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

Високодозна брахитерапија код узрапредовалог карцинома плућа –
анализа присуства плућне ателектазе

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

Високодозна брахитерапија код узнапредовалог карцинома плућа – анализа присуства плућне ателектазе

SUMMARY

Introduction/Objective Locally advanced lung cancer (LC) is often accompanied with 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 (QoL), 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 LC 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 of atelectasis either before or after EBB.

Conclusion HDR-EBB is an efficient method that improved the QoL 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

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 (PFS), као и укупно преживљавање (OS) у односу на присуство/одсуство ателектазе након терапијског третмана.

Метод Студија је обухватила 100 пацијената са узнапредовалим карциномом плућа или метастазама лечених HDR-EBB током 2017. године. Како би се посматрале клиничке карактеристике, PFS и OS пацијенти су сврстани у четири групе у односу на присуство ателектазе пре и након HDR-EBB.

Резултати Након самосталне HDR-EBB или у комбинацији са другим модалитетима лечења, утврђен је статистички значајано повлачење већине симптома, осим кашља ($p < 0.05$). Статистички значајно је продужен PFS, код пацијената код којих је дошло до повлачења ателектазе након третмана ($p = 0.0284$). Најдужи OS је забележен код пацијената код којих се након третмана повукла ателектаза ($p = 0.0028$), или који нису имали ателектазу ни пре ни након третмана.

Закључак HDR-EBB је ефикасан третман у побољшању квалитета живота пацијената. 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

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 [2], 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. 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 TNM (tumor, nodal, metastasis) 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 them, and in 60% of the patients a fatal outcome occurred due to respiratory failure, obstructive pneumonia, and sepsis. EBB is an efficient method for palliative treatment in advance NSCLC resulting in improvement of 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) the hospitalization is not necessary mostly and is administered with a variation of fractionating modalities and dosage, depending it is intended for a curative or palliative effect [4, 6]. EBB can be combined with other treatment modalities, including EBRT, chemotherapy, biological or immune therapy [7, 8].

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 Ethical Board 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 extra pulmonary primary tumor. The patients with a “positive endobronchial status” (the tumor was seen in trachea or 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 3-year survival.

Guided by bronchoscope, endobronchial a Teflon catheter is induced in tumor area. Position of tumor regarding the catheter and segment volume which is necessary to irradiate, is measured on orthogonal X rays, based on which a radiation field is planned with calculation of dose distribution. Application dose is given in 2 fractions of 7Gy, in weekly treatments. Dose is prescribed at 1 cm from the source axis. After connection of catheter to HDR brachytherapy machine, radiation is conducted by remote after loading technique, and radioactive source (isotop Ir192) through catheter is placed in vicinity of the tumor.

The OS assessment started from the moment of bronchial biopsy established diagnosis, 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, 7th revision.

Statistical analysis

The total of 100 patients treated by brachytherapy were classified into two groups according to the presence or absence of lung atelectasis. The description within the group was performed using absolute values and percentiles. The statistical analysis of the clinical features and treatment outcomes was performed by the Pearson Chi Square and Fisher's Exact Test.

The log-rank test was used to compare OS and PFS outcomes between the groups. The OS and 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 computer program, accepting $p < 0.05$ for the statistical significance level.

RESULTS

Patient and tumor characteristics

The total of 100 patients were treated with HDR-EBB in the Oncology Institute of Vojvodina, after placement of an endobronchial catheter by a bronchologist of the Institute for Pulmonary Diseases of Vojvodina. Ninety-eight patients had a primary or recurrent disease of LC, and only 2 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 patients' 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 yrs. The youngest and the oldest patient were at 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 (ECOG) performance status differences registered between the examined (A & B) 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 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 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 endobronchial brachytherapy (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 6 patients, combined with chemotherapy - CHT 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 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 (100) 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 (the patients having no atelectasis prior to EBB, but developed it after the treatment), and Group IV (the patients free of atelectasis before as well as after EBB). Of all the examined patients, 2-year PFS was 9%. One of them 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 and II, III, and IV respectively. The Logrank was 0.028, suggesting 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 OS, the patients were classified into the same groups as for 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, 1 belonging to Group I, 6 to Group II, none to Group III, and 6 patients to Group IV. The total OS median was 10 months, the longest (12 months) was in Group II and the shortest (0) was in Group III. The logrank was $p = 0.002$ suggesting there was statistically significant differences in OS among the examined groups, that is the longest survival was registered in the patients who had atelectasis prior to, but not after EBB (Group I), as well as among the patients free of atelectasis either before or after EBB (Group IV) (Table 5, Figure 2).

During the procedure one patient had life-threatening hemoptysis and but survived and was alive 6 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. External beam radiotherapy 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 because it takes minimally 3 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. have reported their study of 60 patients who received HDR-EBB in three 6Gy fractions (3x6Gy), which resulted in a clinical improvement (76%), chest X-ray improvement (64%), bronchoscopy improvement (84%), with the median OS of 10 months. Speiser and Spratling have reported their study of 66 patients who received HDR-EBB in the dose of 3x10 Gy, registering a clinical and bronchoscopy improvement in 88% and 99% respectively [3, 4].

All the patients included in our study received HDR-EBB in two fractions of 7Gy, treatment was given weekly, in total of 14Gy 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 central airway obstruction (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 lung cancer in our region, as well as a high incidence of smokers among lung cancer 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 and al. 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 [12]. 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 18Gy in 3 fr. of 6Gy in 4-7 day intervals – the patients already treated with EBRT had dose reduction to 50Gy). However, the latest studies report that the published evidence did not provide conclusive evidence to recommend combined endobronchial and external-beam radiotherapy, endobronchial brachytherapy over external-beam, chemotherapy and Nd-YAG laser treatment [6].

EBB later caused the effect on airway recanalization and also provides delayed spirometry improvement (forced expiratory volume in 1s, forced vital capacity), pulmonary ventilation and perfusion and exercise tolerance of 5 min 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. 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 report 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 (PS) scores partially, but not the overall QoL [16, 17]. Neither did we investigate the QoL in our study, but did investigate the PS, obtaining a statistically significant improvement of our patients' PS after the treatment.

Our study focused on the patients' survival related to the presence and "loss" of atelectasis after EBB. Statistically significant differences in 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 it was the case in 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 central airway obstruction (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 risk of exposure to patients and providers [23]. Radiotherapy remains one of the key treatment options for lung cancer in the era of the COVID-19 pandemic [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 PFS and OS have been registered among the examined groups, the longest survival was registered in the patients who had atelectasis prior to, but not after EBB.

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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

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

	Atelectasis before TH			
	Yes	No	p	
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

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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

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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
Logrank	p = 0.0284	p = 0.0028

Group I – patients with atelectasis prior to endobronchial brachytherapy (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;

Group IV – patients free of atelectasis before as well as after EBB

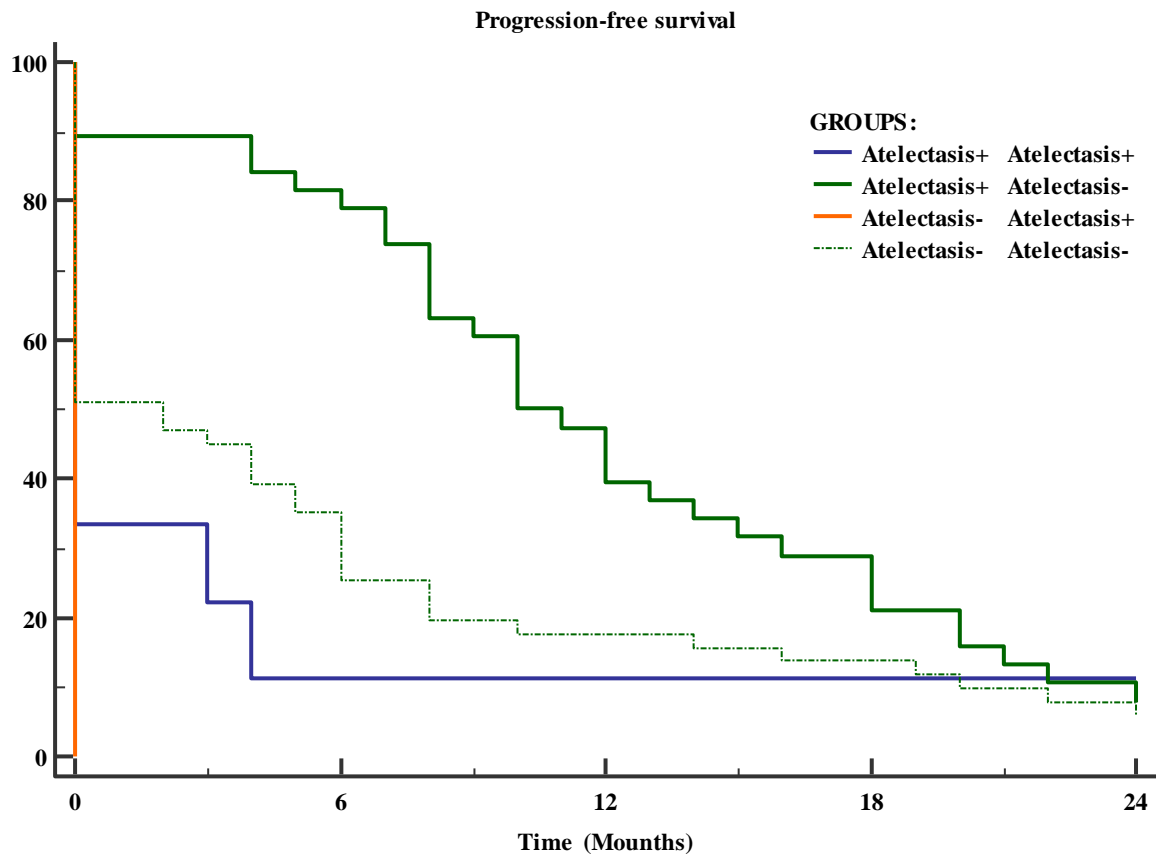


Figure 1. Progression free survival in patients treated with high dose rate endobronchial brachytherapy according to the presence of lung atelectasis

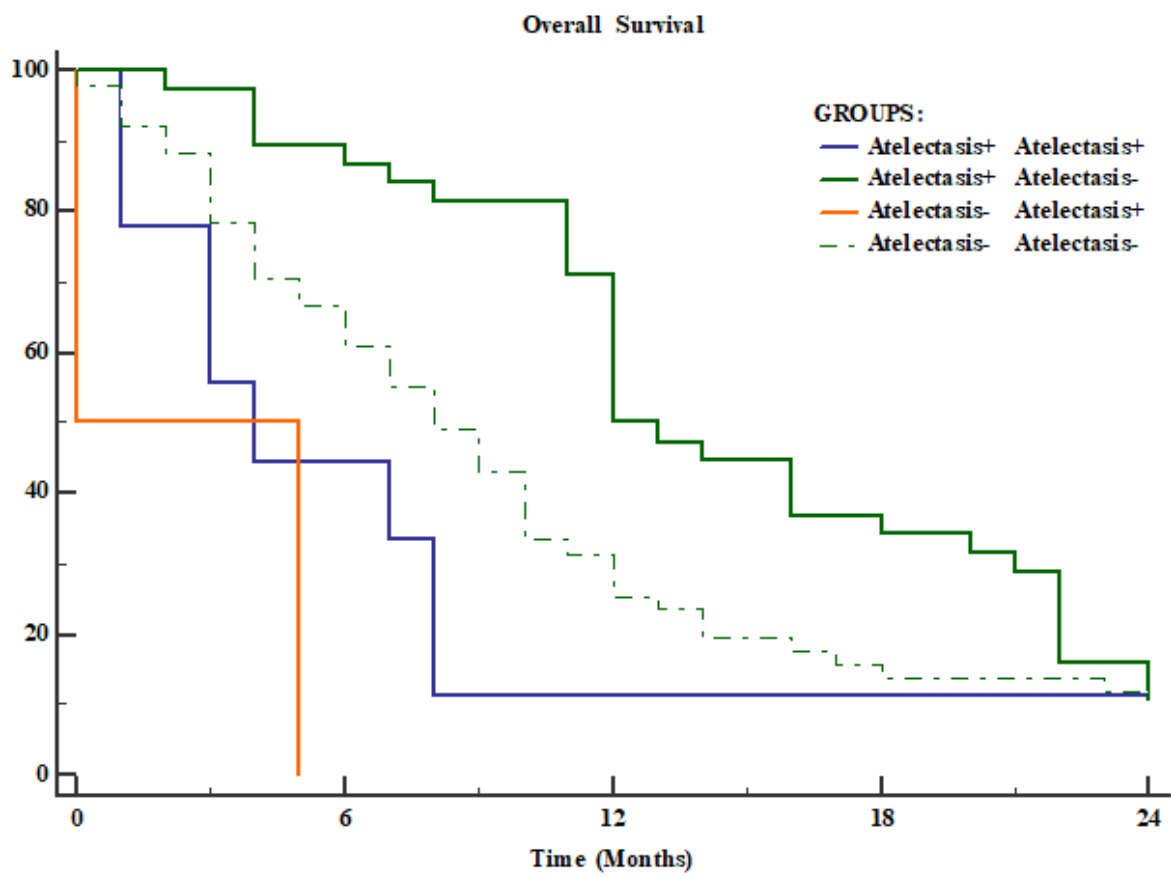


Figure 2. Overall survival in patients treated with high dose rate endobronchial brachytherapy according to the presence of lung atelectasis