The prognostic significance of histopathologic angioinvasion in stage I non-small cell lung cancer

Evre I küçük hücreli dışı akciğer kanserinde histopatolojik damar invazyonun prognostik önemi

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Background: We aimed to analyze the prognostic significance of vascular invasion, which is one of the histopathological features affecting the prognosis in early stage lung cancers.

Methods: Forty early stage ($T_{1-2}N_0M_0$) non-small cell lung cancer patients (32 males, 8 females; mean age 53.8±8.7 years; range 35 to 69 years) who underwent curative surgery with mediastinal lymph node dissection between December 1997 and January 2004 were retrospectively evaluated. Tumor histology, grade, vascular invasion, and the extent of resections were evaluated. Pathological slides were re-examined and invasion of at least two vascular structures and/or presence of tumoral thrombosis in the lumen of vessels were defined as vascular invasion.

Results: Three-year disease free survival was found to be 67.2±7.5% and five-year survival was 64.5±7.6%. When an evaluation was done considering whether there was vascular invasion or not, there was not a significant difference (Log rank: 0.85; p:0.357; p>0.05). However, adenocarcinoma subtype was found to be related with unfavorable outcome with high local relapses and distant metastases (p<0.01).

Conclusion: Despite the limited number of the cases in our retrospective study, it was found that in early stage lung cancer the type histology was far more prognostic than histological vascular invasion.

Key words: Early stage lung cancer; histopathology; vascular invasion.

Amaç: Çalışmamızda akciğer kanserinde prognozu etkileyen histopatolojik bulgulardan vasküler invazyonun, lenfatik yayılım yapmamış erken evre akciğer kanserindeki prognostik önemi araştırıldı.

Çalışma planı: Aralık 1997-Ocak 2004 yılları arasında küratif mediastinal lenf nodu rezeksiyonu uygulanmış erken evre ($T_{1-2}N_0M_0$) küçük hücreli dışı akciğer kanserli 40 hasta (32 erkek, 8 kadın; ort. yaş 53.8±8.7 yıl; dağılım 35-69 yıl) geriye yönelik olarak değerlendirildi. Tümör histolojisi, grade, vasküler invazyon ve rezeksiyon büyüklüğü çalışılan kriterlerdendi. Patoloji kesitleri yeniden incelendi ve en az iki vasküler yapının invazyonu ve/veya damar lümeninde tumoral tromboz bulunması vasküler invazyon olarak tanımlandı.

Bulgular: Üç yıllık hastalıksız sağkalım %67.2±7.5, beş yıllık sağkalım ise %64.5±7.6 olarak hesaplandı. Vasküler invazyonun olup olmamasına göre değerlendirme yapıldığında genel sağkalım süreleri arasında anlamlı farklılık saptanmadı (Log rank: 0.85; p:0.357; p>0.05). Bununla birlikte, adenokarsinomlu olguların lokal nüks veya uzak metastaz nedeni ile kötü prognoz gösterdiği tespit edildi (p<0.01).

Sonuç: Olgu sayımız sınırlı olsa da, geriye yönelik çalışmamızda, erken evre akciğer kanserinde histolojik tipin, sağkalım açısından histolojik vasküler invazyondan daha etkin olduğu görüldü.

Anahtar sözcükler: Erken evre akciğer kanseri; histopatoloji; vasküler invazyon.

Lung cancer is still the most common cause of cancer deaths despite the significant advancements in its treatment. Mortality rates remain high compared to the last 15 years.[1] Numerous studies have been performed on immunohistochemical and histopathologic prognostic factors that may influence the survival in non-small cell lung carcinoma (NSCLC). Vascular invasion determined by histopathologic examination is one of these

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factors. Detection of factors that influence survival or disease-free survival will elucidate the role of adjuvant therapy in early stage NSCLC, which is a common topic of debate nowadays.[2]

PATIENTS AND METHODS

All records of 40 patients (32 males 8 females; mean age 53.8±8.7 years; range 35 to 69 years) with early stage NSCLC ($T_{1\text{-}2}N_0M_0$) that underwent lung resection with mediastinal lymph node dissection in the Heybeliada Teaching and Research Hospital for Chest Diseases and Thoracic Surgery between December 1997 and January 2004 have been reviewed. Blood tests, radiologic examinations (chest X-ray and thorax computed tomography) and bronchoscopy were performed in all patients. Cranial magnetic resonance imaging and bone scintigraphy was used as preoperative staging modalities when required.

Patients that received neoadjuvant treatment or underwent rethoracotomy for synchronous and metachronous tumors were excluded from the study. Particularly for the tumors of the left-side, patients without mediastinal lymph node metastasis proven by preoperative mediastinoscopy or patients who underwent a preoperative mediastinal lymph node dissection were recruited for the study. Therefore, pathologic stage I was confirmed for all patients with tumors localized on the left side. The follow-up procedure included phone calls to all patients or their relatives to receive up-to-date information. Chest X-rays and thorax computed tomographies were performed to all survivors. No advanced imaging techniques were used in patients that were free of symptoms with normal laboratory results.

All pathological slides were re-examined by one pathologist (AE). Slides of paraffin blocks were stained by standard hematoxylin-eosin. Invasion of at least two vascular structures and/or presence of tumoral thrombosis in the lumen of a vessel in the re-examined slides were defined as vascular invasion.

Statistical analysis of the data was performed by SPSS (Statistical Package for Social Sciences) Windows 10.0 version (SPSS Inc., Chicago, Illionis, USA) software. Data analysis included descriptive statistical methods (mean ± standard deviation) along with the comparison of quantitative data by the Student t-test. The Chi-square and Fisher's exact Chi-square tests were used for comparison of the qualitative data. The Kaplan Meier

Table 1. Characteristics of patients according to vascular invasion

	Vascular invasion						*p*
	Positive (n=11)			Negative (n=29)			
	n	%	Mean±SD	n	%	Mean±SD	
Age			57.7±5.8			52.3±9.3	p=0.036*
Smoke (pack. years)			44.1±25.6			38.7±21.1	p=0.496
Disease free survival			995.5±598.8			1300.1±637.1	p=0.178
Sex							
Female	2	18.2		6	20.7		p=0.859
Male	9	81.8		23	79.3		
Tumor status (tm)							
T_1	–	–		4	13.8		p=0.316
T_2	11	100		25	86.2		
Histology							
Squamous carcinoma	8	72.7		20	69.0		p=0.817
Adeno carcinoma	3	27.3		9	31.0		
Resection							
Lobectomy	7	63.6		17	58.6		p=0.811
Bilobectomy	2	18.2		8	27.6		
Pneumonectomy	2	18.2		4	13.8		
Grade							
High	–	–		4	13.8		p=0.180
Moderate	5	45.5		17	58.6		
Low	6	54.5		8	27.6		
Mortalitiy							
None	6	54.5		20	69.0		p=0.406
Distant metastases	3	27.3		3	10.3		
Local recurrence	2	18.2		6	20.7		

*: p<0.05; SD: Standard deviation.

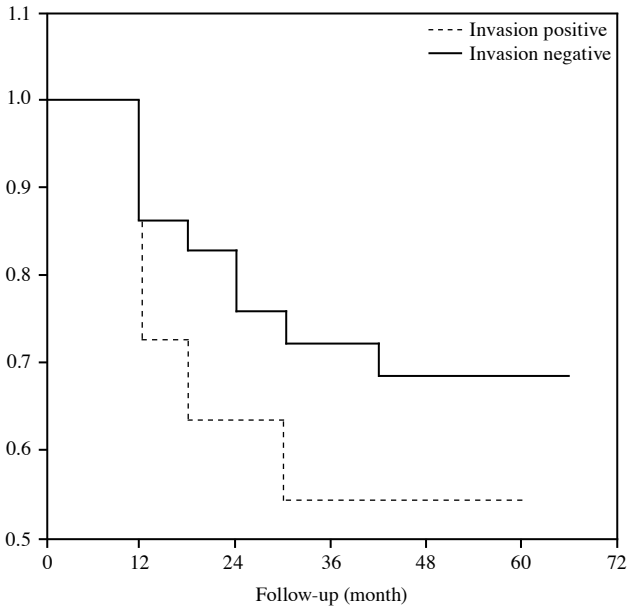

Fig. 1. Survival curve analyses.

survival analysis and the Log rank test were used to evaluate disease-free and overall survival data. Results were presented at a 95% confidence interval and p<0.05 was set as the level of significance.

RESULTS

The demographic characteristics of the patients and the risk factors for vascular invasion observed in 11 patients (27.5%) are presented in Table 1. Excluding the age, no correlation could be established between the gender, T stage, tumor histology, resection size, grade and mortality rates of the patients and the presence of vascular invasion (p>0.05). Vascular invasion showed no correlation with the disease-free survival period either (p>0.05).

In our study, the three-year and five-year disease-free survival rates were 67.2±7.5% and 64.5±7.6% respectively. The five-year survival rate of patients with vascular invasion was 54.6±15.0%; six patients (54.6%) in this group survived whereas five died, and the mean survival period was 38 months. The five-year survival rate of patients without vascular invasion was 68.5±8.7%; 20 patients in this group survived (69.0%) whereas nine died, and the mean survival period was 57 months. According to these results, no significant difference could be demonstrated between the overall survival rates of the groups with or without vascular invasion (Log rank: 0.85; p: 0.357; p>0.05), (Fig. 1).

When each parameter was considered as univariate, the mortality rate was found to be strongly associated with the histologic type (p<0.01; Table 2). The adenocarcinoma group had the highest rate of local recurrence and/or distant metastasis. The relative risk of cases to have adenocarcinoma was calculated as 3.11. Vascular invasion showed no correlation with mortality (p>0.05); and the relative risk for vascular invasion was calculated as 1.46. The histological type was statistically defined as a prognostic factor by the Cox regression analysis (p<0.01; Table 3).

DISCUSSION

The five-year survival rate of lung cancer that had been 12% between 1974 and 1976 has been slightly improved to a value reaching up to 15% between 1992 and 1997. Nowadays, the lung cancer constitutes 12.8% of all cancers in the world and is responsible for 17.8% of all cancer deaths.[3] Up to now, numerous studies have been performed on histopathologic prognostic factors that may influence survival in non-small cell lung carcinoma.[4-6] Basically, all studies aimed to select patients with early stage tumors that were appropriate for adjuvant treatment following resection.

As reported by the studies on large series, the five-year survival rate of stage I tumors range from 50 to 70%.[7,8] In our study, this figure was found to be 64.5%. Vascular invasions were observed in 11 patients that corresponded to 27.5% of our cases; in other studies, this figure was reported to range from 6.2%[9] to 39%.[10] We were unable to detect any statistically significant effect of vascular invasions on the survival rate in our study. Similarly, Pechet et al.[10] had not been able to demonstrate the effect of vascular invasions on the survival rate by a multivariate analysis in their study involving 100 patients with stage 1 tumor. In another study, Ogawa et al.[11] have shown by both univariate and multivariate analyses that an arterial invasion indicated poor prognosis. However, the details of the study revealed that a

Table 2. Univariate analyses of mortality effecting factors

Factors	Category	Relative risk (95%, CI)	*p*
Sex	Male vs female	3.250 (0.496-21.312)	0.136
Tumor stage	T_1 vs T_2	0.611 (0.471-0.793)	0.122
Resection	Lobectomy vs pneumonectomy	0.647 (0.254-1.650)	0.403
Histology	Adeno carcinoma vs squamous carcinoma	3.111 (1.378-7.024)	0.006*
Grade	High, moderate, low differentiate	0.718 (0.311-1.656)	0.445

*: p<0.01; CI: Confidence interval.

Table 3. Cox regression analysis

Factors	Hazard ratio (95%, CI)	SD	*p*
Resection type	1.32 (0.34-5.00)	0.67	0.681
Histology	6.54 (1.88-22.68)	0.63	0.003*
Vascular invasion	3.01 (0.79-11.41)	0.68	0.106
Grade	1.05 (0.32-3.37)	0.59	0.938

*: p<0.001; SD: Standard deviation; CI: Confidence interval.

wedge resection has been performed on some patients, and no information about vascular invasions in these patients was presented. In our study, we did not discriminate between arterial or venous invasions as in the abovementioned studies. Macchiarini et al.[12,13] have been able to demonstrate the prognostic effect of vascular invasions only for tumors treated by a wedge resection. Subsequent studies from this author revealed that these patients who underwent non-anatomic resections constituted approximately 25% of the cases, which was a considerably high ratio. Conclusions from these studies that showed a negative effect on survival stated that these tumors were more aggressive.

Another reason for investigating the correlation between vascular invasions and the survival rate in early stage tumors is that a vascular invasion can easily be demonstrated by simple histopathologic methods. Many other studies involve non-routine examinations such as assays of complex molecules at the level of nucleotides[14] or immunohistochemical analyses.[15] Considered from this point of view, other factors such as perineural invasions and lymphatic vessel invasions that have the potential to influence the prognosis and can be demonstrated by basic histopathologic methods just like vascular invasions become more important. Sayar et al.[6] have demonstrated the prognostic importance of perineural and lymphatic vessel invasions in the absence of any vascular invasions in their retrospective study on 82 cases. These results are promising and results of larger series are also expected.

Ichinose et al.[16] have assessed vascular invasions separately as arterial, venous and lymphatic vessel invasions and suggested the venous invasion as the predominant prognostic factor. However, they have not described how they discriminated the vascular structures.

Although the differentiation level of a tumor has been shown to have a prognostic effect in various studies,[17] the tumor grade had no affect on the prognosis in our study. Additionally, a study including 2410 patients, 767 of which underwent a complete resection, has revealed a 43.9% five-year survival rate in 417 pN0 patients and the only factor that affected survival was the T stage and N status whereas the histologic type and tumor differentiation were shown to have no effect by multivariate and Cox regression analyses.[18] In the same way, Bakır et al.[19] have failed to demonstrate the prognostic importance of either tumor type or histologic differentiation.

There exist several studies that investigated the effects of various histologic cell types on the prognosis, but their results are inconsistent. In general, studies from the western countries report poor prognosis for squamous cell carcinoma,[20,21] but other studies indicate that histologic type has no effect on the prognosis of tumors of the same stage.[18,19] In our study, we found that adenocarcinoma had poorer prognosis compared to squamous cell carcinoma, as it statistically led to early local recurrence/distant metastasis at the same early stage.

In conclusion, the retrospective, single-center design of our study with a limited number of patients selected includes some bias that may affect the results. But determining the prevalence of pathologic vascular invasions in early stage NSCLC patients is critical as it shapes the adjuvant treatment at the early stage, which is currently a subject of active debate. Although prognostic importance of vascular invasions could not be demonstrated in the present study, pathologic examination reports should still include the description of any histopathologic vascular invasions in detail. However, studies with larger series are required to find out similar prognostic factors that can be assessed by simple histopathologic examination.

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