Editor's note:
In the era of personalized medicine, a critical appraisal new developments and controversies are essential in order to derived tailored approaches. In addition to its educative aspect, we expect these discussions to help younger researchers to refine their own research strategies.

Controversies on Lung Cancer: Pros and Cons

Cons: After lung stereotactic ablative radiotherapy for a peripheral stage I non-small cell lung carcinoma, radiological suspicion of a local recurrence is not sufficient indication to proceed to salvage therapy

Meredith Giuliani, Andrea Bezjak

Department of Radiation Oncology, Princess Margaret Cancer Centre, Toronto, ON, Canada

Correspondence to: Dr. Andrea Bezjak, MD. Department of Radiation Oncology, 610 University Avenue, 5th Floor, Princess Margaret Cancer Centre, Toronto, ON M5G 2M9, Canada. Email: andrea.bezjak@rmp.uhn.on.ca.

Related to: Nguyen TK, Palma DA. Pros: After stereotactic ablative radiotherapy for a peripheral early-stage non-small cell lung cancer, radiological suspicion of a local recurrence can be sufficient indication to proceed to salvage therapy. Transl Lung Cancer Res 2016;5:647-50.
Giuliani M, Bezjak A. Rebuttal from Dr. Bezjak and Dr. Giuliani. Transl Lung Cancer Res 2016;5:658-9.
Nguyen TK, Palma DA. Rebuttal from Dr. Nguyen and Dr. Palma. Transl Lung Cancer Res 2016;5:655-7.

Submitted Nov 12, 2016. Accepted for publication Dec 16, 2016.
doi: 10.21037/tlcr.2016.12.10
View this article at: http://dx.doi.org/10.21037/tlcr.2016.12.10

Stereotactic body radiotherapy (SBRT) or stereotactic ablative radiotherapy (SABR) has become the standard of care for inoperable stage I non-small cell lung carcinoma (NSCLC). SBRT for peripheral tumors is well tolerated with minimal side effects (1,2) and results in excellent local control (2). While local recurrence is uncommon following lung SBRT, with the increasing use of SBRT in operable patients, there is a greater need to identify and manage local recurrences.

Radiation induced lung injury (RILI) is a common occurrence after SBRT. RILI is a benign process involving fibrocytes and other inflammatory cells (3). It is complex in its appearance, evolves over time (4,5) and its appearance can vary with treatment technique (6). RILI from SBRT is of a different nature than radiographic changes seen from conventional radiotherapy treatments. It is uncommon for patients to develop symptomatic radiation pneumonitis after lung SBRT (1), but radiographic changes of RILI do occur in the majority of patients starting 3-6 months after SBRT and can evolve for years (7). One classification system describes four patterns of RILI, namely the modified conventional, mass-like and scar-like fibrosis as well as the "no evidence of increased density" pattern (5). Mass-like fibrosis, defined as a "well-circumscribed focal consolidation limited to area surrounding the tumor and the abnormality must be larger than the original tumor" (5) is a particularly challenging form of RILI to distinguish from local recurrence (5,8,9) and leads to clinical concerns relating to whether the changes are suspicious and what, if any, interventions are appropriate (9,10). However, the majority of cases of mass-like fibrosis remain stable over time without development of recurrence, and are thus confirmed as RILI.

There is no uniform definition of local control following SBRT, whether in studies or in clinical practice. RECIST criteria, which classify an increase of ≥20% in

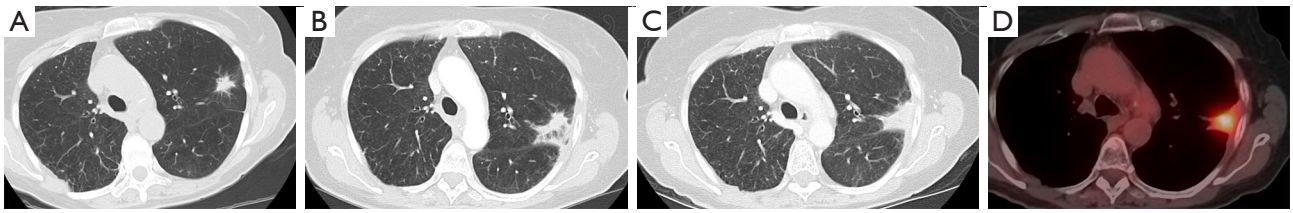

Figure 1 Illustrative case where salvage lobectomy on the basis of high suspicion radiological evidence of local recurrence 7-month post SBRT revealed fibrosis with no evidence of viable cancer. (A) Baseline CT scan image of biopsy proven non-small cell lung cancer, T1N0, that was then treated with SBRT (48Gray in 4 fractions); (B) CT image 3-month post SBRT showing increased consolidation and pleural thickening; (C) CT image 6-month post SBRT, showing increasing mass-like consolidation with craniocaudal growth; (D) FDG-PET scan 7-month post SBRT, SUV_{max} 8.9 (pre-treatment SUV_{max} 4.3).

size as "progressive disease", has been used in early SBRT studies (RTOG 0236) but are limited by RILI (10). The next generation of studies, such as RTOG 0813 have distinguished between local enlargement and local failure, and have required that an increase in tumor dimension of 20% be confirmed with either FDG-PET imaging with uptake of a similar intensity as the pretreatment staging PET, or a biopsy confirming viable carcinoma, before a local failure is declared (11).

Given the limitations of tumor measurement on CT scans in the post-SBRT setting, efforts were made to identify high risk features, beyond size, that would help identify local failure on CT scans. Kato *et al*. proposed the following high-risk features on a series of 27 cases (with 5 local recurrences): a bulging margin, disappearance of air bronchograms, appearance of pleural effusion, or increase in the abnormal opacity after 12 months (12). This work was expanded by Huang *et al*., on a matched-case series of 12 biopsy-proven recurrences; they found the previous criteria valid and added an additional feature cranio-caudal growth (13). Several groups have attempted to validate these high risk radiological features. Halpenny *et al*. found only new bulging margin as a significant predictor; they had 10 local failures, four of which were biopsy proven (14). Peulen *et al*. using a multi-institutional series including 53 local recurrences (13 of which were biopsy proven) suggested a simplified model that combined bulging margin and cranio-caudal growth (15). Studies describing and validating these features have a common significant limitation, which is the lack of biopsy confirmation of all cases that were deemed to be "recurrence". This likely reflects the challenges of considering a biopsy in a predominantly medically inoperable patient population and the ethical considerations of subjecting a patient to a potentially risky procedure if there is not curative salvage therapy that can be offered.

Given the limitations of CT to distinguish RILI from recurrent cancer, several groups have examined FDG-PET as an alternate or complementary approach. One caveat to the interpretation of FDG-PET data is the lack of standard inter-institutional approach to FDG-PET scans, which can impact the measured SUV values. Additional limitations of FDG-PET scans include the hypermetabolic activity seen in RILI (16) and a lack of validated SUV cut-offs for local recurrence. One algorithm proposes SUV_{max} of ≥5 as a high-risk threshold for local failure (17). A series of 128 patients concluded that SUV_{max} of ≥5 should prompt a biopsy; however, the positive predictive value was only 50% (18). A series with 6 biopsy proven local recurrences reported high SUV_{max}, all greater the 5 (19). However, other reports describe cases that exceed that SUV threshold but were proven to be benign changes without any evidence of residual or recurrent tumors (20,21), as illustrated in *Figure 1*. There are other reports of highly suspicious radiographic findings prompting surgical resection without evidence of disease (8,21), but the true frequency of this phenomenon is unclear. Thus, there is currently no established radiological (CT and/or PET) criteria that has sufficient sensitivity and specificity to confirm local failure. Distinguishing RILI from recurrence ideally requires the use of complementary imaging modality to guide the selection of patients most likely to have a local recurrence, who should proceed to biopsy. However, a biopsy done too early after SBRT may result in a false positive biopsy as the time at which patients will develop maximal pathological response to high-dose per fraction radiation such as SBRT is unknown. There have indeed been reports of false positive biopsy following SBRT at 5 and 14 months (3).

The limitations of CT and FDG-PET scans to diagnose

local failure have prompted investigators to explore alternate imaging modalities. One study is using thoracic MRI scans in patients considered to have either stable fibrosis or recurrent cancer; a number of MRI sequences are obtained, that provide anatomic and functional characterization of the area of interest, with the hypothesis that MRI will be able to distinguish fibrosis from tumor recurrence (22). Another study is investigating FLT-PET scans, hypothesizing that the integration of thymidine into DNA as a tool to assess proliferation, can distinguish fibrosis for local recurrence (23). The use of biopsy must be taken in context with a patient's medical status and the options available for salvage. All such cases should be discussed in a multi-disciplinary setting.

The importance of confirming a local failure using pathology before embarking on salvage interventions is impacted by the potential risk and toxicity associated with those salvage treatments. The two main forms of salvage therapy, salvage surgery and re-irradiation, are both associated with potential toxicities. There is limited experience of salvage surgery in the literature. This likely reflects the patient population who received SBRT, as in general, SBRT is used in medically inoperable or high risk patients for surgery, with only a minority of patients currently being medically operable and choosing to have SBRT instead. Given the challenges of operating once post radiation fibrosis has occurred, and patients' age and comorbidities, salvage surgery for local failure post SBRT is clearly a high-risk option and should only be contemplated after careful consideration of risks and benefits. Small series looking at salvage lobectomy have reported low rates of morbidities in very well selected patients in centers with high surgical volume and expertise (20,21,24).

Salvage radiation in the form of additional SBRT has also been reported. A report on 29 patients from the Karolinska University Hospital demonstrated this approach can achieve local control, however there is a significant risk of grade 5 toxicity, massive hemoptysis, particularly with more central tumors and larger volumes (25). It is our recommendations that such risks should be considered only for patients with pathologically proven tumor recurrence.

Systemic therapy, including targeted therapy, chemotherapy and immunotherapy may be an option for patients with isolated local failures but is not considered curative, and is associated with side-effects and risks, and there is no evidence currently that early institution of such therapy would clearly improve patient outcomes, particularly as isolated local failure may not be causing any symptoms.

Conclusions

Radiological suspicion of local recurrence following lung SBRT in the absence of pathological proof of recurrences does not have sufficient sensitivity and specificity to select patients to potentially toxic salvage therapies. While proposed models of high-risk CT features may be helpful, no current models have been adequately validated with confirmed local failure; the "gold standard" evidence is scant. In the future, purely imaging based combinations of CT and novel imaging modalities must be validated against biopsy proven failures to identify local recurrences without a biopsy. Until then, patients with high clinical and radiographic suspicion of local recurrence should undergo, where feasible, biopsy confirmation prior to consideration of salvage therapy to maximize cure rates and the therapeutic ratios for patients with early stage lung cancer.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Taremi M, Hope A, Dahele M, et al. Stereotactic body radiotherapy for medically inoperable lung cancer: prospective, single-center study of 108 consecutive patients. Int J Radiat Oncol Biol Phys 2012;82:967-73.
2. Timmerman R, Paulus R, Galvin J, et al. Stereotactic body radiation therapy for inoperable early stage lung cancer. JAMA 2010;303:1070-6.
3. Singhvi M, Lee P. Illustrative cases of false positive biopsies after stereotactic body radiation therapy for lung cancer based on abnormal FDG-PET-CT imaging. BMJ Case Rep 2013;2013.
4. Faruqi S, Giuliani ME, Raziee H, et al. Interrater reliability of the categorization of late radiographic changes after lung stereotactic body radiation therapy. Int J Radiat Oncol Biol Phys 2014;89:1076-83.
5. Dahele M, Palma D, Lagerwaard F, et al. Radiological changes after stereotactic radiotherapy for stage I lung cancer. J Thorac Oncol 2011;6:1221-8.
6. Senthi S, Dahele M, van de Ven PM, et al. Late radiologic

changes after stereotactic ablative radiotherapy for early stage lung cancer: a comparison of fixed-beam versus arc delivery techniques. Radiother Oncol 2013;109:77-81.
7. Raziee H, Hope A, Faruqi S, et al. Classification and Reporting of Late Radiographic Changes After Lung Stereotactic Body Radiotherapy: Proposing a New System. Clin Lung Cancer 2015;16:e245-51.
8. Takeda A, Kunieda E, Takeda T, et al. Possible misinterpretation of demarcated solid patterns of radiation fibrosis on CT scans as tumor recurrence in patients receiving hypofractionated stereotactic radiotherapy for lung cancer. Int J Radiat Oncol Biol Phys 2008;70:1057-65.
9. Matsuo Y, Nagata Y, Mizowaki T, et al. Evaluation of mass-like consolidation after stereotactic body radiation therapy for lung tumors. Int J Clin Oncol 2007;12:356-62.
10. RTOG 0236: A phase II trial of stereotactic body radiation therapy (sbrt) in the treatment of patients with medically inoperable stage i/ii non-small cell lung cancer. Available online: https://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=0236. Accessed October 12, 2016.
11. Bezjak A, Bradley J, Gaspar L, et al. RTOG 0813: seamless phase I/II study of stereotactic lung radiotherapy (SBRT) for early-stage, centrally located, non–small-cell lung cancer (NSCLC) in medically inoperable patients. 2014. Available online: https://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=0813
12. Kato S, Nambu A, Onishi H, et al. Computed tomography appearances of local recurrence after stereotactic body radiation therapy for stage I non-small-cell lung carcinoma. Jpn J Radiol 2010;28:259-65.
13. Huang K, Senthi S, Palma DA, et al. High-risk CT features for detection of local recurrence after stereotactic ablative radiotherapy for lung cancer. Radiother Oncol 2013;109:51-7.
14. Halpenny D, Ridge CA, Hayes S, et al. Computed tomographic features predictive of local recurrence in patients with early stage lung cancer treated with stereotactic body radiation therapy. Clin Imaging 2015;39:254-8.
15. Peulen H, Mantel F, Guckenberger M, et al. Validation of High-Risk Computed Tomography Features for Detection of Local Recurrence After Stereotactic Body Radiation Therapy for Early-Stage Non-Small Cell Lung Cancer. Int J Radiat Oncol Biol Phys 2016;96:134-41.
16. Hoopes DJ, Tann M, Fletcher JW, et al. FDG-PET and stereotactic body radiotherapy (SBRT) for stage I non-small-cell lung cancer. Lung Cancer 2007;56:229-34.
17. Huang K, Dahele M, Senan S, et al. Radiographic changes after lung stereotactic ablative radiotherapy (SABR)--can we distinguish recurrence from fibrosis? A systematic review of the literature. Radiother Oncol 2012;102:335-42.
18. Zhang X, Liu H, Balter P, et al. Positron emission tomography for assessing local failure after stereotactic body radiotherapy for non-small-cell lung cancer. Int J Radiat Oncol Biol Phys 2012;83:1558-65.
19. Hayashi S, Tanaka H, Hoshi H. Imaging characteristics of local recurrences after stereotactic body radiation therapy for stage I non-small cell lung cancer: Evaluation of mass-like fibrosis. Thorac Cancer 2015;6:186-93.
20. Allibhai Z, Cho BC, Taremi M, et al. Surgical salvage following stereotactic body radiotherapy for early-stage NSCLC. Eur Respir J 2012;39:1039-42.
21. Chen F, Matsuo Y, Yoshizawa A, 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.
22. Stereotactic Body Radiotherapy (RT) for Non-Small Cell Lung Cancer. Available online: https://clinicaltrials.gov/ct2/show/NCT01480973. Accessed October 12, 2016.
23. Piloting the Feasibility of FLT-PET/CT Non-Small Cell Lung Cancer Managed With SBRT (SBRT FLT-PET). Available online: https://clinicaltrials.gov/ct2/show/NCT02456246. Accessed October 12, 2016.
24. Neri S, Takahashi Y, Terashi T, et al. Surgical treatment of local recurrence after stereotactic body radiotherapy for primary and metastatic lung cancers. J Thorac Oncol 2010;5:2003-7.
25. Peulen H, Karlsson K, Lindberg K, et al. Toxicity after reirradiation of pulmonary tumours with stereotactic body radiotherapy. Radiother Oncol 2011;101:260-6.

Cite this article as: Giuliani M, Bezjak A. Cons: After lung stereotactic ablative radiotherapy for a peripheral stage I non-small cell lung carcinoma, radiological suspicion of a local recurrence is not sufficient indication to proceed to salvage therapy. Transl Lung Cancer Res 2016;5(6):651-654. doi: 10.21037/tlcr.2016.12.10

