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

Rebuttal from Dr. Nguyen and Dr. Palma

Timothy K. Nguyen, David A. Palma

Department of Radiation Oncology, London Health Sciences Centre, London, Canada

Correspondence to: Dr. David A. Palma, MD, PhD, FRCPC. Department of Radiation Oncology, London Health Sciences Centre, 790 Commissioners Road East, Room A3-123B, London, ON N6A 4L6, Canada. Email: David.Palma@lhsc.on.ca.

Comment on: 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;5:651-4.

Submitted Dec 01, 2016. Accepted for publication Dec 08, 2016.
doi: 10.21037/tlcr.2016.12.09
View this article at: http://dx.doi.org/10.21037/tlcr.2016.12.09

Our thanks to Drs. Giuliani and Bezjak for a thoughtful commentary on a controversial topic. Upon synthesizing the discussion points, we reframed the debate into four discrete questions, which we will address in this rebuttal.

Are the imaging features used to predict recurrence, namely the CT high-risk features (HRFs), any good?

Drs. Guiliani and Bezjak stress that studies reporting LRs require pathologic correlation to ensure that LR is correctly diagnosed. We agree. Both the Peulen and Huang studies, included LRs that had confirmation of recurrence (1,2). In the Peulen HRF validation study, while it is true that only 13 of 53 LRs were confirmed by biopsy, only those 13 were included in their analyses (1). We cannot require biopsies of patients without recurrence, since such procedures are often not clinically indicated and are associated with risk. Regarding their clinical utility, HRFs have excellent reported sensitivities of 92% (1,2) and specificities of 85% (1) and 92% (2). We conclude that HRFs perform well enough for clinical practice.

If imaging is highly suggestive of LR and biopsy is unsafe, is salvage treatment contraindicated?

If salvage treatment is contraindicated, the only remaining options are best-supportive care and/or palliative interventions, with inevitable morbidity and mortality from progression. There is ample precedent for treating without pathology. Treatment of primary lung cancers when biopsy is unavailable is well-established in surgical guidelines when the risk of cancer is high (3) and similarly, many SBRT series do not require biopsy in all patients (4).

When biopsies are unsafe, salvage surgery may be unsafe as well. However, salvage SBRT (or treatment with other radiation fractionations) remains a possibility. Hearn *et al.* retrospectively identified 10 medically inoperable patients with isolated LRs ≤5 cm, who tolerated salvage SBRT with no grade 3–5 toxicities (5). Another series examined grade 3–5 toxicities after salvage SBRT in 29 patients with LRs (32 tumors: 21 peripheral, 11 central). Toxicities were dependent on tumor location: treatment of central tumors was associated with grade 4 (n=2) and grade 5 (n=3) toxicities. Peripheral tumors, however, had no grade 4–5 toxicities (6). These findings support the use of cautious

salvage SBRT in carefully selected patients. We conclude that in patients with imaging findings highly suggestive of LR, but unable to tolerate biopsy, salvage treatment can be more appropriate than palliation alone.

If imaging is highly suggestive of LR and biopsy was done but is non-diagnostic, is salvage treatment also contraindicated?

When clinical and radiologic suspicions are high, clinicians may be dissatisfied by a negative biopsy. Consider a hypothetical scenario: several HRFs are present, including bulging margins, craniocaudal growth, and sequential enlargement. A PET scan reveals a SUV_{max} of 10. A biopsy returns as non-diagnostic. Is it best to repeat the biopsy, treat, or do nothing? Nishimura *et al*. presented two cases of LR that proceeded to salvage SBRT without pathology. In one case, the biopsy was unsuccessful, and in the second, the tumor board recommended against biopsy given the strong suspicion for LR and patient comorbidities (7). We, like Nishimura *et al.*, conclude that salvage treatment is not contraindicated by a non-diagnostic biopsy. At times, we may be forced to act using the best available evidence when our gold standard (i.e., pathology) fails us.

If imaging is highly suggestive of LR and biopsy is safe, is biopsy necessary?

This is the most controversial of the four questions. Biopsies are imperfect and come with risks of complications (8), non-diagnostic samples (9) and treatment delays. A rule of 'biopsy for all' should not be enforced without careful consideration. As Drs. Giuliani and Bezjak correctly indicate, biopsies in this patient population are at risk for false positives, even 14 months after treatment (10). Furthermore, in a case from their own institution, a patient with LR required 11 needle passes over three different biopsy attempts before a pathological diagnosis was obtained (11).

In conclusion, our differing viewpoints ultimately share common ground. We all agree that there are unclear rules for when imaging is sufficient to guide salvage therapy. Biopsies remain the gold standard in diagnosing LR and should be obtained when feasible. However, we contend that a pathologic diagnosis is not always possible—even with a biopsy attempt. Accepting that a validated, evidence-based approach using HRFs can be sufficient to inform salvage treatment in a multidisciplinary setting, grants clinicians the flexibility to provide appropriate care tailored to a patient's specific situation.

Acknowledgements

Dr. Palma is supported by a Clinician-Scientist Grant from the Ontario Institute for Cancer Research.

Footnote

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

References

1. 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.
2. 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.
3. British Thoracic Society; Society of Cardiothoracic Surgeons of Great Britain and Ireland Working Party. BTS guidelines: guidelines on the selection of patients with lung cancer for surgery. Thorax 2001;56:89-108.
4. Louie AV, Palma DA, Dahele M, et al. Management of early-stage non-small cell lung cancer using stereotactic ablative radiotherapy: controversies, insights, and changing horizons. Radiother Oncol 2015;114:138-47.
5. Hearn JW, Videtic GM, Djemil T, et al. Salvage stereotactic body radiation therapy (SBRT) for local failure after primary lung SBRT. Int J Radiat Oncol Biol Phys 2014;90:402-6.
6. Peulen H, Karlsson K, Lindberg K, et al. Toxicity after reirradiation of pulmonary tumours with stereotactic body radiotherapy. Radiother Oncol 2011;101:260-6.
7. Nishimura S, Takeda A, Sanuki N, et al. Dose-Escalated Stereotactic Body Radiotherapy (SBRT) as a Salvage Treatment for Two Cases with Relapsed Peripheral Lung Cancer After Initial SBRT. J Thorac Oncol 2015;10:e69-71.
8. Heerink WJ, de Bock GH, de Jonge GJ, et al. Complication rates of CT-guided transthoracic lung biopsy: meta-analysis. Eur Radiol 2017;27:138-148.
9. Beslic S, Zukic F, Milisic S. Percutaneous transthoracic

CT guided biopsies of lung lesions; fine needle aspiration biopsy versus core biopsy. Radiol Oncol 2012;46:19-22.
10. 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.
11. 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.

Cite this article as: Nguyen TK, Palma DA. Rebuttal from Dr. Nguyen and Dr. Palma. Transl Lung Cancer Res 2016;5(6):655-657. doi: 10.21037/tlcr.2016.12.09

