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Lung cancer SBRT

# High-risk CT features for detection of local recurrence after stereotactic ablative radiotherapy for lung cancer

Kitty Huang [a,1], Sashendra Senthi [b,1], David A. Palma [a,*], Femke O.B. Spoelstra [b], Andrew Warner [a], Ben J. Slotman [b], Suresh Senan [b]

[a] Department of Radiation Oncology, London Regional Cancer Program, Canada; [b] Department of Radiation Oncology, VU University Medical Center, Amsterdam, The Netherlands

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ABSTRACT

*Background and purpose:* Early detection of local recurrences following stereotactic ablative radiotherapy (SABR) for lung cancer may allow for curative salvage treatment, but recurrence can be difficult to distinguish from fibrosis. We studied the clinical performance of CT imaging high-risk features (HRFs) for detecting local recurrence.

*Materials and methods:* Patients treated with SABR for early stage lung cancer between 2003 and 2012 who developed pathology-proven local recurrence ($n = 12$) were matched 1:2 to patients without recurrences ($n = 24$), based on baseline factors. Serial CT images were assessed by blinded radiation oncologists. Previously reported HRFs were (1) enlarging opacity at primary site; (2) sequential enlarging opacity; (3) enlarging opacity after 12-months; (4) bulging margin; (5) loss of linear margin and (6) air bronchogram loss.

*Results:* All HRFs were significantly associated with local recurrence ($p < 0.01$), and one new HRF was identified: cranio-caudal growth ($p < 0.001$). The best individual predictor of local recurrence was opacity enlargement after 12-months (100% sensitivity, 83% specificity, $p < 0.001$). The odds of recurrence increased 4-fold for each additional HRF detected. The presence of $\geqslant 3$ HRFs was highly sensitive and specific for recurrence (both >90%).

*Conclusion:* The systematic assessment of post-SABR CT images for HRFs enables the accurate prediction of local recurrence.



Over the last decade, stereotactic ablative radiotherapy (SABR, also referred to as SBRT) has been rapidly adopted into clinical practice and has become the preferred treatment for early stage non-small cell lung cancer (NSCLC) patients with medically inoperable tumors [1,2]. Single-institution, population-based and Markov-modeling studies have shown treatment outcomes after the implementation of SABR to be comparable to that of surgery, the historical gold-standard treatment [2–5]. SABR has also been increasingly evaluated in the operable patient population, with favorable outcomes [6,7]. As these fitter patients are more likely to be eligible for salvage treatments, appropriate follow-up for the earliest possible detection of local recurrence is of paramount importance.

Due to the high biologic doses delivered with SABR, the vast majority of patients develop benign post-treatment fibrosis within 2 years post-treatment [8,9]. Although local recurrences after SABR for early stage NSCLC are uncommon when effective schemes with high biological doses are applied, the majority of these manifest within the first 2 years of treatment [3,10]. A failure to distinguish between the appearance of recurrence and benign lung fibrosis may lead to unnecessary imaging, invasive testing, delay in salvage or inappropriate salvage therapy.

An evidence-based approach for choice of imaging modality during follow-up, and for the distinction of recurrence from fibrosis after SABR, is lacking. Current imaging follow-up relies mainly on CT imaging, with the role of FDG-PET/CT being unclear. Several previous studies, including a systematic review, have identified CT-based "high-risk features" (HRFs), which could distinguish recurrence from fibrosis [11]. However, these studies have not been validated, and the sensitivity and specificity of these features are unknown. Previous studies have been limited by a lack of pathology-proven recurrences, due to both the infrequency of recurrence and the lack of biopsy confirmation in the frail patient population traditionally treated with SABR. In addition, several studies have included patients classified as having recurrence based only on CT findings (without pathology), which likely overestimates the performance of CT, since CT is used to both define and predict recurrence. The goals of the present study were to validate the previously reported HRFs of recurrence, to identify and

* Corresponding author. Address: Department of Radiation Oncology, London Regional Cancer Program, 790 Commissioners Rd E, London, ON, Canada.
*E-mail address:* david.palma@lhsc.on.ca (D.A. Palma).

[1] These authors contributed equally to this work.

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test possible novel features, to determine the sensitivity and specificity of each feature in predicting recurrence, and to estimate the increase in recurrence risk as additional HRFs are detected in an individual patient.

## Methods

### *Patient population and treatment*

Details of patients treated with SABR for early stage lung cancer at the VU University Medical Center (VUmc) between April 2003 and July 2012 were retrieved from a prospective database. In the Netherlands, retrospective studies of patient data, such as this study, do not fall under the scope of the Medical Research Involving Human Subjects Act; this study is thus exempt from medical ethics review. Patients with synchronous lung tumors were excluded from our study. Patients were treated to a dose of 54–60 Gy prescribed to the 80% isodose in 3–8 risk-adapted fractions, based on tumor size and location [12]. Radiation treatment planning and delivery techniques have been previously reported [12]. A follow-up CT chest with contrast enhancement (2.5–5 mm slice thickness) was obtained at 3, 6 and 12 months, and annually thereafter. More frequent CT imaging was obtained in cases of suspected recurrence. FDG-PET scanning was not performed routinely during follow-up, but only when disease recurrence was suspected, in patients who were considered to be candidates for salvage therapy.

### *Definition of local recurrence*

Local recurrence was defined radiologically as a growing lesion within the involved lobe on sequential follow-up scans that could not clearly be attributable to lung fibrosis, as previously described [6]. During this time period, 31 patients were classified by a multidisciplinary tumor board as having local recurrence based on suspicious radiologic findings. Of these, 12 had pathology-proven local recurrences and were matched 1:2 to patients without recurrence ($n = 24$), from a group of 507 potential matches, according to baseline factors. Patients were matched using a manual method, selecting matched controls based on the following factors: tumor location (peripheral vs. central), fractionation (3, 5 or 8 fractions) and PTV size (within 10%). All patients without recurrence were required to have available follow-up CT images at time intervals and duration comparable to their matched recurrence counterparts.

### *Image analysis*

CT images were assessed for the presence of benign and HRFs previously reported in the literature [8,13–16]. Benign changes are subdivided into acute (within 6 months after treatment) and late changes (beyond 6 months post-treatment). Acute changes include diffuse consolidation, patchy consolidation, diffuse ground glass opacities (GGO), and patchy GGO; late changes include a modified conventional pattern (defined as volume loss, traction bronchiectasis, and consolidation similar to changes after conventional radiotherapy, but less extensive [8]), mass-like fibrosis, and scar-like fibrosis). High-risk CT features have been previously reported by Kato, Takeda, and Matsuo et al. [14–16]. The HRFs assessed were (1) enlarging opacity at the primary site; (2) sequential enlarging opacity; (3) enlarging opacity after 12 months; (4) bulging margin; (5) loss of linear margin and (6) loss of air bronchograms (including partial loss). Enlarging opacity was assessed according to RECIST 1.1 criteria [17]; specifically, size was measured on axial slices as recommended, and any growth in the transverse plane was recorded.

Scoring was performed by blinded observers, viewing anonymized images projected onto a large screen. For reference, scorers were provided with representative images and detailed descriptions of benign and high-risk features. A minimum of two radiation oncologists assessed scans for both high risk and benign features, and any discrepancies were resolved by consensus or consultation with an additional scorer if necessary. For each patient, the corresponding baseline pre-treatment planning 4D-CT and radiotherapy plan were available for review, and all follow-up images were then displayed in sequential order, with all viewing options and window/level settings used in clinical practice available. Size measurements were made using standard lung window settings. Areas of ground glass opacification were not included in the measurements. Judges remained blinded to the status of the patient with respect to recurrence.

Three new potential HRFs were investigated, namely (1) new axial growth after complete response (2) cranio-caudal growth ($\geqslant$5 mm and $\geqslant$20%) and (3) ratio of cranio-caudal growth to axial growth.

### *Data analysis*

Descriptive statistics were generated for the presence of each of the radiographic changes, stratified by recurrence/non-recurrence and compared using the Chi-square test (or Fisher's exact test where appropriate). Sensitivity/specificity for each individual high-risk feature was calculated, along with the sensitivity and specificity for each additional cumulative high-risk feature (dichotomous cut-points, range: 0–7). Positive- and negative-predictive values (PPV and NPV) are not reported, since they are dependent on the prevalence of the outcome. In this 1:2 matched cohort, PPV would be overestimated and NPV underestimated, relative to an actual clinical scenario where recurrence is less common [18]. Univariable logistic regression models were constructed to identify factors associated with recurrence. Since the study uses a matched study design, adjusted odds ratios were computed by stratifying for patient matching. All statistical analysis was performed using SAS (version 9.2), using two-sided statistical testing at the 0.05 significance level.

## Results

Baseline characteristics of all 36 patients are summarized in Table 1. Patients were well-matched in the recurrence and non-recurrence groups. The median age at diagnosis was 68 years and median post-SABR imaging follow-up was 24 months (range 5–67 months). Fig. 1 shows representative serial CT images for a patient without recurrence (Fig. 1A) and a patient with recurrence (Fig. 1B).

Benign CT imaging features were common, and were identified in 89% of all patients (32 of 36 patients). Most common acute benign features were: patchy consolidation (36%) and diffuse consolidation (17%); the most common late benign features were modified conventional changes (78%). The Supplemental Table (online only) shows the frequency of benign features. The onset of benign features appeared at a median of 6 months after treatment (range 3–40 months).

High risk CT features were observed in 21 of 36 patients (58%), most commonly seen as an enlarging opacity (53%), enlarging opacity after 12 months (44%), cranio-caudal growth (42%) or bulging margin (39%) (Table 2). All previously published high-risk CT features included in our study were significantly associated with local recurrence (all $p < 0.01$, Table 2), and all patients with proven recurrence had one or more HRFs. Of the three new radiological features evaluated, only cranio-caudal growth was identified in

**Table 1**
Baseline characteristics.

| Characteristic | All patients ($n$ = 36) | Recurrence ($n$ = 12) | No-recurrence ($n$ = 24) | $p$-Value |
|---|---|---|---|---|
| Age – median (range) | 68 (57, 86) | 65 (60, 86) | 69 (57, 82) | 0.322 |
| Tumor size mm – mean (SD) | 31 (15) | 33 (15) | 30 (15) | 0.561 |
| Male – *N* (%) | 22 (61) | 7 (58) | 15 (63) | 1.00 |
| Charlson score – mean (SD) | 2.9 (1.6) | 2.9 (1.1) | 3.0 (1.9) | 0.933 |
| *Involved lobe – N (%)* | | | | |
| LUL | 11 (31) | 3 (25) | 8 (33) | 0.427 |
| LLL | 7 (19) | 2 (17) | 5 (21) | |
| RUL | 11 (31) | 4 (33) | 7 (29) | |
| RML | 2 (6) | 2 (17) | - | |
| RLL | 5 (14) | 1 (8) | 4 (17) | |
| *Location – N (%)* | | | | |
| Central | 12 (33) | 4 (33) | 8 (33) | 1.00 |
| Peripheral | 24 (67) | 8 (67) | 16 (67) | |
| PTV ($cm^3$) – median (min, max) | 23 (4, 132) | 22 (4, 132) | 23 (5, 126) | 0.987 |
| *RT technique – N (%)* | | | | |
| Fixed Beam | 28 (78) | 9 (75) | 19 (79) | 1.00 |
| Rapid Arc | 8 (22) | 3 (25) | 5 (21) | |
| *Fractionation – N (%)* | | | | |
| 3 | 10 (28) | 4 (33) | 6 (25) | 0.738 |
| 5 | 13 (36) | 3 (25) | 10 (42) | |
| 8 | 13 (36) | 5 (42) | 8 (33) | |

*Abbreviations*: LUL: left upper lobe; LLL: left lower lobe; RUL: right upper lobe; RML: right middle lobe; RLL: right lower lobe; PTV: planning target volume; RT: radiotherapy; SD: standard deviation.

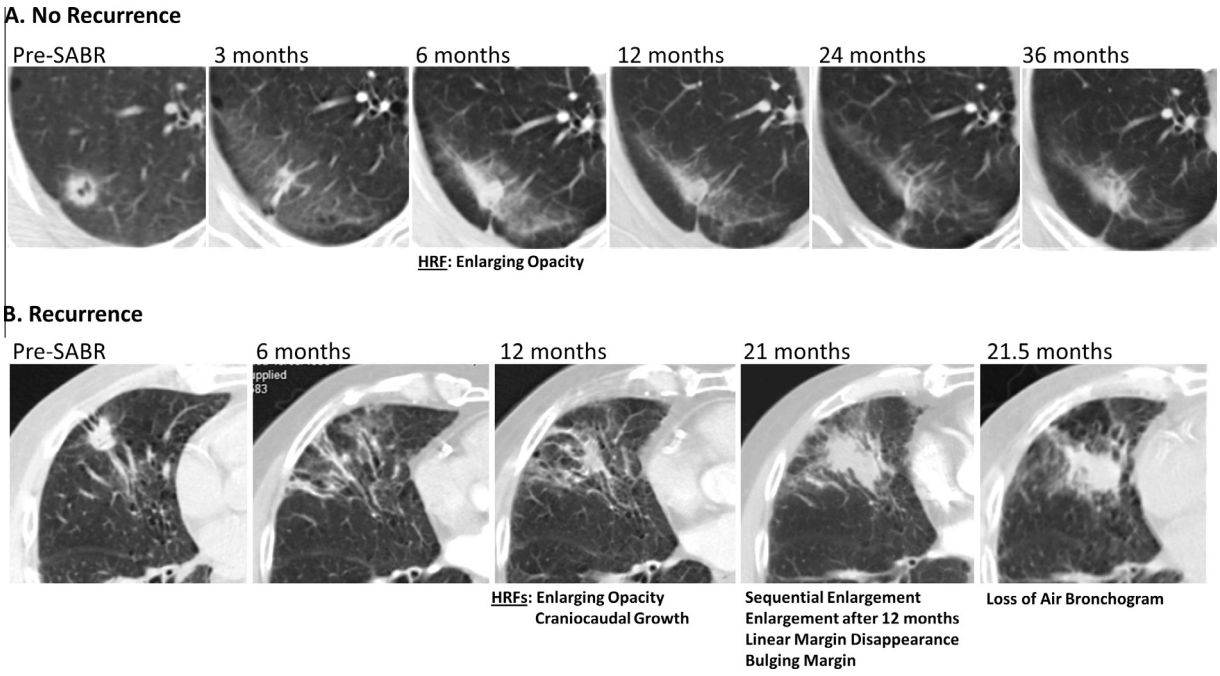


**Fig. 1.** Representative CT images of patients following SABR with benign and high-risk CT features. New high-risk features (HRFs) noted in each scan specified. (A) Patient without local recurrence. A 3 month follow-up scan post-treatment shows diffuse ground glass opacity; a 6 month scan shows a high-risk CT feature: enlarging opacity; however 12, 24 and 36 month scans all show modified conventional pattern of late fibrosis with no additional high-risk CT features. No evidence of local recurrence is seen at 3 years post-treatment. (B) Patient with pathology-proven local recurrence. A 6 month follow-up scan shows diffuse consolidation; a 12 month scan shows modified conventional pattern of late fibrosis and two high-risk CT features: enlarging opacity and cranio-caudal growth (latter not shown); subsequent scans show additional high-risk CT features: sequential enlargement, enlarging opacity after 12 months, linear margin disappearance, bulging margin, followed by loss of air bronchogram. Local recurrence was clinically diagnosed at 22 months and the patient underwent salvage lobectomy at 23 months.

sufficient numbers of patients and with adequate sensitivity and specificity to be clinically useful ($p < 0.001$). The other two features, new axial growth after a complete response, and ratio of cranio-caudal to axial growth, were not adequately sensitive or specific for routine clinical use.

The best individual predictor of local recurrence was an enlarging opacity after 12 months (sensitivity 100%, specificity 83%; Table 2), with the second-most predictive HRF being cranio-caudal growth. The latter was the novel HRF identified in this study (92% sensitivity, 83% specificity). Sequential enlargement was 100% specific, but had a sensitivity of only 67%.

Table 3 shows the sensitivity and specificity of detecting recurrence based on cumulative number of HRFs on CT imaging. The presence of $\geqslant 1$ HRFs had high sensitivity (100%), however the

**Table 2**
Frequency of high-risk features.

| Characteristic | All patients *N* (%) | Rec *N* (%) | No-Rec *N* (%) | *p*-Value | Sens (%) | Spec (%) | Time (months)[a] |
|---|---|---|---|---|---|---|---|
| Any HRF | 21 (58) | 12 (100) | 9 (38) | <0.001 | 100 | 63 | 15 (6, 44) |
| Enlarging opacity | 19 (53) | 11 (92) | 8 (33) | <0.001 | 92 | 67 | 15 (6, 44) |
| Sequential enlargement | 8 (22) | 8 (67) | 0 (0) | <0.001 | 67 | 100 | 19 (9, 46) |
| Enlargement after 12 months | 16 (44) | 12 (100) | 4 (17) | <0.001 | 100 | 83 | 22 (12, 44) |
| Bulging margin | 14 (39) | 10 (83) | 4 (17) | <0.001 | 83 | 83 | 22 (6, 44) |
| Linear Margin disappearance | 5 (14) | 5 (42) | 0 (0) | 0.002 | 42 | 100 | 20 (6, 40) |
| Loss air bronchogram | 9 (25) | 8 (67) | 1 (4) | <0.001 | 67 | 96 | 20 (9, 44) |
| Cranio-Caudal growth | 15 (42) | 11 (92) | 4 (17) | <0.001 | 92 | 83 | 13 (6, 44) |

*Abbreviations*: Rec: recurrence; Sens: sensitivity; Spec: specificity; HRF: high-risk feature.
[a] median (min, max).

**Table 3**
Sensitivity and specificity of CT based on number of high-risk CT features identified.

| Number of HRFs | All Patients *N* (%) | Rec N (%) | No-Rec *N* (%) | *p*-Value | Sens (%) | Spec (%) |
|---|---|---|---|---|---|---|
| ⩾1 | 21 (58) | 12 (100) | 9 (38) | <0.001 | 100 | 63 |
| ⩾2 | 20 (56) | 12 (100) | 8 (33) | <0.001 | 100 | 67 |
| ⩾3 | 13 (36) | 11 (92) | 2 (8) | <0.001 | 92 | 92 |
| ⩾4 | 12 (33) | 10 (83) | 2 (8) | <0.001 | 83 | 92 |
| ⩾5 | 9 (25) | 9 (75) | – | <0.001 | 75 | 100 |
| ⩾6 | 7 (19) | 7 (58) | – | <0.001 | 58 | 100 |
| ⩾7 | 4 (11) | 4 (33) | – | 0.008 | 33 | 100 |
| | Odds ratio (95% CI) | | | *p*-Value | | |
| Per each additional HRF | 4.01 (2.20, 7.32) | | | <0.001 | | |

*Abbreviations*: Rec: recurrence; Sens: sensitivity; Spec: specificity; HRF: high-risk feature.

specificity was low (63%), reflecting a high false-positive rate with a low cut-off. With an increasing number of HRFs, the sensitivity declined while specificity increased. The presence of ⩾3 features was very sensitive and specific (>90%). Each additional HRF identified resulted in a 4-fold increased odds of recurrence.

The median time from start of SABR to clinical diagnosis of local recurrence was 22 months (range 6–46 months). In 50% of patients with recurrences ($n = 6$), the first HRF, in retrospect, appeared 3 months or more before the date of diagnosis of recurrence. In four patients (33% of recurrences), two or more features were present at least 3 months prior to the diagnosis of recurrence. The appearance of an enlarging opacity and cranio-caudal growth were the best early indicators of recurrence: each was detected 3 months or more prior to the date of recurrence in 5 patients (42% of recurrences).

## Discussion

Although survival following local recurrence in early-stage NSCLC is poor, outcomes are significantly improved when patients are able to undergo salvage surgery [19,20]. The American Association for Thoracic Surgery has recommended low-dose CT surveillance for surgical patients eligible for subsequent treatment [21]. With surgical salvage and re-irradiation being feasible post-SABR [22–25], and an increasing proportion of patients undergoing SABR being otherwise operable [7], the importance of early detection of local recurrence is increasingly clinically relevant. The present study validates the clinical utility of previously reported HRFs as being significant predictors of local recurrence. In addition, a novel HRF has been identified, the presence of growth in the cranio-caudal direction. Combining these HRFs permits a highly sensitive and specific diagnosis of local recurrence without functional imaging. These findings are of particular significance, since benign CT-features occurred almost universally, and often at the same time as HRFs, yet the HRFs still perform with good sensitivity and specificity. Finally, the systematic assessment of post-SABR CT images for these HRFs has the potential to diagnose local recurrence sooner than achieved otherwise.

The most accurate predictor of local recurrence was an enlarging opacity after 12 months, however, this criterion inherently cannot allow for detection of recurrence within the first year after diagnosis. As such, other HRFs must be utilized during the first year post-treatment. These findings are supported by previous studies reporting on a combined total of seven histologically confirmed local recurrences, which reported that an enlarging mass, particularly after 12 months, being the most sensitive, but not specific, feature of recurrence [15,16]. One study reported perfect performance for the criteria of three consecutive enlargements (100% sensitive, 100% specific) [26]; however, an important limitation of most studies is the inclusion of patients who had recurrence defined only by CT imaging without biopsy, which risks artificially inflating the sensitivity and specificity values. The drawbacks of a non-systematic approach to diagnosing recurrence is readily evident, and may lead to resection of 'recurrences' without viable tumor cells in one in four patients [15,27]. These findings underscore the limitations of current criteria for defining progressive disease (such as RECIST) and suggest a need for alternative criteria [28].

The novel high-risk CT feature of growth in the cranio-caudal dimension, has not, to our knowledge, been reported previously. The biologic basis to this finding may be that most SABR dose is deposited in the axial plane, where most fibrosis would also be expected as there is a clear relationship between dose and CT density changes [29]. The relatively low amount of low-dose radiation, and more rapid dose fall-off, in the cranio-caudal direction makes CT changes in this axis less likely to be related to radiation injury, and more suggestive of recurrence.

Overall, CT imaging can be very sensitive and also very specific for the diagnosis of local recurrence. When two or fewer HRFs are identified, specificity is low. In such patients, PET/CT may be useful to assist with the diagnosis of local recurrence [30], and also for ruling out distant recurrence prior to salvage. Employing a minimum cut-off of 3 or more HRFs identified, the sensitivity

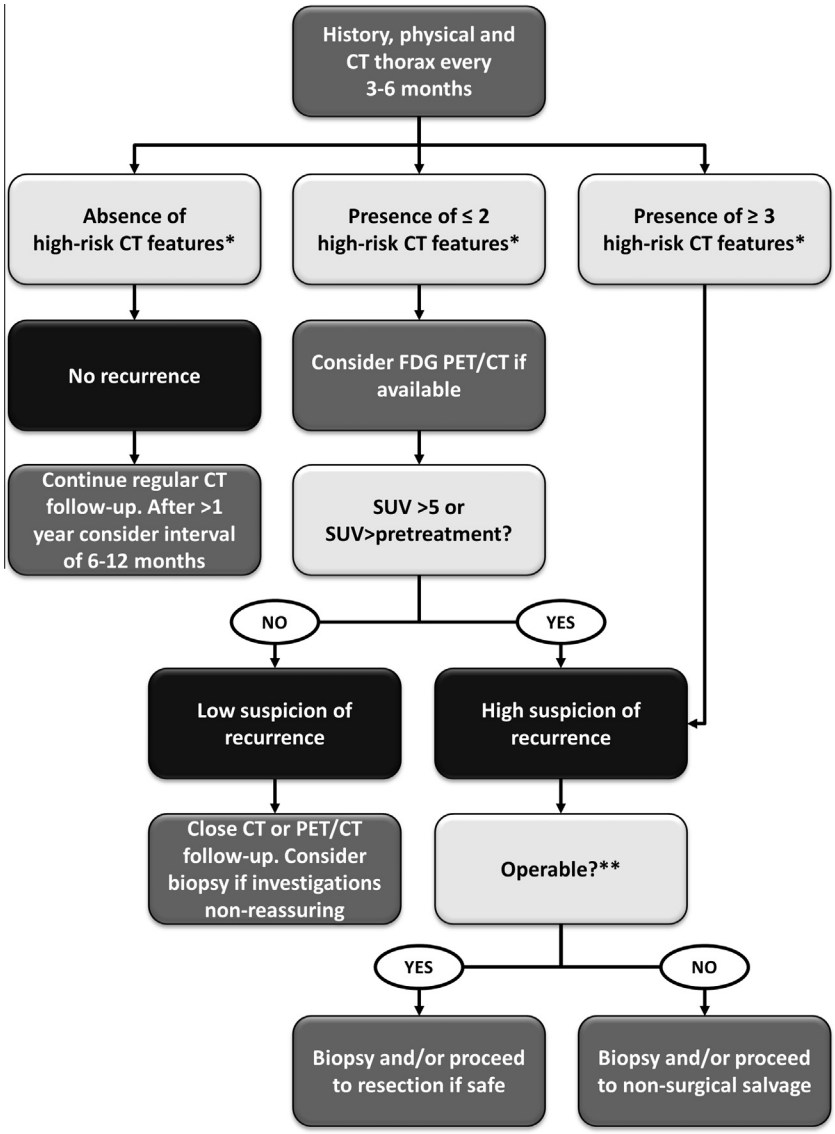


**Fig. 2.** Suggested imaging follow-up algorithm for patients following SABR who are candidates for salvage therapy. The reader is referred to reference #11 for a full discussion of the algorithm. *High-risk CT features include: enlarging opacity, cranio-caudal growth, sequential enlargement, enlarging opacity after 12 months, loss of linear margins, bulging margin and loss of air bronchograms. **Rule out nodal or distant recurrence prior to salvage.

and specificity exceed 90%, suggesting that proceeding to biopsy or salvage treatment may be appropriate, although this finding should be validated in other datasets. These sensitivity and specificity values are promising, since the usual criteria for proceeding with resection, fine-needle aspiration biopsy (FNAB) or core needle biopsy (CNB), have performance characteristics in the same range: sensitivities of 81–91% and 86–97% for FNAB and CNB respectively, and specificities of 75–100% and 89–100% respectively [31]. In such patients with 3 HRFs, omission of PET imaging to assess the primary lesion may be reasonable, particularly if not readily available at the treating institution, although it may provide useful information regarding the presence or absence of distant disease. An updated follow-up imaging algorithm for patients who are candidates for salvage therapy for the detection of local recurrence is provided in Fig. 2, based on a previous systematic review [11].

The management recommendations based on CT imaging presented herein can serve as a useful tool for clinicians, however, a multidisciplinary team opinion is preferred whenever possible. Considerations include risks of diagnostic procedures in frail patients, which may favor close observation. False-negative or indeterminate biopsy results, may favor proceeding directly to salvage therapy, particularly if the clinical suspicion of recurrence is high. Additionally, many patients will require close imaging follow-up for an evolving fibrosis for a number of years before a recurrence can be ruled-out. To address patient concerns, it may be useful to inform patients prior to SABR about the common appearance of post-treatment lung changes and their low risk of cancer recurrence, similar to what patients have found helpful in the discussion of pulmonary nodules [32].

There are inherent limitations of this study. The study is retrospective in nature, and the sample size is modest. The stipulation that patients with recurrence require pathological proof for inclusion in this study is essential to avoid inflating the estimated performance of CT. However, given the excellent local control rates following SABR, the sample size of this study becomes limited, and as such these patients were drawn from a large institutional database (31 recurrences and 507 non-recurrences available, as described above). Nevertheless, to our knowledge, this report still represents the largest study to date detailing the radiographic appearance of pathology-proven local recurrences after lung SABR. Assembling a substantially larger dataset of patients with pathological proof of recurrence would likely require a

multi-institutional pooled analysis. Patients without histologic confirmation of recurrence were not included in our study, since such patients who are diagnosed based on imaging findings only may in fact have benign fibrosis [15]; inclusion of these patients would overinflate the performance of CT imaging. Since patients who had pathologic proof of recurrence are likely different from patients who were unable to undergo confirmatory biopsy, this selection may limit the generalizability of our findings, including the performance characteristics of the HRFs, to the latter group. The clinical impact of this lack of generalizability would likely be minimal, since patients who are unable to have confirmatory biopsies are often unfit for surgical salvage. In this study, 'enlarging opacity' was defined on axial slices; in centers with isotropic reconstructions, defining cranio-caudal growth as a separate risk factor may be redundant if enlargement is measured in all planes. Although all measurements were made using lung window/level settings, standardizing the definition of 'opacity' in terms of HU density changes may be useful to increase generalizability. In addition, there may be underlying differences in tumor biology not captured herein (e.g. volume doubling time) that may help to predict timing of recurrence.

For ethical reasons, our control patients without recurrence were not pathologically confirmed, however, they underwent a minimum follow-up of one year to rule-out local recurrence. We cannot exclude the possibility that a small number of these control patients could develop a late recurrence in the future. In addition, not all of these 'control' patients would be expected to have suspicious CT findings. Since PET/CT was not routinely done on matched controls, the sensitivity/specificity of PET/CT could not be evaluated herein, and the role of FDG-PET/CT warrants further investigation. Finally, there may be variability in the identification of HRFs by physicians, which may be amenable to online training workshops; images herein were analyzed by radiation oncologists, rather than radiologists, as the latter may be unfamiliar with current radiation oncology literature regarding HRFs. More detailed objective measures for the detection of recurrence include CT texture and volumetric analysis, both of which are currently being evaluated [33].

In conclusion, as the use of SABR increases in clinical practice, the need for objective measures to distinguish recurrence from fibrosis on follow-up imaging is pressing. Several HRFs, including one novel HRF, have been validated to be predictive of local recurrence. A systematic assessment of follow-up CTs for HRFs may allow for earlier detection of recurrence. Using a "high-risk count" cut-off of 3 or more features on CT imaging confers excellent sensitivity and specificity for the detection of local recurrence.

## Conflict of interest

The VU university medical center has a research agreement with Varian Medical Systems and Brainlab. SuS and BS have received speaker honoraria and travel support from Varian medical systems, and have participated in advisory boards. The other authors declare that they have no conflicts of interest.

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## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.radonc.2013.06.047.

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