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Lung cancer brachytherapy

HDR endobronchial brachytherapy (HDRBT) in the management of advanced lung cancer – Comparison of two different dose schedules

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ABSTRACT

Purpose: The aim of this work is to compare the results of various treatment protocols used in palliative HDRBT with the view of analyzing differences in survival and diminishing breathing difficulties.
Material and methods: A total of 648 patients with advanced lung cancer were divided into two groups according to their clinical stage and the Zubrod–ECOG–WHO score. 303 (46.8%) patients received a total dose of 22.5 Gy in 3 fractions once a week, and 345 (53.2%) patients received a single fraction of 10 Gy. They were under clinical and endobronchial observation taking into consideration survival rates, local remission and duration of symptom relief such as dyspnoea, breathing, cough and haemoptysis.
Results: There was no difference in the length of survival time between the two groups of patients (log-rank test, $p = 0.055$). Patients showing improvement (objective response) survived longer than those who showed no change or progression (F Cox, $p = 0.000001$). In multivariate analysis the other statistically important prognostic factors were: clinical stage of primary tumor (F Cox, $p = 0.000002$), Zubrod–ECOG–WHO score (F Cox, $p = 0.002$) and age of patients (F Cox, $p = 0.004$).
Conclusions: The two treatment protocols showed similar efficiency in overcoming difficulties in breathing. Prognostic factors that significantly correlated with survival length were: grade of remission after treatment, clinical stage and performance status.
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Only 20–30% of all lung cancer patients are operable at diagnosis and only 40–50% of them can be resected for cure. Local recurrences after external beam radiotherapy (EBRT) occur in 60–70% of patients, and are responsible for 60% of the mortality due to respiratory failure, obstructive pneumonia and sepsis.

Brachytherapy is one of the most efficient methods in overcoming difficulties in breathing that are caused by endobronchial obstruction in palliative treatment of lung cancer [1–6]. Depending on the location of the lesion in some cases brachytherapy is a treatment of choice. Because of uncontrolled local or recurrent disease, patients may have significant symptoms such as: cough, dyspnoea, haemoptysis, obstructive pneumonia or atelectasis. In many cases, these symptoms are primarily attribute to endobronchial obstruction. Efforts to relieve this obstructive process are worthwhile, because patients may experience improved quality of their life. However, many of these patients have a poor performance status and they received multiple other therapies. As a result, treatment options are often limited. In most cases brachytherapy has a palliative aim due to advanced clinical stage [7–11]. Speiser and Spratling [12] considered certain factors for palliative treatment, such as: weight loss of more than 10% in the 6 months prior to diagnosis, poor performance status, tumor stage IIIB or IV, or a recurrent disease following prior external beam irradiation. Lack of clear consensus regarding the value of doses used in brachytherapy is the reason for different fraction doses to be used in clinical treatment [3,13–15]. Due to bad performance status (Zubrod–ECOG–WHO score >2) single high doses ranging from 10 to 15 Gy are being applied [3,14,16,17]. It seems that the results of this procedure are similar to those obtained when doses were given weekly in two or three fractions. A single dose protocol is cost sparing and more comfortable for patients. On the other hand, weekly repeated treatment enables to have a better local control that is visualized with the use of bronchoscopy. Brachytherapy plays a limited but specific role in definitive treatment with curative intent in selected cases of early endobronchial disease as well as in the postoperative treatment of small residual peribronchial disease. The aim of this work is to compare the results of palliative HDRBT using various treatment protocols with the view of analyzing survival rates, differences in diminishing breathing difficulties, as well as remission (objective response).

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Material and methods

Materials

Six hundred and forty-eight patients with advanced lung cancer were treated by HDRBT at the GCC from May 1999 to December 2004. They were disqualified from radical treatment (e.g. surgery, EBRT) due to advanced clinical stage. Brachytherapy was chosen as the sole method of treatment due to endobronchial obstruction caused by a visible tumor and due to intensive dyspnoea. For analysis, only patients treated exclusively with brachytherapy were qualified. Many of the patients underwent earlier palliative or radical treatment and were directed to brachytherapy because of recurrence. In the past, 214 patients (before brachytherapy) were treated with EBRT. Patients with lung cancers without a significant endobronchial component were directed to external beam radiation therapy. In some of the patients with good performance status, brachytherapy was chosen as a treatment of choice because of its good accessibility or patients were disqualified for EBRT because of advanced clinical stage (which is not always correlated with Zubrod score).

All patients have gone through bronchoscopy and X-ray/computed tomography (CT) for histological diagnosis and for evaluation of tumor extent. The age of the patients (540 males and 108 females) ranged from 39 to 81 years (median 63.8 years). In 144 (22.3%) cases tumor was localized in trachea and often infiltrating main bronchus in 318 (49.1%) cases, in main bronchus; in 165 (25.5%) cases, in lobular bronchus, respectively. Most of the patients were in bad performance status (according to Zubrod–ECOG–WHO score), 99 (15.3%) had score 1.261 (40.3%) had score 2.261 (40.3%) had score 3, and 27 (4.2%) had score 4, respectively. The leading clinical symptoms were dyspnoea, cough, hemoptoe, and pain. Some of the patients showed more than one symptom at diagnosis. The symptoms were qualified according to Speiser and Spratling scale for assessing palliative response in endobronchial brachytherapy [12]. Summarized clinical characteristics of patients are presented in Table 1.

Treatment

Endobronchial irradiation was performed under local anesthesia and sedation with midazolam. One or two pieces of bronchial French six catheters were fixed into the bronchus during bronchoscopy and under endoscopical control. The target volume was defined by the prior endoscopical and radiological findings. The treatment was planned with catheter reconstruction on radiographs. Two catheters were used when both main bronchus and trachea with main bronchus were infiltrated. In these cases, an additional lateral radiogram was done and doses were calculated with secure distance greater than 2 cm between both catheters. We gave up 3-dimensional imaging because of palliative aim of the treatment and bad general condition of the patients (intensive dyspnoea).

A high-dose-rate afterloading machine (Gammamed 12i (till 2001), then a microselectron HDR with a l92 Iridium stepping source and a nominal activity of 370 GBq (10 Ci) were used. To calculate the dose distribution the ABACUS (till 2001), then the PLATO computer planning systems were employed. The dose was prescribed at 10 mm distance from the surface of the source. The target volume included the visible tumor with 2 cm margin in proximal and distal directions.

Methods

All the patients were divided into two groups according to their clinical stage and score – those with the Zubrod–ECOG–WHO score higher than 2 points were in most of the cases qualified for a single fraction treatment. In every case the decision of choosing fraction size was carefully analyzed. Three hundred and three (46.8%) patients received a total dose of 22.5 Gy in 3 fractions once a week, 345 (53.2%) patients received a single fraction of 10 Gy. They were under clinical and endobronchial observation with regard to survival rates, local remission and subsiding dyspnoea, breathing, cough and haemoptysis. Survival rate was compared with chosen clinical data: age, sex, histopathology, clinical stage, Zubrod–ECOG–WHO score [18], remission of tumor assessed after 1st month, location of tumor, grade of obturation, and protocol of treatment. The results were assessed after 1st month using bronchoscopy and clinical examination after the end of brachytherapy. The results were divided into four categories: (1) complete remission (CR) – symptoms subsiding and total regression observed during bronchoscopy, (2) partial remission (PR), (3) no remission (NR), or (4) progression. Partial remission (PR) was defined as 50% reduction of tumor volume estimated during bronchoscopy. Complete remission (CR) and progressive disease (PD) were defined as no evidence of local tumor or further tumor growth of more than 25%.

Statistical evaluation

The material was analyzed on the basis of retrospective observation of the course of the disease. The survival time was defined as a time from the beginning of brachytherapy to the death of the patient or to the end of the twelfth month of observation. For survival analysis Kaplan–Meier method was performed, for and univariate categorized data analysis log-rank test and Tarone–Ware test were used. For data showing statistical significance in univariate analysis, multivariate analysis (Cox's regression) model was used.

Results

Four weeks after the end of treatment, some subjective improvements (subsidence of all symptoms) were ascertained in 573/648 (88.4%) patients. In 113 cases (17.4%) complete remission (CR) was found, and in 460 cases (71.0%) partial remission (PR) of the tumor was found. During one year of observation, 423 (65.2%) patients died, and 225 (34.8%) were still alive. In 131 cases (20.3%), recurrence and progression of the disease were noted. After one year, in 94 cases (14.5%) clinical improvement (mostly seen in diminishing of dyspnoea) was observed. The median actuarial survival time for the entire group of patients was 3.71 months. There was a difference in survival between the two groups, but the impact of the fractionation schedule was not statistically different in multivariate analysis. (univariate – log-rank test, $p = 0.003$; multivariate – F Cox, $p = 0.853$) (Fig. 1).

Patients showing improvement had survived longer than those who showed no remission or progression (univariate – log-rank test, $p < 0.0001$; multivariate – F Cox, $p < 0.0001$) (Fig. 2). Other statistically important prognostic factors in multivariate analysis were: clinical stage of primary tumor (F Cox, $p = 0.000002$), Zubrod–ECOG–WHO score (F Cox, $p = 0.002$) and age of patients (F Cox, $p = 0.004$) (Table 2). In univariate analysis, correlations between survival and Zubrod–ECOG–WHO score, grade of cough, hemoptoe and pain were found. Other examined prognostic factors did not show any statistically important correlations.

Discussion

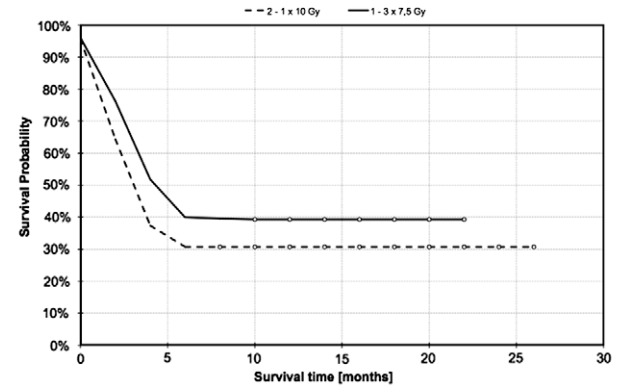
An airway obstruction that is secondary to extensive primary or recurrent intrathoracic cancer, occurs frequently and creates devastating effects in many patients. There are many therapeutic

Table 1
Clinical characteristics of patients and univariate analysis of survival rates (completed data).

Group	Category	Frequency [patients]	Frequency [%]	Completed [patients]	Censored [patients]	Median [month]	SD [month]	p-Value log-rank
Sex	Female	108	16.6	77	31	3.4	0.4	0.104
	Male	540	83.2	346	194	3.8	0.2	
Age (2 groups)*	Age <64 years	336	51.9	213	123	4.1	0.5	0.204
	Age >64 years	312	48.1	210	102	3.4	0.2	
Age (4 groups)*	Age lower than 55 years	147	22.7	113	34	3.1	0.3	<0.001
	Age from 55 to 64 years	168	25.9	85	83	N/A	N/A	
	Age from 64 to 70 years	156	24.1	102	54	3.2	0.3	
	Age higher than 70 years	177	27.3	123	54	3.4	0.2	
Stage	T3 N0	60	9.3	17	43	N/A	N/A	<0.001
	T3 N1-2	153	23.6	75	78	N/A	N/A	
	T4 N0-X M0	192	29.6	136	56	3.7	0.2	
	T1-4 N0-X M1	243	37.5	195	48	2.6	0.2	
Location	Trachea	27	4.2	12	15	N/A	N/A	0.001
	Segmental Bronchus	21	3.2	9	12	N/A	N/A	
	Trachea with Bronchus	117	18.1	93	24	3.3	0.3	
	Main bronchus	318	49.1	204	114	3.7	0.2	
	Lobular bronchus	165	25.5	105	60	3.7	0.3	
Histopathology	Unclassified	36	5.6	15	21	N/A	N/A	0.016
	Squamous cell Carcinoma	456	70.4	306	150	3.7	0.2	
	Adenocarcinoma	66	10.2	42	24	3.3	0.3	
	Carcinoma solidum	33	5.1	18	15	3.5	1.0	
	Anaplastic Carcinoma	57	8.8	42	15	4.3	0.6	
Obturation	Without	N/A	N/A	N/A	N/A	N/A	N/A	0.174
	<50%	54	8.3	33	21	5.0	0.6	
	>50%	123	19.0	86	37	3.5	0.3	
	Almost total	231	35.7	142	89	3.9	0.3	
	Total	240	37.0	162	78	3.5	0.2	
Treatment	1×10 Gy	345	53.2	239	106	3.2	0.2	0.003
	3×7.5 Gy	303	46.8	184	119	4.6	0.5	
Response (1 month)	CR	113	17.4	10	103	N/A	N/A	<0.001
	PR	460	71.0	338	122	3.3	0.1	
	NR	46	7.1	46	0	1.1	0.2	
	Progression	29	4.5	29	0	1.4	0.3	
Zubrod (WHO)	1	99	15.3	42	57	N/A	N/A	<0.001
	2	261	40.3	139	122	5.6	0.6	
	3	261	40.3	224	37	2.5	0.2	
	4	27	4.2	18	9	3.5	0.8	
Dyspnoea	0	18	2.8	9	9	N/A	N/A	<0.001
	1	111	17.1	56	55	5.9	1.3	
	2	261	40.3	161	100	4.5	0.5	
	3	234	36.1	173	61	3.0	0.2	
	4	24	3.7	24	0	1.2	0.3	
Cough	0	21	3.2	3	18	N/A	N/A	<0.001
	1	216	33.3	117	99	5.5	0.6	
	2	378	58.3	270	108	3.1	0.2	
	3	33	5.1	33	0	2.5	0.5	
Hemoptoe	0	117	18.1	66	51	4.8	0.9	<0.001
	1	270	41.7	166	104	4.0	0.2	
	2	192	29.6	136	56	3.0	0.4	
	3	69	10.6	55	14	3.0	0.4	
Pain	0	90	13.9	37	53	N/A	N/A	<0.001
	1	327	50.5	207	120	3.8	0.2	
	2	216	33.3	167	49	2.9	0.3	
	3	15	2.3	12	3	3.0	0.6	

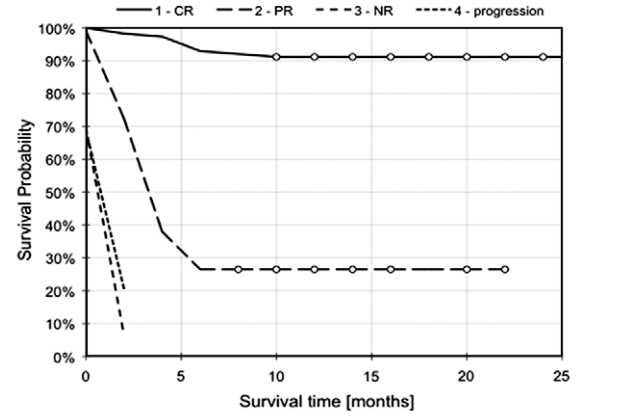
* In the group from 55 to 64 years median survival rate was not estimated because many patients were still alive by the end of the observation period.

modalities available that could be used to relieve this obstruction, including laser therapy, external beam irradiation, chemotherapy and endobronchial brachytherapy [1,4,19,20]. External beam irradiation, however effective, may not be available for many patients (primarily for those who received prior treatment), because of the proximity of dose limiting of structures adjacent to the tracheo-



Interval [months]	[0, 2)	[2, 4)	[4, 6)	[6, 8)	[8, 10)	[10, 12)	[12, 14)	[14, 16)	[16, 18)	[18, 20)	[20, 22)	[22, 24)	[24, 26)	[26, .)
Group 1	291	231	157	121	120	119	54	42	30	24	18	6		
Group 2	330	222	129	106	106	105	66	21	18	15	12	9	3	2

Fig. 1. There was no difference in the length of survival time between the two groups of patients (univariate – log-rank test, $p = 0.003$; multivariate – F Cox, $p = 0.853$).



Number at risk:

Interval [months]	[0, 2)	[2, 4)	[4, 6)	[6, 8)	[8, 10)	[10, 12)	[12, 14)	[14, 16)	[16, 18)	[18, 20)	[20, 22)	[22, 24)	[24, 26)	[26, .)
Group 1	113	111	110	105	104	103	72	48	42	36	27	12	3	2
Group 2	456	333	175	122	122	121	48	15	6	3	3	2		
Group 3	32	3												
Group 4	20	6												

Fig. 2. Patients showing improvement survived longer than those who showed no remission or progression (univariate – log-rank test, $p < 0.0001$; multivariate – F Cox, $p < 0.0001$).

bronchial tree (i.e. esophagus, spinal cord). In addition, the external beam irradiation could have significant side effects (i.e. dysphagia) and result in unnecessary damage of healthy tissues.

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

A lot of investigators have used a range of prescription points and fractional doses which could not be directly compared. Kelly et al. [21] reported significant clinical improvement in 32% of 175 symptomatic patients, a slight improvement in 34% of patients, no relief in 17% of patients and worsening of symptoms in 10% of patients. Patients showing improvement had survived significantly longer than those who showed no change or worsening symptoms. The median actuarial survival time for the entire group was 6 months from the time of the beginning of brachytherapy. For most of the applications, a dose of 15 Gy was given at a distance of 6 mm; therefore, the most common total doses were the multiples of this single dose, or 15 Gy (23%), 30 Gy (58%) and 45 Gy (7%).

Speiser and Spratling [12] observed symptomatic response rates of 85–99% in 342 of the patients receiving a range of HDR protocols who were divided into two groups – one treated with 10 Gy fraction and the other treated with 7 Gy. Response rates were similar in both groups.

In another study [13], the results of treatment of over 100 patients of palliative intent alone were presented. The treatment consisted of three or four weekly fractions, 5 or 7.5 Gy per fraction. The median survival time was only 5.6 months. Objective response, evaluated bronchoscopically, occurred in 84% of the patients. The majority of patients had experienced symptomatic relief by the third fraction of brachytherapy. The frequency of symptomatic relief was as follows: dyspnoea, 54%; cough, 51%; pneumonia, 86%; and haemoptysis, 94%.

Similarly, Gustafson et al. [22] noted significant clinical improvement in 74% of 38 symptomatic patients treated with 21 Gy at 1 cm given in three HDR applications over 3 weeks. In patients without prior irradiation, there was a tendency for higher percentage of clinical and radiographic response. They concluded that a significant proportion of patients can be rendered asymptomatic for the duration of their lives. Nori et al. [23] 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 Bedwinek et al. [24] 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. A German study compared two fractionated HDR regimens; four fractions of 3.8 Gy on a weekly basis and two treatments of 7.2 Gy at a week interval [25]. No significant difference in local control or survival

Table 2
Multivariate analysis, COX Regression for censored data.

Essentiality	$Chi^2 = 280.687$ df = 11 $p = 0.0000$						
	p	Variable force (1 – most)	Beta	Standard	t-Value	Exponent	Wald
Age	0.004	3	0.134	0.047	2.888	1.144	8.339
Location	0.160	5	−0.094	0.067	−1.405	0.911	1.973
Stage	0.000	1	0.263	0.059	4.430	1.300	19.623
Histopathology	0.143	4	−0.066	0.045	−1.465	0.936	2.146
Treatment	0.853	10	−0.019	0.105	−0.185	0.981	0.034
Response after 4 weeks	0.000	1	0.981	0.076	12.990	2.668	168.745
Zubrod	0.002	2	0.279	0.092	3.035	1.322	9.212
Dyspnoea	0.538	9	−0.057	0.092	−0.616	0.945	0.379
Cough	0.403	8	0.091	0.109	0.836	1.095	0.699
Hemoptoe	0.199	6	0.081	0.063	1.284	1.084	1.648
Pain	0.295	7	0.103	0.098	1.047	1.109	1.096

time was found between the two treatment regimens. An incidence of massive hemorrhage was similar within the doses/fractionation schemes, approximately 21–22%. The authors concluded that shorter treatment schedule was more convenient for patients, and did not result in more side effects, as well as it provided equivalent local tumor control.

In our study, we examined the results of treatment of 648 patients with endobronchial tumor, treated with two different protocols of HDR brachytherapy. We found that significant and durable clinical and radiographic responses could be obtained in patients with symptoms, despite prior radiation or metastatic and nonbronchogenic primary disease. There was no statistically important difference in the results between the two groups of patients treated with different doses. The complication rate in our series compares favorably with those reported from other institutions [5,6,26]. The median survival time of 5.9 months is consistent with the advanced stage of this population. Multivariate analysis shows that the grade of remission after treatment, clinical stage and performance status had maintained significance for survival time as well as for treatment response. The Zubrod–ECOG–WHO score is an important prognostic factor in medically inoperable patients treated with HDRBT. It is a powerful predictor of disease-free survival and it could be helpful in selecting patients that are likely to benefit from palliative therapy. We have observed that the Zubrod–ECOG–WHO score predicts which patients would achieve bronchoscopic response and symptom resolution which is positively associated with survival time. 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. For cost sparing reasons, single dose treatment can be chosen in place of weekly repeated fractions.

Conclusions

Brachytherapy treatment in advanced lung cancer is an efficient method that results in retreatment of symptoms and in improvement of quality of the lives of most of the patients. Patients showing improvement after brachytherapy survived longer than those who showed no change or progression. Survival rates were similar in both groups of patients treated with different treatment protocols (in multivariate analysis). The prognostic factors that significantly correlated with survival length were: grade of remission after treatment, age, clinical stage and performance status.

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