

Brachytherapy in lung cancer: a review

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Abstract: Metastatic non-small cell lung cancer (NSCLC) remains the leading cause of cancer death worldwide. Intraluminal brachytherapy (ILBT) has been shown to improve patients' symptoms in some studies. However, its role in the palliation of these patients amidst the other local treatment modalities such as external beam radiotherapy (EBRT), laser and photodynamic therapy (PDT) remains unclear. We have completed a systematic review of the literature to evaluate outcomes of patients with lung cancer treated with ILBT alone and/or in combination with other treatment modalities. We have reviewed tumour and symptom response, overall survival (OS) and toxicities of patients treated with diverse fractionation schemes and those treated with a curative intent. Overall, ILBT is associated with improvement of patients' symptoms in most cases. Its toxicity profile is generally low with small risk of fatal hemoptysis. Further studies are needed to establish an optimal fractionation schedule, although it appears that fractionated treatments (3 fractions) were associated with less toxicity yet similar symptom relief when compared to single fraction treatments. Caution must be taken when prescribing the dose to avoid necrosis and or fistula that may be lead to fatal hemoptysis.

Keywords: Brachytherapy; lung cancer; non-small cell lung cancer (NSCLC); high-dose rate (HDR)

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Introduction

Metastatic non-small cell lung cancer (NSCLC) remains the leading cause of cancer death in men and the second leading cause of cancer deaths in women worldwide (1). It is a debilitating disease that results in a high burden of symptoms including shortness of breath, hemoptysis, cough and pain resulting in poor quality of life. Intraluminal brachytherapy (ILBT) has been shown to improve patients' symptoms in some studies. However, its role in the palliation of these patients amidst the other local treatment modalities such as external beam radiotherapy (EBRT), laser and photodynamic therapy (PDT) remains unclear. Effectiveness in palliation and toxicity profile vary widely between cohorts of patients treated with different fractionation schemes making it difficult to compare them.

Finally, ILBT has also been used in different ways to treat patients in a radical setting in small series.

We have endeavoured to pursue a systematic review of the literature to evaluate outcomes of patients with lung tumours treated with ILBT alone and/or in combination with other treatment modalities. We have reviewed outcomes of patients treated with diverse fractionation schemes and those treated with a curative intent.

Methods and materials

Literature search

The English and French-language literature from 1980 to June 1st 2015 was reviewed according to PRISMA guidelines (2), using PubMed. All relevant abstracts and

articles were thoroughly examined by two independent individuals. Studies were included if they (I) consisted of randomized control trials (RCT), prospective studies or retrospective studies; (II) included patients with biopsy-proven lung cancer and treated with ILBT.

Studies were excluded if they (I) included patients treated for distant lung metastases (II) were non-original studies, i.e., practice guidelines, metaanalyses or systematic review articles (III) did not address patients' outcomes after treatments of their endoluminal lung cancer; (IV) included patients treated with interstitial brachytherapy; (V) patients were treated post-operatively; (VI) treated patients with low-dose rate brachytherapy (LDR), medium dose rate brachytherapy (MDR) or pulse-dose rate brachytherapy (PDR).

The results were divided into into RCTs, prospective studies and retrospective studies. Although meta-analyses, systematic reviews and practice guidelines were not included in our literature search, these were cross-referenced with our search strategies to ensure a complete set of manuscripts for review. The following keywords and MeSH headings were used: "radiotherapy or irradiation or external beam or radiation" and "palliation or palliative or lung cancer or bronchial or endobronchial or lung malignancy" and "thoracic cancer or lung cancer or bronch- or endobronchial" and "palliation or palliative or lung cancer or bronchial or endobronchial or lung malignancy".

Results

Randomized control trials describing the role of ILBT alone or in conjunction with other modalities in the palliative management of lung cancer

ILBT allows the delivery of high-dose radiation to the luminal aspect of the tumour and thereby, relieving patients' symptoms. Few RCTs have attempted to assess the benefit of ILBT in addition to or compared to other treatment modalities, with conflicting results. These are studies with their results are summarized in *Table 1*.

Many RCT have randomized patients to EBRT with or without ILBT to evaluate the impact on outcomes with the addition of ILBT.

Huber *et al.* (8) randomized 93 patients with NSCLC treated with ILBT to a mean delivered dose of 13.4 Gy in 4 weekly fractions or 13.7 Gy in 2 fractions over 3 weeks. The 1-year survival, local control (LC) and fatal hemoptysis rates were not significantly different between the two

groups. Huber *et al.* (7) also randomized 98 patients with inoperable NSCLC to EBRT alone (n=42) compared to EBRT with ILBT (EBRT-ILBT) (n=56). In this trial, although survival rates (and fatal hemoptysis rates) were similar, patients with primary lung squamous cell carcinoma experienced a significantly longer LC when treated with EBRT+ ILBT compared to EBRT alone.

More recently, Langendijk *et al.* (4) randomized previously untreated NSCLC stage I-IIIB in proximal airways to EBRT to 30 Gy in 10 fractions with or without ILBT to a dose of 15 Gy in 2 fractions delivered weekly. This study showed that the addition of ILBT to EBRT improved the rates of re-expansion of collapsed lung from obstructing tumours in the main bronchus resulting in lower levels of dyspnea. There were improved rates of re-aeration (57% *vs.* 35%, P=0.001) and mean dyspnea scores (P=0.02) over time in patients treated with EBRT-ILBT compared to those treated with EBRT alone.

Stout *et al.* (6) randomized 99 patients with inoperable NSCLC to EBRT (30 Gy over 10-12 days) or ILBT (15 Gy). Although patients treated with EBRT had significantly longer survival (9.4 *vs.* 8.2 months), their dysphagia rates were also higher. ILBT and EBRT both provided similar symptom response rates. Of note, in this study, many patients treated with EBRT also received ILBT and vice versa. Patients' tumour size response was not reported.

Niemoeller *et al.* (3) randomized 142 patients with advanced endoluminal centrally located malignant tumours to a different ILBT fractionation schemes, i.e., 15.2 Gy in 4 weekly fractions (n=60) or 14.4 Gy in 2 fractions in 3 weeks. In both groups, survival and symptom response were similar. Interestingly, local tumour response with 2 fractions was significantly higher compared to 4 fractions (median 12 *vs.* 6 weeks, P<0.015) and fatal hemoptysis rate was lower (12% *vs.* 18%), although it did not reach statistical significance. Niemoeller *et al.* attributed the difference in the results to a higher radiation dose per fraction. It is also possible that the larger sample size of Niemoeller's cohort and the difference in the randomization method—performance status in each group was not described and not accounted for—may explain these different findings.

Chella *et al.* (5) evaluated the role of ILBT in addition to Nd-YAG laser in a RCT. Their study included 29 patients with NSCLC involving the central airways between Nd-YAG versus Nd-YAG with ILBT. The addition of ILBT to Nd-YAG increased the symptom-free survival (8.5 *vs.* 2.8 months P<0.05) and decreased the need of further

Table 1 Randomized control trials evaluating outcomes of patients with lung cancer treated with intraluminal brachytherapy

Author, year	Population	N	Treatment	Median follow-up	OS median/1-year OS (%)	Sympt resp (%)	Tumour resp (%)	A/E
Niermoeller et al., 2013 (3)	Endobronchial central NSCLC tumours	Total=142 (I) n= 60 (II) n=82	(I) 3.8 Gy q1wk x 4# (15.2 Gy) @ 1 cm (II) 7.2 Gy x 2# (14.4 Gy) @ 1 cm	20 mos	19 wks/ median 1-yr OS: 11% 18 wks/ median 1-yr OS: 21% (ns)	NR	49% 53%	fHemop: 18% fHemop: 12% (ns)
Langendijk et al., 2001 (4)	Inoperable, biopsy-proven NSCLC with tumor in main or lobar bronchus, Stages I-IIIb (IIb 55%)	Total=95 (I) 47	(I) EBRT alone Radical EBRT: 2.25 Gy x 4# q1wk to 45 Gy + 15 Gy boost, or palliative EBRT: 3 Gy x 4# q1wk to 30 Gy (II) EBRT+BT Radical or palliative EBRT + BT of 7.5 Gy x 2# @ 1 cm q1wk	NR	8.5 mos/NR (95% Ci: 5.4-11.6)	*SOB: 37% *Re-aeration: 35% Hemop 82%	NR	fHemop: 13%
Chella et al., 2000 (5)	NSCLC involving central airway not eligible for other treatments (Sq 72%)	Total=29 (I) n=15	Nd-YAG laser alone: 25-45 Watts using pulses up to 1.2 s to a mean total of 1,850 J	17.8 mo	7.0 mos/NR (95% Ci: 5.3-8.9) P=0.21 7.4 mos/NR	*SOB: 46% *Re-aeration: 57% Hemop: 86%	NR	fHemop: 15% Fistula: 4%
Stout et al., 2000 (6)	Inoperable, histologically proven NSCLC, Sq 82%	n=99 (I) 50 (II) 49	Nd-YAG laser + BT (15 Gy/3# q1wk @ 0.5 cm) EBRT: 30 Gy/8# over 10-12 days BT: 15 Gy /1# @ 1 cm	NR	10.3 mos/NR 9.4 mos/38% 8.2 mos/22% (P=0.04)	100% (hemop, stridor) 76% (SOB), 48% (cough); *15 further endoscopic Rx *Shorter period free-from symptoms 2.8 mos (P<0.05) *3 further Rx (P<0.05) *Free-from symptoms =8.5 mos 67% cough (ns) 50% cough (ns)	NR NR	n=5 (gr2 actinic bronchitis) n=1 (gr 3 actinic bronchitis- dilatation required) fHemop: 0 Massive hemop: 8% Massive hemop: 6% less dysphagia than EBRT
Huber et al., 1997 (7)	Inoperable, histologically proven NSCLC (Sq 69%, Stages I-IV (IIb/IV 77%))	Total n=98 Group 1: n=42 Group 2: n=56	EBRT alone: 2-2.5 Gy/d with 4-5# /wk up to 50 Gy + 10 Gy boost (60 Gy total) Mean= 50.5 Gy EBRT + BT: BT: 4.8 Gy x 2# (1 wk pre- and 3 wk post-EBRT) @ 1 cm; mean BT: 7.44±2.6 Gy; mean EBRT =50 Gy	30 mos	6.5 mos/19% 6.2 mos/25% (ns)	NR	NR	fHemop: 14% fHemop: 19% (P=0.53) longer LC, *SCC

Table 1 (continued)

Table 1 (continued)

Author, year	Population	N	Treatment	Median follow-up	OS median/1-year OS (%)	Sympt resp (%)	Tumour resp (%)	A/E
Huber <i>et al.</i> , 1995 (8)	Histologically proven NSCLC (ns), Sq 49%, Stages I-IV (IIIB/IV 80%)	Total: n=93 Group 1: n=44	BT: 3.8 Gy x 4# q1wk @ 1 cm (mean dose: 13.4±5.2 Gy)	30 mos	4.2 mos/11.4%	NR	CR: 2% PR: 42%	NR
		Group 2: n=49	BT: 7.2 Gy x 2# q3wk @ 1 cm (mean dose: 13.7±4.4 Gy)		4.4 mos/20.4% (ns)		PR: 49%	

A/E, adverse events; BT, brachytherapy; CI, confidence interval; CRT, chemoradiation; EBRT, external beam radiation; Gy, Gray; mo(s), month(s); fHemop, fatal hemoptysis; Hemop, hemoptysis; n, number of patients; NR, not reported; NS, not significant; NSCLC, non-small cell lung cancer; q, every; OS, overall survival; resp, response; Rx, treatment; SOB, shortness of breath; Sq, squamous cell carcinoma; symp, symptom; wk(s), week(s); *, statistically significant; #, fraction(s).

endoscopic treatments (15 *vs.* 3 further endoscopic treatments, $P < 0.05$). It is possible that these two treatments are in fact complimentary. Indeed, Nd-YAG laser may be used to remove bulky tumours-to relieve symptoms rapidly while delivering ILBT provides a longer symptom-free survival and limit the needs of further interventions.

The current data suggests that in patients with endobronchial disease, ILBT given in addition to EBRT may improve LC and symptoms, especially in patients with collapse lung. When ILBT is delivered without EBRT, the use of Nd-YAG laser may be complimentary because it can remove bulky tumours and relieve symptoms rapidly and while ILBT provides a longer period of symptom-free survival. Further studies are needed to better evaluate and quantify the benefits of the addition of ILBT to EBRT in a palliative setting.

Prospective studies describing the role of ILBT alone or in conjunction with other modalities in the palliative management of lung cancer

Ornadel *et al.* (9) reported outcomes of 117 patients previously treated patients undergoing with Nd-YAG laser prior to BT if there was significant endobronchial likely to cause lung collapse before ILBT would have time to relieve obstruction or if patients were in acute distress. ILBT dose was of 15 Gy in 1 fraction, prescribed at 1 cm from the source axis. There was an improvement in symptoms in 59% for cough, 50% for dyspnea and 76% for hemoptysis. Of note, patients with prior laser treatments had a statistically significantly higher risk of subsequent fatal hemoptysis.

Muto *et al.* (10) reported outcomes of 320 patients with stage III NSCLC treated with EBRT (60 Gy in 30 fractions) and with three different schedules of ILBT of 10 Gy in 1 fraction, 14 Gy in 2 fractions and 15 Gy in 3 fractions. The mean OS and rates of symptomatic improvements were not statistically significantly different between the groups. However, the group treated with 3 fractions experienced less toxicity.

Skowronek *et al.* (11) treated 15 patients with 20-30 Gy of EBRT and a weekly high-dose rate (HDR) brachytherapy (3 fractions of 3.5-10 Gy, at 1 cm from the source). In all patients subjective improvement (regression of all symptoms) was found on the first check-up following treatment. In one case complete remission of the tumour lasted for over 6 months, 9 cases had partial remission. The combination of ILBT and EBRT led to regression of

symptoms and improvement of well-being in most patients.

Speiser *et al.* (12) reported one of the largest series of patients treated with ILBT with or without EBRT. The ILBT dose ranged between 22.5 and 30 Gy in 3 fractions. There was a high symptom response rate ranging between 85% (cough, SOB) and 99% (hemoptysis). The rates of procedure-related complications were low, at 3%.

Finally, Freitag *et al.* (13) assessed indirectly whether PDT compared to PDT with ILBT improved tumour response. This prospective study included unresectable endobronchial primary bronchogenic carcinoma (n=15) and recurrent lung tumours (n=17). The complete response rate associated with the initial PDT was of 75%. After patient completed ILBT, the CR was of 97%. These results suggest that perhaps delivering ILBT in addition to PDT may improve tumour control. It would be interesting to evaluate how ILBT alone compares to PDT, with the hope of using only one modality of treatment and minimize toxicities.

Most recently, Goldberg *et al.* (14) reported outcomes of inoperable patients with endobronchial lung cancer treated with ILBT with or without EBRT or chemoradiation. ILBT was delivered with a dose of 14 Gy in 2 fractions. Although the survival was improved in patients with CRT, the mean cough-free survival (4.7 months), mean shortness of breath-free survival (5.8 months) and hemoptysis free-survival (7.7 months) were not statistically significant between groups.

Freitag *et al.* (13) assessed indirectly whether PDT compared to PDT with ILBT improved tumour response. This prospective study included unresectable endobronchial primary bronchogenic carcinoma (n=15) and recurrent lung tumours (n=17). The complete response rate associated with the initial PDT was of 75%. After patient completed ILBT, the CR was of 97%. These results suggest that perhaps delivering ILBT in addition to PDT may improve tumour control. It would be interesting to evaluate how ILBT alone compares to PDT, with the hope of using only one modality of treatment and minimize toxicities.

All these prospective studies used different fractionation schemes and doses. All series report a good rate of symptom relief with low incidence of toxicities. Further studies are needed to determine the optimal dose fractionation scheme.

Retrospective studies describing the role of ILBT alone or in conjunction with other modalities in the palliative management of lung cancer

Many fractionation schemes have been described in

retrospective series. The vast majority of the literature on ILBT discusses its use in the palliation of patients with lung cancers to relieve symptoms such as hemoptysis, cough, dyspnea or atelectasis. The data is summarized in *Tables 1-3*. Its effectiveness in improving symptoms mostly ranges from 43% to 92%, depending on symptoms evaluated. Hemoptysis is the most consistently and effectively palliated symptom, with relief in 70-100% of cases. On the other hand, dyspnea is the symptom the least consistently relieved, with rates ranging from 33-85%.

Technical aspect of ILBT

Prescription point

The prescription point for lung brachytherapy is usually 1 cm from the centre of the source axis. Many authors attempt to treat the entire tumor with the brachytherapy catheters. For tumours in the trachea and mainstem, a prescription point at 1cm from the centre of the source axis is safe. From Goldberg *et al.* experience (18), it appears that prescribing at a depth of 0.5 cm was associated with no toxicities. It is not always possible to treat the entire tumour. Dose prescription points beyond what is recommended above can lead to massive cartilage necrosis causing airway-vascular fistula and massive haemoptysis.

Optimal dose fractionation scheme for palliative endobronchial brachytherapy for patients with lung cancer

In a palliative setting, the ideal treatment schedule aims to balance maximal LC and tumour and symptom response with minimal toxicities from ILBT (such as fatal hemoptysis), number of treatments and overall treatment time. There are innumerable fractionation schemes published in the literature with limited studies comparing them to establish superiority of one over the others.

Huber *et al.* (8) randomized 93 patients with NSCLC to a mean delivered dose of 13.4 Gy in 4 weekly fractions or 13.7 Gy in 2 fractions q3weeks. The 1-year survival, LC and fatal hemoptysis rates were not significantly different between the two groups.

One of the largest study from Niemoeller *et al.* (3) randomized 142 patients with advanced endoluminal centrally located malignant tumors to two fractionation schemes, i.e., 15.2 Gy in 4 weekly fractions (n=60) or 14.4 Gy in 2 fractions over 3 weeks. In both groups, survival and symptom responses were similar. Interestingly, local tumour response with 2 fractions was significantly higher compared to 4 fractions (median 12 *vs.* 6 weeks, P<0.015)

Table 2 Prospective studies evaluating outcomes of patients with lung cancer treated with intraluminal brachytherapy

Author, year	n	Population	Treatment	Symptomatic response (%)	Size response (%)	FU time	OS (mos)	Toxicity
Goldberg et al., 2015 (14)	98	Inoperable endobronchial lung cancer	n=52- BT alone: 7 Gy x 2# n=34- BT 7 Gy x 2# + EBRT (30 Gy/10#) n=6- BT 7 Gy x 2# + CRT (60 Gy/30#) n=6- BT 7 Gy x 2# + Chemo alone @ 1 cm for main and 0.5 cm for segmental bronchi	Mean cough-free survival = 4.7 mos Mean SOB-free survival =5.8 mos Mean Hemop-free survival =7.7 mos (ns) *no difference in sympt-free survival or QOL between treatment groups	NR	12 mos	Mean =4.6 mos Mean =7.5 mos Mean =10.5 mos* Mean =8.4 mos	NR
Skowronek et al., 2009 (11)	648	Advanced lung cancer	n=303- BT: 22.5 Gy/3# @ 1 cm q1wk n=345- BT: 10 Gy/1# @ 1 cm	88% (subsidence of all symptoms at 4 weeks post-ILBT)	CR: 17% PR: 71% (ns)	NR	Median = 3.7 mos (ns)	NR
de Aquino et al., 2013 (15)	78	Primary or metastatic bronchogenic carcinoma	BT (22.5 Gy/3#) + EBRT (60 Gy/30# or 30 Gy/10#)	Overall: 87% Cough: 34% SOB: 57% Hemop: 100% AO: 74% Infection: 80%	CR: 48%	NR	Median =6 mos	Stenosis-stent: 1.3% Fistula 2.6% fHemop 10% (but with PD)
Freitag et al., 2004 (13)	32	unresectable endobronchial primary bronchogenic carcinoma (n=15) and recurrent lung cancer (n=17)	PDT + BT (20 Gy/5# @ 1 cm)	NR	CR: 75% (after PDT) CR: 97% after PDT+ BT	Mean =24 mos	NR	No A/E ≥ grade 3 A/E
Escobar-Sacristan et al., 2004 (16)	81	Primary or metastatic endobronchial cancer	BT: 5 Gy @ 0.5-1 cm +/- surgery, chemo, CRT, laser or EBRT	Overall: 85% Cough: 88%, SOB: 75%, hemop 96%	CR: 57% PR: 41%	Minimum 1 month after BT	NR	Fistula (1%)-no mediastinitis/death
Muto et al., 2000 (10)	320	Biopsy proven NSCLC, KPS >60, Stages IIIA-IIIIB	EBRT (60 Gy/30#) + BT (3 schedules of BT) (i) 10 Gy/1# (ii) 14 Gy/2# (iii) (i) 15 Gy/3# @1 cm (ii) 15 Gy/3# @0.5 cm	Cough: 77%, SOB: 85% Hemop: 94%, atelectasis: 94% Obstructive pneumonia: 90%	NR	5-36 mos	Mean =9.7 mos (ns between groups)	ACUTE: 6-mo bronchitis 16-80% (ss) CHRONIC: Hem: 2.5-6.5% fistula 1-3% 3# associated with fewer A/E but similar OS and sympt relief; trend in higher A/E in C1 vs. C2

Table 2 (continued)

Table 2 (continued)

Author, year	n	Population	Treatment	Symptomatic response (%)	Size response (%)	FU time	OS (mos)	Toxicity
Ofiara et al., 1997 (17)	24	Bronchogenic carcinoma inoperable, recurrent or persistent symptomatic	24 Gy/3# @ 1 cm	Cough: 46% SOB: 33% Hemop: 79% Atelectasis: 54%	62%	NR	NR	NR
Ornadel et al., 1997 (9)	117	Bronchial carcinoma unresectable and not candidate for EBRT	BT: 15 Gy/1# @ 1 cm	Cough: 59% SOB: 50% Hemop: 76%	NR	NR	Median =12 mos	*Prior laser has higher risk of fHemop (P=0.048)
Hernandez et al., 1996 (18)	26	Residual or recurrent lung cancer	Prior EBRT (mean =44 Gy) BT: 7.5-10 Gy x 1-3# (total=7.5-30 Gy) @ 1 cm	Atelectasis 44% Hemop 71% Cough 55% SOB 36% Pneumonitis 50%	42%	NR	NR	n=6/29 (minor hemoptysis <100 mL) n=1/29: (non fatal massive hemop >500 mL) n=1/29: PTx
Trédaniel et al., 1994 (19)	51	Primary carcinoma of tracheobronchial tree	BT alone (14-21 Gy/2-3#) (I) BT radical (n=29) (II) metastatic: BT palliative (n=22)	Overall: 70% Cough: 85% SOB: 55% Hemop: 85%	Group 1: CR: 84% PR: 12% Group 2: CR: 27% PR: 59%	NR	Mean OS (I) 23 mos (II) 5 mos	Abscess: 4% fHemop: 10%
Goldman et al., 1993 (20)	20	Carcinoma in the bronchus	BT alone: 15 Gy/1# @ 1 cm	SOB: 89% (17/19) Cough: 37% (7/19) Hemop: 100% (6/6) Collapse: 69% (9/13)	CR: 42% PR: 47%	NR	NR	NR
Speiser et al., 1993 (12)	(Total: 342) 47	Curative	(I) EBRT (60 Gy/30#) + IDR (30 Gy/3#)	SOB: 86% Pneumonia: 86% Hemop: 99% Cough: 85%	NR	NR	NR	3% procedure-complications 7.3% fHemop
	144	Palliative	(II) EBRT (37.5Gy/15#) + HDR (30 Gy/3#)					
	151	Recurrent	(III) HDR (22.5 Gy/3#) @ 1 cm					
Bedwinek et al., 1992 (21)	45	Recurrent endobronchial carcinoma	6 Gy/1# @ 1 cm	Overall: 76% (29/38) Cough and hemoptysis: 80% SOB: 71% Atelectasis: 64%	CR: 41% PR: 41%	2-12 mos	Median =6.5 mos	fHemop: 32%
Gauwitz et al., 1992 (22)	24	Recurrent endobronchial cancers	9 Gy/1# @ 1 cm	Overall: 88% (21/24) Reoperation: 83% (15/18)	100%	NR	NR	n=1 min hemop n=1 fHemop

Table 2 (continued)

Table 2 (continued)

Author, year	n	Population	Treatment	Symptomatic response (%)	Size response (%)	FU time	OS (mos)	Toxicity
Mehta <i>et al.</i> , 1992 (23)	66	Endobronchial tumours	(I) LDR: 32 Gy/4# BID x 2 days @ 1 cm (II) HDR: 20 Gy/4# BID x 2 days	Overall: 78% Cough: 68%; SOB: 79%; Pneumonia: 82%; hemop 91%; Chest pain: 73%	78%	Median 6.5 mos	Median =5.5 mos; 1-yr 1%	Fistula 11%
Sutedja <i>et al.</i> , 1992 (24)	31	Recurrent endobronchial stage III lung cancer	10 Gy/1# @ 1 cm	SOB: 82% (18/22)	PR: 72%	NR	PR: 7 mos NR: 3 mos	fHemop 33% Fistula 10%
Burt <i>et al.</i> , 1990 (25)	50	Inoperable symptomatic endobronchial carcinoma	BT alone (15-20 Gy/1#) @ 1 cm (n=1 had EBRT, n=1 had chemo also)	Cough: 50%, SOB: 64%, Hemop: 86%, atelectasis: 33%	88% (15/17)	NR	NR	Asymptomatic PTX (n=1)

A/E, adverse events; BID, twice a day; BT, brachytherapy; chemo, chemotherapy; CI, confidence interval; CRT, chemoradiation; EBRT, external beam radiation; Gy, Gray; mo(s), month(s); fHemop, fatal hemoptysis; n, number of patients; HDR, high-dose rate brachytherapy; Hemop, hemoptysis; KPS, Karnofsky performance status; LDR, low-dose rate brachytherapy; NR, not reported; NS, not significant; NSCLC, non-small cell lung cancer; q, every; OS, overall survival; PD, progression of disease; PDT, photodynamic therapy; PTX, pneumothorax; resp, response; Rx, treatment; SOB, shortness of breath; Sq, squamous cell carcinoma; symp, symptom; wk(s), week(s); *, statistically significant; #, fraction(s); †, among evaluated patients.

Table 3 Retrospective studies evaluating outcomes of patients with lung cancer treated with intraluminal brachytherapy

Author, year	Disease description	N	HDREB/EBR treatment	Median FU (mos)	Med OS (mos)	Toxicity hemoptysis (%)	Toxicity (%)	Turnour resp (%)	Symptom response (%)
Rochet <i>et al.</i> , 2013 (26)	NSCLC inoperable stage I-III ineligible Sx/Chemo	35	EBRT (50 Gy) + BT (15 Gy/3#)	26	NR	fHemop (3%)	Hemoptysis (6%), necrosis (3%)	PR (17%); CR (57%)	NR
Chan <i>et al.</i> , 2011 (27)	Early-stage inoperable NSCLC -> RFA+BT	17	Median 18 Gy/1# (14.4-20 Gy)	22 mos	21/2-yr OS: 53%	NR	PneumoTx (11/17) empyema (1/17) pleural effusion (3/17)	NR	NR
Zaric <i>et al.</i> , 2010 (28)	NSCLC	761	14 Gy/2#	NR	NR	1.1%	5% overall acute A/E; severe hypoxemia (1.7%)	NR	NR
Dagnault <i>et al.</i> , 2010 (29)	Iry and metastatic endobronchial tumours <6 mos survival	81	5 Gy x 4# =20 Gy	NR	14.7	1% (gr 1)	46% bronchitis gr1	60% pCR 42% radial resp	SOB: 85% Hemop: 100% Cough: 77%
Skowronek <i>et al.</i> , 2009 (11)	Advanced endobronchial NSCLC non-curative dz, treated with HDR alone	648	(I) 22.5/3# q1wk (n=303) (II) 10 Gy/1# (n=345)	NR	3.71 mos	NR	NR	CR: 17% PR: 71%	15% at 1 yr
Fortunato <i>et al.</i> , 2009 (30)	Primary and recurrent bronchial tree tumour treated with BT, EBRT, chemo, laser	7	EBRT (30-44 Gy) + BT (5-7 Gy/2-4#)	Mean 17 mos	Mean 54 mos	n=1 (14%) fHemop	Fatal hemoptysis 6 mos post-BT due to necrosis of bronchial wall due to PD n=1-grade 1 dysphagia	6/7 (86%) at 72 h	
Ozkok <i>et al.</i> , 2008 (31)	NSCLC st III and palliative patients	Total: 158 n=43	@ 1 cm (I) NSCLC III: EBRT (60 Gy/30#) + BT (15 Gy/3#) @ 1 cm	NR	Median OS: 11 mos CR: 15 mos NR: 9 mos (P=0.03)	fHemop 4%	Fibrous tracheal malacia (n=1) esophagitis gr 3 (n=3) bronchitis (n=6) (P=0.03)	86%	Cough: 58% SOB: 77% Hemop: 100%
		n=74	(II) EBRT (30 Gy/10#) + BT (15 Gy/2#) @ 1 cm			fHemop 11%	Fibrous tracheal malacia (n=1) bronchitis (n=1)	77%	Cough: 57% SOB: 90% Hemop: 94%
		n=41	(III) recurrent: BT (22.5 Gy/3#) @ 1 cm			fHemop 20%	Bronchitis (n=1)	72%	Cough: 55% SOB: 78% Hemop: 77%
Kubaszewska <i>et al.</i> , 2008 (32)	NSCLC + SCLC	270	8-10 Gy/1#; 22.5/3#	NR	NR	NR	NR	80%	Cough: 77% SOB: 76% Hemop: 92% Pneumonia: 82% Re-aeration: 73%

Table 3 (continued)

Table 3 (continued)

Author, year	Disease description	N	HDRE/EBR treatment	Median FU (mos)	Med OS (mos)	Toxicity hemoptysis (%)	Toxicity (%)	Tumour resp (%)	Symptom response (%)
Zorlu <i>et al.</i> , 2008 (33)	Recurrent endoluminal NSCLC	21	Palliative EBRT then BT (10 Gy/1# (n=9) and 15 Gy/1# (n=12) @ 1 cm	NR	5.5 mo (range, 4-12 mo)	fHemop 5%	Intrabronchial edema (5%)	NR	SOB: 71% Hemop: 80%
Mallick <i>et al.</i> , 2006 (34)	Endobronchial, NSCLC, Stages III	All: 95 n=65 n=15 n=15	EBRT (30 Gy/10#) EBRT (30 Gy/10#) + 10 Gy/1# @ 1 cm BT 15 Gy/1#	8 mos	10 mos	0%	No other	61% reduction in obstruction score	SOB: 93% Cough: 81% Hemop 97% Obstructive pneumonia: 91%
Allison <i>et al.</i> , 2004 (35)	NSCLC endobronchial recurrence	10	18/3#	NR	10.5	NR	NR	NR	NR
Magne <i>et al.</i> , 2003 (36)	Pall+curative	31	LDR (n=13) + HDR (n=18) HDR: 36/6# LDR: 21/3#	3.5 yrs	23 mos	16% severe Hemop	22.5%; 6%=PTx 31% stenosis	NR	NR
Gejerman <i>et al.</i> , 2002 (37)	Locally advanced or metastatic lung cancer	33	15/3# q1wk + EBRT (37.5 Gy/15#)	12 mos	Med 5.2 mos	NR	64% odynophagia-fluconazole	54%	72%
Celebioglu <i>et al.</i> , 2002 (38)	Inoperable lung cancer	95	22.5/3# vs. 20/2#	Mean 7.5 mos	NR	3%-Admission	3% (hemoptysis only)	NR (but significant improvement)	NR (but significant improvement)
Harms <i>et al.</i> , 2000 (39)	(I) prior Rx; (II) palliative new; max 3 cm periluminal extension NSCLC	55	(I) BT: 5-27 Gy (med=20); (II) 10-20 Gy (med=15)	12.6 mos	Med A1: 5 mos B1: 20 mos	0% (from DP only)	A: 0% B: 6% gr 1-2. no gr 3-4	A1: CR+PR 53% B1: 77%	NR
Kelly <i>et al.</i> , 2000 (38)	Recurrent/mets, MD Anderson	175	BT alone: 30 Gy/2#	NR	Mean 6 mos	5% fHemop	11%	78%	66% (32% much improved; 34% slight improved)
Hennequin <i>et al.</i> , 1998 (39)	Biopsy proven bronchial malignancies (SCLC 2%, Sq 88%, prior EBR 75%)	149	Mostly @ 1 cm (range, 0.5-1.5 cm)	NR	NR	7.4%	NR	NR	NR
Taulelle <i>et al.</i> , 1998 (40)	Stages I-IV lung cancer, 90% with symptoms of endobronchial disease (SCLC 6%), Sq 84%, WHO ≥2 53%, prior EBR 62%	189	6-10 Gy @ 1 cm q1w x 2-6	NR	NR	Massive hem 7%	NR	NR	74%

Table 3 (continued)

Table 3 (continued)

Author, year	Disease description	N	HDRE/EBR treatment	Median FU (mos)	Med OS (mos)	Toxicity hemoptysis (%)	Toxicity (%)	Tumour resp (%)	Symptom response (%)
Delclos et al., 1996 (41)	Recurrent endobronchial	81	15 Gy x 2# (30 Gy) @ 6 mm	NR	NR	NR	n=2 grade 5 (fistula and tracheal malacia)	NR	Total=84% 32%=excellent 31%=moderate 21%=minimal median Duration=4.5 mos NR
Macha et al., 1995 (42)	Recurrent bronchial carcinoma, Sq 65%, SCLC 9%, majority had prior EBR	365	5 Gy @ 1 cm x 3 (G1) or x 4 (G2) q2w	NR	NR	NR	NR	NR	NR
Gollins et al., 1994 (43)	Inoperable, primary endobronchial or endotracheal, Sq mostly palliative, some curative	406	Group 1 N=324 (80%) previously no-RT -> 1x BT (I) n=218; 1x BT (II) n=106; further EBRT/BT Group 2 (n=65); prior EBRT, now treated with BT Median= 15 Gy/1# (10-20 Gy) qd @ 1 cm Group 3: EBRT (30/8#-50/16#) + BT	NR	Med OS: 5.8 mos 2-yr: 7.2% 5-yr: 1%	fHemop 7.9%	Worsening SOB 5% removing of necrotic debris 0.2%	NR	@ 6 wks: GROUP 1: 92% stridor 88% hemoptysis 62% cough 60% SOB 50% pain 46% atelectasis GROUP 2: 75% stridor 88% hemoptysis 55% cough 52% SOB 60% pain 7% atelectasis
Chang et al., 1994 (44)	Primary lung cancer curative/palliative	76	Median 7 Gy x3# (21 Gy) @ 1 cm if curative, add EBRT 60-70 Gy if pall, add EBRT 20-59 Gy	Mean 7.8 mos	Mean 5 mos	4% fHemop (BT same week as EBRT) 1% mild hemop	4% pneumonitis-steroid 3% mod esoph	CR 35% PR 52% (87% overall)	95% hemoptysis 79% cough 87% SOB 88% post-obs pneumonia

A/E, adverse events; BID, twice a day; BT, brachytherapy; chemo: chemotherapy; CI, confidence interval; CRT, chemoradiation EBRT, external beam radiation; Gy, Gray; mo(s), month(s); fHemop, fatal hemoptysis; n, number of patients; HDR, high-dose rate brachytherapy; Hemop, hemoptysis; KPS, Karnofsky performance status; LDR, low-dose rate brachytherapy; NR, not reported; NS, not significant; NSCLC, non-small cell lung cancer; q, every; OS, overall survival; PD, progression of disease; PDT, photodynamic therapy; PTX, pneumothorax; resp, response; RFA, radiofrequency ablation; Rx, treatment; SOB, shortness of breath; Sq, squamous cell carcinoma; symp, symptom; Sx, surgery; wk(s), week(s); *, statistically significant; #, fraction(s)

and fatal hemoptysis rate was lower (12% *vs.* 18%), although it did not reach statistical significance. Niemoeller *et al.* attributed the difference in the results to a higher irradiation dose per fraction. It is also possible that the larger sample size of Niemoeller's cohort and the difference in the randomization method—performance status in each group was not described and not accounted for—may explain these different findings.

More prospective randomised studies are needed to establish the optimal dose and fractionation can give the best palliation with minimal toxicity in advanced lung cancer.

ILBT-related toxicities

Acute toxicities

One of the most attractive characteristic of ILBT is its sharp dose fall-off curve. It is thus not surprising that its acute toxicities are relatively limited. Although acute bronchitis or pneumonitis has been reported in up to 46% of patients treated (10,31,43), these episodes were usually self-limited or readily treated with inhaled bronchodilators or steroids. Incidences of rapid necrosis of tumours sometimes requiring bronchoscopic removal of the debris have been reported in up to 5% of cases (26,43); patients generally improved after the procedure. Small risks of procedure-related complications such as pneumothorax, infection, empyema and abscess has been reported in up to 6% of cases (12,19,36,45).

Long-term toxicities

The most significant long-term toxicities include fibrosis causing stenosis, fistulisation and fatal hemoptysis.

Rates of bronchial fibrosis causing stenosis range from 2-56% (31,36,45). In most, patients are asymptomatic or minimally symptomatic thus not requiring any intervention. Fistulisation is a more significant complication, as it may lead to uncontrolled infections that may be fatal, albeit these are rare occurrences (41). Rates of fistula are relatively rare, ranging from 1-11% and were not fatal in most series (10,15,16,23,46).

One of most significant toxicity from ILBT consists of hemoptysis that may be fatal. It can occur as soon as a few weeks after ILBT and as late as almost 1 year post-ILBT. Rates of fatal hemoptysis are highly variable and in some series, can be up to 19-33% (7,21,24,31). Ornelas *et al.* (9) suggested that prior laser treatments increased the risk of fatal hemoptysis. Dose prescription point is important in

preventing fatal hemoptysis although this has not been tested in a clinical setting. Hemoptysis also occurs due to disease progression and invasion of blood vessels by tumour and not necessarily from ILBT. In most series, incidences of massive hemoptysis ranged between 2-10% and were almost invariably fatal.

Role of ILBT alone or in conjunction with other modalities in a radical setting

While the most common use of ILBT remains in a palliative setting, small series have reported outcomes of patients treated with EBBT either alone or as a boost to EBRT alone, as shown in *Table 4*.

Kawamura *et al.* (48) have previously reported outcomes of 13 patients with small endobronchial squamous cell carcinomas treated with EBRT and ILBT or ILBT alone. The median ILBT dose was 20 Gy in four fractions and 25 Gy in 5 fractions, respectively. The median dose was 45 Gy (range, 40-61 Gy), delivered at 2 Gy/fraction. The 2-year overall survival (OS) and 2-year LC were 92% and 86%, respectively. The 2-year LC was slightly higher for patients treated with EBRT-ILBT compared to ILBT alone (89% *vs.* 80%). One patient who experience airway stenosis causing cough (n=1/13) and another patient experience dyspnea grade 3 after treatments.

Perol *et al.* (45) reported prospective data on outcomes of 18 patients treated with ILBT alone with a dose escalation scheme from 21 to 35 Gy, prescribed at 1cm from the source axis and delivered at 7 Gy per fraction, weekly. The 2-year LC and OS rates were of 75% and 58%, respectively. Moreover, two patients developed major necrosis of their bronchial wall and two patients died after an episode of fatal hemoptysis. When comparing these results to those of patients treated with stereotactic body radiotherapy in other studies (49), patients treated with ILBT had a lower LC and OS rates. Furthermore, the occurrences of fatal toxicities were relatively high. Further studies are needed to evaluate the role of ILBT in a curative setting. Until further evidence is available, ILBT should be used on a case-by-case basis, and offered only when other better-established treatments such as surgery or stereotactic body radiotherapy have been deemed not feasible.

Fernando *et al.* (50) have reported outcomes of 224 high-risk operable patients with T1-3N0 NSCLC treated with sublobar resection with or without intraoperative brachytherapy (IOBT). The primary endpoint of this study was to assess whether IOBT improved local recurrence

Table 4 Studies describing outcomes of patients treated with brachytherapy with a curative intent

Author (study)	n	Tumour	Treatments	FU (mos)	LC (%)	Tumour resp	Sympt resp	OS (%)	Acute A/E	Long-term A/E
Anacak <i>et al.</i> , 2001 (47) (P)	30	NSCLC stage III	60 Gy + 15 Gy/3#	NR	Median locoregional-free survival: 9 mos	NR	Cough: 43% SOB: 80% Hemop: 95% Chest pain: 88%	Median 11 mos	Bronchitis (70%), esophagitis (6%)	Bronchial fibrosis (25%), esophageal fibrosis (13%), fHemop (11%)
Perol <i>et al.</i> , 1997 (45), pilot study (P)	18	NSCLC <1 cm, exclusive endobronchial involvement (no disease on CT-scan in lung/LNs) with C/A to other therapies	(I) 7 Gy × 3# (21 Gy) (II) 7 Gy × 4# (28 Gy) (III) 7 Gy × 5# (35 Gy) q1wk # @ 1 cm	Mean 28 mos	75%	pCR 83%	NR	1-yr: 78% 2-yr: 58%	n=1 fatal hemoptysis n=1 slight PTx (undrained) n=1 bronchial infection	• Asymptomatic partial fibrous stenosis 10/18 (56%) • n=2 major necrosis of bronchial wall • n=2 fHemop
Kawamura <i>et al.</i> , 2012 (48) (R)	13	SCC endobronchial ca'a <2 cm Roentgenographically occult early endobronchial cancer	n=10: EBRT (median = 45 Gy/22#, range, 40-61 Gy/18-30#) + BT [5 Gy × 4=20 Gy (median)] n=6: BT alone (median 5 Gy × 5=25 Gy/wk	Median 32.5 mos	86% BT alone =80% EBRT + BT =89%			2-year OS 92%	(1/13) SOB grade 3 0% hemoptysis causing cough grade 2	

A/E, adverse event; BT, brachytherapy; C/A, contraindications; EBRT, external beam radiotherapy; fHemop, fatal hemoptysis; FU, follow-up; LC, local control; n: number of patients; mos, months; NR, not reported; NSCLC, non-small cell lung cancer; OS, overall survival; (P), prospective study; PTx, pneumothorax; (R), retrospective study; resp, response; SCC, squamous cell carcinoma; SOB, shortness of breath; sympt, symptom; wk, week; #, fraction.

rates or not. The dosimetry goal of IOBT was to deliver 100 Gy at 5-7 mm along the central axis of the resection margin. IOBT did not reduce local recurrence rates or time to recurrence (HR 1.01; 95% CI 0.51-1.98, P=0.98) nor did it improve 3-year OS rates (71% vs. 71%, P=0.97)

In summary, the role of ILBT in curative treatments remains investigational. Its use alone to treat radically endobronchial tumours is not well established and should not be routinely practiced other than in a clinical trial or if the patient is unsuited for surgery/radical chemoradiation due to any reason. ILBT may be considered either as a boost for endoluminal tumours or post-operatively, if they are not candidates for EBRT. These treatments should be delivered within a clinical trial to document outcomes of these patients.

Conclusions

In conclusion, the current evidence mainly supports the use of ILBT in a palliative setting mostly in combination with other treatments modality, such as EBRT (most commonly) and Nd-YAG laser. When delivered with EBRT, it improves rates of lung re-oxygenation and LC without significantly increasing toxicities. Its role in a radical setting remains investigational. Further studies are required to determine the optimal dose fractionation scheme.

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