THE EFFECT OF CHEMORADIOTHERAPY ON SURVIVAL IN LOCALLY ADVANCED UNRESECTABLE NON-SMALL CELL LUNG CANCER PATIENTS: EXPERIENCE FROM THE SOUTHEAST REGION OF TURKEY

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ABSTRACT

Introduction*: Lung cancer is the leading cause of cancer mortality worldwide. Smoking cigarettes is the predominant risk factor. Chemotherapy (CT) plays an integral part in treating locally advanced-non-small cell carcinoma of the lung (LA-NSCLC) as it improves survival in all subgroups of patients. In this study, our aim was to perform a retrospective overview of our data in LA-NSCLC patients and to explore which CT regimen is more effective during chemoradiotherapy (CRT).*

Materials and methods*: One hundred and thirty-two patients were included in this study. Seventy-six of the patients received 60 Gy radiotherapy (RT) concomitantly with chemotherapy at a weekly dose of 20 mg/m2 docetaxel and 20 mg/m2 cisplatin (P). Five patients received P 50 mg/m2 intravenously (IV) on days 1, 8, 29, and 36 as well as etoposide (E) 50 mg/m2 IV on days 1-5 and 29-33 concurrently with 60 Gy chest RT. Nine patients received weekly doses of carboplatin AUC 2 and paclitaxel 50 mg/m2 and forty-two patients received only cisplatin 20 mg/m2 concurrently with 60 Gy chest RT.*

Results*: The median age of the deceased patients was 61.20±9.96 and 57.70±8.60 for surviving patients. Following concomitant CRT, 26 patients (20%) showed complete response and 66 (50%) showed partial response (total response rate was 70%). The median follow-up period was 22 months (range: 8-36 months). Esophagitis developed in ten (13%) patients, neutropenia in fifteen (9%) patients and pneumonitis in eleven (12%) patients, as grade III-IV toxicity advanced due to concomitant CRT. Consolidation chemotherapy was given to patients with partial response.*

Conclusio*: There are no clinical trials that have established the optimal regimen for concurrent CRT. In our study, the most effective regimen with CRT was carboplatin and paclitaxel. This finding should be evaluated in larger clinical trials.*

Key words*: Locally advanced lung carcinoma, chemoradiotherapy, survival.*

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Introduction

Lung cancer is the leading cause of cancer mortality worldwide. In 2015, an estimated 221, 200 new cases (115, 610 in men and 105, 590 in women) of lung and bronchial cancer will be diagnosed and 158, 040 deaths (86, 380 in men and 71, 660 in women) are estimated to occur because of the disease[1]. After diagnosis, only 16.8% of all patients with lung cancer live beyond 5 years[2].

The majority of data examining the epidemiology of lung cancer comes from the developed world, where smoking cigarettes is the predominant risk factor. In the developing world additional risk factors, such as smoke and air pollution, may be particularly important[1,2]. There are substantial variations in lung cancer incidence between different countries and between men and women. These differences are a reflection in large part of differences in the prevalence of smoking tobacco. Lung cancer mortality has been and continues to be more

common in men than women[2]. However, the magnitude of this difference continues to decline due to increases in the female lung cancer mortality rate while the mortality rate in males has decreased[3,4].

Numerous occupational and environmental carcinogens increase the risk of lung cancer. The best known factors are asbestos and radon. Other exposures that have been associated with lung cancer include arsenic, bis-chloromethyl ether, chromium, formaldehyde, ionizing radiation, nickel, polycyclic aromatic hydrocarbons, hard metal dust, and vinyl chloride. Many of these factors act synergistically with tobacco smoke to produce lung cancer, and are also independent risk factors in nonsmokers[5-7]. Second hand smoke is also a significant cause of lung cancer. Other pulmonary diseases that are associated with inflammation (pulmonary fibrosis, chronic obstructive pulmonary disease, alpha-1 antitrypsin deficiency, tuberculosis) have been associated with a statistically significant increase in the incidence of lung cancer[8-12].

The clinical manifestations of lung cancer can be due to intrathoracic effects of the tumor (eg. cough, hemoptysis, pleural disease), extrathoracic metastases (most commonly, liver, bone, brain), or paraneoplastic phenomena (eg, hypercalcemia, Cushing's syndrome, hypercoagulability disorders, as well as various neurologic syndromes)[13-15].

Surgery remains the cornerstone of treatment for early-stage non-small cell lung cancer. Chemotherapy is an integral part in the treatment of LA-NSCLC as it improves survival in all subgroups of patients, whether treated with surgery or radiotherapy, as shown in meta-analyses based on individual patient data[16,17]. The optimal chemotherapy regimen has not been investigated in randomized trials that were specifically designed for this purpose. Two to four cycles of cisplatin-based doublet chemotherapy are recommended. Combined CRT is considered the standard care for unresectable stage III NSCLC[18]. This recommendation is based on the results of two large randomized controlled trials (RCT) and a meta-analysis[19-21]. There have been limited data comparing outcomes of different agents used for CRT. While radiation therapy has become safer and more effective, investigators are still studying which drugs should be combined and how to optimally administer these agents in conjunction with radiation. In this study, our aim was to complete a retrospective overview of our data in LA-NSCLC patients and to explore which regimen is most effective.

Materials and methods

This retrospective study was performed at our oncology department. Patients' files with NSCLC who admitted to our hospital between 2010 to 2014 were scanned. Eligible patients had stage I, II, IIIA or IIIB NSCLC, baseline performance status of 0 to 1 and less than 5% weight loss. Stage I and II NSCLC patients were not eligible for surgery due to comorbidities so curative concomitant chemoradiotherapy was applied. One hundred and thirty-two patients were included in this study. Seventy-six of the patients received 60 Gy radiotherapy (RT) and weekly 20 mg/m^2 docetaxel and 20 mg/ m^2 cisplatin (P) chemotherapy concomitantly. Five patients received P 50 mg/m^2 intravenously (IV) on days 1, 8, 29, and 36 and etoposide (E) 50 mg/m^2 IV on days 1-5 and 29-33 concurrently with chest RT to 60 Gy. Nine patients received weekly carboplatin AUC 2 and paclitaxel 50 mg/m^2 and forty-two patients received only cisplatin 20 mg/m^2 concurrently with 60 Gy chest RT.

Three-dimensional CT (computed tomography) simulation was used for treatment planning. Radiotherapy for all the patients consisted of 60 Gy administered as 30 fractions over 6 weeks. A total of 40 Gy was delivered with 6-10 MV photons using anterior-posterior opposed fields that included the primary tumor, metastatic lymph nodes and regional nodes. A booster dose of 20 Gy was delivered to the primary tumor and the metastatic lymph nodes. The clinical target volume included the gross tumor volume, including the primary tumor and metastatic nodes (>1 cm at the shortest dimension), plus a 0.5 cm margin. The regional nodes, excluding the contra-lateral hilar nodes, were also included in the clinical target volume.

Median overall survival (OS) was defined as the time from the initiation of the treatment to death from any cause or the last follow-up. The patients who remained alive were evaluated at the date of the last follow-up.

Statistical analysis

Descriptive statistics for the studied variables (characteristics) were presented as mean, standard deviation, minimum and maximum values. Survival analysis was performed to determine the median survival time for the groups. The Kaplan-Meier method was used to estimate the survival of patients. In addition, the Cox regression model was also used to explore the relationships between the survival of a

patient and several explanatory variables.

Statistical significance level was considered as 5 % and SPSS (Statistical Package for the Social Sciences) 19.0 for Windows (SPSS Inc., Chicago, USA) Statistical software was used for all statistical computations.

Results

	Mean(a) day				Median (day)			
	Estimate	Sandard Error	95% Confidence Interval		Estimate	Sandard Error	95% Confidence Interval	
			Lower Bound	Upper Bound			Lower Bound	Upper Bound
PFS 914,087	58.742	798.953	1029.221		854.000	57.818	740.676	967.324
OS 1242,064	73.896	1097.228	1386.901		1288.000	177.075	940.934	1635.066

Table 2: Means and Medians for PFS and OS.

		Exitus		Alive		p
Age		61,20±9,96		57,70±8,60		**0,034**
Gender	**Male**	58	90,60%	62	91,20%	0,912
	Female	6	9,40%	6	8,80%	
Phase 1 RT dose		44,61±7,16		46,62±8,18		0,137
Phase 2 RT dose		60,63±7,6		61,51±1,49		0,439
Pathology	**Adenocarcinoma**	37	57,81%	38	55,88%	0,847
	SCC	21	32,81%	25	36,76%	
	Other	6	9,38%	5	7,35%	
Tumor dimension	**T1**	0	0,00%	7	10,29%	**0,0001**
	T2	14	21,88%	42	61,76%	
	T3	39	60,94%	13	19,12%	
	T4	11	17,19%	6	8,82%	
Lymph node status	**N0**	3	4,69%	17	25,00%	**0,0001**
	N1	5	7,81%	14	20,59%	
	N2	46	71,88%	35	51,47%	
	N3	10	15,63%	2	2,94%	
Metastasis	**M0**	64	100,00%	66	97,06%	0,167
	M1	0	0,00%	2	2,94%	
Staging	**PET**	52	81,25%	61	89,71%	0,368
	MRI	6	9,38%	4	5,88%	
	CT	6	9,38%	3	4,41%	
Chemotherapy Protocol	**Cisplatin**	27	42,19%	15	22,06%	**0,001**
	Cisplatin+Etoposide	3	4,69%	2	2,94%	
	Carboplatin+Paclitaxel	8	12,50%	1	1,47%	
	Cisplatin+Docetaxel	26	40,63%	50	73,53%	
Stage	**I**	0	0,00%	13	19,12%	**0,0001**
	II	8	12,50%	17	25,00%	
	IIIA	41	64,06%	30	44,12%	
	IIIB	15	23,44%	8	11,76%	

Table 1: General characteristics of patients who received CRT.

(RT: radiotherapy; SCC: squamous cell carcinoma of the lung; PET: positron emission tomography; MRI: magnetic resonance imaging, CT: computed tomography)

The general characteristics of the patients were summarized in Table 1.

The median age of the deceased patients was 61.20±9.96 and it was 57.70±8.60 for surviving patients. One hundred twenty patients were men and the remaining were women. Seventy-five patients had adenocarcinoma, forty-six patients had squamous cell carcinoma and eleven were non-specified NSCLC. Staging was done by PET-CT (Positron Emission Tomography), MRI (Magnetic Resonance Imaging) and CT. Following concomitant CRT, 26 patients (20%) showed complete response and 66 (50%) showed partial response (total response rate was 70%). The median follow-up period was 22 months (range: 8-36 months). Mean-median PFS (progression free survival) and OS (overall survival) of patients were summarized in Table 2. The median PFS and OS did not differ according to pathology for patients who received CRT.

Consolidation chemotherapies (cisplatin+gemcitabine, erlotinib, docetaxel, paclitaxel+carboplatin, gemcitabine, vincristine) were given to patients with partial response. PFS of patients according to CT subtype were not statistically significant (Table 3, Figure 1) but OS of patients who received carboplatin and paclitaxel were statistically significantly longer (Table 4, Figure 2). The OS of patients according to stages was statistically significant (Figure 3). PFS and OS according to consolidation CT after relapse were summarized in Tables 3, 4 and Figures 1, 2. Due to concomitant CRT, patients developed grade III-IV toxicity. This resulted in ten patients (13%) contracting esophagitis, fifteen (9%) suffering from neutropenia, and eleven (12%) who were affected by pneumonitis.

According to our data, the most effective chemotherapy regimen for concurrent CRT was carboplatin and paclitaxel (p= 0.01).

CT Protocol	Mean(a) (day)				Median (day)			
	Estimate	Standard Error	95% Confidence Interval		Estimate	Standard Error	95% Confidence Interval	
			Lower Bound	Upper Bound			Lower Bound	Upper Bound
cisplatin	835.892	88.72	662.001	1009.782	714	151.987	416.105	1011.895
paclitaxel+carboplatin	**1562**	0	1562	1562	1562	.	.	.
docetaxel+cisplatin	874.705	69.488	738.507	1010.902	854	49.886	756.224	951.776
cisplatin+etoposide	594	89.257	419.055	768.945	620	185.345	256.724	983.276
Overall	914.087	58.742	798.953	1029.221	854	57.818	740.676	967.324

Table 3: PFS according to chemotherapy (CT) subtype.

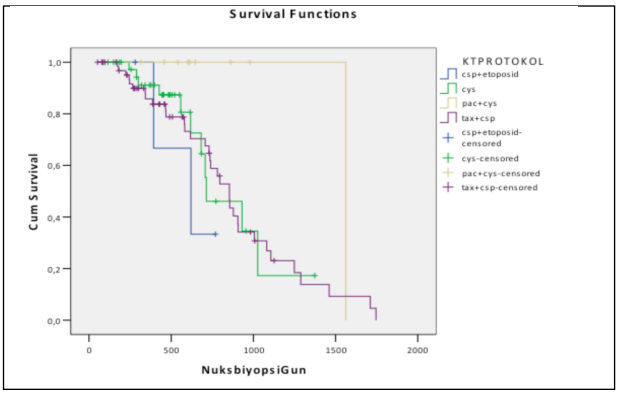

Figure 1: Kaplan-Meier analysis for PFS according to CT subtype.

Discussion

Stage III NSCLC includes a highly heterogeneous group of patients with differences in the extent and localization of disease. The optimal management depends upon multiple factors, including the specific combination of tumor (T) and node (N) staging parameters, the potential to achieve a complete surgical resection of all diseased areas if indicated, and the patient's overall condition and preferences.

There are no clinical trials that have established the optimal regimen for concurrent CRT.

Ct Protocol	Mean(a)				Median			
	Estimate	Standard Error	95% Confidence Interval		Estimate	Standard Error	95% Confidence Interval	
			Lower Bound	Upper Bound			Lower Bound	Upper Bound
cisplatin	1356.063	105.267	1149.74	1562.387	.	.	.	.
paclitaxel+carboplatin	**1803**	170.413	1468.991	2137.009	1562	.	.	.
docetaxel+cisplatin	1075.025	75.385	927.27	1222.78	1006	136.795	737.881	1274.119
cisplatin+etoposide	620	0	620	620	620	.	.	.
Overall	1249.597	74.165	1104.233	1394.96	1288	186.528	922.406	1653.594

Table 4: OS according to chemotherapy subtype.

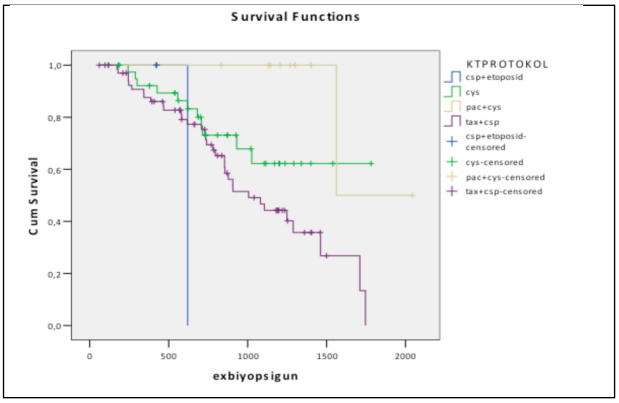

Figure 2: Kaplan-Meier analysis for OS according to CT subtype.

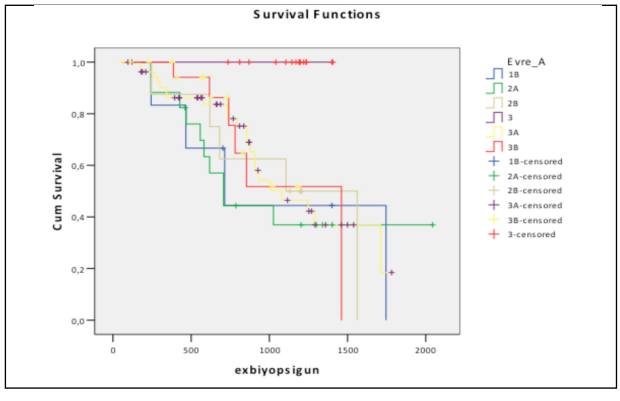

Figure 3: Kaplan-Meier analysis for OS according to stages of patients.

In the absence of such trials, no strict recommendation can be given as to the best combination. Some regimens may be associated with increased incidence of pulmonary toxicity, particularly those including gemcitabine[22]. Widely used regimens include a full dose combination of cisplatin plus etoposide, in conjunction with once daily RT to a dose of approximately 60 Gy, which is followed by two additional cycles of cisplatin plus etoposide[23,24]. An alternative "radiosensitizing chemotherapy" approach uses weekly carboplatin plus paclitaxel with approximately 60 Gy of radiation, followed by two cycles of consolidation with this same chemotherapy combination at standard doses[25]. While the combination of carboplatin and pemetrexed with thoracic radiation is safe[26], a phase III trial to test this regimen was closed early due to futility.

In the EORTC (European Organization for Research and Treatment of Cancer) trial, patients with unresectable N2 disease who showed at least a minimal tumor response after three cycles of very heterogeneous induction chemotherapy protocols; patients were randomized between radiotherapy (60 Gy in 30 fractions in 6 weeks) and surgery[27]. No survival differences were observed. The preferred treatment of unresectable LA-NSCLC is definitive concurrent chemotherapy and radiotherapy with a dose no less than the biological equivalent of 60 Gy in 2.0 Gy fractions.

Induction chemotherapy followed by radiotherapy (mostly to a dose of 60-66 Gy in 30–33 fractions over 6-7 weeks), so-called sequential CRT, was compared with concurrent CRT to the same dose in many phase III trials and in a meta-analysis[28]. Concurrent chemotherapy and radiotherapy lead to higher 5-year survival rates at the cost of a higher rate of reversible esophagitis. In fit patients, this is the standard treatment.

There is no evidence that either induction chemotherapy prior to concurrent CRT or that consolidation chemotherapy after concurrent CRT improve overall survival. However, if the tumor cannot be encompassed within an RT treatment portal with an acceptable risk of radiation pneumonitis, induction chemotherapy may facilitate subsequent concurrent CRT or definitive RT. Following concurrent CRT, surgery is reasonable for carefully selected, otherwise healthy patients with non-bulky mediastinal lymph node involvement whose tumor can be resected with a lobectomy. Whether surgical resection after CRT improves survival compared with definitive CRT alone is uncertain.

In our study, patients were treated with different types of chemotherapy regimens during radiotherapy but the most effective was carboplatin and paclitaxel. This finding should be evaluated in larger clinical trials.

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