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The Role of Rigid Bronchoscopic Intervention for Bronchial Carcinoid

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Bronchial carcinoid is a rare malignant tumor that is categorized as a typical carcinoid or atypical carcinoid. Many institutions use flexible bronchoscopy for diagnosis. However, due to the hemorrhagic nature of the tumor, the amount of specimen obtained is often small, making it difficult to obtain an accurate diagnosis. The use of rigid bronchoscopy may not only contribute to obtaining a diagnosis but also be beneficial in the treatment plan. The aim of this study was to evaluate the efficacy of rigid bronchoscopic interventions for the diagnosis and treatment of bronchial carcinoids. All patients with bronchial carcinoids who underwent rigid bronchoscopic intervention under general anesthesia at our institution between June 2006 and August 2018 were analyzed retrospectively. Eight patients [3 men and 5 women; median age, 71 years (range 45-82 years)] were eligible for the analysis. None of the cases had accurate subtyping preoperatively before intervention. In contrast, all cases were diagnosed as carcinoid with subtypes (5 patients had typical carcinoid and 3 had atypical carcinoid) following rigid bronchoscopic intervention. All respiratory symptoms improved immediately after the procedure. One instance of bleeding occurred, and was easily controlled by argon plasma coagulation and intraluminal administration of epinephrine under flexible and rigid bronchoscopy. Four patients (3 with typical carcinoid and 1 with atypical carcinoid) underwent radical surgery sequentially, and no recurrences were observed. We conclude that rigid bronchoscopic intervention is safe and effective for accurate diagnosis and improvement of respiratory symptoms in patients with bronchial carcinoids.

Keywords: bronchial carcinoid; carcinoid; diagnostic yields; rigid bronchoscopy; safety
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Introduction

Bronchopulmonary carcinoids account for less than 5% of lung cancers and 25% of all carcinoids (Detterbeck 2010; Brokx et al. 2015). Based on pathological features, they are classified as typical carcinoid (TC, < 2 mitoses / 2 mm² of viable tumor) and atypical carcinoid (AC, 2 to 10 mitoses / 2 mm², necrosis, or architectural disruption). When we perform forceps biopsy using a flexible bronchoscope, the amount of specimen obtained is small, so it is often difficult to accurately determine the subtype of carcinoids (40-50%) (Detterbeck 2010). In addition, it was reported that approximately 10% of patients with carcinoids were misdiagnosed as small cell lung cancer or squamous cell lung cancer (Detterbeck 2010). Carcinoid tumors are hemorrhagic and severe bleeding during bronchoscopic biopsy has been reported (Stamatis et al. 1990; Ayache et al. 2018) which may cause carcinoid crisis (Karmy-Jones and Vallieres 1993).

The five-year survival rate (87-100% vs. 56-75%), 10-year survival rate (82-87% vs. 35-56%) (Brokx et al. 2015), and recurrence rate (2.76% vs. 21.26%) (Garcia-Yuste and Matilla 2014) have wide variations between TC and AC, so we need to consider them separately. Moreover, the treatment is decided based on the subtype and tumor size (van der Heijden 2018). Hence, accurate subtyping is of paramount importance.

The central airway lesions often cause respiratory symptoms such as shortness of breath, cough, and hemoptysis. In these lesions, rigid bronchoscopic intervention

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may contribute to relieving the respiratory symptoms as well as diagnosis. Moreover, due to the slow growth of TC, bronchoscopic resection might be a viable option in comparison to surgery in elderly patients or patients with poor performance status. Hence, we assessed the efficacy and safety of rigid bronchoscopic interventions for bronchial carcinoids.

Materials and Methods

Patients

All patients diagnosed with bronchial carcinoid and who underwent rigid bronchoscopic intervention under general anesthesia at our institution between June 2006 and August 2018 were analyzed retrospectively. The main indications for rigid bronchoscopic intervention were as follows: A symptomatic endobronchial tumor in which bronchoscopic resection was considered to be appropriate for relieving symptoms, an endobronchial tumor that was difficult to diagnose, and localized endobronchial tumor in which the surgical resection was not indicated (patients with poor conditions, elderly patients, and patients who refused to undergo surgery). We collected the information including age, sex, tumor location, tumor diameter, treatment options (devices, procedure time, and so forth), treatment efficacy, adverse events, and pathological diagnosis from medical records. The clinical stage was determined according to the 8th edition of tumor-node-metastasis classification for lung cancer. Written informed consent for the procedures was obtained from all the patients. This study was approved by the Institutional Review Board of Nagoya Medical Center (No. 2020-045, approval date: August 27, 2020). Informed consent for this study was waived by the institutional review board because this was a retrospective study.

Procedures

In all cases, we used rigid and flexible bronchoscope under general anesthesia. For tumor resection, we utilized argon plasma coagulation (APC), electrocautery snare, and cryoprobes depending on the tumor location and diameter. The obtained specimens were fixed in formalin and assessed by experienced pathologists.

Assessments

The primary outcome was the safety of rigid bronchoscopic intervention which was evaluated based on adverse events. The secondary outcome was the efficacy, which was evaluated by the diagnostic yield, improvement of respiratory symptoms, recurrence rate, procedure time, and the overall survival time.

Results

Patients

During the study period, 14 patients were diagnosed with bronchial carcinoids. Among them, eight patients [3 men and 5 women; 5 TC and 3 AC; median age, 71 years

Table 1. Patient characteristics and details of procedures.

No	Age (year)	Sex	Preprocedural diagnosis	Final diagnosis	Stage	Location	Symptoms	Atelectasis	Procedures	Complication	Procedure time (minutes)	Surgical resection	Recurrence	Follow-up (months)
1	47	F	Not diagnosed	TC	IA1	RMLB	Cough	Yes	ES, APC	Bleeding	98	Yes	No	55†
2	82	M	Carcinoid	TC	IA1	RB3	Hemoptysis	No	ES, APC	No	23	No	No	18
3	45	F	Not performed	TC	IA2	RULB	Cough, hemoptysis	Yes	ES, APC, cryo	No	53	Yes	No	18†
4	78	F	Carcinoid	TC	IB	LMB	Cough	No	ES, APC	No	33	No	No	12†
5	53	F	Not performed	TC	IB	BI	No symptoms	No	ES, APC	No	16	Yes	No	55†
6	72	F	Not performed	AC	IB	BI	Breathlessness	No	ES, APC	No	33	No	Yes	68
7	70	M	Not performed	AC	IIB	Trachea	Hemoptysis	No	ES, APC	No	58	Yes	No	59†
8	74	M	TC	AC	Recurrence	LMB	Breathlessness	Yes	ES, APC, cryo	No	121	No	No‡	17†

†Survived at the time of data collection.
‡No local recurrence in the left main bronchus was observed at the time of data collection, although multiple liver metastases had occurred at the time of procedures.
AC, atypical carcinoid; APC, argon plasma coagulation; BI, bronchus intermedius; ES, electrocautery snaring; LMB, left main stem bronchus; RB3, anterior segment of right upper lobe bronchus; RMLB, right middle lobe bronchus; RULB, right upper lobe bronchus; TC, typical carcinoid.

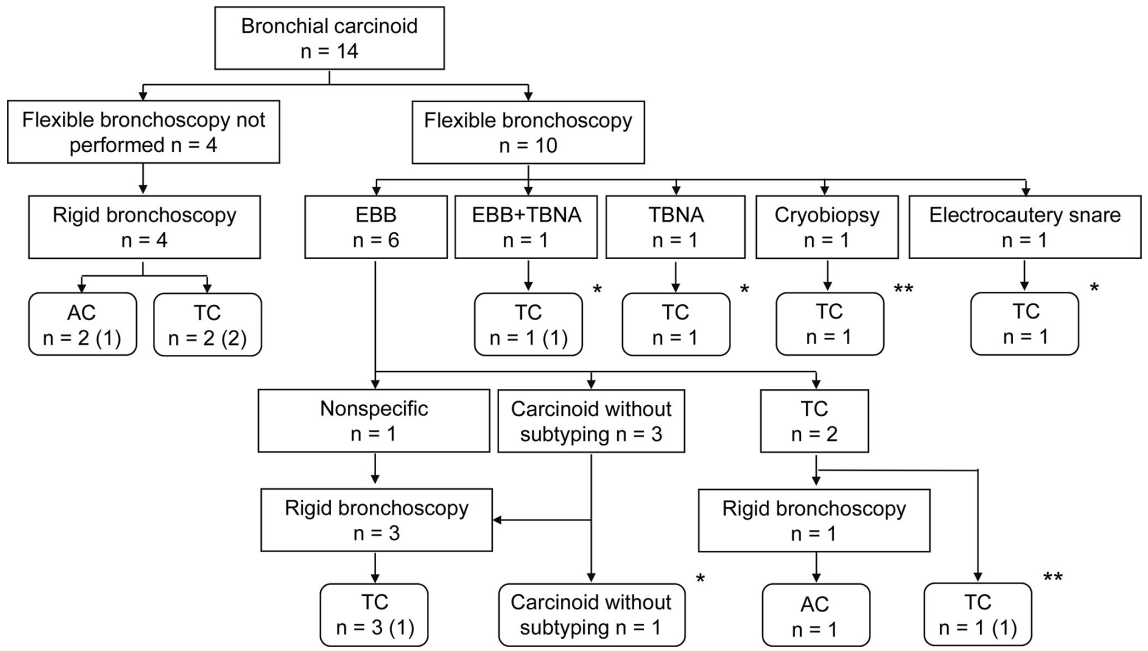

Fig. 1. Diagram illustrates the procedure by which the diagnosis is made.
The number in the parentheses shows the number of patients in whom the final diagnosis is further confirmed from surgically resected specimens. *suggested that patients were asymptomatic and **suggested that patients were symptomatic. Two patients were twenty-four-year-old male and thirty-eight-year-old female, and they had only little respiratory symptoms, so they were able to receive radical resection. Then, we did not perform rigid bronchoscopic intervention.
AC, atypical carcinoid; TC, typical carcinoid; EBB, endobronchial biopsy; TBNA, transbronchial needle aspiration.

(range 47-82 years)] who underwent rigid bronchoscopic intervention were analyzed. The patient characteristics and details of the procedures are shown in Table 1. The diagnostic opportunities were as follows: 5 patients complained of respiratory symptoms, 2 patients were diagnosed by CT scan incidentally, and 1 patient was diagnosed by follow-up CT scan for lung carcinoid. There was no patient with secretion of peptide hormones.

Diagnostic efficacy of rigid bronchoscopy

A diagrammatic representation of the diagnosis is presented in Fig. 1. Flexible bronchoscopy was performed in 10 of the 14 cases of bronchial carcinoid, and only 5 cases (50%) were diagnosed with subtypes. However, rigid bronchoscopy provided a definitive diagnosis of carcinoids with subtype classifications in all eight cases.

Clinical efficacy and outcomes

Seven of the eight patients had respiratory symptoms, such as shortness of breath, coughing, and hemoptysis, and all symptoms were improved after intervention. Two of the three cases with atelectasis were also improved. All the patients underwent pulmonary function tests before intervention but only 3 patients (No. 3, 5, and 8) underwent the tests after intervention, so it was difficult to analyze statistically. However, vital capacity (VC) (from 2.03 to 2.72 L, from 2.38 to 2.66 L and from 2.16 to 2.31 L, respectively), forced expiratory volume in one second (FEV1) (from 1.55 to 2.10 L, from 1.98 to 2.22 L and from 1.48 to 1.65 L, respectively) and peak expiratory flow (PEF) (from 3.68 to 4.84 L/sec, from 6.02 to 6.41 L/sec and from 3.53 to 4.61 L/sec, respectively) were all elevated.

Four patients (3 with TC and one with AC) underwent radical resection sequentially because they were relatively young patients and good performance status with no underlying disease, and none of them had recurrence at the time of data collection. In the study period [median follow-up time was 36.5 months (range 12-68)], recurrence occurred in one AC patient who had not received subsequent management. At the end of this study period, six patients were alive and two patients died, of whom the death of one patient was related to the recurrence of AC, and the other was not related to cancer.

Representative cases (patients No. 3 and No. 7) are shown in Figs. 2 and 3.

Safety

Moderate bleeding occurred in one patient during the rigid bronchoscopic intervention. In this case (patient No. 1), bleeding occurred after right middle lobe bronchial tumor resection using an electrocautery snare. We advanced the rigid bronchoscope into the right main bronchus to prevent blood flooding into the trachea and the left bronchus. Then, we attempted to stop the bleeding by using APC and administering epinephrine under flexible bronchoscopic control. The bleeding was easily controlled without oxygen desaturation.

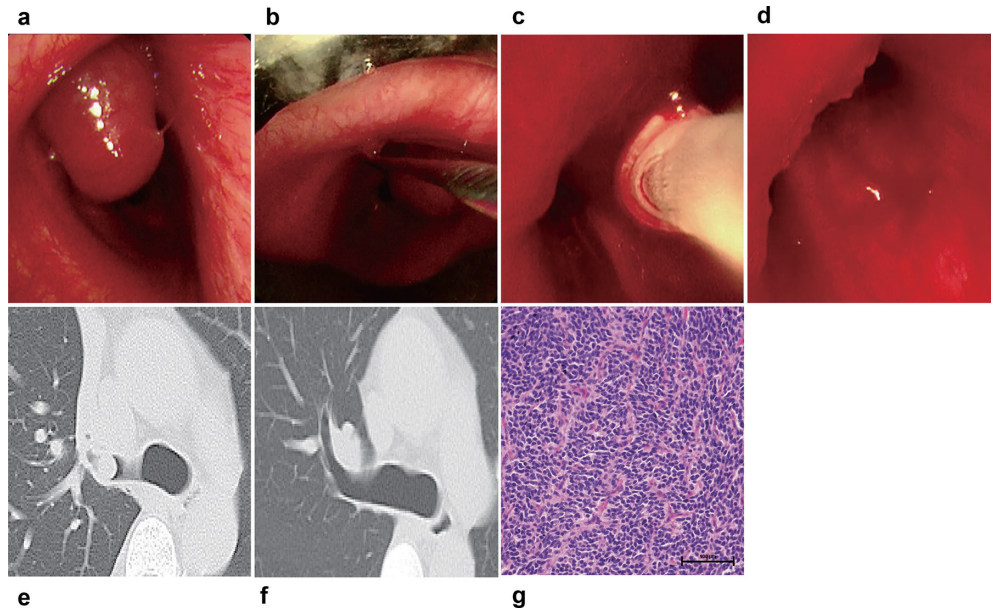

Fig. 2. Bronchoscopic, computed tomographic (CT) and pathologic findings in patient No. 3.
a) Bronchoscopy showing endobronchial tumor occluding right upper lobe bronchus. b) Tumor resection using electrocautery snare. c) Cryorecanalization. d) Reestablished bronchus after bronchoscopic tumor resection. e) A chest CT before bronchoscopic tumor resection showing endobronchial tumor and atelectasis of the right upper lobe lung. f) A chest CT after bronchoscopic tumor resection. g) Microscopic findings of the resected tumor showing typical carcinoid tumor cells with oval nuclear growing monoclonal and subsequencing as alveolar and funicular array, but mitosis is less found (< 2/10 HP) with no necrosis (hematoxylin and eosin staining, × 20 object lens magnification).

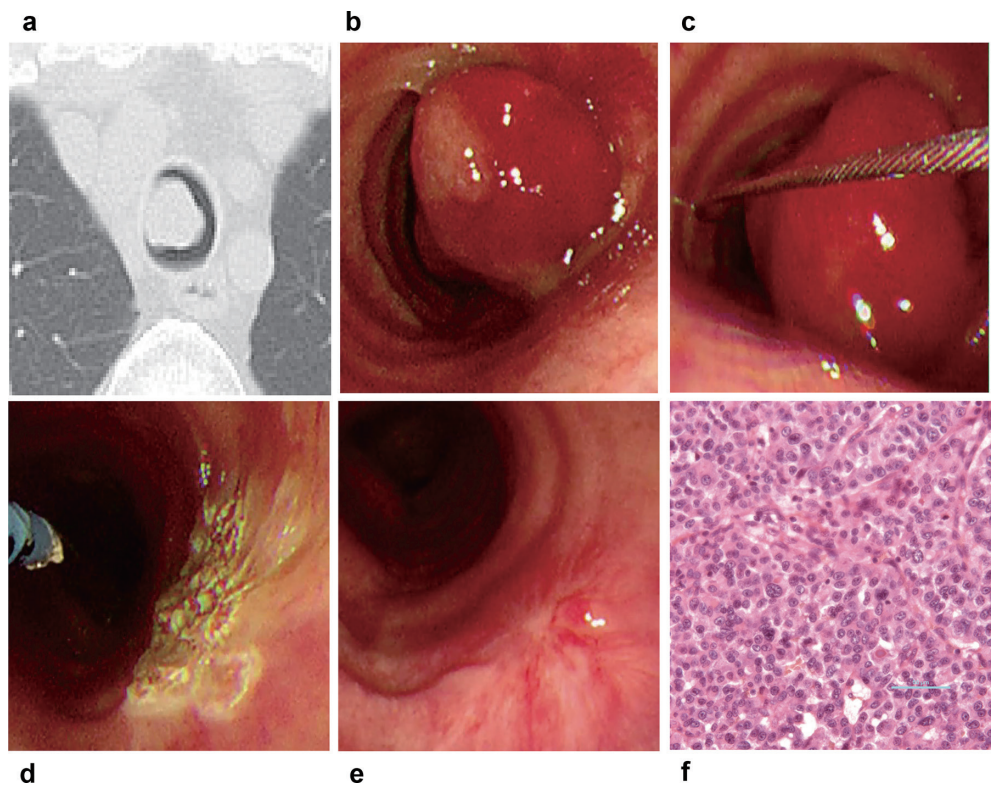

Fig. 3. Bronchoscopic, computed tomographic (CT) and pathologic findings in patient No. 7.
a) A chest CT showing an endotracheal tumor. b) Bronchoscopic findings showing endotracheal tumor. c) Tumor resection using electrocautery snare. d) Argon plasma coagulation. e) Bronchoscopic findings 2 months after procedures. f) Microscopic findings of the resected tumor showing atypical carcinoid tumor cells with dyskaryosis growing and subsequencing as alveolar, funicular and ribbon array, mitosis was often observed (> 2/10 HP) with no necrosis (hematoxylin and eosin staining, × 40 object lens magnification).

Discussion

In our study, eight patients with bronchial carcinoids underwent rigid bronchoscopic intervention, and only one instance of bleeding occurred. Rigid bronchoscopy provided a definitive diagnosis with subtype classification in all patients, and respiratory symptoms improved in all patients. In addition, recurrence was observed in only 1 case.

For the subtype classification of carcinoid, the number of mitotic cells should be calculated in specimens 2 mm^2 in size. If the specimen is small or degenerated by biopsy, the accurate diagnosis is quite difficult. In our study, the diagnostic yield of the subtype by flexible bronchoscopy was 50.0%, the same level as reported in previous reports. Moreover, patient No. 8 was diagnosed with TC by flexible bronchoscopy first; however, the diagnosis changed to AC following rigid brnchoscopic intervention based on the number of mitotic cells.

In addition, bleeding frequently occurs during bronchial carcinoid biopsy. Although the safety of flexible bronchoscopic biopsy is controversial, some investigators have reported cases of serious bleeding. Recently, the usefulness of cryobiopsy for diagnosing carcinoid, which provides larger and higher quality specimens than conventional forceps biopsy, has been reported (Boyd et al. 2014; Gao et al. 2020). However, it is likely associated with a higher frequency of bleeding complications. Fortunately, we experienced four of ten patients with little bleeding administering epinephrine before biopsy, Gao et al. (2020) reported that moderate to severe bleeding occurred in fourteen of forty-nine patients (including four of six patients by cryobiopsy and three of six patients by electrocautery snare) during bronchoscopic sampling for bronchial carcinoids, and 1 patient by cryobiopsy needed treatment in an intensive care unit. On the other hand, rigid bronchoscopy enables the use of hemostatic devices such as balloons and APCs: thus, bleeding can be controlled easily (Stamatis et al. 1990; van Boxem et al. 1998; Bertoletti et al. 2006; Luckraz et al. 2006; Guarino et al. 2016; Reuling et al. 2019). And Ayache et al. (2018) reported that they needed intubation for the maintenance of airway before stopping bleeding and strong cough during bronchoscopy may lead to worsening bleeding. Rigid bronchoscopic intervention is performed under general anesthesia, so there is no cough and it is less painful. We think that this is an advantage for selecting rigid bronchoscopic intervention.

Our study population was relatively older (median 71 years) than in previous studies (Stamatis et al. 1990; van Boxem et al. 1998; Bertoletti et al. 2006; Luckraz et al. 2006; Guarino et al. 2016; Reuling et al. 2019), nevertheless, all patients tolerated the procedures well. Even in elderly patients, rigid bronchoscopy can be performed effectively in terms of improving symptoms and diagnosis without compromising safety.

It is often invasive to resect the central airway lesions. Hence, we carefully choose whether to proceed with surgical resection or not, especially for elderly patients and patients with underlying diseases. Bronchial carcinoids, especially TC, are often growing slowly, so endobronchial resection may be an effective treatment choice.

One of the limitations of this study is that it was a small retrospective study conducted at a single institution. Although the current study demonstrated the high diagnostic yield (100%) of rigid bronchoscopy, we cannot compare it with the yield of flexible bronchoscopy under conscious sedation because of the small patient number and heterogeneity. For the same reason, we cannot compare rigid bronchoscopic resection with surgical resection in terms of radical cure. Another limitation is that the present data were obtained from a special center for bronchoscopic intervention. Seven of the eight patients were referred to our institution from an institution in the neighborhood for rigid bronchoscopic intervention. Thus, the results may not be duplicated in centers with less experienced bronchoscopists.

The current study suggests the usefulness of rigid bronchoscopic intervention for patients with bronchial carcinoids because it can relieve respiratory symptoms and provide a definitive diagnosis more safely and simultaneously than by flexible bronchoscopy. It may play a role for bridge to the following management including surgical resection and simple observation.

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Author Contributions

Atsushi Torii contributed to the conception and design of this study, analysis and interpretation of the data. Masahide Oki contributed to the conception and design of this study. Other authors contributed to acquisition of the data.

Conflict of Interest

The authors declare no conflict of interest.

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