Editorial Commentary

Surveillance imaging for non-small cell lung cancer: mounting evidence that less is more

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Lung cancer is the leading cause of death in both men and women in the United States (1). With increasing implementation of low dose computed tomography (CT) screening in high-risk populations, more patients should be diagnosed with early stage disease in the coming years, amenable to curative intent therapy (2). However, no firm consensus yet guides the frequency and modality of surveillance imaging following definitive treatment, with variable guidelines from large national and international oncologic societies. This largely results from a lack of high-quality data to guide surveillance decisions, and current post-treatment surveillance imaging guidelines from national and international oncologic societies are based on lower-level evidence and expert opinion. The National Comprehensive Cancer Network (NCCN) surveillance guidelines for non-small cell lung cancer (NSCLC) treated definitively recommends a chest CT with or without contrast every 6 months for 2–3 years followed by annual low-dose non-contrast enhanced chest CT for patients with NSCLC stages I–II treated with surgery with or without chemotherapy (3). The American Academy of Chest Physicians (AACP) suggests bi-annual chest CT for 2 years followed by annual chest CT for patients treated with resection (4). The American Association for Thoracic Surgery guidelines for surveillance recommends bi-annual chest CT for the first 4 years after surgical resection of NSCLC stages IA–IIIA followed by annual low-dose chest CT until the age of 79 (5). The European Society of Medical Oncology recommends at least annual chest CT after treatment or bi-annual chest CT if the patient is a candidate for future salvage therapy (6).

Efforts to establish evidence to support a specific modality and frequency for surveillance imaging have led to multiple small retrospective studies with conflicting results. Several retrospective studies have suggested a survival advantage to more frequent imaging (7,8) while others have shown no benefit (9,10). A systematic review by Srikantharajah *et al.* identified 5 relevant studies that investigated the impact of chest CT surveillance in patients who had undergone surgical resection for NSCLC. The authors found conflicting results, with 3 studies that showed a survival benefit and two that did not (11). One prospective trial, the Intergroupe Francophone de Cancerologie Thoracique (IFCT)-0302, randomized patients to Q6 month CT, exam, and chest X-ray (with or without bronchoscopy) to exam and chest X-ray alone. At a median follow up of 8.7 years, no significant survival benefit was identified with the addition of CT, although longer follow up is ongoing.

Still fewer studies have investigated the role of surveillance imaging in NSCLC patients treated with definitive radiation. The available studies suggest more frequent imaging (12,13) or imaging with positron emission tomography (PET)/CT (14) leads to definitive intent treatment in very few patients. One small prospective study enrolled 24 patients who had undergone either definitive

radiation therapy or chemoradiation for NSCLC and surveillance PET/CT every 3 months detected 24 patients at 3 months with recurrence but only 3% were amenable for curative therapy (15).

In aggregate, the available studies addressing frequency of imaging have been largely retrospective, variable in terms of imaging modality, and have shown conflicting results, leading to challenges in creating evidence-based guidelines for practitioners. Most population-based databases do not include whether imaging was performed for surveillance or in response to symptoms, creating challenges in interrogating such databases to better understand the impact of surveillance on outcomes. However, McMurry *et al.* (16), as part of a special study of the National Cancer Database, provide an analysis of a unique population-based dataset that provides fairly robust evidence that more intensive surveillance strategies are not associated with improved survival following surgery for lung cancer. This study analyzed the first surveillance CT imaging for 4,463 patients who had undergone curative surgical resection for stages I–III NSCLC, classified by the interval to scan (3, 6 or 12 months). The dataset included indication, whether imaging was obtained as surveillance or in response to symptoms. The authors of this study conclude that there was not an associated improvement of overall survival with any particular surveillance schedule. This analysis provides additional evidence that more frequent cross-sectional imaging does not affect survival following surgical resection of lung cancer. The general finding that more aggressive surveillance does not impact survival is concordant with the results of the only completed prospective randomized phase III trial to address surveillance imaging in lung cancer, the IFCT-0302. At a median follow-up of 8.7 years, the IFCT-0302 identified no significant survival benefit with the addition of CT to exam and chest X-ray.

The lack of survival benefit to more aggressive surveillance imaging suggests that expedient initiation of salvage therapy does not measurably improve survival, and is congruent with the currently poor prognosis of recurrent lung cancer. Based on available evidence, there is no clear role for frequent cross-sectional imaging in the absence of symptoms in surgically treated lung cancer patients. However, as treatment options improve, the role and impact of surveillance may evolve. New systemic options, most notably immune checkpoint inhibitors, have markedly improved outcomes for the subset of patients who respond. As systemic salvage options continue to improve, early detection of recurrence may have greater impact on survival. Recent randomized phase II trials also suggest that local ablative therapy with stereotactic radiation may improve survival for patients with limited metastatic disease (17-19). Surveillance guidelines will need continual reassessment as salvage options evolve and improve so that patients who may benefit from more aggressive salvage are identified.

Notably, the McMurry study included only surgically resected patients and the results are not applicable to patients treated with definitive radiation, particularly given the challenges of interpreting post-radiation CT scans. Another limitation is that the dataset included only the first surveillance study, rather than capturing ongoing surveillance. The McMurry study also does not address surveillance modality. While the IFCT-0302 suggests the addition of CT to exam and chest X-ray does not improve survival, there is also interest in the role of PET/CT in surveillance, particularly for patients treated with radiation therapy, given the difficulty of differentiating recurrence versus post radiation changes (20), although PET/CT is not currently recommended by any major guidelines as a surveillance modality. The use of blood-based biomarkers in surveillance has also emerged as an area of interest and active investigation. Several studies have sought to elucidate the utility of screening for circulating free tumor DNA and circulating tumor cells (21,22). Such strategies remain investigational at this time, but in the future may supplant or even replace cross sectional imaging for routine surveillance. The impact of surveillance on patient anxiety and quality-of-life is also an important and understudied area in need of investigation.

In summary, a paucity of prospective trials and high-quality population-based data has led to a lack of consensus on the appropriate surveillance strategy following definitive treatment of lung cancer. The McMurry study, using a unique, population-based dataset that includes scan indication, adds to the available evidence that frequent imaging does not affect survival with current treatment approaches and should not be routinely used in asymptomatic patients. However, novel approaches that could replace imaging-based surveillance, such as blood-based biomarkers, may emerge in the upcoming years. Improvements to both local and systemic salvage options may also eventually increase the importance of surveillance and early detection of recurrence.

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Footnote

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

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