Original Article

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STUDY OF EFFICACY AND TOXICITY OF HYPOFRACTIONATED THORACIC RADIOTHERAPY 17 GRAY IN 2 FRACTIONS FOR PALLIATION IN ADVANCED NON-SMALL-CELL LUNG CANCER

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ABSTRACT

Objectives: To determine the efficacy and toxicity of hypofractionated thoracic radiotherapy 17 Gray (Gy) in 2 fractions for palliation in advanced non–small-cell lung carcinoma.

Study design: A quasi-experimental study.

Place and duration of study: Oncology department, Combined Military Hospital, Rawalpindi, from 4th July 2008 to 4th Nov 2009.

Material and Methods: Fifty four patients with histologically and/or cytologically confirmed unresectable stages III and IV non small cell lung cancer, with performance status 2 or 3 and expected survival ≥ 2 months were treated with megavoltage radiation therapy 17 Gy in 2 fractions one week apart, with symptoms due to intrathoracic disease (cough, dyspnea and hemoptysis) and toxicity due to radiation therapy (dysphagia secondary to esophagitis) assessed as per common toxicity criteria adverse event version 3.0 on day 0 before treatment and day 30 after start of treatment.

Results: Grades of cough, hemoptysis and dyspnea showed significant improvement after treatment (p<0.001). A total of 42.68% patients showed an improvement in grade of cough (23 out of 54 patients), 85.7% of patients showed improvement in grade of hemoptysis (36 out of 42 patients) and 55.65% patients showed improvement in grade of dyspnea (30 out of 54 patients). Twenty two point two percent patients (12 out of 54) showed increase in grade of dysphagia. Although, there was a statistically significant increase in grade of dysphagia after treatment but it was limited to grade 1 and 2 only. Considering that no patient had grade 3 or 4 dysphagia, this toxicity was acceptable.

Conclusion: Based on our results hypofractionated thoracic radiotherapy, 17 Gy in 2 fractions, is effective with acceptable toxicity in palliation in advanced non small cell lung cancer and is recommended as it will result in shorter duration of hospital stay and low hospital stay charges.

Keywords: Non–small-cell lung cancer, Palliative, Radiotherapy.

INTRODUCTION

Non–small-cell lung carcinoma (NSCLC) accounts for 75% to 80% of all lung cancers[1]. More than two thirds of patients will present with stage III or IV disease. A majority of these patients will have symptoms from the primary tumor, including dyspnea, cough, and hemoptysis. Thoracic radiotherapy (TRT) is an effective treatment modality in relieving symptoms in up to 90% of patients[2].

Metastatic lung cancer and locally advanced inoperable cancers, not suitable for curative radiotherapy (RT), yield a poor prognosis with relatively short survival (4 to 7 months). Consequently, a limited treatment period using hypofractionated RT is advocated provided adequate palliative efficacy is attained[3].

Thoracic radiation therapy has always been an important treatment modality in advanced NSCLC for patients with symptoms from intrathoracic disease, however, there is still no consensus on which fractionation scheme should be used[3]. If one assumes an α / β of 2 for late responding tissues, 17 Gray (Gy) in 2 fractions is the radiobiologic equivalent of 45 Gy in 25 fractions or 36 Gy in 12 fractions by the linear-quadratic formula[4]. Studies suggest that higher dose per fraction palliative EBRT regimens (eg, 30 Gy/10 fractions equivalent or greater) are associated with modest improvements in survival and total symptom score, particularly in patients with good

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performance status. As these improvements are associated with an increase in esophageal toxicity, various shorter EBRT dose/fractionation schedules (e.g., 20 Gy in 5 fractions, 17 Gy in 2 weekly fractions, 10 Gy in 1 fraction), which provide good symptomatic relief with fewer side effects, can be used for patients requesting a shorter treatment course and/or in those with a poor performance status[5]. Data by Sundstorm et al indicates that protracted palliative TRT renders no improvement in symptom relief, quality of life, or survival when compared with short-term hypofractionated treatment of 17 Gy in 2 fractions in advanced NSCLC[3].

Fractionation scheme for the relief of symptoms in advanced NSCLC needed to be evaluated in our setting. Although, hypofractionated thoracic radiotherapy for symptom relief from intra-thoracic disease in advanced NSCLC is an established protocol and part of Royal College of Radiology and American Society for Radiation Oncology[6] treatment recommendations, after a thorough review of literature we were not able to find a local or loco-regional study which had evaluated the efficacy and toxicity of strict hypofractionated protocols for palliation of symptoms due to intra-thoracic disease progression in NSCLC. This study was aimed at analyzing the efficacy and toxicity of a strict hypofractionated TRT schedule, 17 Gy in two fractions. If efficacious, patients would benefit with fewer visits to the hospital, reducing cost of treatment and leading to better quality of life, decreased workload on our Linear Accelerator, and as a result improving the treatment quality of patients requiring radical treatment.

MATERIAL AND METHODS

This study was carried out at Oncology department, CMH Rawalpindi. The study was conducted from 4th July 2008 to 4th Nov 2009. Fifty five patients with histologically and cytologically confirmed NSCLC, age ≥ 18 years and both genders, stage III or IV disease (among patients with stage IIIA disease only inoperable patients), centrally located tumor causing airway symptoms or without symptoms but threatening central airways, Eastern Cooperative Oncology Group performance status (ECOG PS) 2 to 3 and expected survival ≥ 2 months were included. Patients with relapse in the chest after previous surgery and those who had received previous chemotherapy were also eligible. Patients with past or present history of concomitant second primary, those who had received previous RT or patients with superior vena cava syndrome (SVCS) at presentation were excluded from the study.

After selection and registration, patients were subjected to the following diagnostic work-up: physical examination, radiological examinations like chest x-ray and/or computed tomography (CT) scan of the chest, and biochemical profile (cell counts, erythrocyte sedimentation rate, alkaline phosphatase, alanine transaminase). ECOG PS was documented. Cerebral CT scan or magnetic resonance imaging (MRI) and bone scans were performed if indicated. Disease staging was done according to the 2005 AJCC TNM classification.

Thoracic radiotherapy was delivered at the Oncology department, CMH Rawalpindi, with opposing anterior-posterior fields, individually encompassing the regional mediastinal lymph nodes and the primary tumor with a 1.5- to 2-cm margin. Supraclavicular region was not routinely treated unless palpable regional nodes or primary tumor was located in the apical region of the lung. Portal size did not exceed 200cm^2. Megavoltage RT with a 6- or 15-MV photon beam was used. The RT fractionation scheme was two fractions of 8.5 Gy, on days 1 and 8, to a total dose of 17 Gy. To prevent possible side effects from larger fraction size, Prednisolone 50mg bid was administered prophylactically on days -1, 0 and +1.

Symptoms including cough, hemoptysis, dyspnea, and toxicity (dysphagia) were graded from 1 to 5 according to National Cancer Institute (NCI) Common Toxicity Criteria for Adverse Events Version 3.0 (CTCAE version 3.0) at baseline (day 0) before intervention and at day 30 after start of treatment. Data at day 30 was compared with pre-intervention data to

determine the efficacy and toxicity of hypofractionated TRT in palliation of advanced non-small-cell lung cancer.

Data analysis was computer based with the use of SPSS version 15. Mean and Standard Deviation were calculated for quantitative variables like height, weight and BSA. Frequency and percentages were computed for qualitative variables like gender, histopathology, stage, previous chemotherapy and each symptom grade. Sign test was applied to compare symptoms grade before and after intervention. A *p*-value <0.05 was considered as significant.

RESULTS

A total number of 54 patients of non-small-cell lung carcinoma (NSCLC) were included in the study from Oncology outpatient department. The average age of the patients was 63.65 ± 5.69 years with a range of 51 to 75 years. There were 52 (96.3%) male and 2 (3.7%) female patients. Twenty seven (50%) patients had histopathological diagnosis of adenocarcinoma, 23 (42.69%) patients had squamous cell carcinoma and 4 (7.4%) patients had diagnosis of large cell carcinoma. Thirty patients (55.65%) presented with stage III B NSCLC, 16 (29.6%) with stage IV disease, 7 (13%) with stage IIIA NSCLC, as per 6th edition of TNM classification, and only 1 (1.8%) patient had relapse after surgery. Four (7.4%) patients had previously received chemotherapy and 50 (92.6%) patients were chemo naive.

The pre and post radiation therapy frequency of distribution of grades of cough, hemoptysis, dyspnea and dysphagia is shown in figure 1, 2, 3 and 4 respectively.

The comparative analysis of grades of symptoms assessed, for improvement with treatment, showed that all the symptoms improved significantly (p<0.001) with treatment. Similarly there was a significant difference in grades of dysphagia after treatment i.e the grades of dysphagia increased significantly after treatment at day 30.

DISCUSSION

Most patients with NSCLC present with inoperable advanced tumor and the majority of disease symptoms are related to its local intra thoracic progression. In patients who are not candidates for surgery or radical chemo-radiotherapy, the main aim of treatment is symptom palliation[6]. No consensus has been developed on which fractionation scheme to be used for palliative thoracic radiation therapy. Different treatment protocols have been

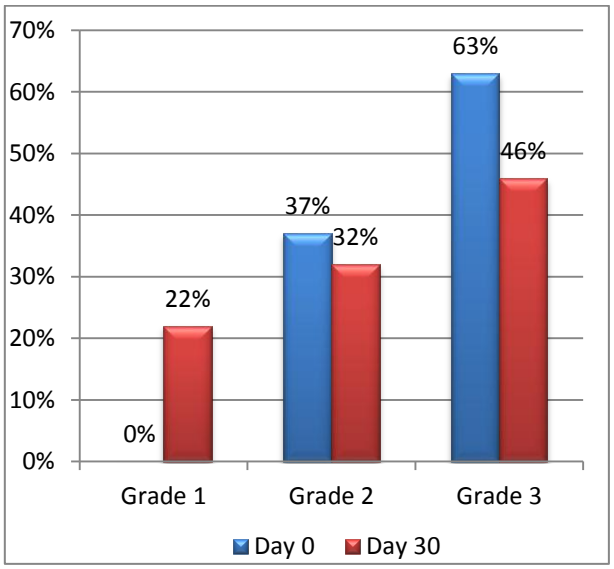

Fig. 1: Distribution of grade of cough at day 0 and day 30.

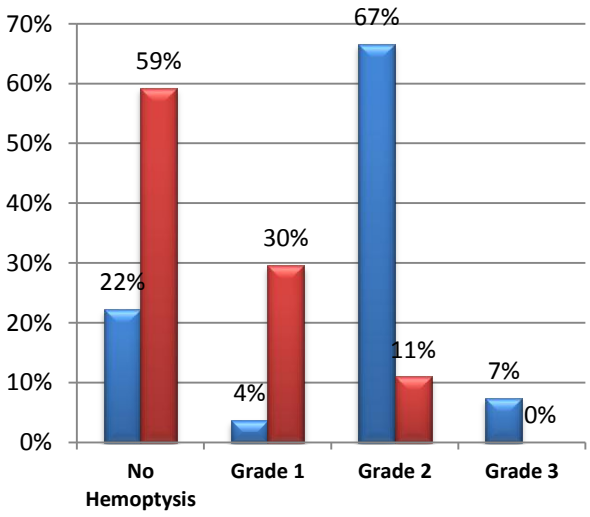

Fig. 2: Distribution of grade of hemoptysis at day 0 and day 30.

developed, leading to a variety of fractionation schedules, ranging from 10 Gy single fraction to 60 Gy in 30 fractions[7]. Fractionation preferences

for palliative thoracic radiotherapy seem to have been influenced more by local institutional RT capacity than by any national, cultural, or attitudinal impacts[8].

Commonly used treatment schedules are based on tradition rather than on clinical research results[9]. The sources of reluctance towards hypofractionated treatment protocols include the lack of experience with large single fraction, concerns about its acute toxicity and uncertainty about the appropriate patient selection for hypofractionated therapy[10].

Considering the limited expected survival, treatment of these patients should be short and non-distressing[3,11]. Over the last 30 to 35 years, several attempts have been made to develop fractionation schedules combining effective symptom control and short treatment period which would improve comfort of patients, minimize hospitalization and save on the use of radiotherapy resources, which are still deficient in many countries including Pakistan.

The equivalence of shorter versus longer radiotherapy schemes in terms of symptom control has been demonstrated in a series of randomized studies, including studies published by Simpson et al in 1985[12], Medical Research Council Lung Cancer Working Party in 1991[13], Medical Research Council Lung Cancer Working Party in 1992[14], Abratt et al in 1995[15], Nestle et al in 2000[16], Kramer et al in 2003[17] and Sundstrom et al in 2004[3]. As a result of published trials by Jassem 18 and Macbeth et al[19], a general conclusion was made that selected advanced and symptomatic NSCLC patients should be treated with just 1 or 2 fractions of palliative radiotherapy (American Society of Clinical Oncology, 1997[9]). The Royal College of Radiologists also recommends 17 Gy in 2 fractions for effective palliation in patients with NSCLC and moderate to poor performance status in patients with unresectable NSCLC ineligible for curative radiotherapy, based on the results of three randomized trials between 1985 and 1992 by Medical research council[13,14].

No such study had been carried out earlier at our centre to determine efficacy and toxicity

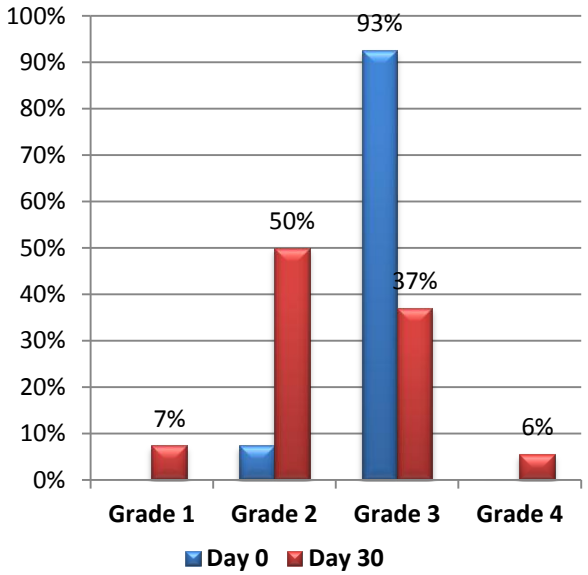

Fig. 3: Distribution of grade of dyspnea at day 0 and day 30.

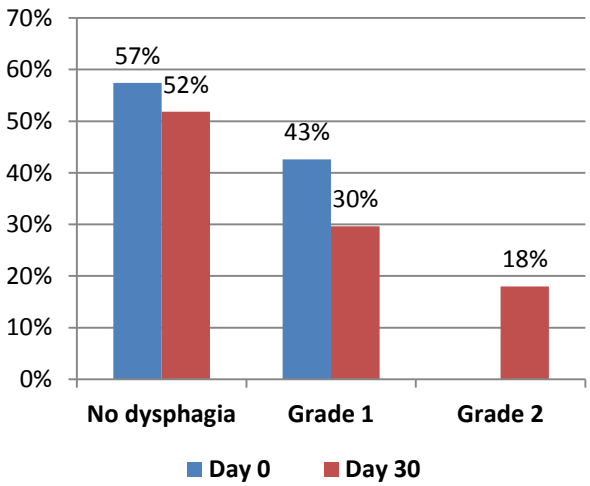

Fig. 4: Distribution of grade of dysphagia at day 0 and day 30.

of hypofractionated thoracic radiotherapy. This study was designed and carried out considering the meagre radiotherapy resources available, huge workload of palliative TRT for advanced NSCLC, lack of consensus, and shakiness in confidence to deliver strictly hypofractionated TRT. As patients in advanced NSCLC have poor prognosis with regard to overall survival (OS), only relief of intra-thoracic disease related symptoms (dyspnea, cough and hemoptysis) was studied along with grade of dysphagia resulting from radiation induced esophagitis, observed as the main toxicity.

Our study showed statistically significant benefit of hypofractionated palliative TRT for

relief of disease related symptoms with grade of cough, hemoptysis and dyspnea showing significant improvement after treatment. Although, there was a statistically significant increase in grade of dysphagia after treatment but only 16 patients (29.6 %) had grade 1 and 10 patients (18.5%) had grade 2 dysphagia. Considering that no patient had grade 3 or 4 dysphagia, this toxicity was acceptable. Results achieved in our study are remarkably similar to those seen in other studies. Norwegian phase III trial of hypofractionated TRT by Sundstrom et al[3] showed improvement in clinicians assessed dyspnea and cough by 40 to 55% and palliation of hemoptysis in 90% after treatment with hypofractionated 17 Gy in two fractions. Polish prospective phase III study by Senkus-konfka et al[6] comparing 16 Gy in 2 fractions to 20 Gy in 5 fractions showed similar results in palliation of cough (57%), dyspnea (65%) and hemoptysis (100%) in 16 Gy arm. Studies by Sundstrom et al and Senkus-konfka et al were multicenter randomized trials comparing hypofractionated and more protracted radiation therapy protocols with longer follow ups compared to our study, but the results seen in the hypofractionated arm for palliation of symptoms arising from intra thoracic disease were quite similar to those seen in our study.

Like all the studies showing equivalence of shorter vs longer radiotherapy treatment schedules, we have used relatively simple 2-D conventional treatment planning system rather than sophisticated three-dimensional methods used in protracted radiotherapy regimens. The results show that this easy to administer and nontoxic regimen has resulted in effective and durable palliation of main symptoms. Apart from purely medical factors, such an approach has logistic and economic benefits as well, which is of particular importance in third world countries like Pakistan.

CONCLUSION

To conclude, our study has confirmed the efficacy and tolerance of hypofractionated TRT for palliation of symptoms resulting from advanced intra-thoracic bronchial malignancy. Short duration treatment is convenient and effective for patients with limited survival. Furthermore hypofractionation may release radiotherapy machines and make radiotherapy equipment available for curative cases requiring higher dose protracted radiation therapy.

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