Editorial

PET-CT limitations in early stage non-small cell lung cancer: to whom more aggressive approach in radiotherapy and surgery should be directed?

Lucyna Kepka[1], Joanna Socha[2]

[1]Department of Radiotherapy, Independent Public Care Facility of the Ministry of the Interior and Warmian-Masurian Oncology Center, Olsztyn, Poland; [2]Department of Radiotherapy, Regional Oncology Center, Czestochowa, Poland

Correspondence to: Lucyna kepka, MD, PhD. Department of Radiotherapy, Independent Public Health Care Facility of the Ministry of the Interior and Warmian-Masurian Oncology Centre, Al. Wojska Polskiego 37, 10-228 Olsztyn, Poland. Email: lucynak@coi.pl.

Abstract: This editorial comments on the study by Paravati *et al.*, which reported on the incidence of occult regional lymph node metastases in PET-CT T1T2N0 non-small cell lung cancer (NSCLC) patients. A central location and the size of the tumor were shown to be the strongest predictors of the risk of occult nodal disease. Authors comment that in view of limitations of modern imaging, as well as the reported negative predictive value (NPV) of invasive staging methods, the choice of therapeutic options as the extent of surgery (lobectomy or sublobar resection) or radiotherapy [stereotactic body radiation therapy (SBRT) or conformal radiotherapy (RT) with some forms of elective nodal irradiation (ENI)] should consider tumor's characteristics and not be based only on imaging and invasive staging modalities.

Keywords: PET-CT; negative predictive value (NPV); non-small cell lung cancer (NSCLC); stereotactic body radiation therapy (SBRT); sublobar resection

Submitted Nov 06, 2015. Accepted for publication Nov 11, 2015.
doi: 10.3978/j.issn.2072-1439.2015.11.34
View this article at: http://dx.doi.org/10.3978/j.issn.2072-1439.2015.11.34

In patients with nonmetastatic non-small cell lung cancer (NSCLC), the N-stage is used to determine the choice of therapeutic options. Although lobectomy with mediastinal lymphadenectomy is the established standard approach for clinical stage (CS) I patients, the increasing use of limited surgical techniques (e.g., wedge resection or segmentectomy) and local, nonsurgical management [e.g., stereotactic body radiation therapy (SBRT)] underscores the need for the accurate identification of lymph node metastasis. In surgically treated patients with planned systemic nodal dissection, the presence of occult N1 disease preoperatively does not have important clinical implications. By contrast, mediastinal metastases preclude curative resection and thus may lead to redirection of the therapy.

The presence of N1 disease is a contraindication for the limited surgical approach. For SBRT, occult lymph node involvement regardless of nodal station is one of the main considerations because any N+ disease would rule out SBRT as an appropriate option. N2 patients should be treated with concurrent chemoradiotherapy and N1 patients with surgery, unless there are contraindications. For N+ patients not amenable to surgery, standard conformal radiotherapy (RT) is an option. The risk of occult nodal disease in PET-CT-staged clinical (c) N0 patients carries an important implication for conformal RT with regard to determination of the target volumes, specifically for the use of elective nodal irradiation (ENI).

PET-CT is being increasingly used as a surrogate for pathology staging, and the routine practice of invasive staging is considered unnecessary and is often abandoned for this group of patients because of the relatively low rate of nodal involvement (1). Evaluation of the accuracy of negative nodal uptake on PET-CT [i.e., the negative predictive value (NPV) for early stage NSCLC] and identification of the potential risk factors for occult nodal

© Journal of Thoracic Disease. All rights reserved.

involvement may allow for the selection of an optimal therapeutic approach for each individual patient.

In a retrospective study, Paravati *et al.* (2) reported on the incidence of occult nodal metastases in PET-CT-staged cN0, T2a or less NSCLC patients. The NPV of PET-CT for detecting nodal disease in these patients was also determined and possible risk factors for nodal involvement were identified. One hundred forty-four NSCLC patients with CS I based on PET-CT underwent definitive surgery with mediastinal staging. Nineteen of these patients were pathologically upstaged because of the presence of nodal metastases, so the overall NPV for nodal disease was 87% (125/144): 90% for T1 and 78% for T2 disease. For N2 (mediastinal metastases), the NPV was 95% for T1 (93/98) and 87% for T2 disease (40/46). Among the factors that may be associated with occult nodal disease, a central tumor location carried the greatest risk of nodal involvement [odds ratio (OR): 7.3, 95% confidence interval (CI), 2.22-24.3, P=0.001]. Patients with a higher T-stage (from T1A to T2B) had a higher risk of occult nodal metastases: a 3.28-fold increase for each higher T category (95% CI, 1.41-7.57, P=0.005). Moreover, an older age at resection significantly predicted a lower risk of unforeseen nodal involvement (OR: 0.95, 95% CI, 0.92-0.98, P=0.002).

The search for predictors of subclinical nodal involvement in cN0 NSCLC has been bringing consistent results in both the pre-PET-CT and PET-CT era. An increasing a tumor size and central location were the strongest clinical predictors of occult N2 disease in the setting of a negative CT scan (3,4). Similar results have been reported in a recent meta-analysis that included 10 studies with 1,122 CS I NSCLC patients staged with PET-CT. In addition to a high FDG tumor uptake and adenocarcinoma histology, tumor size was a predictor of occult nodal disease. The NPV of PET-CT for mediastinal metastases was 0.94 (95% CI, 0.92-0.96) for 649 T1N0 patients from six studies and 0.89 (95% CI, 0.84-0.95) for 130 T2N0 patients from two studies (5).

Gathering all available literature on the accuracy of imaging methods for the detection of mediastinal metastases and pathology data, the European Society of Thoracic Surgeons published guidelines for preoperative mediastinal lymph node staging for NSCLC. In cases of no enlarged regional lymph nodes on CT with no uptake on PET-CT, direct surgical resection with systemic nodal dissection is recommended for tumors ≤3 cm located in the outer third of the lung (6). This way, once more size and location of the tumor were shown to be the strongest predictors of the risk of occult nodal metastases. Consistent with the data reported by Paravati *et al.* (2), these guidelines also support the use of invasive mediastinal staging for PET-CT-staged T2N0 disease and all centrally located tumors regardless of size.

The choice of mediastinal invasive staging methods is between video-assisted mediastinoscopy (VAM) with biopsy or lymph node dissection, and endoscopic staging by endobronchial ultrasonography–endoscopic ultrasonography (EBUS/EUS) with fine-needle aspiration (FNA). However, one question remains: whether the available endoscopic or surgical staging (mediastinoscopy) methods or a combination of both can definitively exclude the risk of occult nodal disease for patients referred for SBRT or sublobar resection. Certainly, all of these methods have proven utility in the establishment of the N stage; however, each has limitations that may affect, to varying extent, the outcome in specific institutions and clinical scenarios.

The low sensitivity of mediastinoscopy in the setting of clinically negative PET-CT has been demonstrated. Of 86 patients with T1T2N0 tumors staged by PET-CT, 23 (26%) were upstaged to the pN1-N2 stage at the time of thoracic surgery, and only one had occult nodal metastases detected at mediastinoscopy (7). These results show the limited value of mediastinoscopy for cN0 patients staged with PET-CT. Additionally, VAM does not evaluate N1 level, which involvement may be crucial when referring patients for SBRT because the elective hilar region is not likely to receive an elective sterilizing micrometastases dose with this RT technique. Nodal stations 10R and 10L may be reached with EBUS. This technique (EBUS—transbronchial FNA alone or combined EBUS/EUS) has a high pooled sensitivity of 83-94% for mediastinal staging of NSCLC (8). However, there still remains some uncertainty about the presence of occult disease.

The results of staging are highly dependent on local expertise and are probably performed less well in community medical centers. Thus, the attitude toward the extent of invasive baseline staging of hilar and mediastinal regions in PET-CT-staged T1T2N0 tumors should be guided by the tumor characteristics (risk of occult metastases) and the planned treatment strategies. If SBRT is planned, ruling out N1 disease would be of value; however, if lobectomy is planned, invasive staging of the hilar region would be less important. In this context, a recent study that reported on an increased risk of regional and distant failure with decreased overall survival (OS) in 295 patients with T2 tumors compared with 993 patients with T1 tumors

© Journal of Thoracic Disease. All rights reserved.

treated with SBRT in five institutions with expertise in the use of this technique between 2004 and 2014 supports the consideration of invasive staging for patients with larger tumors. The 5-year regional failure rates were 24% and 11% for T2 and T1 tumors, respectively (P=0.009) (9). Thus, in cases where some tumor characteristics indicate a risk of occult nodal metastases even if the reasonably chosen and accessible staging procedures show N0 disease, the use of conventional RT with limited ENI should be considered instead of SBRT if the patient can tolerate an increase in radiation volume.

The use of larger radiation fields that includes some forms of ENI for some N0 NSCLC is justified because, as noted by Paravati *et al.* (2), the likelihood of occult nodal metastases must be weighed against the risk of a false-negative result of endoscopic staging, which is generally >10% (8). SBRT is not technically feasible for the treatment of the large volumes required in ENI. Thus, it is not an appropriate technique for tumors at risk of occult metastases. Recently, Lucas *et al.* (10) reported similar results of treatment with SBRT (median dose: 54 Gy in three fractions) and accelerated hypofractionated RT (AHRT) (70.2 Gy in 26 fractions) in 160 patients treated in one institution between 2003 and 2011. The median OS did not differ significantly between the two groups: 38 and 35 months for SBRT and AHRT, respectively. These results compare favorably with other reports of treatment for early stage patients treated with RT. A larger tumor size was related to worse outcome for both techniques, and ENI was omitted in all patients in this study (10). We postulate that addition of moderate-dose ENI for patients with larger tumors treated with AHRT would improve outcomes.

Toxicity of ENI, especially when delivered with a new RT technique, has never been demonstrated and should be weighed against the risk of isolated nodal failure (INF) (11). PET-CT use does not reduce the risk of INF for either SBRT or conventional RT techniques. A recent review of the studies that reported on the risk INF, defined as regional failure without local recurrence regardless of distant metastases status after involved-field RT, demonstrated that PET-CT fails to reduce the rate of INF. There were 136 (6.3%) and 98 (6.6%) INF in 2,158 and 1,487 patients staged with and without PET-CT before RT, respectively (P=0.74) (12). Thus, the tumor characteristics should be considered—sometimes more than the imaging used—when deciding about the radiation volume (ENI *vs.* no ENI) and technique (SBRT *vs.* conventional RT).

The selection of patients for lobectomy versus sublobar resections mirrors problems with referring patients for SBRT *vs.* conventional RT with some forms of ENI. Anatomic lobectomy is considered superior to sublobar resection based on the results of a randomized trial (13). However, some patients are unfit for traditional surgical management, and sublobar resections are considered for them because of the lower morbidity. There are conflicting data about whether sublobar resection is superior to SBRT in such patients (14,15). It is likely that patients with small tumors (<2 cm) and without evidence of nodal involvement on PET-CT may be directed for sublobar resections or SBRT, especially if the risk of an anatomic lobectomy is increased. For patients without evidence of nodal metastases on PET-CT but with tumor characteristics indicating a risk of occult nodal disease, neither sublobar resection nor SBRT is indicated. After careful mediastinal staging that confirms no mediastinal metastases, lobectomy with lymph node dissection or RT with inclusion of at least the hilar region would be a treatment of choice for such patients.

To conclude, a retrospective analysis of the relationship between tumor characteristics and the risk of occult nodal metastases by Paravati *et al.* (2) is in line with a number of similar studies that call for caution in therapeutic decision making based only on imaging and even on inclusion of invasive staging methods. Treatment should be individualized with regard to the patient's condition and tumor characteristics. Although imaging is very helpful, clinical judgment still remains vital to the choice of therapeutic option.

Acknowledgements

None.

Footnote

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

References

1. Meyers BF, Haddad F, Siegel BA, et al. Cost-effectiveness of routine mediastinoscopy in computed tomography- and positron emission tomography-screened patients with stage I lung cancer. J Thorac Cardiovasc Surg 2006;131:822-9; discussion 822-9.
2. Paravati AJ, Johnstone DW, Seltzer MA, et al. Negative predictive value (NPV) of FDG PET-CT for nodal disease

© Journal of Thoracic Disease. All rights reserved.

in clinically node-negative early stage lung cancer (AJCC 7th ed T1-T2aN0) and identification of risk factors for occult nodal (pN1-N2) metastasis: implications for SBRT. Transl Cancer Res 2014;3:313-9.
3. Sawyer TE, Bonner JA, Gould PM, et al. Predictors of subclinical nodal involvement in clinical stages I and II non-small cell lung cancer: implications in the inoperable and three-dimensional dose-escalation settings. Int J Radiat Oncol Biol Phys 1999;43:965-70.
4. Suzuki K, Nagai K, Yoshida J, et al. Clinical predictors of N2 disease in the setting of a negative computed tomographic scan in patients with lung cancer. J Thorac Cardiovasc Surg 1999;117:593-8.
5. 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.
6. De Leyn P, Dooms C, Kuzdzal J, et al. Revised ESTS guidelines for preoperative mediastinal lymph node staging for non-small-cell lung cancer. Eur J Cardiothorac Surg 2014;45:787-98.
7. Fernandez FG, Kozower BD, Crabtree TD, et al. Utility of mediastinoscopy in clinical stage I lung cancers at risk for occult mediastinal nodal metastases. J Thorac Cardiovasc Surg 2015;149:35-41, 42.e1.
8. Fielding DI, Kurimoto N. EBUS-TBNA/staging of lung cancer. Clin Chest Med 2013;34:385-94.
9. Grills IS, Belderbos J, Hope A, et al. Higher risk of failure and death after stereotactic lung radiotherapy for T2 lung cancer. J Thorac Oncol 2015;10:S209 (O-19.02). Available online: http://journals.lww.com/jto/Citation/2015/09001/16th_World_Conference_on_Lung_Cancer_.1.aspx
10. Lucas JT Jr, Kuremsky JG, Soike M, et al. Comparison of accelerated hypofractionation and stereotactic body radiotherapy for Stage 1 and node negative Stage 2 non-small cell lung cancer (NSCLC). Lung Cancer 2014;85:59-65.
11. Belderbos JS, Kepka L, Spring Kong FM, et al. Report from the International Atomic Energy Agency (IAEA) consultants' meeting on elective nodal irradiation in lung cancer: non-small-Cell lung cancer (NSCLC). Int J Radiat Oncol Biol Phys 2008;72:335-42.
12. Kepka L, Socha J. PET-CT use and the occurrence of elective nodal failure in involved field radiotherapy for non-small cell lung cancer: A systematic review. Radiother Oncol 2015;115:151-6.
13. Ginsberg RJ, Rubinstein LV. Randomized trial of lobectomy versus limited resection for T1 N0 non-small cell lung cancer. Lung Cancer Study Group. Ann Thorac Surg 1995;60:615-22; discussion 622-3.
14. Grills IS, Mangona VS, Welsh R, et al. Outcomes after stereotactic lung radiotherapy or wedge resection for stage I non-small-cell lung cancer. J Clin Oncol 2010;28:928-35.
15. Mahmood S, Bilal H, Faivre-Finn C, et al. Is stereotactic ablative radiotherapy equivalent to sublobar resection in high-risk surgical patients with stage I non-small-cell lung cancer? Interact Cardiovasc Thorac Surg 2013;17:845-53.

Cite this article as: Kepka L, Socha J. PET-CT limitations in early stage non-small cell lung cancer: to whom more aggressive approach in radiotherapy and surgery should be directed? J Thorac Dis 2015;7(11):1887-1890. doi: 10.3978/j.issn.2072-1439.2015.11.34

© Journal of Thoracic Disease. All rights reserved.