Review Article

Stereotactic ablative radiotherapy for stage I NSCLC: Recent advances and controversies

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ABSTRACT Stereotactic ablative radiotherapy (SABR) is a technique that has rapidly entered routine care for early-stage peripheral non-small cell lung cancer in many countries in the last decade. The adoption of SABR was partly stimulated by advances in the so-called 'image guided' radiotherapy delivery. In the last 2 years, a growing body of publications has reported on clinical outcomes, acute and late radiological changes after SABR, and sub-acute and late toxicity. The local control rates in many publications have exceeded 90% when tumors of up to 5 cm have been treated, with corresponding regional nodal failure rates of approximately 10%. However, these results are not universal: lower control rates reported by some authors serve to emphasize the importance of quality assurance in all steps of SABR treatment planning and delivery. High-grade toxicity is uncommon when so-called 'risk-adapted' fractionation schemes are applied; an approach which involves the use of lower daily doses and more fractions when critical normal organs are in the proximity of the tumor volume. This review will address the new data available on a number of controversial topics such as the treatment of patients without a tissue diagnosis of malignancy, data on SABR outcomes in patients with severe chronic obstructive airways disease, use of a classification system for late radiological changes post-SABR, late treatment-related toxicity, and the evidence to support a need for expert multi-disciplinary teams in the follow-up of such patients.

KEY WORDS: non-small cell lung cancer; stage I; stereotactic ablative radiotherapy

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Introduction

Stereotactic ablative radiotherapy (SABR) is a form of high-precision radiotherapy delivery, which is characterized by an individualized approach to account for tumor mobility and accurate and reproducible patient setup prior to daily treatments (1,2). The results of SABR for early-stage non-small cell lung cancer (NSCLC) arguably represent one of most significant breakthroughs in curative therapy of lung cancer in the past two decades. SABR for pulmonary tumors is typically delivered in 3-8 daily fractions, resulting in good patient compliance and efficient resource utilization. Key features of SABR are summarized in Figure 1. The use of multiple non-coplanar radiation beams or volumetric modulated arcs results in highly conformal dose distributions, with rapid dose falloff in surrounding normal tissues. A typical dose distribution is shown in Figure 2, illustrating very high doses delivered to the target, with steep dose gradients and low doses to normal tissues.

Update on clinical outcomes

Outcomes of two prospective, single-arm multicenter trials in Europe and North America revealed 3-year local control rates ranging from 92-97% (3,4). A meta-analysis of observational studies of SABR reported a 5-year overall survival after SABR that is significantly higher (42%) than the 20% achieved with conventional radiotherapy (5). No randomized studies comparing the two treatments have been reported, but SABR for early-stage lung tumors has nevertheless gained wide acceptance in countries such as Japan (6), The Netherlands (7) and United States (8). More compelling evidence comes from a population-based cancer registry study of the impact of introducing SABR in a Dutch province, which revealed both an increase in radiotherapy utilization and improvement in median survival of elderly patients following the implementation of SABR (7). Excellent clinical outcomes have also been reported in elderly

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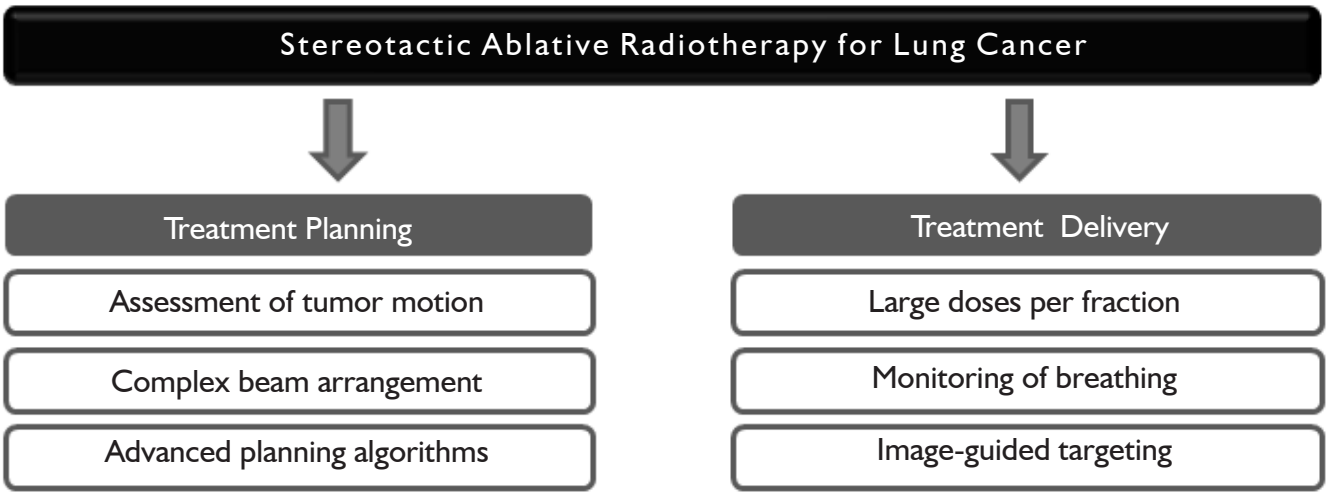

Fig 1. Key features of stereotactic ablative radiotherapy (SABR)

patients with co-existent severe chronic obstructive airways disease (COPD) (9), and a Markov model analysis predicted superior overall and quality-adjusted survival at 5 years in patients with all grades of severity of COPD after SABR versus no treatment (10).

It should be noted, however, that these results have been achieved in the context of rigorous quality control. The introduction of SABR in The Netherlands occurred in the setting of a pre-existing modern radiotherapy infrastructure, together with the introduction of quality assurance programs (11,12). Similarly, much of the available literature on SABR outcomes was derived from treatment of smaller tumors, and data on outcomes of SABR in larger and more centrally-located tumors is still relatively limited (13,14). However, SABR for treatment of central tumors using a 'risk-adapted' dose-fractionation schedule of 7.5 Gy (to a total dose of 60 Gy) reported high-rates of local control and a low incidence of sub-acute toxicity (15).

The issue of whether the excellent results of SABR for lung tumors can also be achieved when patients are treated outside pioneering academic institutions remains a pertinent one. Not all studies have achieved high rates of local control: one center reported an 2-year infield progression free probability of 65% (16), with a 1-year local progression-free survival of less than 80% for lesions measuring more than 4 cm (17). Similarly, other investigators have reported a 2-year local control rate of 70% for T2 tumors (18). Possible explanations for these higher local failure rates are failure to use 4-dimensional CT scans for planning, the limitation of RECIST criteria for assessment of local control, as well as prescribing doses to the tumor isocenter, rather than to the periphery of the target. Centers that prescribe doses to the center of the tumor volume deliver a substantially lower tumor dose than is the case where dose is prescribed to the tumor periphery (Fig 3), an approach which can compromise local control as biological effective doses of more than 100 Gy (BED_{10Gy}) are required for high local control rates (19).

Update on clinical toxicity

A recent review summarized the commoner SABR-related toxicities, which include radiation pneumonitis, bronchial stenosis or necrosis, rib fractures, esophageal injury or injuries to the brachial plexus (13). Only updated results of the more common toxicities, namely chest wall pain and radiation pneumonitis, will be addressed in this current update.

Severe chest wall pain has been reported in approximately 1-2% of patients, with rates of rib fractures ranging from 3-21% in reports evaluating relatively small numbers of patients (13,20). Risk factors for developing chest wall pain are treatment volume and distance from the tumor to the chest wall. Improved planning techniques are now available to reduce chest wall volumes receiving doses in excess of 30 Gy (21). However, the reported incidence of chest wall toxicity may increase in future as increasingly larger lung tumors are now being treated using SABR (14). Nevertheless, chest wall toxicity post-SABR occurs less frequently than post-thoracotomy pain syndromes, which can manifest in about half of surgical patients (22). Up to 30% of post-surgical patients may continue to experience pain after 4 to 5 years (23), although the more widespread use of video-assisted thoracic surgery appears to have reduced this complication (24).

SABR delivery without a pathological diagnosis

In patients who undergo surgery for a growing, peripheral lung nodule suspicious for a lung cancer, a preoperative diagnosis is not always obtained, despite the known morbidity and mortality accompanying a surgical resection (25). For example, a large

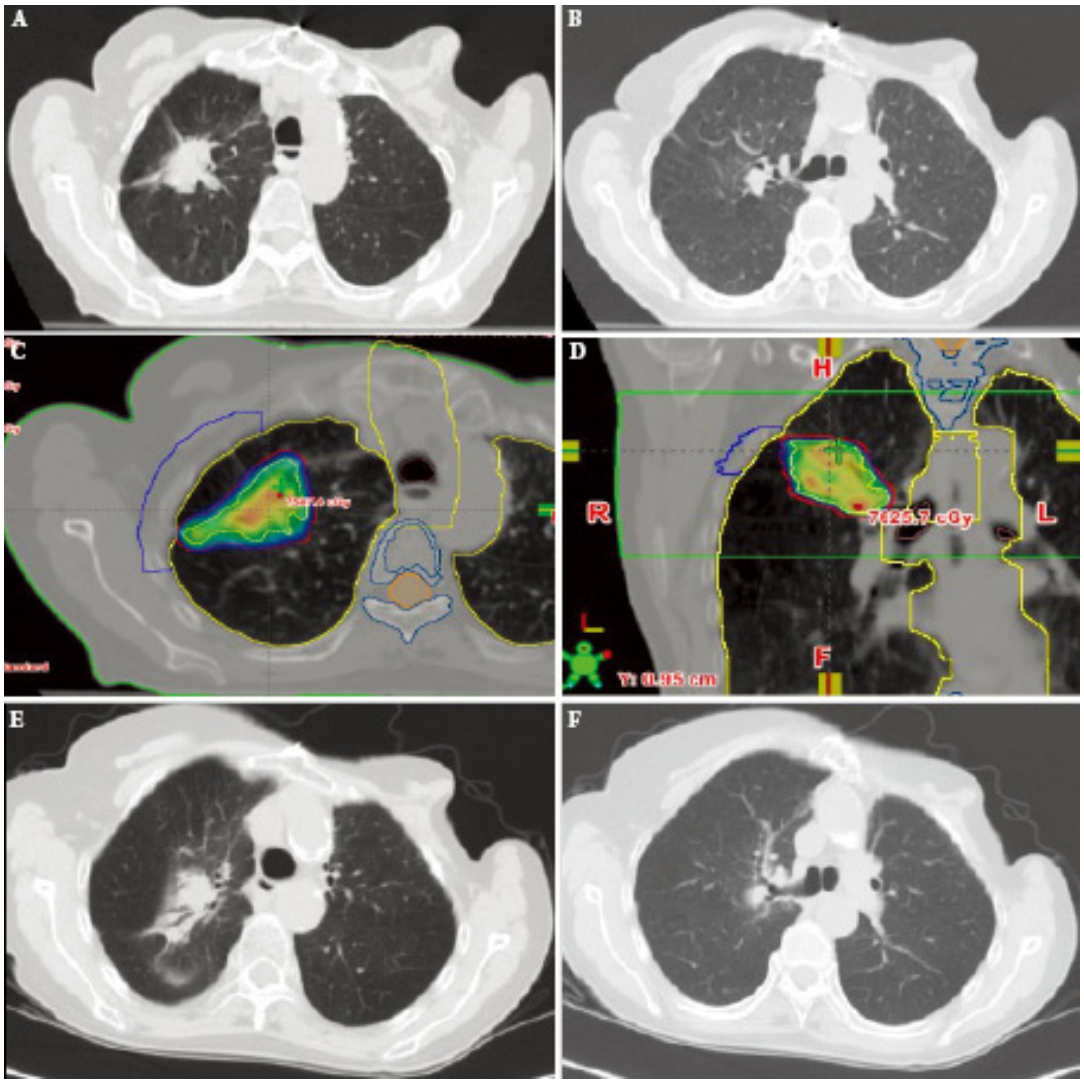

Fig 2. Images of a patient who developed a T2N0M0 adenocarcinoma in the right upper lobe, 30 years after surgery and radiotherapy for a left-sided breast cancer. The lung tumor was treated using SABR in 8-fractions of 7.5 Gy. Pre-treatment images (A, B), the high-dose region receiving 60 Gy in colorwash (C, D), and the post- treatment images at 8 months (E, F) are shown. No evidence for disease progression was observed at two- and-a-half years after SABR.

Japanese study on 1755 operated patients reported that 26% had no preoperative diagnosis (26). The problem of a lack of pre-treatment histological diagnosis is greater in medically inoperable patients who may be at higher risk for complications following a transthoracic needle biopsy. The probability of malignancy in a pulmonary nodule can be calculated using a combination of clinical, radiological and PET findings (27,28).

A number of investigators worldwide have described outcomes after SABR in patients without a pathological diagnosis (3,15,29). With such an approach, the risk of inadvertently treating benign nodules is largely dependent upon the prevalence of benign disease in the population. Current Dutch national radiotherapy guidelines allow for patients without pathology to be accepted for SABR in patients who fulfill all of the following a) a new or growing lesion on CT scans with characteristics of malignancy; b) a high clinical risk for developing lung cancer and c) a FDG-PET positive lesion. This approach is based on data showing a benign diagnosis in less than 4.5% of Dutch patients who underwent surgery after a diagnosis of lung cancer was made based upon CT- and FDG-PET scans (30,31,32). The policy adopted in the Netherlands is consistent with guidelines of the American College of Chest Physicians, which recommends that a likelihood of malignancy that exceeds 60% warrants treatment without further diagnostic procedures (33). A recent population

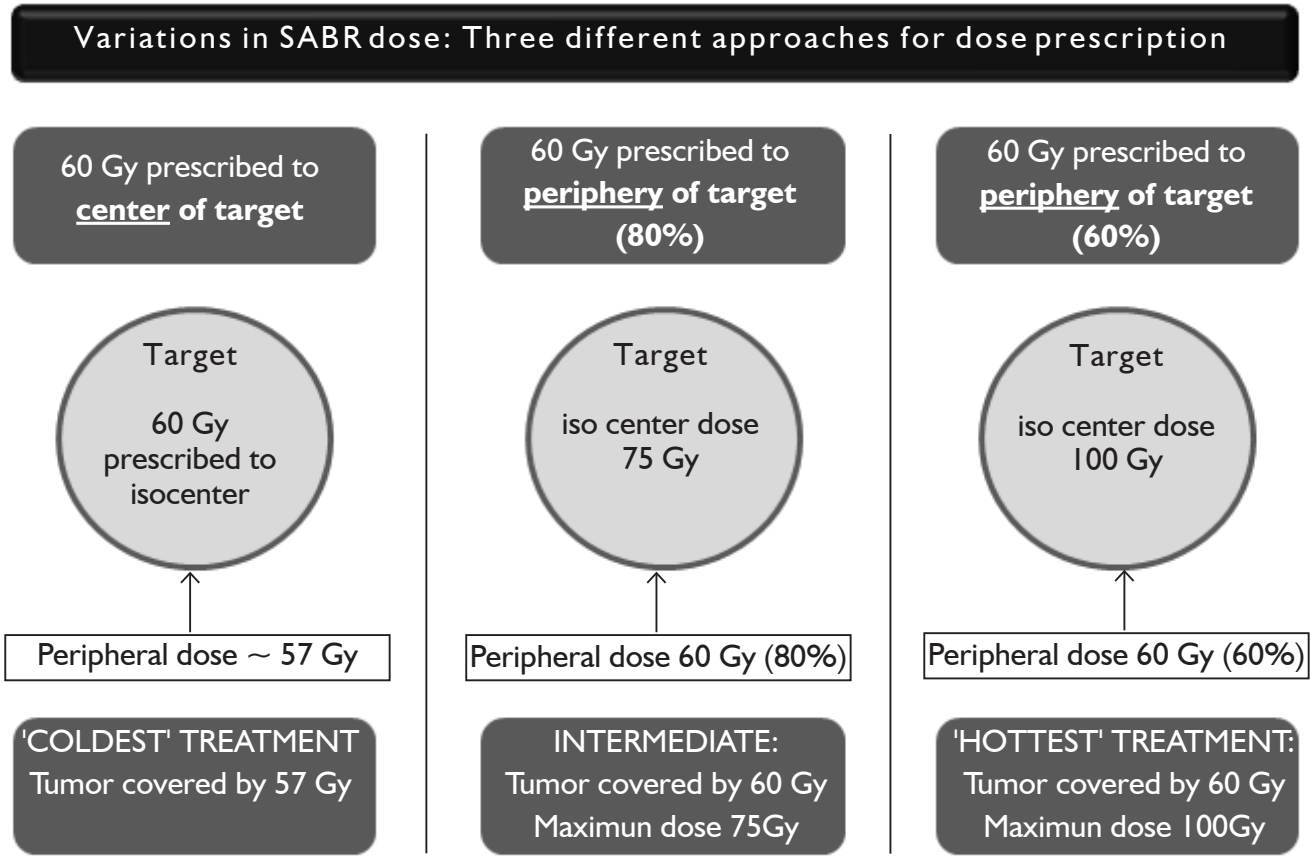

Fig 3. Different approaches described in the literature for dose prescription in SABR.

analysis indicated that inclusion of patients without a histological diagnosis could not have accounted for improvements in survival in an elderly population, as such patients had a poorer survival than patients with histological diagnosis (7).

Nevertheless, the abovementioned approach may be inappropriate in patients living in a region where infections, such as histoplasmosis, can give a false-positive PET uptake (34), thus reducing the specificity of PET. Another study from the United States reported that since institution of routine PET scans for lung nodules, nearly one third of resected nodules were found to be granulomas (35). With the availability of an effective second treatment alternative for patients with a clinical stage I NSCLC, it is clear that more effort should be directed towards obtaining a pathological diagnosis before initiating therapy.

Use of SABR in patients who are fit to undergo surgery

Nearly a third of patients presenting with early-stage disease do not undergo surgery (2). The changing demographics of lung cancer have led to this diagnosis being increasing made in elderly patients in whom the mortality associated with surgery ranges from 5.2-7.4% (25,36). The excellent outcomes of SABR in frail elderly patients has challenged the assumption that surgery should be the preferred treatment for all potentially operable patients with Stage I NSCLC (7,37), and these findings are supported by outcomes from matched comparisons of SABR versus surgery (38,39). SABR is increasingly being performed in potentially operable patients who have fewer co-morbidities (40). A Markov model analysis of outcomes after either SABR or lobectomy for Stage I NSCLC for a 5-year time frame indicated that SABR may offer comparable overall survival and quality-adjusted life expectancy as compared with surgical resection (41). Two single-arm phase II trials of SABR in patients who are fit to undergo surgery have been completed, and the mature results of JCOG 0403 (NCT00238875) and RTOG 0618 (NCT00551369) are awaited. Well-powered prospective studies comparing surgery vs. SABR in early-stage lung cancer are warranted to further investigate the relative survival, quality of life, and cost characteristics of both treatment paradigms.

SABR and lymph node metastases

The rate of regional lymph node failure after SABR has been a question of substantial research interest, since the lymph nodes are not surgically staged. It is well-recognized that some

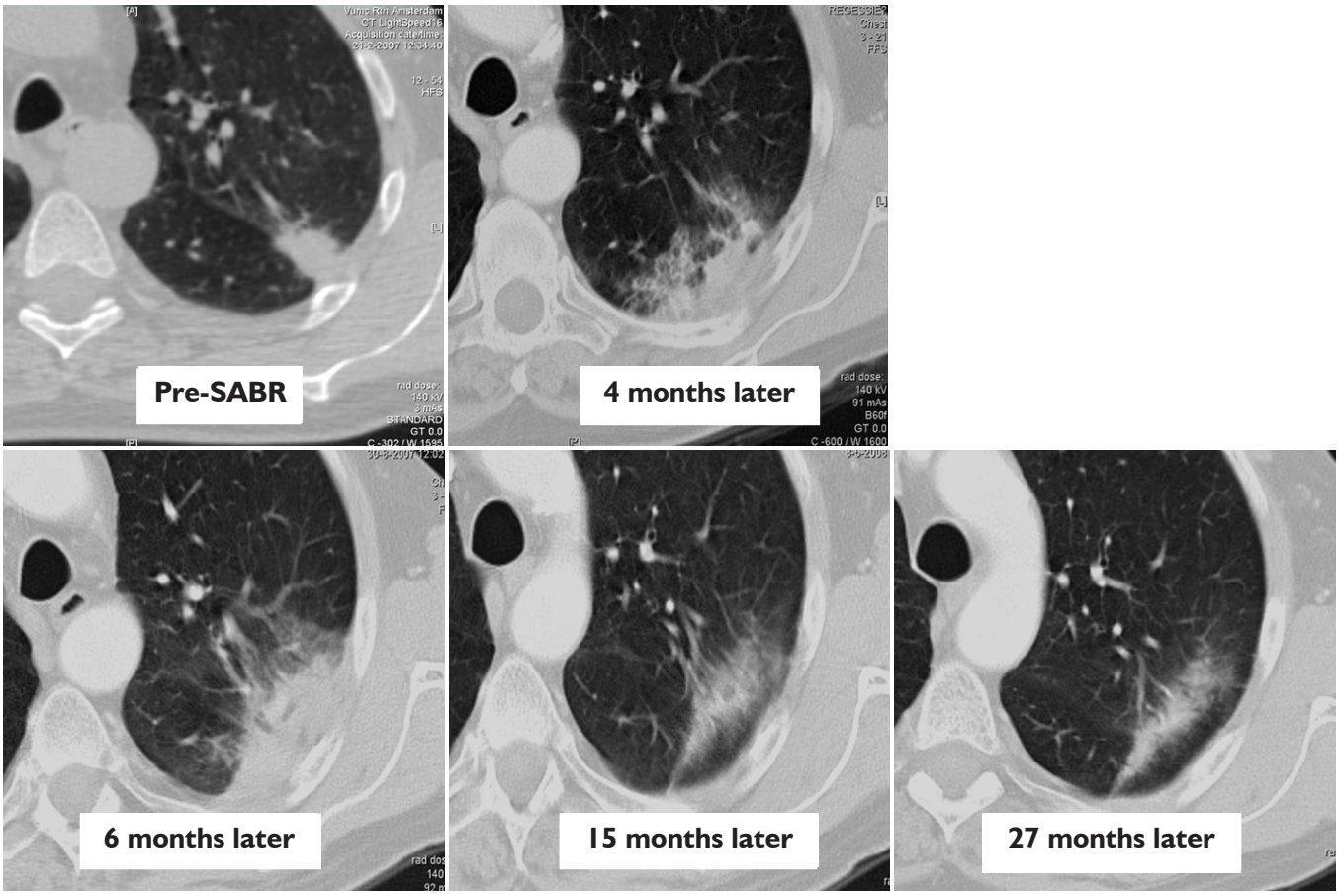

Fig 4. Serial imaging following SABR for a stage I non-small cell lung cancer. The focal radiological changes observed until 6 months were scored as 'patchy consolidation', while the late changes at 15 and 27 months were consistent with the score 'modified conventional' (Table 1).

patients with stage I NSCLC will have occult nodal disease not detectable by pre-operative staging: in a study of 715 patients with clinically-staged stage I disease who proceeded to resection, 16% were found to have occult N1 or N2 disease (34). Despite this, rates of regional failure after SABR are low in PET-staged patients, reported as 10% or less in most studies, comparable to regional recurrence rates after lobectomy (13). For example, a 4% regional recurrence rate was reported after SABR versus 18% after wedge resection (38). The question of why regional recurrence rates are lower than expected after SABR is unanswered, but several plausible hypotheses exist. During SABR, regional lymph nodes near the high-dose volume receive incidental radiation, and as such tumor cells in these nodes may be sterilized (38). In addition, immune activity may play a role: SABR substantially increases T-cell responses in the draining lymphatic tissues in mice, and these T-cell responses have strong anti-cancer cytotoxic activity; this effect is not seen after standard low-dose fractionated radiotherapy (42). Although further research is needed to elucidate these relationships, it remains that regional recurrence rates after SABR are low, even without pathologic staging of the regional nodes.

Patients with occult N1-N2 disease detected at surgery may be offered adjuvant chemotherapy, and SABR does not allow for the identification of such patients. Approximately 66% of patients who are candidates for adjuvant chemotherapy after surgery actually receive chemotherapy (43), and in such patients, adjuvant cisplatin-based chemotherapy is associated with a 5.4% overall survival benefit at 5-years (44). However, this survival improvement is quickly diluted: for a cohort of 100 patients with stage I NSCLC undergoing resection, approximately 16 will have N1/N2 disease, of which 10 would receive chemotherapy, and 0.5 extra patients would be alive after 5 years. Clearly, undertaking nodal dissection for the purposes of identifying chemotherapy candidates is unlikely to offer appreciable improvements in survival. Furthermore, data from patients aged ≥75 who have undergone a resection suggests that the survival in such patients is inferior to untreated controls when adjuvant chemotherapy is administered (45).

Follow-up after SABR

It is important to distinguish treatment-induced changes from

Table 1. A scoring system for acute and late CT changes after stereotactic ablative radiotherapy (SABR) for early stage lung cancer. Standardized classifications will allow for ease of comparisons between different radiotherapy techniques and institutions (modified from reference 46)

ACUTE CT CHANGES (≤ 6 months)		LATE CT CHANGES (> 6 months)	
	Description		Description
Diffuse consolidation	Consolidation > 5 cm in largest dimension. The involved region contains more consolidation than aerated lung.	Modified conventional pattern	Consolidation, loss of volume, bronchiectasis similar to conventional radiation fibrosis, but usually less extensive. May be associated with GGO.
Patchy consolidation	Consolidation ≤ 5 cm in largest dimension and/or the involved region contains less consolidation than aerated lung	Mass-like	Well-circumscribed focal consolidation limited to area surrounding the tumor. The abnormality must be larger than the original tumor size
Diffuse GGO	> 5 cm of GGO, (without consolidation). The involved region contains more GGO than normal lung	Scar-like	Linear opacity in the region of the tumor, associated with loss of volume
Patchy GGO	≤5 cm of GGO, (without consolidation), and/or the involved region contains less GGO than normal lung	No evidence of increased density	No new abnormalities. Includes patients with tumors that are stable, regressing or resolved, or fibrosis in the position of the original tumor that is not larger than the original tumor

GGO: ground glass opacifications.

disease progression in order to avoid both the risk of invasive diagnostic procedures or inappropriate salvage therapy (46). The application of RECIST criteria for evaluation of local response can be difficult because of frequent tumor fibrosis in the high-dose area of SABR (Fig 4). Most studies therefore, have reported local control as an absence of local progression, which can also be challenging. Moderate to intense FDG uptake observed shortly following SABR does not necessarily indicate a residual tumour (47,48).

Consequently, the evaluation of such changes by an experienced multi-disciplinary team of radiation oncologists, radiologists, nuclear medicine physicians and pulmonologists is essential in such a situation. Considerable experience is required to interpret radiological findings post-SABR, and reliable assessment becomes more essential now that increasingly fitter patients are primarily treated with SABR; many of these patients will be long-term survivors. Adequate follow-up imaging allows timely restaging and salvage treatment for local and regional recurrences, and also the detection and treatment of second malignancies that present at a rate of 2-3% per year in this patient population (49,50,51). We recommend re-assessment at 3-, 6- and 12-months after treatment, and every 6-12 months thereafter, with history, physical examination, and CT imaging.

Salvage surgical resections have now been reported in post-SABR recurrences, which were characterized by a rapid enlargement of a mass within a relatively short period (52,53). The role of surgical salvage as a treatment option for recurrences post-SABR is a clinical scenario that will require further study, particularly as it may increase the preference for SABR in some patients who are fit to undergo primary surgery.

References

1. CJA Haasbeek, S Senan, EF Smit, MA Paul, BJ Slotman, FJ Lagerwaard. Critical Review of Non-Surgical Treatment Options for Stage I Non-Small Cell Lung Cancer. Oncologist 2008;13:309-19.
2. Palma D, Senan S. Stereotactic radiation therapy: changing treatment paradigms for stage I non-small cell lung cancer. Curr Opin Oncol 2011;23:133-9.
3. Baumann P, Nyman J, Hoyer M, Wennberg B, Gagliardi G, Lax I, et al. Outcome in a prospective phase II trial of medically inoperable stage I non-small-cell lung cancer patients treated with stereotactic body radiotherapy. J Clin Oncol 2009;27:3290-6.
4. Timmerman R, Paulus R, Galvin J, Michalski J, Straube W, Bradley J, et al. Stereotactic body radiation therapy for inoperable early stage lung cancer. JAMA 2010;303:1070-6.
5. Grutters JPC, Kessels AGH, Pijls-Johannesma M, De Ruysscher D, Joore MA, Lambin P. Comparison of the effectiveness of radiotherapy with photons, protons and carbon-ions for non-small cell lung cancer: A meta-analysis. Radiother Oncol 2010;95:32-40.
6. Nagata Y, Hiraoka M, Mizowaki T, Narita Y, Matsuo Y, Norihisa Y, et al. Survey of stereotactic body radiation therapy in Japan by the Japan 3-D

conformal external beam radiotherapy group. Int J Radiat Oncol Biol Phys 2009;75:343-7.
7. Palma D, Visser O, Lagerwaard FJ, Belderbos J, Slotman BJ, Senan S. The impact of introducing stereotactic lung radiotherapy for elderly patients with Stage I NSCLC: A population-based time-trend analysis. J Clin Oncol 2010;28:5153-9.
8. Pan H, Simpson DR, Mell LK, Mundt AJ, Lawson JD. A survey of stereotactic body radiotherapy use in the United States. Cancer. 2011 Mar 15. doi: 10.1002/cncr.26067. [Epub ahead of print]
9. Palma D, Lagerwaard FJ, Rodrigues G, Haasbeek CJA, Senan S. Curative treatment of stage I non-small cell lung cancer in patients with severe COPD: Outcomes after stereotactic radiotherapy and systematic review of the literature. Int J Radiat Oncol Biol Phys. Forthcoming.
10. Louie AV, Rodrigues G, Hannouf M, Lagerwaard FJ, Palma D, Zaric GS, et al. Withholding Stereotactic Radiotherapy in Elderly Patients with Stage I Non-small Cell Lung Cancer and Co-existing COPD is not Justified: Outcomes of a Markov Model Analysis. Radiother Oncol. Forthcoming.
11. Hurkmans CW, Cuijpers JP, Lagerwaard FJ, Widder J, van der Heide UA, Schuring DD, et al. Recommendations for implementing stereotactic radiotherapy in peripheral stage IA non-small cell lung cancer: Report from the Quality Assurance Working Party of the randomized phase III ROSEL study. Radiat Oncol 2009 4:1.
12. Hurkmans CW, van Lieshout M, Schuring D, van Heumen MJT, Cuijpers JP, Lagerwaard FJ, et al. Quality assurance of 4D-CT scan techniques in a multicenter phase III trial of surgery versus stereotactic radiotherapy (ROSEL). Int J Radiat Oncol Biol Phys Oct 13. [Epub ahead of print]
13. Chi A, Liao Z, Nguyen NP, Xu J, Stea B, Komaki R. Systemic review of the patterns of failure following stereotactic body radiation therapy in early-stage non-small-cell lung cancer: clinical implications. Radiother Oncol 2010;94:1-11.
14. Ong CL, Palma D, Verbakel WFAR, Slotman BJ, Senan S. Treatment of large stage I-II lung tumors using stereotactic body radiotherapy: Planning considerations and early toxicity. Radiother Oncol 2010;97:431-6.
15. Lagerwaard FJ, Haasbeek CJA, Smit EF, Slotman BJ, Senan S. Outcomes of risk-adapted fractionated stereotactic radiotherapy for stage I non-small cell lung cancer. Int J Radiat Oncol Biol Phys 2008;70:685-92.
16. Bral S, Van Parijs H, Soete G, Linthout N, Van Moorter L, Verellen D, et al. A feasibility study of image-guided hypofractionated conformal arc therapy for inoperable patients with localized non-small cell lung cancer. Radiother Oncol 2007;84:252-6.
17. Bral S, Gevaert T, Linthout N, Versmessen H, Collen C, Engels B, et al. Prospective, risk-adapted strategy of stereotactic body radiotherapy for early-stage non-small-cell lung cancer: Results of a Phase II trial. Int J Radiat Oncol Biol Phys. 2010 Aug 12. [Epub ahead of print]
18. Dunlap NE, Larner JM, Read PW, Kozower BD, Lau CL, Sheng K, et al. Size matters: a comparison of T1 and T2 peripheral non-small-cell lung cancers treated with stereotactic body radiation therapy (SBRT). J Thorac Cardiovasc Surg 2010;140:583-9.
19. Onishi H, Shirato H, Nagata Y, Hiraoka M, Fujino M, Gomi K, 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:S94-100.
20. Stephans KL, Djemil T, Tendulkar RD, Robinson CG, Reddy CA, Videtic GM. Prediction of Chest Wall Toxicity From Lung Stereotactic Body Radiotherapy (SBRT). Int J Radiat Oncol Biol Phys 2011 Feb 5. [Epub ahead of print]
21. Ong CL, Verbakel WFAR, Cuijpers JP, Slotman BJ, Lagerwaard FJ, Senan S. Stereotactic radiotherapy for peripheral lung tumors: A comparison of volumetric modulated arc therapy and 3 other delivery approaches. Radiother Oncol 2010;97:437-42.
22. Rogers ML, Duffy JP. Surgical aspects of chronic post-thoracotomy pain. Eur J Cardiothorac Surg 2000;18:711-6.
23. Karmakar MK, Ho AM. Postthoracotomy pain syndrome. Thorac Surg Clin 2004;14:345-52.
24. Sugiura H, Morikawa T, Kaji M, Sasamura Y, Kondo S, Katoh H. Long-term benefits for the quality of life after video-assisted thoracoscopic lobectomy in patients with lung cancer. Surg Laparosc Endosc Percutan Tech 1999;9:403-8.
25. Finlayson E, Fan Z, Birkmeyer JD. Outcomes in octogenarians undergoing high-risk cancer operation: a national study. J Am Coll Surg 2007;205:729-34.
26. Sato S, Koike T, Yamato Y, Yoshiya K, Motono N, Takeshige M, et al. Diagnostic yield of preoperative computed tomography imaging and the importance of a clinical decision for lung cancer surgery. Gen Thorac Cardiovasc Surg 2010;58:461-6.
27. Swensen SJ, Silverstein MD, Ilstrup DM, Schleck CD, Edell ES. The probability of malignancy in solitary pulmonary nodules. Application to small radiologically indeterminate nodules. Arch Intern Med 1997;157:849-855.
28. Herder GJ, van Tinteren H, Golding RP, Kostense PJ, Comans EF, Smit EF, et al. Clinical prediction model to characterize pulmonary nodules: validation and added value of 18F-fluorodeoxyglucose positron emission tomography. Chest 2005;128:2490-6.
29. Inoue T, Shimizu S, Onimaru R, Takeda A, Onishi H, Nagata Y, et al. Clinical outcomes of stereotactic body radiotherapy for small lung lesions clinically diagnosed as primary lung cancer on radiologic examination. Int J Radiat Oncol Biol Phys 2009;75:683-7.
30. van Tinteren H, Hoekstra OS, Smit EF, van den Bergh JH, Schreurs AJ, Stallaert RA, et al. Effectiveness of positron emission tomography in the preoperative assessment of patients with suspected non-small-cell lung cancer: the PLUS multicentre randomised trial. Lancet 2002;359:1388-93.
31. Herder GJ, Kramer H, Hoekstra OS, Smit EF, Pruim J, van Tinteren H, et al. Traditional versus up-front [18F] fluorodeoxyglucose-positron emission tomography staging of non-small-cell lung cancer: a Dutch cooperative randomized study. J Clin Oncol 2006;24:1800-6.
32. Belgers EH, Siebenga J, Bosch AM, van Haren EH, Bollen EC. Complete video-assisted thoracoscopic surgery lobectomy and its learning curve. A single center study introducing the technique in The Netherlands. Interact Cardiovasc Thorac Surg 2010;10:176-80.
33. Scott WJ, Howington J, Feigenberg S, Movsas B, Pisters K; American College of Chest Physicians. Treatment of non-small cell lung cancer stage I and stage II: ACCP evidence-based clinical practice guidelines (2nd

edition). Chest 2007;132:s234-42.
34. Cerfolio RJ, Bryant AS. Survival of patients with true pathologic stage I non-small cell lung cancer. Ann Thorac Surg 2009;88:917-22.
35. May BJ, Levsky JM, Godelman A, Jain VR, Little BP, Mahadevia PS, et al. Should CT Play a Greater Role in Preventing the Resection of Granulomas in the Era of PET? AJR Am J Roentgenol 2011;196:795-800.
36. Wouters MW, Siesling S, Jansen-Landheer ML, Elferink MA, Belderbos J, Coebergh JW, et al. Variation in treatment and outcome in patients with non-small cell lung cancer by region, hospital type and volume in the Netherlands. Eur J Surg Oncol 2010;36:s83-92.
37. Haasbeek CJA, Lagerwaard FJ, Antonisse ME, Slotman BJ, Senan S. Stage I non-small cell lung cancer in patients aged 75 years and older: Outcomes after stereotactic radiotherapy. Cancer 2010;116:406-14.
38. Grills IS, Mangona VS, Welsh R, Chmielewski G, McInerney E, Martin S, et al. Outcomes after stereotactic lung radiotherapy or wedge resection for stage I non-small-cell lung cancer. J Clin Oncol 2010;28:928-35.
39. Crabtree TD, Denlinger CE, Meyers BF, El Naqa I, Zoole J, Krupnick AS, et al. Stereotactic body radiation therapy versus surgical resection for stage I non-small cell lung cancer. J Thorac Cardiovasc Surg 2010;140:377-86.
40. Onishi H, Shirato H, Nagata Y, Hiraoka M, Fujino M, Gomi K, et al. Stereotactic body radiotherapy (SBRT) for operable Stage I non-small-cell lung cancer: Can SBRT be comparable to surgery? Int J Radiat Oncol Biol Phys. 2010 Jul 15. [Epub ahead of print]
41. Louie AV, Rodrigues G, Hannouf M, Zaric GS, Palma DA, Cao JQ, et al. Stereotactic body radiotherapy versus surgery for medically operable Stage I non-small-cell lung cancer: A Markov model-based decision analysis. Int J Radiat Oncol Biol Phys. 2010 Oct 5. [Epub ahead of print]
42. Lee Y, Auh SL, Wang Y, Burnette B, Wang Y, Meng Y, et al. Therapeutic effects of ablative radiation on local tumor require CD8+ T cells: changing strategies for cancer treatment. Blood 2009;114:589-95.
43. Felip E, Rosell R, Maestre JA, Rodríguez-Paniagua JM, Morán T, Astudillo J, et al. Preoperative chemotherapy plus surgery versus surgery plus adjuvant chemotherapy versus surgery alone in early-stage non-small-cell lung cancer. J Clin Oncol 2010;28:3138-45.
44. NSCLC Meta-analyses Collaborative Group, Arriagada R, Auperin A, Burdett S, Higgins JP, Johnson DH, et al. Adjuvant chemotherapy, with or without postoperative radiotherapy, in operable non-small-cell lung cancer: two meta-analyses of individual patient data. Lancet 2010;375:1267-77.
45. Pepe C, Hasan B, Winton TL, Seymour L, Graham B, Livingston RB, et al. Adjuvant vinorelbine and cisplatin in elderly patients: National Cancer Institute of Canada and Intergroup Study JBR.10. J Clin Oncol 2007;25:1553-61.
46. Dahele M, Palma D, Lagerwaard F, Slotman B, Senan S. Radiological changes following stereotactic radiotherapy for stage I lung cancer. J Thorac Oncol. Forthcoming.
47. Matsuo Y, Nakamoto Y, Nagata Y, Shibuya K, Takayama K, Norihisa Y, et al. Characterization of FDG-PET images after stereotactic body radiation therapy for lung cancer. Radiother Oncol 2010;97:200-4.
48. Henderson MA, Hoopes DJ, Fletcher JW, Lin PF, Tann M, Yiannoutsos CT, et al. A pilot trial of serial 18F-fluorodeoxyglucose positron emission tomography in patients with medically inoperable stage I non-small-cell lung cancer treated with hypofractionated stereotactic body radiotherapy. Int J Radiat Oncol Biol Phys 2010;76:789-95.
49. Pasini F, Verlato G, Durante E, de Manzoni G, Valduga F, Accordini S, et al. Persistent excess mortality from lung cancer in patients with stage I non-small-cell lung cancer, disease-free after 5 years. Br J Cancer 2003;88:1666-8.
50. Maeda R, Yoshida J, Ishii G, Aokage K, Hishida T, Nishimura M, et al. Long-term outcome and late recurrence in patients with completely resected stage IA non-small cell lung cancer. J Thorac Oncol 2010;5:1246-50.
51. Murthy SC, Reznik SI, Ogwudu UC, Farver CF, Arrossi A, Batizy LH, et al. Winning the battle, losing the war: the noncurative "curative" resection for stage I adenocarcinoma of the lung. Ann Thorac Surg 2010;90:1067-74.
52. Neri S, Takahashi Y, Terashi T, Hamakawa H, Tomii K, Katakami N, et al. Surgical treatment of local recurrence after stereotactic body radiotherapy for primary and metastatic lung cancers. J Thorac Oncol 2010;5:2003-7.
53. Chen F, Matsuo Y, Yoshizawa A, Sato T, Sakai H, Bando T, et al. Salvage lung resection for non-small cell lung cancer after stereotactic body radiotherapy in initially operable patients. J Thorac Oncol 2010;5:1999-2002.

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