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ORIGINAL ARTICLE

The role of adjuvant chemotherapy in resected stage I non - small cell lung cancer: A Turkish Oncology Group Study

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Summary

Purpose: *The benefit of adjuvant chemotherapy for tumors smaller than 4 cm is not clear. We aimed to evaluate the prognostic impact of adjuvant platin-based chemotherapy in high-risk stage I patients with non-small cell lung cancer (NSCLC).*

Methods: *This cooperative group study included 232 NSCLC patients who underwent curative surgery for stage I disease with tumor size 2-4 cm.*

Results: *Median age at presentation was 63 years (range 18-90). The mean tumor size was 29.6 ± 7.3 mm. The frequency of patients with specified risk factors were: visceral pleural effusion (VPI): n: 82 (36.6%); lymphovascular invasion (LVI): n: 86 (39.1%); Grade 3: n: 48 (32.7%); Solid micropapillary pattern (SMP): n: 70 (48.3%). Adjuvant platin-based chemotherapy was administered to 51 patients. During a median follow-up period of 50.5 months 68 patients (29.3%) developed recurrence, 54 (23.3%) died from any cause and 38 (16.4%) of them died of lung cancer. Patients who received chemotherapy compared with the non-chemotherapy group had a longer 5-years relapse-free survival (RFS) (84.5 vs. 61.1%). Also on multivariate analysis, adjuvant chemotherapy was a significant independent prognostic factor for RFS.*

Conclusion: *Adjuvant platin-based chemotherapy should be considered for patients with small tumors with adverse risk factors.*

Key words: *adjuvant chemotherapy, lung cancer, oncology, lymphovascular invasion, solid-micropapillary pattern, platinum-based therapy*

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Introduction

Surgery is considered the most effective therapeutic modality for early stage non-small cell lung cancer (NSCLC). However, even after optimal approaches, 5-year overall survival for stage IA and stage IB are approximately 85% and 73%, respectively [1-4]. Patients with early stage lung cancer still experience a 20% risk of recurrence after curative resection [5]. Tumor size and lymph node status is the major indicator for adjuvant therapy in patients with NSCLC. Adjuvant platinum-based chemotherapy is accepted as a standard treatment for suitable patients who have undergone surgery for tumors larger than 4 cm with or without positive lymph nodes [6,7]. Despite similar relapse rates, the benefit of adjuvant chemotherapy for smaller tumors with high risk features is not clear. Prior randomized-controlled studies evaluating the role of adjuvant chemotherapy for stage I disease yielded contradictory results. A pooled analysis of over 11,000 patients by the NSCLC Collaborative Group in 2015, reported 3% and 5% overall survival (OS) benefit with adjuvant chemotherapy for patients with stage IA and IB disease, respectively. In this final meta-analysis stage IB patients seemed to derive similar benefit with platinum-based chemotherapy as compared to stage II and III patients [8].

Among non-size predictors for adjuvant chemotherapy evaluated by retrospective multi-center analyses and translational studies of prospective trials; high grade, visceral pleural invasion (VPI), lymphovascular invasion (LVI) and recently solid-micropapillary (SMP) components have been identified as significant prognostic factors for poor outcomes [2, 9-14]. The effect of adjuvant chemotherapy in node-negative tumors measuring 4 cm or smaller is unclear and requires further investigation. In this retrospective analysis, our aim was to evaluate the prognostic impact of adjuvant platinum-based chemotherapy in stage I NSCLC patients measuring 2-4 cm. with high-risk features.

Methods

Ethical approval

The Ethics Committee of Istanbul University Institute of Oncology approved this study with the number 70973125-604.01.01 at 08.01.2018.

This cooperative group study included 232 NSCLC patients who underwent curative surgery between January 2010 and December 2015 at 7 different oncology centers in Turkey. The study cohort comprised of stage I NSCLC patients with tumor size 2 - 4 cm and no lymph node involvement. Centers were selected according to their clinical and pathological quality standards; as well as the ability to ensure adequate follow-up. Demograph-

Table 1. Patient demographics and summary of treatment approach

	n (%)
Age,years	
<65	129 (55.6)
≥65	103 (44.4)
Gender	
Male	174 (75.0)
Female	58 (25.0)
Smoking history	
Yes	126 (87.5)
No	18 (12.5)
Stage	
1A2	18 (7.8)
1A3	71 (30.6)
1B	143 (61.6)
Tumor size, cm	
2 - 3	109 (47)
3 - 4	123 (53)
Surgical procedures	
Lobectomy	160 (86.5)
Anatomic segmentectomy	11 (5.9)
Pneumonectomy	14 (7.6)
Histological types	
Adenocarcinoma	128 (55.2)
Squamous cell carcinoma	85 (36.6)
Large cell carcinoma	11 (4.7)
Other	8 (3.4)
Tumor grading	
Well differentiated	17 (11.6)
Moderately differentiated	82 (55.8)
Poorly differentiated	48 (32.7)
Visceral pleural invasion	
Yes	82 (36.6)
No	142 (63.4)
Solid-micropapillary component	
Yes	70 (48.3)
No	75 (51.7)
Lymphovascular invasion	
Yes	86 (39.1)
No	134 (60.9)
Adjuvant chemotherapy	
Yes	51 (22.4)
No	177 (77.6)
Tumor recurrence	
Yes	68 (29.3)
No	164 (70.7)
Death	
Cancer-related	38 (16.4)
Other reasons	16 (6.9)
No	158 (68.1)
Lost to follow up	20 (8.6)

Table 2. Survival analysis among groups with or without chemotherapy

	Chemotherapy group			*Non-treatment group*			*p value*
	Events/n	*Median*	*5-y Rate*	*Events/n*	*Median*	*5-y Rate*	
RFS	7/51	NR	% 84.5 ± 5.4	61/173	96.3 mo.	% 61.1 ± 4.3	0.010*
CSS	4/49	NR	% 89.7 ± 5	34/162	NR	% 78.1 ± 4	0.114
OS	10/49	NR	%77.4 ± 6.4	43/162	NR	% 74.1 ± 4	0.661

*All values were stratified with respect to potential confounding factors such as age, gender and histology. RFS: Relapse-free survival, CSS: Cancer specific survival, OS: Overall survival NR: Not-reached, Mo: Months

Table 3. Survival results of patients with or without adjuvant chemotherapy

Factors	*Adjuvant chemotherapy (+)*		*Adjuvant chemotherapy (-)*		*p value*[1]
	N of Events	*5y Survival (±SE)*	*N of Events*	*5y Survival (±SE)*	
Relapse Free Survival Results					
Age					
<65	5/38	85.8% (±5.9)	28/86	65.4% (±5.7)	0.037
≥65	2/13	79.5% (±13.1)	33/87	56.3% (±6.4)	0.223
Histology					
Sq.	1/20	94.7% (±5.1)	24/65	60.2% (±6.9)	0.013
Non - Sq.	6/31	77.7% (±8.1)	37/108	61.4% (±5.5)	0.204
Stage*					
1a2+1a3	2/7	66.7% (±19.2)	25/81	63.3% (±6.3)	0.694
1b	5/44	87.2% (±5.4)	36/92	59.1% (±5.9)	0.005
Tumor size					
2 - 3 cm	2/8	71.4% (±17.1)	29/91	68.6% (±5.5)	0.992
3 - 4 cm	5/43	86.8% (±5.5)	31/79	49.5% (±7.1)	0.002
Grade*					
1+2	5/27	79.9% (±8.1)	30/70	53.7% (±6.5)	0.097
3	1/8	80% (±17.9)	14/36	55.9% (±9.8)	0.326
SMP (+)	0/13	100 %	16/51	66.5% (±7.9)	0.018
LVI (+)	2/17	87.5% (±8.3)	28/65	55.7% (±6.8)	0.046
VPI (+)	0/15	100 %	24/60	61.8% (±6.9)	0.013
Cancer specific survival					
Age					
<65	2/36	94% (±4.1)	16/80	74.6% (±6.1)	0.081
≥65	2/13	77.1% (±14.4)	18/82	81.6% (±5)	0.852
Histology					
Sq.	1/19	94.4% (±5.4)	15/57	74.9% (±6.8)	0.121
Non - Sq.	3/30	86.3% (±7.7)	19/105	79.8% (±4.9)	0.436
Stage*					
1a2+1a3	0/7	100 %	13/77	80% (±5.7)	0.276
1b	4/42	87.9% (±5.9)	21/85	76.3% (±5.5)	0.148
Tumor Size					
2 - 3 cm	0/8	100 %	16/86	81.6% (±5)	0.340
3 - 4 cm	4/41	87.7% (±5.9)	18/73	73.3% (±6.3)	0.051
Grade*					
1+2	4/27	81.1% (±8.9)	18/65	72.9% (±6.2)	0.458
3	0/7	100 %	10/32	71.6% (9.8)	0.236
SMP (+)	0/12	100 %	8/50	85.7% (±6)	0.139
LVI (+)	2/17	87.5% (±8.3)	19/60	68.1% (±6.9)	0.224
VPI (+)	0/14	100 %	13/56	82.3% (±5.9)	0.094

[1]Log Rank test, *Stage 1a2 and 1a3 *vs.* Stage 1b; Grade 1 and 2 *vs.* Grade 3 for statistical comparisons NR: Not reached, Sq: Squamous, SMP: Solid - micropapillary component, LVI: lymphovascular invasion, VPI: visceral pleural invasion

ic and pathologic data that including stage, tumor size, age, histology and pathologic prognostic factors were retrieved from patient charts. Patients with lymph node metastasis, large cell neuroendocrine histology or having small cell components, inappropriate lymph node dissection, wedge resections or sublobar resections with close margins, received neoadjuvant therapy and had synchronous or metachronous cancer were excluded. Patients with adverse prognostic factors consisting of VPI, LVI, high grade or presence of SMP components were included in this dataset comprising stage I NSCLC with tumors sized 2-4 cm. Medical records of patients with these pathologic factors were analyzed to investigate the prognostic impact of adjuvant chemotherapy in this specific cohort. Patients were restaged according to the American Joint Committee on Cancer (AJCC) 8th edition [15]. Histologic subtypes of lung cancer were determined according to the World Health Organization classification [16]. Written informed consent was obtained from patients or their relatives. Patients were required to be followed postoperatively for 3- to 6-month intervals for the first two years, and then yearly thereafter with computed tomography for at least 4 years after surgery. Patients lost to follow-up within the specified period were not included in the analysis.

Statistics

Statistical analyses were performed using SPSS 20.0 software (SPSS Inc, Chicago, IL, USA). For evaluation of each prognostic factor separately, patients were grouped into two categories with respect to tumor size; A) ≥2-<3 and B) ≥3-≤4 cm and histology; A) Squamous and B) Non-squamous. The distribution of prognostic factors and demographic variables within each category were compared by using the Chi-square test and Fisher's exact test. Survival analyses and curves were performed according to the Kaplan-Meier method and compared with log-rank test. OS was defined as the time from diagnosis to the date of the patient's death from any cause or last known contact. Cancer specific survival (CSS) was the time from diagnosis to the date of the patient's cancer related death or last known contact. Relapse-free survival (RFS) was the time from surgery to the time until recurrence at any site. Survival analyses were performed according to the Kaplan-Meier method and log-rank test for univariate analysis. Multivariate analysis of prognostic factors related to survival were performed by the Cox proportional hazards model. For multivariate analysis of risk factors, we excluded the SMP group to allow for unbiased histologic evaluation in the model, and grade, due to the high ratio of missing data. Thus, age, tumor size, LVI, VPI, adjuvant chemotherapy and histology were included in the final model. P values ≤ 0.05 were considered significant.

Results

The median age at presentation was 63 years (range 18-90). Male to female ratio was 3 (174/58). The most common surgical procedure was lobectomy (n: 160; 86.5%) and the median number of dissected lymph nodes was 11 (range 1-39). The mean tumor size was 29.6 ± 7.3 mm. Most frequent tumor location was the right upper lobe (n=87, 37.4%) and the most frequent histology was adenocarcinoma (n=128, 55.2%). A total of 51 patients (22.4%) had received adjuvant chemotherapy, mostly with the cisplatin-vinorelbine regimen (n: 41; 85.4%). Other combinations used were carboplatin-paclitaxel (n:1, 2.1%), cisplatin-etoposide (n: 2; 4.2%) and cisplatin-gemcitabine (n:1; 2.1%). Demographic data and management approaches are summarized in Table 1. The frequency of patients with specified risk factors were: VPI: n: 82 (36.6%); LVI: n: 86 (39.1%); Grade 3: n: 48 (32.7%); SMP: n: 70 (48.3%). There were significantly more patients who received chemotherapy in the younger age group (<65 years old *vs.* ≥65 years old) and those with larger tumors (2-3 cm *vs.* 3-4 cm). When the groups were analyzed for any imbalances in the distribution of potential confounding factors, there were more patients with VPI and LVI in the non-squamous histology group despite the smaller tumor size (Supplementary Tables S1,S2).

During a median follow-up period of 50.5 months (range 0.1-102 months), 68 patients (29.3%) recurred and 54 patients (23.3%) died: 70.4% of which died because of lung cancer. The 5-year and 10-year OS rates of the whole group were 74.2% (± 3.5) and 53.1% (± 7.2), CSS rates were 80.4% (± 3.4) and 61.6% (± 7.5), and RFS rates were 66.1% (± 3.7) and 43% (± 13), respectively. Univariate analysis showed that adjuvant chemotherapy had a significant impact on RFS (Table 2). In addition, there was a non-significant trend for improvement in CSS and OS in the chemotherapy group (Figure 1).

Then we analyzed patients with defined adverse risk factors separately, to determine whether adjuvant chemotherapy had a differential prognostic effect as compared to those who had not received chemotherapy. Adjuvant chemotherapy was significantly associated with a longer RFS in all patient groups with adverse risk factors. Younger patients and those with squamous histology seemed to derive more benefit from adjuvant chemotherapy (Table 3). The impact of adjuvant chemotherapy on RFS was independent of age, histology or tumor size (Table 4). Younger patients and those with adverse risk factors had numerically higher CSS with adjuvant chemotherapy. However, the differences remained non-significant, there was a tendency for improved CSS with adjuvant chemotherapy in those having a larger tumor size (p:0.051) (Figure 2, Table 3). Despite numerically higher values, there was no significant association of OS with any of the risk groups analyzed (Supplementary Table S3).

A larger tumor size (≥3 - ≤4 cm) was the single independent risk factor for all prognostic outcomes.

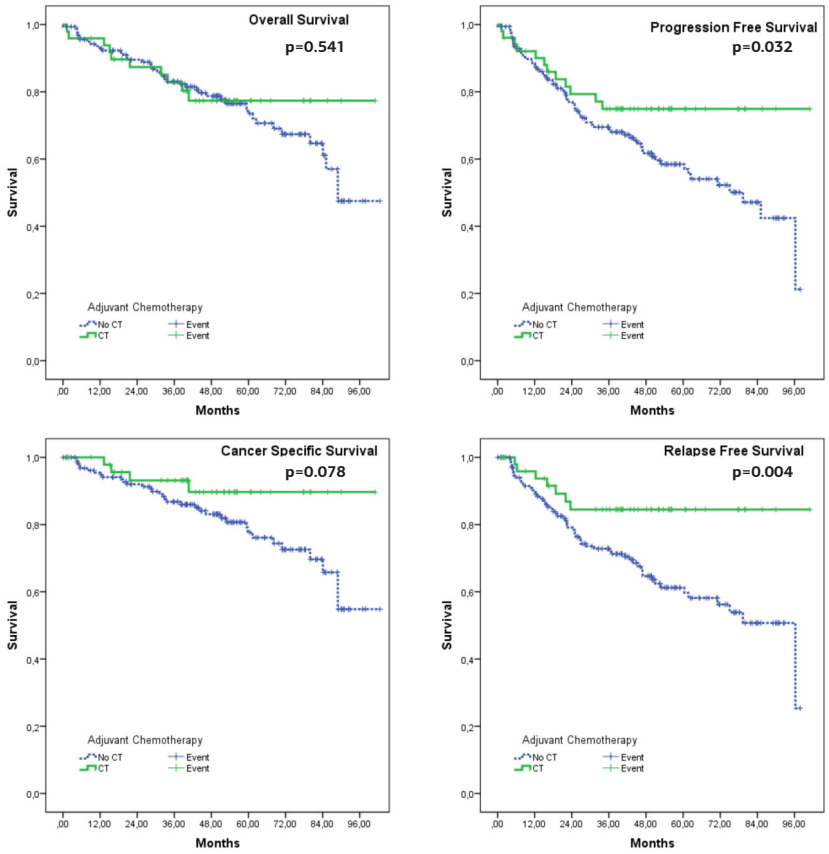

Figure 1. Effects of adjuvant chemotherapy on survival. CT: chemotherapy

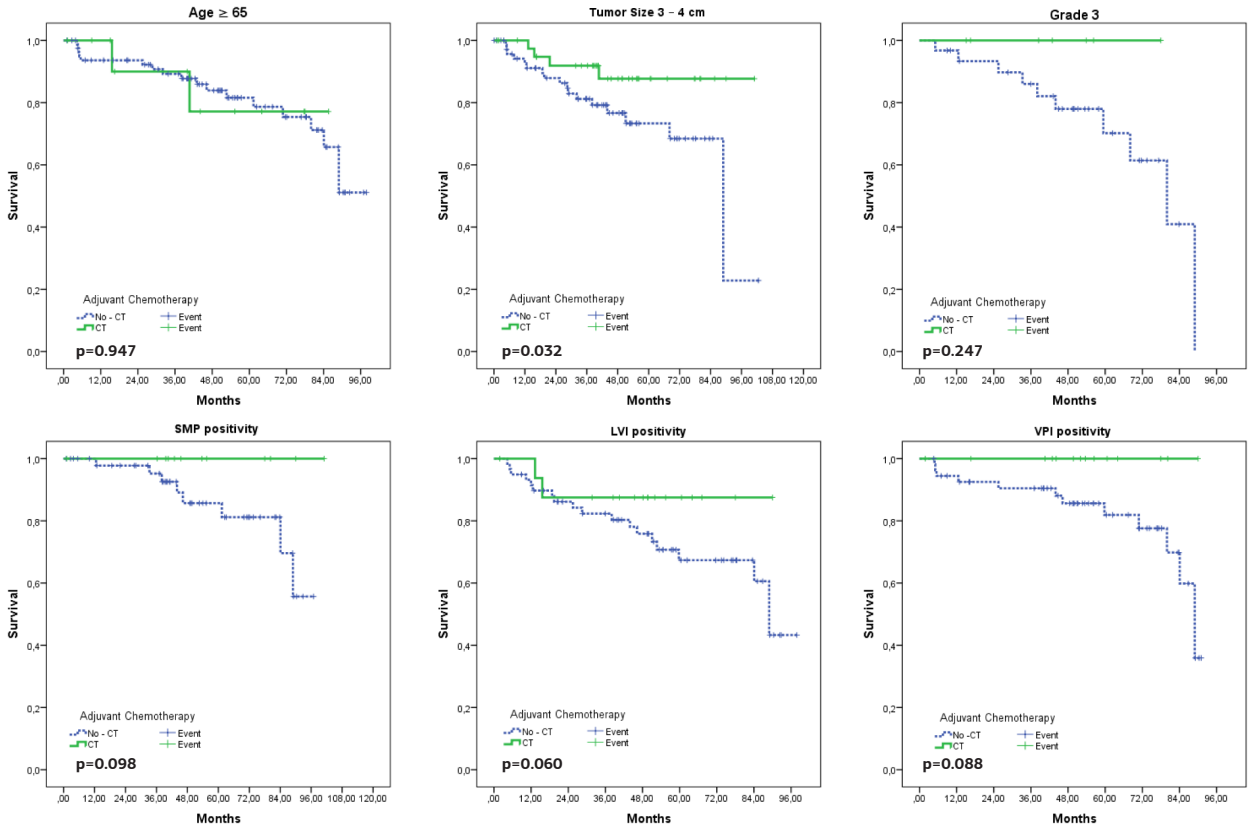

Figure 2. Effects of adjuvant chemotherapy on cancer specific survival of patients with high risk factors. CT: chemotherapy, SMP: Solid - micropapillary component, LVI: lymphovascular invasion, VPI: visceral pleural invasion

Table 4. Cox regression analysis

Factors	*RFS*		*CSS*		*OS*	
	HR (95% CI)	*p value*	*HR (95% CI)*	*p value*	*HR (95% CI)*	*p value*
Age	1.32 (0.78-2.24)	0.31	1.16 (0.57-2.33)	0.69	1.39 (0.76-2.52)	0.29
Tumor size	1.75 (1.01-3.02)	0.046	2.17 (1.05-4.49)	0.038	2.04 (1.08-3.86)	0.03
LVI	1.48 (0.87-2.52)	0.15	2.31 (1.13-4.71)	0.022	2.65 (1.45-4.85)	0.002
VPI	0.94 (0.53-1.65)	0.82	0.77 (0.36-0.65)	0.51	0.60 (0.31-1.15)	0.12
Adjuvant CT.	0.26 (0.10-0.68)	0.006	0.36 (0.12-1.08)	0.07	0.75 (0.35-1.62)	0.47
Histology	1.02 (0.58-1.80)	0.93	0.74 (0.36-1.51)	0.41	0.86 (0.47-1.58)	0.63

LVI: lymphovascular invasion, VPI: visceral pleural invasion, CT: Chemotherapy, RFS: Relapse-free survival, CSS: Cancer specific survival, OS: Overall survival

LVI was determined to be independent risk factor for shorter OS, CSS, RFS, correlated with poorer outcome. Adjuvant chemotherapy was a significant independent prognostic factor for improved RFS, and a tendency for improved CSS, with hazard ratios of 0.47 and 0.36, respectively (Table 4).

Discussion

Numerous studies exist that have focused on adverse prognostic factors influencing the outcome in early-stage NSCLC. Tumor cell differentiation has been regarded as a relevant prognostic factor along with other well-defined clinical poor prognostic factors such as age, male gender and stage, in early-stage NSCLC [2,3,17-19]. Additionally, tumor size has been shown to be a strong prognostic factor in stage I disease [20,21]. In fact, each 1 cm incremental increase in tumor size is significantly associated with reduced survival, which has shaped the new T staging criteria in the revised classification of the 8th TNM staging system [18]. With regards to histologic parameters, adenocarcinoma has been identified as an independent factor with a negative impact on prognosis [2]. Nevertheless, recent studies have shown that not all adenocarcinomas share similar grim outcomes. Collaborative group efforts by the International Association for the Study of Lung Cancer (IASLC), American Thoracic Society (ATS) and European Respiratory Society (ERS) have helped classify lung adenocarcinomas by their predominant histologic patterns as lepidic, acinar, papillary and solid patterns [22]. Solid-micropapillary tumors have been identified as the group with the worst prognosis due to a high relapse rate reaching 48% for solid and 13% for micropapillary predominant adenocarcinoma, whereas predominantly lepidic adenocarcinomas show almost 100 % RFS during follow-up with acinar subtypes placed in between [23]. Also, retrospective studies have shown that patients harboring SMP components had a predilection for early and multi-site recurrence, 75% of which had been observed within 2 years [14,23]. In our cohort we had 70 patients with SMP components, 22.9% of whom had recurrence, with 43.75% relapsing within the first 2 years. Interestingly, none of the 13 patients who received chemotherapy relapsed, accounting for the significant benefit of adjuvant chemotherapy on RFS by univariate analysis in our dataset (p=0.013).

LVI and VPI have been established as significant factors associated with poor outcome in early-stage NSCLC. Aa meta-analysis evaluating 8032 patients enrolled in 20 studies with mixed histology, indicated that LVI is a prognostic indicator of poor outcome for patients with stage I lung cancer [24]. In fact, LVI has been established as a significant prognostic factor for early stage disease and tumors that are smaller than 2 cm [21,25,26]. Kudo et al highlighted the significant role of VPI and LVI as independent predictive factors for lymph node metastasis in patients with small tumor size [27,28]. In concordance with these data, it has been shown that the recurrence rate in patients with LVI and VPI positive tumors ranged between 30.9-33.8 % in a study which focused on small stage I tumors [14]. Additional evidence has been reported by Neri et al who had evaluated the effect of VPI and vessel invasion on 1601 patients with stage I disease and mixed histology. Their analyses showed that 5-year rates of RFS decreased significantly with additional risk factors. In this cohort 5-year RFS for patients with T1a and one positive factor was 72.2% and 50.9% for those who were positive for two factors, whereas RFS for T1b patients with one factor was 64.8%, and 50.6% for those with two factors. By multivariate analysis, LVI and VPI remained as the most important independent prognostic factors in their dataset [10]. Parallel to

these findings, we were able to show that presence of LVI was a significant prognostic factor for OS (63.8% *vs.* 84.2%, p=0.005) and CSS (71.7% *vs.* 88.9%, p=0.021). However, chemotherapy effectively prevented recurrences in our patients with LVI, as only two LVI positive patients (11.8 %) who received chemotherapy relapsed, which compared favorably to those who were followed with no adjuvant treatment (43.07%, p=0.046).

Prior randomized-controlled studies evaluating the role of adjuvant chemotherapy for stage I disease failed to show a significant advantage favoring adjuvant chemotherapy. A pooled analysis of approximately 4000 patients by the Lung Adjuvant Cisplatin Evaluation (LACE) Collaborative Group, reported no benefit of adjuvant chemotherapy for stage IA disease and 7% decrease on the risk of death in stage IB disease with T2N0 tumors [29]. Although updated results from the IALT study showed continued benefit with adjuvant cisplatin-based adjuvant chemotherapy through all stages, long-term follow-up data of both Cancer and Leukemia Group B (CALGB) 9633 and JBR 10 trials which focused on stage I and II patients failed to show a significant benefit of adjuvant chemotherapy in the long run despite positive results at earlier reports [30-32]. Nevertheless, the influence of tumor size as a predictor for survival benefit was shown in an exploratory joint analysis of CALGB 9633 and JBR10 studies, which revealed a statistically significant reduction in the risk of death with adjuvant chemotherapy among tumors ≥4 cm in size (HRs 0.66 and 0.69, respectively) [31,32].

Despite accumulating evidence suggesting that tumors smaller than 4 cm may have a poor outcome, especially if they harbor adverse prognostic factors as summarized above, there is little data on the role of adjuvant chemotherapy for this group of patients following surgery [10,14,21,25]. In fact, two earlier Japanese studies, reporting the results of a phase III trial and a meta-analysis showed significant survival benefit with adjuvant chemotherapy, specifically on the subgroup of tumors larger than 3 cm or VPI positivity, regardless of histological type [33,34]. A subsequent exploratory analysis of the meta-analysis indicated a survival benefit even for p-stage IA disease with tumors larger than 2 cm [35]. Nevertheless, results of these two reports could not be generalized as uracil-tegafur is not available in the Western population and a benefit of adjuvant chemotherapy in earlier stages could not be confirmed in this population.

In concordance with studies showing a poor outcome and a possible benefit with adjuvant chemotherapy in early resected NSCLC, we were able to show a significant benefit of adjuvant platin-based chemotherapy with respect to RFS in our cohort comprising patients with high risk stage I tumors measuring 2-4 cm. We also observed a trend for improved CSS, which did not reach significance, most probably due to the small sample size. The effect of adjuvant chemotherapy was more pronounced in our patients with younger age, larger tumor diameter, squamous histology, higher stage, positive for LVI, VPI and SMP components. In addition, adjuvant chemotherapy seemed to efficiently prevent recurrences in patients with LVI and SMP components. Similar to our results, in two studies evaluating the role of platinum-based chemotherapy, patients who had stage IB lung adenocarcinoma with micropapillary/solid predominant pattern had a significantly improved RFS, despite a lack of OS benefit [36,37]. Furthermore, despite the comparably larger tumor size we observed a larger survival benefit with adjuvant chemotherapy in our patients with squamous cell carcinoma as compared to the non-squamous group, which could possibly be attributed to the lower ratio of patients with VPI in the former group (27.2% *vs.* 42%, respectively; p=0.019). Although VPI was shown to be associated with a shorter RFS by univariate analysis, in the context of a larger tumor size, this finding contradicts our multivariate analysis which has failed to show an independent association of VPI with neither end-point. It is possible that there may be distinct biologic parameters involved in this contradictory finding which requires further evaluation by translational studies.

The impact of age on the efficacy of adjuvant chemotherapy was initially reported in an exploratory analysis from JBR 10 trial, which showed that elderly patients derive a similar benefit from adjuvant chemotherapy, along with similar OS and disease-specific outcomes, as compared to younger patients, despite the higher refusal rate of chemotherapy and a lower dose-intensity of agents utilized [38]. Similar results were confirmed by a combined meta-analysis of randomized trials [39]. Nevertheless, these two studies have also revealed that deaths from non-lung cancer-related causes increased with age, which possibly explains the lack of OS benefit. Combined analysis of BR 18 (which includes metastatic patients) and JBR10 trials focusing on analysis of the elderly group evaluated by the Carlson Comorbidity Index, revealed that a high comorbidity score rather than age was prognostic for OS, highlighting that comorbidity might be more important than chronological age [40]. However,

in daily practice, elderly patients are often either not offered or denied therapy, or prematurely discontinued therapy due to toxicity requiring medical care, contributing to the poor outcomes, which preclude generalizability of clinical trial results to be extended to the general older age population. In our study, only 13 elderly patients had been administered chemotherapy and two had recurrence, limiting our ability to make definite conclusions regarding the prognostic effect of age. Nevertheless, we were able to show that younger patients had a significantly higher RFS, which may be related to the more frequent use of adjuvant chemotherapy in younger patients as a confounding factor (x^2, p=0.002). This finding is similar with previous data that have reported non-adenocarcinoma histology, microvascular invasion and advanced age as poor prognostic features in early-stage disease [28]. Data from the International Adjuvant Lung Cancer Trial, patients aged 70 years or older had less benefit from chemotherapy [30,41]. In another retrospective analysis of early-stage patients, elderly patients had less use of chemotherapy and showed poorer survival results independent of chemotherapy [36]. Despite the incremental increase of elderly patients presenting with NSCLC in the population, they are underrepresented in clinical trials. Whether age constitutes a distinct biologic subgroup is not clear and needs to be addressed by further prospective trials.

There are some limitations of this study that should be mentioned. Since this is a retrospective study, patient selection bias and time trend bias are inevitable. Another limitation pertains to the heterogeneity of the treatment regimens utilized. Although all regimens were platin-based, we cannot rule out differences in administration methods and imbalances in dose intensity, which is an established prognostic factor in patients receiving adjuvant chemotherapy [30]. In addition, our sample size is too small to determine any significant differences between groups associated with chemotherapy.

The strengths of the study are that to our knowledge this is the one of the first reports that evaluate the impact of adjuvant platin-based chemotherapy in a group of high-risk NSCLC patients with very small tumors in a Cooperative Group Setting that meets high quality pathological evaluation criteria.

Although the data clearly show that adjuvant chemotherapy has substantial benefit in patients with high risk small tumors, this finding requires prospective validation. Nevertheless, we believe that it is not feasible to spend more time and financial resources on chemotherapy trials in unselected patients in this era of personalized treatment approaches. The ability to stratify patients into risk groups including prespecified factors evaluated in our study may permit a more individualized approach to adjuvant treatment recommendations. Based on our results, adjuvant platin-based chemotherapy should be considered for this subset of patients having high grade tumors, those with VPI, LVI or SMP components, especially in patients younger than 65 years. We are eagerly awaiting the results from prospective trials incorporating targeted agents and immunotherapy following adjuvant chemotherapy in NSCLC patients.

Conclusion

We found that adjuvant platin-based chemotherapy prevented disease recurrence significantly in patients with stage I NSCLC with tumor diameter 2-4 cm and high-risk factors. Adjuvant chemotherapy was a significant independent prognostic factor for improved RFS. Numerically, adjuvant chemotherapy resulted in an 11 % and 3 % benefit in CSS and OS, respectively. However, these differences did not reach statistical significance due to small sample size, as well as possible impact of post-progression therapies.

Informed consent for participate and publishing

Informed consent was obtained from patients who are alive, and from legal heirs of patient that deceased.

Authors'contribution

Conceptualization: Yesim Eralp, Naziye Ak, Fulden Yumuk; Methodology: All; Software: All; Validation: All; Formal analysis: Naziye Ak; Investigation: All; Resources: All; Data curation: Naziye Ak; Writing - original draft: All; Writing - review & editing: All; Visualization: All; Supervision: All; Project administration: All

Conflict of interests

The authors declare no conflict of interests.

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Supplementary Table S1. Distribution of demographic and pathologic variables with respect to tumor size

Factors	*2-3 cm* *n (%)*	*3-4 cm* *n (%)*	*p value*
Histology			
Squamous	30 (36.1)	53 (63.9)	0.020
Non-Sq.	76 (52.1)	70 (47.9)	
LVI			0.454
+	41 (48.8)	43 (51.2)	
-	58 (43.6)	75 (56.4)	
VPI			0.740
+	38 (48.1)	41 (51.9)	
-	65 (45.8)	77 (54.2)	
SMP			0.593
+	40 (57.1)	30 (42.9)	
-	39 (52.7)	35 (47.3)	
Grade*			0.615
1+2	46 (46.5)	53 (53.5)	
3	19 (40.4)	28 (59.6)	
Age, years			0.458
<65	56 (44.1)	71 (55.9)	
≥65	50 (49)	52 (51)	

*Grade 1 and 2 *vs.* Grade 3; for statistical comparisons. Differences within each category were analyzed by x^2 test. Sq: squamous, LVI: lymphovascular invasion, VPI: visceral pleural invasion, SMP: solid - micropapillary component

Supplementary Table S2. Distribution of demographic and pathologic variables with respect to histology

Factors	*Squamous* *n (%)*	*Non-squamous* *n (%)*	*p value*
Tumor size, cm			0.014
2-3	30 (28.3)	76 (71.7)	
3-4	53 (43.1)	70 (56.9)	
LVI			0.192
+	34 (39.5)	52 (60.5)	
-	44 (32.8)	90 (67.2)	
VPI			0.019
+	22 (26.8)	60 (73.2)	
-	59 (41.5)	83 (58.5)	
grade*			0.317
1+2	49 (49.5)	50 (50.5)	
3	21 (43.8)	27 (56.2)	
Age			0.270
<65	50 (38.8)	79 (61.2)	
≥65	35 (34)	68 (66)	
Adjuvant CT			0.434
+	20 (39.2)	31 (60.8)	
-	65 (36.7)	112 (63.3)	

*Grade 1 and 2 *vs.* Grade 3 for statistical comparisons. Differences within each category were analyzed by x^2. LVI: lymphovascular invasion, VPI: visceral pleural invasion, CT: chemotherapy

Supplementary Table S3. Overall survival results of patients

Factors	???	???	???	???	???	???	???
Age, years							
<65	6/36	NR	82% (±6.7)	18/80	NR	72.4% (±6.1)	0.551
≥65	4/13	NR	64.7% (±14.5)	25/82	88.9 (83.3-94.5)	75.6% (±5.3)	0.629
Histology							
Sq.	4/19	NR	77.1% (±10.2)	17/57	NR	73.3% (±6.8)	0.708
Non - Sq.	6/30	NR	76.8% (±8.6)	26/105	NR	74.4% (±5.1)	0.772
Stage*							
1a2+1a3	1/7	NR	86% (±13.2)	18/77	NR	74.8% (±5.9)	0.615
1b	9/42	NR	75.9% (±7.1)	25/85	88.9 (81.9-95.9)	73.3% (±5.6)	0.672
Tumor size, cm							
2 - 3	1/8	NR	87.5% (±11.7)	21/86	NR	78.4% (±5.1)	0.848
3 - 4	9/41	NR	75.4% (±7.2)	22/79	88.9 (72.1-105.8)	68% (±6.4)	0.285
Grade*							
1+2	7/27	NR	70.6% (±9.6)	18/65	NR	72.9% (±6.2)	0.689
3	2/7	NR	69% (±18.6)	13/32	80 (55.2-104.7)	66.6% (±9.7)	0.993
SMP (+)	1/12	NR	91.7% (±8)	10/50	NR	83% (±6.4)	0.330
LVI (+)	5/17	NR	70.6% (±11.1)	25/60	85.1 (64.5-105.7)	62.4% (±6.9)	0.617
VPI (+)	1/14	NR	92.9% (±6.9)	16/56	88.9 (82.3-95.5)	79.3% (±6.1)	0.199

1Log Rank test, *Stage 1a2 and 1a3 *vs.* Stage 1b; Grade 1 and 2 *vs.* Grade 3 for statistical comparisons. NR: Not reached, Sq: Squamous, SMP: Solid - micropapillary component, LVI: lymphovascular invasion, VPI: visceral pleural invasion