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Original Research

Palliative Fractionated Radiotherapy for Thoracic Non-Small Cell Lung Cancer: A Prospective Comparative Study

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Background: Many patients with lung carcinoma present to the clinic with advanced disease and moderate to severe symptoms. Palliative radiotherapy (PTR) to the chest can alleviate symptoms related to intrathoracic pathology. The timing and fractionation schedule of PTR are critical for achieving symptomatic relief and response. Typically, the effects of radiotherapy become apparent within three months. This study aimed to investigate survival after PTR and evaluate symptomatic relief and adverse effects of different radiotherapy schedules.

Methods: This prospective study included patients with non-small-cell lung cancer (NSCLC) who were scheduled to receive PTR between January 2022 and October 2022 at ATRCTRI Bikaner, Rajasthan. Data collected included pathology, tumor, node, and metastasis (TNM) classification of malignant tumors, stage, indication for PTR, starting date, radiotherapy schedule, completion status (yes/no), performance status (PS), and time of death.

Results: Among 86 patients enrolled, 12 did not complete their radiotherapy course. The remaining 74 patients who received PTR were included in the analysis. Thirty patients (40%) died within 30 days of treatment, and 15 patients died within three months. Only 20 patients remained alive at six months. Symptomatic relief was observed more frequently with 20 Gy in 5 fractions. Survival was associated with PS 1-2 and 30 Gy/10 fractions. Dyspnea, hemoptysis, and superior vena cava (SVC) syndrome were the most common indications for PTR in this study. Almost all patients presented with more than one indication for PTR. The fractionated schedule of 30 Gy/10F was used more frequently in patients with good PS.

Conclusion: This study shows that a significant number of patients who received PTR died before they could achieve the optimal effects of treatment. Performance status and histology were significant prognostic factors, with better outcomes observed in patients with PS 1-2 and squamous cell carcinoma. Based on our findings, we suggest that patients with PS 1-2 should be considered for fractionated PTR, while patients with PS ≥ 2 should be considered for shorter fractionation schedules or best supportive palliative care.

Introduction

Lung cancer poses significant public health challenge and remains one of the most prevalent and deadly form of cancer worldwide. GLOBOCAN 2020 estimates of cancer incidence and mortality produced by the International Agency for Research on Cancer. Worldwide, an estimated 19.3 million new cancer cases and almost 10 million cancer deaths occurred in 2020. Lung cancer still the leading cause of cancer-causing deaths, with an estimated of 1.8 million deaths (18%), followed by colorectal (9.4%), and liver (8.3) [1]. Non-small-cell lung cancer (NSCLC) is the leading cause of cancer related morbidity and mortality [2]. More than 50% of the patients have distant metastases while diagnosis and most of the patients have signs or symptoms of dyspnea, cough, hemoptysis etc [3]. Median overall survival (OS) in all stages of lung cancer with no treatment or with platin-chemotherapy is just seven months and eight to ten months, respectively [4]. Considering the poor prognostic setting and the clinical symptoms which often affect quality of life (QoL), it is important to focus on a best supportive care with meaningful palliative plan. Palliative thoracic radiotherapy (PTR) can relieve symptoms and improves QoL in about one third of all patients [5]. An optimal radiotherapy regimen will alleviate symptoms with less toxicity and consider the time investment for the patient. A recently done systematic review [6] found that long and more fractionated regimens approaches gave no better palliation and there were no significant survival benefits with longer regimens with higher BED. Lung cancer is affected by many factors, such as environmental and behavioral factors; the most important one is smoking cigarettes. The risk of lung cancer in smokers is 20 times higher than non-smokers and it is directly related to the duration, amount, and manner of consumption Occupational exposure to carcinogens (asbestos, arsenic, and other aromatic hydrocarbons), air pollution caused by fuels, underlying lung diseases, family history of lung cancer, nutritional factors (vitamins A, B, and C), substance abuse, and opioids consumption, are other major risk factors for lung cancer. These factors vary according to race, country, and region. Another factor that is HDI (Human Development Index) can affect the incidence and mortality of lung cancer. The index is a function of health, quality of life, health facilities, lack of anxiety, relaxation, and economic and social security. According to various studies, the incidence of lung cancer in developed countries is 1.5 to 2.3 times higher than that of the less developed countries in any age group. Most cancers are not only the result of abnormal genes, but also the result of environmental factors and socioeconomic status [7-10]. Most patients who present with locally advanced or metastatic lung cancer are treated with palliative intent, with the goals of relief of pain and other symptoms, and preservation of quality of life (QoL). Palliative radiotherapy (RT) is effective to improve the symptoms like hemoptysis, cough, chest pain, dyspnea, and airway obstruction in approximately one third of patients hence, improves global QoL [5, 11,12]. Most patients (between 75% and 85%) have non–small-cell lung cancer (NSCLC) (squamous cell, adeno-, and large cell undifferentiated carcinomas), of whom only 15% to 25% will have tumorsthat are potentially curable. The remainder are thought to be incurable, either because of the extent of local tumor or because of known metastases. Radiotherapy to the primarytumor in the chest has been used to treat patients for many years. Although high-dose, radical radiotherapy can be used in a small number of patients with the intention oflong-term disease control or cure, it is more often used in lower doses with the aim of palliating troublesome local.

Materials and Methods

Patients planned for PTR (Palliative thoracic radiotherapy) between the 1st of January 2022 and 30th of October 2022 at our institute ATRCTRI Bikaner (Rajasthan). The standard palliative radiotherapy schedules were 30Gy/10F, 25Gy/5F and 10Gy/1F divided into arm A, B, C respectively. patients with pathologically confirmed NSCLC were included in this study. Age, diagnosis date, TNM classification of tumors, stage, treatment schedule, Performance status at the time of prescription of palliative RT to chest, and time of death were noted before and during radiotherapy. Prescription date was set 1 weeks prior to RT.

Statistical analysis

Statistical analyses were based on intention to treat (from prescription time to death). We investigated PS, pathology, stage, fractionated schedules (30Gy/10F vs 20Gy/5F vs 10 Gy/1F) and age below median age of the population (60 years). A two-sided p-value below 0.05 was considered statistically significant.

Results

A total of 90 patients were referred for PTR between the 1st of January 2022 and 30th of October 2022. Four patients without follow-up were excluded and 12 patients died or stop RT during treatment also excluded from study. A total of 74 patients were included for further statistical analysis.

Patient-characteristics are shown in Table 1.

Patient Characteristics	No (%)
Age at PTR start (Years)	
< 60 years	27
≥ 60 years	47
Histology	
Adenocarcinoma	16
Squamous cell carcinoma	58
Stage	
III	30
IV	44
WHO Performance Status	
1	6
2	26
3	30
4	12
PTR Schedules	
30Gy/10F (arm A)	38
20Gy/5F (arm B)	26
10Gy/1F (arm C)	10

Table 1. Patient-characteristics (n = 74).

We did not note if a patient received chemotherapy after PTR but PTR was in almost all cases the last treatment that the patient received.

Age at RT to thorax was taken as less than 60 and more than 60, in which 27 patients and 47 patients were taken respectively. Twelve patients out of 86 did not finish PTR as 7 stopped coming for RT in middle of treatment and 5 (6%) died during PTR. Of the 74 patients receiving PTR, 30 patients (40%) died within 30 days and next 12 patients died within 3 months of treatment. Only 20 patients remained alive at 6 months. Dyspnea, hemoptysis, and SVC syndrome were the most frequent indications for PTR in our study. Almost every patient noted for >1 indication. Fractionated schedule 30Gy/10F used more frequently.

Overall, the most common fractionated schedule used was 30Gy/10F and then 20Gy/5F and 10 patients received 10Gy in single fraction. Survival at 6 months was more with arm A compare to arm B and arm C (34% vs 27% vs 0 %). The different type of regimes used based on PS due to our

guidelines that suggests a shorter fractionation should be use for patients in higher PS. Patients who had PS 1 and 2 and 3 received either 3Gy /10fr or 20 Gy /5 fr schedule (Table 2).

		Arm A	Arm B	Arm C
Total Patients		38	26	10
1st Month	Death	13	10	7
	Live	25	16	3
6th Month				
	Live	13	7	0
% Survival at 6 months		34%	27%	0

Table 2. Survival of Patients after RT.

Discussion

Multiple randomized trials with different dose/ fractionation schedules have shown that thoracic palliative EBRT can be used to give symptomatic relief in locally advanced or metastatic lung cancer, who cannot be treated with curative intent. In present study we have compared three different dose fractions of palliative thoracic radiation. Arm A patients received 30Gy/10 Fractions (3Gy/fraction once in a day), Arm B patients received 20Gy/ 5 fractions (4 Gy daily AP and PA) and arm C received 10 Gy in single fraction. A study by Jindal and behrar [14] on Indian population showed significance of age and gender in carcinoma lung incidence, in which they found median age of 54.6yrs for males and 52.8 years for females and male to female ratio of 5.6:1. Literature reports development of lung cancer in later decades of life with less than 11% population below the age of 40 years. In our study we divided the patients into 2 groups, less than 60 and more than 60. Most of the patients belong to age more than 60 years. This shows that lung cancer mostly found in later decade of life. Our results support that a significant number of patients in our department received fractionated PTR.

Van Oorschot et al. [15] found, in his study that 12.7% of the patients with NSCLC receiving RT to chest expired within 30 days of completion of treatment. In our study 40% patients died in 1st month after treatment finished that is significantly more than above study. Gripp et al. [16] looked specifically at patients (all diagnosis) dying within 30 days of palliative radiotherapy to identify prognostic factors and found that Karnofsky score < 50% (WHO PS 3-4), brain metastases and dyspnea at rest to be independently associated with an unfavorable prognosis. We found that patients did not live long enough to achieve the optimal effect of the RT since 40% died within 30 days of treatment. This is also seen with our data that PS is very important prognostic factor. We found a significant difference in OS between PS 0-2 and 3-4 in favor of patients in PS 0-2. Van Oorshot et al. [15] took 120 patients for investigation of prognostic factors with NSCLC, receiving different fractionated regimens and found that PS, but not comorbidity, were significant predictors for survival. Few studies also denoted that histology also prognostic factor in palliative radiotherapy but found statistical insignificance [15,16]. Despite these not any study, mentioned above showed that age is also prognostic factor. After this we can say that elderly patients should not be treated different than the younger patients, as showed by Turner et al [17]. In our study we also did not give different fractions based on age. At our institution we found that dyspnea, cough, and pain were the most frequent indications for PTR. Other indication was hemoptysis. Another two studies [18,19] showed that if radiotherapy given to asymptomatic patients, it will not prevent disease symptoms and no impact would be seen on survival. Therefore, if patient is asymptomatic than radiotherapy can be delayed till symptoms appear. Sharma V [20] were randomized Sixty patients to one of the 3 treatment arms; Arm-1: 20 Gy in 5 fractions within one week, Arm-2: 17 Gy in 2 fractions with a one-week interval and Arm-3: 10 Gy in 1 fraction. The purpose of the study was to find the most effective and shorter schedule for palliation of symptoms. the presenting symptoms which included cough, chest pain, dyspnea, and hemoptysis. All symptoms improved significantly

except dyspnea. In our study we divided patients in 3 arms where dyspnea, cough, chest pain and hemoptysis were most common presenting symptoms. dysphasia, fever, neck swelling, pain in other parts were uncommon presentation (5%). These symptoms occur as a result of tumor related compression and irritation. Symptoms relief evaluated at 1 and 3 months after treatment completed. Dyspnea relieved on radiation treatment noticed in both arm A and arm B. More number of patients relieved from dyspnea in arm B. 2 patients treated with 20 Gy/5 fr had reappearance of dyspnea at 3rd month. Another symptom noticed in both arms of this study is cough. In cough it got relieved by radiation in both arms, rapid relief noticed in arm B than arm A. Other symptoms were chest pain and hemoptysis. In both arms' response of chest pain to radiation treatment is good and was noticed that in both arms' chest pain relieved in both arms. Rapid relief of hemoptysis was seen in arm B. Cross CK [21] conducted a prospective study of palliative hypo fractionated radiotherapy (8.5 Gy/ # 2) for patients with symptomatic non–small-cell lung cancer Two "involved-field" fractions of 8.5 Gy were delivered to 23 patients with symptomatic NSCLC for 1 week apart. Patients were assessed for efficacy, toxicity, and tumor response at baseline, treatment completion, and 1 week, 1 month, and 4 months after completing radiotherapy. At 4 months after treatment, the PS had improved for 3 patients, worsened for 1 patient, and remained stable for 19 patients. Six patients experienced mild (Grade 1) skin erythema after RT that improved within 1 month. Grade 2 or greater skin reactions were not seen. No cases of any grade of esophagitis, pneumonitis, or radiation myelopathy occurred. Grade 4 dyspnea developed in 1 patient within 1 month after starting RT. This was due to a progressive pleural effusion and, therefore, most likely was unrelated to RT. In our study toxicities like esophagitis, pneumonitis, skin reaction was noticed. Skin reactions were seen more than other toxicities like pneumonitis and esophagitis in arm A (Table 3).

Symptom Control		1st Month F/U	3rd Month F/U
Dyspnea	Arm A	17/23	13/16
	Arm B	15/18	8/10
Hemoptysis	Arm A	20/23	13/16
	Arm B	16/18	10-Sep
Cough	Arm A	19/23	13/16
	Arm B	13/18	14/16

Table 3. Symptom Control in both Arms.

There is no grade III and grade IV toxicities noticed in this study. Grade 1 and 2 skin reactions are seen in few patients with all fractionation type but more commonly seen with arm A. In our study we observed response of disease to radiation treatment was by imaging technique (x ray chest) at 3rd month and 6th month of treatment. There was no complete response of disease in any of arm. In this study based on Yale's grading SVC symptoms were compared in both arms, here it was observed that rapid relief noticed with arm B than arm A and it was noticed that reappearance of symptoms were more with arm B than arm A. It was observed that most patients expired during the study period more patients expired in arm B. So, in this study based on symptom relief, disease response, toxicity it was observed that arm A is better treatment regime than arm B and depend on PS as higher PS should be treated with shorter fractionation schedule or best supportive care. X ray imaging during follow up for disease response evaluation and smaller number of patients remains the major limitations of this study. Here we can use CECT chest to overcome these problems for follow up, so that accurate evaluation of disease status will possible and we have to take large number of patients for study.

In conclusion, this single institute comparative study evaluated and compared three dose fraction regimes of palliative thoracic radiotherapy for advanced lung cancer. Eighty-six patients of advanced stage carcinoma lung requiring palliation were randomized by simple randomization and based on performance status and divided into three arms to receive palliative RT to chest. Arm A patients received 30Gy/10 Fractions (3Gy/fraction once in a day), Arm B patients received 20Gy/ 5

fractions (4 Gy daily AP and PA). and arm C received 10 Gy in single fraction. All patients were evaluated for symptom relief like cough, dyspnea, chest pain, hemoptysis and radiation induced toxicity like skin reactions, pneumonitis, and esophagitis after 1st and 3rd month and response observed at 3- and 6-months post treatment. To conclude we can say that PS is very important factor to decide fractionation schedule. Symptomatic relief was seen more with 20 Gy in 5 fractions but overall survival was more with 30 Gy in 10 fractions but not statically significant. However, randomized trial with a greater number of patient & longer follow up are further needed to establish this schedule as one of standard palliative regimen.

Informed Consent

Research involving human participants – Informed consent was obtained from all individual participants included in the study.

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