

## Debatable results of surgery for lung cancer in a patient with long existing pulmonary metastases from differentiated thyroid carcinoma.

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**ABSTRACT:** *Introduction:* The appropriate following treatment in a patient with a new presented non-small cell lung cancer (NSCLC) and history of chronic lung metastases of thyroid origin has never been reported. In such cases, the presence of long-standing thyroid metastatic disease with proven “limited malignant potential” could be considered as a minor treatment problem justifying one’s the decision to focus on the primary lung carcinoma as the only serious threat for the patient’s life.

*Case report:* We report the surgical treatment of a new presented NSCLC in a patient with chronic lung metastases of thyroid origin and we present all the diagnostic, staging and treatment problems.

*Conclusion:* The therapeutic results of our surgical approach were not encouraging. This could be owed to our staging problems of NSCLC and the well documented limited immunological response of such patients with multiple neoplasms.

*Key Words:* Lung cancer diagnosis and staging, Lung cancer surgery, Metastasectomy, Synchronous carcinomas, Thyroid cancer.

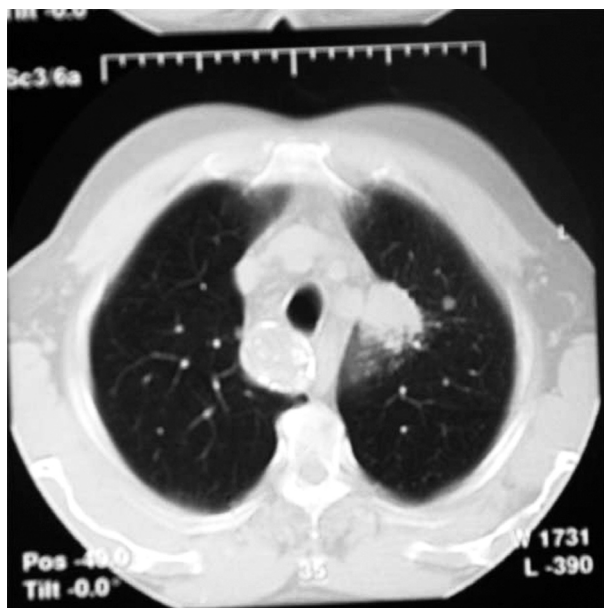
### INTRODUCTION

Unlike most other human cancers, the presence of thyroid metastatic disease does not relate with poor prognosis and the overall long term survival is reported to be approximately 50%<sup>1</sup>. There is no doubt that the usual multiplicity of the thyroid metastatic lesions in both lungs in concordance with their fairly good therapeutic response to <sup>131</sup>I, disables the role of any surgical approach. But similarly, the incidence of thyroid metastatic disease alone does not seem to set a contraindication for thoracotomy in case of a new presented synchronous primary lung cancer.

In such cases the assessment of origin of any neoplastic disease in the lungs or elsewhere (M disease) should be primary based on previous CT scans, which can differentiate the old metastatic thyroid lesions from any new presented ones, which can be considered as of lung origin.

Anyhow, such a similar differentiation concerning the infiltration of mediastinal lymph nodes (N disease) is harder to make, since both NSCLC and papillary thyroid carcinoma tend to metastasize to the anterior mediastinum<sup>2</sup>. As a result, the specificity of all preoperative procedures, including mediastinoscopy, integrated PET/CT and scanning with <sup>131</sup>I, to detect lymph nodes with pulmonary disease is dramatically diminished. *One could propose that nodes detected with PET/CT and not with <sup>131</sup>I are exclusively derived from the lung cancer.* But this can not be the rule, as it is common for longstanding thyroid metastatic lesions to *undifferentiate and thus, not to uptake <sup>131</sup>I.*

According to all the above we considered that the intraoperative complete lymph node dissection could be the only reliable staging procedure for the NSCLC.

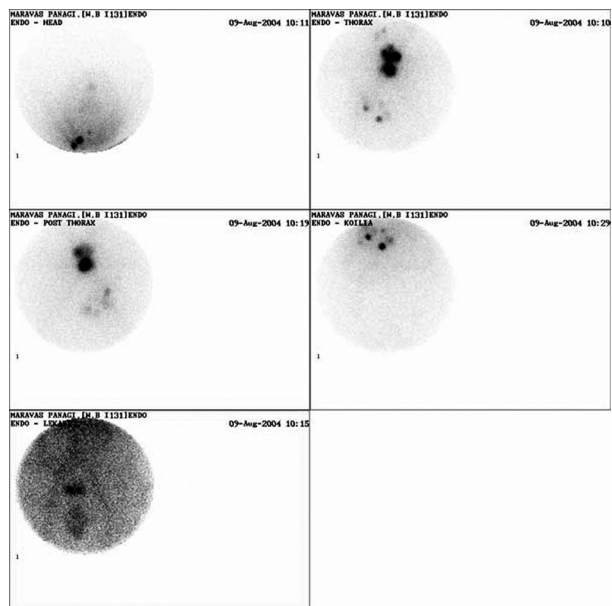


**Figure 1.** Primary malignant lesion and small metastatic nodule in the left upper lobe. Note the egg-shell lymph node calcification in the right paratracheal space causing slight forward displacement of the trachea.

#### Case presentation

A 55-year-old man was referred to our hospital with the diagnosis of squamous cell lung carcinoma and synchronous bilateral pulmonary metastases from papillary thyroid cancer (Figure 1). The patient had history of left thyroid lobectomy for the same thyroid pathology at the age of 15, but despite the existence of multiple pulmonary and mediastinal metastatic lesions he had never received any additional treatment. His follow-up had been based on sporadically taken x-rays and CT scans of the chest, which were almost invariable for 40 years, until recently, when a central located tumor of the upper left lobe was diagnosed. The final diagnosis was set by bronchoscopy and his pretreatment staging including MRI of the brain, CT abdominal scans, and bone scintigraphy revealed absence of any metastatic disease in solid organs.

We considered that the chronic presence of mediastinal lymphatic disease from the thyroid gland (Figures 1, 2) proved by his previous CT scans as well, would affect dramatically the specificity of both mediastinoscopy and integrated PET/CT together with  $^{131}\text{I}$  to detect lymph nodes with pulmonary metastatic



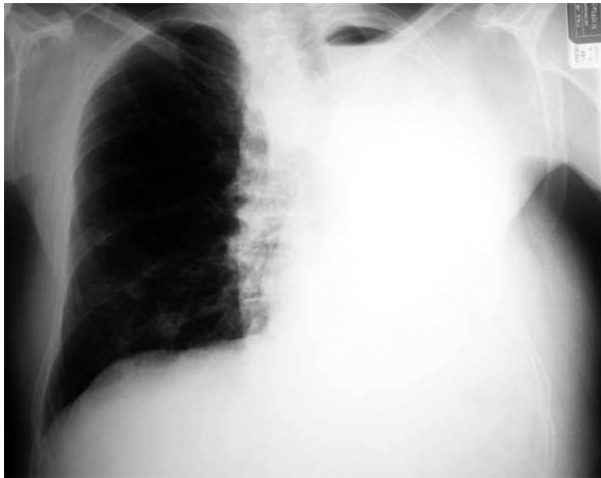
**Figure 2.** Post operative scanning with  $^{131}\text{I}$ . Note the massive  $^{131}\text{I}$  uptake from the mediastinal lymph nodes and from the two longstanding thyroid metastatic lesions in the right lower lobe (present in both thorax and upper abdominal scans). Compare with figure 1c.

disease; therefore we decided to complete the staging of our patient intraoperatively.

At operation, all visible lymph nodes were removed and sent for frozen section. As soon as we got the negative answer for pulmonary metastatic disease (absence of N2 disease preoperative NSCLC staging Ib or IIb), we continued the operation and we performed a typical pneumonectomy (Figure 3) since the tumor was found to extend beyond the fissure invading the lower lobe as well. Following pneumonectomy, the patient underwent also a completion thyroidectomy in order to facilitate the possible postoperative  $^{131}\text{I}$  uptake from the remaining thyroid metastatic lesions.

Permanent sections confirmed the histology for both thyroid metastases (Immunophenotype: Thyroglobulin+, LeuM1-, TTF1-) and the lung carcinoma (Immunophenotype: CK8-18+, CK7+, TTF1+, CK20-, 34 $\beta$ E12+, Thyroglobulin-) revealing also invasion of 2 out of 22 found intrapulmonary nodes [stations 12,13-postoperative staging IIb (T2, N1, M0)]. The patient recovered uneventfully and was discharged home in good condition.

Postoperatively, he received therapeutic doses



**Figure 3.** Post-pneumonectomy chest X-ray showing the remaining thyroid metastatic disease in the right lung.

170 mCi  $^{131}\text{I}$  for the control of the thyroid metastases as well as thoracic radiation therapy (45 Gy over 5 weeks) for his lung carcinoma. Although the suppression of the thyroid metastatic disease proved satisfactory (Figure 2), brain and liver metastases appeared 21 months later. The patient received adjuvant therapy (3 cycles of i.v. docetaxel, cis-platin and gemcitabine HCl), but he died in the next 7 months from disseminated disease.

### DISCUSSION

Thyroid cancer represents an exceptional biological tumor with favorable prognosis even with the existence of distant metastases. It is well-documented that the incidence of thyroid metastatic disease at the time of initial presentation in differentiated thyroid cancer is approximately 4 %<sup>2</sup>.

Metastatic spread of papillary carcinoma occurs to the jugular and the anterior mediastinal nodes, lungs, liver, bones and elsewhere. Pulmonary metastases are usually bilateral and multiple, responding well to radioactive iodine therapy. Therefore they do not fulfil the general selection criteria for metastasectomy: absence of metastases to other nonpulmonary sites, adequate pulmonary function to tolerate resection, lack of any other effective treatment.

The “least malignant” biological behaviour of differentiated thyroid cancer- proved from the long his-

tory of thyroid metastatic disease of our case as well-justified our decision to consider the NSCLC as the only threat for the patient’s life. But unfortunately, the longstanding mediastinal lymphatic disease derived from the papillary thyroid cancer made the assessment of the N2 nodal status for his lung carcinoma very uncertain.

Although there is no definite way for lymphatic spreading in relation to the location of the NSCLC, right lung tumors originating in the upper lobe mainly metastasized to level No. 4, while tumors of the middle lobe spread to stations Nos. 4 and 7, and those in the lower lobe to level No. 7<sup>3</sup>. In our patient the assessment of infiltration or not of these nodes with pulmonary disease was not made preoperatively since thyroid cancer had already metastasized to the same stations (Figure 1).

The specificity of PET/CT together with  $^{131}\text{I}$  scans, to differentiate the pulmonary from the thyroid nodal metastatic disease is null. *One could propose that nodes detected with PET/CT and not with  $^{131}\text{I}$  are exclusively derived from the lung cancer.* But this can not be the rule, as it is common for longstanding thyroid metastatic lesions to *undifferentiate and thus, not to uptake  $^{131}\text{I}$ .*

The interest for the infiltration or not of mediastinal lymph nodes with pulmonary disease is more than theoretic, since it will finally determine the following treatment. Mediastinoscopy has always a central role in the decision-made to proceed or not with lung resection even in the presence of other nodal pathology. For this reason, reconsidering our case we believe that mediastinoscopy should have been performed, despite its predicted low sensitivity in our patient.

On the other hand, aggressive surgical resection is strongly recommended for such individuals with multiple neoplasms which have proven limited immunological response. Re-reviewing our treatment options, we conclude that the decision for surgery was justified, but it should be followed by early aggressive adjuvant treatment as well. This could prolong the limited survival of our patient who finally died from advanced disease.

The only limitation for surgery may result from the pulmonary fibrosis which usually complicates the following radioactive iodine therapy<sup>4</sup>. Any patient

with border respiratory parameters or other pulmonary problems<sup>5</sup> may show impairment of his respiratory function; in such a case an alternative treatment should be considered.

Several additional general conclusions may also arise from this unique report. First of all, in cases of lung cancer with multiple pulmonary nodules the thoracic surgeon must have histologic confirmation about the nature of the satellite lesions, rather than consider them as T4 or M1 originating from the primary site. If such a staging misinterpretation occurs, we may leave inside the patient a quite resectable tumor. Second, if the satellite lesions proved to originate from the thyroid gland as in our case, we must remember that thyroid metastases may respond fairly well to <sup>131</sup>I on condition that the levels of serum thyroglobulin (Tg) after endogenous or exogenous TSH stimulation are higher than 10 microg/L<sup>2</sup>. Of course, total thyroidectomy is essential for the <sup>131</sup>I intake from the satellite lesions<sup>6</sup>. And finally, long-term follow up is crucial as stunning of the thyroid metastases may follow the initial diagnostic or treatment doses of <sup>131</sup>I<sup>7</sup>.

### CONCLUSION

The therapeutic results of lung resection in the presence of multiple chronic thyroid metastases from a differentiated papillary carcinoma are debatable. The reason for this can be the false indication for surgery arising from the staging problems concerning mostly the determination of N disease as well as the limited immunological response of such patients with multiple neoplasms.

### Consent

Written informed consent was obtained from the wife of our deceased patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

### Competing interests

The authors declare that they have no competing interests.

### Authors' contributions

IAK is the main author of the manuscript, DNE and NP interpreted our patients computed tomography and post operative scanning with <sup>131</sup>I, MA collected the data, AN and KT were responsible for the language editing and IPB was one of the surgeons who was involved in the operation.

### Acknowledgements

This article is dedicated to the memory of Antonios Loutsidis. We all miss him too much.

## Αμφίβολα τα αποτελέσματα της χειρουργικής θεραπείας σε ασθενή με καρκίνο του πνεύμονα και χρόνιες πνευμονικές μεταστάσεις από διαφοροποιημένο καρκίνο θυρεοειδούς.

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**ΠΕΡΙΛΗΨΗ:** *Εισαγωγή:* Η πλέον κατάλληλη θεραπεία για τον μη μικροκυτταρικό καρκίνο του πνεύμονα σε ασθενή με χρόνιες πνευμονικές μεταστάσεις θυρεοειδικής προέλευσης δεν έχει μέχρι σήμερα περιγραφεί. Σε ανάλογες περιπτώσεις, η παρουσία χρόνιας μεταστατικής νόσου θυρεοειδικής προέλευσης με αποδεδειγμένη «περιορισμένη κακοήγη δυναμική» θα μπορούσε να θεωρηθεί ως ελλάσον θεραπευτικό πρόβλημα, δικαιολογώντας την απόφαση του θεράποντος να εστιάσει στον πρωτοπαθή καρκίνο του πνεύμονα ως τη μόνη σοβαρή απειλή για τη ζωή του ασθενούς.

*Περιγραφή του περιστατικού:* Παρουσιάζουμε τη χειρουργική θεραπεία πρωτοεμφανιζόμενου μη μικροκυτταρικού καρκίνου του πνεύμονα σε ασθενή με χρόνιες πνευμονικές μεταστάσεις θυρεοειδικής προέλευσης και συζητούμε όλα τα προβλήματα διαγνωστικά, σταδιοποίησης και θεραπευτικής αντιμετώπισης.

*Συμπέρασμα:* Τα θεραπευτικά αποτελέσματα της χειρουργικής μας προσέγγισης δεν ήταν ενθαρρυντικά. Αυτό μπορεί να οφειλόταν τόσο στα προβλήματα που αντιμετωπίσαμε στην σταδιοποίηση του καρκίνου του πνεύμονα όσο και στην γνωστή σε όλους μας καταστολή του ανοσοποιητικού συστήματος που εμφανίζουν τέτοιοι ασθενείς με πολλαπλά νεοπλάσματα.

*Λέξεις Κλειδιά:* Καρκίνος του πνεύμονα διάγνωση και σταδιοποίηση, Χειρουργική αντιμετώπιση καρκίνου του πνεύμονα, Μεταστασεκτομή, Σύγχρονα καρκινώματα, Καρκίνος του θυρεοειδούς.

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