Editorial

Is staging mediastinoscopy necessary before stereotactic body radiotherapy for inoperable early stage lung cancer?

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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. Senthi *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.

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Footnote

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

References

1. Sarwate D, Sarkar S, Krimsky WS, et al. Optimization of mediastinal staging in potential candidates for stereotactic radiosurgery of the chest. J Thorac Cardiovasc Surg 2012;144:81-6.
2. Stephans K. Stereotactic body radiotherapy for stage I non-small cell lung cancer. Cleve Clin J Med 2012;79 Electronic Suppl 1:eS26-31.
3. Baumann P, Nyman J, Hoyer M, et al. Outcome in a prospective phase II trial of medically inoperable stage I non-small-cell lung cancer patients treated with stereotactic body radiotherapy. J Clin Oncol 2009;27:3290-6.

4. Timmerman R, Paulus R, Galvin J, et al. Stereotactic body radiation therapy for inoperable early stage lung cancer. JAMA 2010;303:1070-6.
5. Timmerman RD, Hu C, Michalski J, et al. Long-term Results of RTOG 0236: A Phase II Trial of Stereotactic Body Radiation Therapy (SBRT) in the Treatment of Patients with Medically Inoperable Stage I Non-Small Cell Lung Cancer. Int J Radiat Oncol Biol Phys 2014;1:S30.
6. Senthi S, Lagerwaard FJ, Haasbeek CJ, et al. Patterns of disease recurrence after stereotactic ablative radiotherapy for early stage non-small-cell lung cancer: a retrospective analysis. Lancet Oncol 2012;13:802-9.
7. Rwigema JC, Chen AM, Wang PC, et al. Incidental mediastinal dose does not explain low mediastinal node recurrence rates in patients with early-stage NSCLC treated with stereotactic body radiotherapy. Clin Lung Cancer 2014;15:287-93.
8. Fischer-Valuck BW, Boggs H, Katz S, et al. Comparison of stereotactic body radiation therapy for biopsy-proven versus radiographically diagnosed early-stage non-small lung cancer: a single-institution experience. Tumori 2015;101:287-93.
9. Corso CD, Lloyd S, Harder E, et al. Invasive Mediastinal Staging Does Not Improve Outcomes Over PET Alone in Early-Stage NSCLC Treated with SBRT. Int J Radiat Oncol Biol Phys 2014; 90:S216-7.
10. Paravati AJ, Johnstone DW, Seltzer MA, et al. Negative predictive value (NPV) of FDG PET-CT for nodal disease in clinically node-negative early stage lung cancer (AJCC 7th ed T1-2aN0) and identification of risk factors for occult nodal (pN1-N2) metastasis: implications for SBRT. Transl Cancer Res 2014;3:313-9.
11. Robson JM, Vaidyanathan S, Cheyne L, et al. Occult nodal disease in patients with non-small-cell lung cancer who are suitable for stereotactic ablative body radiation. Clin Lung Cancer 2014;15:466-9.
12. Asamura H, Nakayama H, Kondo H, et al. Lymph node involvement, recurrence, and prognosis in resected small, peripheral, non-small-cell lung carcinomas: are these carcinomas candidates for video-assisted lobectomy? J Thorac Cardiovasc Surg 1996;111:1125-34.
13. Trodella L, Granone P, Valente S, et al. Adjuvant radiotherapy in non-small cell lung cancer with pathological stage I: definitive results of a phase III randomized trial. Radiother Oncol 2002;62:11-9.
14. Feld R, Rubinstein LV, Weisenberger TH. Sites of recurrence in resected stage I non-small-cell lung cancer: a guide for future studies. J Clin Oncol 1984;2:1352-8.
15. Takeda A, Kunieda E, Sanuki N, et al. Stereotactic body radiotherapy (SBRT) for solitary pulmonary nodules clinically diagnosed as lung cancer with no pathological confirmation: comparison with non-small-cell lung cancer. Lung Cancer 2012;77:77-82.
16. Wang J, Welch K, Wang L, et al. Negative predictive value of positron emission tomography and computed tomography for stage T1-2N0 non-small-cell lung cancer: a meta-analysis. Clin Lung Cancer 2012;13:81-9.
17. Al-Sarraf N, Aziz R, Gately K, et al. Pattern and predictors of occult mediastinal lymph node involvement in non-small cell lung cancer patients with negative mediastinal uptake on positron emission tomography. Eur J Cardiothorac Surg 2008;33:104-9.
18. Cerfolio RJ, Bryant AS. Survival of patients with true pathologic stage I non-small cell lung cancer. Ann Thorac Surg 2009;88:917-22; discussion 922-3.
19. Lee Y, Auh SL, Wang Y, et al. Therapeutic effects of ablative radiation on local tumor require CD8+ T cells: changing strategies for cancer treatment. Blood 2009;114:589-95.
20. Formenti SC, Demaria S. Systemic effects of local radiotherapy. Lancet Oncol 2009;10:718-26.

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