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Endobronchial High Dose Rate Brachytherapy for Control of NSCLC

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ABSTRACT

Purpose: To review the role of HDR remotes afterloading brachytherapy in the management of NSCLC as well as to evaluate its effectiveness for palliation of distressing malignant endobronchial obstruction.

Patients and methods: From 1986 to 1995, 88 patients (53 males and 35 females) with obstructive endobronchial malignancies received 215 HDR endobronchial treatments using a high activity Iridium-192 source with remote afterloading. In 60 patients the objective was palliative to treat either symptomatic recurrence (n=48) or metastatic nonpulmonary disease (n=12). The main presenting symptoms were: dyspnea (61%), intractable cough (58%) and hemoptysis (33%). In 28 patients with primary endobronchial carcinoma, the objective was curative using a combination of full course external irradiation (4500-6000 cGy) and HDR with an average dose of 600 cGy at 1 cm from the surface of the source and delivered in one fraction in 41% of cases, 2 fractions in (20%) and 3 fractions in (35%), with 1-2 weeks interval.

Results: At a median follow-up period of 15 months range (3-95), the overall response rate was 641% (CR = 23% and PR = 41%). For the curative group, CR was achieved in 19/28 (68%) patients with median duration of 12 months (range 3-55 m), while a good response was reported in 28/60 (47%) patients in the palliative group, with median response duration of 7 months (range 3-34 m). The median overall survival time was 15.5 months for the entire group,17 months and 11 months for the palliative and the curative respectively. The 1 and 2-year survival rates were 72% and 39% for the palliative group compared with 45% and 35% for the cure group (p .3906). There was statistically a significant difference in survival in favor of stage 2 of the disease (p = 0.0446), as well as with adenocarcinoma histological subtype (p = 0.0497). All patients tolerated treatment well without any acute or late complications.

Conclusion: Outpatient HDR endobronchial brachytherapy is a very convenient treatment modality for the patients, being well tolerated, safe and a short-term schedule. It is a valuable treatment alternative for local palliation in patients with local recurrent or metastatic disease suffering endobronchial obstructive symptoms and signs. Also, this from of treatment may yield high local control rates in earlier stages of endobronchial carcinoma.

Key Words: *Endobronchial - Brachytherapy - NSCLC.*

INTRODUCTION

Long term survival of NSC lung cancer relies on successful surgical resection. However, approximately 75% of primary lung carcinoma cases present with surgically incurable disease and are treated with alternative approaches such as radiation and/or chemotherapy. The survival results are however poor. About 50-60% of patients treated with external radiation therapy will experience local recurrence [9]. Most studies have recommended a dose more than 60 Gy to achieve long-term local control [3], which however will jeopardize the tolerance of the normal surrounding tissues. The rationale of endobronchial brachytherapy stemmed from the fact that it offers a mean to deliver additional radiation to a local disease process even after previous full dose external beam therapy with sparing of the surrounding normal tissues from the early and late effect of X-ray therapy [5]. The main objective of the present study was to review and analyze, retrospectively, the effectiveness of HDR brachytherapy in the management of primary lung cancer with a curative intent as well as palliation of recurrent or metastatic endobronchial malignances with respiratory distress.

PATIENTS AND METHODS

Between 1986 and 1995, 88 patients (53 males and 35 females) with confirmed obstructing endobronchial malignancies, were treated with high dose rate endobronchial brachytherapy (HDR). The average age was 62.8±11.4 years (range 32-90); most of the lesions were located in the right or left upper lobes of the

lung. Squamous cell carcinoma (SCC) was the most frequently recorded histologic type (n = 43 patients) followed by adenocarcinoma (n=22) and large cell type (n=15). Stage III accounted for 59% of cases. Dyspnea was the most frequent symptom in 61% of patients, cough in 58%, hemoptesis in 33% and pain in 25% of cases. The patient characteristics are illustrated in Tables (1 & 2).

The indications for brachytherapy included symptomatic recurrent or metastatic endobronchial obstruction as well as to boost a full course external beam irradiation among patients with primary NSLCC. The patient's categorization is given in Table (3).

According to the treatment modality, patients were classified into two treatment groups. The first group included 28 newly diagnosed irresectable tumors, which were potentially curable. They received external beam irradiation to a total dose of 45-60 Gy (median 45 Gy) followed by HDR brachytherapy in 1-2 weeks to deliver a boost of 1800 cGy with the intention to improve the local control rate as well as its duration. Brachytherapy was started earlier if significant airway symptoms were present. The second group include 60 patients, 48 with recurrent symptomatic NSCLC who had biopsy proven intrinsic disease. Twelve patients had metastatic carcinoma arising from another primary. Treatment consisted of either palliative HDR remote after-loading with the dose varying between 1000 to 2400 cGy delivered at 10 mm depth or external beam therapy and HDR brachytherapy boosts to residual disease. The sequence depended on the presenting obstructive symptoms. Adjuvent laser therapy was used in 13 cases.

Pretreatment evaluation and staging:

Prior to therapy assessment included: Complete clinical history, physical examination, pulmonary function tests, chest radiographs and CT scan, in addition to complete blood, coagulation, renal and hepatic profiles. All patients had biopsy proven bronchoscopic diagnosis. Staging was performed according to the AJCC classification system [2].

Treatment strategies:

A- *Surgery:*

Complete surgical resection was performed in 10 patients through thoracotomy.

B- *High dose rate remote after-loading brachytherapy:*

The procedure was performed by the pulmonogist and radiation oncologist through bronchoscopy, on an outpatient basis, in the department of Radiation Oncology.

The steps include:

1- Anesthesia: Topical 2% xylocaine puffed in the nostrils and 1 mg iv versed.

2- Catheter Insertion: Introduction of an olympus flexible fiberoptic broncoscope transnasally to visualize, identify and localize any intrinsic occlusion, or extrinsic compression and extent of the involved region. Insertion of a guide wire over which is mounted an open ended polyethylene catheter 3 mm in diameter. Both the broncoscope and the guidewire are withdrawn leaving the catheter.

3- Dosimetery: For dose calculation a computer program consisting of dwelling points was used and checked by two physicists. The dose was prescribed in terms of the dose at a depth of 10 mm from the surface of the application using a dummy source placed into the catheter with anteroposterior/lateral radiographs to outline the tumor and set-up the treated volume.

4- Treatment protocol: The patient was transferred to the brachytherapy room, positioned and monitored during treatment. The HDR remote after-loading unit is a Gamma-Med machine with a nominal 10 Ci. Iridium-192 source of 1.2 mm in diameter and 5 mm active length and a stepping sequence which allows up to 24-dwell positions. The mean exposure time was 112 sec with a range of 25-198 sec. After completion of treatment, the catheter was removed and the patient was monitored with the radiation surveymeter, observed for 30 minute then discharged after being instructed as for the date and time of the next treatment or follow-up. A single endobronchial catheter was used per application. Fractionated insertions were performed with 500-1000 cGy (average of 600 cGy delivered per fraction) aiming at 1800 cGy for cure and 10-24 Gy for palliation. Patients received either one (n=40 cases), received 2 (n=23) three (n=28 cases), four (n=5 cases) or six (n=3 cases) brachytherapy sessions Table (4).

C- *External beam therapy (EBR):*

EBR was delivered to 76 patients for both curative and palliative purposes using 6MV linear accelerator. The treatment volume encompassed the lung disease with safety margins and the draining lymph nodes including the supraclavicular, mediastinal and hilar groups to deliver a total dose of 45-60 Gy given as a split course treatment with a rest interval of one week between the courses. The dose was prescribed at the midplane for the lung and lymph nodes and 95% isodose cure for the supraclavicular region. Two opposed anterior and posterior fields were used at 100 cm SSD with shielding of the normal lung tissues. The spinal cord was blocked after 45 Gy. A boost was delivered through oblique or lateral fields with a daily dose of 200 cGy.

Follow-up:

Chest radiographs fiberoptic bronchoscopies and biopsies were repeated 4 weeks after treatment in addition to reporting patients' subjective symptoms, duration of subjective and/or objective relief of symptoms.

Response criteria:

For the group of patients with curative intent, complete remission (CR) was defined as the normalization of clinical, radiological, bronchoscopic and histopathological pretreatment abnormal findings. While, for HDR the objective response with palliative intent was categorized into:

- Local control of the disease as documented by bronchoscopy and biopsy.
- A good response is associated with more than 50% re-open of the airway occlusion and/or resolution of distressing symptoms.
- Poor response is associated with no apparent response.

Statistical analysis:

Disease free survival (DFS) duration was calculated from the date of documented CR to the date of last follow-up or the date of biopsy proven relapse or the date of death. Local control duration was defined as the time from end of treatment with good response until the date of evident disease progression or recurrence. The follow-up period was measured from the date of starting treatment until the date of last follow-up. Overall survival (OAS) was calculated from the date of pathologic diagnosis to the date of death. Continuous variables were analyzed by the unpaired test or one way analysis of variance. Categorical variables were analyzed by contingency table analysis (chi-square). Differences in disease free survival, local control and overall survival were analyzed by the log rank test for the categorical variables and by Cox Proportional Hazards regression for grade and stage which were analyzed as ordinal variables. The Kaplan-Meier product limit method was used to construct DFS, local control and survival curves.

RESULTS

A total of 88 patients were evaluable for response, 53 males and 35 females with an average age of 63±11 years, range (32-90 y). SCC was reported in 49% of cases, adenocarcinoma in 25% large cell 17% and others in 9%. All patients experienced symptoms secondary to endobronchial airway obstruction with dyspnea (61%) and cough (58%) as the most common symptoms. There was no significant difference between sex with respect to smoking history (p = 0.6206); however, patients with SCC had a significantly longer duration of smoking years (mean = 40.0+11.3). There was family history of lung cancer in 9% of the patients (8/88).

The overall response rate was 54% with a median response duration of 15 m (range 3-55 m) with a statistical superiority of the SCC compared to the AD (p = 0.0396) Fig. (1). When stratified by treatment group, the response rates were 68% and 47% for the curative and palliative intents respectively Table (6). The 1 and 2 year disease free survival rates were 38% and 28% for a median DFS of 12 m Fig. (2). At a median follow-up of 15.5 months (range 3-95 m). The 1 and 2-year overall survival rates were 63% and 37% Fig. (3). There was no statistically significant difference between the two groups of patients with respect to OAS (p = 0.3906), the median OAS time for the palliative group was 17 m compared to 11 m for the curative group, while the 1 and 2-year survival rates were 72% and 39% versus 45% and 35% respectively.

There was no significant difference in survival between sex or grades but there was a statistically significant difference in favor of stage II

(p = 0.0446). The one-year survival rates for stages 2, 3A and 3B were 85%, 63% and 59% respectively with median survival time of 30, 14.5 and 14 months respectively, Fig. (4). In addition, a significant difference in survival was shown in favor of the adenocarcinoma histology with a median survival of 27 m compared with 11.5 months for large cell type (p = 0.0497), while the median survival for SCC was 17.5 m Fig. (5). The 1-year survival rates were 68%, 47% and 67% for adenocarcinoma, large cell and SCC respectively.

At the time of analysis, 11.5% of the patients were still alive, while 88.5% had expired. Table (6) illustrates the causes of death. Approximately 50% of cases died because of loco-regional disease progression, while in 1/3 of the patients death occurred due to non-responding local failure, 15% had metastatic disease outside the bronchopulmonary region leading to death. Three patients died of irrelevant causes: heart diseases (n=2) and car accident (n=1). Among patients treated with EBR, only 5 (5.7%) experienced mild oesophagitis. HDR endobronchial brachytherapy was well tolerated by all patients without remarkable acute or long-term complications.

Table (1): Patients characteristics (N = 88 patients).

Characteristic	No. of patients	%
Age (years)	62.8±11.4	
Average range	30-90	
Sex:		
Males	53	60
Females	35	40
Site:		
Right U. lobe	24	27
Left U. lobe	23	26
Other lobes	30	34
Main steam	11	9
Histology:		
SCC	43	49
Adenocarcinoma	22	25
Large cell	15	17
Others	8	9
Stage:		
1	5	6
2	7	8
3A	35	10
3B	17	19
IV	12	13.6
Metastatic	12	18.6
Laser	13	15
External radiation	76	86

Table (2): Distribution of occlusive symptoms.

Symptom*	(%)
Dyspnea	61
Cough	58
Hemoptysis	33
Pain	25
Constitutional	18

* Patients may have multiple symptoms concomitantly.

Table (3): Patient's categorization (No. 88).

Category	No. of patients	(%)
1- Primary bronchogenic carcinoma	28	39
2- Recurrent disease	48	55
3- Metastatic non-pulmonary malignancies	12	13

Table (4): Patient's group stratification according to the clinical presentation N=88 patients.

Group		No. of patients	%	Disease description
Curative intent		28	32	- Residual endobronchial tumor following curative EBR therapy
Palliative intent	60	48	55	- Local recurrence of previously treated primary disease
		12	13	- Metastatic Ca. to endobronchial region

Table (5): Number of brachytherapy applications per patient.

No. of applications/ patient	No. of treatments*	Patients (%)
1	40	41
2	23	20.5
3	28	54.5
4	5	2.5
6	3	2.5
	208*	
Total	215*	

* 7 patients received HDR twice during the course of their disease.

Table (6): Objective response.

	OARR	Curative	Palliative
N	47/88	19/28	28/60
%	54	68	47
Median duration	15 m	12 m	7 m
Range	3-55 m	3-55 m	3-34 m

Table (7): Cause of death.

Cause	No. of patient	%
Local-regional disease progression	38	43
Local recurrence	24	27
Metastatic disease	13	15
Others*	3	3.3
*Heart disease	2	
Car accident	1	

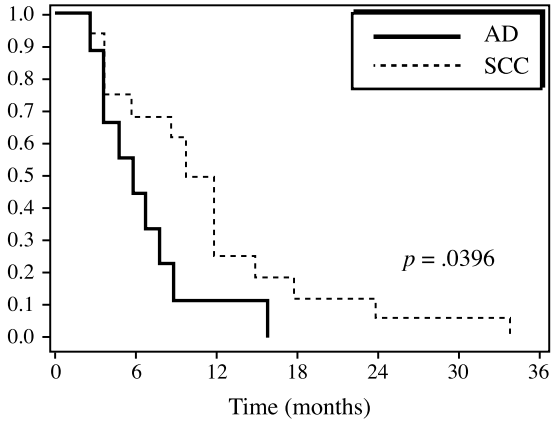

Fig. (1): The local control in relation to histology.

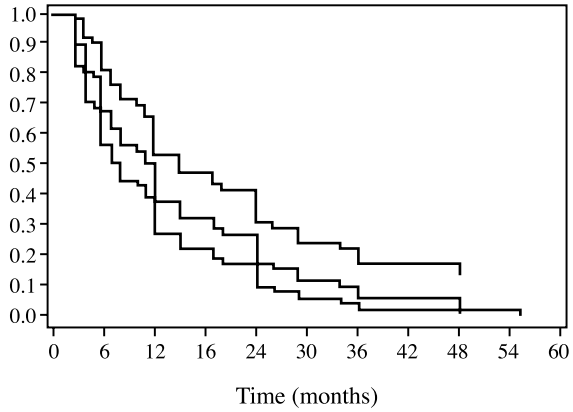

Fig. (2): The kaplan-meier disease free survival (N=88 patients).

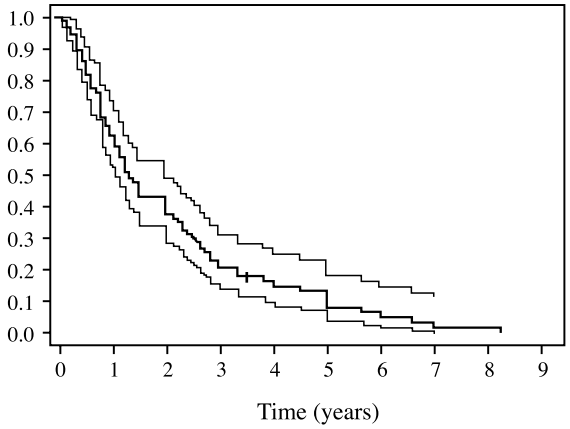

Fig. (3): The overaall survival (N = 88 patients).

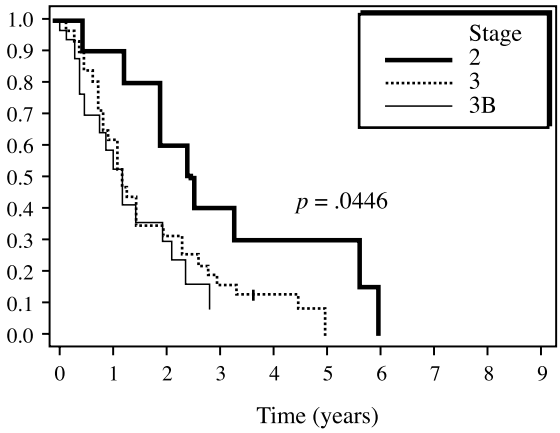

Fig. (4): The survival in relation to disease stages (N = 88 patients).

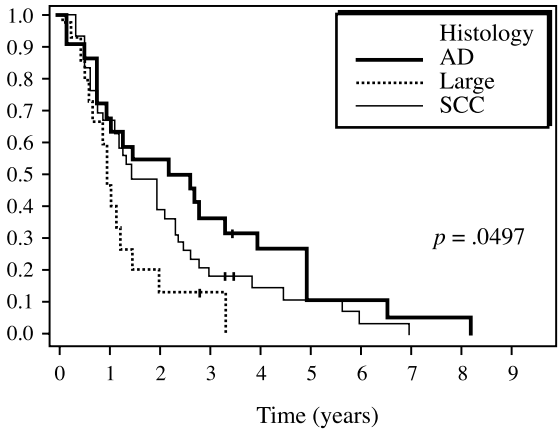

Fig. (5): The overaall survival according to histology.

DISCUSSION

Fifty percent of patients with locally advanced bronchogenic carcinoma die as a result of local failure with the conventional external beam radiotherapy. Therefore, in recent years endobronchial HDR brachytherapy was introduced as a component of radiation treatment of lung cancer. In primary malignancies HDR is used to deliver additional radiation and improve local control, while in recurrent carcinoma with airway obstruction its main objective is to achieve quick and effective palliation.

HDR brachytherapy is a well-tolerated cost effective treatment modality that can be performed on an outpatient basis. In addition, from the physics point of view, the main advantages are: its availability and flexibility to allow customized dose delivery as well as the inverse square law fall-off which offers protection of the normal lung tissues and the spinal cord. In

the present series the overall response rate was 54% which is close to the 60% to 69% reported in literature [6,7]. The median DFS was 12 m, with 38% and 28% overall 1 and 2-year DFS rates respectively. In the curative group, 19/28 of the cases achieved CR for a median DFS and overall survival of 12 m and 15 m respectively, with 45% one year OAS rate and 35% two year survival compared to 7 months median survival and 12% two year survival reported by Speiser, et al. [13] for 29/141 (28%) of patient treated for curative intentions. The higher response rate and borderline better survival rate for the primary cases in our study could be explained by early stage presentation and good performance status of this group in addition to a low symptom profile [4]. At present the role of endobronchial HDR brachytherapy in the curative treatment of lung cancer is well defined. According to Speiser [11] and others [12], the role of brachytherapy as a boost to external beam therapy in the inoperable group of patients is likely to be very small and they reported a median survival of 10.8 months for this particular group of patients. In our opinion this low response profile and decreased survival could be explained by the fact that in almost all studies this patient's category constituted 20 to 30% of the entire groups [5,6,13]. This observation could be clarified through a randomized study including a large number of patients with primary locally advanced NSCLC with good prognostic indicators (performance status and symptomatology) to determine if HDR brachytherapy plays a role in the curability of this disease. While still the latter issue is debated, the palliative role of HDR brachytherapy in recurrent obstructive carcinoma was documented in most studies [5,6,8,13] with a mean or median survival range of 7.5 to 12 m. In the present study, local control was achieved in 28/60 patients in the palliative group for a median duration of 7 m (range 3-34 m). The median survival was 15 m (3-95 m) with 72% of the patients being alive at one year and 49% at two year. A statistically signification difference was reported in favor of stage 2 carcinoma compared to stage 3 (p = 0.0446) with a median survival of 30 months versus 14 months.

In the current study, we believe that the dose range of 600 cGy prescribed at 10 mm from the source surface and delivered in 3 fractions at one week interval was very well tolerated by the patients and we did not record any acute or late complication. The prescribed depth was preferred because it was large enough so that slight errors in position of the delivery catheter did not lead to major radiation dose errors, yet was small enough to be representative of the tumor dose. A review of literature revealed a group of significant complications encountered after higher doses 1000-1500 cGy per fraction [14]. The most common are radiation bronchitis and stenosis (11%) while fatal hemoptysis was recorded in 11.3% of the patients [1].

In conclusion, the primary goal of this retrospective study was to analise the available data aiming at developing more understanding of the rationale for the use of HDR brachytherapy in the management of bronchogenic carcinoma. We believe in the efficacy of this treatment technique to offer an excellent mean of palliation whether subjective or objective in localized malignant obstructive and recurrent endobronchial tumors. As well it may give considerably better control than external beam therapy alone when used as a part of the primary treatment with curative intents in a selected group of patients with good prognostic indicators. Especially that the recent years have seen the development of sophisticated technics designed to enhance the EBR through dose escalation such as 3D-CRT and IMRT which permits delivery of higher tumor doses without increasing the normal tissue complication probability (NTCP) [10].

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