right middle lobe, RUL = right upper lobe, SCC = squamous cell carcinoma, UHCGC = University Hospital Carl Gustav Carus, WHO PS = World Health Organization Performance Score.

From the surgical literature, VPI is a known poor prognostic factor in early stage NSCLC. A negative impact of VPI has been reported on lung cancer specific and overall survival, a higher incidence of involved lymph nodes on lymph node dissection and a higher incidence of lymph node recurrence [9,14–18]. Consequently, it has remained a pathologic descriptor for T2 staging in the 8th edition of the Union Internationale Contre le Cancer (UICC) TNM classification of malignant lung tumours [19,20]. As resected tissue is lacking in patients treated with SABR, we measured and calculated the MPD and the MPD/MTD ratio as a surrogate for VPI. As shown by Imai et al. [11], this ratio as measured on a CT scan correlates with the extent of pleural invasion on pathologic examination. In their study, a ratio of 0.9 resulted in a high sensitivity and specificity for thoracic invasion of 89.7% and 96%, respectively. In the current study, a prognostic effect of the MPD and/or the MPD/MTD ratio could not be demonstrated for any of the studied outcomes on multivariable analysis. Yamamoto et al. [21] conducted a smaller but similar study to ours, measuring the length of pleural contact on pre-SABR CT images of 87 patients with stage I NSCLC. They found a broad attachment to the pleura of >14.7 mm (the median length of contact) to be a negative independent predictor for locoregional control. We did not find evidence to support their conclusion within our large multi-institutional patient cohort. A possible reason why, in contrast to surgical series, a relation between pleural invasion and regional control was not found could be the sterilisation of involved pleura or tumour cells in the pleural cavity as dose deposition continues outside the PTV.

Several other relevant patient, tumour and (pre-)treatment characteristics were tested for a correlation with (isolated) regional and distant recurrence. None of the tested variables was

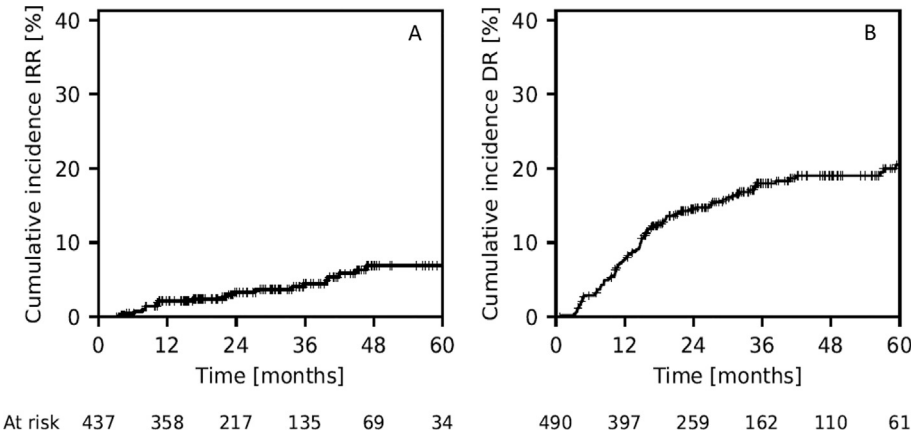

Fig. 3. Cumulative incidence function of (A) isolated regional recurrence (IRR) and (B) distant recurrence (DR).

Table 2
Univariable Cox regression for isolated regional recurrence and distant recurrence.

	Isolated regional recurrence		Distant recurrence	
Parameter	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Age (years)	1.06 (1.00–1.12)	0.033	1.02 (0.99–1.04)	0.18
Gender (male/female)	0.57 (0.24–1.39)	0.22	0.91 (0.60–1.38)	0.67
cT (1 vs 2,3)	0.85 (0.25–2.91)	0.80	3.01 (1.96–4.63)	<0.001
WHO PS (0,1 vs 2,3)	0.48 (0.14–1.64)	0.24	1.18 (0.75–1.83)	0.48
BMI (kg/m^2)	0.96 (0.88–1.06)	0.42	0.99 (0.94–1.03)	0.54
Metformin (no/yes)	1.04 (0.30–3.55)	0.95	1.19 (0.66–2.14)	0.57
Location		**		**
GTV (ml)	1.03 (1.00–1.06)	0.029	1.03 (1.01–1.04)	<0.001
EQD2 95% (Gy)	0.98 (0.95–1.01)	0.24	1.01 (0.99–1.03)	0.42
Pleural contact (none/tag/tumour abuts pleura)		0.28		* 0.55
Pleural contact (none/present)	1.01 (0.29–3.56)	0.98	1.38 (0.75–2.54)	0.31
Pleural tag type (linear lung/linear mediastinal/cord-like mediastinal)		0.64		* 0.25
Pleural categories (remaining *vs* MPD > 23 mm)	1.86 (0.52–6.61)	0.34	1.44 (0.82–2.53)	0.20
MPD (mm)	1.02 (0.97–1.08)	0.37	1.03 (1.01–1.06)	0.006
MPD/MTD ratio	5.25 (0.42–65.8)	0.20	2.70 (0.66–11.1)	0.17

BMI = Body Mass Index, EQD2 95% = 95% of the prescribed dose as an equivalent dose of 2 Gy fractions, using an α/β ratio of 10 Gy for the tumour, GTV = gross tumour volume, HR = hazard ratio, MPD = maximum pleural distance, MTD = maximum tumour diameter, RML = right middle lobe, WHO PS = World Health Organization Performance Score.
* Overall chi-squared test of categorical variables with more than two factors.
** No convergence (no event in RML group).

Table 3
Multivariable Cox regression for isolated regional recurrence and distant recurrence.

	Isolated regional recurrence		Distant recurrence	
Parameter	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Age (years)	1.04 (0.99–1.10)	0.12		
cT (1 vs 2,3)			2.87 (1.67–4.94)	<0.001
GTV (ml)	1.03 (0.99–1.06)	0.10	1.01 (0.98–1.03)	0.64

GTV = gross tumour volume, HR = hazard ratio.

predictive for (I)RR and only a higher cT stage was significantly associated with DR.

We believe further investigation on the prediction of the outcome of patients treated with SABR is warranted, especially as more younger, fitter and operable patients are receiving stereotactic radiotherapy. The main reason for this is the risk of undertreating those patients who are potentially operable and able to undergo adjuvant systemic treatment in case of high risk features predisposing them to regional or distant disease recurrence. In a recent retrospective cohort study, adjuvant systemic therapy was associated with less regional and distant failures in the SABR population [22]. Furthermore, the consequence of the lack of final pathological mediastinal staging in patients treated with SABR is largely unknown. A lobectomy or segmentectomy typically includes a systematic lymph node dissection and in case of lymph node involvement, adjuvant systemic therapy is considered [20]. The available evidence generally does not show an increased risk of RR in patients treated with SABR [2,23,24]. Suggested explanations include incidental mediastinal/hilar dose from SABR (causing sterilisation of micrometasases), mediastinal lymph node dissections inconsistent with available guidelines, differences in follow-up and a higher non-cancer death rate following SABR [2]. However, van den Berg et al. [25] reported more locoregional failures and a trend for more nodal failures following SABR. As the data on nodal failure rates come from mainly retrospective studies in typically medically inoperable patients, the subject remains a

matter of debate [2]. Long-term prospective follow-up data on large cohorts of fit, operable patients receiving SABR is still lacking [2,26]. A pooled analysis of two preliminary closed randomized controlled trials comparing surgery with SABR for operable early stage NSCLC reported no significant difference in regional and distant control, but was underpowered due to the very small number of patients that entered the trials and small number of events [24]. The recently published NRG Oncology Radiation Therapy Oncology Group (RTOG) 0618 trial also showed favourable results with a 4-year locoregional control rate of 88% in operable patients treated with SABR [27]. However, only 26 patients were analysed in this small single-arm phase 2 trial. Several studies are still ongoing attempting to compare SABR with surgical resection in randomized clinical trials (e.g. VALOR, STABLE-MATES, SABRTOOTH) [26]. If successful, these trials can deliver evidence on the likelihood of equivalence of SABR and surgery with respect to RR and the possible consequences of the lack of final pathologic mediastinal staging.

Currently, clinical staging procedures for SABR are comparable to preoperative staging procedures for early stage NSCLC. No additional preoperative mediastinal staging procedures are recommended in patients staged as cN0 through PET/CT with a tumour $\leq$3 cm located in the outer third of the lung [28]. This recommendation is based on a high negative predictive value of >90% of PET/CT and a very low incidence of pN2 disease of 2.9% for peripheral tumours $\leq$3 cm [28]. As the majority of pulmonary nodules treated with SABR is small and peripherally located, it is not surprising that the yield of pre-SABR invasive mediastinal nodal staging (IMNS) with EBUS or mediastinoscopy is minimal in unselected patients: only 3.4% of cN0 patients (based on PET/CT) are upstaged by IMNS [29]. Schonewolf et al. [3] reported similar patterns of failure and overall survival following SABR for patients staged as cN0 with PET/CT combined with IMNS compared to patients staged with PET/CT alone. However, as again mainly medically inoperable patients who are more likely to die from non-oncologic causes were included in these studies, it is unclear whether these results can be extrapolated to a medically operable population.

The indications for SABR are expanding with larger (>5cm) and more centrally located tumours harbouring a risk of nodal involvement of over 10% [30–32]. This, combined with more younger, potentially operable patients receiving SABR, highlights the importance of future studies focussing on improving outcome prediction by incorporating relevant risk factors for recurrence following stereotactic radiotherapy in prediction models. Subsequently, these models can be used to revise mediastinal staging and follow-up strategies and specify the role of adjuvant systemic therapy following SABR [22,30,31,33,34]. In addition, more sensitive (mediastinal) staging procedures might improve staging accuracy and should be investigated. Possibilities include a staging 4D PET/CT or the combination of PET/CT and Dual Energy CT imaging (www.clinicaltrials.gov, NCT03146117) [35].

The retrospective nature of our study has a few limitations. A lack of (systematic) follow-up and the considering of death as a competing risk may have resulted in an underestimation of regional and distant failures: the (regional) disease status at time of death was not recorded if patients were lost to follow-up and OS data were retrieved from a national database. The 60 patients from the UHCGC (11% of the cohort) could not be analysed for (I)RR and DR. However, we believe it to be unlikely that inclusion of these patients in the IRR analyses would have changed our conclusions.

Almost seventy percent of patients were irradiated without histological proof of malignancy. This is quite common in clinical practice, as the risk of a CT-guided needle biopsy complication such as a pneumothorax and/or haemorrhage is considerable and unfortunate in frail, elderly patients with poor pulmonary function. Thus, often, these patients are being offered SABR without histological proof [36,37]. The inclusion of T2 and T3 tumours could have led to a higher rate of nodal involvement than if only T1 tumours had been included. The retrospective nature of the study entails a lack of standardization (e.g. missing information on the management of suspected lymph nodes with respect to biopsy and/or follow-up) and could have given rise to unknown confounding factors. Finally, we attempted to keep the measuring inconsistencies as low as possible by having only one researcher measure the MPDs and MTDs, nevertheless, slight inaccuracies cannot be excluded.

In conclusion, the presence, type and length of pleural contact as surrogate for visceral pleural invasion were not predictive for regional and distant recurrence in patients with early stage NSCLC treated with SABR in the current study. Further studies focussing on risk factors for occult nodal involvement, RR, distant metastases and mortality in early stage NSCLC treated with SABR are warranted for the development of risk adapted diagnostic, treatment and follow-up strategies as more younger, operable and fitter patients receive SABR.

Conflicts of interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2018.11.024.

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