THE REPEATED USE OF HIGH DOSE RATE BRACHYTHERAPY FOR LOCALLY RECURRENT LUNG CANCER

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SUMMARY

Purpose: To assess the effect of repeated palliative treatment with high dose rate brachytherapy in patients with advanced lung cancer.

Material and Methods: Fifty-six patients, 25.3% of a total of 221 patients treated for lung cancer with HDR brachytherapy were treated twice, using High Dose Rate Brachytherapy. All patients were qualified for repeated brachytherapy due to the recurrence of intrabronchial tumour and acceptable remissions after the first treatment. The survival times were compared with selected clinical data. Correlations between survival times and subjective breathing difficulties were analyzed separately.

Results: The median survival time in the whole group of patients was 8.9 months. The period of obtaining a positive clinical response was correlated with a longer survival time (log-rank test, p=0.0009, F Cox test, p=0.007). In the multivariate analysis other statistically important prognostic factors were also included: the clinical stage of the primary tumour (F Cox test, p=0.04), and the interval between the first and second treatment (F Cox, p=0.004). None of the analyzed factors (dyspnoea, cough, haemoptysis and pain) had any influence on survival.

Conclusion: Repeated HDR brachytherapy in advanced lung cancer was an efficient method that in many patients led to regression of symptoms and improvement in life quality.

Key words: Lung Cancer, HDR Brachytherapy, Reirradiation, Recurrence.

INTRODUCTION

Palliative brachytherapy can be applied in three situations: (1) it is often used 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, (2) it is less frequently used in combination with external beam irradiation to deliver an additional "boost" with curative intent to the primary endobronchial lesion, and (3) it is often used in newly diagnosed patients, i.e. those without previous or additional external beam irradiation [1-5].

Because of uncontrolled local or recurrent disease, patients may display signifycant cough, dyspnoea and haemoptysis.
In many patients, these symptoms are primarily attributable to endobronchial obstruction. Efforts to relieve this obstructive process are worthwhile because, as an effect, patients may experience a significantly improved quality of life. However, many of these patients have a poor performance status and/or have a record of receiving multiple other therapies. As a result, treatment options are often limited [6-10].

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 [11-12].

In some cases, this treatment can be repeated when dyspnoea returns. This arises from the fact that local irradiation involves relative good adjacent health tissue sparing. Another reason is that often other modes of treatment are not available.

The present work reports results of repeated palliative treatment using high dose rate brachytherapy in patients with advanced lung cancer. Influence of chosen clinical data and grade of breathing difficulties on survival is analyzed.

MATERIAL AND METHODS

1. Material

Fifty-six patients, that is 25.3% out of 221 patients treated for lung cancer with HDR brachytherapy between May 1999 and May 2001 at the Great Poland Cancer Center, were treated twice using High Dose Rate Brachytherapy. All patients were individually qualified for each irradiation because of the recurrence of intrabronchial tumour and acceptable remission after the first treatment.

The median interval between both treatments was 6 months. The group of patients included 48 men and 8 women, their age ranging from 39 to 81 years (median 61.0 years). In all patients bronchoscopy and computed tomography (CT) were performed for histological diagnosis and for the evaluation of the tumour extent.

Thirty-six patients had squamous cell carcinoma (SCC), eight had adenocarcinoma (ACC), four had anaplastic carcinoma, four had solid cancer, and four had unclassified carcinoma.

In 10 (17.9%) cases, the tumour was localized in the trachea infiltrating the main bronchus, in 29 (51.8%) cases in the main bronchus, and in 17 (30.4%) cases in the lobular bronchus.

Summarized clinical data on the patients are presented in *Table 1.*

Most patients were in a bad performance status (according to the Zubrod score): 12 (21.4%), 28 (50%) and 16 (28.6%) had the Zubrod 1, Zubrod 2 and Zubrod 3 status, respectively. The leading clinical symptoms were dyspnoea, cough, haemoptysis and pain. Some patients showed more than one symptom at diagnosis (*Table 2*). The symptoms were arranged according to the Speiser and Spratling scale for assessing the palliative response in endobronchial brachytherapy [13].

Table 1. Clinical characteristic of patients.

Clinical data	Number of patients
1/ Age:	***Average: 61,0***
≤ 61	29 (51,8%)
> 61	27 (48,2%)
2/ Sex:	
Male:	48 (85,7%)
Female:	8 (14,3%)
3/ *Clinical stage (primary lesion):*	
T3 N1	6 (10,7%)
T3 N2	8 (14,3%)
T4 N0-X	31 (55,3%)
T1-4 N0-X M1	11 (19,6%)
4/ Location of tumour:	
Trachea infiltrating bronchus	10 (17,9%)
Main bronchus	29 (51.8%)
Lobular bronchus	17 (30,4%)
5/ Histopathological type:	
Squamous cell carcinoma	36 (64,3%)
Adenocarcinoma	8 (14,3%)
Carcinoma solidum	4 (7,1%)
Anaplastic carcinoma	4 (7,1%)
Unclassified carcinoma	4 (7,1%)
6/ Obturation grade:	
≤ 50%	4 (7,1%)
> 50%	10 (17,9%)
almost total	25 (44,6%)
total	17 (30,4%)
7/ Interval length between the first and second treatment:	
≤ 6 months	46 (82,1%)
> 6 months	10 (17,9%)
8/ Remission after 4 weeks:	
CR	4 (7,1%)
PR	42 (75%)
NR	10 (17,9%)

Table 2. Performance status of patients in time of repeated brachytherapy

Performance status data	Number of patients
1/ Zubrod (WHO) score:	
1	12 (21,4%)
2	28 (50%)
3	16 (28,6%)
2/ Dyspnoea:	
0	2 (3,6%)
1	12 (21,4%)
2	27 (48,2%)
3	13 (23,2%)
4	2 (3,6%)
3/ Cough:	
0	3 (5,3%)
1	24 (42,8%)
2	27 (48,2%)
3	2 (3,6%)
4/ Hemaptoe:	
0	8 (14,3%)
1	25 (44,6%)
2	18 (32,1%)
3	5 (8,9%)
5/ Pain:	
0	13 (23,2%)
1	29 (51,8%)
2	13 (23,2%)
3	1 (1,8%)

Speiser and Spratling Scale for assessing palliative response in endobronchial brachytherapy [13]

2. Treatment

At the first treatment all 56 patients received a total dose of 22.5 Gy in 3 fractions every week. The second treatment in all cases involved a single 10 Gy fraction.

Endobronchial irradiation was performed after local anaesthesia and sedation with midazolam. The applicator tube, loaded with a ribbon of dummy seeds, was positionned under endoscopical and fluoroscopical control. The target volume was defined by prior endoscopical and radiological findings. A high-dose-rate afterloading machine (Gammamed 12i, Isotopentechnik Dr. Sauerwein, Haan, Germany) with an I92 Iridium stepping source and a nominal activity of 370 GBq (10 Ci) was used. To calculate dose distributions an ABACUS computer programme was employed. The dose was prescribed at a 10-mm distance to the surface of the source. The target volume included the residual tumour visualized by bronchoscopy or proven by biopsy plus 2 cm safety margins in cranial and caudal direction. In all patients, the applications were performed with a 1.8 mm bronchus applicator (length 1300 mm) inserted endoscopically before treatment.

3. Methods

Clinical and endobronchial observations were based on the rating of local remission and regression of difficulties with breathing, cough and haemoptysis. Remission of the tumour was assessed in the first month after brachytherapy, then in the third, sixth and twelfth month.

Partial remission (PR) was defined as a 50% reduction in the tumour volume, measured by CT and bronchoscopy. Complete remission (CR) and progressive disease (PD) were defined as lack of evidence of local tumour or further tumour growth exceeding 25%. No remission (NR) was defined as no change in tumour size or tumor growth of less then 25%.

The results were compared with some selected clinical factors such as age, sex, histopathology, clinical stage, the Zubrod score, remission of the tumour assessed after the 1^{th} month, location of the tumour, grade of obturation, the interval between 1^{st} and 2^{nd} treatment, and the administered dose.

4. Statistical evaluation

The survival time was defined as the time from the beginning of the second bra-

chytherapy to the death of the patient, or to the end of the twelfth month of observation. Univariate and multivariate categorized analysis were made using the Kaplan – Meier method and log-rank, F Cox tests were performed for the overall survival. In none of the categorized data such as age and interval between 1st and 2nd treatment Cox's regression model was used.

RESULTS

The median survival time (Kaplan-Meier) in the whole group of patients was 8.9 months *(figure 1).* After the first month from the end of the second treatment in 46/56 (82.1%) patients subjective and clinical (CR+PR) improvement (regression of all symptoms) was observed *(Table 1).*

A positive response was correlated with longer survival time. Patients with endoscopically controlled complete or partial remission had significantly longer survival times in comparison with patients whose tumour size remained unchanged (figure 2, log-rank test, p=0.0009, F Cox test, p=0.007). After 3 months, CR in 2/56 (3,6%) cases, PR in 37/56 (66,1%) cases, NR in 7/56 (12,5%) cases were noted, and in 10 cases (17,9%) progression was observed. After 6 months, CR in 2/56 (3,6%) cases, PR in 19/56 (33,9%) cases, progression/recurrence in 23/56 (41,1%) cases were noted.

Twelve (21,4%) patients died in the first 6 months of observation. During one year of observation 47 patients (83.9%) died, in 3 alive patients (5.4%) improvement of dyspnoea was noted, and in 6 patients (10.7%) recurrence and progression of the disease was observed. Most frequent cause of death were local recurrence alone or with dissemination.

Univariate categorized analysis revealed no differences in survival times in relation to sex and age (log-rank test, p=0.37 for age, p= 0.6 for sex). Patients' age was classified in two groups: equal or lower than the median and that higher than the median. Absence of statistical significance with age was confirmed by all the categorized factors analyzed (p=0.09).

The influence of the clinical stage of the primary tumour on survival was analyzed. Patients were divided into three groups (*Table 1*). Less advanced stage at the first treatment corresponded to longer survival. In the multivariate analysis we found a significant difference in the survival times between groups (*figure 3*, F Cox test, p=0.04).

Survival was analyzed according to the Zubrod (WHO) score. Statistical analysis revealed a significant difference between patients with the Zubrod score of 1 (12, 21.40%), 2 (28, 50%) and 3 (16, 28.6%), respectively (*figure 4*, log-rank test, p=0.005).

The influence of tumour location on survival was analyzed. For statistical analysis our patients were divided into three groups: those with trachea infiltrating bronchus (10, 17.9%), with the main bronchus (27, 48.2%) and with the lobular bronchus (17, 30.4%). In the univariate analysis tumour location had significant influence on survival (*figure 5*, log-rank test, p=0.04).

The influence of the interval between the first and second treatment on survival times was analyzed. Longer interval (equal or more than 6 months) led to longer survival compared *(figure 6*, log-rank test, p=0.001, F Cox p=0.004).

The influence of the obturation grade on survival was not observed (log-rank test, p=0.8), neither have we found statistically significant correlations between survival and fractionation schema used in the first brachytherapy treatment (3 x 7.5Gy or 1 x 10 Gy) (log-rank test, p=0.3) and histopathology (log-rank test, p=0.3).

Correlations between survival times and subjective breathing difficulties were analyzed separately. None of the analyzed factors *(Table 2)* - dyspnoea, cough, haemoptysis and pain – divided into groups according to Speiser and Spratling [13]) - had any influence on survival (log-rank test, respectively, p=0.18, p=0.06, p=0.3, p=0.25).

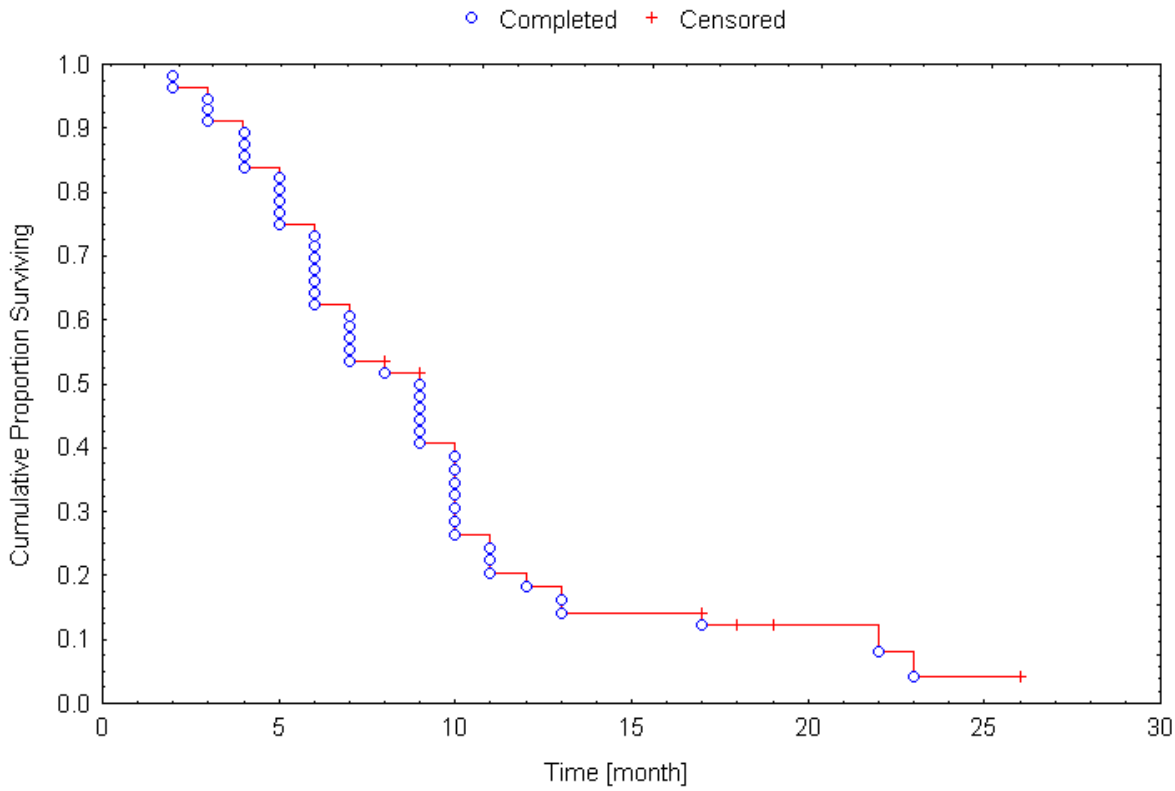

Fig. 1. Surviving for all patients (Kaplan Meier).

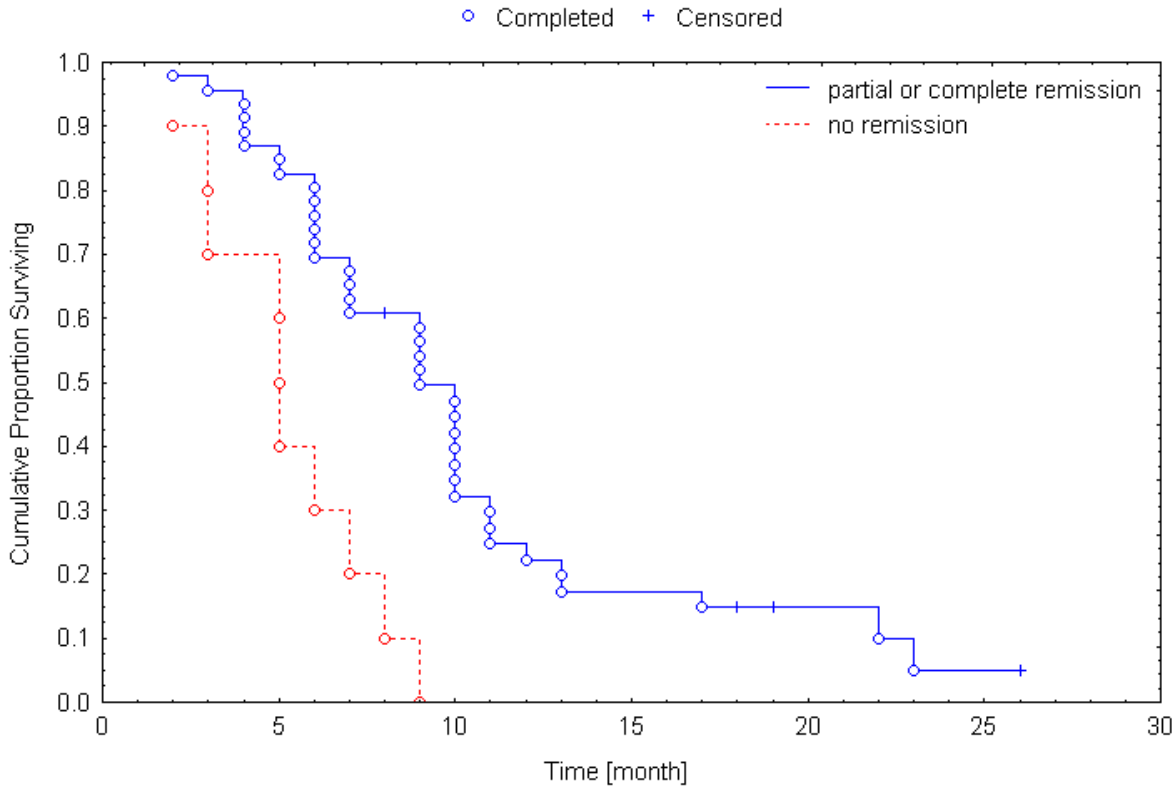

Fig. 2. Influence of local response assessed in 1st month after brachytherapy on survival (log rank p=0,008, F Cox p=0,007).

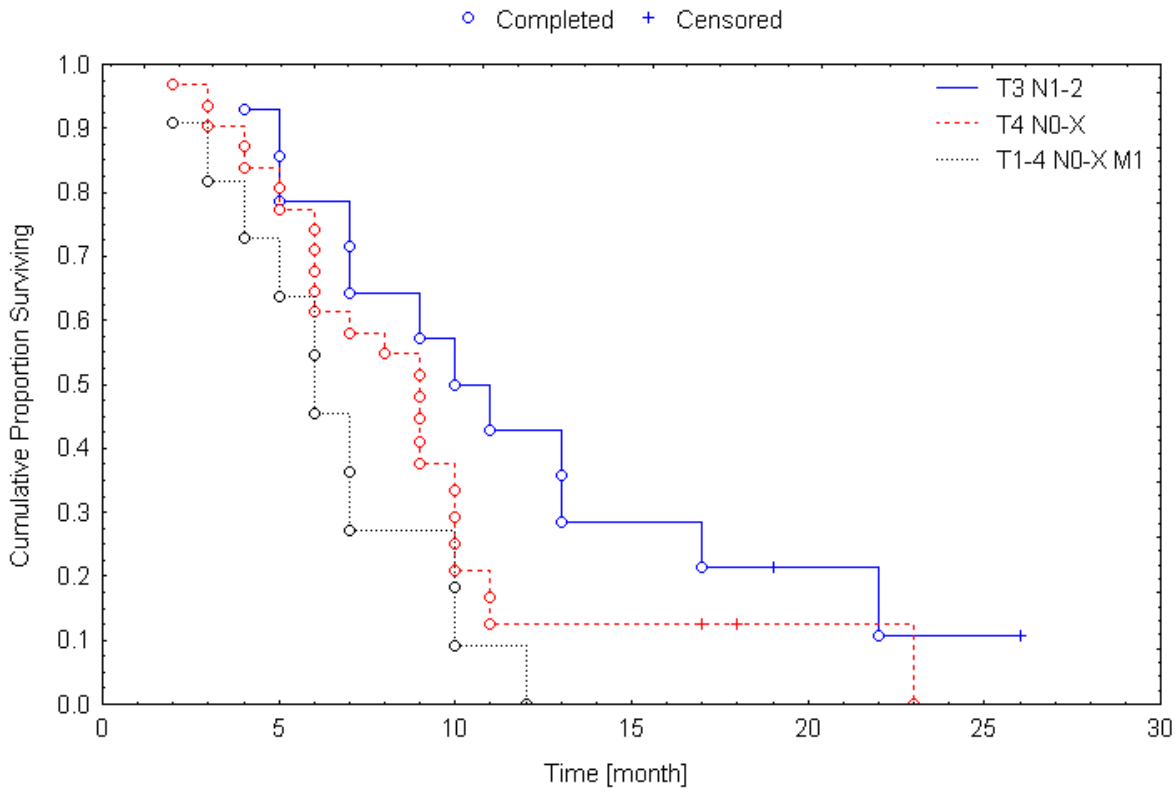

Fig. 3. Influence of clinical stage on survival (F Cox p=0,04).

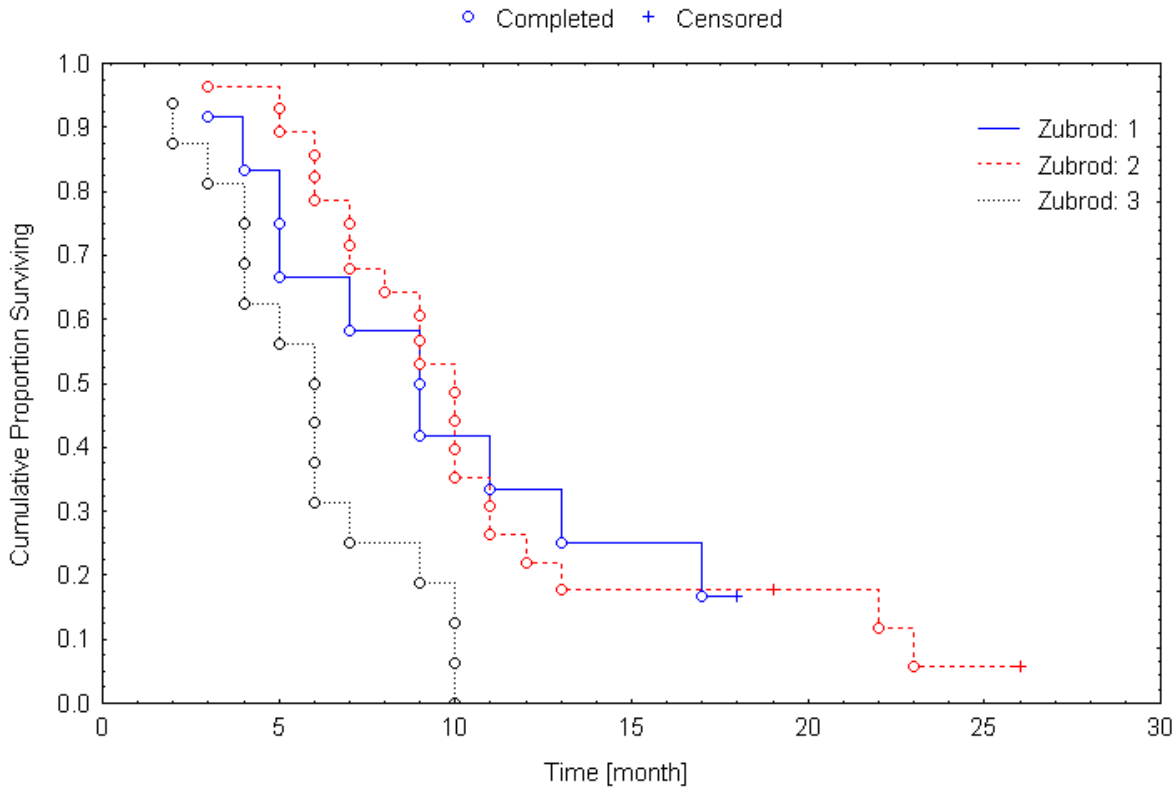

Fig. 4. Survival according to Zubrod (WHO) score (log rank p=0,005).

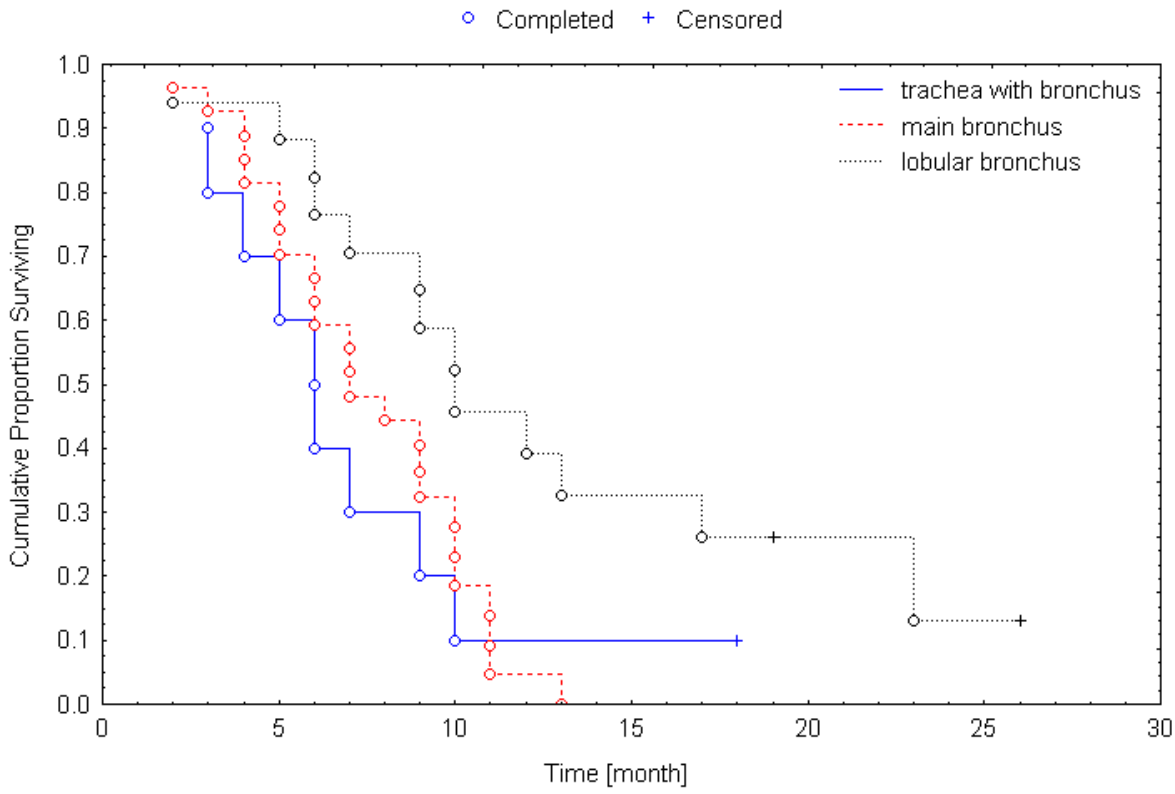

Fig. 5. Influence of tumour location on survival (log rank p=0,04)

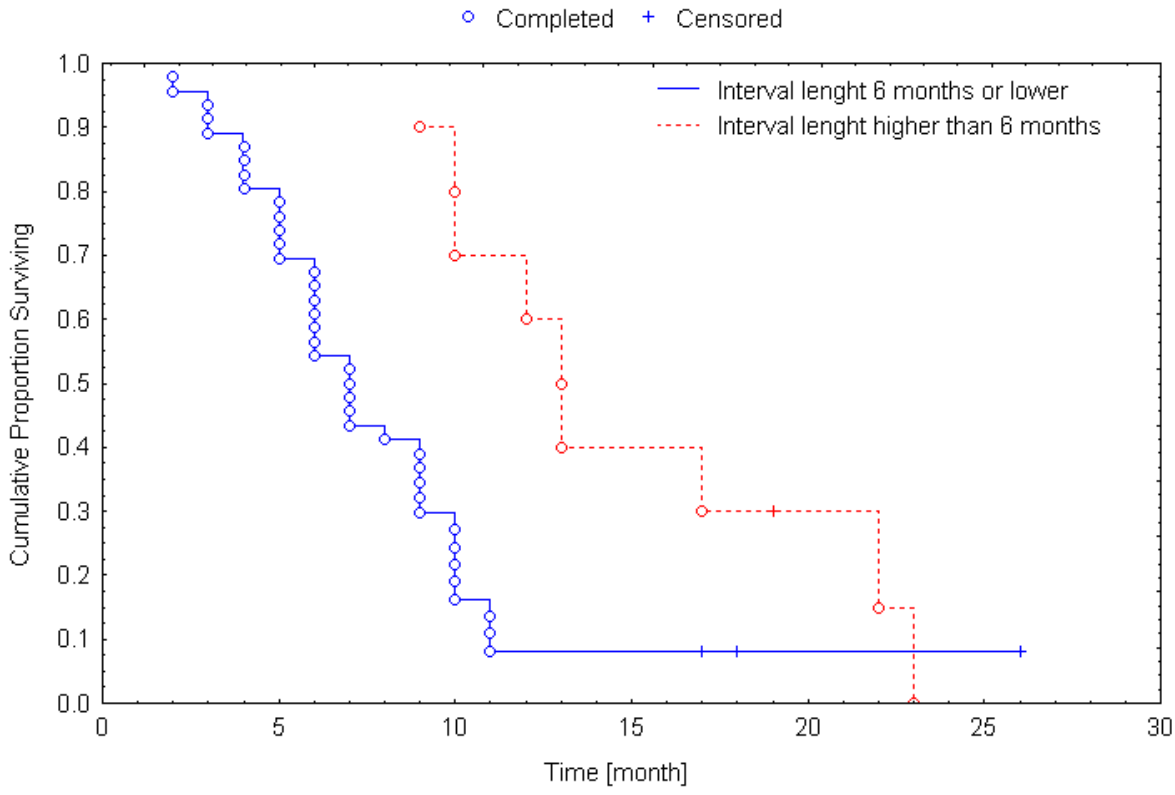

Fig. 6. Influence of interval length between treatments on survival (log rank p=0,001, F Cox p=0,004).

COMPLICATIONS

There were no complications during bronchoscopy and catheter positioning. In monthly repeated bronchoscopy we could observe gradual improvement in all cases with necrosis. Forty-two (75.0%) patients presented with early superficial mucosal necrosis (assessed in 1st month after brachytherapy, SOMA Evaluation – grade 1 and 2) were successfully treated pharmacologically. Higher temperature and exhausting cough were most frequent complications. In 6 cases (10,7%) during 12 months of follow-up we found broncho - esophageal fistula. No early life threatening complications were observed.

DISCUSSION

An airway obstruction, secondary to extensive primary or recurrent intrathoracic cancer, occurs frequently and creates devastating effects on 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 [1,4,14-16].

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). 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 recurrent intraluminal airway tumours [10,16-18].

There are only few papers reporting results of repeated irradiation after previous external beam therapy or brachytherapy. Authors have not found reports concerning repeated second HDR brachytherapy in advanced lung cancer.

In one of the recently published papers authors [17] reviewed a series of patients with local recurrence of lung cancer to evaluate the efficacy and safety of external beam reirradiation. Reirradiation was performed in 18 patients with the aim of achieving a cure or prolongation of survival (radical treatment), while 16 patients were treated for improvement of their symptoms (symptomatic treatment). The overall survival rate after reirradiation was 43% at 1 year and 27% at 2 years, with a median survival time of 8 months. The median survival time after radical treatment was 15 months, with a range of 3 to 58 months, whereas that after symptomatic treatment was 3 months, with a range of 1 to 14 months.

Delclos et al. [2] evaluated toxicity and efficacy of endobronchial brachytherapy for recurrent endobronchial lesions in 81 patients. For most patients, a dose of 30 Gy in two fractions over two weeks was delivered. In sixty-eight patients (84%) some response was obtained. The median duration of response was 4.5 months. Patients with excellent response (32%) had a significantly better survival (13.3 months) compared with that of other patients (5.4 months) (p=0.01). There were only two fatal complications, which were due to fistula and tracheal malacia.

Taulelle et al. [5] analyzed a group of 189 patients treated with HDR brachytherapy. Most patients (69.3%) had received prior treatment and revealed symptomatic bronchial obstruction due to either recurrent or residual endobronchial disease. Treatment was performed weekly and consisted of three to four 8 to 10 Gy fractions. Complete endoscopic response was observed in 54% of cases. The median survival was 7 months for the entire group. Using a univariate analysis, no factor was found to be predictive of late pulmonary toxicity. The study confirmed the usefulness of endobronchial brachytherapy in alleviating symptoms caused by endobronchial recurrence of bronchogenic carcinoma.

Speiser and Spratling [13] observed symptomatic response rates of 85-99% in 342 patients receiving a range of HDR protocols divided into two groups – one treated with a fraction of 10 Gy and the other treated with 7 Gy. Response rates were similar in both groups. The authors have observed a significant decrease in bronchoscopic response in patients treated with palliative brachytherapy for relapse following external beam radiation as

compared with those who had not received previous external beam radiation, i.e., 70% and 84%, respectively.

Micke et al. [19] reported the results of HDR brachytherapy in 16 patients with recurrent lung cancer after external beam radiation (50 – 60 Gy). The recurrences were treated using 2 to 4 applications of 5 to 6 Gy each. The median period of remission was 4 months, whereas the median survival time was 9 months. 56% of patients achieved partial or complete remission, 81.3% achieved improvement in dyspnoea.

Gustafson et al [20] noted significant clinical improvement in 74% of 38 symptomatic patients with recurrent lung cancer treated by 21 Gy given in 3 HDR applications. Twelve patients received prior external beam irradiation (median dose of 58 Gy). Twenty-five patients (69%) had a partial or complete response on radiographic examination. In patients without prior irradiation there was a tendency for a higher percentage of clinical response. None of the factors used predicted an increased risk of complications.

Ornadel et al. [21] have undertaken a prospective analysis of symptom response, duration response and prognostic factors in 117 patients treated with brachytherapy. A single dose of 15 Gy was given. Ninety-two patients had received previous external beam radiotherapy. The external beam radiotherapy dose ranged from 20 Gy in 5 patients to 60 Gy in 30 fractions. The median survival time was 12 months. There was no correlation between the total dose of the prior external beam therapy and the survival rate or rate of fatal haemoptysis.

In the Bedwinek et al. [22] series, 38 patients were treated with high dose rate endobronchial brachytherapy to palliate symptoms caused by endobronchial recurrence of previously irradiated ($\geq$ 5000 cGy) lung cancer. Twenty-nine (76%) patients had symptomatic improvement in response to a dose of 18 Gy, given in 3 HDR sessions weekly. The median duration of symptoms relief was 7.5 months. Bronchoscopy carried out 3 months after brachytherapy revealed that 41% had complete regression and another 41% had partial regression. Location of the recurrence was the most important predictor of pulmonary haemorrhage.

Kelly et al [18] investigated the outcome of 175 lung cancer patients who underwent HDR brachytherapy for recurrent or metastatic tumours. The median actuarial survival for the entire group was 6 months from the time of the first HDR brachytherapy treatment session, 160 patients having previously received external beam radiation. Of the 175 patients (66%) who showed symptomatic improvement, 32% were much improved and 34% were slightly improved. Patients showing improvement survived for significantly longer than those who showed no change or worsening of symptoms (7 vs. 4 months, $p = 0.0032$). Complications occurred in 19 patients (11% crude rate) with an actuarial complication rate of 13% at 1 year from the time of the first brachytherapy treatment session. The authors concluded that HDR brachytherapy effectively palliates most patients' symptoms caused by endobronchial lesions. This relief correlates significantly with an overall survival benefit.

A number of studies concerning brachytherapy for recurrence after external irradiation reported the incidence of these fatal complications as ranging from 0 to 50% [21-27].

One of the published randomized studies [28] was conducted to investigate whether endobronchial brachytherapy (EBB) is a risk factor for massive haemoptysis in 938 patients primarily treated by a combination of EBB and external irradiation (XRT) for lung cancer. One hundred-one out of 938 patients (10.8%) died from massive haemoptysis. The incidence of massive haemoptysis depended signifycantly on the fraction size of brachytherapy. The authors concluded that a combination of EBB and XRT as primary treatment for NSCLC did not lead to a higher risk of massive haemoptysis as compared with XRT alone, when fraction sizes for EBB of 7.5 or 10 Gy are used.

Our results of treatment confirmed the usefulness of repeated brachytherapy in the treatment of advanced recurrent lung cancer. Periodical regression of dyspnoea was found in all patients. In some cases, the improvement occurred within a few hours after the termination of bra-

chytherapy. Regression of dyspnoea was associated with less intense cough, smaller haemoptysis, lower pain in the mediastinum or fewer symptoms of atelectasis.

Complete remission observed in the first month after treatment was the most important prognostic factor indicating prolonged survival. There were other signifycant correlations found in the multivariate analysis: between survival and clinical stage of primary tumour and between survival and interval length between first and second treatment. In the univariate analysis additional correlations were noted between the survival and the Zubrod score and between survival and location of the tumour. Tolerance of repeated treatment was good in most cases, in 42 patients (75,0%) a superficial intermittent mucosal necrosis, in 6 cases broncho-esophageal fistulae were observed. Mucosal necrosis was successfully treated pharmacologycally during observation. A number of complications were not different from the results obtained by other authors. No early life threatening complications were observed..

It seems that complete local remission after brachytherapy is more important in patients with recurrent lung cancer than other clinical factors such as age, sex, histopathology, tumour obturation or method of fractionation used in prior irradiation. The prognostic role of clinical stage is emphasized by many authors, the same is true for the length of the interval between both treatments. The high summary local dose (especially in bronchial wall) did not lead to any increase in complications.

CONCLUSIONS

1. Repeated HDR brachytherapy in advanced lung cancer was an efficient method that in many patients caused regression of the symptoms and led to the improvement of life quality.
2. The survival time was correlated with (1) a positive response (complete or partial) at the first follow-up after the end of the treatment, (2) a clinical stage of the primary tumour and (3) the length of the interval between the first and second treatment.
3. High total doses influenced the frequency rate of temporary early complications, in the majority of patients, however superficial mucosal necrosis was observed.

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