Patterns of disease recurrence after stereotactic ablative radiotherapy for early stage non-small-cell lung cancer: A retrospective analysis

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Patterns of disease recurrence after stereotactic ablative radiotherapy for early stage non-small-cell lung cancer: a retrospective analysis

Sashendra Senthi, Frank J Lagerwaard, Cornelis J A Haasbeek, Ben J Slotman, Suresh Senan

Summary

Background Stereotactic ablative radiotherapy (SABR) is increasingly used in the treatment of medically inoperable early stage non-small-cell lung cancer (NSCLC). Because patterns of late disease recurrence after SABR are not well characterised, we aimed to assess these outcomes in a cohort of patients with NSCLC.

Methods Patients with ¹⁸F-fluorodeoxyglucose (¹⁸F-FDG)-PET confirmed stage 1–2 NSCLC who were treated with SABR at the VU University Medical Center (Amsterdam, Netherlands) were identified from an institutional database. SABR doses were 54–60 Gy, delivered in three to eight once-daily fractions, depending on tumour size and location. Clinical follow-up and CT scans were done at 3, 6, and 12 months, then yearly thereafter. ¹⁸F-FDG-PET restaging was only done when clinically indicated. Initial sites of recurrence were classified as local, regional, and distant, and were differentiated from second primary tumours in the lung at multidisciplinary tumour board review.

Findings Between April 4, 2003, and Dec 5, 2011, 676 patients were treated with SABR and were eligible for assessment of recurrence. The median follow-up was 32·9 months (IQR 14·9–50·9 months). 124 (18%) of 676 patients had disease recurrence. Actuarial 2-year rates of local, regional, and distant recurrence were 4·9% (95% CI 2·7–7·1), 7·8% (5·3–10·3), and 14·7% (11·4–18·0), respectively. Corresponding 5-year rates were 10·5% (95% CI 6·4–14·6), 12·7% (8·4–17·0), and 19·9% (14·9–24·6), respectively. Of the 124 recurrences, 82 (66%) were distant recurrences and 57 (46%) were isolated distant recurrences. Isolated locoregional recurrences occurred in the remaining 42 patients with disease recurrence (34%). 35 (83%) of whom did not develop subsequent distant recurrence. The median times to local, regional, and distant recurrence were 14·9 months (95% CI 11·4–18·4), 13·1 months (7·9–18·3), and 9·6 months (6·8–12·4), respectively. New pulmonary lesions characterised as second primary tumours in the lung developed in 42 (6%) of 676 patients at a median of 18·0 months (95% CI 12·5–23·5) after SABR.

Interpretation Late recurrences after SABR are infrequent and two distinct patterns account for most cases. The predominant pattern is out-of-field, isolated distant recurrence presenting early, despite initial PET staging. A third of patients develop isolated locoregional recurrence; for these patients standardised follow-up is important to ensure that appropriate salvage treatments are considered.

Funding None.

Introduction Surgery is regarded as the standard of care for early stage non-small-cell lung cancer (NSCLC).¹ Patients who are medically inoperable and receiving either no treatment or conventional radiotherapy are significantly less likely to survive than are those who receive surgery.¹⁻³ Local recurrences at the primary tumour site in up to 50% of patients might be responsible for this low survival rate.¹ Stereotactic ablative radiotherapy (SABR), or stereotactic body radiotherapy, is a form of high-precision delivery of treatment that represents the culmination of multiple technological advancements in delivery of radiation.² SABR involves the use of multiple conformal radiation beams that deliver high doses of radiation and that are individually tailored to avoid radiosensitive organs in the proximity of the tumour. Prospective multicentre studies have reported 3-year local control rates in excess of 90%.⁶ This local control has translated into a survival advantage over conventional radiotherapy,⁷ which has led to SABR being increasingly used for early stage NSCLC in Japan, the Netherlands, and the USA.⁸⁻¹⁰ The availability of SABR in the outpatient setting, and the ability to complete treatment in a limited number of fractions, has increased the use of curative treatments in elderly patients,¹¹ who represent an increasing proportion of the global lung cancer burden.¹²⁻¹⁴ Because of the increase in use of SABR, there is a need for data on patterns of recurrence to guide care after treatment. We aimed to assess these outcomes in a cohort of patients with NSCLC.
Methods

Patient population

Patients with stage 1–2 NSCLC (American Joint Committee on Cancer [AJCC] sixth edition T1–2N0M0) who were referred from 70 hospitals to the VU University Medical Center (Amsterdam, Netherlands) for SABR treatment were included in the study. Details of baseline characteristics, treatment, and follow-up findings were entered prospectively into an institutional database. Patients with double lung tumours, other synchronous malignancies, and those without ¹⁸F-fluorodeoxyglucose (¹⁸F-FDG)-PET staging were excluded.

In the Netherlands, retrospective studies of patient records, such as the one undertaken in this study, do not fall under the scope of the Medical Research Involving Human Subjects Act. This study is therefore exempt from medical ethics review.

Procedures

All but the first six patients (for whom the technology was not available at the time) had a planning four-dimensional (4D) CT scan, with patients breathing freely without respiratory coaching or rigid immobilisation. Tumour position was assessed in all phases of the 4D CT scans, which enabled individualised definition of an internal target volume encompassing all respiratory motion. For the six patients without a planning 4D CT, multiple standard planning CT scans were taken and co-registered to generate an internal target volume. An isotropic margin of 3–5 mm was used to create the planning target volume (PTV).

During the study period, two SABR planning and delivery techniques were used. Initially, a fixed beam technique using seven to 12 non-coplanar beams was used. Since 2008, a volumetric intensity-modulated arc technique has been used.18 Because this technique uses a more accurate planning algorithm, the dose delivered per fraction and the PTV margins were adapted to maintain equivalent biologically effective doses. Radiotherapy plans were optimised to minimise the dose given close to radiosensitive organs at risk, including the chest wall, heart, mediastinum, and hilus.19 SABR fractionation was risk adapted and depended on tumour size and location.20 Three fractions of either 18 or 20 Gy were delivered for T1 tumours, five fractions of either 11 or 12 Gy for T2 tumours or T1 tumours with broad chest wall contact, and eight fractions of 7·5 Gy for tumours adjacent to the heart, hilus, or mediastinum. Doses were prescribed to the 80% isodose encompassing the PTV, which resulted in biologically effective doses of at least 151·2 Gy, 115·5 Gy, and 105 Gy for the three, five, and eight fraction schedules, respectively.

Clinical follow-up and CT scans were done at 3, 6, and 12 months, then at yearly intervals. Follow-up contrast-enhanced CT scans of the lower neck, thorax, and upper abdomen, including the liver and adrenals, were routinely undertaken. Routine imaging of the brain was done. ¹⁸F-FDG-PET scans were only done for restaging if this had clinical consequences and potential for subsequent treatment. Recurrences were defined as local, with failure in or adjacent to the PTV; regional, with failure in the ipsilateral hilus, mediastinum, or supraclavicular fossa; or distant, with failure in other organs at risk or bone.

### Table 1: Patient demographics and tumour characteristics

<table>
<thead>
<tr>
<th>Patients (n=676)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>409 (61%)</td>
</tr>
<tr>
<td>Women</td>
<td>267 (39%)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>73 (47–92)</td>
</tr>
<tr>
<td>Past or present smoker</td>
<td>646 (96%)</td>
</tr>
<tr>
<td>TNM¹⁶</td>
<td></td>
</tr>
<tr>
<td>T1N0M0</td>
<td>379 (55%)</td>
</tr>
<tr>
<td>T2N0M0</td>
<td>297 (44%)</td>
</tr>
<tr>
<td>SABR indication</td>
<td></td>
</tr>
<tr>
<td>General state</td>
<td>22 (3%)</td>
</tr>
<tr>
<td>Pulmonary insufficiency</td>
<td>237 (35%)</td>
</tr>
<tr>
<td>Cardiac insufficiency</td>
<td>99 (15%)</td>
</tr>
<tr>
<td>Previous chemoradiation</td>
<td>7 (1%)</td>
</tr>
<tr>
<td>Previous lung surgery</td>
<td>23 (3%)</td>
</tr>
<tr>
<td>Other comorbidity</td>
<td>81 (12%)</td>
</tr>
<tr>
<td>Potentially operable*</td>
<td>207 (31%)</td>
</tr>
<tr>
<td>Gold classification†‡</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>138 (20%)</td>
</tr>
<tr>
<td>1</td>
<td>89 (13%)</td>
</tr>
<tr>
<td>2</td>
<td>233 (33%)</td>
</tr>
<tr>
<td>3</td>
<td>168 (25%)</td>
</tr>
<tr>
<td>4</td>
<td>54 (8%)</td>
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<tr>
<td>ECOG performance status§</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>75 (11%)</td>
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<tr>
<td>1</td>
<td>349 (52%)</td>
</tr>
<tr>
<td>2</td>
<td>218 (32%)</td>
</tr>
<tr>
<td>3</td>
<td>31 (5%)</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
</tr>
<tr>
<td>Not attained</td>
<td>441 (65%)</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>78/235 (33%)</td>
</tr>
<tr>
<td>Bronchoalveolar carcinoma</td>
<td>2/235 (1%)</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>82/235 (35%)</td>
</tr>
<tr>
<td>NSCLC—not specified</td>
<td>73/235 (31%)</td>
</tr>
<tr>
<td>¹⁸F-FDG-PET staging done</td>
<td>6/6 (100%)</td>
</tr>
<tr>
<td>SABR delivery technique</td>
<td></td>
</tr>
<tr>
<td>Fixed beam</td>
<td>413 (61%)</td>
</tr>
<tr>
<td>Arc</td>
<td>261 (39%)</td>
</tr>
<tr>
<td>Number of fractions</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>218 (24%)</td>
</tr>
<tr>
<td>5</td>
<td>296 (44%)</td>
</tr>
<tr>
<td>8</td>
<td>152 (22%)</td>
</tr>
</tbody>
</table>

Data are number (%), median (range), or n/N (%). SABR=stereotactic ablative radiotherapy. ECOG=Eastern Cooperative Oncology Group. NSCLC=non-small-cell lung cancer. ¹⁸F-FDG=¹⁸F-fluorodeoxyglucose. *As defined previously using objective physiological criteria. †Chronic obstructive pulmonary disease staging as defined by the Global Initiative for Chronic Obstructive Lung Disease. ‡Data missing for four patients. §Data missing for one patient. ¶Percentage reported is of those in whom a histological diagnosis was attained.

For more on the Global Initiative for Chronic Obstructive Lung Disease see http://www.goldcopd.org
or distant, with failure at other sites. Recurrence was diagnosed and differentiated from second primary lung tumours by a multidisciplinary tumour board (MDT) review of available imaging and pathology results. Several aspects were considered for differentiating second primary tumours from local recurrences, including the interval between the occurrence of the first and second primary tumours and the location of the new lesion in relation to the SABR treatment plan. The first evidence of disease failure on imaging was used to define the sites and time of initial recurrence. Additional disease sites found on subsequent imaging within 3 months of this event were also defined as initial recurrences to ensure that delays in imaging did not bias the rates of initial recurrence. Additional disease sites identified after 3 months were defined as subsequent recurrences.

**Statistical analysis**

We used descriptive statistics for crude recurrence outcomes. Time to recurrence was calculated from the first SABR treatment. Survival, disease-specific survival, and time to recurrence outcomes were estimated using the Kaplan-Meier method. Median follow-up was assessed using the reverse Kaplan-Meier method. All statistical analyses were two-sided, with p values of 0·05 or less deemed statistically significant, and were done using SPSS version 18.0.

**Role of the funding source**

There was no funding source for this study. All authors had full access to all the data in the study and the corresponding author (FJL) had final responsibility for the decision to submit for publication.

**Results**

Between April 4, 2003, and Dec 5, 2011, 919 patients were treated with SABR. After excluding patients with double lung tumours (n=82), other synchronous malignancies (n=157), and those without ¹⁸F-FDG-PET staging (n=4), 676 patients remained eligible for assessment of patterns of recurrence. Table 1 summarises patient and tumour characteristics of all 676 patients. The median age was 73 years (range 47–92). Respiratory and cardiac disease were the most common reasons at MDT review for deeming patients medically inoperable, probably because most patients (96%) had a smoking history. According to criteria defined previously, 207 (31%) patients receiving SABR had no absolute contraindication to surgery and were considered potentially operable. 224 of 676 patients had a history of malignancy, with lung malignancy being most common (97 patients). The median interval between the previous lung malignancy and SABR was 48·8 months (IQR 10·3–87·3).

Histological confirmation before SABR was obtained in 235 (35%) of 676 patients; the remaining patients had a new or growing lesion with a CT appearance consistent with malignancy and local ¹⁸F-FDG-PET uptake. Findings from surgical studies in the Netherlands have shown that the likelihood of a benign diagnosis in such patients is less than 4%.22,23 The median tumour diameter was 27 mm (range 9–107). The median PTV was 28·9 cm³ (range 3·3–290·6). Tumours were located in the upper, lower, and middle lobes in 427 (63%), 219 (32%), and 30 (4%) of 676 patients, respectively.

Median overall survival was 40·7 months (95% CI 34·7–46·8) and the median disease-specific survival was not reached (figure 1). Actuarial 2-year and 5-year rates of any recurrence were 21·5% (95% CI 17·8–25·2) and

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**Figure 1: Kaplan-Meier curves of overall survival and disease-specific survival**

A

Overall survival

Censored

B

Disease-specific survival

Censored

Number at risk 676 465 284 172 99 34 16 12 12

Follow-up (months) 0 12 24 36 48 60 72 84 96

Number at risk 676 363 224 138 81 37 16 16 16

Disease-specific survival (%)

Overall survival (%)

0 20 40 60 80 100

0 20 40 60 80 100

0 12 24 36 48 60 72 84 96

Follow-up (months)

---

**Figure 1:** Kaplan-Meier curves of overall survival and disease-specific survival
30.0% (24.7–35.3), respectively. Actuarial 2-year rates of initial local, regional, and distant recurrence were 4.9% (95% CI 2.7–7.1), 7.8% (5.3–10.3), and 14.7% (11.4–18.0), respectively. Corresponding 5-year rates were 10.5% (95% CI 6.4–14.6), 12.7% (8.4–17.0), and 19.9% (14.9–24.6), respectively (figure 2). The median follow-up was 32.9 months (IQR 14.9–50.9). At the end of follow-up, 406 patients were alive, with follow-up ranging from 0.2 to 90.7 months.

Table 2 summarises the patterns of disease recurrence. Crude initial local recurrence occurred in 30 patients (4%), 18 of whom had isolated local recurrences and two had local recurrences with regional recurrence. The median time to any local recurrence was 14.9 months (95% CI 11.4–18.4). Local recurrence was not related to the SABR scheme used (p=0.97); crude local recurrence occurred in 11 (5%) of 228, 13 (4%) of 296, and six (4%) of 152 patients treated using the three, five, and eight fraction schedules, respectively. Initial regional recurrence occurred in 43 patients (6%), with 22 (51%) of these being isolated regional recurrence. The median time to any regional recurrence was 13.1 months (95% CI 7.9–18.3). Therefore, 42 patients (6%) presented with isolated locoregional recurrence, representing 34% of all recurrences. Because most patients were medically inoperable, only 13 (31%) of the 42 patients with locoregional recurrence were offered potentially curative treatment. These 13 patients underwent 18F-FDG-PET restaging, which confirmed the absence of distant recurrence. Crude initial distant recurrence was noted in 82 (12%) of 676 patients, 57 (70%) of whom had isolated distant recurrence without locoregional recurrence. The most common site of initial distant recurrence was pulmonary (table 2); other common sites were bone, brain, and liver (table 2). Distant nodal, adrenal, and skin recurrences were uncommon (table 2). The median time to any distant recurrence was 9.6 months (95% CI 6.8–12.4).

No differences in overall survival (p=0.75), local recurrence (p=0.21), regional recurrence (p=0.81), or...
A second primary lung cancer was diagnosed in 42 (6%) patients at a median of 18·0 months (95% CI 12·5–23·5) after SABR (table 2). Second primary tumours were located in the involved ipsilateral lobe (n=8), the uninvolved ipsilateral lobe (n=11), and either contralateral lobes (n=23). Among these 42 patients, 32 (76%) were offered curative treatment for their second primary tumour.

Figure 3 shows the combined rates of either recurrence or second primary tumours in the lung per patient per 6-month period after SABR. The average combined rate of either event during the first 3 years after SABR was 5·9% per patient per 6 months, whereas it was 1·3% per patient per 6 months in the subsequent 2 years.

**Discussion**

In this large cohort of patients with long-term follow-up after SABR for stage 1–2 NSCLC, we found that recurrence after SABR was infrequent overall and that the predominant pattern was one of distant recurrence (panel). These findings are consistent with results reported in two small prospective studies and are within the wide range of results reported in a systematic review. Most recurrences reported fell into two clinically distinct patterns. Firstly, isolated distant recurrence accounted for 46% of all recurrences and occurred at a median of 8·3 months after SABR. This interval suggests that isolated distant recurrence probably represents existing subclinical disease, which was undetectable on baseline 18F-FDG-PET imaging. Secondly, isolated locoregional recurrence accounted for 34% of all recurrences and was the predominant pattern after 18F-FDG-PET imaging. Secondly, isolated locoregional recurrence accounted for 34% of all recurrences. When such recurrences develop after primary surgery, the use of salvage treatments can have a significant positive prognostic effect. The limited fitness of our patients to undergo salvage treatment for locoregional recurrences might have been the reason why only about a third of patients had curative treatment. However, about three-quarters of patients with second primary lung cancers were offered curative treatment, presumably because this involved a less taxing treatment for such patients.

Detailed study of patterns of disease recurrence after treatment enables the identification of optimum post-treatment care. At present, recommendations for post-treatment care are based mostly on findings from surgical series. The need for such data to guide care after SABR is highlighted by the inability of a recent systematic review to provide follow-up guidelines because of the poor quality of available data. In the present study, the combined event rate for recurrences and second primary tumours of almost 6% per patient per 6 months in the first 3 years and just over 1% per patient per 6 months in the subsequent 2 years provides the basis for identifying efficient follow-up schedules. For patients suitable for salvage treatments, an efficient schedule would be 6-monthly CT scans in the first 3 years after SABR.

Comparisons between the data presented here and other published findings on surgical treatment of NSCLC are difficult because of differences in patient populations.
and definitions of recurrences and the absence of pathological staging after SABR. Although the reported crude local recurrence of 4% after SABR is reassuring, there are several reasons why this might be an underestimation of local recurrence relative to surgical reports. The definition of postsurgical local recurrence typically includes any recurrence within the entire ipsilateral lung. By contrast, we defined local recurrence after SABR as being within or adjacent to the PTV, and all other ipsilateral lung recurrences were classed as either distant recurrence or second primary tumours in the lung after MDT review. Additionally, because radiological lung changes after SABR can be difficult to differentiate from local recurrence, all suspicious lesions were coded as local recurrence, even when confirmatory ¹⁸F-FDG-PET imaging or histology were absent, to reduce the risk of underestimation. The assessment of whether local recurrences were full in-field recurrences or marginal recurrences remains difficult because radiological changes after SABR are common, which causes distortion of anatomy and makes reconstruction of dose distributions on co-registered follow-up CT scans difficult.

Published data on surgical treatment of NSCLC suggest that after clinical staging with ¹⁸F-FDG-PET, about 10% of patients who have surgery have pathologically involved nodal disease. Nevertheless, the crude regional recurrence of 6% after SABR that we report here is reassuring but is difficult to compare with postsurgical regional recurrence because the latter typically refers only to regional recurrences in the mediastinum in pathologically staged patients.

Panel: Research in context

**Systematic review**

A systematic review of patterns of recurrence after SABR has been published recently. However, this review included reports that contained small patient numbers, had short follow-up durations, and the biologically effective doses of radiation varied significantly. In the present study, we report findings from a large cohort of patients with long-term follow-up after SABR at biologically effective doses for treatment of stage 1–2 NSCLC.

**Interpretation**

Our findings confirm the long-term effectiveness of SABR. Recurrences are uncommon and are most often isolated distant recurrences that will probably not be affected by the local treatment used. Because most recurrences and second primary events occur in the first 3 years after SABR, 6-monthly assessments during this period might represent an efficient follow-up schedule. This follow-up is important, because isolated locoregional recurrence occurs in a third of patients and the proportion of fit patients undergoing SABR continues to increase. These findings provide reassurance to referring clinicians as technological advances have led to a greater access to SABR worldwide. Our findings also suggest that the availability of an effective non-operative therapy should lead to greater efforts to obtain a pathological diagnosis before SABR, because a diagnosis based on CT scans and ¹⁸F-FDG-PET might not be appropriate outside the Netherlands.
A limitation of our study is that a high proportion of patients did not have a pretreatment pathological diagnosis. The study group included patients referred for SABR after discussion at an MDT at more than 70 hospitals. The rate of pathological confirmation is consistent with the general approach in the Netherlands towards patients with solitary pulmonary nodules, where treatment without histological confirmation is based on an assessment of the likelihood of malignancy of ¹⁸F-FDG-PET-positive lesions. The latter is consistent with recommended practice guidelines, which in the Netherlands have also been influenced by the low rates of benign ¹⁸F-FDG-PET-positive lung disease. Reassuringly, we found no differences in overall survival or patterns of recurrence between patients with and without pathologically proven disease in this study—a finding that was previously reported in detail.

Because a third of the study population had a previous malignancy, we cannot rule out that some of the treated lesions might have been a metastasis from the previous tumour (so-called oligometastasis) or a metastasis from a new primary cancer, and that subsequent extrathoracic or intrathoracic metastases reported might have been additional metastases from this previous malignancy. However, the likelihood of the former is low because the median interval between the initial primary tumour and SABR exceeded 4 years and pre-SABR staging ¹⁸F-FDG-PET did not identify extrapulmonary tumours. Furthermore, previous malignancy was not associated with overall survival or any pattern of recurrence in this series.

The low rates of local and regional recurrence on long-term follow-up are reassuring when one considers the increasing use of SABR worldwide, even as SABR planning and delivery techniques have continued to improve since 2008. The predominant pattern of disease recurrence is rapid isolated distant recurrence, a finding that is unlikely to be affected by the choice of local treatment. In some patients, isolated locoregional recurrence can occur, which potentially represents an opportunity for salvage curative treatment.

### Contributors
FJL, CJAH, BJS, and SuS designed the study. FJL and SuS supervised the study. SaS and SuS did the literature search. FJL and CJAH collected the data. SaS, FJL, and SuS analysed the data. SaS, FJL, CJAH, BJS and SuS interpreted the data. All authors reviewed and provided comments on initial versions and reviewed and approved the final draft of the report.

### Conflicts of interest
The Department of Radiation Oncology at VU University Medical Center has research agreements with Varian Medical Systems. FJL, BJS, and SuS have received honoraria as speakers for Varian Medical Systems. BJ and SaS have participated in advisory boards for and received honoraria from Varian Medical Systems. SaS and CJAH declare that they have no conflicts of interest.

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