Endobronchial Radiotherapy for Malignant Bronchial Obstruction or Recurrence

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Forty-five lung cancer patients who had recurrence and/or endobronchial obstruction were treated with intrabronchial radiotherapy (IBRT). The majority had been heavily treated previously, mainly by external radiotherapy; six patients were treated surgically. IBRT was given with high-dose-rate equipment, either 18 Gy in three fractions or 15 Gy as a single dose was originally planned. For different reasons several patients received other regimens. Palliation of dyspnoea was obtained in 64% of the patients. Palliation of hemoptysis (12/14) and cough (11/17) was registered, as well as improvement in atelectasis in 11/26 patients. Palliation of dyspnoea was enhanced with an IBRT dose >15 Gy. The median survival after IBRT was 13 weeks. Fatal hemoptysis (FH) occurred in 12 patients; 10 of these within 6 months after treatment. The risk of FH significantly increased with an IBRT dose >15 Gy.

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The management of recurrence of bronchial obstruction in patients previously treated for lung cancer is a great challenge. Most of the patients have had radiotherapy for inoperable cancer, and repeated external radiotherapy (XRT) can be given only to a limited extent. Intrabronchial radiotherapy (IBRT) with afterloading equipment has provided new possibilities in the palliation of this group of patients.

The indication for treatment is malignant obstruction, or recurrence, with centrally located endobronchial tumor. IBRT can be combined with laser coagulation in patients with severe obstruction and can also be used as a boost adjuvant to definitive XRT, but this is a more controversial indication (1, 2).

The primary aim of the present retrospective study was to evaluate the palliative effect of IBRT on dyspnoea. It was also of interest to describe the effect on palliation of other symptoms, as well as prognostic factors for survival and the effect of IBRT on risk of fatal hemoptysis.

MATERIAL AND METHODS

Patients

Forty-five patients with primary lung cancer were treated with IBRT for bronchial carcinoma at the Norwegian Radium Hospital during the period 1988–1996. The rather small number of patients may be due to various causes. The traditional treatment for inoperable lung cancer was external radiotherapy (XRT), or in many cases laser coagulation and XRT. Only patients with intrabronchial tumor masses were selected for this modality, never patients who had intact bronchial mucosa and extrabronchial compression. The IBRT was given for malignant obstruction in 26 patients and for recurrence in 19 patients. Patients treated with IBRT for lung metastases from other primary tumors were not included in this study. Patients who had an obstruction at the time of diagnosis and were given IBRT as a planned boost were also excluded. Patient characteristics are presented in Table 1.

If a patient had severe symptoms of obstruction, laser coagulation was carried out before IBRT in order to obtain a fast effect on the symptoms. In some patients laser treatment was considered necessary to make it possible to pass the bronchoscope to the distal margin; 28 patients received 1–2 laser treatments, 5 patients had 3–5 treatments, and 12 patients had no laser treatment.

Treatment

In 1990 a high-dose-rate (HDR) Microselectron became available in our department, and later on all patients except one were treated with this equipment. Before 1990 two patients were treated on an HDR Selectron. The Selectron catheter has a diameter of 8 mm, while the diameter of the Microselectron catheter is 1.9 mm. Owing

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to this, the possibility of brachytherapy in the airways was very limited before 1990. The one patient treated on the Selectron after 1990 had a recurrence in the trachea and was thought to have received a more homogeneous dose to the tracheal wall because of the greater diameter of the Selectron catheter.

Under local anesthesia, a fiberoptic bronchoscope was passed to the upper margin of the obstruction. The point was marked on the skin under fluoroscopy. In most patients the bronchoscope could be passed to the distal margin of the obstruction, which was marked in the same way. The 1.9 mm wide treatment catheter with a dummy wire was inserted through the bronchoscope and positioned according to the marks under fluoroscopy. If either the main bronchi or two lobar bronchi were involved, two catheters were used. The dose was calculated at 10 mm distance from the center of the source.

The length of the source was 40–120 mm (mean 68 mm). Thirteen patients had two catheters each; in 3 patients the catheters were located in the upper and the lower lobe bronchi, and in 10 patients they were located in both of the main bronchi. When adding up all the source lengths, the range was 40–175 mm (mean 82 mm). Although 'high-dose-rate' equipment was used, the dose rate varied by a factor of approximately 3, due to the short half-life of the Iridium source.

During the first years of this treatment program, three fractions at one-week intervals were planned for each patient. If the patient had received XRT, 6 Gy/fraction was given; patients not treated with XRT had 8 Gy/fraction. (Table 2). In the most recently treated patients, a single dose of 10–15 Gy was given. The planned IBRT in three fractions, or as a single dose of 10 Gy or more, was completed in 39 patients. Six patients had less than the planned treatment because of early death or intercurrent disease. The doses given were based on information from the literature. The change from three fractions to a single dose was effected mainly for practical reasons. The doses for XRT and IBRT were the actual given doses. No recalculation according to the LQ model or any other models for biological effect was attempted.

Evaluation and statistical analyses

To assess the relief of dyspnoea, a scoring system graded 1–4 was used. Before IBRT and approximately after 2, 4 and 6 months, the patient was evaluated as having: 'No dyspnoea' (1 on the scoring system), 'dyspnoea at exercise' (2), 'dyspnoea at rest' (3) or 'oxygen dependence' (4). In patients who had the relevant symptoms registered before treatment, the effect on symptoms such as cough, hemoptysis, resolution of atelectasis on x-ray, and improvement of bronchoscopic findings was registered.

The effect of IBRT on dypnoea was analyzed by a mixed model analysis of variance for repeated measures (BMDP3V). The effect of IBRT on hemoptysis, cough, atelectasis, and bronchoscopy findings was evaluated by the sign test. The Kaplan-Meier method was used to estimate survival as measured from time of IBRT to death. In addition, the time from IBRT to fatal bleeding was estimated. Here deaths from other causes were treated as censored observations. Comparisons of survival curves were made using the log-rank test. Variables registered on an ordinal scale were analyzed by the log-rank test for trend. Cox's proportional hazards model was used to analyze the simultaneous effect of possible risk factors on survival. The assumption of proportional hazards was checked by visual inspection of cumulative hazard plots.

Table 1

Characteristics of the patients at primary diagnosis

	No	%
Diagnosis		
Small cell cancer	1	2
Squamous cell cancer	35	78
Adenocarcinoma	5	11
Large cell and other	4	9
Sex		
Males	35	78
Females	10	22
T-stage		
T2	12	27
T3	18	40
T4	15	33
Primary treatment		
Surgery (pulmectomy or lobectomy)	6	13
External radiotherapy alone	31	69
Chemotherapy and radiotherapy	3	7
Laser coagulation	5	11
External radiotherapy dose		
No external RT	4	9
28–40 Gy	7	16
41–50 Gy	29	64
51–60 Gy	5	11
Age	Mean	Range
	62	44–78

Table 2

Doses and fractionation of brachytherapy

No. of fractions	Dose per fraction	Total dose	No. of patients
1	6	6	2
1	7	7	1
1	10	10	2
1	12	12	4
1	15	15	17
2	7	14	1
2	8	16	1
3	6	18	14
3	7	21	1
3	8	24	2

A single fraction of 15 Gy, or 18 Gy in three fractions was the most common regimen.

Possible prognostic factors for obtaining 'No dyspnoea' were analyzed by a logistic regression model. Continuous variables were dichotomized using the median as the cut-off value before being entered into any of the regression models. A p-value below 5% was considered statistically significant. The p-values obtained from pairwise analyses were corrected by the Bonferroni method. The statistical analyses were performed by SPSS and BMDP.

RESULTS

Laser coagulation

Of the 33 patients who had laser coagulation before IBRT, 21 experienced an immediate improvement, in 10 there was no change, the condition of one patient worsened, and one patient was not evaluable.

Palliation of dyspnoea

Before IBRT (but after laser, if given), 16 patients had dyspnoea at exercise, 25 had dyspnoea at rest, and 4 were oxygen dependent. At the first follow-up, at 1–2 months after treatment, 17 patients had no dyspnoea, 17 had dyspnoea at exercise, 7 patients had dyspnoea at rest, and none of them were oxygen dependent. Looking at the individual patients; 29 had improved (64%), 9 remained unchanged, 3 were worse. Four patients could not be evaluated at the first follow-up, because of early death or other reasons. At 3–4 months, 7 patients had no dyspnoea, 14 had dyspnoea at exercise, 7 patients had dyspnoea at rest, and none of the patients were oxygen dependent. Compared to the status before IBRT, 18 were improved, 7 were unchanged, and 3 patients were worse. At 5–6 months only 12 patients were evaluable, owing to short survival. Seven were improved, 3 unchanged, and 2 worse compared to scores before IBRT.

The mean dyspnoea scores and corresponding 95% confidence intervals are charted in Fig. 1. According to the analysis using the mixed model analysis of variance for repeated measures, there was a significant effect of time ($p < 0.0001$). A pairwise analysis of the different times shows that all mean scores after IBRT were significantly different from the mean score before IBRT. There were no significant differences between mean scores after IBRT.

Relief of dyspnoea was better in patients who received high doses of IBRT. We found a significant association between IBRT score (≤ 15 Gy vs. ≥ 16 Gy) and the probability of obtaining complete relief of dyspnoea ($p = 0.022$, logistic regression). No other variables had any influence on the palliative effect of IBRT in this series.

Palliation of other symptoms

Fourteen patients had information on hemoptysis before IBRT. Twelve were improved and 2 were unchanged ($p < 0.001$). Cough was a predominant symptom in 16 patients. Eleven were improved, 4 unchanged, and one patient had progression of cough ($p = 0.006$). Twenty-six patients had roentgenological evidence of atelectasis before IBRT. Improvement was seen in 11 patients, no change in 12, and progression in 3 patients ($p = 0.058$). Only 13 patients had a bronchoscopy during follow-up. Of these, 7 were improved, 2 had no change, and 4 patients had progression ($p = 0.55$).

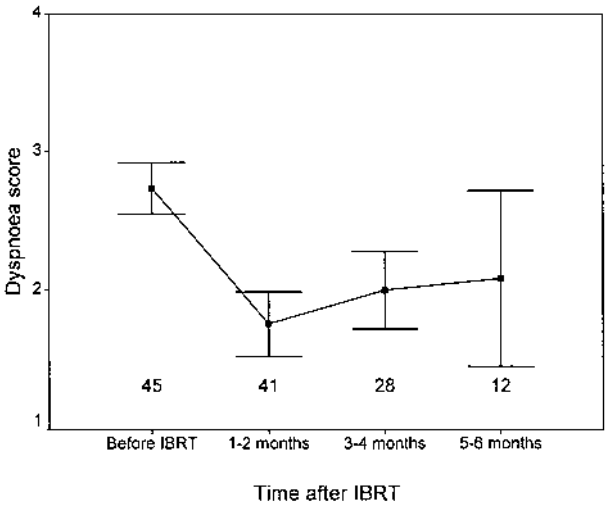

Fig. 1. Mean dyspnoea score and corresponding 95% confidence intervals. The number of evaluable patients at each follow-up is also shown.

Survival

The median survival after IBRT with or without laser coagulation was 13 weeks with a 95% confidence interval (9–19). As shown in Fig. 2, survival was significantly associated with dyspnoea grade before IBRT ($p = 0.007$,

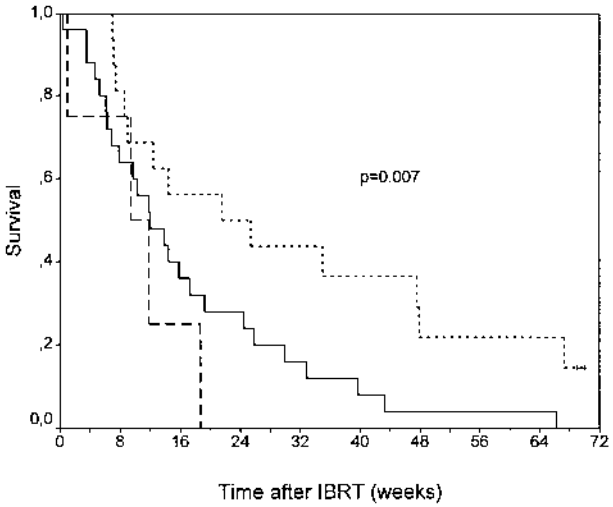

Fig. 2. Overall survival from start of IBRT. Patients with better respiratory function did significantly better. The dotted line represents 'dyspnoea at exercise', the solid line 'dyspnoea at rest', and the dashed line 'oxygen dependence'.

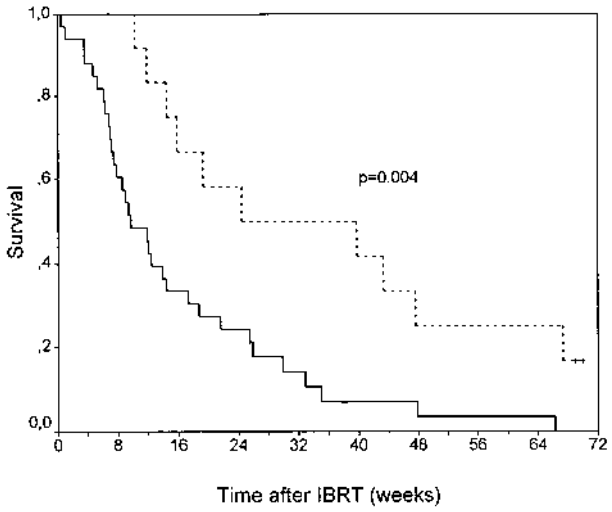

Fig. 3. Overall survival from start of IBRT. Patients given laser treatment had significantly shorter survival. The solid line represents laser treatment and the dotted line no laser treatment.

log-rank test for trend). A statistically significant decrease in survival was demonstrated for patients who had received laser coagulation (Fig. 3, $p = 0.004$, log-rank test).

Dyspnoea grade and laser treatment were included in a Cox's regression model. Both variables were significantly associated with survival. No other factors available (see Tables 1 and 2) significantly affected overall survival. The results of the multivariable analysis are presented in Table 3.

Cause of death is listed in Table 4. In the present series 12 patients had a fatal bleeding from the airways. Ten of these occurred within 6 months and correspond to 30% of the total number of deaths before 6 months. The risk of fatal bleeding was associated with the total IBRT dose, with a higher risk in patients who were given more than 15 Gy, compared with patients with a lower dose, as shown in Fig. 4 ($p = 0.023$, log-rank test). A comparison of patients who received 1×15 Gy and those given 3×6 Gy produced similar results. There seemed to be no association with the length of the source(s), or with the dose rate used. Three patients had treatment in one of the upper lobes, of whom two had a fatal hemorrhage. There was no significant association between laser coagulation and risk of fatal hemoptysis.

Table 3

Prognostic variables. Cox's regression model

Variable	p-value*	Hazard ratio	95% CI
Laser coagulation (yes/no)	0.008	2.77	1.30, 5.92
Dyspnoea grade before IBRT**	0.013	1.91	1.14, 3.18

* Likelihood ratio test.
** Continuous scale (2, 3, 4).

Table 4

Cause of death

	No. of patients
Dead from intercurrent disease	3
Dead from fatal bleeding	12
Dead from progressive cancer	27
Alive with cancer*	3

* Still alive at the time of analysis; 6, 16 and 16 months after IBRT, respectively.

An autopsy was performed in only two patients. One had massive infiltration of tumor in both lungs, and died of respiratory failure. In the other, who had a fatal bleeding, a perforation through the tumor was found between the right main bronchus and the right pulmonary artery.

DISCUSSION

This is a retrospective study, and some of the observations are clearly due to bias in selecting patients for various treatments. The demonstrated better survival with better respiratory function before IBRT is probably an effect of better general condition, which is known to be very important for the survival of advanced lung cancer patients (14). The apparently negative effect of laser treatment is believed to be confounded by grade of obstruction, as patients with the most severe obstruction were selected for laser coagulation.

The effect of IBRT on dypnoea was primarily analyzed by a mixed model analysis of variance for repeated measures (BMDP3V). Such a parametric approach to ordinal data in four categories may be questionable, and we have therefore also used a non-parametric approach; the Friedman test. The drawbacks to this method are that it disre-

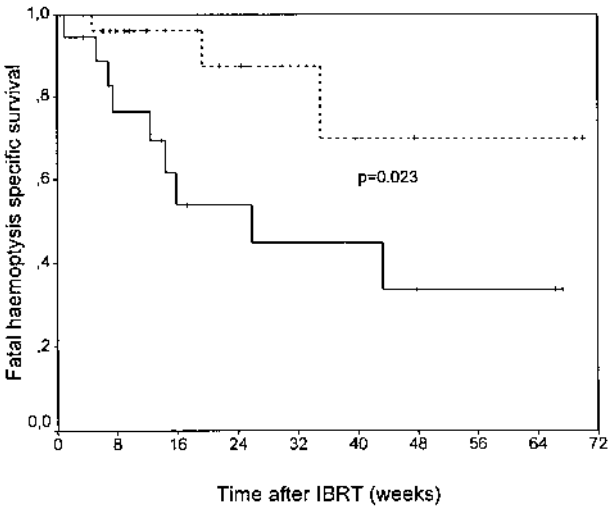

Fig. 4. Fatal hemoptysis specific survival. A high dose of IBRT significantly increased the risk of fatal hemoptysis. The dotted line represents IBRT dose ≤ 15 Gy and the solid line ≥ 16 Gy.

gards the ordering of measurement times and that only cases with no missing data are included in the analysis. The number of patients available for analysis will thus be small, and the results will possibly be biased because of selection of survivors. Therefore the analysis was based on a 'last observation carried forward' technique (LOCF). Here any missing value is replaced by the last value registered. The result of performing a Friedman test using the LOCF technique did not alter the conclusion that there was a significant effect of IBRT; the only difference being that the scores at 5–6 months were now significantly higher than those at 1–2 months.

Only a few retrospective series report on survival after start of IBRT. The survival after brachytherapy in this study was short because of selection of rather advanced cases. However, it corresponds well to results reported previously (15–17). The palliative effect also corresponds well to previous reports (3–5).

In the literature the risk of fatal bleeding varies from 0 to 50%. Chen et al. (18) constructed a dose volume histogram to evaluate the risk of late complications and found an association between IBRT dose and volume. Cotter et al. (6) describe better palliation of symptoms as well as higher complication rates with higher XRT and IBRT dose combined. A comparison of risk of fatal hemorrhage between different series is probably impossible due to different selection of patients, and different reporting of results (5, 7–9, 16). Gollins et al. (10) found higher IBRT dose (20 Gy vs. 15 Gy), prior laser treatment in the same location, and repeated IBRT in the same location to be the main risk factors for fatal hemoptysis. Bedwinek (11) reported 12/38 (32%) patients dying of hemoptysis. As 5 patients were alive at the time of analysis, 36% of the expired patients had fatal hemoptysis.

Possible hypotheses concerning the cause of fatal hemoptysis are tumor progression, the high dose of irradiation produced by the brachytherapy and prior external irradiation, or that the tumor had already created a bronchial-arterial fistula, which was blocked by tumor tissue and resulted in bleeding after tumor shrinkage due to IBRT.

No conclusions can be drawn from the present study concerning the cause of fatal hemoptysis; one can only speculate. As the fatal events occurred at very different times, there is probably more than one cause. The early events might fit well with the hypothesis of a breakdown of a pre-existing tumor infiltration into an arterial wall. The late events could be related to tumor progression, but vascular damage to an arterial wall as a late radiation effect is also a possible explanation. The finding of increased risk with higher IBRT dose in the present report, and as reported by Gollins (10), might suggest radiation injury as a cause in late events. Rupture of an artery in other anatomic regions caused by radiation has been described previously (12, 13, 19).

The frequency of using laser treatment varies between reports. Laser coagulation is reported to be used in 3–40% of patients before IBRT (16, 20–23) compared with 78% of the patients in the present study. Laser coagulation had an immediate effect on the symptoms but no impact on the respiratory function later on. It was not a risk factor for fatal hemoptysis.

CONCLUSION

In advanced inoperable lung cancer patients with symptoms of bronchial obstruction endocavitary radiotherapy may offer relief of respiratory distress for their remaining lifetime. Relief of cough, hemoptysis, and resolution of atelectasis were obtained in the majority of patients. Factors contributing to the outcome in terms of survival and palliation of symptoms are still uncertain, as are the risk factors for fatal hemorrhage. The present results suggest that a higher IBRT dose offers better relief of obstruction, but carries a higher risk of fatal hemoptysis, possibly in combination with a higher external dose of radiotherapy. At the present time we recommend 15 Gy as a single dose, which is practical to carry out, gives a reasonably good palliation of dyspnoea, and carries an acceptable risk of complications.

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