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Measurement of primary tumor volume by PET–CT to evaluate risk of mediastinal nodal involvement in NSCLC patients with clinically negative N2 lymph nodes

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ABSTRACT

Aim: The study aimed to determine a prognostic value of primary tumor volume measured on the basis of integrated positron emission tomography–computerized tomography (PET–CT) in terms of mediastinal nodal metastases (N2) prediction in non-small-cell lung cancer (NSCLC) patients with PET–CT N2 negative lymph nodes.

Methods: The records of 70 potentially operable NSCLC patients treated with surgical resection were analyzed. All patients underwent diagnostic, preoperative PET–CT, which was the basis for tumor volume calculations as well as the evaluation of N2 nodes status. The logistic regression analysis was employed to determine correlation between mediastinal nodal involvement and volume of primary tumor (izoSUV2.5 volume), that is the volume of primary tumor inside SUV 2.5 line, tumor histology, location (peripheral vs. central), hilar node status.

Results: A statistically significant correlation between mediastinal node involvement and izoSUV2.5 volume, tumor histology, locations peripheral vs. central and hilar node status was found. The risk of mediastinal lymph node metastasis is 24% for tumor volume of 100 cm^3 and increases up to 40% for tumor volume of 360 cm^3. An increase of tumor volume by 1 cm^3 increases the risk of lymph node disease by 0.3%. Tumor histology adenocarcinoma vs. squamous cell carcinoma increases the risk of mediastinal lymph node involvement by 195%, location central vs. peripheral by 68% and hilar node involvement by 166%.

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Conclusions: The study demonstrates that izoSUV2.5 volume of primary tumor may be considered as a prognostic factor in NSCLC patients, since it strongly correlates with mediastinal lymph node pathological status. This correlation is modified by primary tumor location, histology and hilar node involvement.

1. Background

The most absorbing issue in modern oncology of non-small-cell lung cancer (NSCLC) is the implementation of integrated positron emission tomography–computerized tomography (PET–CT) to the diagnostic process. PET–CT offers superior sensitivity and specificity compared to CT or PET alone and may improve staging accuracy. Mediastinal lymph nodes status in NSCLC patients has important therapeutic and prognostic implications. The current consensus is that a positive mediastinal nodal uptake on PET–CT should be verified histologically by mediastinoscopy or transbronchial needle aspiration while negative uptake in the mediastinum should proceed to resection. A significant proportion of PET–CT mediastinum negative cases will turn out to be positive following resection. There is a high probability that tumor volume has great value in predicting lymph node involvement, a feature, which decreases 5-year survival by 30–40%.

1.1. Aim

The study aimed to determine a prognostic value of primary tumor volume measured on the basis of PET–CT (izoSUV2.5 volume) in terms of mediastinal nodal metastases prediction in NSCLC patients.

2. Material and methods

2.1. Selection of patients

Between September 2008 and December 2009, a total number of 70 consecutive potentially operable NSCLC patients were treated with a curative intent. From the total number of 425 evaluated by PET–CT newly diagnosed NSCLC patients, 355 (83%) presented a more advanced disease. Diagnostic PET–CT performed in all 70 did not depict mediastinal lymph node involvement (PET–CT N2 negative patients). All these patients were treated radically, 62 of them underwent anatomical resections and 8 of them wedge resections. As regards anatomical resections, 8 pneumonectomies – all left-sided, 6 inferior bilobectomies and 48 lobectomies (22 right-sided and 26 left-sided) were performed. All patients underwent a systematic lymph node dissection and were then examined pathologically. The patients were given antibiotics and antithrombotic prophylaxis perioperatively.

The mean age of patients was 63 years, ranging from 22 to 78; 44 of them were male (62.9%) and 26 female (37.1%). The clinical staging was based on the following criteria: general clinical examination, biopsy, routine blood cell counts, blood chemistry profile, chest X-ray and chest CT, abdominal ultrasonography, bronchoscopy and pulmonary function test. The pathological diagnosis of most patients was squamous cell carcinoma in 35 patients (50%), adenocarcinoma in 26 (37%), large cell carcinoma in 8 (12%) and mucoepidermoid carcinoma in 1 (2%) case. The grading was: G_1 in 1, G_2 in 28, G_3 in 17 and unknown in 24 cases. Primary tumor stage was T1 in 23, T2 in 35, T3 in 12 patients. There were 33 PET N1 positive cases and 37 negative ones. Peripheral location was determined in 55 patients while central in 15.

2.2. Image analysis

All patients underwent PET–CT examination as a routine procedure before the decision of surgery. The whole body scan (Biograph 6 and Biograph 16, Siemens, Erlangen, Germany) was performed for the evaluation of primary tumor, lymph node involvement, distant metastases and tumor volume computations. All patients were fasted for at least 6 h before the examination. Blood glucose levels were determined before injection of 5–7 MBq/kg [^{18}F]fluorodeoxyglucose (FDG). FDG was produced in our own laboratory. Sixty minutes after administration of FDG, PET–CT scans were obtained from the skull base to the ¼ upper level of the hips. Diagnostic CT was done in 6–7 beds, 2 min each, of PET imagining performed according to the height of the patient. Images were reconstructed using 3D iterative reconstruction.[1,2]

Whole body images in DICOM formats were sent online via PACS system (Siemens, Erlangen, Germany) to the external beam radiotherapy treatment planning system. Tumor area was identified and delineated on each PET–CT scan by the oncologist with the assistance of a nuclear medicine specialist, who was unaware of clinical and pathological findings. IzoSUV2.5 volumes, that is the volume of primary tumor inside SUV 2.5 line, were calculated automatically using the True D radiotherapy treatment planning system (Siemens, Erlangen, Germany; Fig. 1).

Lymph nodes greater than 10 mm in the short axis and SUV > 2.5 were interpreted as metastatic.

2.3. Statistical analysis

Pathologically confirmed mediastinal lymph node involvement was the endpoint of the study. The correlation between mediastinal nodal metastasis occurrence (pathologically confirmed) and such parameters as: izoSUV2.5 volume, SUV max, tumor pathological type and grade, primary tumor stage, diameter and location (peripheral vs. central), hilar node status (PET N1) as well as patient's age and sex were determined using the univariate logistic regression. Correlation between statistically significant variables and lymph node involvement were assessed using the multivariate logistic regression

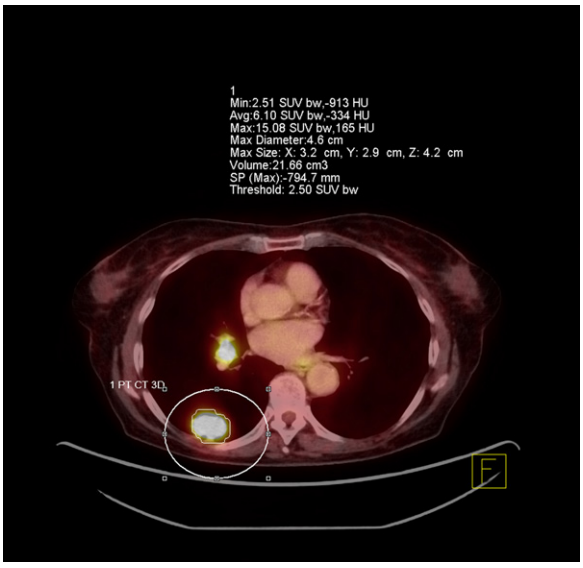

Fig. 1 – PET–CT scan – delineated tumor (white line) is visible as a high-signal mass comprising the peripheral part of the lung. The calculated izoSUV2.5 volume of primary tumor, without N1 mass, is shown.

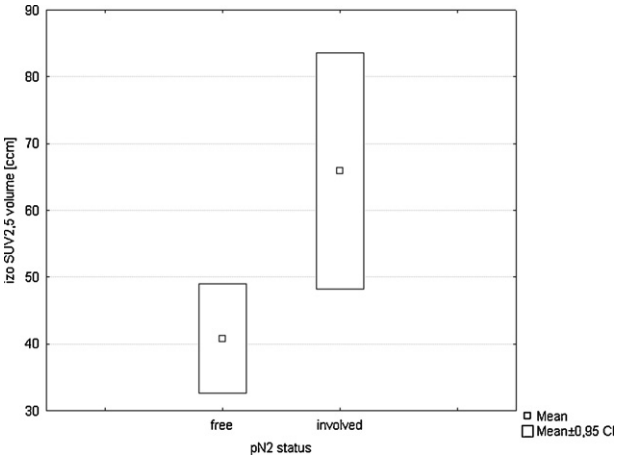

Fig. 2 – Tumor volume parameters categorized into two groups according to the status of mediastinal lymph nodes, pN2 positive (metastatic) lymph nodes, pN2 negative (free) lymph nodes.

analysis. Odds ratio (OR) and its 95% confidential interval (CI) were estimated. Additionally, a sigmoid risk curve was drawn and its coefficient was obtained. The maximum likelihood method enabled drawing the best adjusted risk curve and assessing a statistical significance of the adjustment. A value of $p = 0.05$ was accepted as statistically significant. Tumor volumes were computed for both distinguished patient groups, with and without mediastinal lymph node disease, and compared with the *t-Student* test. All the calculations were made using the Statistica'99 software.[3]

3. Results

Mediastinal nodal metastases (pN2+) were found in 16 (23%) out of 70 operated patients. Thus, 54 (77%) out of 70 patients represented a negative mediastinal lymph node status (pN2−). In the whole group of patients, approximately 9.1 lymph nodes (standard deviation (SD) 5.3; range 1–27) were removed. In groups (pN2+) and (pN2−), approximately 10 (SD 5.8; range 1–23) and 8.8 (SD 5.1; range 1–27) lymph nodes were removed, respectively. In the mediastinal lymph node involvement group a vessel embolism of neoplasm cells in 5 patients and an extracapsular infiltration in 4 others were observed.

The mean izoSUV2.5 volume was 45 cm^3, SD 99 cm^3. In patients with nodal metastases izoSUV2.5 volumes were significantly higher compared to those in patients with no nodal involvement: 65.9 cm^3, SD 113.5 cm^3 vs. 40.9 cm^3, SD 91.3 cm^3; *t* test $p = 0.003$ (Fig. 2).

In the univariate logistic regression analysis the statistical significance was found for six parameters: SUV max, izoSUV2.5 volume, tumor histology type, stage and location peripheral vs. central and hilar node status (Table 1).

In the multivariate logistic regression analysis the statistical significance was found for four parameters only, including izoSUV2.5 volume, tumor histology type, location peripheral vs. central, hilar node status (Table 2).

Fig. 3 represents the risk of mediastinal lymph node involvement as a function of izoSUV2.5 volume defined on the basis of PET–CT images. The probability of mediastinal lymph node metastasis is 24% for tumor volume of 100 cm^3 and increases up to 40% for tumor volume of 360 cm^3. The logistic regression analysis showed that each 1 cm^3 of tumor volume increases the risk of mediastinal lymph node involvement by 0.3%, with odds ratio of 1.0034. The model predicts a 23% risk for the "0" cm^3 izoSUV2.5 volume (invisible tumor). Tumor histology adenocarcinoma vs. squamous cell carcinoma increased the risk of mediastinal lymph involvement by 195%. Tumor location central vs. peripheral increased the risk of mediastinal lymph involvement by 68%. PET–CT N1 metastatic feature increased the risk of mediastinal lymph involvement by 166%.

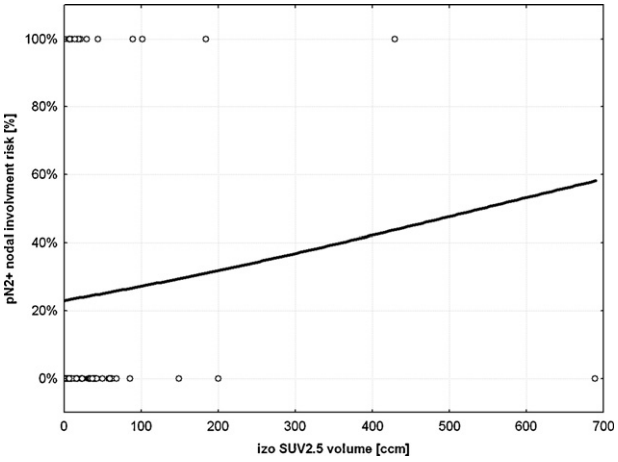

Fig. 3 – Relationship between the risk of mediastinal nodal involvement and tumor volume.

Table 1 – The risk of mediastinal lymph node involvement, the univariate logistic regression analysis.

	Odds ratio	Confidence interval		*p*-Value
		−95%	+95%	
izoSUV2.5 volume	1.0022	1.0006	1004	<0.001
Location peripheral vs. central	1.45	1.02	2.22	0.04
HP adeno vs. squamous	2.1	1.6	2.9	<0.001
N1 PET vs. N0 PET	2.38	1.6	3.4	<0.001
T stage	1.31	1.00	1.73	0.04
SUV max	1.05	1.00	1.12	0.02

Table 2 – The multivariate logistic regression analysis, the risk of mediastinal lymph node involvement as a function of independent variable.

	Odds ratio	Confidence interval		*p*-Value
		−95%	+95%	
izoSUV2.5 volume	1.0034	1.0015	1.0053	0.0004
Location peripheral vs. central	1.68	1.02	2.77	0.04
HP adeno vs. squamous	2.95	2.02	4.30	<0.001
N1 PET vs. N0 PET	2.66	1.76	4.02	<0.001
T stage				0.5
SUV max				0.2

Fig. 4 presents the risk of mediastinal lymph node involvement as a function of izoSUV2.5 volume and tumor histology.

4. Discussion

According to expectations, a statistical significance was demonstrated between the izoSUV2.5 volume and mediastinal lymph node involvement risks, assessed pathologically.

Asamura[4] found that among patients with resected peripheral NSCLC, the prevalence of lymph node metastases increased from 19.5% in tumors 2.0 cm or smaller to 32.5% in tumors 2 to 3.0 cm in diameter. Like Stiles,[5] he highlights that in the group of primary tumors 0–2 cm vs. >2 cm the risk rises 2.4 times.

Lee[6] discovered a growing risk of micrometastasis: 4.8%, 6.5%, 6.3%, 57% for primary tumors 0–2, 2.1–4, 4.1–6 and >6 cm in diameter, respectively.

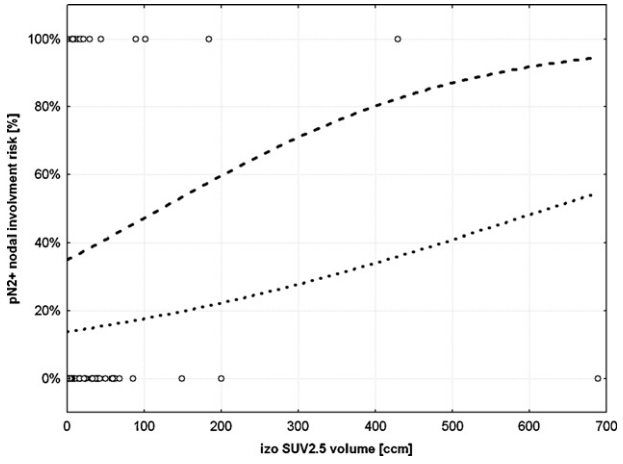

Fig. 4 – Relationship between the risk of mediastinal nodal involvement and tumor volume according to pathological type, adenocarcinoma – dashed, squamous – dotted line.

In our result, the 23% incidence of occult pN2 metastasis approached that given by Melek 20.3%,[7] Periguad[8] 19.6%, Al-Sarraf[9] 16%, Tournoy[10] 16%, Gomez-Caro[11] 14.4%, who recruited from a similar group of patients. At the same time, however, there is much concern about our cutting point (SUV2.5 and 1 cm in short axis) which could be suggested as being too liberal.

Current evidence confirms that there is a connection between adenocarcinoma and an increased risk of understaging: our results support this thesis. Such outcomes are also presented by Gomez-Caro,[11] Melek,[7] Lee,[6] Carnochan,[12] Bille,[13] Stiles.[5]

We agree with Gomez-Caro[11] and Cardia[14] that such variables as side and age are not influential. But in contrast to us, they do not indicate the significance of tumor size, but gender role.

The feature of primary tumor, which is conversely assessed as the risk factor of incidence of occult N2 disease, is SUV max. Lee[6] concluded that tumors with occult N2 metastases had a significantly higher median SUV max compared with those without N2 disease: 6.0 g/mL vs. 3.6 g/mL. And the prevalence of occult N2 disease increased significantly from 1.9% to 10.5% when SUV max of the primary tumor exceeded 4.0 g/mL.

Downey[15] also noted that uptake in patients with pathological nodal involvement was higher than in those who were N0 too. The mean SUV in N0 patients was 8.9 ± 6.3 and the mean SUV in N1–2 patients was 13.6 ± 6.9. In this observation, tumor volume compound is needed to assess the mean SUV of primary tumor. In our group of patients we did not found statistically significant differences between the SUV max of primary tumor in both subgroups, pN2 negative vs. pN2 positive, in the multivariate logistic regression analysis. The statistical significance of the SUV max is disappearing for the benefit of izoSUV2.5 volume, which better explains the risk of mediastinal nodal metastases.

The coexistence of two independent variables, i.e. the size of primary tumor and histology, is suggested by Casali[16] in the assessment of the biological aggressiveness of lung cancer

and, as a result, prognosis. These two factors are relevant in our material as well.

Kanzaki[17] demonstrated that adenocarcinoma, tumors located in the upper or middle lobe, tumor size >3 cm, and SUV_{max} of primary tumor >4.0 g/mL are risk factors for occult MLN metastasis.

The limit of resolution for the PET–CT system can explain the majority of false negative cases.[8] The other cause could be a central tumor location, which obscures adjacent lymph node invasion.[9] On the other hand, the presence of air in surrounding structures (lungs) makes ultrasound visualization of the lymph nodes impossible in opposition to e.g. head and neck cancer patients.[18,19]

Our principal finding is the correlation between tumor volume and lymph node status. The frequency of lymph node metastases was significantly higher in patients with larger tumor volumes compared with those with smaller ones. A change of tumor volume by 1 cm^3 highly alter the risk of mediastinal nodal involvement by 0.3%. This relation is modified as well by histology, tumor locations and hilar nodes involvement.

It is a well known fact, however, that, apart from distant metastases, positive mediastinal lymph nodes are the most significant prognostic factors for recurrence and death in NSCLC patients.

We realize that a relatively small group of patients that might have influenced the statistical power of the analysis is a meaningful limitation of our results. However, the important fact is that our model allowed us to distinguish a group of patients whose risk of lymph node disease is low, for example less than 25% or 33% (predicted for the volume of 48 cm^3 and 210 cm^3, respectively). A more pronounced risk, for example greater than 50% (predicted in our model for 540 cm^3) could suggest an alteration in treatment strategy, for example an exclusion of surgery. Unquestionably, further studies, with a higher number of patients, are required to confirm the presented preliminary results. So far, our retrospective research, restricted to one hospital, does not allow us to suggest any strong recommendations on changing the treatment protocol, depending on tumor volume and thus the risk of mediastinal node metastasis. This is only a monograph to discuss that topic as well as the cost-effectiveness aspect.[20]

Conflict of interest

The authors declare that they have no conflict of interest.

Financial disclosure

None declared.

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