Review Article

Certainty versus practicality: when is histologic proof needed prior to stereotactic ablative radiotherapy for solitary pulmonary nodules?

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Abstract: Stereotactic ablative radiotherapy (SABR) is a radiotherapy technique for treating early-stage non-small cell lung cancer (NSCLC), and is characterized by high dose per fraction, few fractions, and image-guided precision. Multiple studies have consistently demonstrated high rates of local control and a low incidence of serious adverse events, making it an attractive option for patients who are medically unfit for surgery. Although a biopsy is recommended for confirmation of the diagnosis prior to treatment, it is not without its risks. Herein we review the necessity of a biopsy prior to SABR for a solitary pulmonary nodule (SPN) suspicious for early-stage NSCLC. We examine malignancy prediction tools for assessing SPNs and scenarios in which forgoing a biopsy could be reasonable.

Keywords: Lung cancer; biopsy; solitary pulmonary nodule (SPN); stereotactic ablative radiotherapy (SABR); stereotactic body radiation therapy (SBRT)

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While surgery in the form of an anatomic lobectomy is the standard of care for patients with localized, early-stage non-small cell lung cancer (NSCLC), co-morbidities and competing risks may preclude the appropriateness of this procedure (1,2). For patients who are not medically fit for lobectomy, alternatives include sublobar resection, conventional radiation therapy (RT), stereotactic ablative radiotherapy (SABR), other ablative procedures, and observation. With respect to RT-based treatment options, SABR differs from conventional RT in that it is characterized by few fractions (often 5 or less), extreme hypofractionation and a high degree of conformality—factors that necessitate a high degree of accuracy and precision (3). As a testament to the rapid evolvement of SABR, prospective trials have reported on the high efficacy and safety of a single fraction radiosurgery dose of 30 and 34 Gy to peripheral targets (4,5). Generally, prospective studies have demonstrated the 3-year rates of local-regional control with SABR to be greater than 90% (6,7). SABR is typically well-tolerated, with fatigue being the most common side effect (8). More serious toxicities, such as chest wall, esophageal, or airway injury are less common, with increased risks related to proximity of the tumour target to relevant organs at risk (9).

Although tissue evaluation is the gold standard for the diagnosis of solid tumours, current guidelines suggest that a biopsy may not be crucial prior to treatment for a solitary pulmonary nodule (SPN) with a high likelihood of malignancy. Guidelines from the American College of Chest Physicians recommend that for SPNs with a likelihood of

malignancy greater than 65%, surgery is recommended if feasible (1). A multidisciplinary group of Asian physicians published recommendations based on these guidelines in light of characteristics unique to the Asian population, including rates of benign disease and access to functional imaging (10). They recommended a surgical biopsy when the likelihood of malignancy was greater than 60%. The British Thoracic Society, in their appraisal of the literature, suggests a 70% or greater threshold following positron emission tomography-computed tomography (PET-CT) risk assessment (11).

While operating on an SPN that is suspicious for cancer is both diagnostic and therapeutic, radiation with SABR is only therapeutic. Lung SABR in this setting historically has been employed in the least fit patients at highest risk of toxicity from a biopsy. This is best illustrated in the introduction of lung SABR within the Netherlands, whereby approximately one-third of SABR-treated patients did not have histologic confirmation of malignancy (12). On the other hand, recent population-based data from the United States suggest an overtreatment phenomenon (13). In a SEER-based analysis, there was an improvement in cancer-specific survival noted in SPN patients treated with SABR without histologic confirmation compared to those with histologic confirmation. This finding suggested a potential excess of benign disease treated in the cohort of patients without histologic confirmation of malignancy.

In suspected cancer, obtaining a biopsy is desirable to ensure certainty of a diagnosis prior to treatment. However, a transthoracic biopsy is associated with risks, including pneumothorax, hemothorax, hemoptysis, infection and air embolism. These risks are increased with smaller lesions, basal and middle zone lesions, and longer distances from lesion to pleura (14). Furthermore, biopsies can be non-diagnostic, and the rate of a false negative procedure is estimated to be between 3–19% (15,16). From a practical point of view, some may argue for employing SABR generously for suspicious SPNs; however, this may result in unnecessary exposure to SABR risks in an already compromised patient population. The risk of false positives also varies according to geographic jurisdictions, with higher rates of granulomatous disease and tuberculosis endemic within North American and Asian areas, respectively.

To address the uncertainty in this clinical scenario, our research group developed a decision analysis model whereby a hypothetical cohort of patients with a SPN greater than 1 cm in diameter suspicious for early-stage NSCLC undergoes 1 of 3 strategies: PET scan-biopsy-SABR, surveillance, or PET-directed SABR (17). The model incorporated published rates of cancer control, competing risk, quality of life (via utilities), SABR-related toxicities, and biopsy-related toxicities to arrive at a point estimate of 85% as a likelihood of malignancy threshold at which forgoing a biopsy could be reasonable (17). This threshold estimate was most sensitive to the diagnostic performance of biopsy (range, 77–94%), and the detection rate of false negatives on CT surveillance (range, 82–92%).

Various likelihood malignancy calculators for assessing SPNs have been published that consider both clinical and radiographical factors (18). Although these calculators have excellent predictive value in the populations in which they were developed, they may not be generalizable to all patients. Most models derived data from a single country and incorporated the rates of malignancy and benign mimics inherent to their geography. Further, the different models had different recruitment strategies and exclusion criteria.

The Swensen model is a clinical predictive tool that was based on a retrospective cohort analysis of 419 patients in the US with a new diagnosis of SPN on CT (19). This work was expanded upon by the Herder model, adding 18-fluoro-deoxyglucose positron emission tomography (FDG-PET) data to the calculation (20). In contrast, the Brock University model was based on Canadian patients with a history of smoking undergoing screening CT, where the prevalence of malignancy was low (21). Overall, nine predictors of malignancy were identified in at least two or more studies: age, smoking history, pack-years of smoking, previous history of extrapulmonary cancer, SPN diameter, spiculation, upper lobe location, pleural indentation and volume doubling time (11).

With regards to biopsy prior to SABR for SPNs, there remains a lack of consensus guidelines, and the rates of biopsy prior to SABR in the literature are variable. The most current publication from the American Society for Radiation Oncology recommends a biopsy whenever possible, and to seek an opinion from a multidisciplinary committee when this is not possible (22). Our previously published decision analysis model may help guide clinicians in treating patients with SPNs, and was used by the British Thoracic Society to derive their threshold recommendation of 70% (11). Although surgery remains the standard of care for most patients presenting with a SPN, SABR is an attractive option for patients whose comorbidities preclude them from surgery. We feel that a biopsy should be attempted if felt to be feasible after a multidisciplinary

discussion. If a biopsy is not feasible, then a careful discussion should be had with patients with regards to predicted malignancy risk of SPN and the side effects of SABR. If treatment is deferred, then short interval follow-up (e.g., 3–6 months) with a focus to repeat CT imaging for serial growth and growth kinetics that may better advise the appropriateness of when to intervene with SABR.

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Footnote

Conflicts of Interest: Dr. AV Louie has received honoraria from Varian Medical Systems Inc. and AstraZeneca, unrelated to this work. The other author has no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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