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Endobronchial brachytherapy with curative intent: the impact of reference points setting according to the bronchial diameter

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ABSTRACT

Endobronchial brachytherapy (EBB) is an effective treatment for endobronchial tumors. However, bronchial toxicity caused by over-irradiation remains problematic. To decrease bronchial toxicity, we developed a source-centralizing applicator for EBB. The purpose of the present study was to assess the efficacy and safety of EBB with varying reference dose points according to the bronchial diameter, using a source-centralizing applicator. We reviewed 15 patients with endobronchial carcinoma who were treated with curative intent using a combination of external beam radiotherapy (EBRT) and high-dose-rate EBB between 2005 and 2014. During each EBB session, we used a source-centralizing applicator that maintained the source-delivering catheter in the center of the bronchial lumen. Reference dose points were 5–7 mm from the source axis, depending on the bronchial diameter. The median radiation doses of EBRT and EBB were 40 Gy in 20 fractions and 18 Gy in 3 fractions, respectively. The median observation period was 36 months. The 3-year overall survival, progression-free survival and local control rates were 79%, 77% and 100%, respectively. Grade 2 radiation pneumonitis was observed in two cases. Bronchial toxicities, such as hemoptysis or the symptoms of chronic bronchitis, were not observed. EBB with varying reference dose points according to bronchial diameter, using a source-centralizing applicator, is a promising procedure that may be effective for tumor elimination and reducing toxicity to the bronchial wall.

KEYWORDS: lung cancer, endobronchial brachytherapy, reference point

INTRODUCTION

Endobronchial brachytherapy (EBB) has mainly been used in lung cancer treatment for palliative purposes, such as for the treatment of airway obstruction and hemoptysis [1–8]. On the other hand, EBB has also been used for curative tumor treatment [9–17], and excellent outcomes have been reported, especially for patients with roentgenographically occult endobronchial cancer (ROEC) [10, 15, 16].

Although EBB is effective for both alleviating symptoms and eliminating tumors, complications such as hemoptysis, bronchial stenosis and bronchial obstruction remain serious problems [14, 17–25]. It has been suggested that these complications can be caused by eccentric locations of the source-delivering catheter in the bronchial lumen [19]. If the source-delivering catheter is located at one side of the bronchial lumen, this eccentric position of the catheter might cause inappropriate dose distribution to the bronchial mucosa. Uneven dose distributions produce excessive dose areas in the bronchial mucosa and lead to bronchial necrosis. To prevent eccentric positioning of the catheter, we developed an applicator that has two

'wings' to centralize the radioactive source in the bronchial lumen in 1997 [26].

Regarding the reference dose point, it is set at 10 mm from the source axis in most studies [9, 11, 12, 17, 20, 25]. However, the radius of the bronchus is <10 mm on the distal side of main bronchus, and this difference leads to overdosing to the bronchial mucosa. Therefore, it seemed reasonable to hypothesize that varying reference dose points according to bronchial diameter would prevent overdosing to the bronchial mucosa.

The purpose of this study was to provide an initial efficacy and safety assessment of this dose prescription method using the source-centralizing applicator, based on a retrospective analysis of patients receiving curative EBB.

MATERIALS AND METHODS

Patients

We reviewed 15 patients who were treated with EBB with curative intent between November 2005 and September 2014. Patient characteristics are listed in Table 1. This study included 14 men and one woman, with an overall median age of 71 years (range, 59–88 years). Proven histology and tumor sites are also shown in Table 1. Thirteen patients had ROECs that were not identified as tumors via chest radiography examination. In all cases, computed tomography (CT) scanning confirmed the absence of tumor extension outside the bronchial wall and the absence of lymph node involvement. Seven of the endobronchial tumors were found during follow-up periods after surgery for previous lung cancer, while six cases of inoperable endobronchial tumors were diagnosed via endoscopic examination. The remaining two cases involved post-surgical patients who had pathological residual tumor upon surgical anastomosis. Our institutional review board approved this retrospective study.

Treatment protocol

Radiation therapy consisted of a combination of external beam radiation therapy (EBRT) and EBB. Chemotherapy was not concurrently performed, and EBRT was performed prior to brachytherapy. Using megavoltage equipment with 6 MV photon beams, five fractions of 2 Gy were applied weekly for a total dose of 40 Gy. The radiation field was limited to the primary lesion, without extension to the regional lymph nodes. The clinical target volume was delineated with reference to bronchoscopic findings.

Table 1. Patient characteristics

Total number of patients:		15
Age (years)	Median (range)	71 (59–81)
Gender:	Male/Female	14/1
Histology:	SCC/adc/large/ACC	11/2/1/1
Bronchial site:	trachea/main/lobe/segmental	1/4/5/5
Tumor status:	ROEC/post-operative	13/2

SCC = squamous cell carcinoma, adc = adenocarcinoma, ACC = adenoid cystic carcinoma, ROEC = roentgenographically occult endobronchial cancer.

Brachytherapy procedure

The applicator system and application methods were described in an earlier study [26]. Briefly, the endobronchial applicator (Create Medic Co. Ltd, Japan) has two 'wings' on the tip side of the applicator. In the application procedure, first, the source-delivering catheter (Lumencath Applicator®, Nucletron, Elekta Co., Sweden) is inserted via the operating channel of a bronchoscope with a nasal approach. After pulling back the bronchoscope, the endobronchial applicator is inserted overlaying the source-delivering catheter under fluororoentgenography. The 'wings' are self-expandable and adjustable according to the diameter of the bronchial lumen. The applicator is adjusted to the optimal position such that the tumor is located between the two wings: the position is confirmed by bronchoscopy with an oral approach.

After placing an applicator, CT scans were obtained during every treatment session to confirm the applicator's position and to measure the distance between the source axis and the bronchial wall.

Brachytherapy was performed with a fraction dose of 6 Gy using a high-dose-rate ^{192}Ir after-loading machine (microSelectron®, Nucletron, Elekta Co, Sweden). Generally, three fractions of brachytherapy were performed once per week. Reference dose points varied for each patient, depending on the bronchial diameter. The distance from the source axis to the bronchial wall was measured on the planning CT image. When the irradiation length was long, dose prescription points were set for more than one point, for example, for example, 7 mm at central side and 5 mm at peripheral side. The irradiation length was defined according to the length of the tumor, as measured by bronchoscopy, with 2 cm proximal and distal margins.

Statistical evaluation and follow-up

SPSS Statistics Version 16 (SPSS Japan Inc., Tokyo, Japan) was used to calculate Kaplan–Meier estimates of local control and survival rates. Overall survival was defined as the time from the treatment starting date to the date of death from any cause. Progression-free survival was defined as the time from the treatment starting date to the date on which the disease progressed or the date of death from any cause. Local control was assessed by bronchoscopy and chest CT conducted every 6 months after the treatment. Toxicity was evaluated using version 4.0 of the Common Terminology Criteria for Adverse Events.

RESULTS

All patients were treated with a combination of EBRT and EBB. Prescription doses of EBRT and EBB are shown in Table 2. The median doses of EBRT and EBB were 40 Gy/20 fr and 18 Gy/3 fr, respectively. If a tumor was present at the bronchial spur, 2 fractions of brachytherapy were administered to each bronchus equally, and therefore, 4 fractions of brachytherapy were performed. The dose prescription points were 5–7 mm from the source axis in 12 patients, and 5 mm in three patients, according to the bronchial diameter at the treatment site (Table 3). Chemotherapy was

Table 2. Radiation dose

Radiation dose		No. of cases
EBRT	EBB	
40 Gy/20 fr	18 Gy/3 fr	13
40 Gy/20 fr	16 Gy/4 r	1
30 Gy/15 fr	24 Gy/4 fr	1

Table 3. Reference dose points

Reference dose point (from the source axis)	No. of cases
5 mm	3
5–7 mm	12

administered after radiotherapy in one case of histologically proven adenocarcinoma.

The median follow-up period was 36 months, with an interquartile range (25th–75th percentile) of 24–75 months and an overall range of 11–100 months. In all cases, elimination of the tumor was confirmed with bronchoscopy at the last session of brachytherapy. Therefore, the complete remission (CR) rate was 100% in 13 cases, excluding the two post-operative cases.

Five patients died during the observation period. Two deaths were due to lung cancer, including one from progression of locoregional recurrence at 62 months after the beginning of the treatment, and one from progression of liver metastasis without local recurrence. Of the remaining three deaths, one was due to esophageal cancer, one was due to pneumonia, and one was due to liver cirrhosis. One patient was alive with bone metastasis at the end of the observation period. The 3-year overall survival, and progression-free survival rates were 79% (Fig. 1) and 77% (Fig. 2), respectively. As for local control, one patient had local recurrence at 62 months. Therefore, the 3-year local control rate was 100%.

Regarding toxicities, two patients developed Grade 2 radiation pneumonitis. No hemoptysis or other symptoms of chronic bronchitis were seen during the observation period. In recent three cases, in a total of 9 sessions, we analyzed the dose–volume histograms of the bronchial wall as an organ at risk and obtained the data that the mean $D_{0.1\ cm3}$, $D_{1\ cm3}$, and $D_{2\ cm3}$ of the bronchial wall were 155.2% (118.5–202.0%), 105.4% (77.4–119.2%) and 83.6% (65.5–104.3%), respectively.

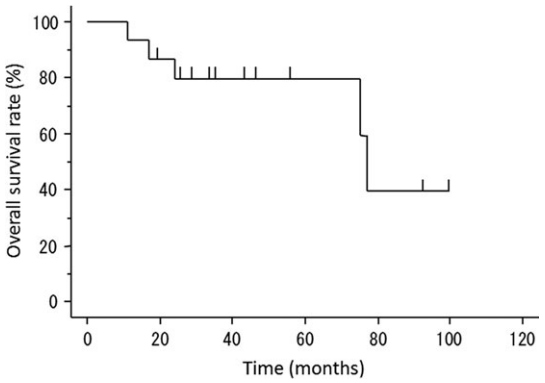

Fig. 1. Kaplan–Meier curve of overall survival.

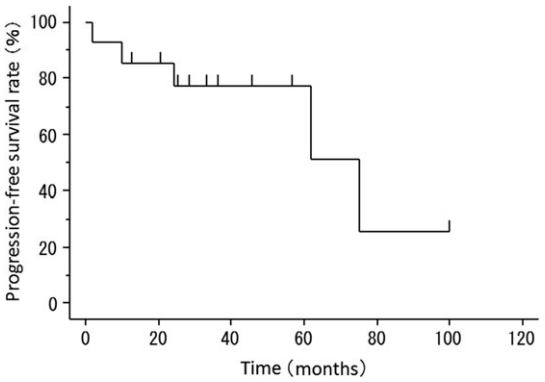

Fig. 2. Kaplan–Meier curve of progression-free survival.

DISCUSSION

In cases of medically inoperable lung cancer, EBB has been widely performed to improve symptoms such as dyspnea, cough and hemoptysis [1–8]. With regard to palliative therapy, EBB has been recognized as a useful treatment for malignant airway obstruction. Although reports on EBB have more commonly considered its use as a palliative treatment, studies of EBB with curative intent have shown promising tumor control and survival outcomes [9–14, 17, 25]. Excellent treatment outcomes, in particular, have been reported for ROECs [15, 16]. It has been recognized that EBB provides good treatment results for centrally located superficial tumors without extension to the outside of the bronchial wall. The local control rates in the present study were consistent with those given in the previous reports. One of the reasons for this excellent local control is probably that all tumors were within the tracheo–bronchial wall. ROEC is often found via endoscopic examination during post-surgical follow-up. In this study, seven of the 15 patients were diagnosed with ROEC during the follow-up period after surgery for lung tumors at other sites. These cases are considered good candidates for EBB with an expectation of excellent tumor control. For curative treatment, EBB is compared with other therapeutic modalities available, such as stereotactic body radiotherapy (SBRT) or photodynamic therapy (PDT). In comparison with SBRT, brachytherapy doesn't need to consider the respiratory movement of the CTV and reduce the high-dose irradiation area. In addition, in SBRT, safety for a tumor that is centrally located has not been confirmed. PDT has an excellent effect on patients with centrally located, early-stage lung cancer who have limited tumor invasion extending over a small area (≤1 cm) [27]. However, the local control rate decreased when the tumor size was >1 cm. In addition, the indication of PDT is restricted to patients in whom the tumor does not infiltrate more deeply than submucosal layer.

Hemoptysis and serious bronchitis are recognized as major toxicities of EBB [17–25]. Although hemoptysis likely relates to tumor recurrence, it has been suggested that its presence after EBB is a complication of the treatment itself. These complications may be partly explained by the placement of the radioactive source-delivering catheter at eccentric locations in the bronchial lumen, which can lead to localized hot spots on the bronchial mucous membrane. Hara *et al.* [19] reported that direct contact between the EBB applicator and the tracheobronchial walls was one of the significant risk factors for massive hemoptysis. Furthermore, Perol *et al.* [17] reported that to prevent massive hemoptysis, a specific spacer should be employed to maintain a safe distance between the applicator and the bronchial wall.

To prevent eccentric positioning of the catheter, we developed an applicator and utilized it in clinical practice [26]. In the current study, we analyzed its efficacy in patients receiving therapy with curative intent. Regarding toxicity, Grade 2 radiation pneumonitis was observed in two cases; however, these toxicities might have been caused by EBRT. We did not observe serious toxicity related to the bronchial tree, such as hemoptysis or bronchitis. We hypothesize that such toxicity was probably absent because the use of the applicator avoided overdosing that area of the bronchial mucosa. In an early follow-up study with bronchoscopic examination, a circumferential white coat was observed on the irradiated bronchial mucosa. The white coat was thin, uniform and surrounded the bronchial wall. There was no local thick white coat. These findings indicate that there were no 'hot spots' in the irradiated bronchial mucosa.

In most studies on EBB, the reference dose point has been set to 10 mm from the source axis. In this setting, the actual radiation dose to the bronchial mucosa might be higher than the prescription dose because the bronchial radius is 7–8 mm or smaller. Additionally, without the use of a source centralizing applicator, an unexpected high-dose area will arise where the source transfer catheter contacts the bronchial mucosa. These situations are speculated to cause bronchial necrosis and lead to massive hemoptysis. To prevent overdosing the bronchial mucosa, we proposed that reference points be set according to the bronchial diameter, using a centrally positioned applicator. When beginning this treatment at our institution, we set reference points according to the irradiation site of the bronchial tree, for example, 10 mm at the trachea, 7 mm at the main bronchus, 5 mm at the lobe bronchus and 3 mm at the segmental bronchus. After CT-based treatment planning was available, we were able to measure the distance between the source axis and the bronchial wall surface directly. Therefore, we could set the reference point according to bronchial diameter. In this study, the reference dose points were 5–7 mm from the source axis, which was approximately equal to the radius of the bronchial tree. In one patient in this study, although the treatment site was the trachea, the actual distance between the source axis and the tracheal wall surface was 7 mm. In this era of image-guided brachytherapy (IGBT), the advantages of application of IGBT in EBB should be considered.

In the setting of these reference dose points, the prescription dose is nearly equal to the dose received by the bronchial mucosa. This procedure may prevent overdosing of the bronchial mucosa and reduce bronchial toxicities. Although, in small cases, from analysis of the dose–volume histogram, there was no hyperdose area or hot spot in the bronchial wall. By using this procedure, it might be possible to estimate the tolerance dose of the bronchial mucosa in the future.

In the present study, we investigated the combination of EBRT with EBB. The aim of EBRT prior to brachytherapy is to reduce the tumor size and obtain a uniform dose distribution to the bronchial wall. Rochet *et al.* [9] reported that it is advantageous to have a smaller target volume and adequately encompass the residual disease within the high-dose field of EBB after EBRT. There have been several previous reports regarding the dose for EBRT and EBB combination therapy. Saito *et al.* [15] reported the combination of EBRT at 40 Gy and low-dose-rate EBB at 25 Gy with excellent outcomes for ROEC. Our treatment protocol was designed in the same fashion, and the EBRT dose was similar. The EBB dose was comparable with the dose conversion of low-dose-rate brachytherapy into high-dose-rate brachytherapy. Hosni *et al.* [28] reported a similar treatment schedule for a combination of EBRT and high-dose-rate EBB, with varying dose prescription points according to bronchial site (10 mm for trachea, 7 mm for main bronchus, 5 mm for lobar bronchus), with excellent outcome.

The retrospective nature and small cohort size are important limitations of this study. Despite these study limitations, this is the first study to demonstrate the efficacy of varying reference dose points according to the bronchial diameter with CT-based treatment planning, and the results of this study will contribute to EBB with curative intent.

In conclusion, EBB with varying reference dose points according to the bronchial diameter, using a source-centralizing applicator, is a promising option that may provide effective and safe treatment for endobronchial carcinoma. Modifying prescription dose points according to the bronchial diameter may reduce toxicity to the bronchial wall.

CONFLICT OF INTEREST

The authors state that there are no conflicts of interest, grants or any assistance to be disclosed.

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