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BRACHYTHERAPY

Brachytherapy 14 (2015) 655–661

A prospective analysis of high-dose-rate endobronchial brachytherapy in the palliation of obstructive symptoms in lung cancer patients: A single-institution experience

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ABSTRACT

PURPOSE: Obstructive symptoms that affect quality of life (QOL) are commonly caused by endobronchial disease in many patients with locally advanced, inoperable lung cancer. High-dose-rate endobronchial brachytherapy (HDREBBT) has been used to palliate these symptoms, yet its role is not well defined in the literature.

METHODS AND MATERIALS: Ninety-eight patients with locally advanced, inoperable lung cancer received HDREBBT. They were prospectively followed for survival, QOL, and toxicity endpoints. QOL measures were captured using the Quality of Life Questionnaire–Lung Cancer 30 and –Lung Cancer 13.

RESULTS: At 1-year follow-up, no significant toxicities were seen. Overall survival was 13.4% at 12 months (mean 192 days). Performance status, additional treatment after HDREBBT and treatment intent affected overall survival on univariate analysis ($p < 0.05$). Mean hemoptysis-free survival for all patients was 232.3 days, cough-free survival was 140.3 days, and dyspnea-free survival was 173.5 days. There was no impact of any treatment- or patient-related factors of these outcomes on multivariate analysis, including additional treatment modalities and HDREBBT dose.

CONCLUSIONS: HDREBBT is a safe and effective way to palliate endobronchial symptoms. Additional external-beam radiation therapy, chemotherapy, or chemoradiation after HDREBBT improves survival, but does not affect QOL measures.

Key words: Lung cancer; Brachytherapy; High dose rate; External radiation; Palliation; Symptom-free survival

Introduction

Lung cancer is one of the most common cancers in Canada. It remains the most common cause of cancer death for both sexes (1). Minimal gains in survival rates have been made over the past few decades, with 5-year survival remaining less than 20% (1). Thirty to 40% of patients are inoperable or have metastatic disease at diagnosis (2). In patients who undergo curative resection, 50% develop recurrent disease within 5 years (2). Patients who undergo radical management with concurrent chemoradiotherapy (CRT) relapse within the irradiated field more than 55% of the time (3). Half of patients with lung cancer will ultimately develop symptomatic endobronchial involvement due to their disease (4). These patients present with typical obstructive symptoms of cough, dyspnea, hemoptysis, and postobstructive pneumonitis that affect quality of life (QOL). Previous irradiation could preclude the opportunity for palliative external-beam radiation therapy (EBRT) due to dose constraints of nearby organs at risk.

Alternative interventions for obstructive symptoms include laser photocoagulation, cryotherapy, photodynamic therapy, stenting, low-dose-rate brachytherapy, and high-dose-rate endobronchial brachytherapy (HDREBBT). A randomized study to compare these modalities closed early due to failure to accrue patients (5).

HDREBBT is an ideal approach given the ability to deliver potentially tumoricidal doses in few fractions with short treatment times and low dose to organs at risk. Although HDREBBT has been in practice since the

Received 21 March 2015; accepted 15 April 2015.

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1538-4721/$ - see front matter
http://dx.doi.org/10.1016/j.brachy.2015.04.005

1920s (6), advances in technology such as the flexible fiberoptic bronchoscope and remote HDR afterloading have made it safer, faster, and more effective. However, mainstream use of this technique is limited to specially trained radiation oncologists, access to a shielded brachytherapy suite, and appropriate multidisciplinary resources. Moreover, the optimal role for HDREBBT in radical or palliative settings is not well defined in the literature.

At the Juravinski Cancer Centre in Hamilton, Ontario, the HDREBBT program was initiated in 2005. Since that time, more than 600 patients have been treated in the definitive or palliative setting. Between 2005 and 2006, eligible patients undergoing HDREBBT were prospectively followed for QOL measures and survival endpoints. This report represents a prospective analysis of 98 patients with at least 1-year follow-up.

Materials and methods

Inoperable patients with endobronchial disease on bronchoscopy or imaging and obstructive symptoms were eligible for HDREBBT. Patients were followed every 3 months, or earlier if indicated. QOL data were assessed at baseline and at follow-up visits using the Quality of Life Questionnaire−Lung Cancer 30 and −Lung Cancer 13 (7, 8). Treatment toxicity was assessed by the radiation oncologist during follow-up. Bronchoscopies were not performed to assess response unless specifically indicated by patient symptoms. All patients were followed for at least 1 year with institutional review board approval.

Patients were premedicated with topical Xylocaine and sedated with intravenous fentanyl and midazolam. Flexible fiberoptic bronchoscopy was undertaken orally or at times nasally by a respirologist to visualize the tumor. Flexible plastic catheters were inserted into the bronchi adjacent to and beyond the tumor under bronchoscopic and fluoroscopic vision. The number of catheters used varied depending on tumor size and location with the intent of encompassing the entire intraluminal visualized tumor and optimizing dose distribution. The bronchoscope was subsequently withdrawn, leaving only the catheter in situ. A marker wire with a centimeter scale was inserted into the catheter for precise treatment delineation under fluoroscopic vision. Fluoroscopy was used and orthogonal films were taken to image and confirm catheter placement, as well as to delineate the target volume. The plans were created in real-time using the BrachyVision Treatment Planning system (Varian, Palo Alto, CA, USA). A usual dose of 7 Gy (range 5−10 Gy) was prescribed to 1 cm from the source axis for tumors in the mainstem bronchus or 0.5 cm from the source axis for tumors in segmental bronchi. The VariSource (Varian, USA) HDR afterloader was used to place an Iridium-192 source at 0.5-cm dwell positions. The patient's cardiorespiratory status was closely monitored throughout. After the treatment, the catheter (or catheters) was removed and the patient was monitored in a recovery room for approximately 1 hour before discharge. Brachytherapy dose and fractionation was determined based on American Brachytherapy Society Recommendations. Treatment parameters used, including dose and fractionation, are described in Table 1. Multiple fractions were scheduled at 1-week, and less often 2-week, intervals. Brachytherapy was not given concurrently with EBRT or chemotherapy. Patients undergoing subsequent chemotherapy treatments were given a 2-week break between modalities.

Survival, QOL, and toxicity data were collected in a prospective fashion over the follow-up period. Survival was defined as time from first consultation to death. Specific symptom-free survival was defined as time from first brachytherapy insertion to symptom return or progression. Statistical analysis of the data was done using the SAS Statistics software (SAS Institute, Cary, NC). Kaplan-Meier curves were compared using the log-rank test. Multivariate and univariate analyses were done using the Cox proportional hazards model. Ethics approval for the study was obtained from the Hamilton Integrated Research Ethics Board.

Results

The mean age was 69 years (range 47−89 years). Most patients had poor performance statuses with comorbidities, such as smoking, coronary artery disease, congestive heart failure, and chronic obstructive pulmonary disease. Baseline patient characteristics are described in Table 2. Presenting symptoms are presented in Table 3.

Most patients (78%) were treated for newly diagnosed disease, whereas 22% of patients had disease recurrence.

Table 1
High-dose-rate endobronchial brachytherapy treatment parameters

	Treatment parameter	N
Catheters used per patient	1	33
	2	49
	3	14
	4	2
Total dose given, Gy	5	1
	7	12
	10	1
	14	44
	15	1
	18	2
	21	36
	28	1
Dose per fraction, Gy	5	1
	6	2
	7	93
	7.5	1
	10	1
Number of fractions used	1	14
	2	45
	3	38
	4	1

Table 2
Baseline characteristics of patients treated with HDREBBT

Patient characteristics	Numbers
Age	Mean 69.41 (range, 47–89)
Sex, M:F	54:44
Smoking, nonsmokers:smokers	5:93
KPS, <50:50–70:>70	33:40:25
Cardiac comorbidity, none:present:unknown	43:54:1
Lung comorbidity, absent:present	68:30
Histology, NSCLC:SCLC:metastatic	93:4:1
Side, left:right:central:unknown	31:62:1:4
Lobe, upper:middle:lower:unknown	34:32:28:4
New diagnosis:recurrent disease	76:22
Therapy before HDREBBT, no:yes	70:28
Previous treatment, EBRT:C:CRT:S	11:4:7:6
Treatment received on study, HDREBBT only:HDREBBT and EBRT:HDREBBT and CRT:HDREBBT and C	52:34:6:6

M = male, F = female, KPS = Karnofsky Performance Score, HDREBBT = high-dose-rate endobronchial brachytherapy, EBRT = external-beam radiation therapy, CRT = chemoradiotherapy, S = surgery, NSCLC = non–small cell lung cancer, SCLC = small cell lung cancer.

Fifty-three percent of patients received HDREBBT alone. All treatments received before or subsequent to HDREBBT are described in Table 2. EBRT given alone was given as 30 Gy in 10 fractions. Patients who received CRT were treated to radical doses, 60 Gy over 30 fractions. No significant toxicities were seen regardless of treatment received.

Survival

Overall survival (OS) was 13.4% at 12 months, with a mean survival of 192 days. The impact of 10 prognostic markers, including sex, age, smoking history, performance status, presence of pulmonary or cardiac comorbidities, tumor location, HDREBBT dose, additional treatments after HDREBBT, treatments before HDREBBT, and treatment intent, were assessed. On multivariate analysis, higher performance status ($p = 0.04$; hazard ratio [HR] 0.831, confidence interval [CI] 0.696–0.992), absence of cardiac comorbidities ($p = 0.0008$, HR 0.379, CI 0.216–0.668), and tumor site (right-sided as compared with left-sided) ($p = 0.0056$, HR 1.673, CI 1.16–2.41) impacted positively on OS. On univariate analysis, only higher performance status ($p = 0.002$), additional treatment after HDREBBT ($p = 0.027$), and treatment intent ($p = 0.0153$) impacted positively on OS.

Table 3
Distribution of presenting symptoms

Symptom	Grade 1	Grade 2	Grade 3	Grade 4	Unknown
Cough	21	22	41	13	1
Hemoptysis	50	17	15	15	1
Dyspnea	14	27	32	24	1
Pain	67	18	10	2	1

Mean survival was not impacted by treatment received *before* HDREBBT. However, mean survival was significantly longer if patients received EBRT, chemotherapy, or CRT *after* receiving HDREBBT ($p = 0.027$), or whether treatment intent was radical (i.e., dose of an additional 60 Gy of EBRT) vs. palliative ($p = 0.0153$) (Fig 1 and Supplementary table 1).

QOL measures

Mean hemoptysis-free survival for all patients was 232.3 days, cough-free survival was 140.3 days, and dyspnea-free survival was 173.5 days. No impact of any treatment- or patient-related factors on these outcomes was detected on multivariate or univariate analysis. Unlike the effect seen on OS, the addition of EBRT, chemotherapy, or both after HDREBBT did not improve these QOL outcomes ($p > 0.05$) (Fig 2). Symptom-free survival for hemoptysis, cough, and dyspnea for patients who presented with the respective symptoms is described in Table 4 according to treatment received.

Discussion

HDREBBT has been shown to result in rapid and sustained palliation of endobronchial symptoms, objective improvements in bronchoscopy findings (9, 10), spirometric indices, radiographic findings, and exercise tolerance (11). Although the advantages of this technique are well received in clinical practice, it lacks the benefit of robust, randomized controlled trials. Most published series are retrospective with small sample sizes of heterogeneous groups of patients. A wide array of dose and fractionation schedules is seen in published case series, complicating interpretation of the literature. Studies have attempted to determine the optimal dose and fractionation but have largely found no significant difference between regimens (9, 12, 13), yet suggestion of a dose response for toxicity and local control has been made (14, 15). Additionally, the role of HDREBBT as a boost has been explored but the results have been mixed (9, 12, 14,16–21). Lastly, there is variation among trials regarding whether EBRT and

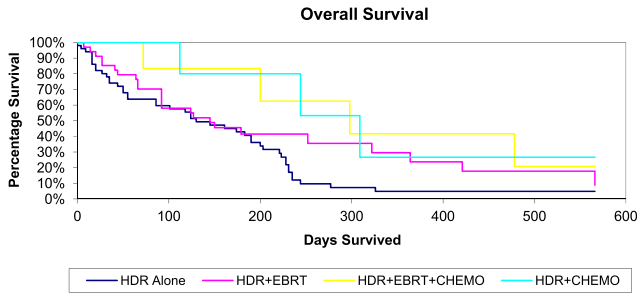

Fig. 1. Kaplan-Meier curves for overall survival by treatment received. HDR = high-dose-rate endobronchial brachytherapy, EBRT = external-beam radiation therapy, CHEMO = chemotherapy.

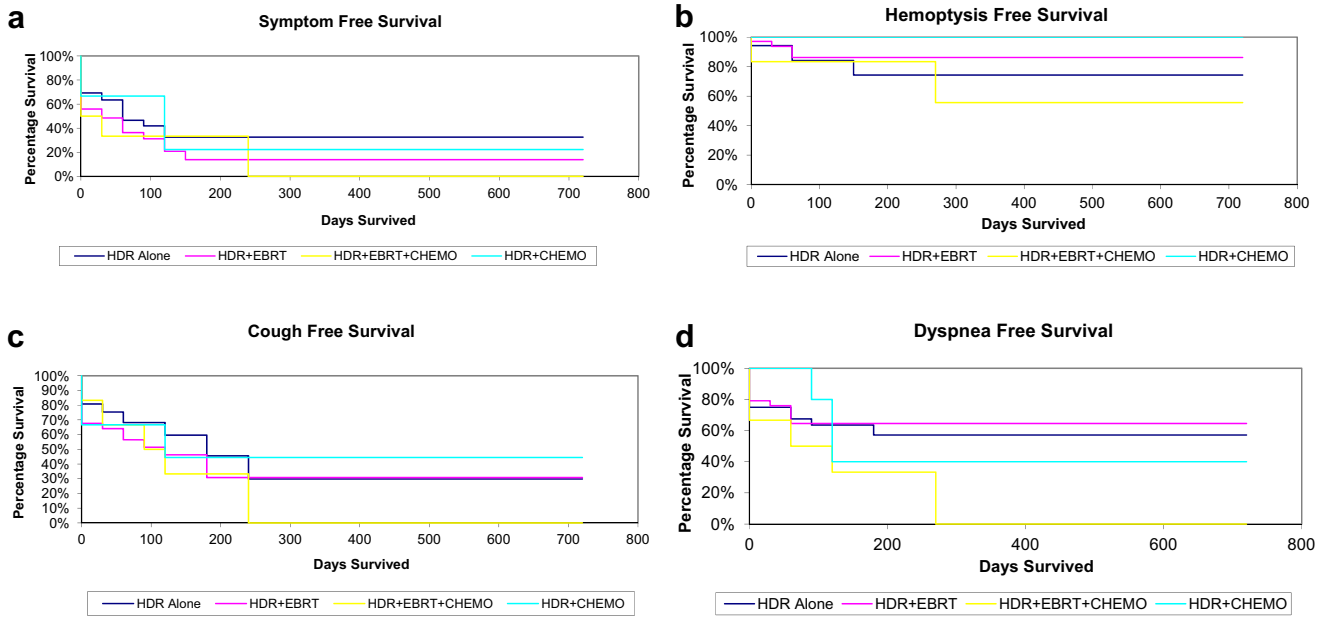

Fig. 2. Kaplan-Meier curves: symptom-free survival (a), hemoptysis-free survival (b), cough-free survival (c), and dyspnea-free survival (d) by treatment. HDR = high-dose-rate endobronchial brachytherapy, EBRT = external-beam radiation therapy, CHEMO = chemotherapy.

HDREBBT is given concurrently or sequentially. Although the role of EBRT has long been established by prospective trials in radical and palliative lung cancer treatment (22), with a modest advantage for survival and duration of palliation over HDREBBT (17), previous irradiation in recurrent patients often precludes further EBRT.

Our center has adapted the use of HDREBBT for symptomatic endobronchial disease in the upfront setting for inoperable patients who might then go on to receive definitive CRT, or more commonly, in the palliative setting. Palliative EBRT may also be used depending on the patient's symptomatology and extrabronchial disease burden. In this study, the vast majority of patients were previously untreated and received primarily HDREBBT alone, allowing for an assessment of the contribution of this technique to symptom palliation and survival.

OS was 13.4% at 12 months, consistent with previously published reports of heterogeneous patient populations (23). On both multivariate and univariate analysis, higher performance status and additional treatment after HDREBBT significantly influenced OS, with patients who received chemotherapy surviving longest. This has been well established; compared with best supportive care, chemotherapy improves survival in patients with metastatic or recurrent non–small cell lung cancer (24). Higher performance status would predict for a greater likelihood of patient eligibility for chemotherapy; thus, these findings cannot be considered separately. Patients who receive additional treatments after HDREBBT represent a select group of patients in better overall condition who are more likely to do better regardless.

In a study by Langendijk *et al.* (18), median survival was found to be similar in patients who received EBRT alone or EBRT with concurrent HDREBBT. However, we report that additional treatment, including EBRT, was associated with improved OS. This difference may be because, at our center, EBRT is not given concurrently with HDREBBT. EBRT when used is given before or subsequent to HDREBBT, making it difficult to directly compare trials. Additionally, concurrent EBRT and HDREBBT may result in added toxicity that has not yet been studied, which could account for the effect on survival seen in the study by Langendijk *et al.* (18).

HDREBBT dose was not found to affect survival or QOL on multivariate or univariate analysis in our patients. This is consistent with previously published data (12, 13, 25).

HDREBBT palliation of QOL measures was found to be effective and sustained at approximately 4 to 5 months. No treatment or patient-related factors were found to affect these outcomes on multivariate or univariate analyses. Similarly, in one of the larger studied cohorts of HDREBBT only, Gollins *et al.* (23) report a sustained

Table 4
Quality of life survival

Treatment	Hemoptysis-free survival, d	Cough-free survival, d	Dyspnea-free survival, d
HDREBBT alone	132.26	159.38	122.43
HDREBBT and EBRT	57.23	99.66	171.63
HDREBBT and C	225	80	114
HDREBBT and CRT	-	120	120

HDREBBT = high-dose-rate endobronchial brachytherapy, EBRT = external-beam radiation therapy, C = chemotherapy, CRT = chemoradiotherapy.

response of QOL measures at 4 and then 12 months. They too did not find any difference in degree of palliation achieved by dose (23).

Speiser and Spratling (9) and Zajac *et al.* (26) reported little to no palliative benefit of HDREBBT in patients with poor performance status, apart from relief of hemoptysis. Performance status was not found to affect any of the QOL outcomes on multivariate or univariate analysis in our series. Furthermore, HDREBBT was performed safely despite a large proportion of patients having poor performance statuses (Karnofsky Performance Status <50).

Similar to other series, the greatest magnitude and durability of response to HDREBBT was seen for hemoptysis (9, 13, 21, 23, 25, 27, 28). Other obstructive symptoms of cough and dyspnea are also related to premorbid conditions (chronic obstructive pulmonary disease, cardiac morbidity, smoking) commonly seen in this patient population.

Additional treatment modalities did not affect QOL measures. In the only published randomized trial Mallick *et al.* (20) report that palliation was similar when comparing EBRT concurrent with HDREBBT, vs. HDREBBT alone. However, palliation of hemoptysis favored the combined modality approach. Few nonrandomized trials have attempted to answer this question, and results have been mixed (21, 23, 29). Although a trend toward improved dyspnea-free survival was noted in our patients favoring HDREBBT and EBRT, this did not reach statistical significance. The trend favored HDREBBT alone for hemoptysis and cough-free survival. It is difficult to make direct comparisons across trials given differences in palliation endpoints (i.e., symptom-free survival vs. response rate), varying dose/fractionation and treatment regimens, and small sample sizes. Our trial was not powered to detect differences between these groups.

QOL outcomes were measured using the Quality of Life Questionnaire−Lung Cancer 30 and −Lung Cancer 13, which have been specifically validated in our unique patient population (7). Few other studies have used these (18, 20, 21). In our experience, these are effective and reproducible tools for this population.

HDREBBT complications of fatal hemoptysis (10,13−15, 18, 20, 23, 25,29−31), bronchitis (9, 13, 31, 32), stenosis (10, 14, 31), pneumothorax (25, 31), necrosis (14, 31), and fistulas (10, 13, 14, 18) have been reported in the literature. No significant toxicities were seen in our patients at 1-year follow-up. Similarly, Sur *et al.* (33, 34) previously reported no complications in patients treated with HDREBBT. Fatal hemoptysis, in particular, has sparked much debate within the literature due to the dramatic nature of the outcome as well as the wide range of reported incidence (0% (35) to 50% (36)). We therefore would be remiss to not consider this in a discussion of our results.

The underlying cause of complications after HDREBBT pertains to the large variation in diameter of the lumen as one moves distally within the airway and the variable position of treatment catheters (37). Bedwinek *et al.* (38) demonstrated that when a source is inserted through a curved catheter, the dose at 1 cm from the source at the mid portion of the curved path is greater than the intended dose on the concave side and considerably colder on the convex side. The true prescription is achieved only when the source travels through a linear path. Subsequently, they reported 12 occurrences of fatal hemoptysis coinciding with curved pathways anatomically placed under pulmonary arteries. Marsiglia *et al.* (39) suggest that the use of multiple catheters allows for better dose distribution to the tumor and less dose to the endobronchial mucosa, resulting in fewer late complications. An Italian series reported that prescribing to 0.5 cm as opposed to 1.0 cm from the central axis resulted in less radiation bronchitis events (13). Dose optimization can be accomplished by using various prescription points, multiple catheters, and real-time planning. A prescription point at 1 cm is appropriate in the main stem bronchi; however, as the lumen diameter decreases within the segmental bronchi, prescribing to 0.5 cm reduces high dose to the bronchial wall reducing severe complications.

The integrity of reported incidences of fatal hemoptysis is influenced by small sample sizes, difference in HDREBBT dosing/fractionation, use with concurrent EBRT or laser therapy, as well as potential loss of follow-up for patients treated in a specialty center but followed thereafter in the community. These variables make it difficult to tease out the exact relationship between HDREBBT and fatal hemoptysis. One must also consider whether this fatal outcome is a result of an intervention or disease progression. Although the latter has been suggested in some series (17, 20, 21, 29, 32, 40), lack of consistent autopsy, radiologic, and pathologic investigations makes this theory difficult to evaluate. Two randomized trials and a matched-pair analysis found no difference in fatal hemoptysis with the addition of HDREBBT to EBRT as compared with EBRT alone (16, 18, 19), adding to the argument that fatal hemoptysis is related to disease progression as opposed to HDREBBT.

The Manchester group's series of 406 patients treated with HDREBBT represents the largest published experience. Fatal hemoptysis occurred in 7.9% of patients and they demonstrated dose greater than 15 Gy, previous laser therapy, second HDREBBT, and possibly concurrent EBRT were significantly associated with massive hemoptysis (15). Ozkok *et al.* (29) also found that radiobiological equivalent dose and number of HDREBBT fractions prognosticated for fatal hemoptysis. Speiser and Spratling (32) reported high-grade stenosis and bronchitis in patients treated with HDREBBT concurrent with EBRT. Most of our patients received fractionated HDREBBT with lower dose per fraction, no treatment was given concurrently with EBRT, and laser therapy was not used. In this largest analysis by the Manchester group, fatal hemoptysis occurred between 9 and 12 months, suggesting our follow-up period was sufficient to identify this adverse event.

Conclusions

HDREBBT is a safe and effective form of palliation for symptomatic endobronchial lesions. The procedure was well tolerated despite poor performance status and cardiorespiratory comorbidities. Although additional EBRT, chemotherapy, or CRT after HDREBBT increases patient survival, it does not significantly affect respiratory QOL measures. There is ongoing uncertainty regarding the optimal dosing, fractionation, and adjunctive treatments to best optimize the palliative effects of HDREBBT while minimizing severe complications. Our series represents one of the larger series within the literature that confirms the role of HDREBBT in durable palliation of this patient population.

Supplementary data

Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.brachy.2015.04.005.

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