



ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

High-dose-rate endobronchial brachytherapy in the management of advanced lung cancer – comparison according to the presence of lung atelectasis

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SUMMARY

Introduction/Objective Locally advanced lung cancer is often accompanied by atelectasis of either a part or the entire lung. The aim of this study was to establish the benefits of brachytherapy on the patients' quality of life, the length of the progression-free survival (PFS), and the overall survival (OS) as related to the presence or absence of atelectasis after the applied treatment.

Methods The total of 100 patients with locally advanced lung cancer or endobronchial metastasis of other malignancy were treated with the high-dose-rate endobronchial brachytherapy (HDR-EBB) in 2017. For observing the patients' clinical characteristics, the PFS and OS, the patients were classified into four groups according to the presence of atelectasis before and after HDR-EBB.

Results After HDR-EBB alone or combined with other treatment modalities, a statistically significant symptom alleviation was registered for all the symptoms except cough ($p < 0.05$). The significantly highest PFS value was registered among the patients with atelectasis prior but not after HDR-EBB. The longest survival was registered in the patients who had atelectasis prior to, but not after HDR-EBB, as well as among the patients without atelectasis either before or after EBB.

Conclusion HDR-EBB is an efficient method that improved the quality of life of most patients. There were improved rates of re-aeration after HDR-EBB treatment alone and as a part of combined treatment. Re-aeration after EBB is a positive prognostic factor with respect to PFS and OS of these patients.

Keywords: atelectasis; brachytherapy; lung cancer; progression-free survival; survival

INTRODUCTION

Worldwide, lung cancer (LC) still has the highest incidence and mortality compared to other malignancies, with 2.1 million new LC cases and 1.8 million deaths predicted in 2018 [1]. Five-year survival rate is still low, it has been registered in only 19% of the cases, despite advances achieved in the fields of surgery, irradiation, and chemo treatment, as well as introduction of entirely new treatment modalities such as molecular and immunotherapy [2]. Among patients with diagnosed non-small cell lung cancer (NSCLC), 25–30% have either stage I or stage II of the disease according to the tumor, nodal, metastasis (TNM) classification, 30% have a locally advanced disease (TNM stage III), and the remaining 40–45% have distant metastases (stage IV). In LC after external beam radiotherapy (EBRT), local relapses of the disease are registered in almost 60–70% of the patients, and in 60% of the patients a fatal outcome occurred due to respiratory failure, obstructive pneumonia, and sepsis. Endobronchial brachytherapy (EBB) is an efficient method for palliative treatment in advance NSCLC resulting in improvement of the QoL in most patients [3, 4].

The total endoluminal obstruction induces atelectasis of the lung – segmental, lobar, or complete, and the resulting pneumonia with prominent symptoms such as dyspnea, elevated body temperature, hemoptysis, cough, suffocation. The bronchial obstruction type determines the optimal therapeutic regimen, and the endoluminal obstruction may be resolved by brachytherapy, laser therapy, photodynamic therapy or cryotherapy, while the extraluminal obstruction may be eliminated by external radiotherapy or stent placement [5]. Interventional bronchoscopy therapeutic procedures may result in a rapid alleviation of the symptoms and are often well tolerated, with minimal toxicity [4].

In locally advanced LC, brachytherapy is most frequently applied as palliative treatment procedure accompanied by other interventional bronchoscopy procedures. For high-dose-rate endobronchial brachytherapy (HDR-EBB), hospitalization is mostly unnecessary and the therapy is administered with a variation of fractionating modalities and dosage, depending on whether is intended for a curative or a palliative effect [4, 6]. EBB can be combined with other treatment modalities, including EBRT, chemotherapy, biological, or immune therapy [7, 8].

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In this study, we report our experience with HDR-EBB to assess its efficacy and tolerability in the treatment of patients with atelectasis caused by endobronchial metastatic tumors and LC.

METHODS

Material

Having obtained the approval for the research of the Board of Ethics of the Institute for Pulmonary Diseases of Vojvodina, a retrospective review of 100 patients (≥ 18 years old) with endobronchial (lung or metastatic) tumor was conducted. The patients had bronchoscopy-established advanced stage (IIIB and IV) LC, or a bronchial metastatic cancer from an extrapulmonary primary tumor. The patients with a “positive endobronchial status” (the tumor was seen in the trachea or the main bronchi) were diagnosed in the period from January 2017 to January 2018, giving a retrospective character to the study and enabling monitoring of the three-year survival.

Guided by bronchoscope, an endobronchial polytetrafluoroethylene catheter is induced into the tumor area. The position of the tumor regarding the catheter and the segment volume which is necessary to irradiate is measured by orthogonal X-ray imaging, based on which a radiation field is planned with calculation of dose distribution. Application dose is given in two fractions of 7 Gy, in weekly treatments. The dose is prescribed at 1 cm from the source axis. After connecting the catheter to the HDR brachytherapy machine, irradiation is conducted remotely after the loading technique, and a radioactive source (isotope Ir192) is placed in the vicinity of the tumor through the catheter.

The OS assessment started from the moment of bronchial biopsy-established diagnosis, lasting to the end of the follow-up period or the date of death according to the Lung Cancer Registry of the Institute. The patients' identity was protected in strict accordance with the Declaration of Helsinki, seventh revision.

Statistical analysis

A total of 100 patients treated with brachytherapy were classified into two groups according to the presence or absence of lung atelectasis. The description within the groups was performed using absolute values and percentiles. The statistical analysis of the clinical features and treatment outcomes was performed by the Pearson χ^2 and the Fisher's exact test. The log-rank test was used to compare the overall survival (OS) and progression-free survival (PFS) outcomes between the groups. The OS and the PFS were compared using the median, with the monitoring period ≤ 36 months, and they were graphically presented using the Kaplan-Meier analysis and the MedCalc statistical software package (MedCalc Software Ltd, Ostend, Belgium), accepting $p < 0.05$ for the statistical significance level.

RESULTS

Patient and tumor characteristics

The total of 100 patients were treated with HDR-EBB at the Oncology Institute of Vojvodina, with a bronchologist of the Institute for Pulmonary Diseases of Vojvodina placing endobronchial catheters. Ninety-eight patients had a primary or recurrent disease of LC, and only two patients had endobronchial metastasis. The patients were classified into two groups: Group A – the patients who had atelectasis at the time of establishing the diagnosis, and Group B – the patients who did not have atelectasis at the time of establishing the diagnosis. The patient and tumor characteristics are summarized in Table 1. Group A included 47 patients, and Group B had 53 subjects. The mean age of the examined patients was 64 years. The youngest and the oldest patient were 44 and 84 years of age, respectively. There were 86 males and 14 females. In endoscopically visible bronchial cancer or bronchial infiltration, no statistically significant sex-related differences regarding the presence of atelectasis at the moment of diagnosing LC were registered. Neither were statistically significant European Cooperative Oncology Group performance status differences registered between the examined groups ($p = 0.196$). Regarding the histological tumor type, squamous lung cancer was most common, followed by adenocarcinoma, small cell and large cell lung cancer, while two patients had an endobronchial metastasis of the colon cancer. There existed a statistically

Table 1. Patient and tumor characteristics before high-dose-rate endobronchial brachytherapy related to the presence of atelectasis

Median age/ range (years)	64 (44–84)	with AT (A)	without AT (B)	p
Sex	Male	42 (89.36%)	44 (83.02%)	0.362 ^a
	Female	5 (10.64%)	9 (16.98%)	
ECOG performance status	0	/	/	0.196 ^a
	1	34	35	
	2	11	19	
	3	1	/	
Histology	Squamous ca.	33 (70.21%)	37 (69.81%)	0.205 ^a
	Adenocarcinoma	7 (14.89%)	10 (18.87%)	
	Large cell ca.	1 (2.13%)	3 (5.66%)	
	SCLC	4 (8.51%)	1 (1.89%)	
	Metastatic	/	2 (3.77%)	
	Others	2 (4.26%)	/	
Site (endobronchial-positive finding)	Trachea	/	16 (30.19%)	0.001 ^a
	Main br. R	15 (31.91%)	11 (20.75%)	
	Main br. L	22 (46.81%)	6 (11.32%)	
	Middle br.	2 (4.26%)	1 (1.89%)	
	Upper br. R	2 (4.26%)	3 (5.66%)	
	Upper br. L	2 (4.26%)	2 (3.77%)	
	Lower br. R	2 (4.26%)	2 (3.77%)	
	Lower br. L	/	4 (7.55%)	
	Br. intermedius	2 (4.26%)	2 (3.77%)	
	Both sides	/	6 (11.32%)	
Total		47 (100%)	53 (100%)	

AT – atelectasis; R – right; L – left; ECOG – European Cooperative Oncology Group; SCLC – small cell lung cancer;

^aPearson's χ^2

significant difference ($p = 0.001$) regarding the localization of the bronchial tumor or bronchial involvement by the tumor: the positive endoscopy finding was most frequently obtained from the left main bronchus, then from the right main bronchus, and finally other endoscopy tumor localizations.

Treatment characteristics

HDR-EBB gave as a palliative and symptom-relieving method in all the patients. Of 100 examined subjects, 47 had atelectasis of a part or the entire lung at the moment of establishing the diagnosis, while 53 patients had no atelectasis. After the palliative EBB had been applied, either alone or in combination with other therapy modes, atelectasis was registered in 11 patients, while 89 patients were without atelectasis (Table 2). For this clinical treatment response, the difference was statistically significant ($p = 0.022$). EBB was administered alone in 26 patients, combined with EBRT in six patients, combined with chemotherapy in 23 patients, and combined EBRT with chemotherapy in 45 patients. There was no statistically significant difference between these therapeutic options in the "loss" of atelectasis following the treatment ($p = 0.186$). These results are reviewed in Table 3.

Palliation rate and clinical response

All the patients were evaluated for subjective symptom response summarized in Table 4. Analyzing the most common symptoms present at the moment of establishing the diagnosis on endoscopy and then after EBB alone or combined with other treatment modalities, a statistically significant symptom alleviation was registered for all the symptoms except cough.

Local control, time to progression, and overall survival

To assess the PFS and OS, all the patients were subdivided into four groups: Group I – patients with atelectasis prior to EBB, persisting after the treatment as well; Group II – patients with atelectasis prior to, but not after EBB; Group III – patients having no atelectasis prior to EBB, but developed it after the treatment, and Group IV – patients free of atelectasis before as well as after EBB. In all of the examined patients, the two-year PFS was 9%. One of the patients belonged to Group I [making 11.11% of the group (1/9)], four patients belonged to Group II [making 10.53% of the group (4/38)], none of the patients belonged to Group III, and four patients belonged to Group IV [making 7.84% of the group (4/51)]. The PFS median was 0, 10, 0, and 2 months in Groups I, II, III, and IV, respectively. The log-rank was 0.028, suggesting a different PFS in the examined groups; the significantly highest PFS value was registered among the patients with atelectasis prior but not after EBB (Group II), as well as in the patients free of atelectasis either before or after EBB – Group IV (Table 5, Figure 1). To evaluate the OS, the patients were classified into the same

Table 2. Local control of the disease before and after high dose rate endobronchial brachytherapy related to the presence of atelectasis

		Atelectasis before TH		p
		Yes	No	
Atelectasis after TH	Yes	9 (19.15%)	2 (3.77%)	0.022 ^b
	No	38 (80.85%)	51 (96.23%)	

TH – therapy;

^bFisher's exact test

Table 3. The presence/absence of atelectasis related to the treatment characteristics

Treatment	AT	Before EBB	After EBB	p
EBB alone	Yes	6	4	0.186 ^a
	No	20	22	
EBB + EBRT	Yes	3	1	
	No	3	5	
EBB + CHT	Yes	12	1	
	No	11	22	
EBB + EBRT + CHT	Yes	26	5	
	No	19	40	

EBB – endobronchial brachytherapy; EBRT – external beam radiotherapy; CHT – chemotherapy

^aPearson's χ^2

Table 4. Symptom response

Symptom	Present	Before EBB	After EBB	p
Temperature* after TH	Yes	7	6	0.003 ^a
	No	15	72	
Cough after TH	Yes	49	4	0.731 ^b
	No	42	5	
Dyspnea after TH	Yes	49	1	0.001 ^b
	No	37	13	
Hemoptysis after TH	Yes	5	6	0.025 ^a
	No	15	74	

TH – therapy; EBB – endobronchial brachytherapy;

^aPearson's χ^2 ;

^bFisher's exact test;

*temperature > 38°C

Table 5. Progression free survival (PFS) and overall survival (OS) in lung cancer patients with and without atelectasis

Group	PFS (median) months	OS (median) months
Group I	0	4
Group II	10	12
Group III	0	0
Group IV	2	8
No accordance to AT	5	10
Log-rank	$p = 0.0284$	$p = 0.0028$

AT – atelectasis; Group I – patients with atelectasis prior to endobronchial brachytherapy; persisting after treatment as well; Group II – patients with atelectasis prior to but not after endobronchial brachytherapy; Group III – patients having no atelectasis prior to endobronchial brachytherapy but developed it after treatment; Group IV – patients free of atelectasis before as well as after endobronchial brachytherapy

groups as for the PFS data. Of 100 patients, a 12-month OS was achieved by 44%, while a 24-month OS was achieved by 13% of the patients, one belonging to Group I, six to Group II, none to Group III, and six patients to Group IV. The total OS median was 10 months, the longest OS (12 months) was in Group II, and the shortest one (0) was in Group III. The log-rank was $p = 0.002$, suggesting there were statistically significant differences in the OS among the examined groups – the longest survival was registered

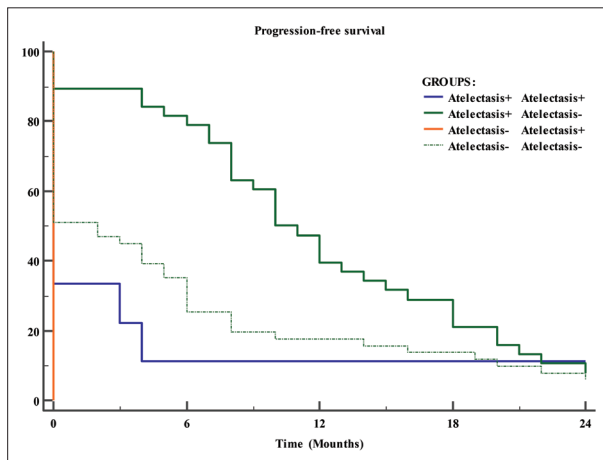


Figure 1. Progression-free survival in patients treated with high-dose-rate endobronchial brachytherapy according to the presence of lung atelectasis

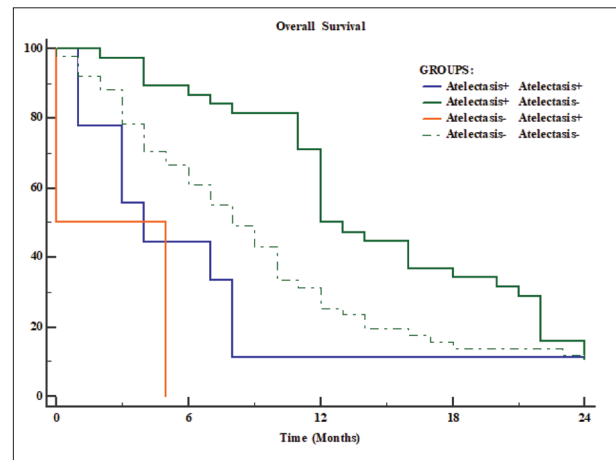


Figure 2. Overall survival in patients treated with high-dose-rate endobronchial brachytherapy according to the presence of lung atelectasis

in patients who had atelectasis prior to but not after EBB (Group I), as well as among patients free of atelectasis either before or after EBB (Group IV) (Table 5, Figure 2).

During the procedure, one patient had life-threatening hemoptysis but survived and was alive six months after therapy.

DISCUSSION

As 30% of LC patients have a locally advanced disease (stage III), and 40–45% have distant metastases (stage IV), palliative treatment procedures are probably a sole option for these patients. EBRT can also be a palliative treatment procedure affecting the tumor size, but its effect is rather slow and limited by the total radiation dose, and the maximal atelectasis regression achieved is 20% provided that other local interventional bronchoscopy procedures are not necessary [9]. Depending on the endobronchial tumor and the tumor compression type, brachytherapy may in some cases be the treatment of choice, either as a single therapy or combined with other interventional bronchoscopic procedures. Brachytherapy stops the obstruction process and removes atelectasis, improving patients' QoL [9]. Brachytherapy is not effective for acute and severe central airway obstruction (CAO) because it takes minimally three weeks for its effect [10]. Our study was aimed at establishing the presence of atelectasis of either the entire lung or its part, which was due to an intraluminal obstruction by the tumor or tumor-infiltrated bronchial mucosa, as well as the effects of EBB on the obstruction and atelectasis removal.

Several studies have reviewed different HDR-EBB regimens correlated to NSCLC stage, EBB fractionation modality mode, the number of installed catheters and delivered doses, as well as a clinical response. Bedwinek et al. reported on 60 patients who received HDR-EBB in three 6 Gy fractions (3×6 Gy), which resulted in a clinical improvement (76%), chest X-ray improvement (64%), bronchoscopy improvement (84%), with the median OS

of 10 months [3]. Speiser and Spratling reported on 66 patients who received HDR-EBB in the dose of 3×10 Gy, registering a clinical and bronchoscopy improvement in 88% and 99%, respectively [4].

All the patients included in our study received HDR-EBB in two fractions of 7 Gy, the treatment was given weekly, in total of 14 Gy locally. In the patients who had the trachea bifurcation infiltrated, we installed two catheters bilaterally in both fractions.

Our examined sample of 100 patients included 86 males and 14 females at the mean age of 64 years. These clinical characteristics correlate to the reported studies of locally advanced NSCLC. Squamous lung cancer is the most common histological type of centrally located and endoscopy visible tumors. Proximal or CAO complicates 20–30% of LC cases and 40% of them originate from squamous NSCLC [11]. In our study, squamous lung carcinoma was diagnosed in 33 (70.21%) patients having atelectasis prior to treatment, and in 37 (69.81%) patients without atelectasis, exceeding the number reported by other authors, which is probably due to the high incidence of squamous LC in our region, as well as a high incidence of smokers among LC patients. After EBB had been applied as a palliative therapeutic procedure, either alone or combined with other treatment modalities, 11 patients had atelectasis and 89 did not. This clinical response was statistically significant ($p = 0.022$). Erickson et al. [12] reported a partial remission (atelectasis elimination) was achieved in 101 of their 188 examined patients, a minor response was registered in 25/188, no response in 29/188, while 33/188 patients developed progression in terms of atelectasis emerging in cases where it was formerly absent. Evaluating the applied treatment modalities, the best treatment response in terms of atelectasis elimination was achieved by EBB combined with a double-agent chemotherapy regimen and then by the EBB and EBRT combined. Mantz et al. [13] reported the best treatment response in terms of the local control of the endobronchial disease applying the treatment regimen with EBB followed by EBRT combined (EBB total dose 18 Gy in three fractions of 6 Gy in 4–7-day intervals

– the patients already treated with EBRT had a dose reduction to 50 Gy). However, the latest studies report that the published evidence did not provide conclusive evidence to recommend combined endobronchial and external-beam radiotherapy, EBB over external-beam, chemotherapy and neodymium-doped yttrium aluminum garnet laser treatment [6].

EBB later caused the effect on airway recanalization and also provides delayed spirometry improvement (forced expiratory volume in one second, forced vital capacity), pulmonary ventilation and perfusion and exercise tolerance of the five-minute walking distance [14]. A control of the symptoms, i.e., their elimination or improvement, is characteristic for all interventional airway recanalization treatment procedures, including EBB as well. In our study, analyzing the most common symptoms present at the moment of establishing the diagnosis and then after EBB alone or combined with other treatment modalities, a statistically significant symptom alleviation was registered for all the symptoms except cough. The presence of cough as the disease symptom may be explained by a definite damage of the tissue zones in the main airways, impossible to be entirely revitalized by palliative EBB. Several authors reported that a temporary dyspnea elimination may even result in a prolonged suffering from the patients' point of view [15]. It is therefore necessary to establish whether the patients' QoL will be clearly improved, as well as the survival benefit after interventional therapy in patients with inoperable malignant CAO. Most studies investigated dyspnea and performance status scores partially, but not the overall QoL [16, 17]. Neither did we investigate the QoL in our study, but we did investigate the performance status, obtaining a statistically significant improvement of our patients' performance status after the treatment.

Our study focused on the patients' survival related to the presence and "loss" of atelectasis after EBB. Statistically significant differences in the OS have been registered among the examined groups, that is – the longest survival was registered in the patients who had atelectasis prior to but not after EBB, as well as among the patients free of atelectasis either before or after EBB. In other studies which

compared the OS according to the presence of atelectasis (with no interventional bronchoscopy procedures applied), the presence of atelectasis emerged as a positive prognostic factor, unlike the results of our study [18, 19].

Comparing our results to those obtained by other authors describing the application of palliative endoscopy procedures such as laser therapy, electrocautery, diathermy, electrocoagulation, phototherapy, cryotherapy, endobronchial stent insertion, and combinations of these techniques, similar results have been obtained regarding the OS of the patients with a CAO [20–23]. Future comparisons with stereotactic body radiotherapy and other ablative techniques are warranted to expand multi-disciplinary management options [24].

Although brachytherapy requires multidisciplinary coordination in a protected operating room or brachytherapy suite, patient sedation, bronchoscopy, and planning that increases the risk of exposure to patients and providers, radiotherapy remains one of the key treatment options for lung cancer in the era of the COVID-19 pandemic [23, 25].

CONCLUSION

Brachytherapy as a palliative interventional airway recanalization endoscopic treatment is a safe therapeutic tool that independently or in association with other therapeutic modalities leads to the improvement of patients' QoL suffering from locally advanced LC. Significant differences in the PFS and the OS have been registered among the examined groups, with the longest survival being registered in patients who had atelectasis prior to but not after EBB.

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Високодозна брахитерапија код узнапредовалог карцинома плућа – анализа присуства плућне ателектазе

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САЖЕТАК

Увод/Циљ Локално узнапредовали карцином плућа се често презентује ателектазом једног дела или целог плућног ткива.

Циљ ове студије је да се утврде утицај високодозне ендобронхијалне брахитерапије (*HDR-EBB*) на квалитет живота болесника, време до прогресије болести, као и укупно преживљавање у односу на присуство/одсуство ателектазе након терапијског третмана.

Метод Студија је обухватила 100 болесника са узнапредовалим карциномом плућа или метастазама лечених *HDR-EBB* током 2017. године. Како би се посматрале клиничке карактеристике, време до прогресије болести и укупно преживљавање, болесници су сврстани у четири групе у односу на присуство ателектазе пре и после *HDR-EBB*.

Резултати После самосталне *HDR-EBB* или у комбинацији са другим начинима лечења, утврђено је статистич-

ки значајано повлачење већине симптома, осим кашља ($p < 0,05$). Статистички значајно је продужено време до прогресије болести код болесника код којих је дошло до повлачења ателектазе након третмана ($p = 0,0284$). Најдуже укупно преживљавање је забележено код болесника код којих се после третмана повукла ателектаза ($p = 0,0028$), или који нису имали ателектазу ни пре ни после третмана.

Закључак *HDR-EBB* је ефикасан третман у побољшању квалитета живота болесника. Након самосталне брахитерапије или комбиноване са другим терапијским модалитетима уочено је значајно повећање степена аерације плућа. Повлачење ателектазе након брахитерапије је добар прогностички фактор, који доводи до продуженог времена до прогресије болести и укупног преживљавања.

Кључне речи: ателектаза; брахитерапија; карцином плућа; време без прогресије; преживљавање