ORIGINAL ARTICLE

Preoperative tumour size as a predictor of the presence of lymphovascular invasion in lung adenocarcinoma

Kemal Grbić[1], Bakir Mehić[2], Dalma Udovičić-Gagula[3], Amina Valjevac[4], Adem Ćemerlić[5], Ferid Krupić[6]

[1]Clinic for Thoracic Surgery, [2]Clinic for Lung Disease, [3]Department of Pathology; University Clinical Centre Sarajevo, [4]Department of Human Physiology, School of Medicine, University of Sarajevo, [5]School of medicine, University of Sarajevo, Sarajevo, Bosnia and Herzegovina, [6]Department of Anaesthesiology, Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, Sweden

ABSTRACT

Aim To examine whether preoperative tumour size may serve as a biomarker for the occurrence of lymphovascular invasion (LVI) in centrally and peripherally located lung adenocarcinoma.

Method The study included 261 patients surgically treated for diagnosed lung adenocarcinoma. A ROC curve was used to determine the biomarker potential of tumour size relative to the occurrence of LVI. Binary logistic regression was used to show changes of tumour size impact on the status of LVI.

Result Tumour prevalence according to localization had no statistical significance (p=0.464), while the presence of LVI in central, as well as peripheral positions, was statistically significantly different (p<0.001). The area under the curve of 0.978 highlights the fact that tumour size is an excellent marker of the presence of LVI in centrally located adenocarcinomas of the lung. A similar finding was confirmed in peripherally located lung adenocarcinomas with an area below the curve of 0.943. Binary logistical regression showed that in centrally localized adenocarcinomas of the lung, each additional centimetre of tumour growth represents an increase in the likelihood of LVI+ by 17.14 times. In peripherally located adenocarcinomas of the lung, this increase in likelihood of LVI for each centimetre of growth was 5.46 times.

Conclusion With a high degree of sensitivity and specificity, preoperative tumour size may serve as an important biomarker and positive predictor of the presence of LVI in lung adenocarcinoma of any location.

Key words: binary logistical regression, CT scanning, histopathological examination, surgical resection, T-descriptor

Corresponding author:
Grbic Kemal
Clinic of Thoracic Surgery,
Clinical Centre University of Sarajevo
Bolnička 25, 71000 Sarajevo,
Bosnia and Herzegovina
Phone: +387 33 297 238;
Fax: +387 33 297 937.
E-mail: kemalgrbic@hotmail.com
ORCID ID: https://orcid.org/0000-0003-3721-6369

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INTRODUCTION

The presence of lymphovascular invasion (LVI) in a tumour represents an independent negative individual prognostic factor in invasive lung adenocarcinoma (1). Majority of studies that tracked the relation of LVI and the disease course showed a direct correlation with the appearance of local and distant metastases, as well as modest results in regards to survival without progression of the disease, disease-free survival, and the overall five-year survival rates, which for all histological pictures of lung adenocarcinoma amounts to a modest 13-18% (2–6).

Lung adenocarcinoma is most commonly characterized by peripheral localization in the lung parenchyma, zones of cavitation and necrosis, slow growth compared to other malignant lung tumours, masked clinical findings, and metastasis in the early course of the disease (6–8). The most common secondary metastases arising from the primary disease are discovered in the central nervous and musculoskeletal systems, as well as the liver and lungs (6–9).

Preoperative tumour size represents a significant parameter of the therapeutic and prognostic course, and is thus included in the current Tumor-Node-Metastases (TNM) classification of the disease (10). Previous research demonstrated a direct association of the clinical T descriptor and the appearance of LVI (11–13), however not enough research has been conducted on the delicate cutoff tumour size at which the presence of LVI may be expected, as well as the reliability of such a finding.

The aim of this study was to examine whether preoperative tumour size may serve as a biomarker for the occurrence of lymphovascular invasion (LVI) in centrally and peripherally located lung adenocarcinoma.

PATIENTS AND METHODS

Study design and patients

This cross-sectional study included 261 surgically treated patients at the Clinic for Thoracic Surgery, University of Sarajevo Clinical Centre (USCC) with previously diagnosed lung adenocarcinoma, from January 2017 to December 2018. Patients who underwent complete tumour resection were stratified according to the localization (central and peripheral position), and according to LVI status, as tumours with the presence of LVI (LVI+) and tumours without the presence of LVI (LVI–).

The approval for this study was obtained from the Ethics Committee of the University of Sarajevo Clinical Centre.

Methods

Preoperative tumour size was determined during standard preoperative CT scanning of the thoracic cage. The examination was performed with a GE LightSpeed VCT multi-slice CT (MSCT) machine, with 64 rows of detectors (General Electric Company, Fairfield, Connecticut, USA) in the native and contrast (Ultravist 370, Schering, Germany) series in slices of 0.625 mm. Transverse sections and 3D reconstruction was used for the analysis. Among other radiological characteristics, tumour size was measured by the thoracic radiologist in three planes; anteroposterior, laterolateral and craniocaudal diameters were measured, with the largest diameter in this study being expressed in millimetres (mm). Tumours that infiltrated lobar and proximal portions of the segmental bronchi were classified as central, while those more distally localized were labelled as peripheral tumours.

All patients underwent preoperative bronchoscopic examination under local anaesthesia with a flexible Olympus series bronchoscope. During the bronchoscopy, fluid and tissue biopsies were taken for cytological and/or histological analysis. Tissue biopsies included sampling of endobronchial tumour lesions, as well as transtracheal and transbronchial needle biopsies. In peripherally localized tumours, transthoracic needle biopsies were performed under the control of CT or ultrasound.

The histopathological analysis of the resected pulmonary tissue was performed at the Department of Clinical Cytology and Pathology of USCC. After the primary sectioning and a 24-hour fixation of the resected tumour specimen in 10% buffered formalin, sliced tissue sections of 4-5 mm thickness were created and automatically processed into the tissue histoprocessor "Logos One Milestone" according to the manufacturer's protocol. These specimens were then moulded into paraffin blocks and cut into slices of 4-5 μ in thickness and were stained using the standard

Hematoxylin-Eosin (H&E) method. Utilizing microscopic examination of the stained sections, the type of tumour according to the current World Health Organization (WHO) classification was determined (14). Without question, the presence of lymphovascular invasion was denoted as lymphovascular invasion positive (LVI+), or absent - lymphovascular invasion negative (LVI–).

Statistical analysis

Continuous variables with normal distribution were expressed as mean ± standard deviation and categorical variables were expressed as a number (percentage). A two sample t-test was used to compare continuous variables with normal distribution and $\chi 2$ or Fisher's exact test (with Yates correction when needed) to compare categorical variables. Sensitivity and specificity of tumour size for predicting lymphovascular invasion in patients with central and peripheral tumour localization were determined, and receiver operating characteristic (ROC) curves were constructed by plotting sensitivity against (1- specificity). The area under the curve (AUC) was calculated and analysed with a one-tail test. Cutoff points were obtained by calculating the Youden index. Binary logistical regression was performed to show that a change in tumour size may impact the status of LVI. The assigned level of statistical significance was $p<0.05$.

RESULTS

In the observed sample of diseased patients (n=261) a statistically significant difference in the incidence of the disease in relation to gender was found (male:female = 1.75:1) ($p<0.001$). The mean age of males was 62.36 ± 6.45 years and it was statistically significantly higher than the female patients, 60.12 ±9.11 years (p=0.022).

The finding of tumours in the central and peripheral positions was almost equal, 136 (52.11%) and 125 (47.89%), respectively (p=0.464), while the presence of lymphovascular invasion (LVI+) was more frequently found than absent (LVI–) in both central and peripheral tumour localizations ($p<0.001$) (Table 1).

The sensitivity of a finding of the presence of LVI in a centrally positioned tumour >4.5 cm in size amounted to 89.7%, with a specificity of 100%; the positive predictive value was 100%, while the negative predictive value was found to be 61.3%. The AUC for tumour size amounted to 0.98 ($p<0.001$) (Figure 1, Table 2).

The sensitivity of a finding of the presence of LVI in a peripherally positioned tumour >4.5 cm in size amounted to 92.7%, while specificity was 90.1%; the positive predictive value was found

Table 1. Relationship of tumour localization and status of lymphovascular invasion (LVI)

Location of the tumour	No (%) of patients			p
	LVI +	LVI -	Total	
Central	117 (44.83)	19 (7.29)	136 (52.11)	
Peripheral	82 (31.41)	43 (16.47)	125 (47.89)	< 0.001
Total	199 (76.24)	62 (23.76)	261 (100)	

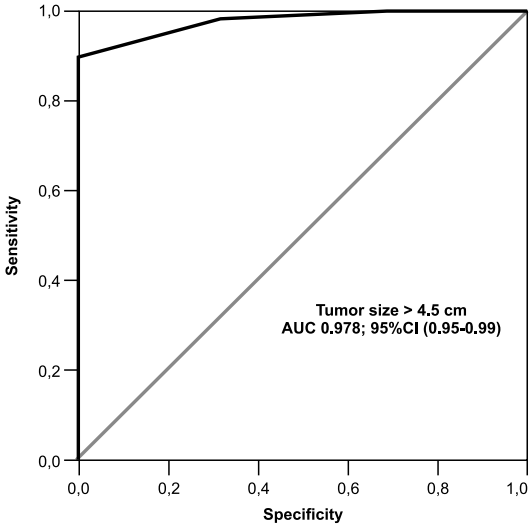

Figure1. Receiver Operating Characteristics (ROC) curve of the tumour size as a potential marker of the appearance of lymphovascular invasion in centrally positioned tumours; AUC, area under the curve; CI, confidence interval

Table 2. Sensitivity and specificity of tumour size as a potential marker for the appearance of lymphovascular invasion in centrally positioned tumours

Variable	AUC	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	95% CI	p
Tumour size (cm) (cutoff – 4.5)	0.978	89.7	100	100	61.3	0.957 - 0.999	<0.001

AUC, area under the curve; PPV, positive predictive value; NPV, negative predictive value; CI, confidence interval

Table 3. Sensitivity and specificity of the tumour size as a potential marker for the appearance of lymphovascular invasion in peripherally positioned tumours

Variable	AUC	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	95% CI	p
Tumour size (cm) (cutoff – 4.5)	0.943	92.7	90.1	92.5	86.7	0.894 - 0.992	<0.001

AUC, area under the curve; PPV, positive predictive value; NPV, negative predictive value; CI, confidence interval

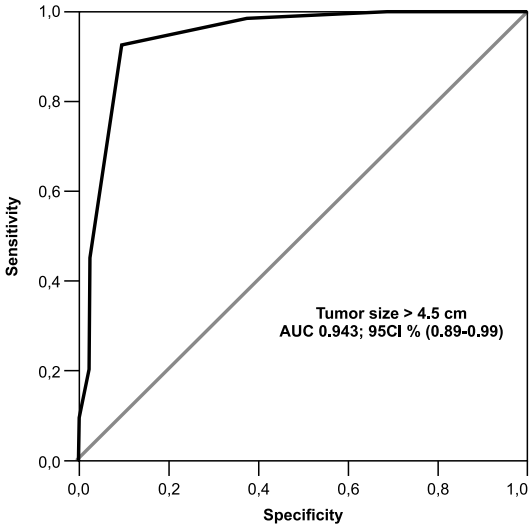

Figure 2. Receiver Operating Characteristics (ROC) curve of the tumour size as a potential marker of the appearance of lymphovascular invasion in peripherally positioned tumours; AUC, area under the curve; CI, confidence interval

to be 92.5%, while the negative predictive value amounted to 86.7%. The AUC for tumour size was 0.94 (p<0.001) (Figure 2, Table 3).

Binary logistic regression showed that the tumour size was an independent positive predictor of the occurrence of LVI in lung adenocarcinoma with central (OR=17.14; 95%CI (4.32–68.04); (p<0.001), but also peripheral tumour locations (OR=5.46; 95%CI (3.053–9.78) (p<0.001).

DISCUSSION

In this study, LVI+ was present in 76.24% resections, which is significantly higher than the results of research by other authors (3-5). LVI as an independent prognostic factor of poor disease outcome has been established by Funai et al.; by following surgically treated patients due to lung adenocarcinoma, up to 3 cm in size, they found that those patients that had LVI in tumours had a worse 5-year survival rate than those in whom tumours LVI was not found (70.9% vs. 94.5%) (15). Fan et al. (16) followed patients with operated adenocarcinoma with tumour size up to 2 cm and found that diseased patients with the presence of LVI had more numerous relapses of the disease within the five-year follow-up period than the patients without LVI (87.5% and 72.1%, respectively). A group of Japanese authors (Norifumi et al.) followed patients with lung adenocarcinoma of all subtypes in whom tumours were smaller than 3 cm and found a higher proportion of the disease in those with LVI present compared to those tumours without LVI (96.2% and 70.7%, respectively) (17).

The prevalence of centrally localized tumours in our study was not statistically significantly more frequent compared to peripherally localized tumours, even though other studies have shown that adenocarcinoma of the lung is more frequently positioned peripherally (7,8,18,19). Our results are not consistent with the report by the American Cancer Society, which unequivocally states that adenocarcinoma of the lung is a peripheral tumour (6).

Yang et al. (20), in their large meta-analysis, which included 397,189 diseased patients with lung adenocarcinoma, found peripheral tumours in 97.5%, and only 2.5% centrally localized tumours; the authors found more aggressive tumours among centrally positioned adenocarcinoma, meaning more frequent local and distant metastases, and shorter overall survival concluding that adenocarcinoma location in the main bronchus may be a predictor of metastasis and poor prognosis of this histologic tumour type. Moon et al. (18), in patients with diagnosed lung adenocarcinoma with present LVI, found more frequent nodal and distant metastases in those with centrally located tumours compared to those with peripheral positions. Sun et al. (19), in following patients with adenocarcinoma, found more frequent nodal metastases and shorter periods without the disease relapse in those with centrally positioned tumours.

The results of this study showed that the size of lung adenocarcinoma is an excellent marker of the occurrence of LVI with a sensitivity of 89.7% and specificity of 100% for centrally positioned tumours, and with 97.2% sensitivity and 90.1% specificity for peripherally positioned tumours. Studies by other researchers have shown that with an increasing tumour size, the proportion of lymphovascular invasion increases linearly (15,21,22). Igai et al. (21) found in lobectomy resectate at lung adenocarcinoma up to 1 cm in size the presence of LVI in only 9% of cases. Funai et al. (15) found LVI present in 15% of the surgically treated patients with lung adenocarcinoma up to 2 cm. Higgins et al. (22), in non-small cell lung cancer (NSC resectate, of which there were 734 patients operated on due to adenocarcinoma

up to 3 cm in size, found involvement of vascular and lymphatic vessels in 22% of patients.

In our study, logistic regression showed that the tumour size was an independent positive predictor of the occurrence of LVI in lung adenocarcinoma with central, but also peripheral tumour positioning meaning that in centrally located lung adenocarcinomas, the growth of the tumour size by each additional centimetre results in an increase in the likelihood of LVI+ by 17.14 times. In peripherally located lung adenocarcinoma this increase in likelihood was lower, and for each additional centimetre the risk increases by 5.46 times. Similarly, a group of Korean authors, following surgically treated patients with lung adenocarcinoma and utilizing regression analysis, showed that preoperative size, central localization, and the presence of LVI in a tumour represent independent negative predictors of the disease recurrence (23). In lung adenocarcinoma patients, Sun et al. showed with multivariate analysis that the tumour size of 1-4 cm in the central lung position is an independent prognostic factor of LVI status, and a period without disease progression (19). Igai et al. (21) analysed several parameters in patients with adenocarcinoma of the lung showing that lymphovascular invasion was a negative prognostic factor for the course of the disease. Conversely, a group of German authors, in 208 patients with NSCLC resectate, of which 57.4% were found to have lung adenocarcinoma, concluded that central positions of tumours with a diameter larger than 3 cm, diagnosed preoperatively, are significant predictive factors of invasion of lymphatic vessels and lymph node drainage networks (24).

In conclusion, preoperative tumour size represents an excellent biomarker and is a trustworthy positive predictor of the occurrence of lymphovascular invasion in adenocarcinoma of the lung, for both central as well as peripheral positions. From a practical standpoint, it is important for clinicians to be cognizant of the fact that a preoperative finding of lung adenocarcinoma greater than 4.5 cm confidently implies that LVI is present. Metastatic lesions which may not be identified with imagining techniques may be encountered intraoperatively, and also that the indicated tumour size may help guide recommendations for therapeutic treatment by multidisciplinary teams of physicians.

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TRANSPARENCY DECLARATION

Competing interest: None to declare.

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