Patterns of Disease Recurrence after SABR for Early Stage Non–Small-Cell Lung Cancer

Optimizing Follow-Up Schedules for Salvage Therapy

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Introduction: Stereotactic ablative radiotherapy is a guideline-recommended treatment for early stage non–small-cell lung cancer. We report on incidence and salvage of local recurrences (LR) and second primary lung cancers (SPLC) in a large series of patients with long-term follow-up, to generate data for evidence-based follow-up regimens.

Methods: We excluded all patients with double tumors, TNM-stages other than T1-T2N0M0, biologically effective dose less than 100 Gy_{10} and previous treatment for the index tumor from our institutional database. LR was defined as recurrence in/adjacent to the planning target volume. A diagnosis of SPLC was determined using criteria described by Martini et al.

Results: The 855 patients included had a median follow-up of 52 months. Forty-six patients developed LR after a median of 22 months (range 7–87 months). Actuarial local control rates at 3 and 5 years were 92.4% and 90.9%, respectively. Fifty-four percent had isolated LR and 13% had LR in combination with regional recurrences. Ten patients underwent radical salvage treatment; surgery ($N = 6$), high-dose radiotherapy ($N = 3$), or chemoradiation ($N = 1$). Median overall survival following LR was 13 months, but it was 36 months in patients who underwent radical salvage. A SPLC was diagnosed in 79 patients, after a median interval of 34 months. Actuarial cumulative incidences of SPLC at 3 and 5 years were 11.7% and 16.7%, respectively. Radical salvage for SPLC was performed in 63 patients (80%).

Conclusions: Both the timing of LR and persistent risk of SPLC serve as rationale for long-term follow-up using computed tomography scans in patients fit enough to undergo any radical treatment.

Key Words: NSCLC, Stereotactic radiotherapy, SABR, Early stage.

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Stereotactic ablative radiotherapy (SABR) is a guideline-recommended treatment for peripheral early stage non–small-cell lung cancer (NSCLC) in patients who are unfit for surgery.[1,2] Although randomized controlled trials comparing surgery and SABR in operable patients have failed to accrue sufficient numbers of patients, comparative effectiveness studies suggest similar outcomes following both treatment modalities.[3,4] In recent years, a shift in treatment patterns has been observed, with SABR increasingly being used in fitter, high-risk surgical patients.[5,6] In such patients, early recognition of a local recurrence (LR) or new second primary lung cancer (SPLC), which is reported to occur in 3–6% per year, is particularly important as they are potentially salvageable.[7] In patients undergoing surgery for early stage NSCLC, treatment of LRs has been shown to be a predictor for postrecurrence survival. Therefore, the surgical resection of isolated LRs has been recommended.[8]

In patients treated with SABR for early stage NSCLC, clinical practice guidelines of the European Society for Medical Oncology recommend computed tomography (CT) imaging every 3–6 months for a period of 2–3 years postradiotherapy followed by annual CT imaging.[1] This advice was updated in 2014 to emphasize that CT should also be performed with a frequency of 6 months for at least 3 years in those patients suitable for salvage therapy.[9] Such recommendations should ideally be based on long-term observational studies, but there is limited data available to guide the optimal follow-up frequency and duration after SABR. Similarly, there is little known about how many patients are eligible for such salvage treatments.

We previously reported on the outcomes after SABR in a group of 676 patients, after a median follow-up of 32.9 months.[10] In this article, we updated our series with more patients and longer follow-up, and pay specific attention to LRs and salvage therapy, to generate data for evidence-based follow-up regimens.

MATERIALS AND METHODS

Details of all patients with ES-NSCLC treated with SABR between 2003 and 2013 at our center are recorded in an institutional database. For this study, we excluded patients with synchronous lung tumors, a TNM-stage other than T1-T2N0M0 and previous treatment for the index tumor and

patients treated with a fractionation scheme with a biologically effective dose <100 Gy_{10}.

As reported previously, SABR was delivered in an outpatient setting, using risk adapted fractionation schemes to a total dose of 60 Gy, with more fractionated schemes for larger lesions and tumors near organs at risk.[11] All fractionation schemes had a biologically effective dose of >100 Gy_{10} prescribed to the planning target volume (PTV).

Posttreatment follow-up generally consisted of contrast-enhanced CT scans of the thorax and upper abdomen at 3 and 6 months post-SABR, followed by 6 months until 2 years after treatment and annually thereafter. Follow-up was performed in our center and/or in the referring center. Where necessary, the general practitioner or pulmonologist was contacted to retrieve follow-up data.

LRs were defined as a recurrence in, or adjacent to, the PTV. A LR was suspected if there was a growing or increasingly dense mass on sequential follow-up CT scans. For this analysis, cases where there was persistent uncertainty between either LR or post-SABR fibrosis were scored as having a recurrence. Identification of high-risk radiological features suspicious for recurrence, such as those recently published, were not used for identifying LRs in the present cohort, as they were published after the study period.[9,12] In the event of a growing lesion suspicious for a LR, and therefore followed up with imaging before a final diagnosis of a LR, we dated the recurrence to the date of initial clinical suspicion. Locoregional recurrence was defined as a LR, either with or without tumor recurrence in regional lymph nodes.

A new, distinct pulmonary tumor was considered a SPLC if it fulfilled the criteria for multiple metachronous lung cancers described by Martini et al.,[13] namely: (A) different histology or (B) the same histology if (1) the disease-free interval between cancers was at least 2 years, or (2) if the origin was from carcinoma in situ, or (3) if the second cancer was in a different lobe or lung without carcinoma in lymphatics common to both and with no extra pulmonary metastases at the time of diagnosis.

Follow-up was calculated using the reverse Kaplan–Meier method.[14] Time-to-event outcomes were analyzed using the Kaplan–Meier method. The risks per year were calculated using actuarial control rates retrieved from the Kaplan–Meier survival tables. Univariate analysis was performed with the log-rank test to investigate the prognostic value of age, sex, tumor stage, fractionation scheme, treatment delivery technique, PTV size, presence of a pretreatment pathological diagnosis, histology, and a history of a prior (pulmonary) malignancy.

RESULTS

A total of 855 patients with early stage NSCLC fulfilling the above-mentioned inclusion criteria were identified. The median follow-up in all patients was 52 months (interquartile range 33–72 months). The major patient characteristics are displayed in Table 1.

In a total of 73 patients (i.e., 8.5% of all patients), a LR was suspected at some point during follow-up after review of CT scans. Of these, a final diagnosis of a LR was made in 46 patients by pathology and/or radiology. In the 27 patients in whom a recurrence was considered unlikely, this was based on a negative fluorodeoxyglucose-positron emission tomography (18FDG-PET) scan in 13 patients (48%) and/or a negative biopsy in three patients (11%). In another 14 patients, a LR was considered to be unlikely based on the subsequent findings of stable or regressing masses on serial CT scans.

In 46 patients with a diagnosis of LR, this diagnosis was established at a median of 22 months (range 7–87 months). The actuarial local control rates at 1-, 3-, and 5 years post-SABR were 98.9%, 92.4%, and 90.9%, respectively. Univariate analysis was performed in the entire patient cohort to identify potential factors influencing local control. None of the investigated factors—age, sex, tumor stage, fractionation scheme, treatment delivery technique, PTV size, presence of a pretreatment pathological diagnosis, histology or a history of a prior (pulmonary) malignancy—correlated significantly with local control, see Table 2.

TABLE 1. Patient Characteristics of All Patients Treated with SABR

Characteristics	*N* (%) or Median (Range)
Age (years)	74 (45–91)
Sex	
Male	516 (60%)
Female	339 (40%)
Pathological diagnosis	
Yes	308 (36%)
No	547 (64%)
WHO performance score	
0	111 (13%)
1	446 (52%)
2	256 (30%)
3	38 (4%)
Charlson comorbidity index[24]	2 (0–11)
COPD	640 (75%)
Medically inoperable	
Yes	613 (72%)
No	242 (28%)

SABR, stereotactic ablative radiotherapy; WHO, World Health Organization; COPD, chronic obstructive pulmonary disease.

TABLE 2. Investigated Factors in Univariate Analysis for Correlation with Local Control

Investigated Factor	*p*
Age	0.336
Sex	0.121
TNM stage	0.183
Fractionation scheme	0.182
Delivery technique	0.650
PTV size	0.630
Pre-SABR pathology	0.584
Histology	0.843
Prior malignancy	0.584

PTV, planning target volume; SABR, stereotactic ablative radiotherapy.

In all but two patients, the diagnosis of a LR was based on findings of a CT scan, either with or without additional investigations. One of the two patients without corroborative CT scan findings had local disease progression on serial chest X-rays only, but did not undergo further diagnostic tests. The second patient had a LR diagnosed at autopsy. Increased uptake on ^{18}FDG-PET scans was seen in 28 patients (61%), whereas other patients did not undergo ^{18}FDG-PET scans. Unfortunately, data on standardized uptake values for these scans was not always available. A final pathological confirmation of LR was available in 18 patients (39%), with pathology obtained using transthoracic biopsy (N = 7, 39%), bronchoscopy (N = 3, 17%), a surgical resection (N = 4, 22%), endobronchial ultrasound (N = 2, 11%), or after autopsy (N = 2, 11%). Of these 18 patients, 15 had both a positive ^{18}FDG-PET scan and pathological confirmation of recurrence.

An overview of the diagnosis and management of LRs is given in Figure 1. Based on the available staging modalities, the recurrence was exclusively local in 25 patients (54%) and locoregional in 31 of the patients (67%). In six patients with a combined local and regional failure, regional failure was limited to ipsilateral hilar nodes in four patients, and two patients had mediastinal (N2) disease. Of 31 patients presenting with locoregional recurrence, only 12 were considered eligible for radical salvage by a multidisciplinary tumor board (MDT). Of these, nine patients underwent radical salvage. Five patients had a surgical resection, followed by either adjuvant chemotherapy (n = 2) or radiotherapy (n = 1). Radical nonsurgical treatments included high dose radiotherapy (n = 3) and chemoradiation (n = 1). Three other patients refused further treatment. A single patient with both a LR and a solitary metastasis in an adrenal gland was planned for radical treatment with a lobectomy to be followed by SABR for the adrenal metastasis. However, due to the detection of pleural metastasis during surgery, the patient was subsequently referred for palliative chemotherapy.

Three out of 12 patients who were considered eligible for radical salvage by a MDT were initially referred for SABR for their primary tumor as they were considered at high risk for surgery. At the time of a LR, these patients were again discussed in a MDT, and the surgical risks were considered as being acceptable. Of these, two patients underwent a lobectomy, and one underwent a wedge resection.

The median overall survival after the diagnosis of a LR was 13 months (95% confidence interval: 8.6–17.4 months). However, patients who underwent some form of radical treatment (n = 10) had a median overall survival after LR of 36 months (mean 32 months, 95% confidence interval: 20–43 months).

A diagnosis of a SPLC was made in 79 patients (9.2%), at a median time of 34 months after SABR (range 3–105 months). The actuarial cumulative incidences of SPLC at 1-, 3-, and 5 years post-SABR were 1.9%, 11.7%, and 16.7%, respectively. The SPLC was located in the same lung in 37 patients (47%) and in the same lobe in 15 patients (19%); all of these had pathology different from the index tumor or an interval exceeding 2 years. Pathological confirmation of the SPLC was available in only 21 patients (27%). Median follow-up after the diagnosis of SPLC was 23 months (range

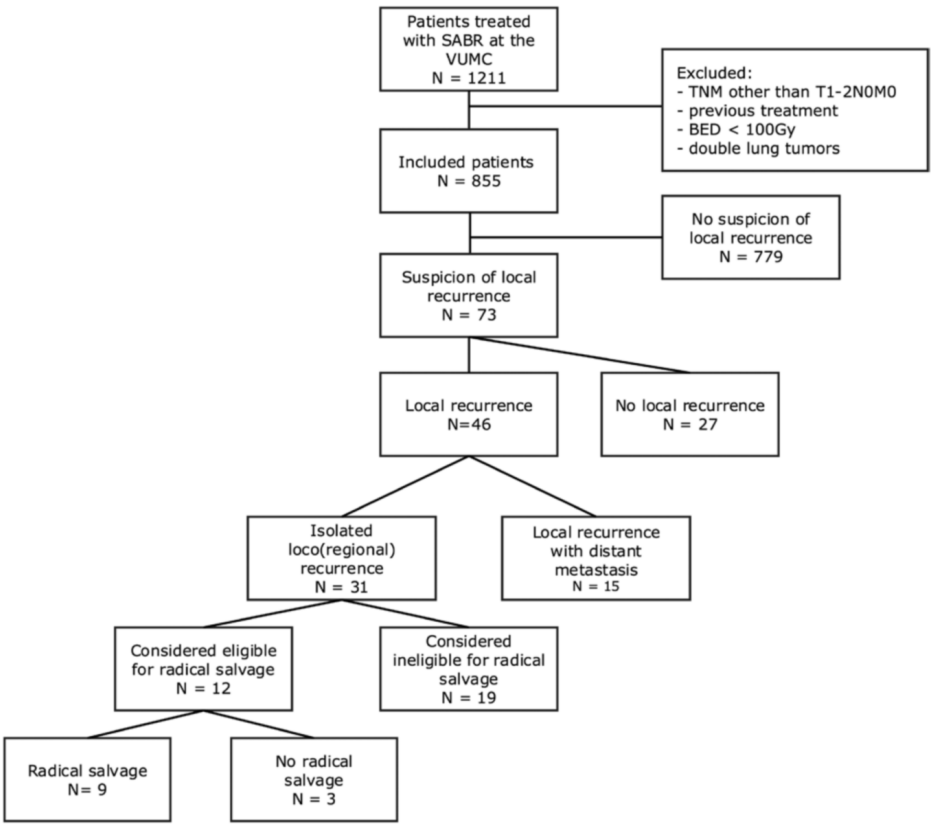

FIGURE 1. Flowchart of staging and salvage in patients with local recurrences after treatment with SABR for early-stage lung cancer. SABR, stereotactic ablative radiotherapy.

3–105 months), and median overall survival after diagnosis of a SPLC was 23 months. An overview of the diagnosis and management of SPLC is shown in Figure 2.

DISCUSSION

The optimal follow-up schedule after SABR for early stage NSCLC is unclear, although the ESMO guidelines suggested CT imaging every 3–6 months for a period of at least 2 or 3 years post-SABR followed by annually thereafter.[9] As the literature on long-term follow-up after SABR is relatively limited, we studied recurrence patterns in 855 post-SABR patients who were followed up for a median of 52 months. Our main finding was a 5-year LR rate of 9.1%, including the cases without a pathological confirmation. Two thirds of patients diagnosed with a LR had either an isolated local- or loco-regional failure, indicating that the majority were potentially eligible for salvage therapy. However, only a minority (10 of 46 patients) finally underwent curative-intent treatment. The latter is likely to be a reflection of the fact that 72% of patients in this cohort were considered inoperable after assessment at a MTB at the time of initial presentation. The favorable median overall survival of 36 months after radical treatment for a locoregional recurrence mirrors that in surgical reports on radical salvage treatment.[8]

Our results compare well to the recurrence rates reported by two prospective trials. In the RTOG 0236 trial, 55 patients were evaluable with a median follow-up of 4.0 years. The estimated primary tumor failure rate reported was 7%, and an additional nine patients had recurrence in the same lobe (16%).[15] In the prospective phase II trial reported by Baumann et al.,[16] 57 patients were treated with SABR for T1-2N0M0 NSCLC, with a median follow-up of 36 months. A local control rate of 92% at 3 years was reported.

An important finding is that three patients, who had been referred for SABR previously after being considered to be at high risk for surgery by a MDT, were considered to be surgical candidates when they presented with LR. This underlines the importance of discussing all patients with a locoregional recurrence in a MDT, as medical inoperability is a grey area, and a reflection of the risks that patients and their physicians are prepared to accept in the absence of other curative options. Similar findings have been reported by other authors in patients who were initially considered inoperable, and who underwent SABR as initial therapy.[17]

Distinguishing radiological changes after SABR due to LRs and radiation-induced fibrosis can be quite challenging and discussion of such cases in a MDT is important in patients fit for salvage options.[18] We recommend the follow-up CT scans to be reviewed by radiologists experienced in interpreting post-SABR findings. In case follow-up occurs outside of the treating center, we encourage centers to consult an experienced radiologist or radiation-oncologist in all cases of a suspected recurrence. Furthermore, ESMO guidelines recommend repeating 18FDG-PET scans if there is a suspected recurrence, and obtaining pathological confirmation whenever possible and when it is of consequence. In this series, pathology and ^{18}FDG-PET scans were obtained in only a minority of patients, largely because of the diagnosis of distant metastases, or because of a combination of age and comorbidity, and the views of an MDT about the lack of treatment options.

Another observation is the wide range in time to diagnosis of LRs. A peak in LRs was seen between 1 and 3 years post-SABR, but late LRs were also observed. With longer follow-up in this study, the median time to LR after SABR has increased to 22 months compared with 14.9 months as

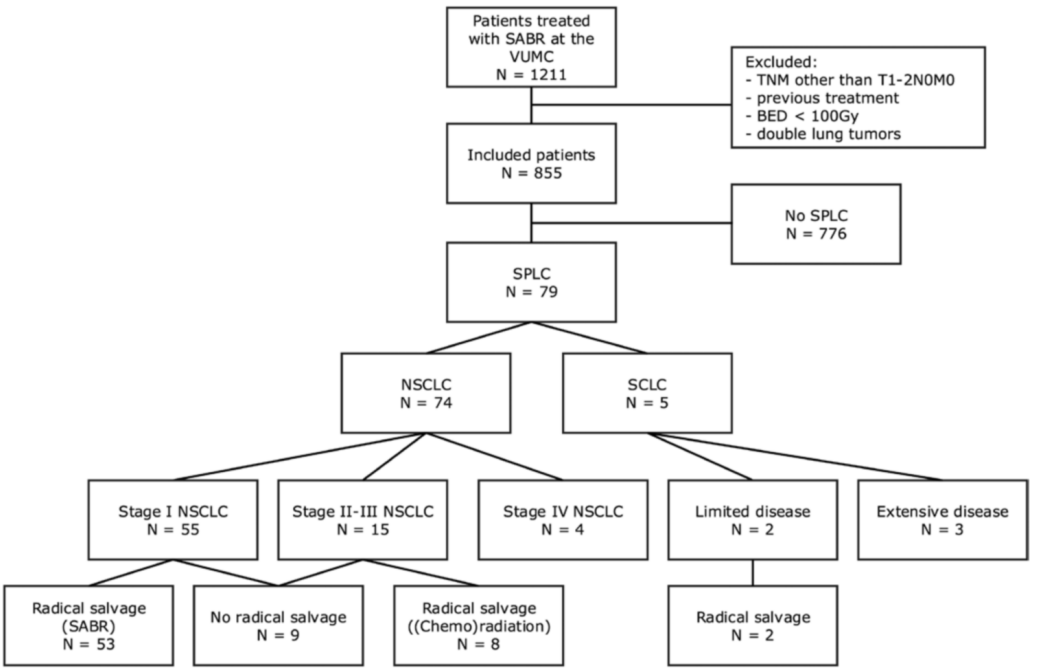

FIGURE 2. Flowchart of staging and salvage in patients with a clinical diagnosis of SPLC after treatment with SABR for early stage NSCLC. SPLC, second primary lung cancer; SABR, stereotactic ablative radiotherapy; NSCLC, non–small-cell lung cancer.

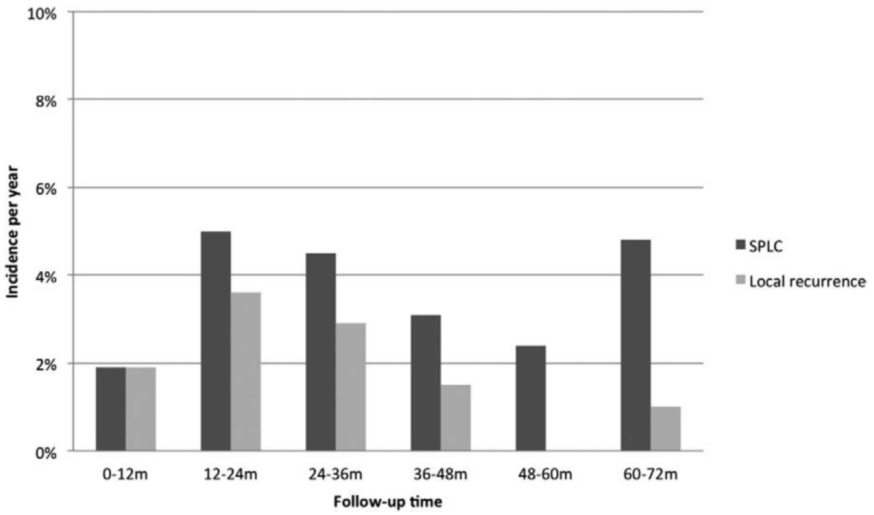

FIGURE 3. Incidence of SPLC and local recurrences per year in patients treated with SABR for early stage NSCLC. SPLC, second primary lung cancer; SABR, stereotactic ablative radiotherapy; NSCLC, non–small-cell lung cancer.

previously reported at our center.[10] This, together with the observed annual rate of SPLC of 2% to 5%, suggests that long-term follow-up of patients is beneficial (Fig. 3). The rates of SPLC identified in our cohort are in agreement with published rates after surgery.[7,19] In total, 80% of patients with a SPLC underwent radical salvage treatment, and because of the high percentage of early stage SPLC, salvage SABR for the SPLC was the predominant treatment. Reported outcomes for SABR for a SPLC have been shown to be similar to results of SABR for a first presentation of NSCLC.[20]

A key limitation of this study is that not all patients had a pathological diagnosis before SABR treatment. However, reported rates of benign disease in patients staged with ^{18}FDG-PET scans in the Netherlands, and who subsequently underwent surgery for a clinical diagnosis of early stage NSCLC, are low.[21,22]

As increasingly fit patients are now undergoing SABR and these patients will have longer follow-up as they have less competing causes of mortality, more emphasis is placed on detection and salvage of LRs, Until now, only limited data on salvage procedures with curative intent, e.g., surgery, has been available and although these studies with limited patient numbers suggest it is feasible, more data on the safety and outcome of such procedures is needed.[17,23,24]

In conclusion, both the timing of LRs after SABR, as well a persistent risk of SPLC, serves as a rationale for long-term radiological follow-up using CT scans, especially in patients fit enough to undergo any radical treatment. Our findings support the use of a similar follow-up strategy after SABR as was recommended for postsurgical cases.[9,25] Therefore, we recommend that all patients eligible for any type of salvage undergo 6 months follow-up CT scans for a period of 3 years post-SABR, followed by annual CT scans thereafter. All patients who are suspected of having recurrence should be discussed in an MDT.

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