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Stereotactic Ablative Body Radiotherapy in Non-small Cell Carcinoma Lung in Elderly: Initial Experience from a Rural Tertiary Cancer Centre

Vinin NV, Joneetha Jones*, Geetha M, Nabeel Yahiya, Shoaib Nawaz PN, Arun P Narendran, Greeshma KE, Nidhin Raj D and Resmi K Bharathan

Department of Radiation Oncology, Malabar Cancer Center, Thalassery, kerala, India,

***Corresponding author:** Joneetha Jones, Assistant professor, Department of Radiation Oncology, Malabar Cancer Center, Thalassery, kerala, India, E-mail: joneetha14@gmail.com

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Abstract

Aim: The aim of this study was to evaluate the efficacy and outcome of early stage non-small cell lung carcinoma in elderly patients treated with SABR in a tertiary care cancer centre in rural India.

Materials and methods: This was a retrospective study. All cases of histopathologically proven, stage 1 lung cancer patients in whom surgical management was not feasible due to various reasons were included. It included patients treated from 2013 to 2018 at our centre. Case records and radiation treatment plans were reviewed and data was collected. All were T1/T2N0 cases. Dose schedules employed were 48 Gy in 4 fractions, 60 Gy in 5 fractions and 60 Gy in 3 fractions. The primary end point was the tolerance and toxicity profile.

Results: A total of 5 patients were treated at our center from 2013 to 2017. All were males. Mean age was 72 years. One had squamous cell and four had adenocarcinoma histology. The dose fractionation schedules employed where 48 Gy in 4 fractions, 60 Gy in 5 fractions and 60 Gy in 3 fractions. All tolerated treatment well. No grade 3 or 4 toxicities were observed.

Conclusion: SABR is a feasible alternative curative treatment modality in stage 1 NSCLC. It is feasible and was tolerated well even in the elderly age group. This can be offered to medically inoperable patients as a curative treatment and is possible in a resource constrained setting also. This modality is a promise to future for operable stage 1 NSCLC also. But more randomized studies need to be carried out before applying it to operable lung cancer patients.

Keywords: SABR; Lung cancer; Elderly; Carcinoma

Introduction

The incidence of lung cancer in India is on a rise. In India, lung cancer constitutes 6.9 per cent of all new cancer cases and 9.3 per cent of all cancer related deaths in both sexes; it is the commonest cancer and cause of cancer related mortality in men [1]. The current standard choice of treatment for stage I non-small cell lung cancer (NSCLC) is lobectomy and mediastinal lymph nodal dissection If nodes are pathologically negative then adjuvant chemotherapy is given. If nodes are involved then adjuvant chemoradiation is given. For inoperable patients or those who refuse surgery, chemotherapy with or without radiation that is delivered in conventional fractionation is the option available [2].

The best outcomes in lung cancer have been achieved with surgery in early stage disease, because in early stages complete tumor ablation by surgery is possible. Many patients with anatomically respectable early lung cancer are not treated with surgery because of older age and multiple comorbidities [3]. Conventional radiation therapy is effective but the problem is that it does not approach surgical cure rates because it has not been possible to achieve ablative radiation dose using conventional techniques because of normal tissue tolerance [4].

Stereotactic ablative body radiotherapy (SABR) uses very short course of very conformal and dose intensive radiotherapy precisely delivered to limited size targets. The rationale for the use of SABR is the assumption that more localized radiation, will spares normal tissue. This allows higher radiation doses to be delivered without increasing toxicity. This can potentially lead to improved disease control and survival. Using SABR very high biologically effective doses in a fewer number of fractions can be delivered. It is also more convenient for the patients as the number of hospital visits is reduced.

Recent technological advances in patient positioning and development of newer immobilization systems have helped a lot in delivering highly conformal radiation treatment. Also tools for tumor motion assessment and control will also make treatment more precise. Accurate target delineation is now possible with the advent of PETCT scanning.

Although the concept of delivering high biologically effective doses is excellent it has to be weighed against the toxicity and efficacy profile. Trials have shown that SABR did not cause any major deterioration in pulmonary function tests even in severe chronic obstructive pulmonary disease [5,6]. This is a boon for many medically inoperable patients with limited lung functions. Ours is a rural based cancer center situated in northern Kerala catering to the needs of a huge population. Most of the lung cancer cases present in advanced stages. Patients who present in early stages go for surgery if they are found to be operable according to the present guidelines. But quite of few numbers of cases are deemed inoperable due to associated

comorbidities or advanced age. Also many patients refuse curative surgery in view of advanced age. Such patients are offered curative stereotactic ablative body radiotherapy if satisfying the criteria for the same.

Materials and Methods

Patients who were cytologically or histopathologically proven stage 1 non-small cell lung cancer patients were enrolled in the study. All had ECOG performance status 0 to 2. All were assessed by thoracic surgeons and were deemed inoperable due to medical comorbidities and age. One patient was not willing for surgical management. Pretreatment CT scans were taken to assess the stage of the disease. Two patients had PETCT scans prior to treatment.

Patients were immobilized with wing board and combifix immobilization system. Planning CT scans were obtained in treatment position. CT cuts were taken at 1.25 mm intervals. Tumor volumes were contoured in normal respiration, inspiratory phase and expiratory phases. The GTV was defined as the radiologically visible tumour in the lung, contoured using lung settings. Mediastinal windows were used for tumours proximal to the chest wall.

Information from PET/CT was incorporated into delineating the GTV whenever available. The Clinical Target Volume is the GTV with no margin for microscopic disease extension. Planning target volume was obtained by adding a 5 mm margin to the gross tumor volume. The dose prescription was chosen such that 95% of the planning target volume (PTV) received at least the nominal fraction dose and 99% of the target volume (PTV)received a minimum of 90% of the fraction dose The dose max within the PTV was preferably not be less than 110% nor exceed 140%.

Radiation treatment plans were generated using non coplanar beams. The aim of planning was that high-dose region should be conformal to the PTV, the medium-dose region surrounding the PTV should be compact and the low-dose region is permitted to be relatively large by comparison to the other regions Beam energy used was 6 Mv in all cases.

On board Cone beam CT images were taken and the treatment set up verified by the treating oncologist and treatment was delivered. Verification was performed to avoid a set up error of more than 5 mm in any direction.

All patients treated in our center were treated with VMAT technique Patients were assessed prior to each fraction. On completion of treatment they were followed up 6 weeks post treatment. Chest X-ray imaging was done in all patients. Subsequent visits were scheduled at 3 monthly intervals for one year and 4 monthly intervals thereafter as per institutional protocol. Chest CT scan was advised only if X-ray showed progression or if the patient was symptomatic due to logistical reasons.

Toxicity was evaluated using the Common Terminology Criteria for Adverse Events, version 4.0 [7]. Local tumor response could not be evaluated according to Response Evaluation Criteria in Solid Tumor (RECIST) in this study because of the absence of CT/PET CT scan uniformly for all patients due to logistical issues.

A consecutive increase in tumor shadow by chest CT or X-ray examination during 6 months, or a histopathologically confirmed recurrent cancer after treatment was considered to be a local recurrence. All images were reviewed by a radiologist.

Results

A total of 5 patients were treated from 2013 to 2017 in our centre. Mean age of the patients was 72 years. All patients were males.4 had adenocarcinoma and one had squamous cell histology. Patient characteristics are depicted in Table 1.

Number	Age	Sex	Histology	Side	Reason for inoperability
1	74	Male	Adenocarcinoma	Right	Comorbidity
2	75	Male	Adenocarcinoma	Left	Refused
3	75	Male	Squamous	Right	Comorbidity
4	70	Male	Adenocarcinoma	Right	Comorbidity
5	68	Male	Adenocarcinoma	Right	Comorbidity

Table 1: Patient characteristics.

All patients were evaluated by thoracic surgeon and anesthesia team and were deemed inoperable due to advanced age and medical comorbidity. One patient refused surgery. The dose fractionation employed where 4 fractions of 12 Gy each, 5 fractions of 12 Gy each and 20 Gy into 3 fractions.

Dosimetrically we were able to achieve plans in accordance with the RTOG criteria [8] and we also adopted schedules as per SABR UK consortium guidelines [9] recently. Dosimetric details are given in Table 2.

Serial no	Dose /Fraction	Vol of PTV	Vol of 100% PTV/Vol of PTV (1.1-1.2)	Vol of 50% PTV/Vol of PTV (5-7)	V20 lung (<10%)	Max dose>2 cm (38.5-44)	Conformity index	Homogenity index
1	12 GY x 4	76.7	1.2	5.3	3.2	28	1.4	0.11
2	12 GY x 4	83.07	1.19	5	1.1	30	1.2	0.42
3	12 Gy x 5	74.39	1.2	5.5	9.08	32	1.1	0.37
4	12 Gy x 5	72.25	1.1	4.6	4.1	41	1.1	0.45
5	20 Gy x 3	80.3	0.82	3.5	9.3	32	1.01	0.32

Table 2: Dosimetric details.

Vol (100%)/Vol (PTV): Ratio of prescription isodose volume to the PTV

Vol (50%)/Vol (PTV): Ratio of 50% prescription isodose volume to the PTV

Max dose >2 cm: Maximum dose at least 2 cm from the PTV in any direction

V20: Percentage of total lung volume – GTV receiving >20 Gy

Organ at risk

Normal organs contoured include spinalcord, esophagus, tracheobronchial tree, brachial plexus and heart. The organ at risk dose (dmax) was calculated for 0.01 cc of spinal cord and 0.1 cc for other organs. The dose achieved for organ at risk is given in Table 3.

Follow up

The first patient treated with SABR in our centre developed disease progression after 6 months in the mediastinum and had liver metastasis and was treated with palliative chemotherapy and succumbed to illness after 9 months.

The second patient is on follow up since 48 months. One and half years post treatment he developed second primary ca floor of mouth and underwent surgery. It was pathologically pT1N0. He is on follow up.

The third patient is on follow up and disease free since 36 months. The fourth and fifth patients are disease free since 22 and 14 months and on follow up. No grade 3 or 4 toxicities occurred during follow up.

Serial No.	Spinal cord (18-22 Gy)	Esophagus (27-28.5 Gy)	Brachial plexus (27-29 Gy)	Tracheobronchial tree (32-35 Gy0	Heart (27-29 Gy)
Case 1	19	16.5	5	6	16
Case 2	20	27	26.9	22	4
Case 3	7	7	6	30	17
Case 4	12	8	20	24	12
Case 5	14	14	15	28	22

Table 3: Organ at risk doses (Dmax).

Discussion

The purpose of this study was to evaluate the tolerance and toxicity of patients treated with SABR in our centre. All the patients were elderly. Median age group was 72 years; this is in contrast to the median age of 67 years in the pooled analysis of two randomized control trials of STARS and ROSEL [10]. The median age group was 70 years in the Japanese Clinical Oncology Group Trial 0403 [11]. 4 patients had adenocarcinoma histology and one had squamous cell histology. The optimal dosing schedule in different studies varied depending on the location of the tumor. RTOG 0915 trial employed a dosing schedule of 48 Gy in 4 fractions [12,13]. The dosage schedules employed in this study were 48 Gy in four fractions, 60 Gy in five fractions and 60 Gy in three fractions.

Initially we had adopted dosage schedules as per RTOG schedules. Later the dosage schedules were in accordance with the SABR UK consortium guidelines [9], We could achieve the dose distribution as well as the organ at risk dose within the tolerance limit for all patients.

All patients tolerated treatment well. Toxicity during and post treatment was graded with Common Terminology Criteria for Toxicity assessment CTCAE version 4.0. The most common symptom encountered was grade 2 cough. No grade 3 or 4 toxicities occurred. No non pulmonary complications were encountered.

The first patient treated with SABR in our centre developed disease progression after 6 months in the mediastinum and also had liver metastasis and was treated with palliative chemotherapy. He took chemotherapy for 3 months and had disease progression and succumbed to disease. The major drawback was that PETCT was not available to accurately stage the patient during initial period. The second patient is on follow up since 48 months.

One and half years post treatment he developed second primary ca floor of mouth and underwent surgery. It was pathologically pT1N0. He is on follow up the third patient is on follow up and disease free since 36 months. The fourth and fifth patients are disease free since 22 and 14 months and on follow up. No grade 3 or 4 toxicities occurred during follow up. Follow up data is given in Table 4.

Case 1	Recurred after 6 months in mediastinal node and systemic metastasis
Case 2	Disease free since 48 months. Developed second primary ca floor of mouth. Underwent surgery and on follow up
Case 3	Disease free since last 36 months
Case 4	Disease free since last 22 months
Case 5	Disease free since last 14 months

Table 4: Follow up of the cases.

Follow up

The major drawbacks of this study was that PETCT evaluation for initial staging could only be done in two patients because of the lack of availability in the initial period when we started doing SABR in 2013 and also due to financial constraints. Also during follow up post treatment baseline CT scans were taken in only two patients due to logistical issues. All patients had X-ray imaging and CT scan was advised only if disease progressed on X-rays or patient was symptomatic. So the radiological response assessment could not be carried out according to set standards in this study. Inspite of our limitations, even in a resource constrained setting like ours SABR was feasible and we can adopt this to our clinical practice especially in medically inoperable and elderly age group.

Most studies of SABR have concentrated mainly on the medically inoperable population. SABR for operable patients is gaining interest recently. The Japan Clinical Oncology Group 0403 phase II trial of SABR for peripheral operable stage IA lung cancer preliminarily found 3-year primary tumor control of 86% and overall survival of 76%in patients with a median age of 79 years [11]. The successes of SABR in achieving high local tumor control and low toxicity bring forth the question of whether SABR can be a viable option in patients with stage I Non-small cell lung cancer (NSCLC), particularly those who are medically inoperable. The choice of this treatment modality in

operable lung cancer patients can be adopted only after the emergence of definite data from prospective randomized studies.

Conclusion

SABR is an accepted curative modality for early stage lung cancer. It is a safe and valuable treatment option for patients who cannot or will not undergo surgery. It is well tolerated even in elderly patients. But more definitive data is needed before drawing conclusions about the applicability of SABR as primary therapy for patients with operable early stage NSCLC. Although our experience is of only with 5 patients even in advanced age group it was feasible and well tolerated. Also the treatment compliance was very good in view of decreased number of fractions when compared to conventional schedule. From our experience it can be used for curative treatment in elderly and also in medically inoperable patients.

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