ORIGINAL RESEARCH

RADIOTHERAPY AS THE PRIMARY AND PALLIATIVE TREATMENT FOR PATIENTS AGED 75 AND OVER WITH LOCALLY ADVANCED AND METASTATIC NON-SMALL CELL LUNG CANCER: ANALYSIS OF 45 CASES WITH A REVIEW OF THE LITERATURE

Görkem Aksu[1], Merdan Fayda[1], Mert Saynak[2], Esra Kaytan Saglamer[3], Ethem Nezih Oral[3], Ahmet Kizir[3], Ahmet Karadeniz[3]

[1]Kocaeli Tıp Fakültesi, Radyasyon Onkolojisi, Kocaeli, Türkiye [2]Trakya Tıp Fakültesi, Radyasyon Onkolojisi, Edirne, Türkiye [3]İstanbul Üniversitesi Onkoloji Enstitüsü, Radyasyon Onkolojisi, İstanbul, Türkiye

ABSTRACT

Aim: To evaluate the prognostic factors and treatment results of Turkish patients aged 75 and over with locally advanced and metastatic non-small cell lung cancer (NSCLC).

Patients and Methods: Forty-five patients ≥ 75 years were evaluated. The median age was 78 (75-93). Thirty-four patients (75%) had stage IIIB and 11 patients had stage IV disease (25%). Fourteen patients (41%) with stage IIIB disease were treated with curative radiotherapy (RT), 18 patients (52%) with palliative RT and 2 patients (5%) were treated with only chemotherapy (CT).

Results: The one-year survival rate was 37%. The overall median survival was 12.7 months in stage IIIB and 7.67 months in stage IV. In univariate analysis, advanced stage (p=0.0006), performance status (p=0.056), absence of radiotherapy (p=0.0008) and weight loss (p=0.0053) adversely affected survival. In multivariate analysis only stage IV was found to be a statistically significant independent poor prognostic factor (p=0.0025 HR=0.2760 (0.12-0.60) 95% confidence interval).

Conclusion: In Turkish patients, with NSCLC, aged 75 or over, stage IV disease was associated with poor prognosis. The higher radiotherapy doses did not improve survival in patients with stage IIIB disease and the prognosis with only radiotherapy is similar to the results of chemoradiation in the literature in this age group.

Keywords: Elderly, Lung cancer, Prognostic factors, Radiotherapy, Chemotherapy

75 YAŞ VE ÜZERİ LOKAL İLERİ VE METASTATİK KÜÇÜK HÜCRELİ DIŞI AKCİĞER KANSERİNDE PRİMER VE PALYATİF TEDAVİ OLARAK RADYOTERAPİ UYGULAMASI: 45 VAKANIN DEĞERLENDİRİLMESİ VE LİTERATÜR İNCELEMESİ

ÖZET

Amaç: Lokal ileri veya metastatik KHDAK tanılı hastalarda prognostik faktörler ve tedavi sonuçlarının değerlendirilmesi

Hastalar ve Yöntem: Yetmiş beş yaş ve üzeri toplam 45 KHDAK tanılı hasta değerlendirildi. Medyan yaş 78 idi (75-93). Otuz dört hasta Evre IIIB (75%), 11 hasta (25%) ise Evre IV olarak evrelendirildi. Evre IIIB tanılı hastaların 14 tanesine (41%) küratif Radyoterapi (RT), 18 hastaya (52%) palyatif RT uygulanırken, 2 hasta (5%) sadece kemoterapi (KT) aldı.

İletişim Bilgileri:
Görkem Aksu, M.D.
Kocaeli Tıp Fakültesi, Radyasyon Onkolojisi, Kocaeli, Türkiye
e-mail: aksugorkem@yahoo.com

Marmara Medical Journal 2008;21(1);011-020

Bulgular: Bir yıllık genel sağkalım oranı %37 olarak tespit edildi. Medyan sağkalım; Evre IIIB hastalarda 12.7 ay olarak bulunurken, Evre IV hastalarda 7.67 ay olarak gözlendi. Tek değişkenli analizde, ileri evre (p= 0.0006), performans durumu (p=0.056), RT uygulanmaması (p=0.0008) ve kilo kaybı (p=0.0053) sağkalımı olumsuz olarak etkileyen faktörler olarak tespit edildi. Çoklu değişkenli analizde ise; sadece Evre IV hastalık, anlamlı kötü prognostik faktör olarak bulundu (p=0.0025 HR=0.2760 (0.12-0.60) 95% güvenlik aralığı).

Sonuç: ≥ 75 yaş KHDAK tanılı Türk hastalarda, evre IV hastalığın kötü prognozla ilişkili olduğu saptandı. Evre IIIB hastalıkta ise, küratif RT dozlarının sağkalımı iyileştiremediği ancak, tek başına RT ile elde edilen sağkalımın, bu yaş hasta grubunda literatürde kemoradyoterapi ile elde edilen sonuçlara benzer olduğu tespit edildi.

Anahtar Kelimeler: Yaşlı, Akciğer kanseri, Prognostik faktörler, Radyoterapi, Kemoterapi

INTRODUCTION

Lung cancer is still the leading cause of cancer death in developed countries. NSCLC accounts for 80% of all lung cancers and about one-third of all patients with NSCLC are older than 70 years of age[1,2]. Older age is an independent and important factor for evaluating patients' prognosis in many diseases, since the choice of treatment is more difficult in elderly patients because of the higher incidence of co-morbid conditions. The cytotoxic nature of the cancer treatment can also have a more hazardous effect on elderly patients. Therefore; although it is clear that a combination of chemotherapy and radiotherapy is more effective than using these treatment modalities alone in locally advanced NSCLC, some of the elderly patients are contraindicated for the combination therapy because of accompanying cardiovascular or pulmonary diseases. In such cases, the choice of treatment is radiotherapy since it has been shown that older patients with good functional status tolerate radiotherapy as well as younger patients and with the proper techniques the complication rates are within tolerable limits[1-5].

Lonardi et al evaluated the outcome of 48 patients, aged 75 years and over, treated with radiation therapy alone for locally advanced NSCLC. A median dose of 50 Gy was delivered to the primary site and mediastinum with standard fractionation. Toxicity was negligible and mainly consisted of grade I-II esophagitis. The overall median survival was 5 months, but dose-related survival was much better in patients given at least 50 Gy than in those treated with lower doses: 52% versus 35% at 6 months, and 28% versus 4% at 13 months[1].

Tombolini et al. analyzed 41 medically inoperable IIIA and IIIB elderly patients (aged > or=70 years), treated with radiotherapy alone and showed that the 2-year overall survival and disease free survivals were 27% and 14.6% respectively. Patients presenting with weight loss > 10% experienced 14% overall survival at 2 years compared to 58% for those without weight loss (p=0.0027). Patients with tumor size less than 4 cm had an overall survival rate of 64% at 2 years while patients with tumor size > 4 cm had only a 2 year survival of 7% (p=0.0009)[2].

Rengan et al. analyzed 72 patients with Stage III NSCLC and gross tumor volumes (GTV) of greater than 100 cc, who were treated with three dimensional conformal radiotherapy (3D-CRT) alone, by dividing patients into two subgroups: those treated to less than 64 Gy (37 patients) and those treated to 64 Gy or higher (35 patients). The median survival time for patients treated to 64 Gy or higher was 20 months vs. 15 months for those treated to less than 64 Gy (p=0.068). The 1-year and 2-year local failure rates were 27% and 47%, respectively, for Stage III patients treated to 64 Gy or higher, and 61% and 76%, respectively, for those treated to less than 64 Gy (p=0.024). The results showed that a 10 Gy increase in dose resulted in a 36.4% decreased risk of local failure and the authors concluded that administration of higher doses using 3D-CRT improves local control in Stage III NSCLC patients with large GTV's[3].

The results of these trials show that radiotherapy is also a good treatment for locally advanced NSCLC in elderly patients, assuring good quality of life, high rates of relief of symptoms and overall and disease free survival similar to those obtained with chemotherapy and chemotherapy plus radiotherapy.

Regarding these results, we evaluated the demographic features, treatment outcomes, prognostic factors, toxicity and tolerability profiles of Turkish patients aged 75 or over with locally advanced and metastatic NSCLC and reviewed the recent literature.

PATIENTS AND METHOD

Forty-five patients with stage IIIB and IV NSCLC aged 75 years or over, referred to our clinic between 1993 and 1999. The median age was 78 (75-93). 42 patients (93%) were male and 3 patients (7%) were female. The male:female ratio is different from the rest of the European countries probably because smoking is far less common among Turkish women than among other European women. Histopathologically, 32 patients (71%) had epidermoid carcinoma and 13 (29%) had adenocarcinoma. 34 of 45 patients (76%) were in stage IIIB and 11 of them (24%) were in stage IV. The metastatic pattern of these 11 patients was: four patients had lung metastases, three patients had brain metastases, one patient had brain and lung metastases, one patient had renal, brain and bone metastases, one had liver and the other both liver and surrenal metastases. 42 of 45 patients (93%) had a smoking history. Lactate dehydrogenase (LDH) levels were found elevated (above 400 IU/lt) in 4 patients (8%). An anemia (hemoglobin level below 12g/dl) was found in 18 patients (40%). ECOG performance status was 0 in 5 patients (11%), 1 in 30 patients (68%) and 2 in 10 patients (22%). Fourteen patients (31%) received radical radiotherapy. 24 patients (53%) were treated with palliative thoracic radiotherapy. Four patients (9%) received only chemotherapy. One patient (2%) received both curative radiotherapy and chemotherapy. Due to poor performance status, two patients (4%) had only supportive care. The treatments chosen for each stage are shown in Table I. The median follow-up time was 9.87 months.

Table I. Treatment according to the stage and performance status.

	Performance Status	Curative RT*	Palliative RT*	CT	Curative RT+CT	Best supportive care
Stage IIIB	ECOG=0	1	3¥	--	1	--
	ECOG=1	11	13¥	2	--	--
	ECOG=2	1	2	--	--	--
Stage IV	ECOG=0	--	--	--	--	--
	ECOG=1	1¶	2	1	--	--
	ECOG=2	--	4	1	--	2

* Curative radiotherapy doses were accepted as 55 Gy and above. Palliative RT was accepted as doses below 55 Gy.
¥ The patients had accompanying diseases.
¶ As the patients' lung metastases could be included in a single radiotherapy field, the curative dose was given

RADIOTHERAPY: Thirty-nine patients (86%) were treated with thorax radiotherapy (RT). RT fields included the primary tumor and regional lymphatics in the ipsilateral hilum and mediastinum for all of the patients. Fourteen of 34 patients (41%) with stage IIIB, were treated with radical RT. Among these patients only one received also two cycles of cisplatin-based chemotherapy (CT). Palliative RT was defined as the doses below 55 Gy in daily 2 Gy/fraction. RT for palliative purpose was given to 24 patients (54%). The decision concerning curative versus palliative radiotherapy, was given considering the patient's performance status and co-morbid diseases. Sixteen patients with stage IIIB whose performance status was ECOG 0 and 1 did not receive radical RT doses because of accompanying co-morbid diseases (a history of ischemic heart disease in 7 patients and chronic obstructive pulmonary disease in 9 patients).

CHEMOTHERAPY: CT was applied to 5 patients (17%). Cisplatin-based chemotherapy regimens were chosen. Median 2 (2-7) cycles of CT were administered. After two cycles, the patients were re-evaluated and CT was stopped in cases of progressive disease, grade 4 neutropenia or deterioration of performance status.

STATISTICS: The statistical analysis was made using the SPSS 7.5 package program. Survival times were determined with the Kaplan-Meier method. Factors associated with poor prognosis were determined and multivariate analysis was done with the Cox-regression FORWARD:LR method.

RESULTS

The overall median survival of patients with stage IIIB was 12.7 months. In a subgroup analysis, 13 of 34 (38%) patients treated with curative RT had a median survival of 11.03 months. In contrast, median survival was found to be 13.10 months for 18 patients (52%) treated with palliative doses. The difference was insignificant (p=0.44). 2 patients (5%) at the same stage were only treated with chemotherapy and their survivals were 3.53 and 7.57 months. Only 1 patient tolerated two cycles of induction CT and radical radiotherapy and he was alive for 16.6 months.

Overall median survival of 11 patients with stage IV was 7.67 months. Six patients (53%) treated with palliative RT lived for a median of 4.67 months. Two patients (18%) treated with CT lived for a median of 7.67 months. Two patients (18%) who were only given best supportive care lived for a median of 3.80 months. One patient (1%) was treated with curative RT (lung metastasis treated with the same radiation portal) and lived for 13.43 months.

The median survival of our group was 10.33 months regardless of stage. One-year survival was 37%. In univariate analysis, stage IV disease, poor performance status, absence of radiotherapy and weight loss (10% loss in the last six months) adversely affected survival (p=0.0006, 0.056, 0.0008 and 0.0053 respectively). In multivariate analyses, only stage IV disease was found to be statistically significant (p=0.0025 HR=0.2760 (0.12-0.60) 95% confidence interval) (Figure 1). Histopathology (adeno vs. epidermoid ca), gender, treatment response (complete/partial vs. stable/progressive), haemoglobin level (12g/dl upper vs. lower) and lactate dehidrogenase level (400 IU/lt upper vs. lower) were not found to affect survival (Table II).

In the radiotherapy group, grade 1-2 dysphagia was seen in 28 patients (61%) and grade 3 dysphagia was seen in only two patients (both in radical RT group) (4%). No patient had grade 3 pneumonitis and only five patients in the radical RT group (11%) had grade 3 odinophagia. Grade 3 neutropenia was seen in three patients (6%) (Table III). In the chemotherapy group, grade 4 febrile neutropenia was seen in 3 of 5 (60%) patients. No death was directly associated with radiotherapy and chemotherapy.

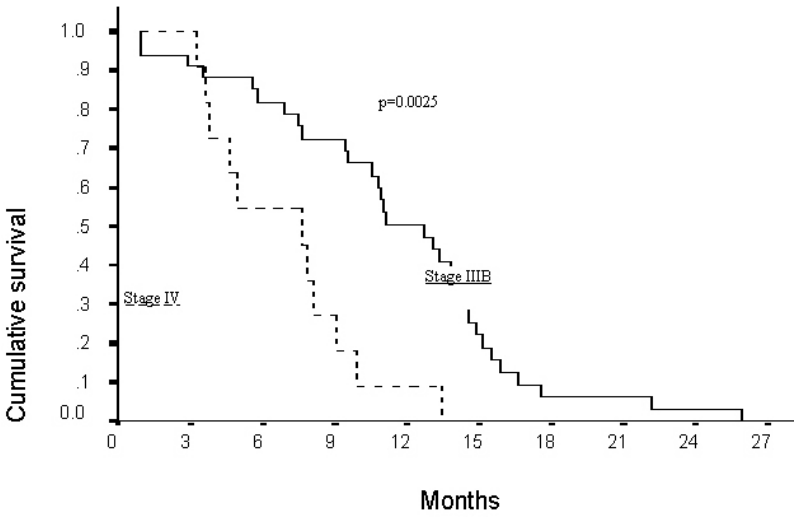

Figure 1: Stage and survival relationship.

Table II. The analysis of factors associated with survival.

		No of patients (%)	Median survival (Month)	Univariate Analysis (p)	Multivariate Analysis (p)
STAGE	Stage 3B	34 (75%)	12.70	0.0006	0.0025 HR=0.2760 (0.12-0.60) (95% CI)
	Stage 4	11 (25%)	7.67		
PERFORMANCE STATUS	ECOG =0	5 (11%)	15.5	0.056	Not significant
	ECOG=1	30 (66%)	11.03		
	ECOG=2	10 (23%)	5.0		
THORAX RADIOTHERAPY	None	6 (14%)	5	0.0008	Not significant
	Yes	39 (86%)	11.03		
WEIGHT LOSS	Yes	16 (35%)	7.50	0.0053	Not significant
	None	29 (65%)	13.10		
HISTOPATHOLOGY	Epidermoid Cancer	32 (71%)	10.9	0.16	Not computed
	Adenocarcinoma	13 (29%)	9.87		
TREATMENT RESPONSE	Stable/Progressive	15 (33%)	7.67	0.23	Not computed
	Complete/Partial Response	30 (67%)	11.10		
TREATMENT OPTIONS	Palliative thorax RT	24 (54%)	10.83	0.017	Not computed
	Curative RT	14 (32%)	12.70		
	CT	4 (8%)	3.80		
	Curative RT+ CT	1 (2%)	16.63		
	Best supportive care	2 (4%)	5		
GENDER	Male	42 (93%)	10.33	0.65	Not computed
	Female	3 (7%)	7.7		
SMOKING HISTORY	Positive	42 (94%)	10.83	0.29	Not computed
	Negative	3 (6%)	7.73		
HAEMOGLOBIN LEVEL	<12g/dl	18 (40%)	8.13	0.37	Not computed
	=12g/dl	27 (60%)	10.83		
LACTATE DEHYDROGENASE LEVEL	=400 IU/lt	4 (8%)	12.70	0.10	Not computed
	<400 IU/lt	41 (92%)	9.87		
CHEMOTHERAPY	None	40 (89%)	10.9	0.47	Not computed
	Yes	5 (11%)	7.70		

Table III. Toxicities associated with radiotherapy in 39 patients (NCI common toxicity criteria)

	Grade 1	Grade 2	Grade 3	Grade 4
Dysphagia	20 (44%)	8 (17%)	2 (4%)	--
Pneumonitis	22 (48%)	4 (8%)	--	--
Odinophagia	10 (22%)	9 (20%)	5 (11%)	--
Febrile Neutropenia	--	--	3* (6%)	--

*One patient also received chemotherapy.

DISCUSSION

The role of age as a prognostic factor for survival has been evaluated by several studies for patients with NSCLC. In a study of The Eastern Cooperative Oncology Group (ECOG), age was not a significant prognostic factor[4]. On the other hand, The Southwest Oncology Group reviewed patients with extensive-stage NSCLC and determined that being 70 years of age and older was a favorable prognostic factor[5]. The European Lung Cancer Working Party analyzed data from patients with unresectable NSCLC, treated with cisplatin- or carboplatin-based CT, and showed that increased age was associated with a significantly greater response to CT[6]. But in a different study that evaluated patients with inoperable lung cancer, age was not a significant prognostic factor. The most important prognostic factors for survival were performance status, extent of disease, and weight loss in the past six months[7].

According to these findings, it may be observed that; age alone is not a poor prognostic factor for overall survival or response to treatment for patients with NSCLC, and treatment decisions should be based on performance status rather than age. Despite these findings, there is a tendency to undertreatment older patients. Hillner et al. and Smith et al. showed more patients aged 65 years and older receive no treatment when compared with younger patients[8,9].In onfirmation of this, in our group, over half the patients with stage IIIB received palliative doses of RT and no CT was given. Older patients are also less likely to receive surgery for localized disease and CT for metastatic disease[8,9].

Another study which evaluated prognostic factors among 169 stage III NSCLC patients treated with hyperfractionated RT (64–68 Gy) with or without etoposide and/or carboplatin chemotherapy revealed that, younger age (<60 years), Karnofsky PS 80%, weight loss 5%, lower disease stage (IIIA), and female gender were all associated with improved survival[10]. The role of concurrent versus sequential chemotherapy and thoracic radiation for older patients with locally advanced NSCLC was analyzed in the Radiation Therapy Oncology Group 94–10 which compared concurrent cisplatin-based chemotherapy and thoracic radiotherapy (given once or twice daily [hyperfractionated]) versus sequential CT and RT. Data were analyzed by age (younger than 70, n = 488; 70 years and older, n = 104), revealing that older patients had a survival benefit with concurrent chemotherapy and radiation compared with sequential treatment. The risks for Grade 3 neutropenia and Grade 4 toxicities were increased in the older patient, but there was no difference in long-term toxicity. Grade 4 toxicities occurred mostly in older patients regardless of the treatment, but they were most common with the concurrent daily chemotherapy and radiation schedule[11]. In our group, there was no grade 4 toxicity associated with RT and grade 2-3 toxicities were comparable with the

result of younger patients in other series. But in the CT group, 3 patients had grade 4 neutropenia, although no patient was treated with concurrent CT and RT.

In the Intergroup trial, patients under 60 years of age had superior survival rates with sequential chemotherapy and radiation (15 months sequential treatment, 12 months radiation therapy alone, and 12 months for hyperfractionated radiation). In contrast, patients over 70 years of age had superior survival rates with radiation therapy alone (13 months for radiation therapy alone; 11 months for sequential treatment). All deaths from chemotherapy toxicity occurred in patients over 70[13]. Our results are similar with these findings. The patients in our series who were treated with only curative RT, had a median survival of 12.70 months.

RT is used for both cure and palliation in patients with stage IIIB/IV NSCLC. With increasing age, the likelihood of receiving radiation is higher than with any other therapy ($P < .0008$)[9]. In a different study, it was shown that; among 1,706 patients with NSCLC, patients 65 years of age and older were more than twice likely to receive radiation for local disease (14% of patients younger than 65 versus 31% of patients 65 and older) than younger patients[8].

Although radiation can be given with curative intent to patients with early-stage lung cancer who are not surgical candidates; the survival rates are lower than those reported after surgery. In a retrospective review of patients with Stage I NSCLC (median age, 70 years) who received radiation therapy with curative intent, overall survival and recurrence-free survival rates were similar in older and younger patients, with a trend for older patients to fare better. For patients who were aged 70 years and older, the overall survival rate at five years was 34% and the median survival time was 26 months. Age did not adversely influence the tolerability or delivery of the radiation[12].

In a different study with 1,208 patients who had received thoracic irradiation, there was no significant difference in the survival rate between patients aged under 65, 65 to 70, and over 70 ($p = .82$). Age had no effect on acute or late radiation toxicity, including nausea, dyspnea, esophagitis, or weakness. Older patients, however, were more likely to experience weight loss than were younger patients ($P = .002$). Weight loss has been found to be an independent predictor of death in older community-dwelling adults, and thus close attention should be paid to nutritional status in older patients who receive radiation[14].

Pooled data from six prospective Phase II or III Radiation Therapy Oncology Group studies of patients with locally advanced lung cancer were analyzed with respect to age. Data were included for 979 patients with Stages II to IIIB inoperable NSCLC who had received one of six treatment regimens of either concurrent chemo-radiation or RT alone. Patients under 60 years of age had an improved survival rate and quality-adjusted survival scores with CT and RT compared with patients who had radiation therapy alone. Patients 60 to 70 years old had a trend toward improved outcome with combined therapy. Patients over 70 achieved the best quality-adjusted survival rate with radiation alone. For patients receiving concurrent chemo-radiation, lung and upper gastrointestinal toxicities had the greatest effect on quality-adjusted survival[15]

In summary, RT can be given with curative or palliative intent to older patients with lung cancer. Radiation alone may represent the best choice for many older persons when both toxicity and survival rate are weighed[16].

The goals of chemotherapy in stage IV NSCLC patients are to treat symptoms of the disease and lengthen survival time. In a meta-analysis of chemotherapy trials, treatment with a cisplatin-based regimen leads to a reduced risk of death by 27%, and improvement in one-year survival rate by 10% (95% CI, 5%-15%) compared with outcomes in similarly healthy patients randomized to receive best supportive care[17]. Subgroup analysis revealed no difference in benefit through age or performance status

(KPS 60%); however, most (78%) patients included in the clinical trials were under 65 years of age and patients with KPS 50% were not included. In a retrospective review of 6,232 patients over 65 years of age with Stage IV NSCLC, treatment with chemotherapy increased one-year survival rate by 9%[18].

In the ELVIS trial, which evaluated patients aged 70 years and older with Stage IIIB or IV NSCLC, Vinorelbine vs. best supportive care was compared. The results showed that, vinorelbine had improved quality of life and lengthened the one-year survival rate from 14% with best supportive care to 32%[19].

In The Multicenter Italian Lung Cancer in the Elderly (MILES) trial, which included patients aged 70 years and older, the investigators found no difference in response rates or survival rate for older patients with NSCLC who received combination chemotherapy with gemcitabine-vinorelbine compared with vinorelbine alone or gemcitabine alone. Quality of life was similar for the combination versus single-agent therapy; however, toxicity was greater for patients who received combination chemotherapy[20]. In the Southern Italian Cooperative Oncology Group (SICOG) trial which included 120 patients aged 70 years and older with Stage IIIB or IV NSCLC, patients treated with combination chemotherapy had an improved one-year survival rate (30% for gemcitabine plus vinorelbine versus 13% for vinorelbine alone) [21]. Based on the conflicting results of these Phase III trials, the benefit of single-agent versus combination chemotherapy in the older patient is an area that needs additional study.

The role of cisplatin-based combination therapy in the treatment of older patients with NSCLC is another controversial area. In ECOG 5592, the results were stratified by age (under 70 versus 70 years and older) and it was seen that there was no significant difference in response rates (p= .67) or survival rate (p= .29). Toxicity between the two groups was similar, except that older men were more likely to experience Grade 4 leukopenia than were their younger counterparts (42% versus 17%; p< .001) and they had a higher incidence of neuropsychiatric effects[22].

There is also data indicating that a cisplatin-based combination may be too toxic for an older patient. In an analysis of the Southwest Oncology Trials 9509 and 9308, 46% of the patients aged 70 and older who received vinorelbine plus cisplatin, discontinued treatment, secondary to toxicity compared with 16% of the patients who received paclitaxel plus carboplatin; but only 19% of the patients in these clinical trials were 70 years or older[23]. Our results also support these findings since three of five patients (60%) who received cisplatin based CT had grade 4 neutropenia.

The substitution of carboplatin for cisplatin may help to ameliorate toxicity. A retrospective review revealed similar response and survival rates and toxicity patterns for patients aged under 70 years, compared with those aged 70 years and older[24]. In a study from the Cancer and Leukemia Group B, which analyzed combination chemotherapy with carboplatin and paclitaxel compared with paclitaxel alone for patients with Stage IIIB or IV NSCLC; patients aged over 70 also revealed a benefit from combination chemotherapy, although this was not statistically significant[25].

The epidermal growth factor receptor tyrosine kinase inhibitor, gefitinib (Iressa; ZD1839), can also be used for patients with advanced NSCLC with disease progression or intolerance to cisplatin or carboplatin and docetaxel based on two Phase II trials[26,27].

In our series, one-year survival was 37% and overall median survival was 12.7 months in stage IIIB and 7.67 months in stage IV. In univariate analysis, advanced stage, performance status, absence of radiotherapy and weight loss adversely affected survival (p=0.0006, 0.056, 0.0008 and 0.0053 respectively). In multivariate analysis, only stage IV was found to be statistically significant, independent of poor prognostic factors (p=0.0025 HR=0.2760 (0.12-0.60) 95% confidence interval). The median

survival in our series is interesting and intriguing since most of the patients were treated with radiotherapy alone, but the survival rates were comparable with the series that used combined chemoradiotherapy. Although our study has some limitations such as its retrospective nature and the relatively small number of patients for making significant statistical comparisons it is clear that radiotherapy alone can also be a treatment of choice for patients aged over 75. Further studies evaluating the impact of chemotherapy and radiotherapy with more conformal techniques or different fractionations in this age group are warranted.

REFERENCES

1. Lonardi F, Coeli M, Pavanato G, Adami F, Gioga G, Campostrini F. Radiotherapy for non-small cell lung cancer in patients aged 75 and over, safety, effectiveness and possible impact on survival. Lung Cancer 2000; 28: 43-50.
2. Tombolini V, Bonanni A, Donato V, et al. Radiotherapy alone in elderly patients with medically inoperable stage IIIA and IIIB non-small cell lung cancer. Anticancer Res 2000; 20,:4829-4833.
3. Rengan R, Rosenzweig, KE, Venkatraman E, et al. Improved local control with higher doses of radiation in large-volume stage III non-small-cell lung cancer. Int J Radiat Oncol Biol Phys 2004;60:741-747.
4. Finkelstein DM, Ettinger DS, Ruckdeschel JC. Long-term survivors in metastatic non-small cell lung cancer: an Eastern Cooperative Oncology Group Study. J Clin Oncol 1986;4:702–709.
5. Albain KS, Crowley JJ, LeBlanc M, Livingston RB. Survival determinants in extensive-stage non-small cell lung cancer: the Southwest Oncology Group experience. J Clin Oncol 1991; 9: 1618–1626.
6. Borges, M., Sculier, JP., Paesmans, M., et al. Prognostic factors for response to chemotherapy containing platinum derivatives in patients with unresectable non-small cell lung cancer (NSCLC). Lung Cancer 1996;16: 21–33.
7. Stanley, KE. Prognostic factors for survival in patients with inoperable lung cancer. J Natl Cancer Inst 1980;65:25–32.
8. Hillner BE, McDonald MK, Desch CE, Smith TJ, Penberthy L, Retchin SM. A comparison of patterns of care of nonsmall cell lung carcinoma patients in a younger and Medigap commercially insured cohort. Cancer 1998;83: 1930–1937.
9. Smith TJ, Penberthy L, Desch CE, et al. Differences in initial treatment patterns and outcomes of lung cancer in the elderly. Lung Cancer 1995;13:235–252.
10. Jeremic B, Shibamoto Y. Pre-treatment prognostic factors in patients with stage III non-small cell lung cancer treated with hyperfractionated radiation therapy with or without concurrent chemotherapy. Lung Cancer 1995; 13: 21–30.
11. Langer C, Hsu C, Curran D, et al. Do elderly patients with locally advanced non-small cell lung cancer benefit from combined modality therapy? A secondary analysis of RTOG 94-10. Int J Radiat Oncol Biol Phys 2001; 51: 20–21.
12. Gauden SJ, Tripcony L. The curative treatment by radiation therapy alone of Stage I non- small cell lung cancer in a geriatric population. Lung Cancer 2001; 32: 71–79.
13. Sause W, Kolesar P, Taylor SI, et al. Final results of phase III trial in regionally advanced unresectable non-small cell lung cancer: Radiation Therapy Oncology Group, Eastern Cooperative Oncology Group, and Southwest Oncology Group. Chest 2000; 117: 358–364.
14. Newman AB, Yanez D, Harris T, et al. Weight change in old age and its association with mortality. J Am Geriatr Soc 2001; 49: 1309–1318.
15. Movsas B, Scott C, Sause W, et al. The benefit of treatment intensification is age and histology-dependent in patients with locally advanced non-small cell lung cancer (NSCLC): a quality-adjusted survival analysis of radiation therapy oncology group (RTOG) chemoradiation studies. Int J Radiat Oncol Biol Phys 1999; 45: 1143–1149.
16. Numico G, Russi E, Merlano M. Best supportive care in non-small cell lung cancer: Is there a role for radiotherapy and chemotherapy? Lung Cancer 2001; 32: 213–226.
17. Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomized clinical trials. Non-small Cell Lung Cancer Collaborative Group. BMJ 1995; 311: 899–909.
18. Earle CC, Tsai JS, Gelber RD, et al. Effectiveness of chemotherapy for advanced lung cancer in the elderly: instrumental variable and propensity analysis. J Clin Oncol 2001; 19: 1064–1070.
19. Effects of vinorelbine on quality of life and survival of elderly patients with advanced non-small cell lung cancer. The Elderly Lung Cancer Vinorelbine Italian Study Group. J Natl Cancer Inst 1999; 91: 66–72.
20. Gridelli C, Perrone F, Gallo C, et al. Chemotherapy for elderly patients with advanced non-small cell lung cancer: the Multicenter Italian Lung Cancer in the Elderly Study (MILES) phase III randomized trial. J Natl Cancer Inst 2003, 95: 362–372.
21. Frasci G, Lorusso V, Panza N, et al. Gemcitabine plus vinorelbine versus vinorelbine alone in elderly patients with advanced non-small cell lung cancer. J Clin Oncol 2000; 18: 2529–2536.
22. Langer CJ, Manola J, Bernardo P, et al. Cisplatin-based therapy for elderly patients with advanced non-small cell lung cancer: implications of Eastern Cooperative Oncology Group 5592, a randomized trial. J Natl Cancer Inst 2002; 94: 173–181.
23. Kelly K, Giarritta S, Akerley W, et al. Should older patients (Pts) receive combination chemotherapy for advanced stage non-small cell lung cancer (NSCLC)? An analysis of Southwest Oncology Trials 9509 and 9308. Proc Am Soc Clin Oncol 2001; 20: 329a.
24. Hensing TA, Socinski MA, Schell MJ, et al. Age does not alter toxicity or survival for patients (pts) with stage IIIB/IV non-small cell lung cancer (NSCLC) treated with carboplatin (C) and paclitaxel (P). Proc Am Soc Clin Oncol 2001; 20: 346a.
25. Lilenbaum RC, Herndon J, List M, et al. Single-agent (SA) versus combination chemotherapy (CC) in advanced non-small cell lung cancer (NSCLC): a CALGB randomized trial of efficacy, quality of life (QOL), and cost-effectiveness. Proc Am Soc Clin Oncol 2002; 21: 1a.

26. Kris MG, Natale RB, Herbst RS, et al. A phase II trial of ZD1839 ('Iressa') in advanced non-small cell lung cancer (NSCLC) patients who had failed platinum- and docetaxel-based regimens (IDEAL 2). Proc Am Soc Clin Oncol 2002; 21: 292a

27. Fukuoka M, Yano S, Giaccone G, et al. Multi-institutional randomized phase II trial of gefitinib for previously treated patients with advanced non-small cell lung cancer. J Clin Oncol 2003; 21: 2237–2246.