Patients with stage I non-small lung cancer (NSCLC) who are managed with stereotactic body radiotherapy (SBRT) do not routinely undergo mediastinal lymph node sampling, although a significant proportion of these patients can harbor metastatic subclinical mediastinal disease. For instance, results of a retrospective analysis by Sarwate et al., in which 59 patients with medically inoperable NSCLC, had pathologic mediastinal staging prior to SBRT consideration, indicated that 16% of patients had positive mediastinal disease, which prompted alternative treatment options (1).

Nevertheless, in addition to excellent primary tumor control and overall survival rates that are comparable to historical data of patients who undergo lobectomy, the incidence of mediastinum disease recurrence rates in patients treated with SBRT without pathological staging appear to be limited in currently available data (2). Baumann et al. reported only 5% regional nodal recurrence rate with a median follow-up of 35 months, in a prospective phase II trial of 57 patients with medically inoperable stage I NSCLC treated with SBRT (3). Similarly, in RTOG 0236, a phase II trial of 55 patients with medically inoperable disease, Timmerman et al. reported a 3.6% mediastinal failure rate with a median follow-up of 34.4 months (4). However, in their recent update with long-term follow-up, Timmerman et al. noted an increased 5-year loco-regional failure rate at 38%, while the 5-year primary tumor control remained high at 93%, and without increased late toxicity (5). Data from retrospective series have also shown low mediastinum failure rates with limited follow-up. Senthil et al. reported outcomes of a series of 676 patients with T12N0M0 treated with SBRT, where they obtained a 6.4% overall regional recurrence rate with a median follow-up of 32.9 months (6). In our single institutional retrospective analysis of 46 patients with stage I NSCLC treated with SBRT, we achieved a 4.9% regional (i.e., ipsilateral and contralateral mediastinum plus supraclavicular node regions) nodal recurrence rate at a median follow-up of 16.8 months (7).

Emerging data suggest no differences in outcomes regardless of whether or not surgical staging is performed before SBRT. Fischer-Valuck et al. analyzed outcomes of 88 patients with early stage NSCLC, in whom 73.9% had biopsy-proven disease compared to radiographic only diagnosis in the remaining group (8). They found no differences in 3-year local progression-free survival, regional lymph node metastasis-free survival and overall survival rates between the two groups (8). Another recent study from Yale University demonstrated that loco-regional recurrence free-survival and overall survival were similar in 286 patients treated with SBRT with or without mediastinal staging with a median follow-up of 20.3 months (9).

In the article by Paravati et al., they evaluated the negative predictive value (NPV) of PETCT for nodal disease in 144 patients with clinically node negative stage I NSCLC who underwent surgical resection at single institution (10). Of the 144 patients, 19 patients were upstaged due to the presence of nodal metastases resulting in an overall nodal NPV of 87%. On multivariate analysis they noted that larger tumor size, age at surgery and central tumor location were significant predictors of occult nodal metastasis (10). Of note, they defined central tumors as those within the inner third of lung parenchyma, unlike RTOG 0236 criteria, that defines central tumors as those within 2 cm of the bronchial tree, major vessels, esophagus, heart, trachea, pericardium, or vertebral body (4). Data
from other surgical series suggest potentially significant rates of occult nodal metastases after pathologic mediastinal staging of patients with stage I NSCLC. In a series by Robson et al. (11), of 128 patients with stage I NSCLC who underwent surgery, they found an 8.9% incidence of hilar/mediastinal occult metastatic disease in peripheral tumors compared to 33.3% for central tumors (defined as per RTOG criteria).

Surgical series report mediastinum failure rates that are comparable to SBRT data but with longer follow-up. A retrospective analysis by Asamura et al., of 337 patients with peripheral stage I (94.7% T1) NSCLC who underwent lobectomy (97%) or pneumonectomy (3%) with lymphadenectomy, of whom 305 patients had clinical N0 status, 68 (22.3%) were found to have mediastinal and hilar LN involvement after mediastinoscopy (12). With a follow-up of at least 5 years, there was a 5.3% (1 of 213) incidence of mediastinal recurrence. Trodella et al. reported results of a phase III trial comparing postoperative radiotherapy to surgery alone in 104 patients with stage I NSCLC who underwent at least a lobectomy with lymphadenectomy (13). In the surgery alone arm there was a 9.4% mediastinal recurrence rate with a mean follow-up of 63 months. An analysis of patterns of recurrence of patients with resected stage I NSCLC from a multicenter Lung Cancer Study Group trial and showed a 7% mediastinal recurrence with a mean follow-up of 41 months (14).

One could expect higher regional relapse rates in surgical series than observed, if preoperative mediastinal lymph node sampling were omitted, simply based on the potentially significant rates of occult nodal metastases that can be discovered prior to surgery. On the other hand, it is also possible that the low mediastinum relapse rates noted in most SBRT series may be due to shorter follow-up than in surgical series, such that occult disease may take a long time to manifest clinically. Moreover, some SBRT series report results of patients treated without biopsy confirmation of cancer, which would artificially lower the incidence of mediastinum recurrence if benign lesions are inadvertently included (15).

So when does it make sense to subject patients to an invasive staging mediastinoscopy in patients with inoperable stage I NSCLC? It seems reasonable for patients with larger tumors and centrally-located tumors to undergo routine mediastinoscopy, as suggested by Paravati et al. and others, since there is an increased risk of subclinical nodal disease [mainly N2 (13)], as this can alter treatment recommendations (10,16,17). However, can we still be on par with surgery while avoiding a mediastinoscopy in low-risk inoperable patients (i.e., small peripheral tumors)? We propose that in patients with borderline resectable disease, it can be useful to advocate for a pathologic lymph node sampling procedure as the reported high NPV, PETCT can still under-stage up to 32% of patients with stage I NSCLC (18). Yet, the low regional nodal relapse rates observed after SBRT with PETCT staging only, are somewhat are paradoxical and may not be fully explained by inadequate follow-up with SBRT. Given that incidental SBRT dose to the mediastinum while treating stage I NSCLC is too low (i.e., <5 Gy) to account for subclinical nodal disease clearance, alternative mechanisms that are increasingly supported by emerging data proposing immune-mediated effects of SBRT outside the primary target, may play a role (7,19,20). However, further studies are warranted to further elucidate the impact of abscopal effects of ablative radiotherapy on overall disease control in early stage NSCLC.

In summary, in patients with inoperable disease who may not live long enough to develop regional recurrences, we should not change our practice to recommend an invasive staging procedure before SBRT without clearly defined evidence-based guidelines from prospective randomized data.

Acknowledgements
None.

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

References


