JBUON 2020; 25(2): 842-847
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
Email: editorial_office@jbuon.com

ORIGINAL ARTICLE

A randomized study comparing two hypofractioned 3-D conformal radiotherapy for stage IIIb-IV non small cell lung cancer

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Summary

Purpose: *We compared the safety and efficacy of two hypofractionated irradiation schedules for elderly and low performance status patients with inoperable symptomatic non-small cell lung cancer (NSCLC).*

Methods: *Patients that entered the study were either unfit or without response concerning chemotherapy. We randomized 14 patients (group A) vs 15 patients (group B) who underwent two different hypofractionated radiotherapy schedules. Group A patients underwent a scheme of 13x3 Gy, while group B patients received 2x8.5 Gy and one fraction of 6 Gy one week apart. Efficacy was assessed in terms of disease-free survival (DFS), tumor response and overall survival (OS). Toxicity according to RTOG/EORTC criteria and duration of symptoms were also evaluated.*

Results: *Median follow up was 3 years. Median age was 64.5 years (group A) and 73 years (group B). Mean values for symptom palliation were higher for group B vs group A (3.20±1.21 vs 2.21±0.97, p=0.037), respectively. EORTC/RTOG toxicity was significantly higher (p=0.046) for group A (1.57±0.51) vs group B (1.13±0.35). Duration of toxicity was significantly lower in group B compared to group A (p=0.001). Median OS was similar between groups, while DFS was better in group B than group A (p=0.023).*

Conclusions: *Although safe conclusions are difficult to be ascertained, hypofractionated schedule B might be an alternative scheme in elderly and low performance status patients offering adequate palliation, good tumor control and acceptable toxicity.*

Key words: *non small lung cancer, radiotherapy, hypofractionated, toxicity, randomized study*

Introduction

Many randomized trials [1-9] have been published on the alternative clinical role of hypofractionated radiotherapy, confirming to be at least as safe and effective. In patients with locally advanced inoperable stage of non small cell lung cancer (NSCLC), hypofractionation offers acceptable palliation compared to conventional schedules and without severe toxicity, probably due to lower biologic total dose [5-16]. In a previous study, we have reported our experience with weekly schedule of

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Received: 17/08/2019; Accepted: 24/09/2019

25.5 Gy in 3 fractions, showing acceptable toxicity and palliation for elderly patients unfit for chemotherapy [17].

The purpose of the current study was to perform a comparative evaluation between two hypofractionated schedules in terms of the optimum schedule for PFS, symptom palliation, toxicity, duration of toxicity and overall survival.

Methods

The randomization for the trial was performed by a computer software through a random number generator (even numbers for group A and odd numbers for group B).

In this study, we analyzed the outcome between two hypofractionated schedules. The technique used was 3D conformal in all cases. The study has been approved from the local ethical committee and the inclusion criteria were as follows:

1. Stage IIIb, IV.
2. Performance status >1.
3. Unfit for chemotherapy due to comorbidities (renal failure, cardiac failure, etc) or alternatively no response after chemotherapy in terms of RECIST radiological criteria [18] or symptom palliation.
4. No metastatic disease.
5. Dyspnea and thoracic pain.
6. FEV1 >50%.

Exclusion criteria were as follows:

1. Candidate for second line of chemotherapy or other clinical trial.
2. Previous thoracic irradiation.
3. Bulky disease - unable to perform irradiation and candidate for palliation only.

The power analysis with an alpha=0.05 and beta=0.2, showed a minimum of 34 patients entering the study. Initially 45 patients entered the study. Eventually, 29 patients were evaluated due to lost to follow-up. The main reason for this was the fact that several patients were inhabitants of isolated areas outside Athens, specifically in small islands in Aegean sea. Thus, the study finally included 14 patients in the first schedule (group A) and 15 patients in the second schedule (group B). Their median age was 64.5 in group A and 73 years in group B. Ten patients of group A and 8 patients from group B were referred for radiotherapy after chemotherapy without response. These patients had received platinum doublet (carboplatin/paclitaxel, carboplatin/gemcitabine, carboplatin/navelbine, carboplatin/ permetrexed).

The patient characteristics are shown in Table 1. The patients were referred either to Attikon University hospital or Aretaieion University hospital, after histological confirmation of malignancy and after the completion of TNM staging. Also, all patients underwent a respiratory evaluation before starting treatment.

All patients underwent a treatment planning computed tomography (CT) scan of 2mm slice thickness in supine position and arms sited above the shoulder and immobilized. All the data was transferred for contouring either to Prosoma® virtual simula¬tion or to PLATO (Nucletron, Veenendaal, The Nether¬lands). The treatment planning used was CADPLAN® (Varian Oncology Systems Inc, Palo Alto, California, USA) or PLATO (Nucletron, Veenendaal, The Nether¬lands). The following structures were delineated: gross target volume (GTV), clinical target volume (CTV) and planning target volume (PTV) according to the ICRU criteria. The GTV was defined from either PET-CT or CT enhanced imaging. The heart, ipsilateral and contralateral lung, spinal cord and esophagus were outlined as organs at risk (OARs). Radiation therapy was delivered by using either a 6 MV (VARIAN 600 clinac or SIEMENS concort) or 15MV (VARIAN 2100 clinac) linear accelerator. Group A received 30 Gy in 13 daily fractions with 3 Gy/fraction. Group B received 17 Gy to the tumor bed in weekly schedule of 2x850 cGy and one fraction of 6 Gy.

The biological effective dose (BED) for normal tissues was calculated using the following formula [19]:

$$BED=nd\,[1+d/\alpha/\beta]$$

where D is the total dose, d is the dose per fraction, α and β are the coefficients for the linear and quadratic terms in linear quadratic (LQ) model. We considered that α/β=3 and 3.9 for tumor, and α/β=10 for acute toxicity [19,20]. Calculations of BED for tumor local control are shown in Table 2.

The dose was calculated at the isocenter according to International Commission on Radiation Units

Table 1. Patient characteristics

Characteristics	*Group A (N=14) n (%)*	*Group B (N=15) n (%)*	*p*
Stage			0.57*
IIIB	7/14 (50)	8/15 (53.3)	
IV	7/14 (50)	7/15 (46.6)	
ECOG performance status			0.71*
II	7/14 (50)	6/15 (40)	
III	7/14 (50)	9/15 (60)	
Age median, years (median, range)	64.5 (57-85)	73 (54-87)	0.093**
Pre RT chemotherapy	10/14 (71.4)	8/15 (53.3)	0.45*

* x^2, ** Mann-Whitney U test

Table 2. Calculated BED values for the two RT schedules

	Group A (3 Gy)	*Group B (2x8.5 Gy+6 Gy)*
Physical dose	39 Gy	21 Gy
BED (α/β=3)	78.0 Gy	83.16 Gy
BED (α/β=3.9)	69.0 Gy	69.28 Gy
BED (α/β=10)	50.7 Gy	41.5 Gy

and Measurements (ICRU point). For quality assurance purposes double-exposure portal films were obtained weekly and compared with the corresponding digitally reconstructed radiograph from the initial simulation. The dose within the PTV ranged between 95% and 107% of the isocentric dose, according to ICRU recommendations. In all cases, the maximum radiobiological equivalent dose to the OARs was according to the Quantitative Analyses of Normal Tissue Effects in the Clinical Trial for the dose constrains (QUANTEC: Quantitative Analyses of Normal Tissue Effects in the Clinic) [21]. The radiological equivalent dose for OARs was performed with a transformation method of relevant dose volume histograms in terms of α/β=3 [22].

Patient monitoring and follow up

The follow up was monthly for the first 3 months, every 6 months for the next 2 years and yearly thereafter. The follow up evaluation included physical examination, blood and serum exams and CT scan of the thorax and ultrasound of the abdomen annually. The evaluation of response was according to Response Evaluation Criteria In Solid Tumors (RECIST) criteria [18]. The combined RTOG/EORTC [23] criteria were employed to assess toxicity for esophagus and lung. The recurrence was estimated in the treated field of radiation therapy.

In the current study, the primary endpoints were the PDFS, OS and symptom palliation. Secondary endpoints were toxicity and duration of toxicity of the two schedules. The hypothesis made was the potential superiority of the irradiation course of 3 weekly fractions (2x8.5Gy+1x6Gy), in terms of primary endpoints.

Statistics

Pearson x^2 test was used to test the relationships between categorical variables. Mann-Whitney U nonparametric test was used for statistical comparisons between mean values. Survival was analyzed using Kaplan Meier method and log rank test. A p value less than 0.05 was considered as statistically significant. All statistical analyses were performed using the SPSS 8.0 package (SPSS, Inc, Chicago, IL).

Results

As shown in Table 1, the patient characteristics, regarding T, N stage, ECOG performance status and age were homogeneous between the two groups indicating satisfying randomization.

The calculated values of BED for either tumor or acute responding normal tissues are shown in Table 2.

The calculated BED for tumor control (α/β=3-3.9) in group A-schedule was 69 Gy vs 69.28 Gy in group B. This demonstrates that schedule B might slightly be more effective in favor of tumor control due to higher BED delivered to the tumor bed.

By calculating BED for acute toxicity (α/β=10), the toxicity in group B was lower. On the contrary, BED for late responding normal tissues (α/β=3) was higher in group B (83.16 vs 78 in group A) , which might increase the probability of late toxicity (chronic pulmonary fibrosis and esophagitis..

Radiotherapy was more effective in group B (Figure 1), since DFS was better in group B than in group A (p=0.023, log rank test). However, median OS had no significant difference between groups (p=0.231, log rank test), as shown in Figure 2.

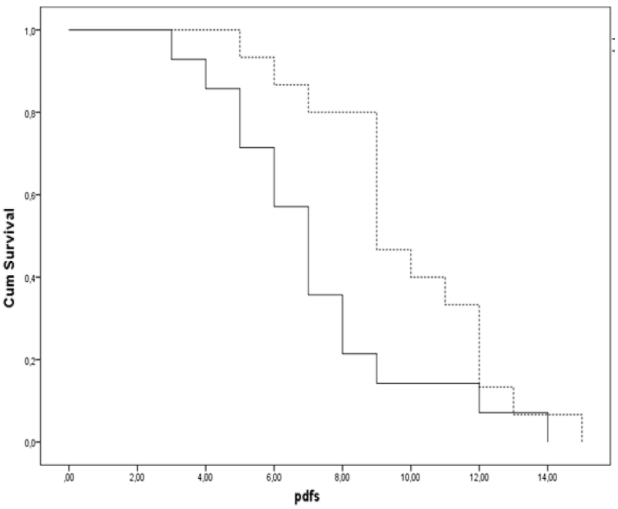

Figure 1. Median PDFS in months was 4.78 (SE:0.61) for group A versus 7.07 (SE:0.59) for group B (p=0.023, Log rank test).

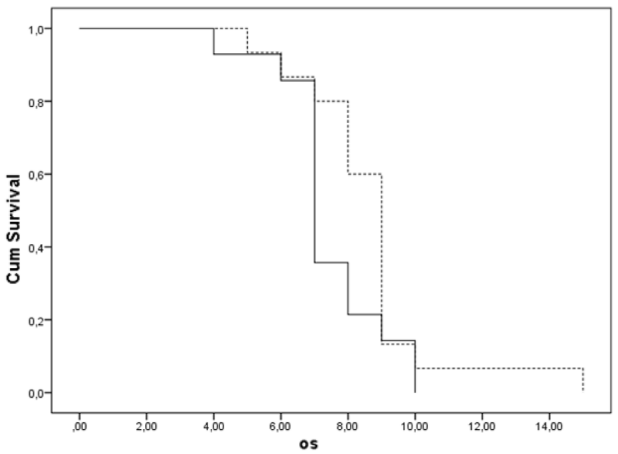

Figure 2. Median OS in months was 7.43 (SE:0.42) in group A versus 8.67 (SE:0.57) in group B. (p=0.231, Log rank test).

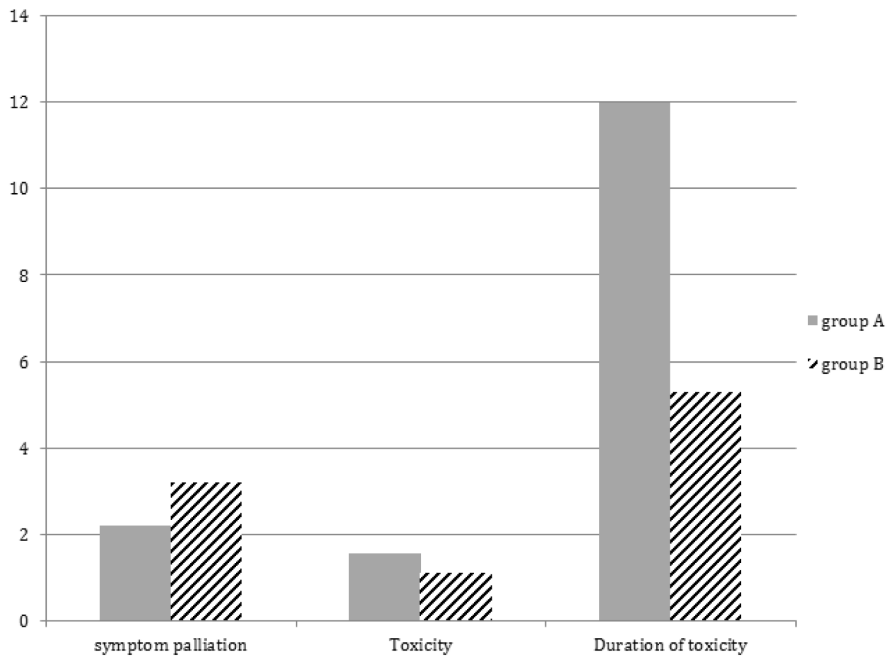

Figure 3. Symptom palliation was 2.21±0.97 and 3.20±1.21 in group A and B respectively (Mann Whitney U test p=0.037) EORTC/RTOG toxicity was 1.57±0.51 in group A versus 1.13±0.35 in group B (Mann Whitney U test p=0.046). Duration of toxicity was 12.0±4.5 days in group A versus 5.3±4.7 in Group B (Mann Whitney U test p=0.001).

Figure 3 shows symptomatic outcome and duration of radiation-induced toxicity. Mean values for symptom palliation was higher in group B 3.20±1.21 and 2.21±0.97 in group A (p=0.037, Mann-Whitney U test). EORTC/RTOG toxicity was higher in group A (1.57±0.51 vs 1.13±0.35 in group B; (p=0.046, Mann-Whitney U test). Duration of toxicity was lower in group B compared to group A (p=0.001, Mann-Whitney U test).

Discussion

Hypofractionated radiotherapy with high doses per fraction has been avoided in the treatment of NSCLC with curative intent, due to the fear of increasing toxicity for late-reacting normal tissues, which is quite logical. On the other hand, shortening of overall treatment time increases the biological effect on tumors [15,16]. Hypofractionated radiotherapy in locally advanced inoperable symptomatic patients with NSCLC is well established by a number of studies, as it offers acceptable palliation compared to conventional schedules and lacks severe toxicity, probably due to lower biologic total dose and in cases of tight radiotherapy design [15]. In fact, hypofractionation could achieve a positive change in the therapeutic ratio, using modern highly conformal radiation techniques, as lung toxicity is volume-dependent and the major volume of normal tissues is about to receive lower total dose with lower dose per fraction compared to the actual tumor itself [1,2,16].

In a phase II trial [3] in locally advanced NSCLC patients, after induction chemotherapy, the delivery 65-68 Gy hypofractionated radiotherapy (50 Gy/20 fractions and then a fraction of 3 Gy), without elective nodal irradiation, resulted in minimal toxicity. In another randomized trial by Macbeth et al [4] in the same group of inoperable not suitable for radical treatment NSCLC patients, but with good performance status, the delivery of 17 Gy in 2 fractions 1 week apart or 39 Gy in 13 fractions 5 days/week were compared. The palliative effect was more rapid in the first group and dysphagia was less common and lasted fewer days, the same results with our study. What is of great interest is that when patients were asked to participate in the RT-schedule decision-making, in a study by Tang et al [5], 55% of them preferred the longer schedule due to promising prolonged survival, when 45% chose the shorter one due to duration, lower cost and rapid symptom relief despite the reported lower survival. All patients reported satisfied being able to participate in the decision, even though the radiation oncologist had the right to alter schedules and eventually did so in 56% of the second group [5].

However, a larger phase III trial in 421 advanced NSCLC patients with stages III/IV [7], which compared hypofractionated thoracic radiotherapy of 17 Gy/2 fractions or 42 Gy/15 fractions or conventional 50 Gy/25 fractions demonstrated no differences in symptom relief, quality of life or survival between schedules.

Another prospective randomized trial in 120 patients by Slawson et al [6], once-a-week 5 Gy up to 60 Gy vs conventional fractionation, revealed an advantage of hypofractionation in rates of complete response, survival, tolerance and no difference in late toxicity.

As regards to patients with poor performance status (ECOG PS≥2), a prospective trial [8] suggested that the delivery of 2 fractions of 8.5 Gy a week apart, provided sufficient symptom relief 4 months after RT ,reported no esophagitis, pneumonitis or myelopathy and outlined the importance of reducing treatment time, providing patients with additional time at home. Additionally, a multicenter randomized trial by MRC (Medical Research Council) in 235 patients not candidates for radical treatment proposed a single 10 Gy fraction (F1) compared with 2x8.5 Gy (F2), with equal palliation from symptoms, less dysphagia and slightly longer reported survival, as an acceptable alternative for patients with poor performance status [9]. A different schedule with 4 fractions of 5 Gy per week up to 20 Gy was suggested by Bhatt et al, which provided adequate symptom relief without severe acute toxicity, which was convenient for patients with difficulties to access daily treatment [10].

Other hypofractionated schedules suggested by Plataniotis et al included 3 fractions of 4.25 Gy the first day and 2 fraction of 4.25 Gy the second day compared to 2x8.5 Gy a week apart, resulted to equal symptom relief and median survival and have been proven convenient for distal habitants [13]. The same authors also suggested that the total tumor volume had no impact on symptom control rate, but could have on survival [14].

A systematic review of the literature in 2015 by Stevens et al [11], including 14 randomized trials and 3576 patients receiving 19 different palliative radiotherapy regimens for thoracic symptoms of NSCLS, from single 10 Gy fraction to conventional 60 Gy/30 fractions, provided no strong evidence for greater or more durable palliation with any regimen and concluded that the speculation of prolonged survival is not adequately evidence-based. A meta-analysis in patients with poor performance status revealed no difference in 1-year survival [11].

Additionally, a large study with 1250 patients with advanced/metastatic NSCLC, treated with short, split-course palliative thoracic radiotherapy reported adequate palliation and good tolerance in 92% of them [12]. Acute pneumonitis was reported in 2.3% and more rare nausea, hemorrhage and severe esophagitis (0.6%), while 6 patients developed chronic pulmonary fibrosis, 1 myelopathy and 0.2% broncho-oesophageal fistula, which were considered as relatively acceptable toxicity [12].

NSCLC remains a disease with dismal prognosis affecting patients' quality of life [24]. Observing all previous studies in patients with poor performance status, hypofractionated radiotherapy is established in advanced/metastatic NSCLC patients. Thus, in our study we compared two hypofractionated radiotherapy schedules in a homogeneous population of patients for parameters like stage, ECOG performance status and age. By calculating BED for α/β=3.9, group B schedule seems to have an advantage in delivering a higher BED to the tumor (69.28 vs 69 Gy). Moreover, esophageal toxicity seems to be a main criterion for radiation induced toxicity [25]. The expected acute toxicity seemed lower by calculating BED for α/β=10 (41.5 vs 50.7) vs group A schedule. The above were noted as a clinical outcome in terms of lower radiation-induced esophageal toxicity in favor of group B. This was related to either lower or lesser duration of esophagitis for group B. On the contrary, BED for late-responding normal tissues (α/β=3) seems higher in group B (83.16 vs 78 in group A), which could increase the probability of chronic pulmonary fibrosis. However, this might not be the case for this kind of patients with poor prognosis. This was actually the reason for choosing this schedule for our routine clinical practice focusing on elderly patients with advanced stage NSCLC and unfit for chemotherapy [17]. Yet, considering that our study aimed to focus on elderly patients with poor performance status, a more convenient schedule which offers adequate palliation, good tumor control and acceptable toxicity and which offers less hospitalization, could be an obvious clinical advantage for patients with dismal prognosis and in accordance with the evidence from the literature.

However, the original goal could not be met, due to poor accrual and rather rely on descriptive statistics. Moreover, the shorter schedule could be an option, but it is definitely not possible to claim superiority. It should be also stated that no safe conclusion can be drawn due to the small number of patients included and evaluated in the study. Definitely, related to the limitations of the current report, another prospective study with increased number of patients stands in need.

Conflict of interests

Nothing to declare. All authors state that subjects have given their informed consent and that the study protocol has been approved by the institute's committee on human research. Further, we also state that animal experiments were not performed in our study.

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