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Research Article

Definitive Radiotherapy for the Treatment of Non-Small Cell Lung Cancer in Patients Aged 70 Years and Older

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Abstract

Background: The factors affecting survival were evaluated in patients aged ≥ 70 years with Non-Small Cell Lung Cancer (NSCLC) treated with definitive Radiotherapy (RT).

Methods: Between January 1996 and April 2012, 52 patients were treated. The median age was 73 (range 70-80) and 73% and 75% of patients with stage III according to AJCC 2002 and AJCC 2010 staging, respectively. Radiotherapy was performed median 6160 cGy (range: 3600-6660 cGy) and CHE were given 75% of the patients.

Results: Median follow-up was 12.5 (range: 2.5-103) months. Median overall (OS) and Disease-Free (DFS) Survival were 22 and 18.5 months, respectively. Radiotherapy related death was not observed. In Univariate analysis; AJCC 2002 stage I-II, RT dose, RT duration, for OS and RT dose, RT duration, neoadjuvant CHE ≤ 3 cycles, complete response, ≥ 4 cycles of CHE for DFS were significant ($p < 0.05$). In multivariate analysis, RT duration > 49 days related with higher RT dose (≥ 60 Gy) were found a positive impact on OS (HR: 3.235, 95% CI: 1:25 to 8:32 $p = 0.01$).

Conclusion: In our study, elderly patients with NCSLC can be given ≥ 60 Gy without complications and was seen positively impact on survival.

Introduction

The median age of lung cancer patients is 70 years [1]. In clinical studies, it is reported that the number and severity of comorbid conditions increase and limit the treatment options in patients with ≥ 70 years of age [2]. It has been reported that 51% with local, 35% with regional and 27% with metastatic disease of lung cancer patients aged 65 years or older receive guidelines-recommended treatment [3]. In the SEER study, 47% of the patients were older than 70 years and it was reported that mortality due to lung cancer is increased in this age group (5-year Overall Survival (OS); 15% *vs* 12% *vs* 7%, for < 70 *vs* 70-79 *vs* > 80 years, respectively; $p < 0.0001$) [4].

Curative or palliative Radiotherapy (RT) is an important therapeutic option in elderly lung cancer patients, in whom surgical-systemic therapeutic options are limited due to multiple comorbidities. In their prospective study, Pergolizzi et al. found 5-year OS as 12% with a median 60 Gy in 40 stage IIIA patients aged ≥75 years and reported that a radiation dose of 66 Gy can be tolerated in these patients [5]. Bayman et al. performed a review including only RT studies in patients aged ≥ 70 years and reported median OS was 37 and 8 months in stage I-II and III cases, respectively [6].

For locally advanced Non-Small Cell Lung Cancer (NSCLC), current treatment approach is concurrent Chemotherapy (CHE) and RT [7]. Retrospective analysis of the RTOG 94-10 study revealed increased survival with concurrent chemo-RT as compared to sequential chemo-RT (22 *vs* 16 months, p=0.06) in those ≥ 70 years (104/595) [8]. Other studies as well reported improved survival with combined therapy in elderly patients (2-year OS 44% *vs* 7%, $p < 0.001$) and emphasized that the use of RT only and the presence of co morbidity are independent and significant poor Prognostic Factors (PF) in terms of survival [9,10].

The present study aimed to determine the factors that influence survival in elderly NSCLC patients treated with definitive RT with or without CHE in our department.

Methods

Fifty-two patients treated between January 1996 and April 2012, were retrospectively evaluated. Data were retrieved from the medical records of the patients (Table 1). Written informed consent was obtained from all patients.

All cases were staged using chest "Computed Tomography (CT)", bone scintigraphy, cranial "Magnetic Resonance Imaging (MRI)" and additionally "Positron Emission Tomography (PET/

Table 1: Clinical characteristics.

Clinical features (n: 52)	N (range/ %)	
Age (median, year)	73 (70-80)	
Sex		
Male	50 (96)	
Female	2 (4)	
KPS (median)	90 (70-100)	
Smoking		
absent	2 (4)	
present	50 (96)	
Smoking pack-year (median)	50 (0.6-186)	
Histology		
Squamous cell carcinoma	35 (67)	
Adenocarcinoma	11 (21)	
NSCLC	6 (12)	
Tumor size (median, cm)	4.5 (2-10)	
TNM staging	**AJCC 2002**	**AJCC 2010**
IA	1 (2)	3 (6)
IB	4 (8)	3 (6)
IIA	-	1 (2)
IIB	8 (15)	5 (10)
IIIA	11 (21)	22 (42)
IIIB	27 (52)	17 (32)
IV	1 (2)	1 (2)
Localization		
Right	28 (54)	
Left	24 (46)	
Neoadjuvant CHE		
absent	34 (65)	
present	18 (35)	
Neoadjuvant CHE cycles (median)	4 (1-9)	
Symptom time (median, months)	3 (0-12)	
RT dose (median, cGy)	6160 (3600-6660)	
RT fraction dose (median, cGy)	180 (180-300)	
RT duration (median, days)	49 (31-88)	
Treatment break (median, days) (n: 30)	3 (1-42)	
Concurrent CHE		
absent	30 (58)	
present	22 (42)	
weekly	11 (21)	
standart	11 (21)	
Concurrent CHE cycles (median)	2 (1-3)	
Response		
Complete	8 (15)	
Partially	31 (60)	

Stable	7 (13)
Progression	2 (4)
Unevaluated	4 (8)
Adjuvant CHE	
absent	37 (71)
present	15 (29)
Adjuvant CHE cycles (median)	3 (1-6)
Chemotherapy	
absent	13 (25)
present	39 (75)
CHE cycles (median)	4 (1-9)
Family history of cancer	
absent	36 (69)
present	16 (31)
Comorbidity (COPD, Tuberculosis, CAD, Hypertension, abdominal aortic aneurism, Diabetes, CVA)	
absent	28 (54)
present	24 (46)
preRT-Hb (median, gr/dl) (n: 50)	11.9 (9.4-15.8)
midRT-Hb (median, gr/dl) (n: 49)	11.4 (8.2-16.2)
postRT-Hb (median, gr/dl) (n: 50)	11.7 (7.2-16)
Albumin (median, gr/dl) (n: 41)	4.1 (2.8-5.1)
Body mass index (median) (n: 26)	24.1 (16.5-37.5)

CT)" after 2006. Radiotherapy was performed by a LINAC as two-dimensional RT (n: 42) before June 2008 and then as "Three-Dimensional Conformal RT (3DCRT)" or "Intensity-Modulated RT (IMRT)" (n: 10). Since the study was between 1996 and 2012 and different imaging was used, staging was done for both AJCC 2002 and AJCC 2010 and the compliance with each other and effects on survival were examined.

Multi-agent standard CHE regimens with cisplatin (paclitaxel, docetaxel, gemcitabine, etoposide) were administered as neoadjuvant, concurrent or adjuvant therapies. In patients who received concurrent chemo-RT with weekly CHE, the number of CHE cycles was calculated as the equivalent cumulative dose of standard CHE. Comorbidity status of the patients was evaluated according to the presence of pulmonary, cardiovascular, renal or neurological conditions, history of cancer and presence of diabetes [11].

Response was assessed in the 1st month by CT. Toxicity was evaluated according to the "Common Terminology Criteria for Adverse Events", version 4 [12]. The patients with local recurrence or distant metastasis at follow-up received CHE, palliative RT or supportive care.

Statistical analysis was performed in January 2016 using SPSS version 21. Overall survival was calculated from the time of diagnosis to death or last follow-up. Disease Free Survival (DFS) and Loco Regional Progression-Free Survival (LRPFS) were calculated from the time of diagnosis to progression or last follow-up. Survival was analyzed using Kaplan-Meier method with Univariate analysis (log-rank test). Cox regression analysis was used for multivariate analysis and variables were compared by chi-square test. A p value ≤ 0.05 was considered significant.

Results

The median age was 73 (range, 70-80) years, male to female ratio was 50 to 2 and the median Karnofsky Performance Status (KPS) was 90 (range, 70-100) (Table 1). One case had solitary brain metastasis at diagnosis. According to the AJCC 2002 and 2010 staging, 73% and 75% of the cases were stage III. The consistency of AJCC 2010 with AJCC 2002 staging was 33%, 67%, 80%, 57%, 94% and 100% for stage IA, IB, IIB, IIIA, IIIB and IV, respectively. Stage migration of patients to early stage was detected in AJCC 2010 staging.

Mediastinoscopy revealed nodal involvement in two of 4 cases. Pulmonary Function Tests (PFT) were available in 19 cases and the median values were as follows; FEV1 50% (range, 36-105%), FVC 69% (range, 30-108%) and FEV1/FVC 86% (range, 61-135%). Thirteen cases (54%, 13/24) had multiple co morbidities. Of the cases, 21% had ≥ 5% weight loss at diagnosis.

Radiotherapy was given at a median dose of 6160 cGy (range, 3600-6660 cGy). The median RT duration was 49 (range, 31-88) days. While the median dose of RT was 5940 cGy (range, 3600-6300 cGy) in patients with a median RT duration ≤ 49 days, it was 6300 cGy (range, 5940-6660 cGy) in those with a median RT duration > 49 days. Treatment interruption was a median 3 (range, 1-42) days in a total of 30 cases due to machine breakdown/official holiday (n: 18), hematological toxicity (n: 8), esophagitis (n: 3) and infection (n: 1). Chemotherapy was given to 75% (n: 39) of the cases with median 4

cycles (range, 1-9). Twenty-two patients received concurrent chemo-RT with standart CHE (n: 11) or weekly paclitaxel (30-60 mg/m2), vinorelbine (20 mg/m2) or cisplatin (20 mg/m2) as monotherapy (n: 11). Two cases discontinued treatment at 3600 cGy and 4800 cGy because of progression or on their own decision. Two cases could not receive the planned total dose of RT due to hematological toxicity. Compliance with RT was 92% (48/52).

Complete, objective and stabil response to treatment was 15%, 75% and 13%, respectively. Acute esophagitis and neutropenia were observed in 86% and 27%, while ≥ G3 esophagitis and neutropenia was present in 6% and 10% of the cases, respectively. Acute grade 1 and 2 pneumonia was seen in 15% and 10% of patients in a median of 3 (range, 1-5) months, respectively. Late esophagitis did not develop in any of the 43 cases, which had been followed up for six months or longer. Pulmonary fibrosis was found in 4 cases (9%, 4/43) in a median of 20 (range, 6-21) months. Two cases developed pericardial effusion in 7 and 11 months, respectively; one of these died of adrenal insufficiency, whereas the other was still alive throughout a 75-month follow-up period.

Of the 13 cases eligible for surgery at diagnosis, 5 were medically inoperable, 6 of them refused surgery and two cases were considered inoperable during thoracotomy. Two stage III cases underwent surgery after curative chemo-RT and pathological partial response was obtained. These cases died of respiratory failure or distant metastasis in 8.5 and 20 months, respectively.

Excluding the cases with progression during and immediately after treatment and those that could not be evaluated, Loco Regional Control (LRC) was 78% (36/46). Loco regional recurrence was seen in a median of 7 (range, 5-24) months in 6 (13%), distant recurrence was seen in a median of 6.5 (range, 2-28) months in 10 (21%) and loco regional plus distant metastasis was observed in a median of 26 (range, 14-56) months in 4 (9%) cases. The sites of distant metastasis were the bones (n: 5), brain (n: 4), lungs (n: 4), liver (n: 1), adrenal glands (n: 1) and distant lymph nodes (n: 2) with multiple metastasis in three cases. The causes of death (n: 33) were disease progression in 26%, complication of CHE in 12%, cardiac-respiratory failure in 15%, infection in 6%, adrenal insufficiency in 3%, second primary tumor in 3% and unknown reasons in 24%. However, 43% (7/16) of cases, which were lost to follow-up, had local/distant recurrence. A predisposing co morbid condition was present in three of six cases, which died of cardiac-respiratory failure had received median 5940 cGy (range, 5940-6300 cGy).

The median follow-up was 12.5 (range, 2.5-103) months. In the assessment, three (6%) cases were alive, 33 (63%) had died and 16 (31%) were lost to follow-up. Median and 2-year OS, DFS and LRPFS were 22 months (95% CI 12-31) and 50%, 18.5 months (95% CI 7-29) and 47%, 25 months (95% CI 15-34) and 52%, respectively.

Table 2: Univariate and multivariate analysis for survival.

Significance in univariate analysis:	**Median OS (95% CI) (months)**	***P* value**	**Median DFS (95% CI) (months)**	***P* value**
	22 (12.99-31.00)		**18.5 (7.45-29.54)**	
AJCC 2002 stage	**72.5 (0-150) *vs* 20 (9-30)**	**0.057**	72.5 (0-165) *vs* 18.5 (7-29)	0.063
I-II *vs* III-IV				
Neoadjuvant CHE cycles	Mean 58 (33-82) *vs* 23 (15-32)	0.069	**Mean 58 (33-82) *vs* 19 (11-28)**	**0.031**
≤ 3 *vs* > 3				
RT dose (Gy)	**27.5 (22-32) *vs* 12.5 (9-15)**	**0.011**	**25 (15-34) *vs* 11 (7-14)**	**0.022**
≥ 60 *vs* < 60				
RT duration (days)	**31 (0-94) *vs* 11 (8-13)**	**<0.001**	**26.5 (0-87) *vs* 10.5 (7-13)**	**<0.001**
> 49 *vs* ≤ 49				
RT dose stratification				
≥ 60 Gy	**72.5 (7-137) *vs* 7.5 (1-13)**	**0.006**	**33 (6-138) *vs* 5 (2-7)**	**0.01**
> 49 (n: 20) *vs* ≤ 49 day (n: 8)				
< 60 Gy	**13 (4-21) *vs* 12 (7-16)**	0.41	**8.5 (5-11) *vs* 11 (7-14)**	**0.739**
> 49 (n: 6) *vs* ≤ 49 day (n: 18)				
Response	Mean 62 (31-92) *vs* 25 (18-33)	0.084	**Mean 62 (31-92) *vs* 20 (14-26)**	**0.033**
Complete *vs* partial + stable				
CHE	25 (15-34) *vs* 8 (0-30)	0.081	25 (14-25) *vs* 8 (3-12)	0.073
Presence *vs* absence				
Total CHE cycles	31 (9-52) *vs* 13 (8-17)	0.067	**25 (2-47) *vs* 11 (6-15)**	**0.052**
> 4 *vs* ≤ 3 CHE				
Significance in multivariate analysis:	**HR (95% CI)**			
RT duration (days)	**3.235 (1.25-8.32)**	**0.015**		
> 49 *vs* ≤ 49				

In Univariate analysis; AJCC 2002 stage I-II (72.5 *vs* 20 months, p=0.05), RT dose ≥ 60 Gy (27.5 *vs* 12.5 months, p=0.01) and RT duration > 49 days (31 *vs* 11 months, p < 0.001) were significant factors for OS. The difference in OS was found significant when patients were stratified of the dose and duration of RT (72.5 months in those with ≥ 60 Gy and > 49 days *vs* 7.5 months in those with < 60 Gy and ≤ 49 days, p=0.006). Neoadjuvant CHE ≤ 3 cycles (mean 58 *vs* 23 months, p=0.069), receiving CHE (25 *vs* 8 months, p=0.081), CHE ≥ 4 cycles (31 *vs* 13 months, p=0.067) and complete response to RT (72.5 *vs* 22 months, p=0.084) demonstrated a trend toward improved OS (Table 2, Figure 1).

Neoadjuvant CHE ≤ 3 cycles (mean 58 *vs* 19 months, p=0.03), RT dose ≥ 60 Gy (25 *vs* 11 months, p=0.02), RT duration > 49 days (26.5 *vs* 10.5 months, p <0.001), complete response to RT (72.5 *vs* 18.5 months, p=0.03) and CHE ≥ 4 cycles (25 *vs* 11 months, p=0.05) were found significant for DFS. The difference in DFS was found significant in terms of the dose and duration of treatment (33 months in those with ≥ 60 Gy and > 49 days *vs* 5 months, p=0.01). AJCC 2002 stage I-II (72.5 *vs* 12 months, p=0.063) and receiving CHE (25 *vs* 8 months, p=0.073) demonstrated a trend toward improved DFS (Table 2, Figure 2).

Other PFs as age, KPS, smoking, T stage, N stage, AJCC stage 2010, histology, tumor size, symptom duration, treatment break, fx dose, localization, weight loss, family history, co morbidity, pre-mid-post RT Hb level, albumin level, body mass index were not found to be significant for survival (p > 0.05).

Multivariate analysis revealed that RT duration > 49 days related with higher RT dose is a good PF for OS (HR: 3.235, 95% CI: 1.25-8.32, p=0.01) (Table 2).

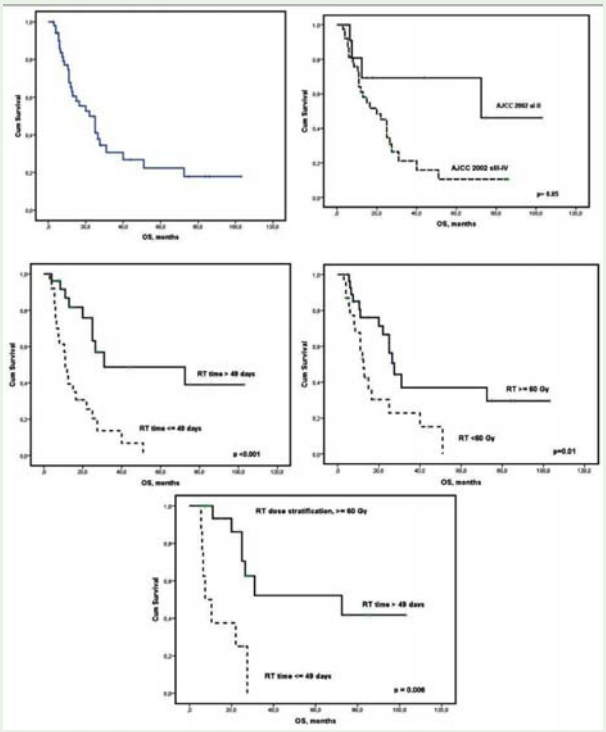

Figure 1: Overall survival and prognostic factors.

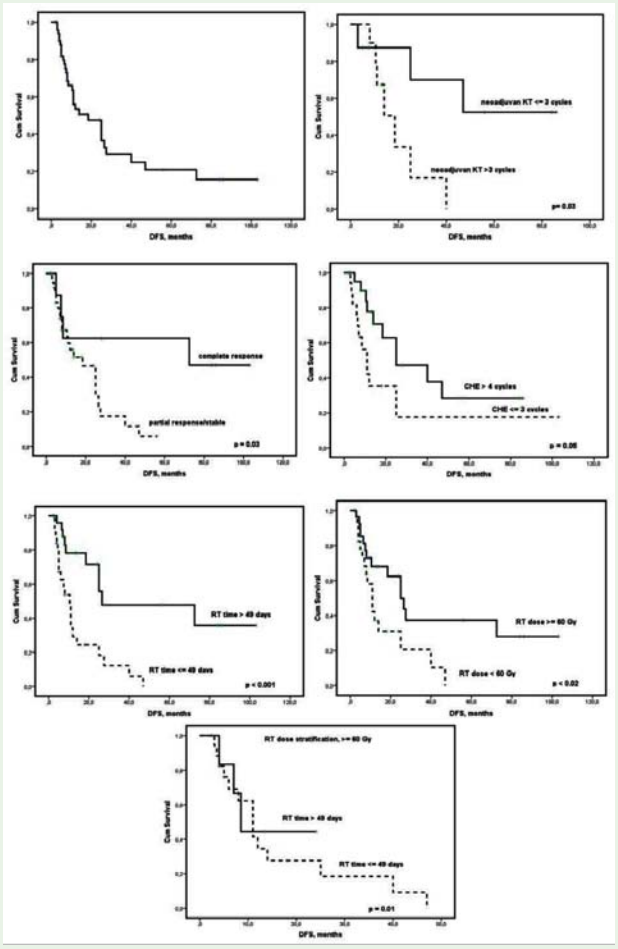

Figure 2: Disease-free survival and prognostic factors.

Discussion

The number of elderly lung cancer patients has been increased with the prolongation of human life [13]. The percentage of patients of ≥ 70-years enrolled in clinical studies is 30% and it is reported that these patients are unable to complete the treatment, have high mortality and poor survival [14,15].

In our study, all patients were ≥70 years of age and no significant relationship was determined between median age and survival. Jenssen-Heijnen et al. reported that age is a more significant PF than the presence of a co morbid disease in 4076 lung cancer patients [16]. In that study, the rate of surgery with or without RT in local disease was reported to be 92% *vs* 9%, whereas the rate of CHE with or without RT in advanced stage was reported to be 24% *vs* 2% for ages < 60 and ≥ 80, respectively. The "Swedish Lung Cancer Study Group" reported that the patients younger than 55 years have a better OS and seem to benefit more from the addition of surgery or CHE to RT in 1146 NSCLC patients treated with at least 50 Gy [17]. On the other hand, in studies on elderly patients receiving curative RT, survival rates decrease with the presence of a co morbid condition, but there is no difference with age [6]. It has been reported that increased severe pulmonary toxicities in patients have high co morbidity score treated with chemo-RT when compared RT alone and this complication also

unfavorably impacts on survival [18]. Semrau et al. reported that baseline cardiac-pulmonary dysfunction is the worst PF for survival in elderly patients receiving curative chemo-RT [15].

Sequential or concurrent chemo-RT was found to be superior to RT alone in terms of survival for lung cancer patients [7,19]. On the other hand, Hsu et al. reported the rate of receiving CHE as 73%, 41% and 12% for all cases, aged 70-79 years and ≥ 80 years, respectively [20]. The SEER study determined that 66% of the elderly NSCLC patients could receive treatment, 41% received RT alone while 45% received chemo-RT [10]. In that study, chemo-RT was found superior to RT alone with an absolute increase of 11% in one-year OS (32% *vs* 43%, p=0.001), however, concurrent chemo-RT increases mortality and thereby induction CHE would be more appropriate in geriatric cases. In our study, the rate of receiving CHE was 75% and a total of > 4 cycles of CHE were associated with an increasing trend in OS and significant for DFS. Neoadjuvant CHE was given only 9 patients with no significant difference in OS between those who received or not. Increase in DFS with ≤ 3 cycles of neoadjuvant CHE was thought to be associated with the administration of early curative RT before repopulation of the tumor cells.

Which CHE regimen is better for elderly patients remains unknown. It has been reported that treatment compliance and LRC are increased and toxicity is reduced with daily or weekly treatment and that monotherapy with 3rd generation CHE agents should be a routine practice [14]. Lilenbaum et al. compared paclitaxel monotherapy with the combination of paclitaxel and carboplatin in 561 advanced-stage cases in a randomized trial [21]. In that study, response rate and recurrence-free survival were increased with combination regimen and they failed to demonstrate any difference with age in terms of hematological toxicity. Wang et al also found that concurrent chemo-RT with standard CHE was superior to weekly CHE in terms of 3-year OS in 65 unresectable stage III cases (33% *vs* 13%, p=0.04) [22]. In a randomized study, no difference was found between concurrent chemo-RT with standard, daily and weekly CHE administered after 2 cycles of carboplatin-paclitaxel in terms of survival, emphasizing that unfavorable effect of induction CHE on tumor repopulation [23]. The incidence of esophagitis was reported to be lower (8% *vs* 20-19%) and response rate was found to be higher (70% *vs* 33-45%) in the daily chemo-RT arm in that study. Survival benefit cannot be demonstrated in the studies conducted with targeted agents yet [24].

The relationship between RT dose and LRC and survival is known. With the analysis of RTOG chemo-RT studies, 2-year OS and LRC were reported to be 38% and 46%, respectively in locally advanced NSCLC [25]. These results are associated with a 4% increase in OS and a 3% increase in LRC with a 1 Gy increase in Biologically Effective Dose (BED). It has been reported that a dose of 66 Gy can be tolerated in elderly patients, acute toxicity is more common (23%), but there is no difference in terms of G3-4 late esophagitis/pneumonia incidence (< 4%) [5,8,26]. In the randomized NCCTG trial, no difference was found between the age groups in terms of OS in the patients receiving concurrent chemo-RT, but it was reported that G4 hematological and pulmonary toxicity showed an increase with age (56% *vs* 78% (p=0.003) and 1% *vs* 6% (p=0.02), for < 70 *vs* ≥ 70 years, respectively) [27]. In a study, using definitive RT alone a total dose of 66 Gy at 30 fraction for elderly patients unfit for combined treatment was reported that median, 2-year overall and cause-specific survival rates were 19 months, 39% and 57%, respectively with no significant difference for acute toxicities with age [28]. In another study; Topkan et al. reported the median OS and LRPFS as 22 and 10.5 months, respectively with concurrent standart chemo-RT using high dose of RT (66 Gy/33 fraction) in 89 stage III cases aged ≥ 70 years with no grade 4/5 acute toxicity [29]. In the present study, the median OS, DFS and LRPFS rates were 22, 18.5 and 25 months, respectively. It was observed that complete response to RT had a favorable effect on survival. Overall and DFS were significantly better in the patients receiving 60 Gy and higher doses and no patient died of complications during RT.

There were limitations of our study. Heterogeneous CHE regimens were used and higher rate of patients lost to follow-up. Early stage patients accounted for 25% of the study population. Because of the limited patients that underwent PET/CT for diagnosis and response assessment, statistical comparison could not be made for survival analysis. Ten percent of patients died of cardiac or respiratory complications, but the negative effects of RT could not be distinguished due to already existing co morbidities.

In conclusion, age alone is not a poor PF for survival. It was observed that definitive RT at a dose ≥ 60 Gy with or without CHE can be safely used without causing complications and with a favorable impact on survival in cases over 70 years in our study. Further studies are required to evaluate combination therapy with new agents in elderly patients with no co morbidities and a good performance.

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