High-Dose Rate Brachytherapy of Bronchial Cancer: Treatment Optimization Using Three Schemes of Therapy

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ABSTRACT

Purpose. Our aim is to demonstrate that a fractionated high-dose rate endobronchial brachytherapy (HDRBT) treatment is tolerable for patients with advanced (IIIA-IIIB) non-small cell lung cancer and gives an improvement of symptoms.

Patients and Methods. From January 1992 to July 1997, we treated 320 patients with external beam radiotherapy (EBRT) and concomitant HDRBT with Ir192. Eighty-four patients received 10 Gy in one fraction from January 1992 to March 1993 (Group A); 47 patients received two fractions of 7 Gy each from April 1993 to December 1993 (Group B), and 189 patients received three fractions of 5 Gy each from January 1994 to July 1997 (Group C).

Results. Mean survival from diagnosis is 11.1 months and mean survival from last HDRBT is 9.7 months. The symptomatic response rate is 90% for dyspnea, 82% for cough, 94% for hemoptysis and 90% for obstructive pneumonia. Performance status was improved in 70% of patients. Follow-up is in the range of 5-36 months with 280/320 evaluable patients (87.5%) (40 patients were lost to follow-up). For the patients treated with three fractions of HDRBT plus EBRT, a smaller number of side effects occurred while relief from symptoms linked to bronchial obstruction and survival was similar for the three groups.

Conclusions. A three-fraction brachytherapy results in fewer side effects, such as bronchial fibrosis with or without stenosis, while survival and symptomatic relief are similar in the three groups treated. The Oncologist 2000;5:209-214

INTRODUCTION

Lung cancer is the leading cause of cancer-related mortality among men [1]. Surgical resection is considered the treatment of choice for stage I-IIIA non-small cell lung cancer (NSCLC); unfortunately, only 30% of patients with lung cancer are in these stages. External radiotherapy (RT), with chemotherapy, is the usual treatment for inoperable patients. Though it only offers a potential for cure for very few patients, it may achieve local control [1-4]. In patients presenting with airway obstruction, endobronchial intervention is frequently required considering the severity of symptoms and risk of respiratory failure [4-6]. Macha and Loddenkemper reported that bronoscopic intervention was required in the course of the disease in 6% of all NSCLC observed since 1983 and in 15% of all squamous lung cancers [7, 8]. Endobronchial brachytherapy (BT) may be employed alone or combined with other endobronchial treatments such as laser [8, 9] or external beam RT (EBRT) [2, 5, 6, 10]. Some authors believe that BT administered simultaneously with chemotherapy is better tolerated than a course of EBRT and chemotherapy [11, 12].

Several long-term side effects have been reported following the procedure (e.g., broncho-vascular fistulae, radiation bronchitis and stricture); incident rates are variable according to different authors’ experiences [7, 8, 13, 13-15].

Our first objective was to obtain palliation for patients with advanced NSCLC with obstructive pneumonitis or atelectasia of the main or secondary bronchi by tumor. Second,
we tried to evaluate the effectiveness of the combination of EBRT and high-dose rate brachytherapy (HDRBT) in a curative approach, and search the optimal dose schedule using different fractionations. Finally, one of the aims of the present study was to retrospectively evaluate the safety of endobronchial BT in patients with NSCLC undergoing concomitant EBRT.

**Materials and Methods**

From January 1992 to July 1997, we treated 320 patients with EBRT with concomitant HDRBT with Ir192. Patient selection criteria were: biopsy proved to be histology (non-small cell cancers), Stage IIIA-IIIIB, Karnofsky Performance Score >60, expectancy of life >6 months, presence of cough and/or dyspnea, hemoptysis, obstructive pneumonia, and no chemotherapy before or during treatment. Staging was realized with chest x-rays, total body computerized tomography scan, bronchoscopy, liver ultrasonography, and bone scan. All patients had tumors with a preponderant bronchial involvement resulting in a total or partial obstruction of the bronchus demonstrated at bronchoscopy. The patients with total bronchial obstruction (17/320; 5%) were first treated with laser. We excluded patients in whom it was not possible to resolve the total obstruction of the bronchus before therapy. No control group has been considered. EBRT was performed after a three-dimensional planning, for all patients considered, using a 15 MV linear accelerator and delivering 60 Gy to the tumor bed and 50 Gy for mediastinum. The daily dose was 2 Gy; all patients were treated with Ap-Pa fields until 50 Gy (including the supraclavicular fossae in those with upper bronchus tumors, with personalized treatment fields), then oblique fields were used in order to avoid irradiation of the spinal cord (the total dose at that level was always ≤5 Gy).

In this prospective study, we divided the patients that received HDRBT into four groups according to the dose prescribed at the reference point, corresponding to four different periods in which we performed HDRBT. In fact, we started treating the Group A patients in January 1992, Group B in April 1993, and Group C in January 1994. This last group can be divided into two others groups, Group C1 and Group C2, according to the distance at which the BT dose was prescribed.

Group A consisted of 84 patients and the dose prescribed was 10 Gy delivered in a single fraction (dose calculated at 1 cm from the central axis of the endobronchial catheter). In 75/84 patients, single catheter HDRBT was used; in nine patients we used two catheters. In this group the treatment was performed before starting EBRT.

In Group B, 47 patients received a total dose of 14 Gy delivered in two fractions of 7 Gy each, calculated at 1 cm (41 patients with single catheter HDRBT and six with double catheter for both fractions). This group received BT before the first EBRT and after the last EBRT treatment.

One-hundred and eighty-nine patients were included in Group C. They received a total dose of 15 Gy delivered in three fractions of 5 Gy each (170 patients received a single catheter HDRBT, and 19 were treated with two catheters for all fractions). Patients were treated every 15 fractions of EBRT (the day before the beginning of EBRT, after three and six weeks of treatment). In Group C1 (50 patients) dose was calculated at 1 cm from the central axis of the catheter of treatment and in C2 (139 patients), it was calculated at 0.5 cm from the central axis.

The choice between the prescribed dose at 0.5 cm or 1 cm was made after the diameter of the bronchial tree involved was measured during the bronchoscopy.

One-half hour before the procedure, patients were premedicated with i.m. Atropine (0.5 mg), Diazepam (5 mg) and Clobutinol (20 mg). Betametasone (2 mg) was also employed if there was no contraindication. Oxygen was administered through a nasal catheter at a rate of 4 l/min. Oxygen saturation and pulse rate were monitored continuously. A more accurate assessment of tumor extension was generally possible at the time of the second or third session due to tumor regression. After each procedure, the occurrence of side effects occurring within one hour from the procedure was recorded. We also asked the patients and their families to annotate the increase or decrease of intensity of symptoms during treatment and during the follow-up period.

**Results**

Follow-up is in the range of 5-36 months with 280/320 evaluable patients (87.5%) (40 patients were lost to follow-up). We have 78 evaluable patients from Group A, 46 from Group B, 36 from group C1 and 120 from Group C2. We performed a chest x-ray after one to three months from the last HDRBT, a bronchoscopy after six months (or if necessary after three months), histological samples and a CT scan after six months.

The mean survival from diagnosis was 44 weeks (11.1 months) and the mean survival from last HDRBT was 39 weeks (9.7 months). There was no difference in survival between the four groups.

The symptomatic response rates, recorded by the patients one month after treatment, were 85% for dyspnea, 77% for cough and 90% for hemoptysis. At the six-month bronchoscopy, response rates were 90% for dyspnea, 82% for cough, 94% for hemoptysis and 90% for obstructive pneumonia. Seventy percent of patients in the three groups reported an improvement in general conditions one month after the treatment began. The improvement of symptoms is
reported in Table 1. In this table we describe the percentage of patients in each group that were affected by each symptom before, during and one month after radio-brachytherapy (the value recorded during RTs represents the median value of the score recorded each week by the same patients). These data are obtained from a personal observation of each patient and they could be influenced by the subjective tolerance to these symptoms, so we compared them to the information scored by the physician during therapy and follow-up. All the data have a statistical relevance \(p < 0.01\).

Radiological improvement (i.e., reduction of more than one-third of tumor volume at the chest x-rays performed at one month from the end of treatment) was recorded in 45\% of all patients treated, with no difference between the three groups.

One of the most common complications was the radiation bronchitis (with or without concomitant bronchial stenosis), which was found at the six-month bronchoscopy in 61/78 (80\%) patients evaluable from Group A, in 22/46 (48\%) evaluable from Group B, in 8/36 (22\%) evaluable from Group C1 and 19/120 (16\%) from Group C2. The values have a statistical relevance \(p < 0.01\). The complete distribution of radiation bronchitis by grade of reaction in each group, according to the \textit{Speiser} and \textit{Spratling} classification [14], is shown in Table 2. These clinical changes, which occurred in the tracheobronchial tree following radiation, were less frequent for the groups in which the prescribed dose was lower.

In 22/78 (28\%) patients from Group A, 11/46 (24\%) from Group B, 4/36 from Group C1 (11\%) and 11/120 (9\%) from Group C2, biopsy proved the presence of neoplastic cells in the bronchus \(p < 0.01\). Another severe complication was fatal hemoptysis that was recorded in Group A for 2/78 (2.5\%) patients, Group B in 3/46 (6.5\%), Group C1 in 1/36 (3\%) and in Group C2 in 3/120 (2.5\%). In this case there is not a statistical relevance of data. More frequently, we recorded the appearance of spontaneous bleeding after treatment which resolved in a few minutes and without any further complications. There was no difference in the hemoptysis rate in patients with upper or lower lobe tumors.

We also documented some complications linked to the procedure of bronchoscopy, generally to the local anesthesia or introduction of the bronchoscope. In Group A it was recorded in 22/78 (2.5\%) patients, in Group B in 2/46 (4.3\%), in Group C1 in 0/36 (0\%) and in Group C2 in 3/120 (2.5\%) \(p > 0.01\). Bronco-esophageal fistulas were not common. In Group A they were recorded in 1/78 (1\%) patients, in Group B 1/46 (2\%), in Group C1 1/36 (3\%), and none in Group C2 \(p > 0.01\).

No patient received further RT for local recurrence, but 39/280 (14\%) were treated with EBRT for metastatic disease. Only five patients have been treated with HDRBT alone for bronchial obstruction due to tumor recurrence.

| Table 1. Symptomatic subjective response rate (presence of symptoms before, during and after one month from treatment) (%) |
|-----------------|-----------------|-----------------|-----------------|-----------------|
|                 | Dyspnea (%)     | Cough (%)       | Hemoptysis (%)  |                 |
|                 | Before (%)      | During (%)      | After 1 month (%) | Before (%)      | During (%)      | After 1 month (%) | Before (%)      | During (%)      | After 1 month (%) |
| Group A         | 90              | 72              | 20              | 92              | 80              | 42              | 10              | 2               | 0               |
| 78 Patients     |                 |                 |                 |                 |                 |                 |                 |                 |                 |
| Group B         | 87              | 68              | 15              | 96              | 82              | 28              | 7               | 1               | 1               |
| 46 Patients     |                 |                 |                 |                 |                 |                 |                 |                 |                 |
| Group C1        | 88              | 71              | 10              | 90              | 79              | 12              | 8               | 2               | 1               |
| 36 Patients     |                 |                 |                 |                 |                 |                 |                 |                 |                 |
| Group C2        | 85              | 73              | 5               | 91              | 83              | 11              | 12              | 2               | 0               |
| 120 Patients    |                 |                 |                 |                 |                 |                 |                 |                 |                 |

| Table 2. Distribution of radiation bronchitis by grade of reaction in each group |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| Grade           | 1               | 2               | 3               | 4               | TOTAL           |
| Group A         | 19/78           | 13/78           | 17/78           | 12/78           | 61 Patients     |
| Group C1        | 2/36            | 0/36            | 3/36            | 3/36            | 8 Patients      |
| Group C2        | 6/120           | 3/120           | 5/120           | 5/120           | 19 Patients     |
| TOTAL           | 39/280          | 20/280          | 28/280          | 23/280          |                 |
Moreover 42/280 patients (15%) underwent chemotherapy after our treatment.

**DISCUSSION**

Endobronchial BT has been used since the introduction of the after-loading technique and the advances in RT technology [16]; thus it is now generally performed as HDRBT. It has been used in some cases as primary treatment for cure of small endobronchial tumors [17], a boost to complete a course of external RT [8], or as palliative therapy in patients with recurrent tumors treated with EBRT and/or chemotherapy [12, 13, 18, 19].

Palliation of endoluminal obstruction is the main application of HDRBT [5, 13, 16, 20]. The symptomatic relief (of cough, breathlessness, hemoptysis) is generally rapid [4, 8, 18, 21] and a favorable impact on survival time has sometimes been observed [5, 20, 22, 23]. In either case HDRBT seemed to increase local control [6].

In 1992 we started treating patients with advanced (IIIA-IIIB) NSCLC who were not suitable for surgery, but had general conditions and performance status that allowed a “potentially curative” treatment.

The aim of our prospective study was to use EBRT plus HDRBT in order to have an expedient and lasting relief of symptoms. The decision of where to prescribe the dose of HDRBT was made after the measurements of bronchial diameters and the dimensions of tumor.

We asked the patients to record any change of the three most frequent symptoms: dyspnea, cough, and hemoptysis, during and after the therapy period. The symptomatic response rate, both at one and six months, was documented with questionnaires given to the patients and confirmed during the follow-up, so any information was scored both by the patients and the physicians. All the patients considered in this study answered properly. In all groups there was a gradual improvement of symptoms, but the groups in which brachytherapy was delivered in a multifractionated treatment seemed to have more advantages from therapy. During treatment there was no difference in outcome between the four groups but, in the follow-up at one month, dyspnea was present in 10% of group C1 and 5% of group C2, while it was 20% in Group A and 15% in Group B. The same thing happened for cough. After one month, it was present in 42% of patients in Group A, in 28% of Group B, but only in 12% and 11% of Groups C1 and C2. Hemoptysis is so rare in our experience that we cannot draw a conclusion on its response. In any case, no difference in patients with upper or lower lobe tumors has been found for this symptom before or after treatment.

In our department, the operating room is used for patient preparation and designed to enable precise localization of applicators for accurate delivery of HDRBT. Therefore, in the same room, anesthesia, endoscopy, x-rays and therapy are performed without the need to transfer patients elsewhere, which can lead to catheter displacement.

The incidence of side effects is variable, according to different authors, probably due to the heterogeneity of study populations as well as the differences in the technique employed [7, 8, 10, 13-15, 21].

Immediate side effects are likely due to the bronchoscopic procedure per se (not to the effects of radiation). It is well known that fiberoptic bronchoscopy usually causes a temporary increase in airflow resistance, which may result in hypoxia and, more rarely, hypercapnia [24]. Inappropriate sedation may further increase the risk of respiratory complications, so care in identifying patients at risk is recommended [24]. Major complications have been reported following fiberoptic bronchoscopy in 0.3%-5% of cases, and the reported mortality rate of the procedure is reported to range between 0.01%-0.5%. The majority of the fatalities are, however, related to endobronchial procedures, like transbronchial biopsy [25]. There were only 7/280 (2.5%) incidences of side effects linked to endoscopic procedure. In all the cases the problems were transient.

In our study, we did not record cases of laryngospasm or respiratory failure requiring mechanical ventilation while bronchospasm occurred in two patients and resolved quickly with inhaled beta-2 agonists. Transitory supraventricular arrhythmia was observed in four patients and resolved spontaneously in all the cases. Pulmonary edema, observed in two patients, required standard therapy (oxygen, diuretics, and cardio kinetics) and resolved within 2 h. Thus our incidence of complications is comparable to that reported in other series of fiberoptic bronchoscopy [15, 21], though it is reasonable to think that patients in our series were more severely ill, due to the criteria for eligibility for EBRT with or without HDRBT (NSCLC not suitable for surgery for advanced stage or poor cardiorespiratory function).

In this prospective study, treatment changed as years went by and personal experience increased. We first modified the prescribed dose of HDRBT and then the distance of optimization from the central axis of the treatment catheter. We noted that doses and “distance” of HDRBT had an impact on the percentage of side effects, and we have reduced these phenomena with more fractions.

The most frequent complication linked to endobronchial irradiation currently recorded is radiation bronchitis (with or without a concomitant bronchial stenosis). We proved this at the six-month bronchoscopy in 80% of patients in Group A, 48% in Group B, 22% in Group C1 and 16% in Group C2. The distribution of this symptom by
grade in each of our groups is shown in Table 2. According to the Speiser scale [14], Grade 1 reactions occurred in 39/280 (14%) patients evaluated after six months with bronchoscopy. Grade 2 reactions occurred in 20/280 (7%), Grade 3 in 28/280 (10%), and Grade 4 in 23/280 (8%). As is possible to see, there are few differences in the incidence of each grade of reactions in all groups, as in other experiences [10, 14, 21]. Biopsy, performed during the follow-up bronchoscopies, proved the presence of neoplastic cells in the bronchus in 28% of Group A, 24% of Group B, 11% of Group C1 and 9% of Group C2. We don’t know how much of this fibrosis and bronchitis, with or without stenosis, is linked to HDRBT and how much is linked to EBRT, both of which are performed at the same time. Our policy of reducing the dose per fraction seems to give results with the incidence of radiation fibrosis (but not the grade of it) reduced from 80% to 18% in patients evaluated at six months. In this way, we have obtained a relief of symptoms while trying to minimize side effects.

We believe that increasing the number of fractions is useful in decreasing the incidence of these kinds of side effects. At the same time, with increasing number of fractions, a corresponding reduction in the presence of neoplastic cells in the samples taken during the six-month follow-up bronchoscopy (from 29% to 3%) is seen. We believe that the patients controlled with biopsy are few; we need further analysis of these data.

At this time we have no definitive data that shows an improvement of symptoms in patients treated with the dose prescribed at 0.5 cm instead of 1 cm from the central axis of the bronchial catheter, but preliminary data show us a partial decreasing of side effects in these patients. In fact we have obtained a persistence of dyspnea in 5% of patients in Group C2 versus 10% in Group C1, while for cough and hemoptysis there is no difference.

Passing from Group C1 to C2, we considered not only the dose in itself but the treated volume. With a reference dose of 5 Gy calculated at 1 cm from the central axis, in a standard treatment the volume that receives such dose is 23 cc. The volume that receives a double dose is 7 cc. With the same dose calculated at 0.5 cm, the volume that receives the prescribed dose is 7 cc, the one that receives the double dose is 3 cc. At the moment any effort in optimizing HDRBT is linked to the optimal definition of treated volume.

Late toxicity on the bronchial wall is attributed mainly to contact between the catheter and the bronchial mucosa [5]. The reduction of the irradiated volumes can lead to a reduction of stenosis and fibrosis. In fact in Group C2 (dose of 5 Gy prescribed at 0.5 cm from the axis of the catheter), there seems to be a reduction of radiation bronchitis if compared to that obtained in Group C1 (same dose but prescribed at 1 cm from the central axis). In Group C2 this symptom has been recorded in 19/120 patients (16%) versus 8/36 (22%) in Group C1.

Moreover, soon after the first HDRBT, some patients reported an improvement of symptoms that led them to therapy, which had an immediate positive impact on the psychological attitude of patients.

We believe, although we have no definitive data, that a fractionated HDRBT is more tolerable and effective than a single-time procedure. At the same time, we tried to obtain an initial immediate relief of symptoms by starting the combined therapies (EBRT+HDRBT) with HDR in order to obtain an immediate partial relapse of symptoms. We also recorded a median survival of 11.1 months from diagnosis and 9.7 months from the first BT, comparable to the 10 months of Aygun et al. [2] and to the 9.5 months of Speiser and Spratling [10] or the seven months of Taulelle et al. [1]. The use of endobronchial BT as a boost to conventional EBRT has not yet demonstrated improvement of survival compared to EBRT alone for inoperable lung cancer [5]. We must consider that prolonging survival is probably not the first goal of these therapies.

Another point that has to be discussed is the fact that despite the good symptomatic improvement, the radiological/endoscopic results were not as good. In fact, we recorded a radiological improvement (i.e., a shrinking of tumor dimensions) in only 45% of patients treated. This is because in many cases, fibrosis takes the place of the tumor in the bronchial lumen [25]. Our first goal is to obtain a long-lasting improvement of symptoms, not radiological remissions of tumors.

CONCLUSIONS

Endoluminal BT seems to be an effective palliative modality to relieve endoluminal obstruction that can be used alone or definitively to boost the primary site before, during or after a course of external irradiation. No differences have been found in disease-free survival or overall survival using different therapy schemes. At the moment we believe that it is very important to consider the importance of the prescribed dose, but above all, at what distance from the catheter this dose is prescribed and the volume treated. As our experience confirms, the smallest irradiated volume and a fractionated HDRBT are associated with fewer side effects. We believe this is of enormous importance with a palliative tool like HDRBT.

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REFERENCES


