HIGH DOSE RATE ENDOBRONCHIAL BRACHYTHERAPY IN THE MANAGEMENT OF ADVANCED LUNG CANCER – COMPARISON OF DIFFERENT DOSES – PRELIMINARY ASSESSMENT

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ABSTRACT

Purpose: Brachytherapy is one of the most efficient methods of overcoming endobronchial obstruction in palliative treatment of lung cancer. In single cases, brachytherapy is performed as radical treatment, however in most of cases, due to advanced clinical stage it has a palliative aim. In the absence of clear consensus regarding the value of doses used in brachytherapy different fraction doses are used in clinical treatment. The aim of this work is to compare results of palliative high dose rate brachytherapy using various treatment protocols with the view to analysing differences in survival and diminishing breathing difficulties.

Material and methods: Between May 1999 and February 2000 at the Greatpoland Cancer Center, 69 patients with advanced lung cancer were treated by high dose rate brachytherapy. They were disqualified from radical treatment due to advanced clinical stage. The age of the patients ranged from 39 to 76 years (average 53,2 years). Fifty-one patients received a total dose of 22,5 Gy in 3 fractions once a week, 18 patients received one single fraction of 10 Gy. All the patients were divided into two groups according to their clinical stage and the Karnofsky score – those with the Karnofsky score lower than 50 were qualified for a single fraction treatment. They were under clinical and endobronchial observation as regards survival rates, local remission and subsiding dyspnoea, breathing, cough and haemoptysis in the first, third, sixth and twelveth month of observation.

Results: Four weeks after the end of treatment subjective improvement (subsidence of all symptoms) was ascertained in 61/69 (88,4%) patients. In 12 cases (17,4%) complete remission (CR), in 49 cases (71,0%) - partial remission (PR) of the tumor were found. During one year of observation 45 (65,2%) patients died, in 10 cases (14,5%) improvement of in dyspnoea was observed and in 14 cases (20,3%) recurrence and progression of the disease were noted. There was no statistical difference in the survival rates between the two groups of patients treated with different fractions protocols.

Conclusions:

1. Brachytherapy in advanced lung cancer is an efficient method that led in most of patients to subcidence of symptoms and to improvement of the quality their lives.
2. The two treatment protocols showed similar efficiency in overcoming difficulties in breathing.
3. Survival rates were similar in both group of patients treated with different treatment protocols.

Key words: lung cancer, HDR brachytherapy.

INTRODUCTION

Brachytherapy is one of the most efficient methods in the overcoming difficulties in breathing caused by endobronchial obstruction in palliative treatment of lung cancer [1-5]. Depending on the location of the lesion in some cases brachytherapy is a treatment of choice. Because of the uncontrolled local or recurrent disease, patients may have significant symptoms: cough, dyspnoea,

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haemoptysis, obstructive pneumonia or atelectasis. In many patients, these symptoms are primarily attributable to endobronchial obstruction. Efforts to relieve this obstructive process are worthwhile because patients may experience a significantly improved quality of life. However, many of these patients have a poor performance status and have received multiple other therapies. As a result, treatment options are often limited.

In most cases brachytherapy has a palliative aim due to the advanced clinical stage [6-9]. Lack of clear consensus regarding the value of doses used in brachytherapy is the reason why different fraction doses are used in clinical treatment [3,10-12].

Due to bad performance status (Karnofsky score < 50) single high doses ranging from 10 Gy to 15 Gy are used [3,11,13]. It seems that the results achieved are similar to those when doses are given weekly in two or three fractions. A single dose protocol is cost - sparing and comfortable for patients. On another hand, weekly repeated treatment makes it possible to have an better local control visualized on bronchoscopy.

The aim of this work was to compare results of palliative high dose rate brachytherapy using various treatment protocols, especially with a view to analysing differences in survival rates and the diminishing breathing difficulties.

MATERIAL AND METHODS

Between May 1999 and February 2000, 69 patients with advanced lung cancer were treated palliatively using High Dose Rate brachytherapy at the Great Poland Cancer Centre. They were disqualified from radical treatment (eg. surgery, external beam therapy) due to advanced clinical stage. Brachytherapy was chosen as the only method of treatment due to endobronchial obstruction caused by a visuable tumour and because of intensive dyspnoea was selected instead of external beam therapy.

The age of the patients (54 males and 15 females) ranged from 39 to 76 years (average 53,2 years). Fifty-six patients had T3N1-2 and 13 – T4Nx clinical stage, respectively. In most cases (n=56) more than 50% of the bronchus were obturated by the tumour.

In all the cases tumour was localized in one of the main bronchus. The intrabronchial tumour occlusion in this group was single cause for dyspnoea.

The most frequent histopatological type was *squamous cell carcinoma* (n=61), *adenocarcinoma* being diagnosed in 8 patients *(Table 1)*.

Tab. 1. Clinical characteristic of patients

Clinical data	Number of patients
(1) Age:	
<53,2	30 (43,5%)
>53,2	39 (56,5%)
Average: 53,2	
(2) Sex:	
Male:	54 (78,3%)
Female:	15 (21,7%)
(3) Symptoms:	
Dyspnoea:	69 (100,0%)
Caugh:	60 (87,0%)
Hemoptysis:	37 (53,6%)
Pain:	13 (18,9%)
Atelectasis:	11 (15,9%)
(4) Histopathological type:	
squamous cell carcinoma	61 (88,4%)
adenocarcinoma	8 (11,6%)
(5) Clinical stage:	
T3 N1	33 (47,7%)
T3 N2	23 (33,3%)
T4 N0-X	13 (18,9%)
(6) Methods of treatment:	
3 x 7,5 Gy	51 (73,9%)
1 x 10 Gy	18 (26,1%)

Patients were divided into two groups according to their clinical stage and the Karnofsky score; patients were qualified for single fraction treatment (10 Gy) when the Karnofsky score was lower than 50.

A single bronchial catheter (diameter of 1,8 mm) was fixed in the bronchus during bronchoscopy. The target volume included the tumor with a 2 cm margin proximally and distally. The dose was measured 1 cm from the catheter axis. An iridium 192 source with 10 Ci nominal activity and GAMMAMED 12i and an ABACUS planning system were used.

Fifty-one patients received a total dose of 22,5 Gy in three fractions given once a week, whereas 18 patients received one single fraction dose of 10 Gy.

Clinical and endobronchial observations included rating of local remission and subciding difficulties with breathing, cough, pain and haemoptysis in the first, third, sixth and twelveth month of observation. The results achieved were assessed using bronchoscopy and clinical examination after the end of brachytherapy. The results were divided into four categories: (1) complete remission (CR) – subciding symptoms and total regression observed during bronchoscopy, (2) partial remission (PR), (3) no remission (NR), or (4) progression. Local (assessed during bronchoscopy) and clinical (subjective) remission and survival rates were compared with two different fractionation protocols. The material was analyzed on the basis of retrospective observation of the course of the disease. Statistical analysis was performed using the F. Cox test. Survival rates were analyzed using the Kaplan-Meier method.

RESULTS

After four weeks from the end of the treatment subjective improvement (subcidence of all symptoms) was ascertained in 61/69 (88,4%) patients (*Table 2*). In 12 cases (17,4%), complete remission (CR), in 49 (71,0%) partial remission (PR) of the tumour and in 8 (11,6%) no remission (NR) or progression were found on bronchoscopy and X-ray examination.

Tab. 2. Improvement in symptoms in comparison with clinical data (CR + PR).

Clinical data	N =	1 month	3 month	6 month	12 month
(1) Age:					
< 53,2 years	30	86,7%	80,0%	46,7%	6,7%
> 53,2 years	39	89,7%	84,6%	61,5%	20,5%
(2) Sex:					
Male:	54	90,7%	88,9%	57,4%	14,8%
Female:	15	80,0%	60,0%	46,7%	13,3%
(3) Histopathology:					
squamous cell carcinoma	61	88,5%	83,6%	57,4%	14,8%
adenocarcinoma	8	87,5%	75,0%	37,5%	12,5%
(4) Clinical stage:					
T3 N1	33	90,1%	87,9%	57,4%	33,3%
T3 N2	23	86,6%	82,6%	55,1%	8,3%
T4 N0-X	13	84,6%	53,9%	38,5%	0,0%

CR – complete remission

PR – partial remission

After three months, CR was noted in 10/69 (14,5%) cases, PR in 47/69 (68,1%) cases, NR in 9/69 (13,0%) cases and three cases (4,3%) showed progression. After 6 months, CR was observed in 8/69 (11,6%) cases, PR in 30/69 (43,5%) cases and progression/recurrence in 19/69 (27,5%) cases. Twelve (17,4%) patients died in the first 6 months of observation. After 12 months of observation, in 10 (14,5%) cases improvement in dyspnoea (CR + PR) was seen and in 14 (20,3%) cases recurrence and progression of the disease (*Table 3*) was noted. During one year of observation 45 (65,2%) patients died.

Four weeks after the end of treatment the results in both groups of patients were compared. In a group of 51 patients treated with three fractions of 7,5 Gy CR was observed in 9 (17,7%) cases, PR in 37 (72,6%) cases and NR/progression in 5 (9,8%) cases. In a group of 18 patients treated with a single 10 Gy fraction the following results were obtained: CR in 3 (16,7%) cases, PR in 12 (66,7%) cases and NR/progression in 3 (16,7%) cases. The median survival time for both groups was 26 weeks. The greatest risk of death was observed in the 24th week in both groups. There was no statistically important difference in the results (the length of survival time) between the two groups of patients treated with different doses (p = 0,26) (*Figure 1*).
Also failed to observe any differences after 3,6 and 12 months (*Table 4*).

In fifteen cases, superficial necrosis was observed in the third and sixth month of observation. Another frequent early complications were: cough, high temperature and weakness. In four cases (5,8%), during 12 months of observation, we found a broncho - esophageal fistula – two in both groups of patients. Complications occurred also in both groups of patients.

Tab. 3. Improvement in symptoms in patients examined (CR + PR).

Symptoms	N =	1st month	3rd month	6th month	12th month
Dyspnoea	69	88,4%	83,2%	55,1%	41,7%*
Caugh	60	91,7%	88,7%	65,7%	41,7%*
Hemoptysis	37	91,9%	79,3%	65,7%	37,5%*
Pain	13	76,9%	76,9%	70,1%	37,5%*
Atelectasis	11	90,1%	90,1%	82,2%	37,5%*

* relating to living patients
CR – complete remission
PR – partial remission

Tab. 4. Comparison of the effectiveness of both methods of treatment (CR = PR).

Methods of treatment	N =	1st month n = %	3rd month n = %	6th month n = %	12th month n = %
1/ 3 x 7,5 Gy	51	46 (90,2%)	44 (86,3%)	27 (52,9%)	7 (13,7%)
2/ 1 x 10 Gy	18	15 (83,2%)	13 (72,3%)	11 (61,1%)	3 (16,7%)
Total	69	88,4%	82,6%	55,1%	14,5%

CR – complete remission
PR – partial remission

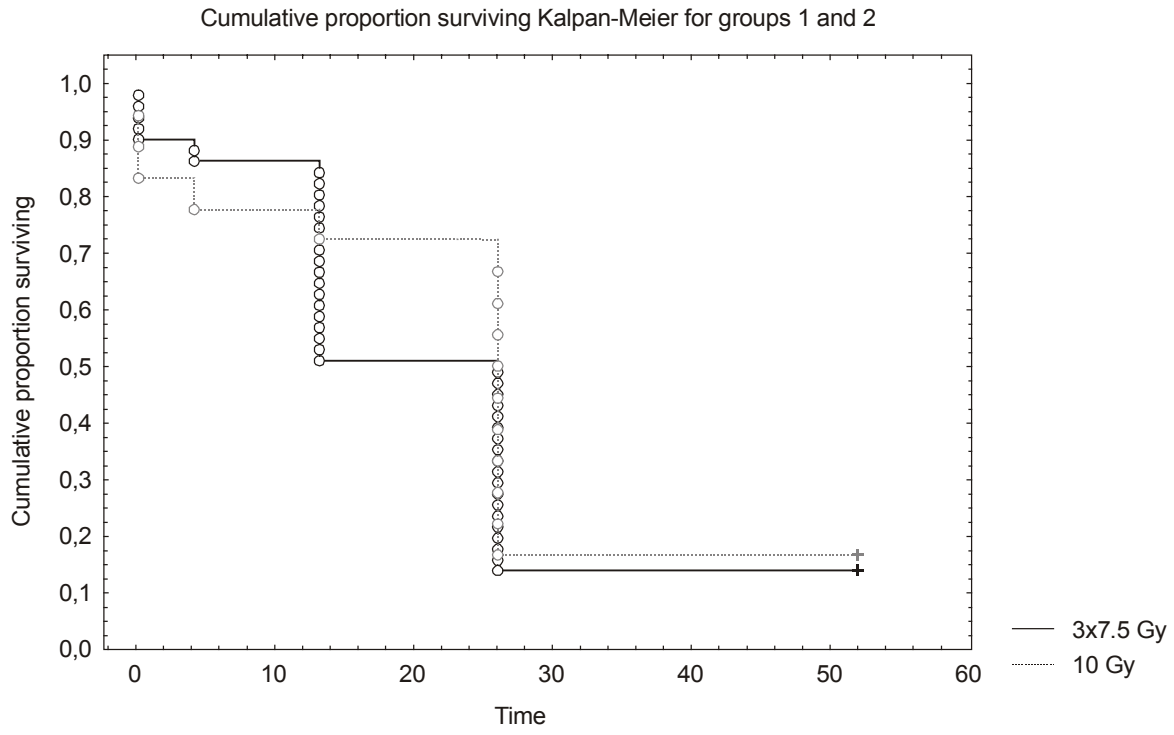

Fig. 1. Cumulative proportion (surviving Kaplan-Meier) for groups 1 (3 x 7,5 Gy) and 2 (1 x 10 Gy). F Cox test (p = 0.26).

DISCUSSION

An airway obstruction secondary to extensive primary or recurrent intrathoracic cancer, occurs frequently and creates devastating effects for many patients. There are many therapeutic modalities available that can be used to relieve this obstruction, including laser therapy, external beam irradiation, chemotherapy, and endobronchial brachytherapy [1,4,14,15].

External beam irradiation, although effecttive, may not be possible in many patients (primarily those received prior treatment) because of the proximity of dose limiting structures adjacent to the tracheobronchial tree (i.e. esophagus, spinal cord). In addition, external beam irradiation can have significant side effects (i.e. dysphagia) and result in unnecessary normal tissue damage.

Endobronchial brachytherapy provides prompt relief of symptoms in patients with intraluminal airway tumours. Although external-beam radiation therapy could also be used for this purpose, it cannot be often used because patients have already received irradiation.

A lot of investigators have used a range of prescription points and fractional doses which may make direct comparisons between series difficult.

Kelly et al. [16] reported significant clinical improvement in 32% of 175 symptomatic patients, slight improvement in 34% of patients, no relief in 17% of patients and worsening of symptoms in 10% of patients. For most of the applications, a dose of 15 Gy was given at a distance of 6mm; therefore, the most common total doses were multiples of this single dose, or 15 Gy (23%), 30 Gy (58%) and 45 Gy (7%).

Speiser and Spratling [17] observed symptomatic response rates of 85-99% in 342 patients receiving a range of HDR protocols divided into two groups – one treated with fraction of 10 Gy and the second treated with 7 Gy. Response rates were similar in both groups. Similarly, Gustafson et al [18] noted significant clinical improvement in 74% of 38 symptomatic patients treated to 21 Gy at 1 cm given in 3 HDR applications over 3 weeks. Nori et al. [19] reported palliation rates ranging from 84% to 100% in 15 patients

receiving 12-16 Gy at 1 cm delivered in 3-4 HDR treatments given over one month. In the Bedwinek et al. [20] series, 76% of the patients had symptomatic improvement in response to a dose of 18 Gy, given at a distance of 1 cm in 3 HDR sessions weekly.

In our study, we examined the results of treatment of 69 patients with endobronchial tumour treated with different doses of HDR brachytherapy. We found that significant and durable clinical and radiographic responses can be obtained in patients with symptoms despite prior radiation therapy or the presence of the metastatic, nonbronchogenic primary disease. There was no statistically important difference in the results between the two groups of patients treated with different doses. In addition, the morbidity associated with HDR endobronchial brachytherapy appears acceptable despite late complications directly related to the procedure. The complication rate in our series compares favorably with those reported from other institutions [5,6,21]. Given these findings, we believe that HDR endobronchial brachytherapy can provide a safe, quick, and effective palliation method and should be recommended in patients with a symptomatic endobronchial disease.

CONCLUSIONS

1. Brachytherapy in advanced lung cancer is an efficient method that lead to subsidence in most of patients symptoms and to improvement in life quality.
2. Both treatment protocols were characterized by similar efficiency in overcoming dyspnoea, cough, pain and haemoptysis.
3. Survival rates were similar in both group of patients treated with different protocols.

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