RESEARCH ARTICLE

Prognostic Factors for Lymph Node Negative Stage I and IIA Non-small Cell Lung Cancer: Multicenter Experiences

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Abstract

Background: Surgery is the only curative treatment for operable non-small lung cancer (NSCLC) and the importance of adjuvant chemotherapy for stage IB patients is unclear. Herein, we evaluated prognostic factors for survival and factors related with adjuvant treatment decisions for stage I and IIA NSCLC patients without lymph node metastasis. Materials and Methods: We retrospectively analyzed 302 patients who had undergone curative surgery for prognostic factors regarding survival and clinicopathological factors related to adjuvant chemotherapy. Results: Nearly 90% of the patients underwent lobectomy or pneumonectomy with mediastinal lymph node resection. For the others, wedge resection were performed. The patients were diagnosed as stage IA in 35%, IB in 49% and IIA in 17%. Histopathological type (p=0.02), tumor diameter (p=0.01) and stage (p<0.001) were found to be related to adjuvant chemotherapy decisions, while operation type, lypmhovascular invasion (LVI), grade and the presence of recurrence were important factors in predicting overall survival (OS), and operation type, tumor size greater than 4 cm, T stage, LVI, and visceral pleural invasion were related with disease free survival (DFS). Multivariate analysis showed operation type (p<0.001, hazard ratio (HR):1.91) and the presence of recurrence (p<0.001, HR:0.007) were independent prognostic factors for OS, as well visceral pleural invasion (p=0.01, HR:0.57) and LVI (p=0.004, HR:0.57) for DFS. Conclusions: Although adjuvant chemotherapy is standard for early stage lymph node positive NSCLC, it has less clear importance in stage I and IIA patients without lymph node metastasis.

Keywords: Non-small cell lung cancer - lymph node negative - adjuvant chemotherapy - prognosis

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Introduction

Surgery has long been standart therapy for operable non-small cell lung cancer (NSCLC) however five-year survival has been reported as 50-70% for stage I and II patients (Bouchard et al., 2008). Even in stage I disease relapse rate has been documented as 30% (Visbal et al., 2005). Randomized trials have confirmed the benefit of adjuvant chemotherapy in operated NSCLC, because of the micrometastasis after completely resected NSCLC which lead the recurrences after surgery. Meta-analysis of 5 large trials indicated the 4.2% absolute benefit for 5-year overall survival (OS) with cisplatin-based adjuvant chemotherapy (Pignon et al., 2008). Adjuvant chemotherapy is not effective for all patients so prognostic factors predicting disease free survival (DFS) or OS should be evaluated before treatment decision. Although larger trials included International Adjuvant Lung Trial (IALT), Canada Cancer Therapeutics Group JBR.10 trial, Adjuvant Navelbine International Trialist Association (ANITA) reported significant OS advantages with cisplatin based adjuvant chemotherapy for stage II and III NSCLC, they failed to demonstrate improvement OS of stage IB patients. With a median 5.2 years of follow-up in LACE metaanalysis, the overall hazard ratio of death was 0.89 (95%CI=0.82-0.96), p=0.005. The benefit varied with stage as HR were 1.40, 0.93 and 0.83 for stage IA, IB and II respectively (Suehisa and Toyooka, 2009) .Only small number of patients with stage IA NSCLC were enrolled into clinical trials and adjuvant chemotherapy is not recommended for stage IA disease (Custodio, et al., 2009).

Although adjuvant chemotherapy, recurrence rates have been reported as 40-60% for stage I or II disease (Custodio et al., 2009). So, the determination of adjuvant chemotherapy in the light of the prognostic factors might

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be an important. Pathological stage based on the tumor size and lymph node status were the most important factors in determining adjuvant therapy decision for early stage NSCLC (Ioannidis et al., 2011). Other poor prognostic factors in early stage disease are age, male gender and non-squamous histology (Ioannidis et al., 2011). Grade, lymphovascular invasion (LVI), visceral pleural invasion have been reported as important for poor prognosis in retrospective analysis (Sun et al., 2006; Ioannidis et al., 2011). These parameters have been used for decision in adjuvant chemotherapy in early stage NSCLC (Ioannidis et al., 2011). In our country early stage diagnosis can not be possible everytime, because of screening programs has not been routinely performed in our country so there is no certain rules in determining adjuvant chemotherapy in these group. The aim of this study was to provide general aspect of the adjuvant chemotherapy for lymph node negative stage I and IIA NSCLC in our population and to evaluate the prognostic factors and the association of the clinicopathological factors with adjuvant chemotherapy.

Materials and Methods

This study consisted of 302 NSCLC patients who had undergone curative surgery in different oncolgy center in Turkey between May 2001 and December 2012. All patients underwent either lobectomy, pneumonectomy or wedge resections with mediastinal lymph node dissections. Patients were staged according to American Joint Committee on Cancer (AJCC) 7th edition (Edge et al., 2010). pT1 and T2 tumors without lymph node metastasis were included. Patients with distant metastasis or lymph node metastasis at diagnosis were excluded from the study. None of the patients received neoadjuvant therapy. This study is a retrospective, observational and reviewed-based study of medical records of patients. Clinical informations about age, gender, smoking history, resection type, histolopathology, tumor stage, tumor size, histologic grade, visceral pleural invasion, lymphatic, perineural and vascular invasion, the type of adjuvant chemotherapy, recurrence and survival were obtained from patients charts after written informed consent had been obtained from patients or their relatives.

The patients who were received adjuvant chemotherapy were compared with other patients who were not given adjuvant chemotherapy in regarding clinicopathological factors such as age, gender, smoking history, ECOG performance status (PS), operation type, histopathological type, tumor diameter, pT stage, pathological stage, LVI, PNI, grade, visceral pleural invasion and recurrence. In addition, the importance of these factors and presence of adjuvant chemotherapy in predicting DFS or OS were analyzed.

Statistical analysis

Statistical analyses were performed using SPSS 17.0 (SPSS Inc., Chicago, IL,USA) software. Clinicopathological parameters who received adjuvant chemotherapy were compared with those who did not receive adjuvant chemotherapy by using the Chi-square test and Fisher's exact test. The factors which were predicted adjuvant chemotherapy were investigated by logistic regression analysis. Survival analysis and curves were established according to the Kaplan-Meier method and compared using the log-rank test. Median follow-up time was calculated as the median observation time among all patients. DFS was defined as the time from surgery to the last follow-up and the time until relapse was defined as the time since surgery to the first evidence of relapse. In addition, OS was described as the time from diagnosis to the date of the patient's death or last known contact. Univariate and multivariate analysis of prognostic factors related to survival were performed by the Cox proportional hazards model. Multivariate p values were used to characterize the independence of these factors. A 95% confidence interval (CI) was used to quantify the relationship between survival time and each independent factor. All p values were two-sided in tests and p values less than or equal to 0.05 were considered significant.

Results

A total of 302 patients with radically resected lung cancer were retrospectively analyzed. Forty-nine patients were women and 253 (83.8%) were men. The median age was 69 ranging from 20-84 years. Twenty-six patients were younger than 50 years (44%) and nearly 90% had smoking history. When the patients had been applied to department of medical oncology, ECOG PS were 0, 1 or 2 for 55.2%, 42.7% and 2.1% of patients in order of frequency. Although 267 patients underwent optimal surgery as lobectomy (70.9%) or pneumonectomy (17.5%), wedge resection was performed in 35 (11.6%) patients. The median number of dissected lymph nodes was 6 (range, 1-38). All patients had a histologically proven NSCLC. Over 40% had a squamous histology (SCC), and the remaining of them had non-squamous (58.6%), adenocarcinoma (43%), adenocarcinoma with neuroendocrine differentiation (2.3%), large cell carcinoma(5.3%) and NSCLC non otherwise specified (NOS) (7%). Based on the tumor diameter, 189 (62.5%) tumors were equal and smaller than 4cm, 113 (37.5%) were greater than 4cm. The majority of patients were T2a-stage (150 patients, 49.7%), others were T1a (18.2%), T1b (16.2%) and T2b (15.9%) in order of frequency. At the median follow-up of 22.6 months (range; 1-132), recurrence was diagnosed in 132 patients (43.7%). Five-year DFS and OS rates were 34.8% and 53.8% for all patients, respectively. The median DFS time was 34.4 months (SE:3, 95%CI; 28.4-40.3) and the median OS time was 67.5 months (SE:10.7, 95%CI; 46.4-88.7) (Figure 1).

One hundred thirty-five patients (44.7%) received

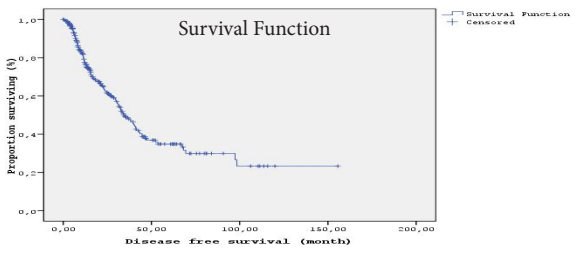

Figure 1. Disease Free Survival Curve of the Patients

Table 1. The Relationship between Adjuvant Chemotherapy and Clinicopathological Characteristics

Characteristics		Present (%)	Absent (%)	p
Age	≤50	26(44)	33(56)	0.9
	>50	109(44.8)	134(55.2)	
Gender	Female	22(44.8)	27(55.2)	0.9
	Male	113(44.6)	140(55.4)	
PS	0	68(43.5)	88(56.5)	0.7
	1	62(46.6)	71(53.4)	
	2	5(38.4)	8(61.6)	
Smoking	Present	119(44.7)	147(55.3)	0.9
	Absent	16(44.4)	20(55.6)	
Operation type	Optimal	119(44.7)	147(55.3)	0.9
	Wedge resection	16(44.4)	20(55.6)	
histopathological type	SCC	46(36.8)	79(63.2)	0.02
	non-SCC	89(50.2)	88(49.8)	
Tumor diameter	≤4cm	71(37.5)	118(62.5)	0.01
	>4cm	64(56.6)	49(43.4)	
Stage	IA	31(29.8)	73(70.2)	<0.001
	IB	72(48.6)	76(51.4)	
	IIA	32(64)	18(36)	
LVI	Present	23(46.9)	26(53.1)	0.8
	Absent	91(45.2)	110(54.8)	
PNI	Present	9(52.9)	8(47.1)	0.5
	Absent	102(44.7)	126(55.3)	
Grade	Low	22(46.8)	25(53.2)	0.5
	Intermediate	40(43.9)	51(56.1)	
	High	36(53.7)	31(46.3)	
Pleura invasion	Present	26(48.1)	28(51.9)	0.5
	Absent	107(43.8)	137(56.2)	
Recurrence	Present	55(41.6)	77(58.4)	0.3
	Absent	80(47)	90(53)	

*Performance status, LVI:lymphovascular invasion, PNI: perineural invasion

adjuvant platin based chemotherapy. Platin were combined with vinorelbine (n=70, 52%), taxane (n=23, 17%), etoposide (n=28, 20.7%) or gemcitabine (n=14, 10.3%). Median chemotherapy cycle was 4 in the range of 2 and 6, only 6 patients stopped the adjuvant chemotherapy because of disease progression in 1 patient and hematological toxicity in the remaining patients. There was no treatment related death. Grade 3-4 toxicities were detected in 52 patients, 29 with hematologic (55.8%), 5 with febril neutropenia (9.6%), 15 with gastrointestinal system (28.8%) and 3 with nephrotoxicities (5.8%). The correlation between the presence of adjuvant chemotherapy and the clinicopathologic findings are shown in Table 1. The adjuvant chemotherapy was received significantly more frequently in cases with non-squamous histology, tumor ≥4cm, pathological stage IB and II. On the other hand, the presence of adjuvant chemotherapy was not associated with age, gender, operation type, LVI, PNI, grade, pleural invasion or recurrence. While 18 of 50 patients with stage IIA disease didn't receive adjuvant chemotherapy on the other hand, 76 of the 148 stage IB patients were not treated with adjuvant chemotherapy. Tumor stage and histopathological type were the most powerful predictors of adjuvant chemotherapy (p=0.02, OR: 0.92, 95%CI: 0.87-0.99, vs p=0.01, OR:1.96, 95%CI: 1.17-3.30). Table 2 shows the results of the regression analysis.

The univariate analysis showed that operation type (p=0.01), LVI (0.02), grade (<0.001) and recurrence (p<0.001) were important prognostic indicators for OS, in addition, operation type (p=0.03), T stages (p=0.04), LVI (p<0.001) and visceral pleural invasion (p=0.01)

Table 2. Independent Factors Predicting Adjuvant Chemotherapy

Characteristics	Wald	p	HR	95%CI
Gender	0.20	0.6	0.82	0.35-1.89
Age	0.01	0.9	1.03	0.55-1.02
Ps	0.16	0.6	0.91	0.59-1.40
Smoking	0.10	0.7	0.86	0.34-2.15
T Stage	2.33	0.1	1.55	0.88-2.71
Grade	2.30	0.1	1.20	0.94-1.53
Histopathology	6.52	0.01	1.96	1.17-3.30
Operation	0.54	0.4	1.08	0.7-1.5
Tumor Diameter	0.02	0.8	1.04	0.5-1.8
Stage	5.16	0.02	0.92	0.87-0.99
Pni	0.09	0.7	0.90	0.48-1.69
Pleura Invasion	0.03	0.8	0.94	0.50-1.74
Lvi	0.80	0.3	1.26	0.75-2.12
Recurrence	2.12	0.1	0.69	0.42-1.19

*PNI: perineural invasion, LVI: lymphovascular invasion, CT: chemotherapy, HR: hazards ratio; CI: confidence interval

were found to be related DFS. OS and DFS for patients with optimal surgery were better than those of patients with wedge resection in addition the presence of LVI decreased both OS and DFS. The results of univariate analysis are listed in Table 3. Although 5 year OS rate of patients who were received adjuvant chemotherapy was 56.6% compared to 53.6% for patients without adjuvant chemotherapy, this was not statistically significant (p=0.6). We carried out multivariate analysis with Cox proportional hazards model in order to further evaluate the prognostic significance of these parameters and multivariate analysis indicate that the visceral pleural invasion and LVI were independent prognostic factors (p=0.01, HR:0.57; 95%CI :0.3-0.9 and p=0.004, HR: 0.57; 95%CI:0.3-0.8, respectively) for DFS, as were operation type and recurrence were important for OS (p<0.001, HR:1.91; 95%CI :1.3-2.7 and p<0.001, HR: 0.007; 95%CI :0.001-0.055, respectively). Table 4,5 shows the results of multivariate analysis.

If we excluded tumor ≤3cm, 119 tumors were equal or smaller than 3 cm (39.4%) and DFS was longer for patients with tumor equal or smaller than 3 cm by univariate analysis. Although OS was also better for tumor ≤3cm than >3 cm, it was not significant statistically (98.3 vs 63.4 month, p=0.1). After stage IA was excluded, we found that LVI (p<0.001) and visceral pleural invasion (p=0.02) were related to be DFS. In addition, smoking (p=0.01), operation type (p=0.05), LVI (p=0.009) and recurrence (p<0.001) were important factors predicting OS. Moreover, during 22.6 months of follow-up time, 3 years OS rates were 73.1% and 63.4% for patients who were given chemotherapy or not in stage IB and IIA patients, respectively (p=0.9).

Discussion

NSCLC is the leading cause of cancer related death worldwide. Even patients are diagnosed in early stage, recurrence rates are high (Kelsey et al., 2009). 5-year OS rates are 73-25% for stage IA through stage IIIA (Sangha et al., 2010). Cisplatin based adjuvant chemotherapy

Table 3. Results of the Univariate Analysis

		No. (%)	Median OS (month)	Range	p	Median PFS (month)	Range	p
Age	≤50	59 (19.5)	86.4	37.2-135.5	0.6	29.4	17.4-41.4	0.1
	>50	243 (80.5)	68.3	55.9-80.7		37	30.7-43.3	
Gender	Female	49 (16.2)	nr	nr	0.7	33.4	28.2-38.6	0.7
	Male	253 (83.8)	67.5	46.4-88.7		35.5	28.9-42.0	
PS	0	79 (55.2)	69.4	47.4-9	0.7	38.4/34.1	27.3-49.4/28-40.1	0.8
	1	61 (42.7)	67.5	nr		34.1	28.0-40.1	
	2	3 (2.1)	nr	nr		27.7	nr	
Smoking	Present	266 (88.1)	67.3	56.2-78.4	0.7	34.4	28.2-40.6	0.5
	Absent	36 (11.9)	86.4	8.9-163.8		33.4	12.7-54.1	
Operation type	lobectomy	214 (70.9)	58.4	43.9-72.8	0.01	32.9	29.8-35.9	0.03
	pneumonectomy	53 (17.5)	nr	nr		nr	nr	
	wedge resection	35 (11.6)	47.8	16.3-79.2		28.3	2.2-54.3	
Histopathological type	SCC	125 (41.4)	68.3	56.3-80.4	0.3	33.4	26.9-39.8	0.6
	non-SCC	177 (58.6)	67.5	35.9-99.1		39.5	30.3-48.8	
Tumor diameter	≤4cm	189 (62.6)	69.4	33.4-105.4	0.5	38.1	31.2-44.9	0.07
	>4cm	113 (37.4)	67.5	52.2-82.8		25.7	13.1-38.2	
T evresi	T1a	55 (18.2)	nr	nr	0.2	69.4	23.3-115.5	0.04
	T1b	49 (16.2)	67.3	0.0-137.4		31.8	20.8-42.7	
	T2a	150 (49.7)	63.4	46.5-80.3		31.2	23.8-38.6	
	T2b	48 (15.9)	67.5	41.2-93.9		32.9	nr	
Stage	IA	104 (34.4)	98.3	48.4-148.3	0.4	42.8	27.6-58.1	0.06
	IB	148 (49)	63.4	40.2-86.5		31.4	26.7-38.6	
	IIA	50 (16.6)	56.8	43.2-70.3		32.9	nr	
LVI	Present	49 (19.6)	27.7	14.5-40.8	0.02	15	10-20	<0.001
	Absent	201 (80.4)	35.7	27.7-43.6		40.4	31.5-49.2	
PNI	Present	17 (6.9)	32.1	9.2-54.9	0.1	22.5	13.3-31.7	0.1
	Absent	228 (93.1)	67.5	57.1-77.9		35.5	29.9-41	
Grade	Low	47 (22.8)	41.3	16.4-66.1	<0.001	40.4	28.5-52.2	0.4
	Intermediate	91 (44.2)	45.2	41.2-49.1		39.8	30.9-48.7	
	High	68 (33)	41327	7.6-36.7		30	22.6-37.4	
Pleura Invasion	Present	54 (18.1)	43.6	27.7-59.5	0.09	22.9	16.4-29.4	0.01
	Absent	244 (81.9)	68.3	45.4-91.2		39.5	33.1-46.0	
Adjuvant Ct	Present	135 (44.7)	67.3	45.1-89.7	0.6	37	27.2-46.8	0.3
	Absent	167 (55.3)	105.9	40.4-171.5		33.8	25.3-42.4	
Recurrence	Present	132 (43.7)	37.7	29.7-45.8	<0.001			
	Absent	170 (56.3)	nr	nr				

*OS: overall survival, PFS: progression free survival, PS: performance status, nr: not reached, SCC: squamous cell cancer, LVI: lymphovascular invasion, PNI: perineural invasion, CT: chemotherapy

Table 4. Results of Multivariate Analysis of PFS

Characteristics	Wald	p	HR	95%CI
Gender	0.22	0.6	0.69	0.9-
Age	2.14	0.1	1.34	0.9-2
Smoking	0.07	0.9	1.02	0.5-1.7
Tstage	1.37	0.2	1.06	0.9-1.18
Grade	0.36	0.5	1.05	0.71-2.47
Histopathology	0.13	0.7	1.20	0.44-3.21
Operation	0.19	0.6	1.06	0.7-1.4
Tumor Diameter	0.26	0.6	0.89	0.6-1.3
Stage	2.38	0.1	1.03	0.9-1
PNI	2.17	0.1	1.45	0.8-2.3
Plevra Invasion	5.59	0.01	0.57	0.3-0.9
LVI	8.19	0.004	0.57	0.3-0.8
Adjuvant CT	2.09	0.1	1.30	0.9-1.8

*PNI: perineural invasion, LVI: lymphovascular invasion, CT: chemotherapy, HR: hazards ratio; CI: confidence interval

Table 5. Results of Multivariate Analysis of OS

Characteristics	Wald	p	HR	95%CI
Tstage	0.08	0.7	1.02	0.8-1.1
Grade	2.61	0.1	1.21	0.9-1.5
Histopathology	2.22	0.1	0.69	0.4-1.1
Operation	13.1	<0.001	1.91	1.3-2.7
Tumor Diameter	0.88	0.3	1.31	0.7-2.3
Stage	0.61	0.4	1.02	0.9-1
PNI	0.48	0.4	0.78	0.3-1.5
Plevra invasion	0.46	0.4	0.80	0.4-1.4
LVI	1.12	0.2	0.77	0.4-1.2
Recurrence	22.9	<0.001	0.007	0.001-0.055

*PNI: perineural invasion, LVI: lymphovascular invasion, CT: chemotherapy, HR: hazards ratio; CI: confidence interval

can reduce the recurrence risk but there is no consensus in decision of adjuvant chemotherapy in lymph node negative early stage I and IIA NSCLC patients. IALT trial demonstrated the 4% survival advantage at 5 year but this has not been continued at 7 year follow-up in stage II and III NSCLC patients (Arriagada et al., 2010). JBR.10 trial reported survival advantage for resected NSCLC patients over 9 years of follow-up (Butts et al., 2010). They included stage IB (45%) and II (55%) patients. In our study, 49% of the 302 patients were stage IB and 16% were stage IIA. We included also stage IA disease. The Cancer and Leukemia Group B (CALGB) 9633 trial was evaluated adjuvant chemotherapy in only stage IB(T2N0)

NSCLC patients (Strauss et al., 2008). Although 3-year OS was significantly better than observation group, at 4 year the statisticaly significance was lost but significant survival difference is demonstrated in favor of adjuvant chemotherapy for patients with tumor >4cm in the subgroup analysis. In updated staging of NSCLC (7th edition) provide an important distinction between early stage as T2 was subdivided according to tumor diameter as T2a (3cm<tm<5cm) and T2b (5cm<tm<7cm) and tumor>7cm in the original T2 was reclassified as T3 so previous stage T2N0 categorized as T2aN0 (IB), T2bN0 (IIA) and T3N0 (IIB) (Carbone, et al., 2011). In CALGB study T2N0 patients were included according to AJCC 6th addition, means that all tumors were >3cm were included. The median tumor diameter was 4cm ranging 0-14cm. They also made subgroup analysis and they showed no survival advantages for adjuvant chemotherapy for tumor smaller than 4 cm, mean tumor diameters were 2.73 for adjuvant chemotherapy group and 2.71cm for observation group. The vast majority of patients included CALGB study would be shift to stage II on the basis of the AJCC 7th edition. Japan Lung Cancer Research Group (JLCRG) reported the survival advantages of adjuvant UFT for stage IB NSCLC patients. They included both stage IA and IB patients but OS advantages was detected for only stage IB (27%) of them (Kato et al., 2004). If we excluded IA tumors, 119 were equal or smaller than 3 cm (39.4%) and DFS was longer for patients with ≤3 cm by univariate analysis. OS was also better for tumor ≤3cm than >3 cm, but not significant statistically(98.3 vs 63.4 month, p=0.1). Although retrospective, our study is noteworthy in evaluating stage of patients according to AJCC 7th edition.

We analyzed the decision of adjuvant chemotherapy and prognostic factors predicting survival in lymph node negative stage I and IIA NSCLC patients as Anatolian Society of Medical Oncology Study Group. Although toxicities were acceptable, only 44.7% of the patients were received adjuvant chemotherapy. This may be related clinicopathological factors or preference of surgeon. We herein evaluated which factors were affected the decision of adjuvant chemotherapy. Bouchard et al analyzed 249 operated NSCLC patients, 100 patients were treated with adjuvant chemotherapy. Age, histopatology, stage, operation type, PS were different between patients who taken adjuvant chemotherapy or not. In our study, in addition to histopatological type and stage, tumor diameter were also higher in adjuvant chemotherapy group. Also we compared LVI, PNI, pleural invasion, grade and recurrence between two groups as different from their study. They reported the tumor stage and PS were independent predictors for adjuvant chemotherpy, (Bouchard et al., 2008). we also found stage was an most important factor in predicting adjuvant chemotherapy as well as histopatological type. The differences may be related that 13 patients with small cell lung cancer group were included in their study. We classified histopatological types as squamous and non-squamous histology. Over half of them were (58.6%) non-SCC histology. Winget et al. (2011) reported 226 stage IB (69%) or II (31%) NSCLC patients consultated with medical oncology after operation. Nearly 40% of them received adjuvant chemotherapy, similar to our study as 135 out of the 302 patients (44%). We had 148 (49%) patients with stage IB, 16% stage II and 34% stage IA disease. They found to be association between patient'age and stage with the presence of adjuvant chemotherapy. Younger than 70 years were more taken chemotherapy than older one (Winget et al., 2011). In our study, not age but tumor diameter, stage at diagnosis and histopatological type of the tumors were related with adjuvant chemotherapy. Non-SCC and >4cm tumors with advanced stage (IIA) were taken more adjuvant chemotherapy compared the small, stage I tumor with SCC histology. When we excluded the stage IA patients, stage (p=0.04) and histopatological type (p=0.006) were also found to be related with the presence of adjuvant chemotherapy.

In JBR-10 trial, 53% of tumors were adenocarcinoma and they reported the better survival and lower recurrence rate for SCC than adenocarcinoma or large cell carcınoma (Butts et al., 2011). We couldn't prove an importance of histopatological type for OS or PFS. If we might determined the subgroup of non-SCC histology, the results might be more definite. Kelsey et al evaluated local recurrence of 975 stage I and II NSCLC, herein 7% were received adjuvant chemotherapy nearly half as carboplatin and paclitaxel and 5-year DFS rate was reported to be 42%. Sublobar resection, increased tumor size, lack of mediastinal lymph node sampling, high grade, SCC histology, LVI, visceral pleural invasion were related with risk of local recurrence. SCC histology and sublobar resection were independent risk factor for local recurrence by multivariate analysis. Operation type, T stage, LVI and visceral pleural invasion were also related with DFS in our study but we didn't report recurrence pattern as local or distant. Total recurrence rate was 43.7% similar to their study (Kelsey et al., 2009). Cushodio et al. (2008) analyzed the platin-taxan combination as adjuvant chemotherapy in 41 NSCLC patients with stage IB, II or stage IIIA (Cushodio et al., 2008). Recurrence was documented in 15 (37%) patients within median 12.1 months of relaps free survival(RFS). Five-years DFS and OS rates were 34.8% and 53.8% for all patients, respectively during 22.6 months of follow-up period. They couldn't find any variables to be related with RFS other than PS in patients treated with adjuvant chemotherapy. After stage IA was excluded, we found LVI (p<0.001) and visceral pleural invasion (p=0.02) were related to be DFS. In addition, smoking (p=0.01), operation type (p=0.05), LVI (p=0.009) and recurrence (p<0.001) were important factors predicting OS. The visceral pleural invasion, T stage and grade were found important prognostic indicators for recurrence in resected 110 stage IB NSCLC patients (Cho et al., 2012). Grade and moleculer marker survivin were the independent prognostic factors in predicting recurrence. Recently, the prognostic factors for survival of stage IA (according to 7th editiıon) was analyzed in 1929 NSCLC patients and intratumoral vessel invasion and grade were important factors for stage 1A disease (Zhang et al., 2012). In another study, age, grade, tumor size, number of removed mediastinal lymph nodes and visceral pleura invasion were found to be associated with mortality in 147 stage IB upper lobe tumor (Wang et al., 2011). We

also supported the visceral pleural invasion and stage as predicting DFS, as were LVI and operation type which was consistent with the literature. Furthermore visceral pleural invasion and LVI were significant for DFS by multivariate analysis. These parameters might be changed according to population or patologist who evaluated the resection specimens. Although our results indicate the prognostic factors in our Anatolian population, because of the analysis of the resection material from multicenter, the results may be variable.

The overall rate of grade 3 or 4 toxicity was 66% predominantly as a result of neutropenia in LACE metaanalysis (Sangha et al., 2010). We detected grade 3-4 toxicities in 52 patients (38.5%) which smaller than the literature. This may be related with the different chemotherapy regimen that we used (cisplatin or carboplatin with vinorelbine, etoposide, taxan or gemcitabin). During 72 months of follow-up time, 72% of the patients in Winget's trial and 69% of the patients at JBR trial were alive who were randomized according to the presence of adjuvant chemotherapy and 57% and 54% were alive who didn't receive chemotherapy postoperatively. In the present study, during 22.6 months of follow-up time, 3 years OS rates were 73.1% and 63.4% for patients who were given chemotherapy or not in stage IB anad IIA patients, respectively (p=0.9).

Decision in regarding adjuvant chemotherapy depends on true evaluation of risk and benefit for OS. For patients with low risk of recurrence, adjuvant chemotherapy may be excluded. Accurate staging is important for treatment decision. Tumor stage, histopatological type, LVI, visseral pleural invasion or grade were important in our study predicting OS or DFS. Retrospective nature of our study is the major limitation. Our results don't support the recommendation of adjuvant chemotherapy for lymph node negative stage IB or IIA NSCLC. Furthermore we evaluated all patients who had stage I, IIA without lymph node metastasis. If number of patients increase in the future, we should reevaluate patients as stage IA, IB and IIA respectively.

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