Prognostic significance of tumor extension to the main bronchus in the patients with resected right upper lobe lung cancer

Sağ üst lob akciğer kanserli rezeksiyon uygulanmış hastalarda tümörün ana bronşa yayılımının prognostik önemi

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Background: We evaluated the prognostic role of main bronchial extension of right upper lobe tumors in patients with non-small cell lung cancer (NSCLC).

Methods: Between 1998 and 2007, the results of surgery in 302 patients with right upper lobe NSCLC were investigated retrospectively. One-hundred-sixty-nine patients with completely resected pT2 or pT3 tumor without lymph node metastasis were analyzed. The patients were divided into three groups; patients with NSCLC staged as pT2 (n=82), pT3 with invasion of the main bronchus (pT3-MB; n=41), and pT3 patients without main bronchial involvement (n=46).

Results: The five-year survival rate of patients with pT3-MB was 36.7%, whereas it was 55.1% for patients with pT2 and 50.7% for patients with other pT3 tumor (p=0.28). Survival of the patients who had undergone pneumonectomy was poorer than that of others (p<0.01). The hilar or interlobar N1 was found to be predictive for poor prognosis (p<0.001).

Conclusion: The survival of patients with resected right upper lobe NSCLC with pT3-MB is poor. Our study confirmed that extralobar N1 is frequently seen and it worsens the prognosis. This coexistence could be the another reason of poor prognosis in patients with main bronchus invaded T3 tumor.

Key words: Adenocarcinoma/pathology/mortality; carcinoma, squamous cell; pneumonectomy; prognosis; survival analysis.

Amaç: Küçük hücreli dışı akciğer kanseri (KHDAK) bulunan hastalarda sağ üst lob tümörlerinin ana bronşa yayılımın prognostik önemi araştırıldı.

Çalışma planı: 1998-2007 yılları arasında sağ üst lob KHDAK ameliyatı uygulanan 302 hastanın sonuçları geriye dönük olarak incelendi. pT2 veya pT3 tümörü tamamen çıkarılmış olan ve lenf nodu yayılımı bulunmayan 169 hasta analiz edildi. Hastalar üç gruba ayrıldı; pT2 (n=82), pT3 olup ana bronş invazyonu olanlar (pT3-MB; n=41), ana bronş invazyonu bulunmayan pT3 olgular (n=46).

Bulgular: Beş yıllık sağkalım oranları pT3-MB'li hastalar için %36.7, pT2'li hastalar için %55.1 ve pT3 tümörlü hastalar için %50.7 (p=0.28) idi. Sağkalım pnömonektomi uygulanan hastalarda diğerlerine göre daha kötü idi (p<0.01). Hiler veya interlober N1 varlığının kötü prognoz için belirleyici olduğu bulundu (p<0.001).

Sonuç: Sağ üst lobu alınmış KHDAK-pT3-MB'li hastaların sağkalım olasılığı kötüdür. Bizim çalışmamız ekstralober N1'in sık görüldüğünü ve prognozu kötüleştirdiğini doğrulamıştır. Bu birliktelik ana bronşa T3 invazyonu bulunan hastalardaki kötü prognozun bir diğer nedeni olabilir.

Anahtar sözcükler: Adenokarsinom/patoloji/mortalite; karsinom, skuamöz hücre; pnömonektomi; prognoz; sağkalım analizi.

Tumors extending to the main bronchus <2 cm distal to the carina, without involving it are classified as "T3" according to the TNM staging for non-small cell lung carcinoma (NSCLC) that has been described by Mountain in 1997.[1]

The length of the right main bronchus is approximately 1.2 cm.[2] Therefore tumors of the proximal part of the right upper lobe that have extended to the right main bronchus should be directly classified as T3. This proposal could be questioned. Tumors classified as T3

Received: July 10, 2009 *Accepted:* January 12, 2010

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due to extension from the right upper lobe to the main bronchus may be accepted as a special subgroup of tumors classified as T3 due to bronchial causes.

In this study, the survival of NSCLC patients who have tumors extending from the bronchus of the right upper lobe to the main bronchus was compared with survival rates of patients classified either as T3 due to other causes or as T2.

PATIENTS AND METHODS

The records of 302 patients with NSCLC localized to the right upper lobes that were deemed operable and had resection performed in our hospital between January 1998 and February 2007 were reviewed. Appropriate pulmonary resection and systematic lymph node dissection were performed in all cases. The study group included 169 patients who were classified as T2 or T3 and had complete resection of tumor. The following patients were excluded: (a) patients with T1 (n=29) and T4 (n=23) tumors; (b) patients with multiple lung tumors (n=2); (c) patients who underwent neoadjuvant therapy (n=16); patients who were found to have mediastinal nodal tumor involvement (n=17); (d) patients with incompletely resected tumor (n=27); (e) patients who had metastatic carcinoma (n=7) and (f) patients who had a superior sulcus tumor (n=12).

Preoperative work-ups included routine biochemical tests, electrocardiography (ECG), basic pulmonary function tests with or without the diffusing capacity of lung for carbon monoxide (DLco), ventilation/perfusion (V/Q) scan, and blood gas analysis. Moreover, all had a preoperative chest X-ray, thorax computed tomography, fiberoptic bronchoscopy and some had thoracic magnetic resonance imaging (MRI). For preoperative staging; cranial tomography or MRI were also carried out in majority of cases bone scan and abdominal ultrasonography or positron emission tomography was performed in some cases.

Some characteristics of the patients are presented in Table 1. The mean age was 58.3 (range of 38 to 79), seven (3.9%) were female, and 162 (95.9%) were male. Mediastinal lymph node sampling consisted of stations 2, 4 (both left and right), and 7 in the recent mapping system for lymph nodes using cervical mediastinoscopy that was carried out in 91.1% (n=154) patients. Patients in whom no mediastinal lymph node metastasis was detected underwent thoracotomy. Lobectomy was performed in 102 cases (60.4%), sleeve lobectomy was performed in 23 cases (13.6%) and pneumonectomy was performed in 44 cases (26%). Systematic mediastinal lymph node dissection was routinely carried out in all patients. In addition to lung resection, en-bloc resection of the thoracic wall was performed for 34 patients. Overall morbidity rate was 29.9%. This rate was 25.3%, 4.5% and 55.0% for lobectomy, sleeve lobectomy and pneumonectomy, respectively. Operative mortality occurred in four of 102 lobectomy cases (3.9%), in six of 44 pneumonectomy

Table 1. Demographics and medical characteristics of the patients (overall and subgroups)

Variable	Overall (n=169)			pT2 patients (n=82)			Main bronchus pT3 (n=41)			Other pT3 (n=46)			*p*
	n	%	Mean±SD	n	%	Mean±SD	n	%	Mean±SD	n	%	Mean±SD	
Age			57.9±9.1			57.1±8.9			58.1±8.1			59.3±9.6	0.44
Gender													
Male	162	95.9		79	96.3		39	95.1		44	95.7		0.95
Female	7	4.1		3	3.7		2	4.9		2	4.3		
Histology													
Squamous cell	82	48.5		35	42.7		32	78.0		15	32.6		<0.001
Non squamous	87	51.5		47	57.3		9	22.0		31	67.4		
Tumor size			5.7±2.2			5.8±2.3			5.0±1.9			5.9±2.2	0.09
Postoperative mortality	10	5.9		3	3.7		2	4.9		5	10.9		0.24
Resection type													
Lobectomy[a]	125	74.0		68	82.9		18	43.9[b]		39	84.8		<0.001
Pneumonectomy	44	26.0		14	17.1		23	56.1		7	15.2		
N1 status													
N0	74	43.8		43	52.4		8	15.9		23	50		
Intralobar N1	52	30.8		25	30.5		12	29.3		15	32.6		<0.001
Extralobar N1	43	25.4		14	17.1		21	51.2		8	17.4		
Anemia[c]	30	17.8		14	17.1		9	22		7	15.2		0.70
Hypoalbunemia[d]	12	7.1		4	4.9		3	7.3		5	10.9		0.45

SD: Standard deviation; [a]: Including sleeve lobectomy; [b]: Only sleeve lobectomies; [c]: Preoperative hematocrit less than 35%; [d]: Preoperative albumin less than.

cases (13.6%), making a total of 10 cases (5.9%), but no mortality was observed in patients who had sleeve resection (n=23).

Resected specimens were examined histopathologically, and histological typing was done according to the World Health Organization classification.[3] Histopathological types of tumors were as follows: 82 patients (48.5%) had squamous cell lung carcinoma, 68 patients (40.2%) had adenocarcinoma, and 19 patients (11.2%) had other types of NSCLC. Surgical-pathologic staging was performed according to the Sixth International Staging System for Lung Cancer.[1]

Tumor extending from the bronchus of the right upper lobe to the main bronchus (pT3-MB) was detected in 41 cases (24.3%). This group also included patients who had tumor invading the main pulmonary artery, superior pulmonary vein, pericardium or mediastinal pleura together with main bronchial invasion. In 46 of the remaining cases (27.2%) tumors were staged as pT3 due to reasons other than main bronchial invasion, and 82 of the cases (48.5%) were staged as pT2. N1 nodal involvement was divided into two subgroups; tumor involvement in hilar and/or interlobar (# 10 and/or 11) lymph nodes (extralobar N1), and tumor involvement in intralobar lymph nodes (# 12, 13 or 14). Extralobar N1 was determined in 51.2% of pT3-MB patients (n=21) whereas it was discovered in 17.4% of other patients with other pT3 tumors (n=8); and it was found in 17.1% of pT2 patients (n=14). Other characteristics of the patients are shown in table 1 regarding to T stages.

The hospital records were reviewed for survival data. If hospital records of patients could not be found, three methods were used to obtain the survival data. Their status was checked from the social security system. Some of the patients were reached by telephone. For the patients with only address information, we communicated with the reeve of the town. Mean period of follow-up was 28.6±20.7 months (range 6 to 106 months). Alive patients were followed-up at six-month intervals and examined for local recurrence or metastasis. A chest computed tomography was done in every six months until the postoperative 5th year. Sixteen patients (9.5%) had developed local, 15 patients (8.9%) developed both local and distant, and 16 patients (9.5%) developed distant metastases. A total of 36 patients (21.3%) died for cancer. One patient (0.006%) died due to a non-cancer cause. Cause of mortality could not be determined in 13 patients (7.7%). Survival period until death or until the last follow-up was determined assuming the date of operation as the onset of survival period.

Since it was a retrospective study without disclosure of patients' identities, no institutional review board approval had been required.

Statistical analysis

Frequencies and means were compared using Chi-square and one-way ANOVA tests. Univariate and multivariate survival analysis were performed for prognostic factors (i.e. cell type, T stage, N stage, type of resection) Survival was determined according to the "Kaplan-Meier" survival analysis system assuming the date of resection as day "0". The effect of each variable on survival was analyzed by "log-rank" test. Variables shown to have a possible effect on survival by this test were examined by Cox's proportional hazards model to evaluate whether they had an independent effect (multiple variable analysis). Statistical significance was set as $p \leq 0.05$.

RESULTS

No difference was observed between pT2, pT3 due to other causes and pT3-MB patients in terms of age (p=0.44), gender (p=0.11), tumor size (p=0.09), and postoperative mortality rates (p=0.48). But the incidence of squamous carcinoma in the pT3-MB group was 78%, which was considerably higher than other groups (p<0.001). In addition, the extralobar N1 rate was 51.2% and the pneumonectomy rate was 56.1%, which were also considerably higher in the pT3-MB group than that of the corresponding rates in the other groups (p<0.001 and p<0.001 respectively, Table 1). The mortality rate was 13% for patients who underwent pneumonectomy and zero for patients who underwent a sleeve lobectomy. No statistically significant difference was found between the mortality rates (p=0.07). The five-year survival rates of patients who underwent lobectomy (including sleeve lobectomy) and pneumonectomy were 51.6% and 38.1%, respectively. When compared, this difference in survival rates was statistically significant (p=0.01; Table 2). The five-year survival rate of sleeve lobectomy patients was calculated as 43.3%. This superior rate was not statistically significant when compared with the survival of pneumonectomy patients (p=0.07). Three-year survival rates were 67% and 22% for patients who had sleeve lobectomy and pneumonectomy for extralobar N1 involvement, respectively (p=0.08).

The existence of extralobar N1 indicated poor prognosis (p<0.001, Table 2, Figure 1). However, intralobar N1 did not influence the prognosis when compared with N0.

The five-year survival rate was 36.7% in pT3-MB patients, 50.7% in pT3 for other causes and 55.1% in pT2 patients (Figure 2). The survival of pT3-MB

Table 2. Results of univariate and multivariate analyses for suggested prognostic factors

Variable	n	%	Five-year survival (%)	Univariate *p*	Multivariate *p*	Hazard ratio (95% CI)
T status				0.30	0.64	
T2	79	49.7	57.7	0.13	0.35	1
T3-MB	39	24.5	39.4			0.69 (0.33-1.48)
T3 other	41	25.8	57.4	0.31	0.60	0.79 (0.34-1.89)
Histology						
Squamous cell	78	49.1	52.8	0.99	0.64	1
Non squamous	81	50.9	49.8			1.16 (0.62-2.18)
Resection type						
Lobectomy[a]	121	76.1	53.3	0.09	0.54	1
Pneumonectomy	38	23.9	44.1			1.25 (0.62-2.51)
N1 status				<0.02	0.09	
N0	73	45.9	51.7	0.67	0.54	1
Intralobar N1	50	31.4	60.3			1.25 (0.61-2.56)
Extralobar N1	36	22.6	37.5	0.01	0.03	2.34 (1.08-5.09)

T3-MB: Main bronchus invasion T3: [a]: Including sleeve lobectomy; 95% CI: 95% confidence interval.

patients was not significantly different than that of patients with pT2 (p=0.13) and pT3 for other causes (p=0.64).

In multivariate analysis, being either pT3-MB, pT3 for other causes, or pT2 (p=0.58); along with histological type (p=0.52), and type of resection (p=0.48) showed no effect on survival. The presence of extralobar N1 was found as an independent prognostic factor (p=0.01; Table 2).

DISCUSSION

According to TNM staging, a NSCLC extending to the main bronchus less than 2 cm away from the carina but not invading it is staged as T3. The right main bronchus is only 1.2 cm long.[2] A tumor located at the orifice of the right upper lobe bronchus is less than 2 cm away from the carina and therefore directly advances into T3 stage. Hence, even a small tumor that has not extended proximally can be classified as T3. Solid data is required to claim that this condition exerts a negative effect on prognosis.

Previously, both Riquet[4] and Pitz[5] reported better survival rates for patients with bronchial T3 NSCLC when compared with survival of patients with NSCLC classified as T3 for other causes, though these were not statistically significant. We previously found similar results.[6,7] Okada[8] reported significantly better prognosis in patients with main bronchial invasion when

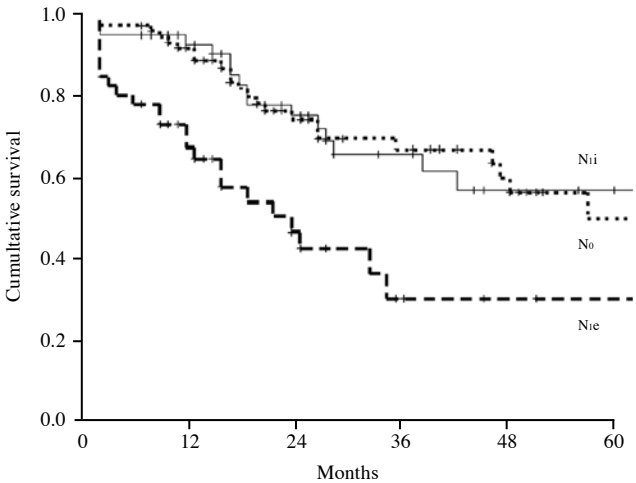

Fig. 1. Survival curves after resection for patients with N0, intralobar N1 and extralobar N1. N0 and intralobar N1 curves are superimposed. N1e: Extralobar N1; N1i: Intralobar N1.

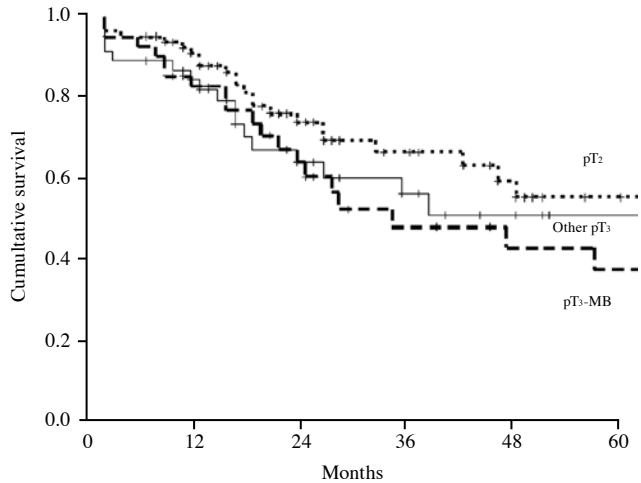

Fig. 2. Survival curves for patients after resection of lung cancer according to T status. pT3-MB: Main bronchus invasion, pT2 and other pT3.

compared with the survival of other T3 patients. Thus the effect of bronchial T3 stage on survival should be questioned compared to other causes of T3 staging. Additionally the role of tumor laterality on prognosis of bronchial T3 patients has not been discussed appropriately until now.

Results of our study showed that patients with tumors extending from the proximal right upper lobe bronchus to the main bronchus did not have better prognosis. In fact poorer prognosis, though not statistically significant, was found in these patients. This discrepancy can be explained by several factors; because the right pulmonary hilum is closely associated with the pulmonary artery, vein, pericardium and mediastinal pleura, tumors of the right upper lobe extending to the right main bronchus invade these adjacent structures frequently. In this series, a number of patients with tumor invading the main bronchus, tumor also invaded adjacent structures. This situation can affect general survival. We have not found any study comparing survival rates for right and left main bronchial invasion. A new study can be designed to expose the role of right and left main bronchial invasion.

Additionally, hilar or interlobar lymph nodes are frequently involved in T3-MB patients due to their approximation. Hilar-interlobar lymph node involvement is known as a poor prognostic factor.[9,10] Our study confirmed that extralobar N1 worsened prognosis. This result can be another cause of the poor prognosis in the main bronchial invasion group.

When complete anatomic resection is performed, the type of resection has not been found to of prognostic value.[11] Complete resection can be achieved by pneumonectomy or sleeve upper lobectomy in T3-MB patients. Pneumonectomy is known to carry a higher risk of morbidity and mortality.[12-14] It is reported that sleeve resection maintains satisfactory survival rates with lung preservation without high morbidity or mortality rates.[14] So we preferred a sleeve lobectomy in many of the cases (44% of T3-MB patients) but due to adjacent structure invasion, pneumonectomy was needed in some patients. Owing to similar long-term survival rates of pneumonectomy and sleeve lobectomy, we recommend performing right upper sleeve upper lobectomy for T3-MB lung cancer of right upper lobe whenever possible.

The main bronchial invasion of right upper lobe tumors is a poor prognostic factor for T3 NSCLC patients. Extralobar N1 involvement, as a poor prognostic factor, is not seen infrequently. Sleeve lobectomy, if technically suitable, should be performed to achieve a complete resection.

Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding

The authors received no financial support for the research and/or authorship of this article.

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