

High dose rate endobronchial brachytherapy for the management of non-small cell lung cancer with an endobronchial or peribronchial component

Review Article

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Abbreviations: Complete response, (CR); external beam radiation, (EBRT); high dose rate, (HDR); high-dose-rate endobronchial brachytherapy, (HDREB); intermediate dose rate, (IDR); low dose rate, (LDR); non-small cell lung cancer, (NSCLC); partial response, (PR)

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Summary

The primary aim of this study was to determine whether a dose response exists for bronchial obstruction caused by non-small cell lung cancer (NSCLC) when treated with increasingly higher radiation doses delivered by a combination of external beam radiation (EBRT) and high-dose-rate endobronchial brachytherapy (HDREB). The secondary aim was to document the tolerability of EBRT combined with HDREB. Thirty patients with medically inoperable or surgically unresectable non-small cell lung cancer were treated in this phase I/II study with both EBRT and HDREB. All patients had a peribronchial or endobronchial component with bronchial obstruction of 50% or more on clinical examination. EBRT was delivered via megavoltage photons at standard fractionation schedules to a total dose of 66 Gy. The HDREB was delivered using the Nucletron HDR remote after loading unit with a 10 Ci Ir-192 source. Each treatment of HDREB was delivered at 1 cm depth. The first group of 10 patients received 3 treatments of HDREB at 7 Gy per fraction. The second group of 10 patients received 3 treatments of 8 Gy per fraction. And the last group of 10 patients received 3 treatments of HDREB of 9 Gy per fraction. HDREB was delivered once weekly. Improvements of obstructions and acute adverse reactions were evaluated for each group of patients before escalating to the next higher-level dose level of HDREB. The median follow-up time for all 30 patients was 14.5 months. The median survival for all 30 patients was 13 months (Range 1 month to 38 months). There was no significant difference of survival among the 3 groups. Complete response or partial response of bronchial obstruction was seen in 60% of patients in Group 1 compared to 90% of patients in both group 2 and 3 (p=0.05). One patient in Group 1 and one patient in Group 3 developed grade IV toxicity, and 1 patient in Group 2 developed grade III toxicity. HDREB of 27 Gy in 3 divided weekly treatments following 66 Gy of external beam radiation is well tolerated for the treatment of NSCLC. A statistically significant dose response for bronchial obstruction from NSCLC is seen when treating with the combination of EBRT and HDREB beyond 24 Gy.

I. Introduction

Radiation is an effective treatment modality in the management of locally advanced non-small cell lung cancer (NSCLC), both in definitive or palliative settings.

The dose of external beam radiation is usually limited to 60-70 Gy due to the surrounding critical normal structures in the treatment field (Dosoretz et al, 1993; Hernandez et al, 1996; Nguyen et al, 1999). However, with this dose delivered using conventional fractionation, the proportion

of patients obtaining partial or complete local response ranges from 20-60% only (Slawson and Scott, 1979; Majid et al, 1986; Chetty et al, 1989). This leaves considerable room for improvement.

The use of high dose rate endobronchial brachytherapy (HDREB) in the treatment of non-small cell lung has been well documented (Macha et al, 1987; Cotter and Ellingwood, 1988; Lang et al, 1988). Combining external beam radiation with endobronchial brachytherapy allows for delivery of significantly higher dose to a limited area. By combining external beam radiotherapy (EBRT) and HDREB, higher partial or complete local response rates ranging between 67-99% can be achieved (Huber et al, 1987; Cotter and Ellingwood, 1988; Chang et al, 1994).

Although HDREB has been frequently used to treat non-small cell lung cancer with an endobronchial or peribronchial component, ideal fractionation schemes and dosages have not yet been fully established. Doses and fractionation schemes are selected empirically because there is little prospective data on tolerance doses of the human bronchial wall after HDREB. Furthermore, the complications caused by the various dose and fractionation schemes using HDREB are not well characterized.

This prospective phase I/II study was conducted for the following purposes: to determine whether a dose response exists for NSCLC when treated with a combination of 66 Gy external beam radiation and escalating doses of HDREB; and to establish a well tolerated dose schema in patients with NSCLC who undergo high dose rate endobronchial brachytherapy.

II. Patients and methods

A. Patient selection

Thirty patients with medically inoperable or surgically unresectable stage III NSCLC were treated in this institutional phase I/II study with both external beam radiotherapy and high dose rate endobronchial brachytherapy. Tissue diagnosis of NSCLC was mandatory for enrollment into the study. All patients had a peribronchial or endobronchial component with bronchial obstruction of 50% or more on bronchoscopy examination. Pre-radiotherapy evaluations included a complete history and physical examination, pulmonary function test, complete blood counts and serum electrolytes, chest X-ray, CT scan of chest, and bronchoscope. Patients with metastatic disease, malignant pleural effusion, history of any other malignancy other than skin cancer, poor performance status (Karnofsky performance status of less than 60), pathology other than non-small cell carcinoma, surgically treated lesions, prior history of radiotherapy to the chest, and those who refused to receive brachytherapy were excluded from the protocol. Written consent was obtained from all patients before starting the treatment.

B. External beam radiotherapy

External beam radiation treatment and high-dose-rate endobronchial brachytherapy were delivered in a sequential manner.

External beam radiotherapy was administered via megavoltage (6MVx) photons. The planned treatment dose of EBRT was 66Gy using a conventional fractionation (2 Gy/fraction) delivered 5 days per week over 33 days. The initial treatment portal included primary tumor, ipsilateral hilar lymph nodes, and mediastinum through opposed parallel AP and PA

fields. Treatment of supraclavicular fossa was not mandatory. After a total of 40 Gy delivered through the initial fields, patients were treated with boost field(s) include the tumor and enlarged lymph nodes defined by chest CT scan. The EBRT boost dose was 26 Gy. Dose to the spinal cord was limited to 45 Gy or less.

C. High-dose-rate brachytherapy

High-dose-rate brachytherapy was delivered using the Nucletron HDR remote afterloading unit with a 10 Ci Ir-192 source. HDREB were delivered prior to the EBRT if the endobronchial or peribronchial component could be fully covered by the HDR brachytherapy dose distribution. For patients with larger tumors, or with complete or near complete bronchial obstruction, HDREB were delivered after the completion of EBRT.

The length of bronchus treated included gross tumor visualized on the bronchoscopy with 2 cm margins proximally and distally. Each treatment of HDREB was delivered at 1 cm depth from the central axis of the radiation source regardless of the size of the tumor at the time of brachytherapy. The first group of 10 patients received three treatments of HDREB at 7 Gy per fraction (Group 1). The second group of ten patients received three treatments at 8 Gy per fraction (Group 2). The last group of ten patients received three treatments of HDREB at 9 Gy per fraction (Group 3). HDREB was delivered once weekly. Bronchoscopy was performed during placement of the brachytherapy catheters during each HDREB session to evaluate any acute side effects or complications. Dose escalation and thus the protocol would be terminated if there was treatment related death or more than 3 Grade 3 or 4 toxicities were observed in any treatment groups. Evaluation of tumor response was not performed until three months after the completion of the treatment.

D. Chemotherapy

All patients in this study had locally advanced disease and received systemic chemotherapy in addition to external beam radiation and brachytherapy. All 30 patients received cisplatin or carboplatin based chemotherapy concurrently during external beam radiation but not during HDREB.

Two patients in Group 1 also received a short course of neoadjuvant chemotherapy before entering this protocol. The pre-radiation baseline CT scan and bronchoscopy evaluations were performed for both patients after the completion of their neoadjuvant chemotherapy but within one week before the starting of radiation. Both patients had more than 50% obstruction at the primary sites in their baseline evaluations before the starting of radiation treatment.

E. Post-treatment Evaluation

All patients were followed up by their radiation oncologists and pulmonologists after the completion of the treatment. All patients were required to receive monthly fiberoptic bronchoscopy for toxicity and response evaluation starting at two to four weeks after the treatment for at least 4 months. CT scan of the chest were required for all patients at 3 months time after the completion of treatment. After that, follow up clinical examinations were performed every three months in either the radiation oncology or pulmonology clinics.

Response to treatment was graded by objective findings include both bronchoscopic and radiological studies at 3 months after the completion of radiotherapy. Subjective findings, including symptomatic changes, were not used to define the response to therapy. Complete response (CR) was defined as the complete disappearance of all clinical and radiological evidence of bronchial obstruction at the primary site; partial response (PR)

as a 50% or greater decrease in the bronchial obstruction on both CT of the chest and bronchoscopy examination; stable disease as a response less than 50% decrease but not more than 25% increase of the bronchial obstruction on either chest CT or bronchoscopy examination; and progressive disease as more than 25% increase in the size of the obstruction in either examination.

Acute and late toxicities from treatments were graded according to the Radiation Therapy Oncology Group criteria. Late toxicities were defined as symptoms first occurring 90 days after treatment or lasting beyond 90 days after the completion of treatment. Toxicities were evaluated weekly during the radiation treatment and at each follow-up after the completion of treatment (Cox et al, 1995).

III. Results

A. Patient characteristics

The median age of all 30 patients was 65 (range 50-72). Twenty-six patients were male and 4 were female. All patients have either AJCC stage IIIa or IIIb non-small cell lung cancer with endobronchial or peribronchial components. Twenty-nine patients received both external beam radiotherapy and brachytherapy according to the protocol. One patient in Group 2 received three applications of HDR brachytherapy (total brachytherapy dose was 24 Gy) followed by external beam radiation but stopped external beam radiation at 60 Gy for non-medical reasons. Two patients in Group 1, 2 patients in Group 2, and 1 patient in Group 3 received HDREB prior to the starting of EBRT.

Patients' characteristics are listed in **Table 1**.

B. Follow up

The median follow up time for all 30 patients was 14.5 months (range 1 to 38 months). One patient in Group 1 died of local disease progression approximately 5 weeks after treatment. All other patients had more than 3 months follow-up and received examinations according to the

requirement of the protocol including a CT scan of the chest at 3 months after the completion of treatment.

C. Response and survival

Complete or partial response at the primary site was obtained in 6 cases (60%), 9 cases (90%), and 9 cases (90%) in the three groups of patients, respectively (**Table 2**). We compared the response data of patients in Group 1 with the response of patients in Group 2 and 3 combined because of the identical response rates (CR and PR combined), and found the difference reached statistical significance (p=0.05).

The medial survival for all 30 patients was 13 months (range 1 to 36 months). Significant difference of survival among the three groups was not expected for this small group of patients with locally advanced disease.

D. Toxicity

Documentation of severe acute and late toxicities (defined as Grade 3 and Grade 4 toxicities according to RTOG toxicity criteria) was mandatory for all patients. Although documentation of Grade 1 and Grade 2 toxicities was required by our radiation oncology department policy, it was not required by this research protocol.

One patient in Group 1 developed Grade 4 toxicity (hemorrhage from the bronchus at the HDR treatment site), 1 patient in Group 2 and 1 patient in Group 3 developed radiation bronchitis. All 3 patients developed toxicities within 90 days after the completion of their brachytherapy (**Table 3**). Although Grade 1 or 2 radiation induced toxicity of esophagus and bronchus was observed during follow-up examinations in multiple cases, no other substantial acute or late toxicities were observed and reported. There were no treatment-related deaths.

The planned treatment with external beam radiation therapy with HDR boost was well tolerated in the majority of the patients.

Table 1. Characteristics of eligible patients. Total patient number: 30

Characteristics	Number (%)
Sex	
Male	24 (80%)
Female	6 (20%)
Age	
50-60	2 (6.7%)
60-70	25 (83%)
>70	3 (10%)
Median	65
Stage (AJCC 1997)	
IIIa	13 (43.3%)
IIIb	17 (56.7%)
KPS (minimum)	>60 (100%)

Table 2. Response and complications after external beam radiotherapy combined with HDR endobronchial brachytherapy. Median follow up time=14.5 months.

Group	No. of Pt.	Brachytherapy Dose	Substantial Response *
1	10	21 Gy/3 weeks	6 (60%)
2	10	24 Gy/3 weeks	9 (90%)
3	10	27 Gy/3 weeks	9 (90%)

*Substantial response is defined as complete or partial response. Difference of response rate reached statistical significance when response rate of group 1 are compared to group 2 and 3 combined. ($p=0.05$)

Table 3. Acute complications after external beam radiotherapy combined with HDR endobronchial brachytherapy.

Group	HDREB Dose	Severity	No. of Pt.	Complication
1	21 Gy/3 wks	Grade 4	1 (10%)	Hemoptysis
2	24 Gy/3 wks	Grade 3	1 (10%)	Bronchitis
3	27 Gy/3 wks	Grade 4	1 (10%)	Bronchitis

IV. Discussion

Patients with locally advanced non-small cell lung cancer are generally treated with external beam radiotherapy combined with chemotherapy; however, previous experience has confirmed that this combined treatment can only achieve limited clearance of the disease because the dose of the treatment is generally limited by other critical structures in the chest. Endobronchial brachytherapy for NSCLC has been well studied extensively previously. Palliative effects ranging from 50-100% for different types of symptoms have been reported.

Endobronchial brachytherapy can be delivered at low dose rate (LDR), intermediate dose rate (IDR), or high dose rate (HDR). HDR brachytherapy units, which deliver radiation at more than 12 Gy per hour, are now widely available in most cancer treatment centers. Because the radioactive sources are more precisely controlled and safety of the treatment delivery is improved, it is the more commonly utilized brachytherapy modality for lung cancer treatment.

Even though HDREB is widely used to treat locally advanced NSCLC, no specific clinical guidelines have been established. The most commonly accepted dosage of HDREB used with external beam radiotherapy has been 3-5 fractions of 5 Gy HDR brachytherapy, but other HDR brachytherapy schedules have also been used. The brachytherapy dose and schedule are chosen mostly empirically. Theoretically, higher dose per fraction may increase the rate of complications, but it may also improve the rate of local control and/or palliation.

Because of the rapid fall of dose with distance, the complication rates from brachytherapy treatments are generally tolerable given the relatively high doses delivered. Rates of severe complications from the HDREB are reported to be 3-11% (Burt et al, 1990; Aliberti, 1995; Langendijk et al, 1998; Kotsianos et al, 2000). Common complications from HDREB include hemoptysis, radiation bronchitis, and esophagitis. Fatal hemoptysis and tracheoesophageal fistula caused by HDREB have been

reported but the occurrence is relative rare. Burt et al. retrospectively reported that patients tolerated well with a single fraction of 15-20 Gy prescribed to 1 cm from the center of the source (Burt et al, 1990). Aliberti analyzed 9 series in the literature and reported 11.3% hemoptysis in 576 cases (Aliberti, 1995). In a retrospective study reported by Langendijk et al, external beam radiotherapy combined with endobronchial brachytherapy as primary treatment for NSCLC did not lead to a higher risk of massive hemoptysis as compared to EBRT alone when fraction sizes for brachytherapy of 7.5 or 10 Gy were used (Langendijk et al, 1998). Kotsianos et al, (2000) analyzed 48 biopsy specimens of three-dimensional miniorgans of the human bronchial wall histologically after high-dose-rate brachytherapy with escalating dosage. The range of the high-dose-rate irradiation was around 75 Gy. The authors found that there was no histologically apparent tissue damage regardless of the irradiation dose and concluded that normal bronchial epithelium has a high tolerance to early epithelial damage by irradiation (Kotsianos et al, 2000). Several other clinical studies attempted to define the optimum doses and fractionation schemes in brachytherapy for lung cancers (Huber et al, 1987; Speiser and Spratling, 1993; Gollins et al, 1994). These trials confirmed a high tolerance of bronchial epithelium to brachytherapy; however, the maximal tolerance dose has not been defined in any prospective studies.

In our series, only 3 patients (one patient from each group) developed Grade 3 or Grade 4 toxicities. All patients developed treatment induced esophagitis with mild to moderate severity (Grade 1 to 3) during or shortly after the completion of external beam radiotherapy. However, no new symptoms of esophagitis were observed and no existing esophagitis worsened during the HDREB. We have confirmed that the total dose of up to 27 Gy in 3 weekly fractions of HDR endobronchial brachytherapy after a definitive course of external beam radiation treatment to the lung is well tolerated. Further dose escalation may be possible in light of our results.

Most studies reported significant symptomatic improvement after HDREB (Burt et al, 1990; Chang et al, 1994; Gollins et al, 1994; Kelly et al, 2000). In a retrospective review reported by Kelly et al, significant and slight improvement of HDREB were reported in 32% and 34% patients, respectively (Kelly et al, 2000). However, repeated bronchoscopy after HDREB demonstrated that overall objective response rate correlated with subjective response and symptomatic relief in less than 80% of the cases. The response rates of our study were measured by both CT scan of the chest and follow up bronchoscopy examinations. All study results were confirmed by the treating pulmonologist and radiation oncologist. Subjective response information such as dyspnea, cough, amount of hemoptysis or other symptoms reported by patients, was not used to measure the response rate. Patients treated with higher dose HDREB (24 Gy or more) achieved significantly higher response rates compared to patients received 21 Gy of HDREB.

Many patients with locally advanced NSCLC have relatively bulky primary disease; however, the therapeutic range of HDREB is limited and may not cover the primary tumor completely. Therefore, HDREB should be used after EBRT for the majority of patients unless the initial primary tumor volume can be covered by HDREB. In our study, only a few patients with small primary tumors were treated with HDREB first. Comparison between patients treated with HDREB before or after EBRT was not done because of the limited number of patients in each group.

The response rate of patients in groups 2 and 3 is identical (90%). We do not know whether further increase of HDREB dose will further improve the local response or not. It was originally planned to escalate the HDREB dose to 30 Gy delivered in 3 weekly fractions; however, to detect any significant but small improvement of response over 90% would require a substantially larger sample size, and such study may not be feasible in a single institution.

Patients with unresectable and locally advanced non-small cell lung cancer are generally treated with definitive radiotherapy with chemotherapy, either sequentially or concurrently (Perez et al, 1987; Dillman et al, 1990; Le Chevalier et al, 1991). All patients in this protocol received concurrent chemotherapy according to our institutional chemotherapy regimen. Two patients in Group 1 also received a short course of neoadjuvant chemotherapy. Both patients received brachytherapy after EBRT and had partial response after the completion of radiotherapy. The post-treatment evaluations for these 2 patients were compared to the chest CT scan and bronchoscopic findings after the completion of neoadjuvant chemotherapy. It is unlikely that this slight deviation from chemotherapy schedule would have any substantial effect on our overall conclusion.

The prognosis of patients with locally advanced non-small-cell lung carcinoma is generally poor. The overall 2-year survival rate is less than 25% (Perez et al, 1987; Hazuka and Turrisi, 1993), and the median survival is around 12 months with external beam radiation and concurrent chemotherapy (Sause et al, 1995). Distant metastasis is common in this group of patients and is the

most common cause of death. The median survival time for our patients was 13 months, which is comparable to the historical data. Because the end points of this study are the overall response rates and the rate of Grade 3 and 4 complications at different dose regimens, follow up for patients' survival data was not required by this prospective protocol. Nevertheless, our clinical chart review data showed that the majority of patients deceased developed distant metastasis. Thus, improvements in survival will also depend on better systemic control.

V. Conclusion

High-dose-rate brachytherapy of 27 Gy in three divided weekly treatments, plus 66 Gy of external beam radiation is well tolerated and effective for the treatment of obstruction from non-small cell lung cancer with endobronchial or peribronchial component. A statistically significant dose response for NSCLC is seen when treating with a combination of external beam radiation and high dose rate endobronchial brachytherapy with a dose of 24 Gy or higher in 3 weekly fractions. EBRT followed by fractionated adjuvant HDREB is a strategy that deserves to be optimized and then tested in a larger scale prospective trial to learn if it can improve outcome.

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