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Primary radiotherapy with endobronchial high-dose-rate brachytherapy boost for inoperable lung cancer: long-term results

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ABSTRACT

Background. To retrospectively evaluate the outcome of patients with inoperable non-small-cell lung cancer treated with primary external beam radiotherapy combined with high-dose-rate endobronchial brachytherapy boost.

Patients and methods. Between 1988 and 2005, 35 patients with non-small-cell lung cancer (stage I-III) ineligible for surgical resection and/or chemotherapy, were primarily treated with external beam radiotherapy with a median total dose of 50 Gy (range, 46-60). A median of 3 fractions high-dose-rate endobronchial brachytherapy was applied as a boost after external beam radiotherapy, the median total dose was 15 Gy (range, 8-20). High-dose-rate endobronchial brachytherapy was carried out with iridium-192 sources (370 GBq) and prescribed to 1 cm distance from the source axis.

Results. With a median follow-up of 26 months from the first fraction of high-dose-rate endobronchial brachytherapy, the 1-, 2- and 5-year overall (local progression-free) survival rates were 76% (76%), 61% (57%) and 28% (42%), respectively. Complete or partial remission rates 6 to 8 weeks after treatment were 57% and 17%, respectively. Significant prognostic favorable factors were a complete remission 6-8 weeks after treatment and a negative nodal status. In patients without mediastinal node involvement, a long-term local control could be achieved with 56% 5-year local progression-free survival. Common Toxicity Criteria grade 3 toxicities were hemoptysis (n = 2) and necrosis (n = 1). One fatal hemoptysis occurred in combination with a local tumor recurrence.

Conclusions. The combination of external beam radiotherapy with high-dose-rate endobronchial brachytherapy boost is an effective primary treatment with acceptable toxicity in patients with non-small-cell lung cancer ineligible for surgical resection and/or chemotherapy.

Key words: external beam radiotherapy, high-dose rate endobronchial brachytherapy, irradiation, non-small-cell lung cancer.

Competing interests: The authors declare they have no competing interests.

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diotherapy (EBRT). However, a potential benefit was noted regarding local control[7].

The aim of this retrospective single-center analysis was to evaluate the long-term effect and toxicity of combined EBRT and high-dose-rate endobronchial brachytherapy (HDREB) in patients with medically inoperable NSCLC treated with a curative intent.

Methods

Patient characteristics

Between 1985 and 2005, 35 patients with a mean age of 64 years (range, 45-75), all of them ineligible for surgical resection and/or chemotherapy, were treated for histologically proven NSCLC UICC stages I to III. There were no cases with distant metastases. Patient characteristics are listed in Table 1. Patients with tumors confined to the bronchial or tracheal wall, with a maximum periluminal tumor extension of 3 cm were selected. An airway recanalization using bronchoscopic mechanical removal or laser vaporization had been performed in 21 of the 35 patients before initiating the radiotherapy.

EBRT

Radiotherapy was started by EBRT. The aim of the procedure was to reduce the tumor size before applying brachytherapy as a boost. EBRT was performed by simulator-based or 3D-computerized multifield treatment planning techniques using megavoltage equipment (6 to 23 MeV). Five fractions of 2 Gy were applied weekly to a median total dose of 50 Gy (range, 40-60). The target volume included the primary tumor and the mediastinal lymph nodes. In patients with tumors located in the upper lobe or centrally located, the supraclavicular lymph nodes were included in the planning target volume. CT scans were performed before and after EBRT. A reduction of the median tumor diameter from 2.0 to 1.0 cm (range, 0.9-1.1) after EBRT was observed.

Endoluminal brachytherapy

After local anaesthesia and sedation, the applicator tube containing a dummy probe was positioned under bronchoscopic and radiological control. The target volume was defined by the prior bronchoscopic and radiological findings. A high-dose-rate afterloading machine (microSelectron, Nucletron, Veenedaal, The Nederlands) with an iridium-192 stepping source and a nominal activity of 370 GBq was used. Depending on the source activity, this resulted in a dose rate of 0.5 to 1.3 Gy/min in the reference point. According to Speiser *et al.*[6], the reference point was defined as 10 mm distant from the source axis. A standard single dose of 5 Gy was applied once or twice weekly[6]. The irradiated length encompassed the pathological endoscopic and CT-scan findings with a safety margin of 0.5 to 1 cm. The treatment length ranged from 2 to 12 cm (median, 7). The median endoluminal dose applied was 15 Gy (range, 8-20).

Table 1 - Patient characteristics

Variable/category	Distribution (n = 35)
Age, median (range), yr	64 (45-75)
Gender	
Male	29
Female	6
Karnofsky score	
90	6
80	17
70	10
60	2
Histology	
Squamous cell	31
Adenocarcinoma	2
Others	2
Tumor localization	
Trachea or bifurcation	11
Main stem bronchus	4
Upper lobe bronchus	11
Lower lobe bronchus	9
TNM stage	
T1	7
N0	7
T2	6
N0	1
N1	2
N2	2
N3	1
T3	14
N0	1
N1	1
N2	7
N3	2
Nx	3
T4	8
N0	3
N3	2
Nx	3
UICC stage (1997)	
I	8
II	3
IIIA	10
IIIB	8
IV	0
Unknown	6

Follow-up

Response to treatment was evaluated after 6 to 8 weeks by bronchoscopy, clinical examination and in 30 of 35 cases by computer tomography. It was classified as complete response requiring no detectable disease; partial remission, tumor mass reduction of at least 50%; no change, less than 50% tumor mass reduction); or as progressive disease. Toxicity was assessed using the Common Toxicity Criteria (CTC 2.0). Clinical data were obtained from medical records and contact (letter and/or telephone) with the referring

physician, general practitioner or the registration office.

Statistics

Statistical analyses were performed using the logrank test and Kaplan-Meier estimation for overall survival (OS), progression-free survival (PFS) and local progression-free survival (LPFS), using the SPSS package (version 10.0.0, SPSS Inc., Chicago, IL, USA). End points were death from any cause (OS), disease recurrence at any site (PFS), and in-field local-regional relapse (LPFS). Patients lost from the sample before the final outcome was observed or patients alive or recurrence free at last control were censored (right censoring). All time estimates began with first application of HDREB. For OS, PFS and LPFS, separate univariate Cox models were fitted individually for each covariate, producing risk ratios, 95% confidence intervals (95% CI) and significance levels (*P*). Covariates included age, gender, Karnofsky performance score, T stage, nodal status, UICC stage, response to treatment after 6 to 8 weeks, tumor localization, median dose for EBRT, median dose for HDREB, median total dose, and treatment length (HDREB). Significance was defined as $P < 0.05$.

Results

Survival

The median observation time from the onset of HDREB to death or to the end of the observation period was 26.4 months (range, 4-117). At the last follow-up, 5 patients (14%) were still alive and 30 patients (86%) had died. The median follow-up for the right censored patients (alive at last follow-up) was 22.8 months (range, 4.9-30.6).

The most common cause of death was local progression with poststenotic complications in 9 patients and metastases of the disease in 6 cases. Intercurrent death occurred in 2 patients. One patient died due to a fatal hemoptysis associated with a local recurrence of the tumor 6 months after radiotherapy. The precise cause of death in the remaining patients was not documented.

The 1-, 2- and 5-year OS rates were 76%, 61% and 28%, respectively with a median OS of 39.1 months (95% CI, 18.6-59.6). The 1-, 2- and 5-year PFS rates were 66%, 43% and 32%, respectively with a median PFS of 17.4 months (95% CI, 11.5-23.6). The 1-, 2- and 5-year LPFS rates were 76%, 57% and 42%, respectively, with a median LPFS of 42 months (95% CI, 2.2-83.7). Survival curves plotted according to the Kaplan-Meier method are shown in Figure 1.

In patients without mediastinal node involvement (N0), the 5-year OS rates were 55% *vs* 11% in patients with mediastinal node metastasis (N+) (logrank test, $P = 0.008$). In N0 cases, a long-term local control could be reached with a 5-year LPFS of 56% *vs* 26% in N+ cases

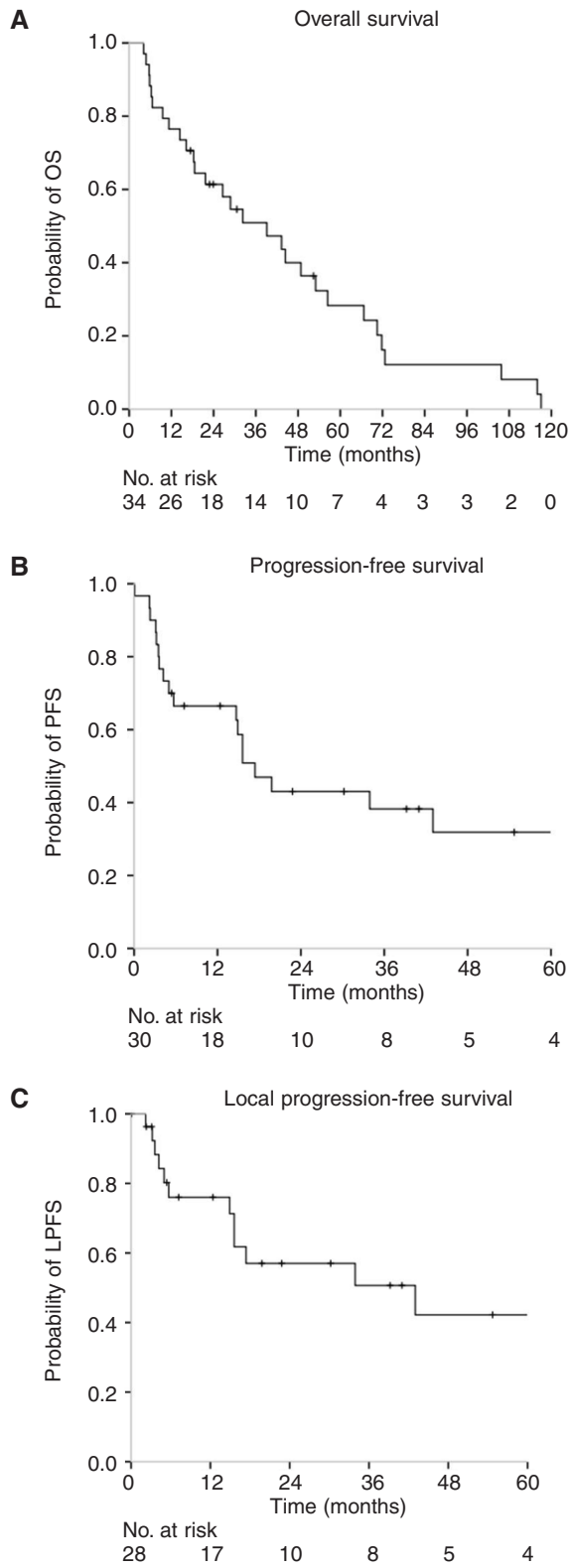

Figure 1 - Kaplan-Meier survival estimates. Thirty-five patients with inoperable non-small-cell lung cancer were treated with primary external beam radiotherapy combined with endobronchial high-dose-rate brachytherapy boost. A) Overall survival. B) Progression-free survival. C) Local progression-free survival. The number of patients at risk remaining each year is reported on the abscissa.

(logrank test, $P = 0.024$), as shown in Figure 2. The local results of HDREB about 6 to 8 weeks after treatment in terms of remission are shown in Table 2.

Using the Cox proportional hazards model, a univariate analysis assessed the effect of prespecified prognostic factors on OS, PFS and LPFS (results are indicated in Table 3).

Patients with a complete remission 6 to 8 weeks after treatment showed a significantly improved OS, PFS and LPFS ($P = 0.014$, $P = 0.015$ and $P = 0.021$, respectively). Patients with a distal location of the tumor (in the upper or lower lobe bronchus) had a significantly better LPFS than patients with a tumor centrally located in the trachea or in the bifurcation ($P = 0.035$). A median dose of EBRT ≥50 Gy was a significant factor for better PFS ($P = 0.045$). Age <64 years showed a trend for better PFS ($P = 0.031$). Gender, Karnofsky score, T stage, UICC stage, median dose for HDREB, median total dose or treatment length (HDREB) did not show significant benefit. A negative nodal status was a predictive factor for complete remission ($P = 0.038$, two-sided Fisher's exact test).

Toxicity

Adverse events are shown in Table 4. One case of CTC grade 1 pneumonitis related to the external irradiation was documented. There were no acute side effects caused by bronchoscopy or by applicator positioning. The patient who died due to a massive hemoptysis associated with a local recurrence of the tumor 6 months after radiotherapy had received a total dose of 56 Gy EBRT and 4 × 5 Gy HDREB. At the control-bronchoscopy 6 weeks after radiotherapy, a partial remission had been documented. We observed 2 further cases of hemoptyses – nonfatal and not requiring blood transfusion – classified CTC grade 3. One of them occurred in a patient with persistent local tumor 14 months after radiotherapy (52 Gy EBRT and 4 × 5 Gy HDREB). The other case was observed in a patient with locally controlled disease 3 months after treatment (50 Gy EBRT and 3 × 5 Gy HDREB). One case of bronchial necrosis occurred 18 months after radiotherapy (total dose of 56 Gy EBRT and 4 × 5 Gy HDREB). It was associated with a local recurrence of the tumor. Bronchoscopy confirmed the destruction of the bronchial wall to be caused by a local recurrence within the boosted area. Two locally controlled patients presented with a CTC grade 2 radiogenic bronchitis 28 and 48 months respectively after treatment (total doses of 50 Gy + 2-3x 5 Gy respectively). Tracheomalacia with stenosis occurred in 2 patients one year after radiotherapy (total doses of 50 Gy EBRT and 10-16 Gy HDREB, respectively).

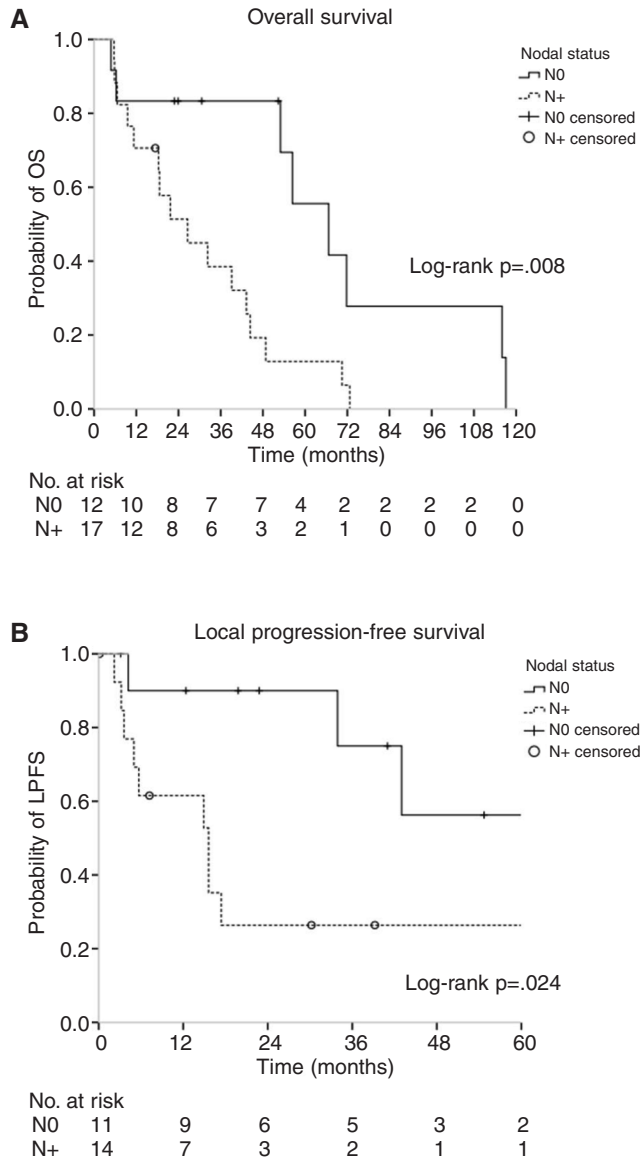

Figure 2 - Kaplan-Meier survival estimates plotted according to the mediastinal nodal status. A) Probability of overall survival (logrank, $P = 0.08$). B) Probability of local progression-free survival (logrank, $P = 0.024$). N0, no mediastinal node involvement; N+, mediastinal node metastasis.
The number of patients at risk remaining each year is reported on the abscissa.

Discussion

This is a single institutional retrospective analysis of 35 patients with inoperable NSCLC treated with a combination of EBRT and HDREB between 1985 and 2005.

Radiotherapy is the treatment of choice in patients with NSCLC who are ineligible for surgical resection and/or chemotherapy. Local control is improved when radical radiotherapeutic doses are administered[1]. To date, endobronchial brachytherapy has been predominately used as a palliative treatment for malignant airway obstruction with excellent results[2-6].

There is little in the literature concerning the implementation of endobronchial brachytherapy combined with EBRT in a potentially curative concept. The results of other authors are reported in Table 5[6-14]. Most of the

Table 2 - Local remission status at first endoscopic post-treatment control

Response to treatment	Distribution (n = 35)
CR	20 (57%)
PR	6 (17%)
NC	2 (6%)
PD	2 (6%)
Not stated	5 (14%)

CR, complete response; PR, partial remission; NC, no change; PD, progressive disease.

series are small, non-controlled and not prospective. Furthermore, technical details of treatment, such as timing relative to EBRT, fractionation scheme or dosing, vary and have yet to be resolved in a general consensus, which makes comparison difficult.

Regarding the endoscopic remission 6 to 8 weeks after HDREB, our results are consistent with other reports. However, our data concerning long-term local control and overall survival are much more optimistic than in the literature. The present study showed 1-, 2- and 5-year LPFS rates of 76%, 57% and 42%, respectively with a median LPFS of 42 months (95% CI, 2.2-83.7). Anacak *et al.*[8] reported a 5-year median LPFS of 10% in 30 patients with stage III NSCLC. In contrast, a Japanese study reported a nearly 100% endoscopic remission rate over a follow-up period of 41 months. However, the patients had radiologically occult, inoperable endobronchial carcinoma, which is an unusual diagnosis. In this group, the 5-year disease-free rates were 87% and the 5-year OS rates were 72%[13].

We observed a median survival of 29 months and 1-, 2- and 5-year OS rates of 76.5%, 61.4% and 28.3%.

Table 3 - Univariate analysis of prognostic factors affecting survival using Cox regressions

Covariate	OS			PFS			LPFS		
	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*
Age, yr			.298			**.031**			.179
≥64	0.7	0.3-1.4		2.7	1-16.8		0.4	0.1-1.4	
<64	1			1			1		
Gender			.622			.855			.556
Female	0.8	0.3-2.1		0.9	0.2-3.1		0.5	0.1-4.3	
Male	1			1			1		
Karnofsky score			.929			.771			.397
≥80	1.03	0.4-2.4		0.9	0.3-2.2		1.7	0.5-5.8	
≤70	1			1			1		
T stage			.502			.749			.871
T3-4	1.3	0.6-2.9		0.8	0.3-2.2		0.9	0.3-2.8	
T1-2	1			1			1		
Nodal status			**.012**			.063			**.037**
N+	3.4	1.3-8.9		2.8	0.9-8.4		4.2	1.1-16.0	
N0	1			1			1		
Tumor localization			.856			.989			**.035**
Distal	1.1	0.5-2.3		0.9	0.3-2.7		0.1	0.0-0.8	
Central	1			1			1		
UICC stage			.502			.117			.729
III	1.4	0.5-3.3		0.4	0.1-1.2		0.8	0.2-2.6	
I/II	1			1			1		
Complete remission after 6-8 weeks			**.014**			**.015**			**.021**
No	3.6	1.2-10.2		3.7	1.3-10.9		4.7	1.2-17.8	
Yes	1			1			1		
Total dose EBRT + HDBRT			.999			.496			.806
≤65 Gy	0.9	0.5-2.1		1.4	0.5-3.4		1.1	0.4-3.7	
>65 Gy	1			1			1		
Total dose HDREB			.573			.582			.697
<15 Gy	0.7	0.3-2.0		0.7	0.2-2.4		0.7	0.2-3.4	
≥15 Gy	1			1			1		
Total dose EBRT			.254			**.045**			.082
≤50 Gy	0.6	0.2-1.4		3.0	1-9.2		3.4	0.8-13.6	
>50 Gy	1			1			1		
Treatment length HDREB			.240			.714			.765
>7 cm	1.6	0.7-3.6		1.3	0.4-4.4		1.3	0.3-5.8	
≤7 cm	1			1			1		

Significance was defined as $P < 0.05$. EBRT, external beam radiotherapy; HDBRT, high-dose-rate brachytherapy; HR, hazard ratio; 95%CI, 95% confidence interval; OS, overall survival; PFS, progression-free survival; LPFS, local progression-free survival; HDREB, high-dose-rate endobronchial brachytherapy.

Table 4 - Adverse events

Adverse events	Distribution (n = 35)		
	CTC grade 2	CTC grade 3	CTC grade 4
Bronchitis	2	0	0
Tracheomalacia/stenosis	2	0	0
Necrosis	0	1	0
Hemoptysis	0	2	1

CTC, Common toxicity criteria.

Anacak *et al.*[8] reported a median survival of 11 months and a 5-year actual survival of 10%. In the report of Aygun *et al.*[9], endoscopic complete remission and median survival were 36% and 13 months, respectively. The treatment schedule in the study was similar to ours, with the exception that brachytherapy was performed during EBRT. Cotter *et al.*[10] reported 1- and 2-year survival rates of 38% and 23%, respectively, with a median survival of 8 months.

Aygun *et al.*[9] found, as we did, a correlation of mediastinal node involvement with treatment outcome. Gejerman *et al.*[14] also reported a correlation between bronchoscopic response and survival. We found that a median dose of EBRT ≥50 Gy was a significant factor for PFS. Mantz *et al.*[12] confirmed that using EBRT doses ≥65 Gy combined with a brachytherapy boost optimized local control results and that lower EBRT doses were associated with increased likelihood for primary disease failure. In addition, patients who underwent endobronchial treatment after completion of EBRT were noted to have better local control rates than patients treated with brachytherapy during EBRT. Therefore, the authors emphasized the necessity to perform the brachytherapy after the completion of EBRT, in order to maximize the likelihood for residual disease to be adequately cytoreduced and to be encompassed within the high-dose field of the HDREB treatment. Treatment with insufficient EBRT doses prior to HDREB or the initiation of treatment during EBRT present the risk of a poor tumor coverage by brachytherapy.

Addressing the question whether additional HDREB after EBRT improves local control and survival, Huber *et al.*[7] published the results of a prospective randomized trial. Ninety-eight patients with inoperable NSCLC were assigned to receive either EBRT alone (total dose of 60Gy) or EBRT combined with 2 additional brachytherapy fractions (to a total dose of 2 × 4.8 Gy). Local control was increased in the brachytherapy group, with a median local control of 21 weeks *vs* 12 weeks with EBRT alone. Results were significant only in the subgroup of patients with squamous cell carcinoma. The brachytherapy group showed also an advantage in median survival with borderline significance.

The role played by HDREB combined with EBRT in the occurrence of severe adverse events is controversial. Hemoptysis is a potentially fatal side effect of brachytherapy. It is not clear whether the incidence of lethal hemoptysis is related to tumor invasion into pulmonary vessels or to a radiation necrosis of the bronchial wall, creating an arterial fistula or exposing a pre-existing fistula due to tumor shrinking. According to Cox *et al.*[15], hemoptysis is the cause of death in lung cancer patients in about 2-8% of all cases when external irradiation has been applied. In the present study, we observed one fatal hemoptysis associated with a local tumor recurrence.

Predictive factors for late toxicity after endobronchial brachytherapy were determined in a multivariate analysis by Hennequin *et al.*[11] The endobronchial tumor length seemed to be strongly associated with hemoptysis ($P = 0.02$). The authors concluded fatal hemoptysis to be more likely related to disease progression, with bleeding being facilitated by brachytherapy. Some rare cases could be a direct complication of brachytherapy itself, particularly when tumors are located in the upper lobe. In contrast, they found that radiation bronchitis occurred more frequently in patients with controlled disease and was significantly influenced by tumor location and technical factors (dose and volume treated). They observed radiation bronchitis in 8.7% of the patients; we reported 5.7%.

Altogether, we observed a low complication rate compared to the published data. This may be explained by the rather small single doses we applied (5 Gy). Furthermore, putting the HDREB at the end of the treatment has the advantage of a smaller target volume, thereby reducing the toxicity.

We observed a significantly worse local control in patients with centrally located tumors (trachea or carina) than in patients with peripheral tumors (bronchi). The finding might be explained by the fact that centrally located tumors were more locally advanced than peripheral tumors. As regards peripheral tumors, correctly placing the brachytherapy application tube in the upper or lower lobe bronchus can be challenging. In this case, electromagnetically navigated brachytherapy could be a new option[16]. Another alternative for high-precision radiotherapy is stereotactic body radiation. It can be used either as hypofractionation or as a single-dose treatment schedule (radiosurgery). Stereotactic body radiation is suitable for peripheral lung tumors. However, Timmerman *et al.*[17-19] warned clinicians of the excessive grade 3 to 5 toxicities seen in patients with central lesion locations.

Our study has several limitations. First, the patient population we analyzed was very small and heterogeneous, so that it is difficult to draw any firm conclusions. Second, our favorable results concerning survival and local control are not in accord with other outcomes reported in the literature. This may be explained by the fact that in our institution only patients with peribronchial tumor extension and with a good response after EBRT were selected for an HDREB boost. Third, we

Table 5 - Comparison of results of endobronchial high-dose rate brachytherapy combined with external-beam radiotherapy (EBRT) in non small-cell lung cancer

Author	No. of cases	Patient collective	Total dose EBRT (Gy)	Single dose HDREB (Gy)/fractionation	Total dose HDREB (Gy)	No. fractions	Prior laser debulking	Sympto. success (%)	Endoscopic remission (%)	Median time to progression (mo)	Radiogenic bronchitis (%)	Fatal events	Fatal events (%)	Median survival (mo)
Speiser *et al.* 1993[6]	47	Inoperable NSCLC	60	7.5/3x	30	3	NI	87	NI	NI	9	2 hemoptysis	4.2	8
Aygun *et al.* 1992[9]	62	Inoperable NSCLC	50-61.6	5	15-25	3-5	NI	NS	36 CR	NI	1.6	9 hemoptysis	15	13
Cotter *et al.* 1993[10]	65	Inoperable NSCLC	55-66	2.7-10	6-35	2-4	NI	66	63 CR 23 PR	NI	7	1 hemoptysis 3 fistulae	6.1	8
Huber *et al.* 1997[7]	56	Inoperable NSCLC	37.5-62.5	4.8/2x	9.6	2	9	NI	NI	5.25	NI	11 hemoptyses	18.9	6.75
Hennequin *et al.* 1998[11]	56	Inoperable NSCLC	40-60	7/2x, 2 weeks after EBRT	14	2	0	60.3	NI	NI	3.5	1 hemoptysis	3.4	24.6
Saito *et al.* 2000[13]	64	Tis-2N0M0	40	5/1-2x 3-9mm distance	25[a]-(35[b])	5	0	NI	86	>30	3		0	>44
Anacak *et al.* 2001[8]	30	NSCLC stage III	60	5/[c]	15	3	NI	>42	53 CR 23 PR	9±4	70	2 hemoptyses	10.5	11±4
Gejerman *et al.* 2002[14]	33	NSCLC stage III-IV	37.5	5/3x concomitant to EBRT	15	3	NI	72	54 CR+PR	NI	NI		0	5.2
Mantz *et al.* 2004[12]	39	Inoperable NSCLC	54-76.5	4-9/weekly	10-30	3	NI	NI	NI	9	NI		0	NI
Present study	35	Inoperable NSCLC	50	5/2x	15	3	0	80	63 CR 26 PR	17.4	5.7	1 hemoptysis	2.8	29

[a]Low dose rate (LDR) brachytherapy with ^{192}Ir.
[b]The patients received only LDR brachytherapy with 35 Gy.
[c]Following every 10 fractions of EBRT.
NI, no information; NS, not significant; CR, complete remission; PR, partial remission.

had to exclude some patients from the risk set for PFS and LPFS. This can be explained by the fact that patients were often discharged to other institutions after completing the radiotherapy and did not come back to perform the scheduled follow-up bronchoscopy and/or CT scan. Others were completely lost to follow-up. As a result, important information concerning local control was sometimes missing, which might have led to bias. Fourth, because we included patients treated from 1988, the PTV described for EBRT in the study (inclusion of uninvolved mediastinal and/or supraclavicular nodes in the PTV) does not correspond to the current standard PTV definition (i.e., elective nodal irradiation). However, despite such limitations, we felt that our work is a valuable contribution to the published literature.

In conclusion, primary EBRT combined with HDREB boost is an effective treatment with an acceptable toxicity in patients with NSCLC who are ineligible for surgical resection and/or chemotherapy. In the subgroup of patients without mediastinal nodal involvement, a long-term local control can be reached (5-year LPFS, 56%). A dose prescription of 50 Gy EBRT followed by 3 × 5 Gy HDREB specified to 1 cm distance from the source axis can be safely applied. Putting the HDREB at the end of the EBRT has the advantage to have a smaller target volume and to adequately encompass the residual disease within the high-dose field of the HDREB treatment. Patients with centrally located tumors and/or endobronchial growth are especially suitable for such an approach.

Fatal events like hemoptysis did not occur in locally controlled patients. However, possible radiogenic side effects demand a periodic endoscopic control. Further prospective randomized studies are required to determine the role and the technical aspects of brachytherapy in the treatment of inoperable NSCLC.

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