

Characteristics of lymphovascular metastatic spread in lung adenocarcinoma according to the primary cancer location

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ABSTRACT

Aim To compare the localization of lung adenocarcinoma with tumour size and lymphovascular invasion (LVI) presence, and to determine the frequency of metastasis findings in hilar and mediastinal lymph nodes depending on the localization of the tumour and status of lymphovascular invasion.

Method This observational cross-sectional study included 261 patients with complete resection of confirmed lung adenocarcinoma. The dependence between categorical variables were performed with χ^2 and Fisher's exact tests. A $p < 0.05$ was considered as statistically significant.

Result Metastases to hilar lymph nodes at lung adenocarcinoma with central localization and presented lymphovascular invasion were more frequently found than tumours with peripheral localization ($p < 0.001$). In tumours with peripheral localization, lymphovascular invasion was less frequent; even in tumours greater than 7 cm in the largest dimension the presence of LVI was not 100%. Metastases to mediastinal lymph nodes in tumours with central localization and presented lymphovascular invasion were less frequent than in tumours with peripheral localization and presented lymphovascular invasion ($p = 0.002$).

Conclusion In invasive adenocarcinoma, lymphovascular invasion was much more common in centrally positioned than in peripherally positioned tumours. Metastases to the hilar and mediastinal lymph nodes, regardless of the findings of lymphovascular invasion, usually originated from upper lobe tumours.

Key words: Frequency, relationship, post-resection histopathological findings, clinical pathological characteristics

INTRODUCTION

Lung cancer is commonly diagnosed cancer in both genders (11.6%) and the leading cause (18.4%) of the total cancer deaths (1). The incidence of adenocarcinomas is steadily increasing, contributing to 40-45% of newly diagnosed cases in the last 10 years, so that now prevalence of adenocarcinoma is higher than epithelioid cell carcinoma; the last one was previously leading among non-small cell lung carcinomas (NSCLC) (2).

Lung adenocarcinoma is often characterized by a peripheral localization in the pulmonary parenchyma, and therefore has a disguised clinical picture, and is discovered at late stages of the disease (3). This type of cancer is most commonly found among non-smokers, women of up to 45 years of age, younger male and people with proven family malignancies (1,2,4). The trend of lung adenocarcinoma is increasing in developed countries, as well as on the Asian continent (2,5,6).

Lymphovascular invasion (LVI) in the tumour tissue is one of the most important diagnostic, prognostic and predictive factors of this disease, and it is listed in the current histopathological classification (7). Although this classification has been multidisciplinary prepared for years, the “invasiveness” parameter is multifactorial, imprecisely defined and it is a subject of discussion (1,8). According to previous research, the existence of LVI leads to an expected bad course of the disease in terms of invasion to draining lymph nodes and frequent distant metastases (as the first signs of the disease), frequent relapses and recurrences, and shorter overall survival (9-12). The status of regional lymph nodes is a strong prognostic indicator and has a major impact on treatment decisions for patients with NSCLC (13).

The aim of the study was to find out frequency of LVI in centrally located lung adenocarcinomas (compared to peripherally located adenocarcinomas) by analysing definitive post-resection histopathological findings, and the relationship between LVI and clinical and pathological characteristics (localization, tumour size, N status, and frequency of metastasis in hilar and mediastinal lymph nodes depending on a tumour localization).

PATIENTS AND METHODS

Patients and study design

This cross-sectional study included 261 patients with complete resection with confirmed lung adenocarcinoma at the Clinic for Thoracic Surgery, University of Sarajevo Clinical Centre (USCC), between January 2017 and December 2018. The study approval was obtained from the Ethics Committee of the University of Sarajevo Clinical Centre, Sarajevo, Bosnia and Herzegovina.

Methods

The preoperative diagnostic protocol consisted of at least contrast computed tomography (CT) scan of the thoracic and upper abdominal organs with the determination of clinical Tumour Node Metastasis (cTNM) disease stage, a bronchoscopy with biopsies, or transthoracic biopsies, histopathological, cytological and immunohistochemical analysis, a functional lung status for the planned resection level, and cardiological evaluation of the patient's ability to be introduced into general anesthesia.

Operative procedures were performed in general separated anesthesia, with a prior zonal exploration of mediastinal lymph nodes and thoroscopic exploration of the pleural cavity. In addition to the tumour resection (done with a cutter/stapler or by placing a double proximal or transfixation ligatures), the enlarged hilar and mediastinal lymph nodes were resected. An intraoperative temporal histopathological resection margin analysis was performed in order to find residual tumour tissue. Pathohistological analysis of the resections was performed at the Department of Clinical Cytology and Pathology of USCC. Resected lung or lobe with tumour was fixed in 10% buffered formalin for 24 hours, dehydrated in alcohol-growing concentrations, illuminated in chloroform, moulded into appropriate paraffin blocks, slit on a sliding microtome at the thickness of 4-5 μ , deparaffinised and stained with standard (Hematoxylin-eosin) staining.

In the pathohistological finding, the status of lymphovascular invasion in the tumour was described as LVI+ (lymphovascular invasion present) and LVI- (non lymphovascular invasion). Surgical-pathologic staging (tumour size – T and lymph node status – N) was assigned according to the 8th edition of the lung cancer tumour – node – metastasis classification system (18). Tumour size: T4

>7 cm in greatest dimension, or invades any of the following structures: diaphragm, mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina, or associated with separate tumour nodule(s) in a different ipsilateral lobe to that of the primary); T3 >5 and ≤7 cm in greatest dimension, or directly invades any of the following structures: chest wall (including parietal pleura and superior sulcus tumours), phrenic nerve, parietal pericardium; or associated with separate tumour nodule(s) in the same lobe as the primary); T2b >4 and ≤5 cm in greatest dimension), T2a >3 and ≤4 cm in greatest dimension; T2 >3cm and ≤5 cm, or tumour with any of the following features: involves main bronchus regardless of the distance from the carina, but without involvement of the carina, invades visceral pleura, associated with atelectasis or obstructive pneumonitis that extends to the hilar region, involving part or all of the lung; T1c >2 and ≤3 cm in greatest dimension, T1b >1 and ≤2cm in greatest dimension; T1a ≤1 cm or less in greatest dimension.

Lymph node status: N0 (no regional lymph node metastasis), N1 (metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension), N2 (metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)).

Tumours localized in the main, lobular and segmental bronchi were classified as centrally positioned (C), and more distal tumours were classified as peripherally positioned (P). The tumour localization was also related to the corresponding lobe in which it was located.

Statistical analysis

The data is presented as absolute value (N), percentage (%), and mean value ±standard deviation. The distribution of variables was tested with the Kolmogorov-Smirnov or Shapiro-Wilk test. For continuous variables, comparison between the groups was performed by Student’s t-test. In the analysis of the dependence between categorical variables, the χ² and Fisher’s exact tests were performed. A p<0.05 was considered statistically significant.

RESULTS

There was a statistically significant gender difference among the patients (male:female= 1.75:1) (p<0.001); female population was younger than

male one (p=0.022). The most commonly found tumour size was T3 in 107 (40.99%) cases; T2b was detected in 43 (16.75%) cases; T1b was occasionally presented, in 13 (4.98%) cases; T1a was not found.

N1 (hilar lymph nodes) was found in 125 cases (47.89%), N2 (mediastinal lymph nodes) in only 38 (14.59%) cases; in 98 (37.52%) cases no lymph nodes were affected (p<0.001) (Table 1).

Table 1. Characteristics of patients and cancer characteristics

Characteristic		P
Age (± SD) (years)		
Male	63 (±1.6)	0.022
Female	62 (±2.4)	
	No (%) of patients	
Gender		
Male	166 (63.60)	< 0.001
Female	95 (36.40)	
Tumour localization (C/P)		
Central	136 (52.11)	0.464
Peripheral	125 (47.89)	
Tumour localization (lobe)		
Right upper	93 (35.73)	
Middle	12 (4.51)	0.057
Right lower	41 (15.71)	
Left upper	80 (30.65)	
Left lower	35 (13.41)	
Tumour descriptor (T)		
T1b	13 (4.98)	
T1c	30 (11.69)	
T2a	33 (12.64)	< 0.001
T2b	43 (16.75)	
T3	107 (40.99)	
T4	35 (13.40)	
Lymphovascular invasion (LVI)		
Present	199 (76.24)	< 0.001
Absent	62 (23.76)	
N descriptor		
N0 (negative)	98 (37.52)	< 0.001
N1 (positive)	125 (47.89)	
N2 (positive)	38 (14.59)	

The LVI was more frequently found in lung adenocarcinoma of central position, comparing to the one of peripheral position, 117 (44.83%) and 82 (31.42%), respectively (p<0.001). In terms of anatomical division of the lung lobes, tumours located in the upper lobes were more frequently affected than other ones; the upper right lobe was the most frequent localization, in 93 (35.73%) cases (p=0.625) (Table 2).

In cases of central position adenocarcinoma no LVI was found at T1b. The prevalence of LVI in centrally located tumours T1c size was 22.22% (two cases out of nine), and in the T2a size almost 3 times higher, (62.5%) (10 cases out of 16). In centrally located tumours with T2b, T3 and T4 size, the prevalence of LVI was 100% (p<0.001).

Table 2. Relationship of tumour localization and status of lymphovascular invasion (LVI)

Location of the tumour	No (%) of patients			p
	LVI +	LVI -	Total	
Central /Peripheral (C/P)				
C	117 (44.83)	19 (7.28)	136 (52.11)	p < 0.001
P	82 (31.42)	43 (16.47)	125 (47.89)	
Lobe				
Right upper	73 (27.97)	20 (7.76)	93 (35.73)	p = 0.625
Middle	9 (3.45)	3 (1.15)	12 (4.51)	
Right lower	34 (13.03)	7 (2.68)	41 (15.71)	
Left upper	57 (21.84)	23 (8.81)	80 (30.7)	
Left lower	26 (9.96)	9 (3.45)	35 (13.41)	
Total	199 (76.25)	62 (23.75)	261 (100)	

In tumours with peripheral localization, the frequency of LVI was rare, even in T4 tumors, 18 (94.74%). However, there was statistically significant dependence between the presence of LVI and T descriptors in tumours with peripheral localization (p<0.001), i.e. with higher T descriptor, finding of LVI had greater probability (Table 3).

Table 3. Relationship of T descriptors (tumour size) and central/peripheral (C/P) localization according to the presence of lymphovascular invasion (LVI+)

Tumour localization in LVI+T1b	No (%) of patients with T						p
	T1c	T2a	T2b	T3	T4		
C	0 (22.22)	2 (62.50)	10 (100)	28 (100)	16 (100)	16 (100)	<0.001
P	0 (4.76)	1 (29.41)	5 (93.33)	14 (95.65)	44 (95.65)	18 (94.74)	<0.001

Out of the total of 117 patients who had a centrally located tumour and present LVI, 64.10% (75/117) had affected N1 (hilar) lymph nodes, and in patients with a peripherally located tumour with presented LVI, 52.38% (43/82) had affected hilar lymph nodes (p<0.001) (Figure 1).

Out of the total of 117 patients with central tumour localization and present LVI, 18 (15.38%) had N2 metastasis in ipsilateral mediastinal and/or subcarinal lymph nodes and in patients with a peripheral tumour position and present LVI 18 (out of 82), 21.96% had mediastinal lymph nodes affected (p=0.002).

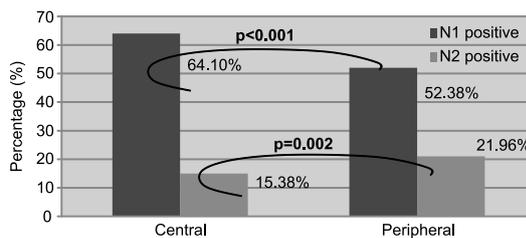


Figure 1. Nodal status in the presence of lymphovascular invasion (LVI) depending on the tumour position central/peripheral (C/P)

There was a statistically significant relationship between LVI findings and metastasis of adenocarcinoma to the hilar lymph nodes in tumours located in any lobes of the lung (p<0.001), except in the middle lobe (LVI finding in the middle lobe tumour will not always mean metastasis to the local hilar lymph nodes). There was no significant relationship between LVI findings and metastasis in mediastinal lymph nodes at tumours located in any lobes of the lung, e.g. the presence of LVI in the tumour of any lobe will not always mean metastasis to the mediastinal lymph nodes (Table 4).

DISCUSSION

The presence of centrally and peripherally located tumours in the observed sample was almost identical, although lung adenocarcinomas are usually characterized as peripheral lung cancers (14-16). The most common localization of the tumour in our study was the upper lobes, which is in accordance with the most studies (3,16,17), but in our study there was no statistically significant difference in the prevalence of tumours according to a position (centrally-peripherally) or anatomical localization (between five lung lobes).

The absence of the T1a in our sample, as well as the finding that at 5% of tumours the largest diameter was 2 cm, is probably a result of the covert initial course of the disease and therefore a relative delay in diagnosis (2,3,8). The highest

Table 4. Frequency of N1 and N2 metastasis depending on anatomical tumour localization and lymphovascular invasion (LVI) status

Anatomical position of the tumour (lobe)	No (%) of patients			p	No (%) of patients			p
	LVI +	LVI -	Total		LVI +	LVI -	Total	
Right upper	36 (94.74)	2 (5.26)	38 (100)	<0.001	12 (92.31)	1 (7.69)	13 (100)	0.175
Middle	7 (87.50)	1 (12.50)	8 (100)	0.236	1 (100)	0	1 (100)	0.750
Right lower	22 (100)	0	22 (100)	0.002	7 (100)	0	7 (100)	0.238
Left upper	39 (92.86)	3 (7.14)	42 (100)	<0.001	10 (90.10)	1 (9.90)	11 (100)	0.112
Left lower	14 (93.33)	1 (6.63)	15 (100)	0.029	5 (83.33)	1 (16.66)	6 (100)	0.507
Total	118 (94.4%)	7 (5.6%)	125		35 (92.1%)	3 (7.9%)	38	

prevalence of tumours > 5cm and > 7cm in size in the analysed sample contributed greatly to the statistically significant difference between tumour descriptors.

The presence of LVI was found in 76.24% of the tumours, which corresponds with the data from the current WHO classification of lung tumours, where it was found in 70-90% of the lung adenocarcinoma resections (7).

The difference in the representation of the N descriptor in our patients was statistically significant, where node negative was found in 37.52%, N1 in 47.89% and N2 in 14.59%, which is partially compatible with the results of other studies (19, 20, 21). In the total of 1526 NSCLC resection samples, Higgins et al. found 80% node-negative (N0), 15.4% node-positive (N1) and only 4.72% node-positive (N2) (19). Similar results were reported by Kotoulas et al. (20), who found 40.1%, 32.1%, and 24.5% respectively, out of 557 operated patients with NSCLC. In 171 patients with resected NSCLC up to stage IIIA disease, a group of Korean authors found no metastasis in hilar and mediastinal lymph nodes in 77.8% cases, while the N1 and N2 descriptors were found in 11.7% and 10.5 % cases, respectively (21). Chao-Yu L et al. (22) have found that hilar/interlobar nodal involvement and poorly differentiated histological grade were significant predictors of worse overall survival.

Lymphovascular invasion was a much more frequent finding in centrally than peripherally located lung adenocarcinoma in our study. A group of Chinese authors has found more frequent LVI in centrally located tumours sized 1-4 cm, which showed higher levels of nodal metastases compared to peripherally located adenocarcinomas (14). Youngkya et al. also showed more frequent LVI in central tumours and a worse course of illness (16). When talking about anatomical tumour localization, in this research 63.5% of all positive LVI were found in the adenocarcinomas located in the upper lobe of the lungs. Studies of Kotoulas et al. indicate that the size of the primary tumour with metastases was lower in adenocarcinomas compared to squamocellular carcinomas, and that adenocarcinomas, although smaller in size, are more aggressive than squamocellular carcinomas due to a greater presence of LVI (20). Sakao et al. found metastases to the

hilar lymph nodes in 11, and in 34 (out of 170) cases metastases to the mediastinal lymph nodes in patients with resected NSCLC of the middle lobe; metastases to the upper mediastinal lymph nodes meant a negative prognostic factor in these patients (23).

The LVI finding follows the tumour size in our study, suggesting that the LVI finding is more certain in tumours with a larger diameter. Other studies have shown similar findings, where increasing LVI involvement linearly tracks tumour growth (24-26). In a large meta-analysis of 20 studies with a total of 8032 patients with NSCLC's with maximal tumour size of 3 cm, LVI is identified as a strong prognostic indicator for poor outcome for patients with surgically managed stage I lung cancer, and the most frequent finding of LVI had the largest observed T descriptor (T1c) (24). Funai et al. have found positive LVI in early stages of lung adenocarcinoma (T1A and T1B), in 22 cases out of 143 analysed patients, concluding that LVI is an independent predictive factor (25). With the aim to evaluate the characteristics and prognostic factors of NSCLC larger than 5 cm, Cho et al. have found that patients with node-negative NSCLC >5 cm had a lower prevalence of lymphovascular invasion and more common contralateral recurrence than patients with node-positive NSCLC (26).

Sun et al. found that 81.5% patients with operated lung adenocarcinoma (size 1-4 cm) had nodal metastases when the tumour was centrally positioned, and 42.6% in peripherally positioned tumours (14). In our study, there were 79.48% nodal metastases in tumours with the central position and 74.34% of nodal metastases in peripheral tumours. Unlike these two studies, a retrospective study by Youngky et al. reported only 31.7% of nodal metastases in cases of central localization of tumours, and 14.9% of nodal metastases in peripheral tumour localization (16). Yang et al. found significantly more nodal metastases in adenocarcinoma of central localization, concluding that the localization of the tumour associated with the major bronchi is an independent predictor of metastasis and has a worse outcome regardless of illness stage and treatment (15).

N2 disease in this study was more common at peripheral than central tumour localization. Ketcherdjian et al. had similar findings (27).

A positive LVI was most frequently found in upper lobe tumours, and in this connection, the occurrence of nodal metastases was most frequent in tumours localized in the upper lobes. Koutoulas et al. found that the most nodal metastases originated from upper right and middle lobe tumours (20). Cerfolio et al. concluded that right lateral lesions were more frequently followed by N2 disease (28). In the study conducted by Seok et al. on 413 pulmonary adenocarcinoma resectates, the authors found 74 metastatic sites in N1 and N2 lymph nodes, with tumours of the upper lobes giving 55% of these metastases (29).

In conclusion, peripherally located lung adenocarcinomas had more metastases to the mediastinal lymph nodes compared to centrally

located tumours. Metastases to the hilar and mediastinal lymph nodes, regardless of the findings of lymphovascular invasion, usually originated from upper lobe tumours. From a clinical point of view, this means that the surgeon can expect to find more enlarged lymph nodes intraoperatively when it comes to the adenocarcinomas of the upper lobes (especially to the right) compared to the adenocarcinomas located in the middle and lower lobes of the lung.

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