The use of high dose rate endobronchial brachytherapy to palliate symptomatic recurrence of previously irriadiated lung cancer

M. KUBASZEWSKA, J. SKOWRONEK*, A. CHICHEŁ, M. KANIKOWSKI

Department of Brachytherapy, Greatpoland Cancer Center, 15 Garbary Street, 61-866 Poznań, Poland, e-mail: janusz.skowronek@wco.pl

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Endobronchial obstruction associated with lung cancer represents a common and potentially life threatening complication of newly diagnosed or recurrent disease. The vast majority of patients with obstructive lesions are not curable so it is desirable to palliate these patients as quickly as possible without compromising quality of life. High dose rate brachytherapy (HDR-BT) represents a therapeutic option with several advantages over external beam radiotherapy (EBRT), particulary in previous irradiated patients. The primary objective of this retrospective analysis was to assess palliation efficacy and complication rate of repeated brachytherapy treatment in previously irradiated patients. Between July 2000 and December 2005, 270 patients with endobronchial recurrence after prior given HDR-BT and / or another treatment modality were again treated with HDR-BT. It makes 270 of 1036 patients (26 %) treated on lung cancer with HDR-BT at all in this period. Brachytherapy was delivered with a dose per fraction 8 or 10 Gy specified from the center of the source at 0,5 or 1,0 cm. The symptomatic response rate were as follows: dyspnea had a 76 % response rate, cough 77 % response rate, hemoptysis 92 % response rate, and postobstructive pneumonia 82 % response rate, respectively. Among 270 of the patients 218 had follow up endoscopic examination (1 – 3 months after brachytherapy completion). Total response rate in this group was 80 %. Of 200 patients whose chest x-ray showed evidence of collapse or atelectasis caused by endobronchial recurrence obstruction, 146 (73 %) had evidence of reaeration. The median duration of palliation, marked by symptoms or a chest x-ray that worsened was five months, the range varing from 2 to 14 months. We have noticed superficial mucosal necrosis in 166 of patients (61,5 %) and broncho – osephagal fistula in 6 of patients (2,2 %). Repeated HDR-BT effectively relieves the symptoms of endobronchial obstruction due to recurrent lung cancer and can be given safely as an outpatient procedure. Future studies should aim to determine the maximum tolerated dose and appropriate patient selection.

Key words: repeated HDR brachytherapy, reirradiation, endobronchial recurrence, palliation.

Lung cancer is the leading cause of cancer death with five-year survival rates reaching only 10-12 % during the last 20 years. Numerous efforts have been made to improve the survival rate for this patient cancer group. The lung cancer failure rate remains unacceptably high, despite major advances over the past 40 years in the field of surgery, radiotherapy and chemotherapy. The most common primary malignant tumors occurring in the respiratory tract arise from the endobronchial epithelium. They are subdivided into small cell lung cancer (SCLC, +/- 25 %) and the majority non-small cell lung cancer (NSCLC, +/- 75 %). In general, upon diagnosis 25 – 30 % of the NSCLC patients present with tumors confined to the lung (stage I or II) and only 40 – 50 % of them can be resected for cure, 30 % have locally advanced disease (stage III), the remaining 40 – 45 % have distant metastases (stage IV). Unfortunately, lung tumour recurrences develops in up to 40 – 60 % and are responsible for 60 % of the mortality due to respiratory failure, obstructive pneumonia and sepsis. The most common symptoms in those patients suffering from endobronchial obstructive recurrences are: cough (45 – 75 %), hemoptysis (25 – 35 %), dyspnea due to atelectasis (40 – 60 %) or postobstructive pneumonia (25 %) [1, 2]. Successful treatment of these recurrences is difficult, as chemotherapy has limited value in this matter and often surgery or EBRT can not be safely applied. The most important consideration in this situation is to relieve distress from symptoms caused by endobronchial recurrences and the restoration of patency of the airway. In order to palliate symptoms, and improve the quality of the remaining life for these patients, it is preferable to use a method that is relatively easy to perform and has mini-

* Corresponding author

mal complications. Removal of the tumour recurrence mass by endoscopic biopsy forceps combined with cryosurgery, electrocautery, or laser ablation can achieve only limited clearance and short – term palliation, because the tumour kinetic is not altered. Therefore, HDR-BT is the option of treatment endobronchial recurrences tumours which can increase the efficiency of the control of malignant airway obstruction and the duration of palliation [3–6].

The primary objective of this study was to report palliation effect in corelation with established prognostic factors in patients with endobronchial recurrence of lung cancer after previously given treatment (including as main condition) using HDR-BT.

Materials and Methods

Patients. Between July 2000 and December 2005, 270 patients, (206 males, 76,3 % and 64 females, 23,7 %) with tracheobronchial recurrence of lung cancer, after prior given treatment including HDR-BT were again treated using this treatment modality at the Greatpoland Cancer Center in Poznań. Patients age was ranging was from 29 to 85 years old with the median age of 62 years old. Histologies of the tumours varied, with squamos cell carcinoma accounting for 63,7% (Table 1).

The site of the endobronchial recurrence treatment was variable. The location of recurrent lesions and endobronchial treatment sites are shown in Table 2 (Table 2). 158 (58,5 %) of patients presented with proximal airway obstruction (14 trachea, 32 trachea + main bronchus, 112 main bronchus). The right and left mainstem bronchus were the most commonly treated sites.

The previous and concurrent treatments in endobronchial recurrence are assumed in Table 3 (Table 3). A total of 334 HDR-BT procedures were performed on 270 patients as repeated treatment due to endobronchial recurrence and acceptable remission after first given HDR-BT. Among 270 patients treated again with HDR-BT, 220 were irradiated once, 38 patients – twice, 10 patients – trice and 2 patients four times in a row. Repeated HDR-BT was delivered as single fraction with dose level 8 or10 Gy depending on size of recurrent tumour, general condition, previously given total dose including EBRT and BT, tolerance of the mucosa in irradieted area. Single dose fraction of 8 Gy was decided to be given, when previous high EBRT dose over 60 Gy/T was delivered. Recurrent patients who had previously received full course of EBRT and had no parenchymal disease were treated with HDR-BT alone. Recurrent patients who previously had not been treated with EBRT, were given HDR-BT. During first treatment 172 patients received total dose of 22,5 Gy in 3 fractions every week while 98 patients received one single fraction of 10 Gy (Table 4).

Table 1. Patients characteristic

Clinical data	Number of patients	Rate (%)
Age:		
< 60	66	24,4
60 -70	95	35,2
70 -80	80	29,6
> 80	29	10,7
Sex:		
Male	206	76,3
Female	64	23,7
Histology:		
Squamous cell carcinoma	172	63,7
Adenocarcinoma	27	10
Non small cell carcinoma	14	5,2
Small cell carcinoma	13	4,8
Large cell carcinoma	6	2,2
Undetermined	21	7,7
Metastases	9	3,3
Cell carcinoma	8	2,9
Stage of primary lung cancer #		
I	10	3,7
II	27	10
IIIA	34	12,6
IIIB	104	38,5
IV	51	18,9
Undetermined	44	16,3

According to American Joint Committee on Cancer Staging System

Table 2. Endobronchial recurrence location

Endobronchial location	Number of patients	Rate (%)
Trachea	14	5,2
Trachea + main bronchus	34	12,6
Main bronchus	112	41,5
Lobular bronchus	85	31,4
Segmental bronchus	17	6,3
Stump	8	2,9

Table 3. Characteristic of given treatment modality.

Treatment	Number of patients	Rate (%)
Previous treatment for recurrent patient:		
Radical treatment:	61	22,6
1. EBRT + BT as "boost"	16	5,9
2. Surgery + BT	4	1,5
3. Surgery + BT + EBRT	8	2,9
4. EBRT + BT + CHTCH	33	12,2
Palliative treatment:	209	77,4
1. EBRT + BT	122	45,2
2. EBRT + BT + CHTCH	54	20
3. Salvage BT	33	12,2
Concurrent treatment for all patients:	144	53,3
1. EBRT	65	24
2. EBRT + CHTCH	42	15,6
3. CHTCH	37	13,7
No concurrent treatment	126	46,6

EBRT = external beam radiotherapy; BT = brachytherapy; CHTCH = chemotherapy

Methods

There were several following criteria for inclusion in this retrospective analysis: 1. history of tracheobronchial carcinoma, bronchogenic or metastatic, 2. the patient must have been previously given HDR-BT (main condition), 3. bronchoscopically documented endobronchial recurrence, producing local symptoms (cough, hemoptysis, dyspnea or obstructive pneumonia), 4. suitable endobronchial location for afterloading catheter placement, 5. general condition according to WHO score ≥ 3.

The definitive decision for repeated brachytherapy was based on: clinical examination, flexible bronchoscopy with precise documentation of the location and the amount of obstruction, supplemented by a chest X-ray and sometimes by computed tomography. It was important to determine tumour extent as clearly as possible, especially in recurrence of disease in previously irradiated area.

The proximal and distal margin of the intraluminal gross tumour volume were estimated by direct visualization of endobronchial involvement. Additional informations from chest X ray were helpful to estimate the length of the obstruction, mainly in completely obstructing lesions in which assessment of the distal margin were not possible by endoscopy. In the longitudinal direction, a safety margin of 2 cm was usually added to both sides of the macroscopic tumour to define the target volume. If there was a doubt about the distal margins, an extra 2 – 3 cm were added to be insure the covering of the whole endobronchial recurrence tumour extent. The application of brachytherapy were performed usually on an outpatient basis, under local anaesthesia, supplemented by sedatives and vagolitic drugs. It was important to suppress the coughing, in order to prevent displacement of the inserted applicator. The area of carcinomatosus obstruction was identified during bronchoscopy and the brachytherapy catheter was then passed directly through the operating channel of the bronchoscope and placed beyond the region of the tumour. The bronchoscope was than removed, leaving the catheter in place. The bronchoscope was reinserted to recheck the right position of catheter. Orthogonal x-ray were used to verify the position of the catheter and to assist in the treatment planning. The position of the applicator on these radiographs were checked and compared with the clinical and radiographic documentation. On the radiograph, the target was drown, taking into account all diagnostic findings. Than patient was moved to the HDR brachytherapy suite. A remote afterloading High Dose Rate Unit (GAMMAMED 12i® until 2001 year, then microselectron HDR Nucletron®) was used to deliver the radiation with a high intensity Iridium 192 source. The total dose for second brachytherapy, consisted in all cases of single fraction 8 or 10 Gy specified on 5 -10 mm from the axis of the source, depending on several factors – taking into account of previous treatment (prior given dose from brachytherapy, EBRT), performance status, size and location of recurrence tumor, accepted tolerance of mucosa, time following the last brachytherapy and/or EBRT. Afterwards, the applicators were removed, and the patients were discharged after a brief observation period.

Clinical, endobronchial and radiological observations were undertaken with rating palliation effect as a main objective

Table 4. HDR – BT schedule

Brachytherapy procedure:	Number of patients	Rate (%)
At first treatment time:		
3x 7,5 Gy	172	63,7
1x 10 Gy	98	36,3
At second treatment time:		
1x	220	81,5
2x	38	14,1
3x	10	3,7
4x	2	0,7
Degree of bronchus obturation at recurrent time:		
< 50 %	22	8,1
> 50%	61	22,6
Almost total	84	31,1
Total	91	33,7
Stump	12	4,4

Table 5. Speiser and Spratling Scale for assessing palliative response in endobronchial HDR – BT [7]

DYSPNEA	
Score	
0	no
1	on moderate exert
2	with normal activity, walking on level ground
3	at rest
4	requires supplemental oxygen
COUGH	
Score	
0	none
1	intermittent: no medication necessary
2	intermittent: non-narcotic medication
3	constant or requiring narcotic medication
4	constant or requiring narcotic medication, but without relief
HEMOPTYSIS	
Score	
0	none
1	less than 2 per week
2	less than daily, more than 2 x per week
3	daily, bright red blood or clots
4	requiring hospitalization and transfusion
PNEUMONIA / ELEVATED TEMPERATURE	
Score	
0	normal temperature, no infiltrates, WBC less than 10.00
1	temperature greater than 38,5 infiltrate, WBC less than 10.000
2	temperature greater than 38,5 infiltrate, and/or WBC over 10.000
3	lobar consolidation on radiograph
4	pneumonia or elevated temperature requiring hospitalization

Table 6. Symtomatic and endoscopic response to HDR – BT.

Response	Number of patients, (%)	P (%)	NR (%)	PR (%)	CR (%)	TR (%)
Symptomatic						
Cough	267 (99)	21 (8)	40 (15)	125 (47)	81 (30)	206 (77)
Dyspnea	243 (90)	26 (11)	32 (13)	145 (60)	40 (16)	185 (76)
Hemoptysis	178 (66)	0 (0)	15 (8)	96 (54)	67 (38)	163 (92)
Pneumonia	124 (46)	4 (3)	12 (10)	76 (62)	32 (26)	102 (82)
Endoscopic	218 (80)	4 (2)	39 (18)	158 (73)	17 (7)	175 (80)

P = Progression; NR = No Response; PR = Partial Response; CR = Complete Response;
TR = Total Response

of study and local remission, complication and survival rate as second end points at first, third, sixth and twelveth month of observation.

The influence of the following variables on the palliative effect was studied: age, sex, WHO score, histology, total brachytherapy dose, total external beam irradiation dose, escalation of clinical, radiological symptoms in recurrence bronchogenic carcinoma according to Speiser and Spratling scale [7] (Table 5).

The treatment efficacy was evaluated in 1 to 3 months after the end of brachytherapy, based on subjective symptomatic attenuation, bronchoscopy and by radiological assessment, depending on patient's clinical situation.

Subjective symptomatic relief was recorded as the patients were asked specific questions about the severity of their symptoms, activity level, and whether their general condition had improved since the last endobronchial treatment. Speiser's scale (four major symptoms were recorded: dyspnea, cough, haemoptysis, pneumonia) and assessment of performance status according to WHO score were used. Endoscopic response were evaluated based on visual intraluminal assessment. Radiological observation (x-ray) were performed once in every three months after treatment completion. For symptomatic responses, progression (P) was recorded when patient had worsening symptoms, no response (NR) was recorded when there was no symptomatic relief, partial response (PR) was recorded when patient had significant relief, complete response (CR) was described when patients had complete relief of symptoms.

For endoscopic findings, P was recorded when increasing size of tumour mass, and/or new cancer focus appeared, NR was described for patients without significant tumour regression, PR was recorded when there was at least 50 % of reduction in the tumor mass, CR was described when there was a total regression of all measurable tumours. Radiation bronchitis was defined as all mucosa reactions (swelling, fibrinous membranes) associated with new respiratory symptoms (cough, dyspnea, pain).

Results

All patients had symptoms secondary to obstruction. Cough was most common symptom occurring in 99 % of all patients. Dyspnea was the second most common symptom, occurring in 90 % of all of the patients in analyzed group. Hemoptysis was occurring in 66 % of patients and lastly, obstructive pneumonia occurred in 46 %. In our analysis, hemoptysis had the highest correlation with the initial response rate (92 %). Dyspnea seems to have the lowest correlation with complete response rate (16%), yet 60 % showed significant improvement. The response rate for cough was 77 %. Patients with postobstructive pneumonia had 82 % of total response rate. Both – dyspnea and cough showed less impressive response rate, in part due to pre-existing pulmonary disease and radiation bronchitis. 218 of patients were reexamined with bronchoscopy at least once between 1 and 3 months after completing HDR-BT. The rest of patients did not have endoscopic reexamination due to rapid deterioration or death.158 of patients had at least 30 % of decrease of tumour size or obstruction. 17 patients were responding completely with no evidence of residual tumour, except some postirradiation changes (bronchial edema, fibrosis). The total response rate according to bronchoscopic finding were 80 % (Table 6).

About 200 (75 %) patients had chest x-rays that showed collapse of one or more lobes or atelectasis due to endobronchial tumour recurrence. Out of the 200, 146 (73 %) patients achieved reaeration, as defined by decreased atelectasis on subsequent chest x-ray. In 54 whose chest x-ray did not change, 15 had definitive symptomatic improvement. Overall, symptomatic palliation was very satisfactory. The majority of the responsive patients enjoyed improved quality of life and some duration of the palliation. The duration of symptomatic relief, including complete and partial remission (interval from retiring of symptoms to recurrence of symptoms or death), ranged from 2 to 14 months with median of 5 months.

Univariate and multivariate analysis revealed differences in duration and degree of symptoms relief after second HDR-BT treatment according to: the performance status (Kruskal – Wallis test, $p = 0{,}016$), the degree of dyspnea (Kruskal – Wallis test, $p = 0{,}010$), the prior given treatment with radical or palliative intent (Mann – Whitney test, $p = 0{,}002$). Including variables such as: better performance status, less degree of dyspnea, more radical prior given treatment, the duration of overall symptomatic palliation effect was more satisfactory and improved quality of life of the patients.

Table 7. Literature review of HDR – BT applications.

Author	Number ofpatients	HDR doseschedule (fractions, Gy)	Clinicaleffect (%)	Radiological improvement (%)	Endoscopic Improvement (%)	Mediansurvival (months)
Speiser [7]	144	3 x 10	85 – 99	-	80	-
	151	3 x 5-7				
Bedwinek [11]	38	3 x 6	76	64	82	10
Jacobson 13]		3 x 6	74	-	65	-
Gauwitz [14]	24	-	88	-	88	8
Sutedja [15]	31	3 x 10	82	-	-	7
Burt [16]	50	1 x 15-20	50 – 86	46	88	-
Miler [17]	88	3 x 10	-	-	80	-
Stout [18]	100	1 x 15-20	88	46	-	-
Aygun [19]	62	3-5 x 5	85 – 99	36	76	-
Mehta [20]	31	4 x 4	82	71 – 100	85	-
Zajac [21]	82	1-5 x 10	82	-	74	-
Chang [22]	76	3 x 7	79 – 95	-	87	-
Delclos [23]	81	1-2 x 15	85	75	80	-
Gollins [24]	406	1 x 10-20	-	-	65	-
Macha [25]	365	3-4 x 5	66	-	-	-
Skowronek [26]	101	3 x 7,5	69,9	-	-	5,9
	115	1 x 10				
Kelly [27]	175	2 x 15	66	-	78	6

Tolerance of repeated treatment using HDR-BT was good in most of the cases with superficial mucosal necrosis observed in 166 of patients and broncho – oseophageal fistula recorded in 6 patients. No patient died as a result of the therapy. There were two factors incriminated the complication rate, which were corelated with the development of more sever degree of radiation bronchitis: 1. tumour location in trachea or main stem bronchus, 2. the dose of radiation given previously, including total HDR-BT dose plus EBRT dose and fractionation schedule (Mann – Whitney test, p = 0,002).

Discussion

Endobronchial obstruction associated with lung cancer represents a common and potentially life threatening complication of newly diagnosed or recurrent disease. The vast majority of patients, presented with obstructive lesions are not curable so it is desirable to palliate this patients as quickly as possible [1, 8–10]. Endobronchial radiation therapy, especially in previously irradiated area with dose limitations set by radiation tolerance of normal tissue represents a therapeutic option with several advantages over conventional external beam radiotherapy and another therapeutic modalities [6, 11, 12].

This retrospective study supports the efficacy of HDR-BT in the palliation of malignant airway obstruction due to recurrence of endobronchial carcinoma. From the literature review, which is summarized in Table 7, HDR-BT demonstrate excellent palliation (Table 7).

There are three main methods which are available for treatment of endobronchial recurrence:

1. External beam radiotherapy (EBRT) usually palliates cough, hemoptysis, dyspnea in the previously unirradiated patient with intrathoracic parenchymal tumours. Concern about radiation overdose and toxicity has caused reluctance to retreat these patients with such modality, especially when endobronchial obstruction appeared [8, 11, 19, 28, 29]. Slawson and Scott reported that although 60 – 84 % of patients with dyspnea, hemoptysis benefited from EBRT, only 23 % of patients with endobronchial obstruction and distal atelectasis had positively responded [30]. In contrast, HDR-BT is highly effective in alleviating clinical symptoms caused by intraluminal tumour [9, 10, 27, 31, 32].
2. Intrabronchogenic laser therapy is another therapeutic approach. There is no potential of enhanced radiation toxicity in previously radiated patients, although increased bleeding and anatomic deformity may render the treatments more hazardous. Because only the intraluminal extent of the tumour can be treated, rapid recurrence can occur. Laser resection is the method of choice especially in emergencies, often giving fast symptomatic relief, but it provided only short-term palliation, due to limited tumor clearance [10, 17, 33–36].
3. Endobronchial brachytherapy (HDR-BT) is the third alternative. By placing a radioactive source near or in the tumour, a high dose of radiation is given to the tumour with the dose fall off in accordance of the inverse square law. The chance of damaging healthy tissues is reduced, since only a small amount of tissue receives therapeutic dose of radiation. HDR-BT delivers the dose rapidly and palliation is likely to be prompt. The advantages of this technique over EBRT are: 1. it can be performed on an out-patient basis, 2 it decreases radiation exposure of the staff, 3. it permits optimization of dose distribution, 4. the treatment time is short, measured in minutes, 5. it reduces healthy tissue damages, caused by rapid dose fall off, which is particularly important for previous irradiated area [1, 7, 23, 27, 33, 34, 37]. In recent years there has been a rapid increase of the use of HDR-BT [1–5, 10, 28, 33, 38, 39].

There are many factors, which are likely to effect the response of HDR-BT given as repeated time treatment caused by endobronchial recurrence. The prior given total dose, the dose rate, the time of recurrence, the adequacy of source placement, the performance status of a patient, the degree and duration of obstruction, the size of extrabronchial part of disease are among the most important factors, which are likely to effect outcome [1, 5, 7, 11, 28, 29]. Bedwinek et al. observed that the extent of extrabronchial disease is the most important predictor of response to brachytherapy [11]. Complete endobronchial clearance was achieved in 67 % of patients treated with HDR-BT whose extrabronchial tumour was less than 5 cm. In contrast, no patient with tumour greater than 5 cm had a complete response. Similarly, the probability of symptom resolution was higher for those with extrabronchial disease less than 5 cm. Schray et al. reported that a previous response to irradiation of more than one year was associated with a high response rate (83 %) to subsequent brachytherapy compared to only 31 % when a response to external beam radiotherapy was less than six months [19]. The performance status (PS) is powerful prognostic and predictor factor in previously irradiated patients [31]. Multivariate analysis demonstrated in our study, shows that PS maintained significant factor for treatment response. It predicts which patient with endobronchial recurrence will achieve positive HDR-BT response and symptom resolution.

To be more accurate in delivering optimal doses to the tumour locally and spare healthy structures, Speiser and Spratling suggested a multiple catheter approach to decrease dose inhomogenity [40]. This should be done especially where the tumour straddles a bifurcation area. Fritz et al. [41] proposed kind of centralized brachytherapy which uses a new applicator that can be positioned in the center of the tracheobronchial lumen. By using this new aplicator, it became possible to improve dose distribution and avoid extreme under and / or over dosage. This new device may decrease any possible bronchus wall perforation and bronchial – arterial fistula [8, 11, 14, 15].

In our study endobronchial brachytherapy provided satisfactory symptomatic relief, which was comparable to other HDR study results. The patient selection criteria differed slightly from other published series on HDR brachytherapy. All 270 patients had failed prior HDR brachytherapy and / or another treatment modalities and all patient were also treated in a uniform method – one single fraction with dose of 8 or 10 Gy at distance of 0,5 to 1 cm from the centre of the source. Our patients had 83 % chest x-ray reaeration rate, which was comparable to other HDR results [10, 32, 38]. Palliation was the main end-point of our study.

We observed that HDR-BT effectively palliates the symptoms of endobronchial recurrence of lung cancer in previously irradiated patients resulting in improved quality of life along with a low complication rate of a patient. It can be done on an outpatient basis, and palliation effect could be rapid. HDR brachytherapy provides an excellent modality to deliver adequate dose to the intraluminal tumour. We do not recommend HDR brachytherapy to be used in situation of the airway obstruction due to external compression by the tumour. The efficacy in this case is less and may lead to higher morbidity. Future randomized multi – center trials are needed to better define the dose size, fractionation, total dose and patient selection, but firstly in previously irradiated endobronchial recurrence group. A variety of doses, fractionation schemes, and prescription points have been used, which precludes meaningful comparison between studies.

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