

Management of screening-detected stage I lung cancer

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Easily the biggest development in the fight against lung cancer since the 1964 US Surgeon General's report directly linked tobacco use to lung cancer, is the emergence of high-quality data clearly establishing the efficacy and cost-effectiveness of computed tomographic (CT)-screening as a means of improving lung cancer survival (1-4). Only tobacco control for primary prevention can have greater population-level impact on lung cancer mortality and survival statistics (5). Given the tight link between stage at treatment and survival, CT screening, by allowing early identification, leads to high lung cancer cure rates (3). Participation in screening is also a tremendous teachable moment that can potentially enhance smoking cessation, thereby contributing to primary (and secondary) prevention.

As great as the opportunity presented by CT screening, is the challenge of implementation. Translating the efficacy of CT screening in relatively controlled environments to real-world effectiveness will be a decades-long challenge. Part of this challenge will be determining the optimal management of screening-detected lung cancer, the objective being to limit treatment-related morbidity and mortality, while preserving benefit. For full benefit, optimal treatment must accompany screening-detected lung cancer. Part of the challenge is understanding how the biology of screening-detected lung cancer is similar to, and different from, lung cancer serendipitously detected on imaging studies done for unrelated reasons, and lung cancer detected on the basis of clinical symptoms.

Currently, the Tumor-Node-Metastasis (TNM) staging system is our best prognostic and treatment guide. This system, which continues to undergo modification as knowledge expands, has mostly been developed in lung cancer detected serendipitously in unselected patients, and during evaluation of clinically symptomatic patients. The extent

to which the prognostic parameters of the TNM system apply to screened populations, especially those at the earliest of stages, and therefore, the approach to risk mitigation during treatment, should be an area of great interest (6). For example, the thoroughness of application of nodal staging is the major quality of care deficit in conventionally diagnosed and treated lung cancer patients, associated with the greatest survival disparity, especially in potentially curable, early stage non-small cell lung cancer (7-12). Multiple investigators have demonstrated the depth, and breadth, of the suboptimal nodal staging problem in surgical and non-surgical patients, ranging from the use of radiologic and invasive nodal staging tests, through to the surgical retrieval and pathologic evaluation of directly and indirectly retrieved lymph nodes in resection specimens (7-17).

Are these concerns relevant to screening-detected early stage patients, or are there subsets of such patients for whom the rules of surgical and non-surgical staging (and treatment) need to be modified because of biologic differences in screening-detected lung cancer? There may be an opportunity to tailor management to patient risk and temper the rules for risk-mitigation in the screen-detected population. Which patients can dispense with invasive and non-invasive staging procedures? What about surgical versus non-surgical treatment options: are early screening-detected patients potentially candidates for non-surgical treatments, thereby avoiding the morbidity and mortality risk of surgical intervention? When surgery is chosen, can we limit the extent of surgical resection, thereby preserving functional lung volume and limiting long-term morbidity, thus improving postoperative quality of life? Can we heed the lesson of breast cancer, in which the use of lumpectomy has superseded mastectomy, an evolution accelerated by mammographic detect of tumors at much earlier stage? Can

we dispense with hilar and mediastinal nodal examination in certain early stage screening-detected lung cancer patients, again heeding the lesson of breast cancer (18)? Bluntly put, are there patients who can do without nodal examination, without extensive resection, without surgery?

The recent publication by Flores *et al.* in the *Annals of Surgery*, addresses the question of nodal examination (19). In a retrospective analysis of the International Early Lung Cancer Action Program (I-ELCAP) database of CT screening-detected lung cancer from 1992 to 2014, limited to patients with resected clinical T1a/b N0M0 non-small cell lung cancer, they identified 462 patients with, and 145 patients without, mediastinal lymph node resection (MLNR). In further analyses, they separated the cohort into those whose cancer manifested as a sub-solid nodule (151 *vs.* 52 patients) and those with a solid nodule (311 *vs.* 93 patients). They compared certain demographic, disease and treatment characteristics as well as long-term survival between those with and without MLNR. They found similar survival between those who had and did not have MLNR: 92% *vs.* 96% (P=0.19) for the whole group; 100% *vs.* 100% for those with subsolid nodules; 87% *vs.* 94% (P=0.24) for those with solid nodules. They identified advancing age, central tumor location, tumor size >20 mm, and invasion beyond the lung stroma as independent risk factors for death (19). They conclude that MLNR is not mandatory when screening-diagnosed NSCLC manifests as a sub-solid nodule.

The ELCAP and I-ELCAP group have performed tremendous, ground-laying work in the lung cancer screening arena, prior to the National Lung Screening Trial (1,2). Despite initial criticism of their uncontrolled prospective observational study design and concerns about the dangers of lead-time, length and over-diagnosis bias, the randomized NLST results have largely validated their early findings on the value of screening CT (3,4,20,21). IELCAP's prospective multi-institutional cohort has the advantages of rigorous data definition, standardized data collection and end-point ascertainment practices, and a long duration of follow up. However, the current report is a retrospective analysis, with all the limitations inherent in such analyses. As with the NLST, there is no pre-specification for cancer treatment (where the rubber meets the road), but rather a pragmatic approach is used, in which treatment decisions are left to the managing clinicians. This methodologic approach has the advantage of potentially improved external validity (generalizability to 'real-world' populations), but a disadvantage of weakened internal

validity, especially in the comparability of ad-hoc internal cohorts, such as in the analyses by Flores *et al.* Additional potential sources of bias are the absence of information on use of invasive preoperative nodal staging (how much preoperative invasive nodal staging did the cohorts receive?). There was no separation between operative mortality and cancer mortality: the investigators (by their admission) have conflated all deaths resulting from treatment as lung cancer deaths, making it difficult to evaluate the challenges of surviving the cancer versus surviving the surgery.

Illustrating the inherent biases of this study design, by their reported demographic and clinical comparisons, the MLNR population appears to be at higher risk than the no MLNR cohort in terms of central location, smoking history, and tumor size. No surprise then that that group's outcomes seem to be worse. One could speculate that the outcome difference might have been greater without the added information from the nodal dissection, given the additional detection of more advanced pathologic stage than initially suspected, and the likely post-operative management response triggered by detection of nodal metastasis in more contemporary patients in the era of beneficial adjuvant therapies. Whilst it is impossible to know if the 'no MLNR' cohort had similar nodal involvement, the suggestion is probably not, given the paucity of hilar/intrapulmonary nodal metastasis (assuming relatively similar patterns of lymph node gross dissection in the provided parenchymal resection specimens), although the higher rate of sublobar resection (with its likely impact on nodal examination) makes even this unknowable.

It is instructive that even in this ostensibly low risk population, 11% of patients with a solid nodule who had MLNR, all of whom were clinically node-negative, had unexpected pathologic nodal metastasis, including 6% with N2 disease. Similar data on the patients with sub-solid nodules are not reported. This is not reassuring, as we have previously pointed out (22). At this time, a recommendation against pathologic nodal evaluation seems akin to opening Pandora's box: the unreported procedures for selection between the MLNR and no-MLNR approaches that directed the I-ELCAP surgeons will not be communicated in general practice. All the average practitioner will hear is that 'MLNR is unnecessary', without communication of the nuances of the decision-making involved in careful selection of such a strategy, and, worse, without prospective evaluation of the soundness of such selection strategies. We have seen out of Pandora's box, the wrong interpretation of ACOSOG Z0030, which some have erroneously cited

as license to perform suboptimal nodal dissection. Finally, minor pedantry: it is unclear why Flores *et al.* have referred to lesions >20 mm as T1a. These are pT1b, although in the absence of nodal or other metastases the aggregate stage remains IA, but that is not the same thing...

The above reservations notwithstanding, the report by Flores *et al.* provides great food for thought. It is almost certain that nodal examination, extensive resection and (albeit well beyond the scope of this report) even surgical intervention, are not necessary in all patients with lung cancer. This hypothesis-generating report reminds us of the need to systematically evaluate which patients can dispense with more morbid processes of care delivery. A reasonable place to start this inquest is in screening-detected patients with small sub-solid nodules or ground-glass opacities. However, more rigorously controlled, prospective studies are needed to validate any recommended practice change. This report should provide greater equipoise to clinical investigators, allowing them to overcome ethical concerns that inhibit enrollment of patients into ongoing prospective trials that seek to help interrogate each of the three clinical questions: the minimum oncologically sound extent of pulmonary parenchymal resection; the extent of nodal evaluation; and the use of surgical *vs.* non-surgical treatment modalities.

In the absence of results from such studies, it is important to remain aware of the limitations of ad-hoc retrospective analyses. Let us bear in mind the paradox of retrospective timeliness of care studies, which consistently show that recipients of delayed lung cancer care have significantly better survival than recipients of timely care (23–25). Clearly, the conclusion from such studies cannot be that delaying delivery of care for a lethal disease such as lung cancer leads to better survival. Consequently, these studies have not led to recommendations for postponing definitive care for lung cancer. Rather, the results are widely acknowledged to reflect the existence of overwhelming and uncorrected asymmetry in the comparative populations.

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Footnote

Provenance: This is an invited Commentary commissioned by the Section Editor Feichao Bao (Department of Thoracic Surgery, the First Affiliated Hospital, Zhejiang University,

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