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COMMENTARY

Response evaluation after stereotactic ablative radiotherapy for localised non-small-cell lung cancer: an equipoise of available resource and accuracy

¹ANDRE G GOUVEIA, MD, ²OSBERT C ZALAY, MD, ^{3,4}KEVIN LM CHUA, MD and ²FABIO YNOE MORAES, MD

¹Oncologia D'or Duque de Caxias, Duque de Caxias, RJ, Brazil

²Department of Oncology - Division of Radiation Oncology, Kingston General Hospital, Queen's University, Kingston, ON, Canada

³Division of Radiation Oncology, National Cancer Centre, Singapore, Singapore

⁴Oncology Academic Programme, Duke-NUS Medical School, Singapore, Singapore

Address correspondence to: Dr Fabio Ynoe Moraes

E-mail: fabio.ynodemoraes@kingstonhsc.ca

ABSTRACT

There is growing evidence supporting the use of stereotactic ablative radiotherapy (SABR) on the treatment of localised stage non-small-cell lung cancer (NSCLC). Distinctive imaging challenges are posed post-SABR treatment. Thus, it is imperative to provide guidance on assessing treatment response, especially for new adopters. This commentary is about filling a gap in response evaluation after SABR for localised NSCLC.

Lung Cancer is the primary cause of cancer mortality worldwide, with almost 1.8 million deaths in 2018.¹ Furthermore, in low- and middle-income countries (LMIC), lung cancer is a growing problem due to high rates of cigarette smoking and other environmental factors, and will persist as a major challenge for at least the next decade. Stereotactic ablative radiotherapy (SABR) has emerged as a highly effective curative treatment for patients with inoperable localised stage I/II non-small-cell lung cancer (NSCLC).² With an increased number of patients being treated with SABR in areas with limited resources, it is imperative to provide guidance on assessing treatment response.³ For example, distinguishing treatment-related lung fibrosis from early tumour recurrence is key to preventing inappropriate salvage treatment, as well as avoiding unnecessary invasive procedures and imaging. Furthermore, in LMIC where trained radiation personnel are in short supply and standardised machine maintenance and quality assurance programmes are lacking,⁴ treatment and service delivery audits are vital to ensure consistency in the delivery of quality RT and central to this, is accurate response evaluation to facilitate outcome measures.

The Response Evaluation Criteria for Solid Tumors (RECIST) v. 1.1 provides a method for determining objective tumour response using CT images⁵ and has traditionally been broadly accepted as standard criteria for post-SABR evaluation. However, owing to a difference in

dosimetric profile, SABR can lead to lung changes that are distinct from those observed following traditional radiation treatment, in either radiologic presentation and/or time to development.⁶ As a result of these challenges in interpreting post-SABR lung abnormalities, RECIST alone is poorly predictive of disease recurrence. For instance, diffuse consolidation (consolidation measuring 5 cm or more and that contains more than 50% abnormal lung) can mistakenly satisfy the criteria for disease progression. Although the overall accuracy of RECIST for predicting tumour relapse following SABR improves with duration of time post-treatment, there is some agreement that the RECIST criteria alone is insufficient for determining tumour recurrence in the post-SABR setting.

Thoracic oncologists should therefore be aware of common post-SABR CT changes. Two major categories of chest CT findings post-SABR are expected changes; and less commonly high-risk features (HRFs). Acute expected changes (within 6 months post-SABR) include patchy consolidation, diffuse consolidation, patchy ground glass opacity (GGO) and diffuse GGO. Late expected changes (6 months or longer post-SABR) are mass-like fibrosis, scar-like fibrosis and a modified conventional pattern.⁷

The HRFs described for early detection of recurrence with CT are enlarging opacity at the primary site, sequential enlarging opacity, enlargement after 12 months, bulging

margins, loss of linear margin, loss of air bronchograms and growth in the craniocaudal direction.⁷ The relevance of growth in the craniocaudal direction can be explained due to post-SABR changes/fibrosis being expected to occur predominantly within the axial plane, as a significant amount of the radiation dose is deposited in this plane. On the other hand, CT changes in the craniocaudal axis are less associated with radiotherapy damage, and more indicative of tumour growth, due to the fact that there is a greater dose fall off, and lower volume receiving radiation dose in this plane. Craniocaudal growth is a fairly predictive HRF (sensitivity [Sn] 92%, specificity [Sp] 83%)⁷ but the single best predictor of local relapse appears to be the presence of an enlarging opacity after 12 months (Sn 100%, Sp 83%).⁷ However, waiting for at least 12 months to determine whether there has been a recurrence can be problematic, especially in patients where salvage options are available, and therefore acute HRFs are still more applicable in the first few months of follow-up.⁷ To this end, when ≥ 3 HRFs features are present, the combination is very sensitive and specific ($>90\%$) for tumour recurrence.⁷ Except for loss of linear margin and enlargement 12 months after SABR where a consensus could not be achieved, these HRFs have been unanimously adopted by an international panel of thoracic radiation oncologists, providing guidance in the management of patients post-SABR.⁸

PET or PET-CT is frequently applied to the initial staging of NSCLC and can help to estimate treatment response or disease progression. The precision of PET to predict local recurrence post-SABR is still debatable as most lesions can exhibit persistent moderate hypermetabolic uptake 12–24 months after SABR.⁹ During the first 6 months after SABR, the treatment region can exhibit PET hypermetabolic activity secondary to either inflammatory changes or remaining activity within reproductively sterile tumour cells.⁹ As a result, Zhang advised doing the first PET no sooner than 6 months after SABR.¹⁰ The same study described that using a cut off of maximum SUV >5 from 6.1 to 12 months after SABR should increase suspicion of local recurrence (Sn 100%, Sp 91%, 50% positive predictive value and 100% negative predictive value).¹⁰ Finally, consolidations with initial hypermetabolic activity post-SABR but with later decrease in SUV and size are not considered tumour relapse, and a 30% decline in SUV characterises a treatment response.¹⁰

However, some challenges in the broad use of PET or PET-CT include the lack of availability and expertise to estimate the SUV and report response in a consistent way between different imaging centres. Therefore, because of inconsistencies in reporting and false-positive results on PET, a biopsy should be carried out to confirm the recurrence if salvage therapy is being considered. When the imaging findings are highly suspicious, and a biopsy is not feasible, or an attempted biopsy is inconclusive, it is acceptable to offer local salvage therapy without pathological proof of tumour relapse.⁸

Recently, a prospective trial from Palma et al assessed post-SABR pathological response with pre-planned surgical resection 10 weeks after SABR.¹¹ The reported pathological complete response (PCR) rate was 60%, inferior to the 90% initial PCR prediction

post-SABR but higher than those described using neoadjuvant immunotherapy (PCR 15%) or radiofrequency ablation (PCR $<40\%$).¹¹ The difference between PCR in this trial and the 90% or higher local control observed in other studies using imaging criteria for follow-up¹² could be due to the 10-week time point¹³ or difficulties in assessing cell viability but also highlights the challenges inherent to response evaluation post lung SABR using radiologic criteria.

Addressing this clinical challenge in the context of LMIC, we recommend that post-SABR follow-up should be tailored to individual patient's fitness for salvage (Figure 1). This would provide much needed resource optimisation in countries with stretched resources. As such, for fitter patients, CT imaging should be performed every 3 months for the first 2 years following treatment, while conversely, every 6 months when dealing with inoperable patients who have multiple comorbidities and poor performance status (early CT imaging has minimal impact on the management of these patients). PET-CT should not be routinely used until there is stronger evidence for its advantages over conventional CT. Thereafter, CT imaging should be performed annually up to 5 years following the completion of treatment in both groups. Continued surveillance is important as late failures are possible, particularly in untreated regions of the chest.¹²

Ideally, an expert radiologist in thoracic imaging should assess the CT images looking out for HRFs mentioned above, as indicators of disease recurrence and suspicious imaging findings should then be confirmed with a biopsy when feasible, if salvage therapy is to be considered. In reality, there is a shortage of oncology professionals in LMIC¹⁴ and the severe demands in clinical practice preclude the effective development of subspecialty expertise. Overcoming this challenge is complex since the clinical adoption of SABR requires a concerted effort and 'buy-in' from all disciplines across lung cancer management. Education of lung cancer physicians to make them aware of the imaging challenges and aforementioned common post-SABR imaging changes is a start. To this end, multidisciplinary team meetings (MDT) have demonstrated significant impact upon patient assessment and management and provide a crucial platform for the implementation of timely, multi disciplinary evidence-based care. In fact, up to 35% of patients discussed at MDT meetings experience changes in diagnostic reports, more patients are likely to be completely staged by appropriate imaging modalities and accuracy of staging improves as well.¹⁵ The creation of MDT platforms can be difficult in LMIC where geographical distribution of services limits access to comprehensive cancer care and radiotherapy expertise. Capitalising on information and communications technology either to centralise radiology reporting services or to provide remote consults on complex cases may allow more remote regions to overcome these geographical limitations.

To conclude, lung SABR has a major role to play in the management of early stage inoperable lung cancer and accurate response evaluation is vital but remains a challenge. The education of stakeholders and setting up of evidence-based clinical practice guidelines with resource optimisation in mind and MDT platforms to guide clinical practice will be crucial in tackling this

Figure 1. Post-SABR imaging based follow-up schema in. Legend: CT: Computed tomography; q3: every 3; HRF: high-risk features; PET-CT: Positron emission tomography CT.

challenge, particularly in LMIC. To this end, organisations such as the International Atomic Energy Agency (IAEA), the International Association for the Study of Lung Cancer (IASLC) and

Union for International Cancer Control (UICC) with their global reach and resources will play an important role in implementing these measures.

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