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ORIGINAL ARTICLE

Is re-irradiation effective in symptomatic local recurrence of non small cell lung cancer patients? A single institution experience and review of the literature

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Summary

Purpose: *To determine reirradiation results of patients with recurrent non-metastatic non-small cell lung cancer (NSCLC).*

Patients and methods: *38 NSCLC patients who showed clinical and/or radiological progression and were retreated with hypofractionated irradiation (RT) were retrospectively evaluated. Two parallel or oblique opposed fields were used for reirradiation of the recurrent tumor while excluding the spinal cord. "Improvement" and "complete or near complete response" were defined as ≥ 50% and 75-100% regression of symptoms, respectively. Log-rank test, chi-square test and Cox regression analysis were used for statistical analyses.*

Results: *Median age was 58 years (range 33-80) and only 3 patients were females. Median follow-up was 13.5 months (range 4-65). In the initial and second course of RT the total dose was 30 Gy (range 28.8-67.2) and 25 Gy (range 5-30) and the number of fractions was 10 (range 9-33) and 10 (range 1-10), respectively. The median interval between the two RT courses was 35 weeks (range 4-189). After reirradiation improvement was observed in 86% of the patients assessable for hemoptysis, in 77% with cough, in 69% with dyspnea, and in 60% with thoracic pain. After reirradiation, the median survival time was 3 months (range 0-55). Two-year survival rates from diagnosis were 28.8% and from reirradiation 5.8%. An interval more than 35 weeks between the end of initial RT and the start of reirradiation was found as the only independent prognostic factor affecting survival. No grade III-IV RTOG late side effects were observed.*

Conclusion: *In initially non-metastatic NSCLC patients, reirradiation can be a safe and effective treatment for palliation after recurrence. Large prospective studies are needed to confirm the safety, effectiveness and economical advantages of this modality.*

Key words: lung cancer, non-small cell, palliative radiotherapy, reirradiation, symptomatic recurrence

Introduction

Lung cancer represents a major problem in health care. It is one of the most frequent cancers and ranks first among cancer-related deaths [1]. Most of the patients present with advanced disease. Surgery is the standard and curative approach of the early-stage NSCLC but only 20-30% of patients can be candidates for such a treatment. The appropriate treatment in suitable patients with locally advanced stage NSCLC is concomitant chemoradiotherapy [2].

Even with an aggressive treatment, locoregional and/or systemic failure are frequent according to the Radiation Therapy Oncology Group (RTOG) data [3]. After RT 34% of patients develop isolated locoregional recurrence, while 16% show locoregional recurrence plus distant metastasis. Even after definitive doses of RT, local failure can be observed in up to 85% of patients, after evaluation with several diagnostic methods [4]. After recurrence the patient can be treated with surgery, external RT, chemotherapy (CHT), brachytherapy or with a combination of these modalities [5]. Patients with poor prognostic factors can be treated with palliative RT. Nestle et al. reported similar rates of survival and palliation in patients treated with palliative or conventional definitive RT in advanced NSCLC [6]. Sundstrom and colleagues reported similar survival and palliation rates in patients with advanced NSCLC

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treated with hypofractionated RT or 50 Gy conventional RT [7].

Reirradiation can be another option for the treatment of patients with recurrent NSCLC. However, because of concerns over lung or other normal tissue toxicities, this modality is not widely used. Up to now 8 articles exist in the literature evaluating the role of reirradiation in lung cancer [8-15].

In this study, the treatment results of reirradiation in recurrent NSCLC are reported, evaluating symptom palliation as the primary, and survival as the secondary endpoint.

Patients and methods

Thirty-eight patients who initially had non-metastatic NSCLC and who recurred after primary radiotherapy were reirradiated at Dokuz Eylul University Hospital, Radiation Oncology Department, between April 1992 and May 2006. Most of the patients (81%) were previously treated with palliative aim because of poor prognostic factors such as advanced disease not suitable for radical RT, weight loss and poor performance status. At the time of initial irradiation the clinical stage was II B in 2 (5%) patients, III A in 4 (10%) and III B in 32 (84%) patients. A total dose of 28.8-67.2 Gy in 9-33 fractions with 2-3.2 Gy per fraction was delivered during initial RT: On starting reirradiation, distant metastasis was observed in 6 (16%) patients: bone metastasis in 1, brain metastasis in 1, bone and liver metastasis in 1, bone and brain metastasis in 2 and lung metastasis in 1 patient.

All computed tomographic (CT) scans of the patients were reevaluated in order to determine the initial exact size and location of the primary lung tumors. Radiological progression was evident in all patients causing clinical distressing symptoms in 36 of them. The stage reevaluation was performed with CT scan of the chest and upper abdomen in all patients, as well as brain CT scan and bone scintigraphy if needed (clinical suspicion of metastasis in these areas). Radiological progression was defined as obvious enlargement of the primary tumor or regional lymph nodes in the follow up CTs. The major clinical symptoms were dyspnea, cough, thoracic pain, hemoptysis and superior vena cava syndrome (SVCS). Oral or written informed consent was obtained from all patients.

The aim of reirradiation was purely palliative in all patients because of poor prognostic factors. Reirradiation was defined as the second course of RT to the initially irradiated volume. All patients were simulated conventionally before reirradiation. The treatment field was tailored individually by taking into account the tumor motion during breathing observed under fluoroscopy of the simulator. Thoracic mass causing clinical symptoms or radiologically progressive disease was included in the treatment field with 1-2 cm safety margin. Elective nodal irradiation was not performed in order to minimize normal lung tissue included in the treatment field. Two oblique, parallely opposed fields were used with isocentric technique in centrally located tumors to exclude the spinal cord. Normal tissues were protected with individually prepared cerrobend alloy blocks. Patients were reirradiated with megavoltage photon beam (Cobalt ^{60}, 6 or 23 MVX). Lung density correction was not performed during both hypofractionated RT courses. A total dose of 5-30 Gy in 1-10 fractions was delivered during reirradiation to the midpoint, with daily fraction size of 2-10 Gy. There was no strict restriction for CHT either before or during reirradiation.

Disease-related clinical symptoms were subjectively evaluated to determine the effectiveness of palliative reirradiation. The symptom relief was recorded after each follow-up visit according to the general subjective perception of symptom improvement by the patient. "Improvement" was defined when a palliation rate $\geq 50\%$ was stated by the patient and "no response" when the response was $< 50\%$ within 2 months after RT. Response of $> 75\%$ was defined as "complete or near complete". The symptomatic improvement could not be evaluated in patients who died or were lost to follow-up during or just after the end of RT.

RTOG toxicity scales were used for the assessment of treatment toxicity.

The interval between the initial RT and reirradiation was calculated from the last treatment day of initial RT to the first day of reirradiation.

The exact dates of death of all patients were obtained from patient relatives by phone calls. Overall survival was calculated from the date of initial diagnosis to the date of death or last follow-up visit. In order to evaluate the impact of repeat RT on survival, another calculation was carried out from the first day of reirradiation to the date of death or last follow-up visit of the patient.

Statistical considerations

Survival analyses were performed using Kaplan-Meier method. Log-rank test, chi-square test and Cox regression hazard model were used for evaluating differences in survival, symptom relief and performing multivariate analysis, respectively. Initial tumor size (<6 vs. ≥ 6 cm), initial tumor location (central vs. peripheral), and previous irradiation aim (radical vs. palliative) were the factors assessed for symptom relief. Age (≤ 58

vs. >58 years), initial tumor size, initial tumor location, and interval (<35 vs. ≥35 weeks) between the primary RT and reirradiation were evaluated as factors influencing overall survival. SPSS version 11.0 statistical software was used to perform all statistical analysis.

Results

The median age at diagnosis was 58 years (range 33-80). All patients but 3 (8%) were males. The tumor histology was squamous cell carcinoma in 23 (60.5%), adenocarcinoma in 5 (13.2%) and unclassified NSCLC in 8 (21%) patients. Histological diagnosis could not be obtained in 2 (5.3%) patients despite the effort done (Table 1).

During the initial course of RT a median dose of 30 Gy (range 28.8-67.2) in median 10 fractions (range 9-33), and median 2-3.2 Gy per fraction were delivered to the primary tumor and metastatic lymph nodes (Tables 2 and 3). It was found that a median of 162.5 cm^2 (range 36-405) treatment field size was used during initial RT.

During the initial course of RT 10 patients received sequential, cisplatin-based CHT and 3 concurrent chemoradiotherapy.

The median interval between the two RT courses was 35 weeks (range 4-189).

During reirradiation, a median total dose of 25 Gy (range 5-30) in median 10 fractions (range 1-10), with median 3 Gy (2-10 Gy) per fraction, were delivered to the midpoint (Tables 2 and 4).

Table 1. Patient characteristics

Characteristic	*Number of patients (%)*
Age	
Years, median (range)	58 (33-80)
≤ 58	19 (50)
> 58	19 (50)
Sex	
Males	35 (92)
Females	3 (8)
Histology	
Squamous cell	23 (61)
Adeno	5 (13)
Unclassified	8 (21)
No histological diagnosis	2 (5)
Initial stage	
II B	2 (5)
III A	4 (11)
III B	32 (84)
Initial tumor size (cm)	
< 6	17 (45)
≥ 6	21 (55)
Initial tumor location	
Central	29 (76)
Peripheral	9 (24)

Table 2. Treatment characteristics

Characteristic	*Range*	*Median*
Initial RT		
Total dose (Gy)	28.8-67.2	30
Treatment field size (cm^2)	36-405	162.5
Fraction dose (Gy)	2-3.2	3
Fraction number	9-33	10
Interval between treatments (weeks)	4-189	35
Reirradiation		
Total dose (Gy)	5-30	25
Treatment field size (cm^2)	25-244.5	88.65
Fraction dose (Gy)	2-10	3
Fraction number	1-10	10

Before reirradiation 9 patients received CHT. Of these, 3 patients had progressive disease and 5 showed stable disease under CHT. In 1 patient response to CHT could not be determined. One patient received concurrent weekly cisplatin during reirradiation. The planned reirradiation course could not be completed in 5 patients. Three patients died during RT at the 5th, 7th and 9th fractions due to uncontrolled disease and 2 patients abandoned RT at the 8th and 9th fractions. The cause of death could be detected in 34 patients. Of these, 12 patients died because of distant metastasis and the other 22 patients because of uncontrolled local disease. Eleven patients out of 38 (29%) lived more than 24 months after the first diagnosis. Only one patient was alive at 65 months at the time of analysis.

In 38 patients there were 72 symptoms. Thirteen patients had only one symptom, 15 patients had 2, 6 had 3 and 2 patients had 4 symptoms. Seventeen (44.7%) patients suffered from dyspnea, 12 (31.5%) from thoracic pain, 16 (42.1%) from cough, 12 (31.5%) from hemoptysis and 2 (5%) from SVCS. The symptom palliation could not be assessed in 11 patients (2 patients had only radiological progression without any symptom, 3 patients died during reirradiation, 2 patients died within 2 days after the end of RT, 2 patients abandoned RT and

Table 3. Fractionation scheme for initial RT

Fraction number	*Fraction dose (Gy)*	*Total dose*	*Number of patients (%)*
28	2.4	67.2	1 (0.26)
33	2	66	7 (18)
27	2	54	1 (0.26)
25	2	50	1 (0.26)
12	2.5	30	3 (0.7)
11	3	33	1 (0.26)
10	3	30	23 (60)
9	3.2	28.8	1 (0.26)

Table 4. Fractionation scheme for reirradiation

Fraction number	*Fraction dose (Gy)*	*Total dose*	*Number of patients (%)*
10	3	30	15 (39)
10	2.5	25	10 (26)
10	2	20	1 (0.26)
9	3	27	1 (0.26)
9	2.5	22.5	2 (0.5)
8	3	24	1 (0.26)
7	3	21	1 (0.26)
5	4	20	2 (0.5)
5	3	15	2 (0.5)
4	1	4	1 (0.26)
1	10	10	1 (0.26)
1	5	5	1 (0.26)

died 3 and 8 weeks after RT, and 2 who finished RT but could not be seen for symptom evaluation died 2.5 and 9 weeks after reirradiation). Thus, symptom palliation could be assessed in 27 patients with 44 symptoms.

Improvement was seen in 21(78%) patients and 18 (67%) of them had complete or near complete response. Sufficient palliation could not be obtained in the remaining 6 (22%) patients. Improvement was observed in 6 of 7 (86%) patients assessable for hemoptysis, in 10 of 13 (77%) with cough, in 9 of 13 (69%) with dyspnea, and in 6 of 10 (60%) with thoracic pain (Table 5). The symptom relief of centrally located tumors was significantly better compared with the peripherally located ones (90 vs. 75%, p=0.01). In tumors < 6 cm, the observed improvement was not significantly better compared with tumors > 6 cm (92 vs. 64%, p=0.08). Previous irradiation aim was also not significant for symptom palliation after reirradiation (p >0.05) (Table 6).

The median overall survival time was 13.5 months (range 4-65) and median survival after reirradiation was 3 months (range 0-55). One-year survival was 57.8% after initial diagnosis and 8.7% after reirradiation. Two-year survival rate was 28.8% after initial diagnosis and 5.8% after reirradiation.

In the univariate analysis only the interval between the two RT courses was the statistically significant factor affecting survival. Patients who were reirradiated within an interval of 35 weeks had a longer median survival (25 vs. 9 months, p <0.001). Age could not be shown to affect overall survival (21 vs. 13 months, p=0.33), as well as tumor size (21 vs. 13 months, p=0.18) and tumor location (21 vs. 13, p=0.82) (Table 7).

Table 7. Results of univariate analysis for overall survival

Prognostic factors	*n (%)*	*Median OS (mo)*	*p-value*
Age (years)			
≤ 58	19 (50)	21	0.33
> 58	19 (50)	13	
Tumor size (cm)			
< 6	17 (45)	21	0.18
≥ 6	21 (55)	13	
Tumor location			
Peripheral	9 (24)	21	0.82
Central	29 (76)	13	
Interval (weeks)			
≥ 35	19 (50)	25	< 0.001
< 35	19 (50)	9	

OS: overall survival, mo: months

Table 5. Symptom response evaluation in 27 patients after reirradiation

Response	*Number of patients (%)*					
	Thoracic pain	*Cough*	*Hemoptysis*	*Dyspnea*	*SVCS*[§]	*Total*
Complete - near complete*	4 (40)	6 (46)	5 (72)	8 (62)	–	23 (52)
Partial**	2 (20)	4 (31)	1(14)	1 (7)	1	9 (21)
No response***	4 (40)	3 (23)	1(14)	4 (31)	–	12 (27)

*Symptom response 75-100%; **Symptom response 50-75%; ***No response <50%; [§]Superior vena cava syndrome

Table 6. Results of symptom relief evaluation according to tumor characteristics in 27 patients

Response	*Number of patients (%)*					
	Tumor size (cm)		*p-value*	*Tumor location*		*p-value*
	<6	> 6		Central	Peripheral	
Complete - near complete*	10 (77)	8 (57)		15 (75)	3 (43)	
Partial**	2 (15)	1 (7)		3 (15)	–	
No response***	1 (8)	5 (36)	0.08	2 (10)	4 (57)	0.01

*Symptom response 75-100%; **Symptom response 50-74%; ***No response <50%

Table 8. Results of multivariate analysis for overall survival

Prognostic factor	*p-value*
Age	0.244
Tumor size	0.671
Tumor location	0.256
Interval	< 0.001

According to the multivariate analysis, the interval between the two RT courses was the only significant prognostic factor as in the case of univariate analysis ($p < 0.001$) (Table 8). In 10 patients with tumor < 6 cm who were reirradiated after 35 weeks, the median overall survival was 26.5 months (range 6-65). The 1, 2 and 3-year survival rates were 80, 70, and 20%, respectively in this subgroup. Conversely, in 12 patients with tumor > 6 cm who were reirradiated before an interval of 35 weeks, the median overall survival was 9 months (range 4-26) with 1-year survival of only 25%.

Toxicity could be evaluated in 26 patients. After reirradiation RTOG grade I-II acute esophagitis was observed in 20 and grade III acute esophagitis in only 1 patient. There was no grade III or IV radiation pneumonitis or esophageal late effects.

Discussion

Lung cancer represents one of the most important health problems in oncology. It is frequent and the leading cause of cancer mortality [1]. According to the Izmir Cancer Registry data, lung cancer is the most common cancer among men in Izmir, Turkey [16]. Göksel et al. reported that the majority (86.7%) of the Turkish NSCLC patients present initially at stage III or IV [17]. Only 25% of the NSCLC patients can be candidates for curative surgery. Unfortunately, the prognosis of locally advanced NSCLC is not satisfactory with about 10% 5-year survival and 20% locoregional control rates [18]. Local recurrences cause severe, distressing symptoms impairing the patients' quality of life and they are life-threatening if left untreated. In this incurable patient population, improving the quality of life becomes the main objective of all the subsequent therapeutic manipulations. Nearly 30 years ago, RT has been found to be very effective to palliate the symptoms caused by lung cancer [19-21]. Palliation rates over 80% have been reported, especially for SVCS and hemoptysis [19]. Symptoms such as pain, cough, dyspnea and hemoptysis are frequently seen and when they occur, CHT, intraluminal therapies, surgery, external beam RT or a combination of these methods can be used for palliation [5]. These retreatment options depend on the general status of patients, previous treatments and tumor characteristics.

After local recurrence of NSCLC, surgery for curative intent can be effectuated in only 1-17% of patients [22-25]. Unfortunately the median survival obtained with that modality was not encouraging. Second-line, and even third and fourth-line CHT can also be used as salvage treatment after recurrence. In Massarelli et al. retrospective study, the response rate decreased dramatically from 16% in second-line to 0% in fourth-line CHT [26]. No response was observed in 8 evaluable patients given CHT before reirradiation in our series. One-year survival was in the range of 29-32% in two recent randomized trials using docetaxel [27,28].

Reirradiation of primary lung tumor is thought to be associated with radiation injury of normal tissues causing severe morbidity, even mortality. Therefore it is not frequently used and data about reirradiation is rare in the literature [8-15]. In a recent longitudinal study done in Australia, it was observed that only 12 patients out of 219 [5%] required retreatment to the primary site with a second course of RT [29].

There are, currently, 8 articles in the literature published in English, evaluating the role of reirradiation, containing 19-34 cases [8-15]. Our study includes 38 reirradiated patients, making it the largest series until now. The initial RT doses in these series vary between 28 to 80 Gy. During reirradiation, 6-70 Gy were delivered, with 1.8-8 Gy per fraction. Symptomatic improvement was evaluated subjectively in our series as performed in the majority of previously published studies. In those series, symptomatic improvement was obtained in 48-87.5% of patients, with 3-15 months median survival time after reirradiation [8-15].

In fact, there are some differences between our study and the others. In all other studies, initially, higher doses (median 53-60 Gy) of definitive RT were delivered to the patients with good performance status (Table 9) [8-15]. Here, we report the treatment results of two courses of RT delivered to the primary tumor of patients with NSCLC, with symptom palliation as the primary, and survival as the secondary endpoint. In our study, patients with poor prognostic factors, having limited life expectancy, were initially treated with a median 30 Gy (range 28.8-67.2) hypofractionated palliative RT. Only 8 patients with good prognostic factors received higher doses in the initial course of RT. The indication for reirradiation was either palliative or definitive in other series, with different total (16-50 Gy) and fraction (1.8-8 Gy) doses [8-15]. In our study, all of the patients received palliative reirradiation with a total median dose of 25 Gy (range 5-30), in median 10

Table 9. Reirradiation series for locally recurrent lung cancer

Author (year)	*Reference*	*Number of patients*	*Initial radiation doses (Gy, median)*	*Reirradiation doses (Gy, median)*	*Symptomatic improvement (%)*	*Median survival time (months)*
Green (1982)	8	29	53	35	48	5
Jackson (1987)	9	22	55	30	55	5.4
Montebello (1992)	10	30	60	37	70	5
Gressen (2000)	11	23	59	30.3	72	4.9
Okomoto (2002)	12	34	60	50	75	8
Wu (2003)	13	23	66	51	88	14
Kramer (2004)	14	28	46-60	16	71	5.6
Tada (2005)	15	19	50-69.6	50	88	7.1
Cetingoz	This study	38	30	25	78	3

fractions (range 1-10). The median interval between the initial RT and reirradiation was 5-23 months in the previous series, the longest reported by Okomato et al. [8-15]. We observed a median interval of 7 months in our patients, the majority of them being initially treated with palliative intent. Small and non-small cell histologies were also included in the other series, but we dealt only with NSCLC patients [11-13].

Despite these variations, we obtained comparable results with other series. Symptomatic improvement was reported in 48-87.5% of patients in the previous series [8-15]. We observed improvement of symptoms in 78% of patients, 67% of them achieving complete or near complete palliation. In the literature, symptomatic response rate for hemoptysis is reported to be 33-100%, for cough 15-67%, for dyspnea 35-100%, and for thoracic pain 40-80% [8-15]. Like in the other series, hemoptysis was the best palliated symptom also in our study, which was followed by cough, dyspnea and thoracic pain. Symptomatic improvement with reirradiation was obtained in 6 of 7 (86%) assessable patients suffering from hemoptysis, 5 (71%) having complete or near complete response. As hemoptysis is one of the most important and distressing symptoms of relapsed lung cancer, it is important to remind that it can be palliated in most patients with reirradiation. We obtained overall improvement of 77% for cough, 69% for dyspnea and 60% for thoracic pain, which are in accordance with the literature.

Tumors < 6 cm had better palliation rate than greater tumors but the difference did not reach statistical significance (p=0.08). This may be due to the relatively small number of patients. Symptomatic improvement was significantly better in centrally located tumors (p=0.01). As tumors of that location can cause more frequent and severe symptoms, this finding is not surprising. The aim of previous irradiation also was not found as a significant factor influencing the palliation rate of reirradiation (p >0.05) which may be attributed to the patient number.

In the previous series, the median survival time after reirradiation was 5.6 months (range 4.4-15), with a median dose of 37 Gy (range 16-50) [8-15]. We obtained 3 months (range 0-55) of median survival after hypofractionated palliative reirradiation. Considering the poor prognostic factors in our patients and that 6 of them had metastatic disease before treatment, this survival time was predictable. One of the best median survivals has been obtained in the study of Wu and colleagues with 14 months median (range 2-37) after reirradiation [13]. In this interesting phase I-II prospective study, reirradiation was effectuated with 3-dimensional conformal RT (3D-CRT). Only 23 patients developing late (>6 months) locoregional recurrence, with both small and NSCLC, who were in good performance status, were included in that study. Depending on the previous dose, a median dose of 51 Gy (range 46-60) was delivered during reirradiation using 3D-CRT technique, with optional sequential CHT. The overall and progression-free survival at 2 years were 21% and 42% respectively, with only 2 patients having clinical symptoms due to treatment-related pulmonary fibrosis. Okomoto et al. reported median survival of 15 months (range 3-58) after radical reirradiation with a median dose of 50 Gy (range 30-70) in 18 patients, 6 of them living > 20 months [12]. It should be taken into account that these favorable results are obtained in selected patients of good general status in whom better survival is expected. The results of these studies should be evaluated carefully because they also contain small cell histology and CHT is used for patients in good condition.

The median overall survival of our patients after diagnosis was 13.5 months, with 11 (29%) of them living > 24 months after diagnosis, The majority of our

patients died because of uncontrolled local disease, showing the importance of local control on survival. Because of the palliative aim of reirradiation, we delivered a maximum of 30 Gy in 10 fractions. As dose/response relationship in RT is well-known, high doses can be delivered if the aim of the reirradiation is cure or prolongation of survival.

Most of the trials using definitive RT with or without CHT report median survival of 12 to 22 months [30-32]. Obtaining 13.5 months of median survival after two RT courses in our patients, having one or more poor prognostic factors, merits attention, but it has to be evaluated cautiously because of the relatively small number of patients.

Like in the study published by Tada et al., it was confirmed also in our patients that those having longer interval between the two RT courses showed an increased overall survival (25 vs. 9 months) [15]. Interpretation of that issue may probably be different natural history of tumor growth and/or tumor sensitivity to irradiation. However, in the study published by Gressen and colleagues, a relationship between treatment interval and survival could not be demonstrated [11].

Five (13%) patients died because of uncontrolled disease, during or in two days after reirradiation, due to late referral. Referral timing is one of the most important problems in oncology. Early referral for RT is crucial because it is one of the main treatment modalities to improve the quality of life the patients with symptomatic disease. The treatment decision, in every cancer patient, in every stage, necessitates multidisciplinary approach with the participation of a radiation oncologist.

The cumulative median dose in our study was 57.5 Gy (range 35-96). Median cumulative doses up to 110 Gy with reirradiation have been reported in the literature [12]. As the main objective of reirradiation in our study was palliation, protracted fraction numbers and high total doses were not used. Kramer et al. used two-weekly fractions of 8 Gy with acceptable toxicity. This retreatment modality, with a median field size of 9.5×11 cm, was found very effective, especially for patients suffering from hemoptysis and SVCS [14]. In all previous studies, the retreatment volume was restricted as much as possible in order to reduce the treatment related side effects and only to include the recurred macroscopic tumor [8-15]. We also treated the relapsed tumor causing clinical symptoms, without elective nodal irradiation, avoiding especially the spinal cord. The median treatment field size in our study was 86.15 cm^2 (range 100-244.5), while it was 65 cm^2 in the study of Okamoto and 104.5 cm^2 in the study of Kramer et al. [12,14]. These restricted treatment volumes are well tolerated with acceptable toxicities in almost all studies.

If the chest region receives high doses of RT some side effects such as radiation pneumonitis, esophagitis, myelopathy, pulmonary fibrosis and myocardiopathy can occur. These complications are dependent on dose per fraction, total dose, treated volume and patient characteristics. In the previous studies reirradiation was found to be well tolerated with only one death due to a radiation pneumonitis in the study of Gressen et al. [11]. It was reported in the study by Kramer et al. that one patient died of bronchoesophageal fistula after laser treatment [14]. Radiation pneumonitis incidence after reirradiation has been reported to range between 0 and 56% [7-14]. The highest incidence was reported in the study of Okamoto et al. with 19 grade 2-3 symptomatic radiation pneumonitis out of 34 patients (56%), without any treatment-related death [12]. Also, the highest radiation esophagitis incidence (18%) was reported in the same study. In that study the highest median cumulative dose in the literature (110 Gy) was delivered. We observed only one patient with grade 3 acute esophagitis. No grade 3-4 radiation pneumonitis or late esophageal toxicity was observed. In all previous studies, as well as ours, reirradiation has been found to be safe. Until now 248 (including our patients) reirradiated patients for recurrent lung cancer have been reported (Table 9). Although not a standard treatment modality for the moment, if the effectiveness and safety of such a treatment will continue to accumulate, it can be an option for the treatment of locally recurrent lung cancer refractory to CHT.

Considering the promising results obtained in this retrospective study and previously published series, a national prospective study is being planned using validated scales measuring quality of life and symptomatic improvement and using modern RT techniques in order to properly define the role of reirradiation in NSCLC.

Conclusion

In this relatively small retrospective study, it is demonstrated that locally recurrent NSCLC patients can be retreated with hypofractionated RT using conventional techniques. As it was also demonstrated in previous relative studies, this retreatment modality appears to be safe and effective. Considerable symptomatic improvement, as well as survival prolongation, is possible with such a treatment. In order to decrease treatment-related side effects, special attention has to be given to reduce the treatment volume and to tailor the treatment according to the tumor and patient characteristics. Sparing of normal tissues while delivering higher doses to the tumor can be accomplished through the use of current modern treatment facilities like conformal RT. Prospective tri-

als, including large numbers of patients, are necessary in order to confirm its efficacy and safety.

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