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High-Dose Rate Endobronchial brachytherapy (HDREB) for palliation of lung cancer: An Observational study

KEYWORDS: Lung cancer, endobronchial, high-dose-rate endobronchial brachytherapy

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ABSTRACT *Aim: Our aim was to evaluate safety and effectiveness of out-patient HDREB for palliation of advanced malignant endobronchial tumors in the context of a multidisciplinary approach.*

MATERIALS AND METHODS: Fifteen patients of advanced malignant endobronchial tumors were treated with palliative intent according to a prospective observational protocol. Intra Luminal HDR Brachytherapy was performed using the high dose rate 192Ir thin wire remote after loading system. HDREB was delivered as two fractions of 7 Gy at weekly intervals. All patients presented with advanced lung cancer primaries and were treated because of lesions located in the trachea and/or main bronchi.

RESULTS: Overall, there was 84.53% improvement, with migration of patients from lower to higher performance status. The symptom that presented the best response was hemoptysis 93.3% followed by postobstructive pneumonia 87 % Symptomatic improvement in dyspnea was observed in 73.3% Radiological and endoscopic partial response was seen in 67% and 73.3% respectively. Palliation was obtained in all patients. Temporary radiation bronchitis was observed in three patients. No fatal complication occurred.

CONCLUSION: This non-comparative, prospective observational study showed HDREB is an excellent modality for palliating malignant airway obstruction with advanced lung cancer primaries and control of haemoptysis resulting in better quality of life. The safety of the procedure was good and the rate of non-fatal serious complications was very low.

Introduction

Out-patient high-dose-rate endobronchial brachytherapy (HDREB) is a possible option in the palliation of symptoms in patients with advanced lung cancer, but literature data is limited and the technique is still under development in developing countries.

Intraluminal brachytherapy (ILBT) is widely performed in medically inoperable endobronchial carcinoma as a palliative and second line treatment [1-4]. On the otherhand, some reports showed high response rates and the potential of curative treatment of ILBT in selected patients [5-11]. Palliative brachytherapy can be applied for palliative purposes in patients with a recurrent endobronchial disease after prior external irradiation to relieve life-threatening symptoms, such as haemoptysis and airway obstruction with an associated atelectasis and pneumonia. [12]. Due to the location of the lesion inside the bronchial tube, the degree of clinical advancement, and the patient's general condition, in some patients brachytherapy is a treatment of choice, which, when carried out on an out-patient basis, takes a short time and leads to a small number of early complications [13-14]. High dose- rate endobronchial brachytherapy (HDREB) relieves the symptoms of endobronchial tumour, including spirometric indices and exercise tolerance, increasing the ventilation/ perfusion ratio

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and reducing airway obstruction. Our study was designed to evaluate the safety and effectiveness of out-patient HDREB for palliation of malignant endobronchial tumors in the context of a multidisciplinary approach.

Study Population

The study design was accepted from our institutional scientific committees. A written consent was taken from all patients before starting radiotherapy. Fifteen patients with previously untreated, inoperable, locally advanced lung cancer were recruited into this prospective observational study between January 2011 to February 2015. All patients had endoscopically proven endobronchial disease and one or more symptoms of endobronchial disease (dyspnea, cough, hemoptysis or obstructive pneumonia). A KPS score of ≥ 50 was required for eligibility into a palliative protocol. Previously treated patients with radiotherapy were not considered eligible. Patients with respiratory or other organ failure and patients with bleeding disorders were excluded from the study, The extent of tumor involvement was assessed by bronchoscopy, chest X-ray, chest computed tomography (CT) using contrast medium. A total of 30 HDREB sessions were carried out in fifteen patients. The median patient age was 55 yrs (range 42–61years) and males were clearly predominant (14 of 15 patients, 93.3%) with male female ratio 14:1. Tumour sites were located mainly in the left main stem bronchus 8 (53.33%), right main stem bronchus 4 (26.66%) and left upper lobe bronchus 1 (6.66%). Summarized clinical data on the patients are presented in Table 1.

Methods:

Radiation technique and radiation dose

Intraluminal brachytherapy (ILBT)

Each patient was prepared for the procedure with local anesthesia and monitored sedation. A Trans-nasal fiber-optic videobronchoscope was introduced through the nostril and used to locate the tumour site. A polythene catheter of diameter 6 Fr and length 150 cm was introduced through the working channel of the bronchoscope and then pushed to at least 2 cm beyond the distal end of the endobronchial lesion. The bronchoscope was then withdrawn while maintaining the catheter in place. CT based Treatment planning was done with the help of Oncentra master plan treatment planning system.

The target volume included the tumour visualized by bronchoscopy, proven by biopsy plus 2 cm safety margins in cranial and caudal direction. CT based dose distribution done with the aim 95% of the clinical target volume received more than 90% of the prescribed dose (Showing in Figure 1). The distances between the radiation source and the mucosal surface were provisionally standardized of 5 mm from the center of the source. In all patients, the applications were performed with a 1.8 mm bronchus applicator (length 150 cm) inserted endoscopically before treatment. A Nucletron High Dose Rate microselectron® with an Ir192 source was used for treatment.. The therapeutic protocol consists of sessions carried out at 1-week intervals in which a total dose per session of 700 cGy was applied (BED=24Gy).All patients received steroids for three days after the procedure. The predominant clinical manifestations before treatment were as follows: cough (n=15, 100%); haemoptysis (n=14, 93.3 %); dyspnoea (n=15, 100%); chest pain(n=12, 80%) and stridor (n=8, 53.3%).

The main objective of the study was to determine if HDREB relieved the symptoms of endobronchial tumour with an acceptable rate of complications. There was no intention to quantify the degree or duration of palliation. Endoscopic evidence of the regression of lesions is the best indicator of a positive response to treatment. The clinical response was categorised in terms of the remission of previous symptoms as complete, less than complete (partial) or absent. Bronchoscopy was performed at 6 week after the last HDREB session. The response to HDREB was judged to be complete when there was no endoluminal pathology or signs of tracheobronchial wall infiltration. The response was considered partial when the lesions and obstruction had decreased, but tumoural infiltration persisted. Nonresponse existed when the pathology remained unchanged after treatment. Patients were scheduled for follow-up 1 month after the last HDREB session. Overall survival was measured from the first day of radiation therapy on study until death of any cause.

Stastical Analysis

A descriptive statistical study was made of the sample. Proportions of repeated observations were compared with McNemar's symmetry test. A value of $p<0.05$ was accepted as significant (95% confidence interval).

Results

An overall clinical response was observed in 84.53% of the symptoms analysed [Table 2]. From 14 patients who had haemoptysis at baseline, only one patient had haemoptysis after HDREB and it was very scanty. This was equivalent to 92.8% palliation (McNemar test p=0.0001). Of 15 patients with coughing at baseline, coughing disappeared or returned to the pre-tumoural situation in 13 (86.6 %; McNemar test p=0.0001). From 15 patients with dyspnoea at baseline, 11 (73.3%) experienced considerable improvement or their dyspnoea disappeared (McNemar test p=0.001). Of eight patients who had increased expectoration at baseline, expectoration decreased or disappeared in four (50%; McNemar test p=0.125). Stridor disappeared in all eight patients who suffered from it before treatment (100%;

McNemar test p=0.08). The endoscopic response was complete in 1 patient (6.6%; Figure 2). The response was partial or less than complete in 10 patients (66.6%) and there was no response in 4(26.6. %). Radiological response assessed by follow up CECT thorax after 1 month there was complete response in one patient (6.6%). There was partial response in 9 patients (60%) and 5 of these patients showed radiological improvement in collapsed lung after intrabronchial obstruction was relieved with endobronchial brachytherapy. There was no radiological response seen in 5(33.3%) patients. Complications were infrequent and included reversible radiation bronchitis (n=3, 20%), pneumonitis in the area proximal to the treated bronchus (n=1) and catheter migration because of severe cough in one patient. Re-planning was done in this case. At the completion of study, 11 patients had died due to disease. 6 patients completed the prescribed adjuvant chemotherapy. The median survival time (Kaplan-Meier) in the whole group of patients was 7 months (Figure 3). The 6 month and 1year Overall survival was 73.3% and 20 % respectively.

Discussion

The value of brachytherapy was recognized early at beginning of 20th century. Following initial interest, the procedure declined in the middle of the 20th century due to the amount of radiation exposure to the operator from the manual application of radioactive sources. The new imaging technique CT and ultrasound with guided procedure

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and three-dimensional treatment planning in the 1980's allows and extends the application of brachytherapy[16]. ILBT has mainly been performed to relieve tumor related stenosis of the trachea and/or main bronchi. Palliative-intent endobronchial ILBT has been reported to have a high response rate, and most patients who have undergone it have improved rapidly after the beginning of treatment. Many investigators therefore believe that ILBT is effective in relieving symptoms and is indicated for palliative treatment of endobronchial tumors[17]. In this study, there was improvement in clinical symptoms as regards to cough, dyspnea, hemoptysis and chest pain after intraluminal brachytherapy intervention with a significant control of hemoptysis.

J.A. Escobar Sacrista et al noted that symptoms of airway obstruction improved with HDREB in 84.53% of the studied patients. A clinical response was elicited in 95.83% of patients with haemoptysis, 88.23% of patients with cough and 50% of patients with expectoration. The two symptoms most directly related with obstruction, stridor and dyspnoea had a clinical response of 100% and 75%, respectively.[15] External beam irradiation, although effective, may not be possible in many patients (primarily in those who had received prior treatment) because of the proximity of dose limiting structures adjacent to the tracheobronchial tree (eg. esophagus, spinal cord). Endobronchial brachytherapy provides prompt relief of symptoms in patients with recurrent intraluminal airway tumours .[12] In this study, the overall rate of complications was very low. All acute complications were mild and self-limiting. All cases of odynophagia and mild cough subsided within 3 weeks of treatment. None of the cases required admission or parenteral medications. Only three cases showed radiological evidence of mild fibrosis and even these patients were asymptomatic. Studies by Gollins et al and Langendijk et al have identified 'dose per fraction' of EBBT as a predictive factor for hemoptysis, with a greater incidence when doses above 15-20 Gy were used.[18,19] In our study, none of patient showed procedure induced haemopysis and Bronchial stenosis. Although bronchial stenosis and irreversible radiation bronchitis reported as long-term complications but this was not encountered in our study probably because EBBT was administered for a maximum of two sessions for palliative intention , resulting in a lower total dose to the bronchial mucosa. Few studies, other than that of Tredaniel et al. [20], have demonstrated that HDREB increases survival in patients with malignant endobronchial processes. These authors claim that HDREB monotherapy, in strictly selected cases of small tumours limited to the bronchial lumen, can increase survival and response duration by producing a complete remission of the tumour; however, the authors remark that the same survival would be achieved with more conventional treatment. Huber et al. [21] reported a nonsignificant increase in survival with HDREB and external radiotherapy and Kelly et al. [22] recently cited an improvement in symptoms in relation to endoscopic response and increased survival. In our study,no patient died of procedure related death only one patient died within one month due to progression of disease. The procedure was well tolerated by all patients and each session required 24 h-48h of hospitalisation. Only one patient had catheter migration because of severe cough and no treatment was discontinued for catheter-placement problems.

These advantages confirm reports in the literature regarding shorter hospital stay, better tolerance and less catheter displacement [24, 25]. Recently, peripheral small lung cancers in medically inoperable patients have been well controlled with hypofractionated schedules by stereo-tactic radiotherapy (SRT). However, central lesions are not indicated of SRT because of the normal tissue complications [23]. ILBT is a promising alternative method for treatment of central small lesions. Medically inoperable patients are increasing and alternative approach should be investigated. We treated only patients whose tumours were inoperable, either for technical or functional reasons. Also, our patients had a substantial tumour burden in the tracheobronchial tree. The prognosis for these patients is poor. The results in our study were surprisingly good, with 11 patients were alive at 6 month. Also encouraging is the fact that no serious side effects were observed during this aggressive treatment protocol.

Our main interest in this study was to acquire initial data regarding the feasibility and efficacy of this regimen. As a result, we did not use a randomized trial design. However, our results are extremely encouraging we believe that further controlled trials of this treatment regimen are warranted.

Conclusion:

The high symptom palliation rates due to endobronchial treatment and the low complication rates indicate that the dose schedule in HDREB is safe and effective in palliation of advanced malignant endobronchial tumors. This non-comparative, prospective observational study showed that HDREB is an excellent modality for palliating malignant airway obstruction and control of haemoptysis resulting in better quality of life.

Table 1. Clinicopathological Characteristics of patients.

Patient Characteristic		Entire Cohort N=15 (100%)
Median Age(Range)year		55 (42-61) year
Sex	Male	14(93.3%)
	Female	1(6.66%)
Karnofsky Performance Status		
≥60		13(86.6%)
< 60		2 (13.3%)
Histology		
Small cell carcinoma		2 (13.3%)
Non small cell carcinoma		12 (80%)
Carcinoid		1 (6.66%)
AJCC Stage		
IIIA		8 (53.3%)
IIIB		4 (26.6%)
IV		3(20%)
Tracheal Lesion		2 (13.33%)
Left Main Bronchus		8 (53.33%)
Right Main Bronchus		4 (26.66%)
Left upper Lobe Bronhus		1 (6.66%)
Obstruction grade		
≤ 50%		3(20%)
>50%		7(46.66%)
Total		5(33.33%)
Bronchoscopy		15
CECT Chest		15

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Table 2. Symptoms response after 6 weeks of endoscopic brachytherapy.

	Symptoms	Response(Percentage)
1.	Haemoptysis (n=14)	13 (92.8%)
2.	Cough (n=15)	13 (86.6%)
3.	Dysponea (n=15)	11 (73.3%)
4.	Chest Pain (n=12)	10 (83.33%)
5.	Postobstructive Pneumonia (n=15)	13 (86.6 %)
6.	Endoscopic Response	11 (73.3%)
	Partial Response	10
	Complete Response	1
	No Response	4
8.	Radiological Response	10 (66.6%)
	Partial Response	9
	Complete Response	1
	No Response	5

Table 3. Post treatment complications.

	Complications	Number of patients (Percentage)
1.	Acute Haemoptysis	0 (0%)
2.	Cavitation of Lung	1(6.66%)
3.	Reversible Radiation Bronchitis	3(20 %)
4.	Pneumothorax	0 (0%)
5.	Esophagitis	0 (0%)
6.	Pneumonia	0 (0%)
7.	Catheter Migration(Replanning)	1(6.66%)
8.	Tracheoesophageal Fistula	0(0%)

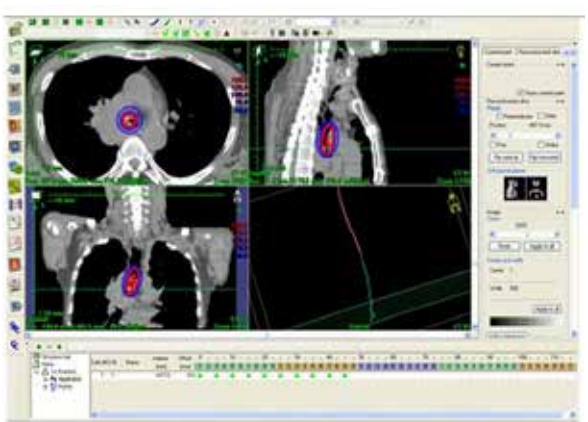

Figure 1: CT based dose distribution. A CT based dose distribution. Red thick line is a delineated contour of clinical targetvolume (CTV) and magenta line indicates 100% of prescribed dose (7Gy). 98% of the CTV receives more than 90% of the prescribed dose.

Figure a. (Pre HDREB) Figure b. (Post HDREB)

Figure 2. Showing the endoscopic response after Ir-192 HDR endobronchial brachytherapy application.

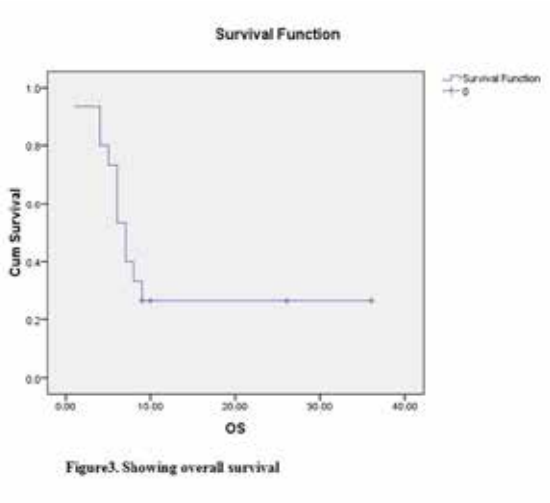

Figure3. Showing overall survival

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