

# Is single-station N2 disease on PET-CT an indication for primary surgery in lung cancer patients?

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*Provenance:* This is an invited Editorial commissioned by the Section Editor Laura Chiara Guglielmetti (Cantonal Hospital Winterthur, Kantonsspital Winterthur, Winterthur, Switzerland).

*Comment on:* Honguero Martínez AF, García Jiménez MD, García Vicente A, *et al.* Is the prognosis of occult N2 disease similar to that of positive positron emission tomography-computed tomography (PET/CT) scan single-station N2 disease in patients with non-small cell lung cancer treated by surgical resection? *Rev Esp Med Nucl Imagen Mol* 2017;36:350-5.

Submitted Oct 03, 2017. Accepted for publication Oct 26, 2017.

doi: 10.21037/jtd.2017.10.154

**View this article at:** <http://dx.doi.org/10.21037/jtd.2017.10.154>

Despite development of novel systemic treatment and radiation strategies, surgery remains the most successful method of radical treatment of non-small-cell lung cancer (NSCLC). However, in patients with locally advanced disease it is recommended to combine surgery with chemotherapy, sometimes with an addition of radiation, to improve the cure rate and distant survival. Authors of the recently available article (1) which is the subject of our polemic compare late survival of two groups of patients with minimal N2 disease who are considered candidates to combined treatment with the predominant role of surgery according to current recommendations. Namely, they compare patients with occult mediastinal lymph node metastases (false negative N2 disease in preoperative positron emission tomography) with those with single-station clinical N2 (cN2) disease which was not confirmed microscopically before surgery. Due to the latter, in both groups of patients no preoperative chemotherapy was administered. This was not a usual situation because in most patients with suspicion of N2 disease, metastases to mediastinal lymph nodes can be confirmed preoperatively and only an “obscured” location of N2 lymph nodes in patients accrued to this study allowed authors to formulate the hypothesis and create the study protocol. According to current recommendations, patients with preoperatively confirmed N2 disease should receive neoadjuvant

chemotherapy while in patients with metastases diagnosed only on the basis of postoperative specimen (so called occult metastases) adjuvant chemotherapy is recommended.

Authors conclude that mean overall survival and mean disease-free survival are similar in both groups. They even extrapolate these results from patients with “obscured” single-station N2 into all patients with single-station N2 disease. This extrapolation seems justified because prognosis of patients with N2 disease is similar regardless of the exact location of lymph nodes. When this conclusion is extrapolated into all patients with single station N2 disease, it rationalizes primary surgical treatment in a significant number of patients who nowadays are treated with neoadjuvant chemotherapy prior to surgery. Although only few direct comparisons of neoadjuvant and adjuvant chemotherapy are available (2,3), these two approaches seem to be comparable in terms of survival (4,5). Moreover, latest development of immunotherapy, molecularly targeted agents, biomarkers and radiation therapy speaks in favor of adjuvant treatment over neoadjuvant cytotoxic chemotherapy.

Numerous factors have been analyzed as predictors of occult metastases to mediastinal lymph nodes (not discovered by preoperative PET scan). Some of them have been confirmed as predictors of false-negative results of PET scan [Table 1 (6-15)]. Among these factors

**Table 1** False negative results of PET scan according to N2 status of patients with an early-stage lung cancer

Author, year	Number of patients	Number of false negative	% of false negative	Predictors of false negative
Al-Sarraf <i>et al.</i> , 2008 (6)	153	25	16	Centrally located tumor, right upper lobe, PET positive uptake in N1
Park <i>et al.</i> , 2010 (7)	147	7	4.8	Primary tumor SUV <sub>max</sub> >7.3
Gómez-Caro <i>et al.</i> , 2012 (8)	153	17	11	Adenocarcinoma, tumor size ≥5 cm, pN1
Iskender <i>et al.</i> , 2012 (9)	107	4	3.7	Right upper lobe
Miyasaka <i>et al.</i> , 2013 (10)	265	24	9.0	Primary tumor SUV <sub>max</sub> >10, consolidation/tumor dimension ratio
Cho <i>et al.</i> , 2014 (11)	1,821	196	10.8	Adenocarcinoma, cN1, tumor size >3 cm, right middle lobe
Trister <i>et al.</i> , 2014 (12)	201	63	31	Primary tumor SUV <sub>max</sub> >10
Lin <i>et al.</i> , 2016 (13)	284	24	8.5	Primary tumor SUV <sub>max</sub> >2.6
Kaseda <i>et al.</i> , 2016 (14)	324	40	12.3	Primary tumor SUV <sub>max</sub> >3.9, adenocarcinoma, tumor size >3 cm
Bille <i>et al.</i> , 2017 (15)	1,667	146	9	Adenocarcinoma, vascular invasion

cN1, clinical N1; pN1, pathological N1; SUV<sub>max</sub>, maximum standardized uptake value.

adenocarcinoma histology, right upper or middle lobe location of the primary tumor, high maximum standardized uptake value (SUV<sub>max</sub>) of the primary tumor, large tumor diameter, vascular invasion, central location of tumor, positive <sup>18</sup>F-FDG uptake in intrapulmonary and/or hilar lymph nodes and consolidation/tumor dimension ratio are best documented. These analyses mostly show the tendency of lung cancer to metastasize to ipsilateral mediastinal lymph nodes regarding tumor location (e.g., vascular invasion) and histology (biology) of the tumor. Application of two models of an Artificial Neural Network to predict metastases into mediastinal lymph nodes showed 89% and 92% accuracy with two factors (SUV<sub>max</sub> >2.8 and lymph node length >15 mm) being most sensitive (16) but their value should be assessed in a larger and prospective analysis.

The analyzed paper aims to provide new data on the role of primary surgery in lung cancer patients with metastases to the ipsilateral mediastinum. This topic is a matter of ongoing debate, full of limitations and concerning a heterogeneous group of patients. Since prospective randomized trials (17,18) did not show any advantage of surgery combined with preoperative chemotherapy over chemoradiotherapy, before recommending primary surgery in any subgroup of patients with N2 disease a comparison of late results of such treatment with chemo-radiotherapy should be performed, at least on the basis of meta-analysis or best—based on the results of a prospective randomized trial. It has been announced previously that patients with metastases to ipsilateral lymph nodes consist of several sub-

groups of different prognoses. The current paper provides with new data on late survival of patients with an “obscured” single-station N2 disease and shows that the prognosis in this group is similar to that in occult N2 metastases. The 5-year survival rate reaching almost 40% in this small group of patients is encouraging but without comparison of this survival to late results of chemoradiotherapy in this subgroup of patients recommendation of primary surgery in this subgroup does not seem justified.

False-negative results of PET-CT in the diagnosis of mediastinal nodal involvement in lung cancer patients prompts several authors to recommend performing a routine mediastinoscopy even in the absence of suspected N2 disease in CT scan or PET-CT. The most commonly accepted recommendations are as follows:

- (I) Adenocarcinoma (except types A, B and C according to Noguchi classification) (9,12,15,16);
- (II) Centrally located tumor (7,19,20);
- (III) High risk of postoperative complications (e.g., pneumonectomy is considered, concomitant diseases) (19);
- (IV) Superior sulcus cancers (21);
- (V) cN1 disease in CT scan or PET-CT (7,9,12,22);
- (VI) High diameter of the tumor (9,12) although the recommended diameter varies;
- (VII) High SUV<sub>max</sub> of the tumor (this parameter is not standardized and varies depending on institution) (8,11,13-15,20);
- (VIII) Right upper lobe (7,10); middle lobe (12) location

of the primary tumor;

- (IX) Known or suspected very limited small cell lung cancer (23).

Implementation of novel non-cytotoxic agents in the systemic treatment sheds new light on the issue of adjuvant treatment, forcing surgeons and pathologists to provide better quality material for molecular tests. On the other hand, the implementation of minimally invasive surgery (VATS lobectomies and VATS segmentectomies) facilitates the use of adjuvant treatment (24,25). By shifting importance towards molecular tests, the advantage of primary surgery and surgical biopsy over fine needle aspiration is increasing. It also prompts to operate patients with locally advanced disease, including patients with minimal N2 disease, before administration of systemic treatment. Whether it will improve quality of life, time to progression and distant survival is not obvious yet and will have to be confirmed in prospective randomized trials.

### Acknowledgements

None.

### Footnote

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

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**Cite this article as:** Kowalewski J, Szczesny TJ. Is single-station N2 disease on PET-CT an indication for primary surgery in lung cancer patients? *J Thorac Dis* 2017;9(12):4828-4831. doi: 10.21037/jtd.2017.10.154