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ORIGINAL ARTICLE

Effects of the recurrence pattern on patient survival following SABR for stage I lung cancer

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ABSTRACT

Background: Information on the effect of the recurrence pattern on survival for stage I lung cancer following stereotactic ablative radiotherapy (SABR) is limited.

Materials and Methods: The recurrence pattern was analyzed for 100 consecutive stage I non-small-cell lung cancer patients treated with SABR using predominantly 12 Gy × 4. Recurrences were classified as local, regional lymph nodes and distant. Distant recurrences included recurrences in the lung and outside the chest. Single lung recurrences were named solitary, if no other location was involved. Kaplan–Meier survival estimates were calculated for different locations of recurrence. Clinical and dosimetrical factors affecting survival were also analyzed.

Results: Median follow-up was 32 months (3–123), median age 70 years (49–95). In total, 31 patients had recurrences after a median 21 months (4–60): 5 local; 10 regional; 8 distant outside the chest; 25 non-local lung recurrences, of which 15 were single – 10 of which solitary – and 10 multiple lung nodules. Patients with a solitary lung recurrence had longer survival compared to local or distant recurrences ($p = .04$ each), and compared to multiple lung nodules ($p = .09$). 3-year local recurrence-free survival was 92%, disease-free survival 69% and overall survival 59%. On multivariate analysis, disease-free survival was associated with statin use ($p = .038$) and tumor location ($p = .035$). Smoking history predicted overall survival ($p < .0006$).

Conclusions: A total of 81% of recurrences involved the lungs. Patients with solitary lung recurrences/second primary lung cancers had the longest overall survival suggesting definitive treatment should be considered. The effects of statin use need to be explored further.

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Introduction

With longer follow-up data becoming available after stereotactic ablative radiotherapy (SABR) for early-stage lung cancer, recurrence patterns are increasingly being analyzed. Investigating the effect of different recurrence patterns on patient outcome is important to determine appropriate surveillance and treatment options at the time of recurrence. Excellent local control rates have repeatedly been demonstrated [1–3], but regional and distant recurrences require better characterization as well. Of particular interest in our study is the incidence and management of solitary lung recurrences or second primary lung cancers (SPLCs), which have been reported to occur at a rate of 2–5% per year [4]. The definition of single metachronous lung nodules as SLPC includes the presence of a different histological and genomic type on a histologic specimen, occurrence at least 2 years after tumor-free interval following first lung cancer, location in different lobes or contralateral lung among other factors [5]. Definitive treatment for SPLCs has been advocated, but mostly for surgically treated patients [5–8]. Little information exists on the outcome following diagnosis of SPLC in medically inoperable patients treated previously with SABR [4,9].

Various fractionation schedules are in clinical use for SABR of inoperable stage I non-small cell lung cancer (NSCLC). The best fractionation schedule is, however, unknown [1,10]. SABR using 12 Gy × 4 has more recently been investigated in prospective trials [2,11]. While this fractionation scheme has been in use for over 10 years [12], long term experience with more commonly used prescription methods is limited.

Various clinical and treatment-related factors have previously been investigated for their prediction of patient outcome. Older age [13], chronic obstructive pulmonary disease COPD)/pulmonary function [13], female gender [14], better performance [15], smaller tumors [3,9,13–17], adenocarcinoma [14], lower SUVmax [18] and tumor location in the upper lobes [19] have been associated with improved outcome. Higher tumor dose has been associated with better tumor control [3,9]. Also, commonly prescribed medications have been associated with cancer treatment outcomes. For example, metformin is currently investigated for its effect on lung cancer treated with radiotherapy [20]. Possible mechanisms for its anti-cancer activity include induction of apoptosis, reductions in the levels of circulating insulin, and activation of specific metabolic pathways [21]. ACE-inhibitors

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have been shown to increase the cancer risk for several tumors including lung cancer [22]. Preclinical pharmacologic and genetic studies suggest that ACE-Is may affect tumorigenesis through effects on angiogenesis and immunosurveillance by macrophage and T-cell lineages [23]. For statins, synergistic effects with radiotherapy through induction of apoptosis and inhibition of DNA repair have recently been described [24]. At present, none of these medications have been shown to influence the patient outcome following SABR for lung cancer.

The present single-institution review with a consistent treatment approach over >10 years investigates recurrence patterns and associated outcomes using a predominantly 12 Gy × 4 fractionation approach. Our study focuses on the outcome of patients with different recurrence patterns, particularly with solitary lung recurrences and SPLCs. Clinical and treatment factors predictive for patient survival are analyzed as well.

Material and methods

Patient population

This IRB-approved project includes all 100 consecutive patients with inoperable stage IA/IB NSCLC (T1-2a N0 M0, AJCC 7th edition) who were treated definitively with SABR at our institution between 2007 and 2016. After obtaining medical history including smoking history and a physical exam, comorbities and medications were recorded. Patients were staged with diagnostic CT chest and PET-CT, and underwent pulmonary function testing. Patients reporting neurological symptoms underwent brain imaging (preferably brain MRI) to exclude metastatic brain disease. Operability was determined by a multidisciplinary tumor board depending on various factors including general performance status, comorbidities including oxygen use, and pulmonary function tests. Patients with FEV-1 (forced expiratory volume in 1 s) <40% predicted and DLCO (diffusion capacity for carbon monoxide) <40% predicted were deemed medically inoperable. Depending on the tumor location, biopsies were obtained through endobronchial ultrasound (EBUS) or transthoracic CT-guided approach. Regional lymph nodes were biopsied with EBUS, if tumor involvement was suspected for lymph nodes with >1cm short-axis diameter and >3.5 maximum standardized uptake value (SUV_{max}) on PET-CT.

Treatment planning

All patients were positioned on individually molded vacuum bags with wing board and underwent treatment planning with free-breathing 4-dimensional computed tomography (4D CT) (Brilliance Big Bore, Philips Medical Systems, Andover, MA). Three additional CTs with active breathing control (ABC, Elekta, Stockholm, Sweden) and short breaks between the scans were obtained for tumor motion >1 cm on 4D CT. For treatment planning, internal gross tumor volumes (iGTV) were generated that were either based on the reconstructed maximum intensity projection (MIP) images from the free-breathing scans or on the three ABC scans. All 10 individual respiration phases of 4D CT scans were used for contouring for tumor locations next to structures with similar density such as the mediastinum and diaphragm. Planning target volumes (PTVs) were generated through 5 mm expansion of the iGTV in all directions. Treatment planning was performed on the 30% phase of the 4D CT or on one of the ABC scans using heterogeneity correction. Patients were treated with 3D conformal radiotherapy (3DCRT) until 5/2011(43 patients), then with IMRT until 12/2014 (34 patients), followed by VMAT since 2015 (23 patients). Dose was prescribed to the PTV covering isodose (typically 80% isodose). IGTV and PTV volumes and biologically effective prescription doses (BED_{10}, $\alpha/\beta = 10$ Gy) were calculated.

Treatment delivery and follow-up

Treatment was initiated after a median 7.5 weeks following diagnosis and was delivered every other day excluding weekends. Planar kilovoltage images and cone-beam CTs (CBCT) were used in all patients for image-guided tumor-based treatment set up according to a departmental protocol.

Patients were followed with diagnostic chest CT scans every 3 months for the first 2 years, then at 6-month intervals until 5 years, followed by annual scans. For equivocal findings on CT imaging, additional PET or other imaging and depending on the estimated risk, biopsies were obtained to rule out tumor recurrence. Recurrences were classified as local (in field), regional (hilar or mediastinal lymph nodes) and distant. Distant recurrences were subdivided into recurrences involving the lungs (outside treated field) and locations outside the chest. Lung recurrences were further divided into single or multiple lung tumors. If single lung recurrences were not associated with recurrences in other locations, these were called solitary lung recurrences.

Statistics

Local recurrence-free survival, disease-free survival and overall survival, as well as subgroup-specific overall survival rates for different recurrence patterns were calculated using the Kaplan–Meier method. The hypotheses of no difference in survival were tested using the log-rank test comparing solitary lung recurrence with other patterns of recurrence. Univariate and multivariate analyses to investigate prognostic factors for disease-free and overall survival were performed using logistic regression. Stepwise forward selection was used to build the models with significantly associated risk factors. Investigated factors included gender, age, race, Karnofsky index, body mass index (BMI, potentially worse outcome with larger BMI due to higher positioning uncertainty [25]), COPD, smoking history and pack years, medications (metformin, ACE-inhibitor, statins), tumor location (upper and middle lobes versus lower lobes), histology (adenocarcinoma versus squamous cell versus NSCLC without further differentiation), SUV_{max} on pretreatment PET scan, treatment technique, BED_{10} of the prescription dose, maximum BED_{10} of PTV, and PTV volume (Table 1). All analyses used the statistical software SAS (Analytical Software and

Table 1. Demographic, clinical and radiation treatment characteristics ($N = 100$).

Characteristics	No. (%) or Median (range/SD)
Age (years)	70 (49–95)
Sex	
Female/male	53/47
Race	
AA/Caucasian	43/57
KPS (%)	
≥80/60–70/≤50	45/52/3
BMI (kg/m^2)	25 (12–44)
COPD	
FEV-1/FVC < 70%	57
Smoking	
Never smoker	1
Pack years	49 (6–240)
Diabetes	
Present	20
Metformin	10
Statin use	
Present	50
ACE-I use	
Present	33
Tumor location	
Upper and middle lobe/lower lobe	62/38
Maximum tumor diameter (mm)	
In axial plane	18 (5–46)
Stage (AJCC 7th ed)	T1 96/T2 4
ITV (cm^3)	13.8 (0.7–70.3)
PTV (cm^3)	35.6 (5.8–135.9)
Pathology	
Adenoca/SCC/NSCLC	41/41/10
No biopsy	8
PET SUV_{max}	6.1 (1.1–30)
Fractionation	
12 Gy × 4	82
Other	18
BED_{10} $D_{prescribed}$ (Gy)	105.6 (72–180)
BED_{10} PTV D_{min} (Gy)	99.5 (29.8–208.5)
BED_{10} PTV D_{mean} (Gy)	124.0 (79.7–235.0)
BED_{10} PTV D_{max} (Gy)	144.0 (83.8–261.9)

AA: African American; ACE-I: angiotensin converting enzyme inhibitor; adenoca: adenocarcinoma; AJCC: American Joint Committee on Cancer; BED_{10}: biologically effective dose for $\alpha/\beta = 10$ Gy; BMI: body mass index; COPD: chronic obstructive pulmonary disease; $D_{max/mean/min/prescribed}$: maximum/mean/minimum/prescribed dose; FEV-1: forced expiratory volume in 1 s; FVC: forced vital capacity; ITV: internal target volume; KPS: Karnofsky performance status; N: number; NSCLC: non-small cell lung cancer; PET: positron emission tomography; PTV: planning target volume; SCC: squamous cell cancer; SD: standard deviation; SUV_{max}: maximum standard uptake value.

Solutions, https://www.sas.com) v9.4 and R (The R Project for Statistical Computing, https://r-project.org) v3.3.

Results

Biopsies revealed squamous cell carcinoma in 41 (41%), adenocarcinoma in 41 (41%), and NSCLCs without further differentiation in 10 (10%) patients. Biopsies were not deemed feasible in 8/100 patients at the time of initial diagnosis due to the presumed high risk for complications, such as pneumothorax. The most common fractionation scheme was 12 Gy × 4 in 82 patients. Other prescriptions ranged from 8 Gy × 5 to 20 Gy × 3. IGTV and PTV volumes and BED_{10} doses for iGTV and PTV are shown in Table 1. Prescribed doses resulted in median (range) PTV_{min} doses of 46.3 Gy (21.9–65.5 Gy), PTV_{mean} doses of 53.3 Gy (42.9–70.3 Gy), and PTV_{max} doses of 59.0 Gy (44.4–76.4 Gy). The median PTV coverage by $D_{prescribed}$ was 99% (range 95–100%). See Table 1 for further patient characteristics.

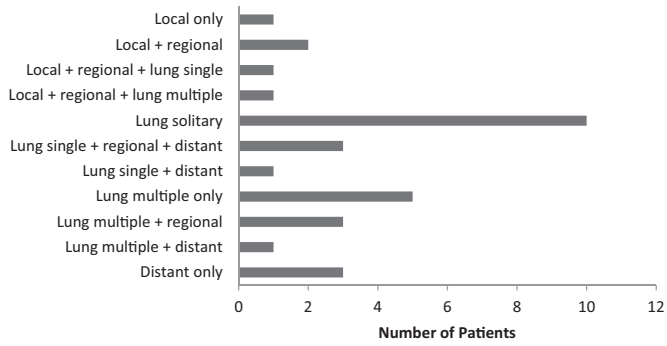

Figure 1. Distribution of tumor recurrences per location for all 31 patients with recurrences.

Recurrence pattern

Median follow-up was 32 months (mo) (3–123 mo). 31 (31%) patients developed recurrences after a median 21 mo (4–60 mo); see Figure 1 for information on the distribution of recurrences. Recurrences were confirmed with biopsy in eight of 31 patients (26%).

Local recurrences: Five (5%) patients developed local recurrences after 16 mo (10–31 mo). Of the five patients with local recurrence, two patients underwent a biopsy. Four of the five patients had also other locations of tumor recurrence (Figure 1). Patients with local recurrences underwent repeated radiotherapy (1, 20%), radiofrequency ablation (1, 20%), and palliative symptom management (3, 60%).

Solitary lung recurrences: Of all recurrences, 10/31 (32%) patients had a solitary lung nodule only and had a median time to recurrence of 31 mo (4–60 mo) Seven of the 10 (70%) patients developed a solitary lung tumor after >2 years from initial therapy. Biopsy of the solitary lung recurrence was performed in three (30%) patients (2× different histology), but in none of the patients recurring less than 2 years after initial therapy. The location of recurrence for the solitary recurrences was contralateral lung in seven (70%), different lobe in two (20%) and same lobe outside the initial radiotherapy field in one (10%) patient. As not all patients with solitary lung recurrence had a 2-year interval or biopsy-confirmed histology different from the original tumor, the presence of SPLC per existing definitions can only be claimed for seven (70%) patients [5]. Of the 10 patients with solitary lung recurrence, eight (80%) patients underwent SABR and all had local control during follow-up, one (10%) patient with recurrence <2 years from initial therapy was offered systemic therapy due to concern for increased toxicity given previous SABR treatment and developed multiple lung metastases, one (10%) patient also with solitary recurrence <2 years from initial therapy was offered palliative management due to poor performance and died shortly afterwards.

Regional, lung and distant recurrences: Regional recurrences were diagnosed in 10 (10%) patients simultaneously with local or other lung recurrences after 12 months (5–51 mo). Eight (8%) patients had distant metastases outside the lung after 10 months (4–22 mo) involving the brain (3), liver (2), adrenal gland (1) and bone (2). In addition, to the 10 (10%) patients with solitary lung recurrences, 15 (15%) other patients recurred in the lung outside the treated

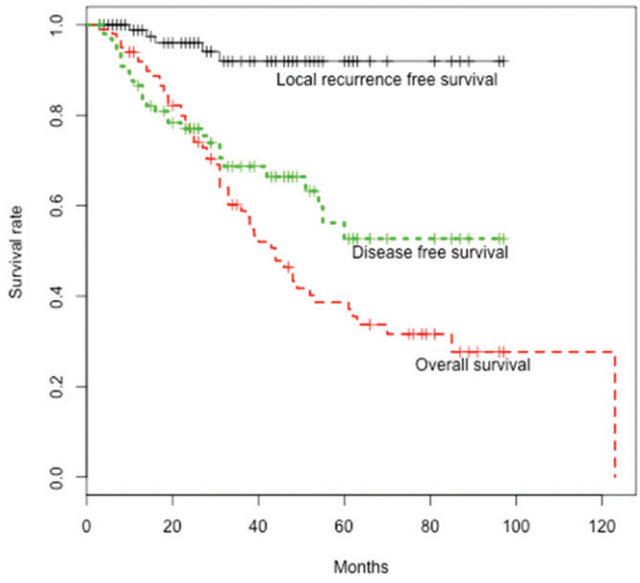

Figure 2. Kaplan–Meier curves for local recurrence-free survival, disease-free survival and overall survival ($N = 100$). 3-year local recurrence-free survival was 92% (95%CI 0.85–0.99), disease free survival 69% (95% CI 0.59–0.80) and overall survival 59% (95%CI 0.49–0.70). Survival data were censored for loss to follow up and last follow-up without recurrence.

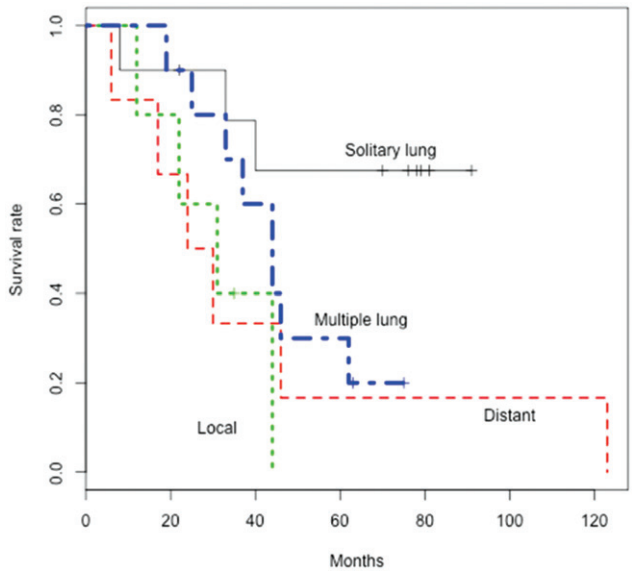

Figure 3. Overall survival depending on the recurrence pattern ($N = 31$). Solitary lung recurrence resulted in longer 3-year survival compared to local or distant recurrences ($p = .04$ each), and compared to multiple lung recurrences ($p = .09$).

volume of which 5 (5%) had a single non-solitary lung nodule after 24 mo (4–60 mo), and 10 (10%) had multiple lung nodules after 8 mo (5–51 mo). Patients with regional, non-solitary lung or distant recurrences underwent further radiotherapy (2, 13%), systemic treatment (9, 56%), or palliative management (5, 31%).

Survival

Kaplan–Meier curves show a 3-year local recurrence-free survival of 92% (95%CI 0.85–0.99), disease-free survival of 69% (95% CI 0.59–0.80) and overall survival of 59% (95%CI 0.49–0.70) (Figure 2). Patients with a solitary lung recurrence had longer 3-year survival (79%, 95% CI 0.564–1.0) compared to patients with local (40%, 95% CI 0.137–1.0) or distant (33%, 95% CI 0.108–1.0) recurrences ($p = .04$ each), and compared to patients with multiple lung recurrences (70%, 95% CI 0.467–1.0; $p = .09$). With longer observation, patients with solitary recurrences showed even larger survival advantage (Figure 3).

Risk factors for disease-free and overall survival

On univariate and multivariate analyses, not taking statins and having a lower lobe tumor predicted for worse disease-free survival (Table 2). In addition, older age was associated with increased disease-free survival on univariate analysis. Regarding overall survival, pack-years smoking history was associated with higher risk on univariate and multivariate analyses. None of the other factors listed under 'Statistics' section were found significant for predicting disease-free or overall survival.

Table 2. Significant parameters on univariate and multivariate analyses.

Characteristics	DFS UVA	DFS MVA	OS UVA	OS MVA
Age	$p = .046$ HR 0.96			
Pack years smoking			$p < .0001$ HR 1.013	$p < .0001$ HR 1.018
No statin use	$p = .043$ HR 2.11	$p = .016$ HR 2.58		
Tumor location lower lobe	$p = .052$ HR 2.02	$p = .025$ HR 2.42		

Patients without statins and tumors in the lower lobes had worse disease-free survival on both univariate and multivariate analyses. Younger age improved disease-free survival. Longer smoking history predicted worse overall survival. BED: biologically effective dose; DFS: disease free survival; D_{max}: maximum dose; MVA: multivariate analysis; OS: overall survival; PTV: planning target volume; UVA: univariate analysis.

Discussion

Local control and survival rates with 12 Gy × 4 fractionation schedule

Standard fractionation schedules for lung SABR in the US were established initially based on the RTOG 0236 protocol using 3 fractions of 18 Gy [1]. A recent analysis of dose prescription patterns shows that its use has been declining [10]. Fractionation schemes with lower doses per fraction were investigated when a prescription BED_{10} dose of at least 100 Gy was identified as the minimum required dose for tumor control more than 10 years ago [26,27]. Reports from Japan were the first to report local control results using 12 Gy × 4 [12,28]. In the meantime, this fractionation scheme has been more commonly used, e.g., as the standard arm in RTOG 0915 and in the SABR arm of the TROG 09.02 Chisel study [2,11]. Outcomes with this fractionation have also been reported in several single-institution reports [16].

Local control rates >90% with SABR are frequently reported. Local control rates in our study compare well to other studies using 12 Gy × 4 [2,17,29–32]. Reported local

control rates are often lower in reports where dose is prescribed to the isocenter rather than the PTV-covering isodose line [26,28], or to higher isodose lines resulting in more homogeneous dose delivery [3,33]. Nagata et al. [12] observed a 3-year local control rate of 87.3% for inoperable patients and 3-year overall survival of 59.9% compared to 92% and 59%, respectively, in our cohort with similar median tumor diameters of about 2 cm. As for recent randomized studies, in the Chisel study 2-year local control rate was 89% in the SABR arm where 87% of patients were treated with 12 Gy × 4 [11]. In RTOG 0915, the 5-year local failure rate for 12 Gy × 4 was 6.8% [2].

Lung recurrences and SPLC

Time to diagnosis: Solitary lung recurrences or SPLCs have been the focus of recent interest. Similar to our study, the median time to diagnosis of metachronous solitary lung nodules was longer than for local, regional or distant recurrences in other reports. Both Sun et al. [9] with a median follow-up of >7 years and Verstegen et al. [4] with a median follow-up of 52 months reported median time to diagnosis of SPLC of 35 months and 34 months, respectively, which is similar to 31 months in our study. These findings indicate the need for prolonged surveillance [4,9,14].

Incidence: The observed SPLC rates varied between 9.2% and 18.5% [4,9], likely due to different follow-up times. Spratt et al. [14] reported a 5.2% SPLC rate after a median follow-up of 16.5 months. Our solitary lung recurrence rate of 10% agrees well with these reports. Overall, SPLC incidence rates of about 2-5% per year have been reported [4,9]. *Treatment:* Treatment of SPLC is typically aggressive. In our study, patients with solitary lung nodules as first recurrence received salvage treatment, most of them with a second course of SABR. Salvage treatment has been reported in about 80% of patients with SPLC [4,14] *Outcome:* Outcomes after SABR for SPLC have been reported to be similar to the outcomes of initial lung cancer treated with SABR or surgery. Griffioen et al. [34] reported 3-year survival rates of 60% for SABR of SPLC following initial surgical treatment. 3-year survival was 79% for patients with solitary lung tumor recurrence/SPLC in our study. Median overall survival was 23 months in the Verstegen et al. [4] study, and Sun et al. [9] reported a median survival time of 13.1 months until either death or last follow-up.

From the practical perspective, a curative treatment approach appears justified in these patients, particularly if solitary lung nodules appear more than 2 years after initial treatment [5]. This recommendation cannot be applied to recurrences earlier than 2 years from treatment, as two of our patients with early solitary recurrence either deceased or developed multiple lung metastases.

Regional and distant recurrences

Despite excellent local control, recurrences occur frequently, in about one-third of our patients during the observed follow-up period. The number of recurrences including regional recurrences accumulates with longer observation [2,14,35]. Similar to our study, where 10% of patients were diagnosed with lymph node recurrences, regional recurrence rates in prospective, large retrospective and review studies range between 4 and 20% [9,11,36,37]. Regional lymph node control rates at 2-7 years have been reported as 80–90% [38].

Distant recurrence rates typically by far exceed local and regional recurrence rates and have been reported to be between 10% and >40%, with increasing rates over time [2,9,11,14,36,38]. Distant metastases including lung occurred in 28% of our patients, whereas distant metastases outside the lungs were observed in only 8%. With 25/31 (81%) the vast majority of recurrences involved the lung outside the treatment area either as single or multiple lung tumor manifestations. Combining all local, lung and regional recurrences in our cohort, chest CTs would have identified the presence of recurrences in 28/31(90%) of our patients.

Clinical and technical factors predictive of disease-free and overall survival

Given the prevalence of multiple comorbidities in this cohort of inoperable stage I lung cancer patients, survival may also be affected by demographic and clinical factors such as underlying lung disease and the smoking situation. In addition, various medications are being investigated for potential effects on cancer patient outcomes such as medications for diabetes, hypercholesterolemia and blood pressure treatment [13,20,22,24]. The identification of factors that influence patient survival is important as some of these factors may be modified to the patients' benefit.

From the factors investigated in our study, patients not taking statins were found to have poorer disease-free survival. While statins have been found to reduce radiotherapy related toxicity [39,40], little is known about the effects of statins as radiation sensitizers [24,41]. Further investigation appears warranted. The observed effect of smoking on overall survival is well known [42]. Given the competing risk of non-cancer, but also smoking-related factors on overall survival such as COPD and vascular disease, the effects of smoking history on overall survival are not surprising [43]. Interestingly, smoking was identified as a risk factor for developing SPLC by Spratt et al. [14]. While none of the never smokers developed SPLC, 15% of the continuing smokers had SLPC. These observations again support the recommendation for smoking cessation for all lung cancer patients to improve survival and reduce secondary cancer risk.

The moderate cohort size in this investigation is a limitation; however, inclusion of all treated patients in this single-center analysis, homogeneous treatment and median follow-up of >2.5 years provide reliable outcome data. Ideally, both initial diagnosis and recurrence should be confirmed by biopsy. Patients ineligible for biopsies used supplemental oxygen continuously, had large emphysematous bullae and/or tumor locations close to lobe fissures or close to large vessels. History of previous pneumothorax also limited further biopsies in the lung. Multidisciplinary imaging review of multimodality imaging including CT chest and PET-CT

through fellowship-trained chest radiologists and longitudinal observation of chest pathologies showing tumor growth over time were performed to limit the risk of misdiagnosis. In addition, smoking history and tumor shape such as speculations were included in the risk assessment for lung cancer diagnosis in the absence of a biopsy. Recurrences were often not biopsy-confirmed due to similar reasons as for primary diagnosis and due to obvious tumor spread including regional lymph nodes, new lung metastases or distant metastases on imaging studies.

Conclusion

A mostly 12 Gy × 4 fractionation scheme results in excellent local control. 25/31 recurrences involved the lung excluding local recurrences. Patients with solitary lung nodules/SPLC fared better than patients with other recurrences, and have significantly improved survival compared to patients with local or distant recurrence. Salvage treatment options should be considered for these patients. The potential benefits of statin use need to be explored further.

Disclosure statement

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References

[1] Timmerman R, Paulus R, Galvin J, et al. Stereotactic body radiation therapy for inoperable early stage lung cancer. JAMA. 2010; 303:1070–1076.

[2] Videtic GM, Paulus R, Singh AK, et al. Long-term follow-up on NRG oncology RTOG 0915 (NCCTG N0927): a randomized phase 2 study comparing 2 stereotactic body radiation therapy schedules for medically inoperable patients with stage i peripheral non-small cell lung cancer. Int J Radiat Oncol Biol Phys. 2019;103: 1077–1084.

[3] Zhao L, Zhou S, Balter P, et al. Planning target volume D95 and mean dose should be considered for optimal local control for stereotactic ablative radiation therapy. Int J Radiat Oncol Biol Phys. 2016;95:1226–1235.

[4] Verstegen NE, Lagerwaard FJ, Hashemi SM, et al. Patterns of disease recurrence after SABR for early stage non-small-cell lung cancer: optimizing follow-up schedules for salvage therapy. J Thorac Oncol. 2015;10:1195–1200.

[5] Martini N, Bains MS, Burt ME, et al. Incidence of local recurrence and second primary tumors in resected stage I lung cancer. J Thorac Cardiovasc Surg. 1995;109:120–129.

[6] Johnson BE. Second lung cancers in patients after treatment for aninitial lung cancer. J Natl Cancer Inst. 1998;90:1335–1345.

[7] Lou F, Huang J, Sima CS, et al. Patterns of recurrence and second primary lung cancer in early-stage lung cancer survivors followed with routine computed tomography surveillance. J Thorac Cardiovasc Surg. 2013;145:75–81.

[8] Lamont JP, Kakuda JT, Smith D, et al. Systematic postoperative radiologic follow-up in patients with nonsmall cell lung cancer for detecting second primary lung cancer in stage IA. Arch Surg. 2002;137:935–938.

[9] Sun B, Brooks ED, Komaki RU, et al. 7-year follow-up after stereotactic ablative radiotherapy for patients with stage I non-small cell lung cancer: Results of a phase 2 clinical trial. Cancer. 2017; 123:3031–3039.

[10] Corso CD, Park HS, Moreno AC, et al. Stage I lung SBRT clinical practice patterns. Am J Clin Oncol. 2017;40:358–361.

[11] Ball D, Mai GT, Vinod S, et al. 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. Lancet Oncol. 2019;20:494–503.

[12] Nagata Y, Hiraoka M, Shibata T, et al. Prospective trial of stereotactic body radiation therapy for both operable and inoperable T1N0M0 non-small cell lung cancer: Japan Clinical oncology group study JCOG0403. Int J Radiat Oncol Biol Phys. 2015;93: 989–996.

[13] Eguchi T, Bains S, Lee MC, et al. Impact of increasing age on cause-specific mortality and morbidity in patients with stage I non-small-cell lung cancer: a competing risks analysis. J Clin Oncol. 2017;35:281–290.

[14] Spratt DE, Wu AJ, Adeseye V, et al. Recurrence Patterns and Second Primary Lung Cancers After Stereotactic Body Radiation Therapy for Early-Stage Non-Small-Cell Lung Cancer: Implications for Surveillance. Clin Lung Cancer. 2016;17:177–183.

[15] Van den Berg LL, Klinkenberg TJ, Groen HJ, et al. Patterns of recurrence and survival after surgery or stereotactic radiotherapy for early stage NSCLC. J Thorac Oncol. 2015;10:826–831.

[16] Allibhai Z, Taremi M, Bezjak A, et al. The impact of tumor size on outcomes after stereotactic body radiation therapy for medically inoperable early-stage non-small cell lung cancer. Int J Radiat Oncol Biol Phys. 2013;87:1064–1070.

[17] Nath SK, Sandhu AP, Kim D, et al. Locoregional and distant failure following image-guided stereotactic body radiation for early-stage primary lung cancer. Radiother Oncol. 2011;99:12–17.

[18] Takeda A, Yokosuka N, Ohashi T, et al. The maximum standardized uptake value (SUVmax) on FDG-PET is a strong predictor of local recurrence for localized non-small-cell lung cancer after stereotactic body radiotherapy (SBRT). Radiother Oncol. 2011;101: 291–297.

[19] Lee HW, Lee C-H, Park YS. Location of stage I–III non-small cell lung cancer and survival rate: Systematic review and meta-analysis. Thorac Cancer. 2018;9:1614–1622.

[20] Chae YK, Arya A, Malecek M-K, et al. Repurposing metformin for cancer treatment: current clinical studies. Oncotarget. 2016;7: 40767–40780.

[21] Chuang M-C, Yang Y-H, Tsai Y-H, et al. Survival benefit associated with metformin use in inoperable non-small cell lung cancer patients with diabetes: a population-based retrospective cohort study. PLoS One. 2018;13:e0191129.

[22] Hicks BM, Filion KB, Yin H, et al. Angiotensin converting enzyme inhibitors and risk of lung cancer: population based cohort study. BMJ. 2018;363:k4209

[23] Morris ZS, Saha S, Magnuson WJ, et al. Increased tumor response to neoadjuvant therapy among rectal cancer patients taking angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. Cancer. 2016;122:2487–2495.

[24] Chen YA, Shih HW, Lin YC, et al. Simvastatin sensitizes radioresistant prostate cancer cells by compromising DNA double-strand break repair. Front Pharmacol. 2018;9:600

[25] Zhao J, Zhang M, Zhai F, et al. Setup errors in radiation therapy for thoracic tumor patients of different body mass index. J Appl Clin Med Phys. 2018; 19:27–31.

[26] 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:S94–S100.

[27] Wulf J, Baier K, Mueller G, et al. Dose-response in stereotactic irradiation of lung tumors. Radiother Oncol. 2005;77:83–87.
[28] Nagata Y, Takayama K, Matsuo Y, et al. Clinical outcomes of a phase I/II study of 48 Gy of stereotactic body radiotherapy in 4 fractions for primary lung cancer using a stereotactic body frame. Int J Radiat Oncol Biol Phys. 2005;63:1427–1431.
[29] Navarria P, Ascolese AM, Mancosu P, et al. Volumetric modulated arc therapy with flattening filter free (FFF) beams for stereotactic body radiation therapy (SBRT) in patients with medically inoperable early stage non small cell lung cancer (NSCLC). Radiother Oncol. 2013;107:414–418.
[30] Taremi M, Hope A, Dahele M, et al. Stereotactic body radiotherapy for medically inoperable lung cancer: prospective, single-center study of 108 consecutive patients. Int J Radiat Oncol Biol Phys. 2012;82:967–973.
[31] Thibault I, Poon I, Yeung L, et al. Predictive factors for local control in primary and metastatic lung tumours after four to five fraction stereotactic ablative body radiotherapy: a single institution's comprehensive experience. Clin Oncol (R Coll Radiol). 2014;26:713–719.
[32] Tsurugai Y, Kozuka T, Ishizuka N, et al. Relationship between the consolidation to maximum tumor diameter ratio and outcomes following stereotactic body radiotherapy for stage I non-small-cell lung cancer. Lung Cancer. 2016;92:47–52.
[33] Stephans KL, Woody NM, Reddy CA, et al. Tumor Control and Toxicity for Common Stereotactic Body Radiation Therapy Dose-Fractionation Regimens in Stage I Non-Small Cell Lung Cancer. Int J Radiat Oncol Biol Phys. 2018;100:462–469.
[34] Griffioen GH, Lagerwaard FJ, Haasbeek CJ, et al. A brief report on outcomes of stereotactic ablative radiotherapy for a second primary lung cancer: evidence in support of routine CT surveillance. J Thorac Oncol. 2014;9:1222–1225.
[35] Grills IS, Hope AJ, Guckenberger M, et al. A collaborative analysis of stereotactic lung radiotherapy outcomes for early-stage non-small-cell lung cancer using daily online cone-beam computed tomography image-guided radiotherapy. J Thorac Oncol. 2012;7:1382–1393.
[36] Senthi S, Lagerwaard FJ, Haasbeek CJ, et al. Patterns of disease recurrence after stereotactic ablative radiotherapy for early stage non-small-cell lung cancer: a retrospective analysis. Lancet Oncol. 2012;13:802–809.
[37] Wink KCJ, van Baardwijk A, Troost EGC, et al. Nodal recurrence after stereotactic body radiotherapy for early stage non-small cell lung cancer: Incidence and proposed risk factors. Cancer Treat Rev. 2017;56:8–15.
[38] Bezjak A, Paulus R, Gaspar LE, et al. Safety and efficacy of a five-fraction stereotactic body radiotherapy schedule for centrally located non-small-cell lung cancer: NRG oncology/RTOG 0813 Trial. J Clin Oncol. 2019;37:1316–1325.
[39] Anscher MS, Chang MG, Moghanaki D, et al. Lovastatin may reduce the risk of erectile dysfunction following radiation therapy for prostate cancer. Acta Oncol. 2016;55:1500–1502.
[40] Vasiljevic D, Arnold C, Neuman D, et al. Occurrence of pneumonitis following radiotherapy of breast cancer - A prospective study. Strahlenther Onkol. 2018;194:520–532.
[41] Sanli T, Liu C, Rashid A, et al. Lovastatin sensitizes lung cancer cells to ionizing radiation: modulation of molecular pathways of radioresistance and tumor suppression. J Thorac Oncol. 2011;6:439–450.
[42] Christensen CH, Rostron B, Cosgrove C, et al. Association of Cigarette, Cigar, and Pipe Use With Mortality Risk in the US Population. JAMA Intern Med. 2018;178:469–476.
[43] Shah S, Blanchette CM, Coyle JC, et al. Survival associated with chronic obstructive pulmonary disease among SEER-Medicare beneficiaries with non-small-cell lung cancer. COPD. 2019;14:893–903.