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ORIGINAL ARTICLE

Toxicity and efficacy of a hypofractionated (3 weekly fractions of 850c Gy) irradiation schedule for stage IIIb / IV non-small cell lung cancer elderly patients with low performance status and unfit for chemotherapy

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Summary

Purpose: *To evaluate in an observational way the clinical impact of a hypofractionated irradiation schedule in patients with unresectable non-small cell lung cancer (NSCLC).*

Methods: *Forty elderly patients (24 men/16 women) diagnosed with unresectable stage IIIb/IV NSCLC unfit for chemotherapy, were treated with once-a-week hypofractionation schedule. All patients had a poor performance status. A dose of 255 Gy in 3 weekly fractions was prescribed while a 3D conformal technique (3D-CRT) was used for irradiation. The primary study endpoints were to assess the therapeutic impact of this schedule in terms of relapse free survival (RFS), overall survival (OS) survival and palliation of symptoms. The secondary endpoints were the evaluation of acute toxicity of the lung, esophagus and the skin. The intended follow-up was 3 years. The median age was 73.5 years (range 71-85).*

Results: *The median RFS was 12 months, while the median OS was 17 months. Symptoms relief was up to 20% for cough, 52.5% for haemoptysis, 40% for thoracic pain and 17.5% for dyspnoea. Acute lung toxicity in terms of radiation pneumonitis was recorded as 6/40 (15%) grade 1, 26/40 (65%) grade 2 and 8/40 (25%) grade 3. Additionally, grade 1 and 2 acute esophageal toxicity was recorded in 10/40 (25%) and 30/40 (75%) patients, respectively. Acute skin toxicity with grade 2 erythema was recorded in only 2/40 (5%) patients while most patients developed grade 1 skin erythema. Grade 3 late lung toxicity was recorded in 10/40 (25%) patients.*

Conclusions: *This study showed that the proposed scheme has a moderate radiation-induced lung toxicity rate and an acceptable therapeutic ratio. Taking into consideration its cost effectiveness, the proposed hypofractionated scheme is a good alternative to conventional fractionation.*

Key words: *hypofractionation, non-small cell lung cancer, palliation, radiotherapy, toxicity, survival*

Introduction

Lung cancer is the second most common malignancy in the US, behind only prostate cancer in men and breast cancer in women. It represents the first cause of death in the US and worldwide [1]. The prognostic factors of lung cancer remain the stage of disease, weight loss (> 10% body weight over 6 months), performance status, K-ras oncogene activation and pleural effusion [2,3]. Radiotherapy (RT) for NSCLC is still a challenging topic since the target volume is surrounded by a

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relatively sensitive structure, such as the normal lung. The limitation of RT dose is related to the sensitivity of the normal lung, especially if large volumes of the lung are exposed to ionizing radiation. Palliative RT applies to all elderly and unfit patients with poor performance status, who suffer from unresectable disease with thoracic symptoms, such as chest pain, hemoptysis and shortness of breath [4]. Several trials have shown a dose-response relationship, so dose escalation can improve tumor control [5]. It has been already demonstrated that for sufficiently high prescription doses, hypofractionation tend to decrease the damaged volume of the lung as predicted by a local threshold dose model [6].

Hypofractionated RT is the delivery of RT with a dose per fraction that exceeds 2.2 Gy. It is an attractive treatment choice related to both logistics and patients convenience. Hypofractionation may allow dose escalation and treatment acceleration while accelerated hyperfractionation has shown an increase in cost [7,8]. Particularly, accelerated RT has been shown to improve tumor control in NSCLC [9].

We studied a weekly regimen, of an equivalent biological effective dose to many commonly used schedules in order to assess efficacy, toxicity, convenience and mainly correlation with either RFS or OS [10].

The irradiation schedule was specially designed for patients who were unfit for conventional fractionation, mainly due to either medical problems or patients in long-distance areas that made daily attendance for lengthy outpatient RT impractical. Patients referred for irradiation through a local tumor board are often unfit for surgery with advanced stage of disease and various co-morbidities, contributing to poorer prognosis [11].

The aim of this study was to investigate the efficacy and potential toxicity using an accelerated hypofractionated irradiation schedule. Special attention was given to the patients' preference as far as RT fractionation schedule was concerned, and to the cost and benefit of the irradiation scheme.

Methods

In an observational way, patients with advanced NSCLC that were not eligible for surgery or conventional fractionation RT selected for this protocol, at the University of Athens, at either University hospital "Attikon" or Aretaieion. The study was approved from the local ethics committees of both University hospitals. The study protocol conformed with the ethical guidelines of the 1975 Declaration of Helsinki. Moreover, informed consent was obtained from each patient included in the study.

Between 2007 and 2012, 40 patients with histologically confirmed NSCLC received dose-escalated radiation, using a hypofractionated schedule of 3x 8.5 Gy, once a week. Their median age was 73.5 years (range 71-85). Twenty-four patients were men and 16 women. The patient characteristics are summarized in Table 1.

Table 1. Patient and disease characteristics (n=40)

Characteristics	*n*
Age (years)	
Median	73.5
Range	71-85
Sex	
Male	24
Female	16
Histology	
Adenocarcinoma	12
Squamous cell carcinoma	28
Stage	
IIIB	22
IV	18
Grade	
G2	0
G3	40

Inclusion – exclusion criteria

The selection of candidates was done through the local tumor board and was based on the following criteria:

Age >70 years; Unresectability of the disease but no evidence of metastasis; Low performance status; Clinical judgment that patients would find it difficult to attend a program of daily hospital visits for a period of approximately 6 weeks, in order to complete the conventional radical RT regimen of 8.5 Gy in 30 fractions; Patients unable to receive chemotherapy due to comorbidities (renal failure, cardiac failure, etc); Residence in isolated areas or islands unable to attend daily irradiation; Symptoms or signs like cough, dyspnea, hemoptysis, obstructive pneumonia, pleural effusion, chest pain, hoarseness, Pancoast or Horner's syndrome were evaluated and played an important role to the medical decision for the selection of the certain RT schedule.

The patients were referred either to Attikon University hospital or Aretaieion University hospital, after a histological confirmation of malignancy and after the completion of the staging that proved the conformity of the above-mentioned criteria. The pretreatment evaluation included pathology review, clinical examination, measuring of the weight loss, smoking and ECOG performance status. Laboratory studies including blood count, BUN, liver function tests, alkaline phosphatase, creatinine, uric acid and finally imaging studies like computed tomography (CT) of the chest were obtained before starting treatment. Also, all patients underwent a respiratory evaluation before starting treatment. Patients were staged using TNM classification system

[12] and all of them had an ECOG performance status of two. Eligible patients had histologically confirmed clinical localized, unresectable, non-metastatic NSCLC with loco-regionally advanced disease as well as poor performance status. In general, this schedule applied to elderly patients, with comorbidities, with advanced lung disease but without evidence of metastases and in general not suitable for radical RT.

Exclusion criteria were as follows: age ≤70 years, ECOG performance status <2, resectable disease, possibility of systemic therapy - chemotherapy, psychiatric disease and second primary cancer. All patients had to sign informed consent concerning the side effects of irradiation.

Radiotherapy technique

For treatment planning purposes, each patient underwent a virtual CT simulation with bilateral arms abducted in a supine position with customized immobilization device. Immobilization was succeeded with a wingboard. Planning CT scan of the thorax was then performed with a 0.2-cm spacing between slices. The CT datasets were transferred either to CADPLAN® (GE Ltd, Stanford, CT,USA) or to Prosoma® virtual simulation or to PLATO (Nucletron, Veenendaal, The Netherlands) and contouring system through the DICOM network. The following structures were delineated: gross target volume (GTV), clinical target volume (CTV) and planning target volume (PTV) according to the ICRU criteria. Organs at risk (OAR) were delineated. The normal lung was manually contoured as the parenchyma of lung minus the PTV of the lesion. In addition heart, spinal cord and esophagus were also contoured. No patient received full mediastinum node or supraclavicular node irradiation, while PET-CT images were used for irradiation of the involved areas [11]. The GTV consisted of the gross primary and regional nodal disease, according to PET-CT images. The CTV typically included GTV plus 1cm margin. The PTV included CTV plus a 0.5 cm margin. The entire target was treated using a multiple field technique with 3D conformal RT and 6 MV X-ray energy beams (typically three-field technique). In order to improve dose homogeneity, we used weighted beams, wedges and/or compensating filters. Dose volume histograms were also generated, whereas mean, median and maximum dose were also evaluated. The target dose that was administered weekly and was prescribed to 95% at the International Commission on Radiation Units and Measurements (ICRU) reference points, at the intersection of the central axis of the treated beam in the midplane of the target volume, was 85 Gy. A total dose of 25.5 Gy was prescribed in 3 weekly fractions. All patients were treated either on a VARIAN 2100C (Palo Alto, CA, USA) or on VARIAN 600C (Palo Alto, CA, USA) linear accelerator or ONCORDE Siemens with 6 MV photons. Dose calculations were performed using either the treatment planning system Eclipse (Varian Associates, Palo Alto, CA), or the PLATO (Nucletron, Veenendaal, The Netherlands), to deliver the prescribed dose according to the ICRU [12,13]. Patient setup was monitored weekly using portal imaging devices.

The linear-quadratic (LQ) modeling was used in order to assess the equivalent to 2 Gy-fractions of the hypofractionation schedules to the Normalized Total Dose (NTD) [10]:

$$NTD = D_{new} [(d_{new} + \alpha/\beta)/(2 + \alpha/\beta)]$$

Where, D_{new} and d_{new} are respectively the total dose and dose per fraction for a suggested hypofractionation scheme. Normalized Total Dose (NTD) has been calculated and tabulated for both lung cancer (α/β=10 Gy) and late reacting tissues (α/β=3Gy) [7,9].

When considering that α/β = 10, the NTD was 39.3 Gy. When considering that α/β = 3, the NTD was 58.7 Gy. Every DVH delivered from the TPS was transferred to radiobiological equivalent one using a model based in the Niemierko model [16].

In terms of dose limitations in OARs, we used the QUANTEC dose-volume data for normal tissues as follows [17]:
V20 <30% for lung (acute pneumonitis);
V35 < 50% for esophagus (acute esophagitis);
V25 < 10% for heart (late toxicity);
50 Gy maximum dose for spinal cord (myelopathy).

All doses to OARs were transferred to conventional schedule (2 Gy per fraction) using and α/β ratio equal either to 10 (lung, esophagus), or 3 (heart), or 2 (spinal cord).

Clinical evaluation

The primary study endpoints were to assess the therapeutic impact of this schedule in terms of RFS, OS and palliation of symptoms. Survival was assessed after the completion of RT. The secondary endpoints were the evaluation of acute toxicity of the lung, esophagus and the skin. Patients were monitored weekly during RT and reviewed every month post-irradiation. Acute and late lung radiation-induced toxicities were monitored. Data at diagnosis (baseline), at the end of RT and at all monthly follow up visits 6 months after finishing RT have been analyzed. The radiological response to treatment was assessed with CT images by using the RECIST criteria (Response Evaluation Criteria In Solid Tumors) version 1.1 [18]. Palliation of symptoms such as cough, chest pain, hemoptysis and dyspnea were also evaluated before RT and 3 months after the completion of RT.

For the radiological evaluation of radiation-induced pneumonitis we used a grading scale based on CT images of the thorax, which has been already reported [19]. Acute radiation-induced toxicity was also analyzed prospectively using the EORTC/RTOG toxicity criteria [20]. In all cases, maximum acute toxicity scores were confirmed as the final toxicity score.

Statistics

Kaplan-Meier survival analysis was performed for both RFS or OS. The correlation between either V20 dosimetric parameter for the lung or radiological response and the pneumonitis radiological grading were assessed with the Spearman's-rho non parametric test. A significant level of 0.05 was set for the analysis. Any difference in the incidence of symptoms before and

after RT was evaluated with the chi square test. The whole analysis was performed with the SPSS version 10 software (Chicago, IL, USA).

Results

All patients completed the planned 3D-CRT. The intended follow-up duration was 36 months. All patients were evaluated through CT scans of the thorax, 3 and 9 months after treatment. Treatment compliance was excellent.

Three fractions given 1 week apart could be delivered with less inconvenience. All patients received 25.5 Gy in 3-weekly fractions. There were 6/40 (15%) patients with grade 1, 26/40 (65%) with grade 2, and 8/40 (25%) patients with grade 3 radiation pneumonitis. Acute toxicity resolved with completion of RT; at 3 months, 6 patients had grade 1 and 26 patients had grade 2 toxicity. After 9 months of follow up, 6 patients had grade 3 radiation pneumonitis (Table 2). The median V20 as calculated from the treatment planning system was 25%. All patients undergoing the treatment schedule of 3-weekly fractions were assessed with a new grading scale for radiation-induced pneumonitis that has been suggested by our department [19]. According to the proposed grading scale, the patients were categorized as grade 0, 1, 2, 3 or 4, depending on the radiation-induced lung symptoms. The toxicity grading scale's scores are shown in Table 3.

Grade 1 and 2 acute esophagitis was developed in 10/40 (25%) and 30/40 (75%) of patients, respectively. Acute skin toxicity was as follows: 14/40 (35%) did not demonstrate any kind of skin toxicity, 24/40 (60%) showed grade 1 and 2/40 (5%) grade 2. Late toxicity was evaluated with CTs at 9 months from RT and 8/40 (25%) of patients demonstrated grade 3 toxicity.

The median RFS was 12 months, while the median OS was 17 months (Figure 1). No patient survived after 27 months during follow up. No fatal or life threatening toxicities have occurred. The Spearman's-rho test between V20 and pneumonitis grading showed a significant correlation with a rho=0.7422 (p=0.0018).

According to RECIST criteria, 3 months post-irradiation no progressive disease (PD) was noticed, while 13/50 (%) patients showed complete response (CR) and 37/50 non CR and non PD. The Spearman's rho test revealed a significant correlation (rho=-0.48) between radiopneumonitis scores based on our radiological scale and response rate according to RECIST criteria (p=0.0014).

Palliation of symptoms was achieved as all our patients reported clinical improvement in terms of cough, chest pain, hemoptysis and dyspnea 3 months after completion of treatment (Table 4).

Table 2. Acute toxicity of irradiated patients according to EORTC/RTOG toxicity criteria

RT acute toxicity	*n (%)*
Lung	
Grade 1	6/40 (15)
Grade 2	26/40 (65)
Grade 3	8/40 (25)
Grade 4	0
Esophagus	
Grade 1	10/40 (25)
Grade 2	30/40 (75)
Skin	
Grade 0	14/40 (35)
Grade 1	24/40 (60)
Grade 2	2/40 (5)

Table 3. Radiological grading scale of radiation-induced pneumonitis

Acute	*n (%)*
Grade 0	0
No findings	
Grade 1	6/40 (15)
Ground glass opacities without fuzziness of the subjacent pulmonary vessels	
Grade 2	26/40 (65)
The findings may vary from ground glass opacities, extending beyond the radiation field, to consolidations	
Late	*n (%)*
Grade 3	8/40 (25)
Clear focal consolidation ± elements of fibrosis	
Grade 4	-
Dense consolidation, cicatrisation atelectasis, aerobronchogram and bronchial extension (traction bronchiectasis), significant pulmonary volume loss, and pleural thickening	

Table 4. Disease related symptoms before and 3 months post-irradiation

Symptoms	*Before RT n (%)*	*3 months post RT n (%)*	*Difference (%)*	*p value*
Cough	32/40 (80.0)	24/40 (60.0)	20.0	<0.01
Chest pain	24/40 (60.0)	3/40 (7.5)	52.5	<0.01
Hemoptysis	17/40 (42.5)	1/40 (2.5)	40.0	<0.01
Dyspnoea	30/40 (75.0)	23/40 (57.5)	17.5	<0.01

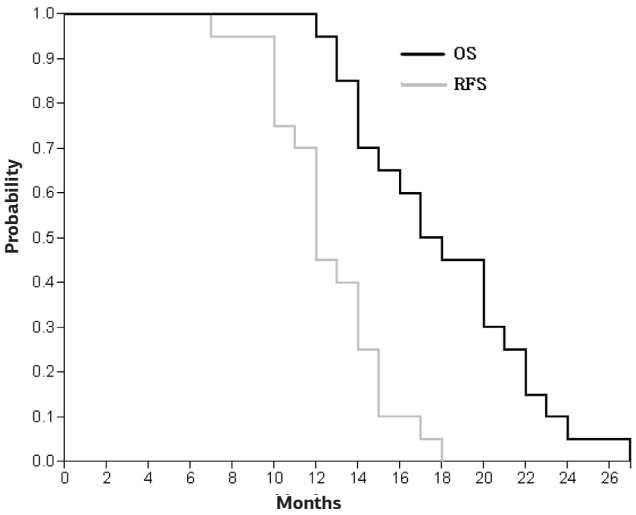

Figure 1. Kaplan Meier survival curves. Median RFS=12 months (SE=1), median OS=17 months (SE=1). SE: standard error.

Discussion

Lung cancer is one of the leading causes of cancer death worldwide. Although surgical approach is the standard treatment, many patients are not surgical candidates because of advanced age, poor medical condition and / or compromised lung function. Lung cancer occurs commonly in heavy smokers, who may suffer also from other comorbidities such as cardiac and respiratory diseases and have difficulty in attending a daily treatment for 6 weeks. RT plays an important role in the management of unresectable, non-metastatic, measurable, loco-regionally advanced disease in patients with poor performance status. These patients may be unable to tolerate the acute morbidity of a conventional radical radiotherapy schedule and the onset of symptoms such as cough, chest pain and shortness of breath, which worsen their quality of life [1].

Hypofractionation is an alternative fractionation schedule concerning logistics and patient convenience [8]. According to a review from Patridge et al. published in 2011, who analyzed data from 24 clinical trials of NSCLC, there is indeed a dose-response relationship of the tumor. Since then various dose escalation schedules have been examined, usually in the setting of phase II or open clinical studies [21]. Ruggieri et al. supported the idea that hypofractionation can create non-homogeneous tumor dose delivery that counteracts tumor hypoxia. In this way, a severe hypofractionated schedule could perform simultaneously dose-boosting with highly clinical efficacy [20]. Additionally, Jin et al. demonstrated that for sufficiently high prescription doses, hypofractionation would tend to decrease the damaged volume of the lung as predicted by a local threshold dose model [6].

One of the major problems of hypofractionation is the risk of radiaton pneumonitis, which increases as the number of fractions decreases for the 3-dimensional conformal radiotherapy (3D-CRT) plan. The present study shows that even with standard values of α/β of 3 and 10 Gy for normal tissue and tumor respectively, lung toxicity after hypofractionation is predicted to be comparable to that of standard fractionation. This is in accordance with the current literature using the model of normal tissue complication probability (NTCP) with clinically estimated parameters [6,23]. The significant correlation between V20 and pneumonitis grading is in accordance with QUANTEC study [17], while the validation of the scale used for radio-pneumonitis scoring has been already reported [16,19].

A phase II trial published in 2011 studied the safety and efficacy of accelerated hypofractionated RT in combination with chemotherapy in patients with locally advanced NSCLC. Although 34 patients received two cycles of induction chemotherapy and underwent a progressive hypofractionated RT regimen, the radiation toxicity was minimal with promising results rates of the OS and PFS. This report suggested that accelerated hypofractionated radiotherapy using 3D-CRT could be used in combination with chemotherapy in unresectable lung cancer [24]. Another randomized controlled study compared 2-fraction RT with more prolonged regimens. The study has shown that the chance of obtaining relief of lung symptoms and dysphagia appeared to be better for the 2-fraction scheme given 1 week apart than for the multiple daily fractionation schedules. In

addition, toxicity appeared to be equivalent [25-28]. Similarly, in our study there was only grade 2 esophageal toxicity. Thus, the patients suffered from mild to moderate dysphagia, or odynophagia, but they controlled these symptoms with narcotic analgesics and diet based on puree or liquids.

Another study from Jin et al. showed that hypofractionation was associated with less relative damage-volume than with that of conventional fractionation for very high prescription doses. This result seems to contradict the common belief, because lung tissue has a lower α/β ratio. However, this new observation could be explained by the fact that both the common belief and the clinical experience mostly come from the 2-dimensional era. According to data from the past, the referring dose was low, the radiation fields were large, radiation was mostly confined to the irradiated volume and the dose distribution within the irradiated volume was relatively uniform. The situation can be different today with 3D-CRT. Hypofractionation was preferred for small tumors and higher normalized total doses, and conventional fractionation was better for large tumors and lower normalized total doses. Hypofractionation could be beneficial for intermediate-sized tumors, or large peripherally located tumors, for which high dose escalation can be performed with some risk of lung toxicity [6].

All previous data are in accordance with a large study from the Department of Radiation Oncology of the University of Maryland. More specifically, according to a large randomized clinical trial, a once-a-week hypofractionation schedule in lung cancer showed better tolerance than conventional RT. There was no weight loss and no fatal or life threatening toxicities in general [28]. Three other published studies demonstrated that 2 palliative weekly fractions of 85 Gy in advanced NSCLC offer acceptable palliation with minimal toxicity [29,30].

For the symptomatic disease control, many trials have demonstrated that hypofractionated RT is effective and equivalent to classic RT schemes. In a study from India published in 2000 from Bhatt et al., 47 patients with NSCLC were treated with 4 weekly fractions of 5 Gy. The authors reported that this scheme was effective in palliating of various intrathoracic symptoms of all the patients [31]. In a well-designed randomized trial from Sundstrøm et al. 421 patients with locally advanced stage III/IV NSCLC were randomly assigned to either 17 Gy in two fractions or standard-fractionation RT. The authors did not find any difference in symptom palliation between the treatment arms and concluded that hypofractionated RT was equivalent to standard RT [32]. Finally, in the recently published Cochrane update review with data from 13 randomized controlled trials, the hypofractionated RT was found as effective as longer RT courses [33]. All these studies demonstrated the efficacy of accelerated hypofractionation in the relief of the symptoms in patients with advanced lung cancer not amenable to daily treatment.

In another study with palliative RT by Reinfuss et al. [34] 1250 patients were analyzed after split-course RT consisting of 2 series of 20 Gy in 5 fractions each, 4 weeks apart. This schedule was quite similar in radiobiological terms with the one presented here with an NTD up to 56 Gy vs 58.56 Gy, respectively (α/β=3). The authors reported disappearance of symptoms up to 24% for cough, 37.8% for thoracic pain, 52% for haemoptysis and 18.3% for dyspnoea. As the two irradiation schedules were equivalent radiobiologically, it was more than expected that our results are in accordance with the above analysis, with relevant results up to 20, 40, 52.5 and 17.5%, respectively.

In general, our trial is part of a series of studies from the Medical School of Athens through the last decade, and is related with the efficacy of hypofractionation in locally advanced NSCLC. More specifically, the first report was published in 2002 and showed the good results of accelerated hypofractionation of 2-weekly fractions of 8.5 Gy and the compliance of all patients even when they had to undergo a scheme of 3 fractions of 4.25 Gy on the first day and 2 fractions of 4.5 Gy on the second day [35]. Another trial demonstrated that patients with symptomatic lung tumors which did not respond to induction chemotherapy, could benefit from RT of 2x8.5 Gy, one week apart [36]. In a review concerning patients treated with a very short regimen of RT, the observed toxicity was minimal, the relief of the symptoms was significant and the compliance of the patients was excellent, since they spent the minimum of their remaining survival time in the hospital [37]. Interestingly, in an independent study, it was found that despite the longer average survival associated with longer fractionation, nearly half of the patients believed that this was not as important, as a shorter duration of treatment and lower cost [26,27]. Additionally, as reported already, more advanced tumors, like in our study, may be treated with hypofractionated doses to achieve palliation and a modest degree of survival benefit equivalent to conventional schemes [36-38].

Last but not least, the radiobiological approach of response related rate and correspondence α/β ratio seems potentially as high as 20-50

Gy for stereotactic schedules [39]. Since our dose per fraction of 85 Gy has a trend to approach the radioablation fractionation, the NTD with an α/β either 20 or 50 Gy is modulating equal to 33 Gy or 28.7 Gy, respectively [40]. However, Ma et al. [41] have already reported that no significant difference was noted for doses lower or higher than 30 Gy in terms of symptom relief for NSCLC. Thus, a dose escalation of more than 30 Gy in NSCLC for palliation might be useless for unfit patients like our patient group. By all means, the schedule of 2.55 Gy in 3 weekly fractions might be as effective and safe for radiopneumonitis. Moreover, the Spearman's rho test revealed a significant correlation between response rate and radiopneumonitis, which is in accordance with the observation of Dang et al. [42]. In any case, the prognosis of inoperable NSCLC remains dismal compared to patients undergoing surgical excision even with postoperative chemoradiotherapy due to relapse [43].

Conclusions

Our study showed that 3D-CRT is a feasible and safe modality allowing for hypofractionation up to 25.5 Gy in 3 weekly fractions. Our results are in accordance to those reported in the literature, regarding the safety and efficacy of palliative hypofractionated RT and demonstrate that in patients unsuitable for surgery or standard daily radical RT, it is possible to deliver hypofractionated 3D-CRT to the lung with an acceptable acute toxicity rate and a lower cost. More prospective trials are needed for the confirmation of our results. Nevertheless, in any case the proposed irradiation schedule should be considered under a multidisciplinary approach through a local tumor board [44].

Conflict of interests

The authors declare no conflict of interests.

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