

## Results of bronchoscopic excision in typical carcinoid tumors of the lung in Turkey

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### ABSTRACT

**Aim** Carcinoid tumors of the lung are the tumors originating from the neuroendocrine cells. Surgical excision remains the gold standard for the treatment. Treatment with interventional bronchoscopic excision has also been reported as an alternative option in typical carcinoid tumors of the lung. The aim of this study was to present results and outcomes in patients who were bronchoscopically treated and followed-up.

**Methods** Data of 14 patients, who had undergone bronchoscopic excision due to typical carcinoid tumor of the lung between April 2008 and July 2015 were retrospectively evaluated. Bronchoscopic excision procedures were performed under general anesthesia, while control bronchoscopies were carried out with flexible bronchoscopy. Time between the first and last bronchoscopies was accepted as the follow-up duration.

**Results** A total of 14 patients was evaluated with eight (57.1%) males. Mean age was 43.57±14.07 (23-68) years. The most common symptoms were shortness of breath and coughing. Mean of 5.69±3.35 (2-12) bronchoscopy procedures were performed in the patients during the diagnosis, treatment and follow-up. Mean follow-up duration was 32.0±19.22 months. At the long-term follow-up, two patients developed 50% stenosis and one patient developed granulation tissue in the endobronchial treatment site. None of the patients developed recurrence during the mean 32-month follow-up.

**Conclusion** Endobronchial treatment is a safe and successful treatment method in well selected typical carcinoid tumor cases that are centrally located, having no radiological suspicion of local or distant metastasis, distally visible but not located on the bronchi with a wide base on bronchoscopy.

**Keywords:** bronchoscopy, safety, carcinoid tumor, lung neoplasms, neuroendocrine tumors

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## INTRODUCTION

Carcinoid tumors of the lung are low grade malignant tumors originating from the neuroendocrine cells (1). These tumors are accounted for about 1% of all primary lung tumors (2). It is reported that the incidence of pulmonary carcinoid tumors has increased in the last 3 decades and these tumors are more common in Afro-American and Asian persons (3). This increase in incidence is thought to be associated with the increase in awareness of the disease (3).

Neuroendocrine tumors of the lung have a wide range from typical carcinoid to small cell lung cancer. Carcinoid tumors are classified as typical and atypical carcinoid tumors according to mitosis number, architectural disruptions and necrosis status (4). While  $<2$  mitoses/ $2\text{ mm}^2$  are expected in typical carcinoid tumors, atypical carcinoid tumors are expected to exhibit 2 to 10 mitoses, necrosis and architectural disruptions (4).

Currently recommended gold standard treatment in carcinoid tumors of the lung is surgical excision (5). However, it is recommended to spare the pulmonary tissue as much as possible as in all lung cancer types (5). Therefore, recent several studies have reported that bronchoscopic excision might be an alternative treatment option for typical carcinoid tumors of the lung (6-10). However, patients to be planned for bronchoscopic excision must be carefully selected (11).

The objective of this case series was to share the results and follow-up outcomes of endobronchial treatment patients with carcinoid tumors of the lung.

## PATIENTS AND METHODS

### Patients and study design

Data of the patients diagnosed and treated due to typical carcinoid tumors in the Yedikule Chest Diseases and Chest Surgery Education and Research Hospital (Turkey) between April 2008 and July 2015 were retrospectively evaluated.

Exclusion criteria for endobronchial treatment were: atypical carcinoid tumors, peripherally located carcinoid tumors, radiologically suspected local or distant metastasis or cartilage invasion, failure to bronchoscopically visualize distal part of the lesion and being located on the airway with a wide base.

There were 25 patients presented due to pulmonary carcinoid excisions. Four of these patients were excluded from the study because of suspected lymph node metastasis in the mediastinum or distally not visible of the lesion. Two patients had been previously operated for carcinoid tumors and presented for control bronchoscopy. Biopsy outcome of one patient was reported as atypical carcinoid tumor. These seven patients did not undergo bronchoscopic excision and were excluded from the study. Additionally, four patients with typical carcinoid tumor who had undergone endobronchial treatment were excluded because they did not continue their controls. Thus, data of 14 patients were evaluated.

After the diagnosis was established for typical carcinoid tumor, all the patients were informed about potential benefits and complications of surgical and bronchoscopic excision. Patients who preferred bronchoscopic excision gave a necessary written consent for rigid bronchoscopic intervention. Yedikule Chest Diseases and Chest Surgery Education and Research Hospital's Ethics Committee approved the study.

### Methods

Histopathologic diagnosis was established first with flexible bronchoscopy (Olympus Medical Systems, Tokyo, Japan) in six and with rigid bronchoscopy (Karl Storz Instruments, Germany) in eight patients. All bronchoscopic excisions were performed with the rigid bronchoscope under general anesthesia. After the excision procedure, control bronchoscopies were carried out with the flexible bronchoscope.

All the rigid bronchoscopy procedures were performed under general anesthesia. General anesthesia was performed using total intravenous anesthesia and the patients were ventilated with air oxygen mixture during the procedure. During the flexible bronchoscopy, lidocaine was used for local anesthesia and midazolam for conscious sedation. Argon plasma-coagulation (APC), laser, electrocautery, mechanical excision and cryotherapy were used during the endobronchial treatment.

Time between the first and last bronchoscopies was used when calculating the follow-up duration.

**Statistical analysis**

Mean, percentage distribution and standard deviation values were calculated with descriptive statistical methods and the results were evaluated at 95% confidence interval and 0.05 significance level.

**RESULTS**

A total of 14 patients with eight males (57.1%) were evaluated. No significant difference was found between genders (p=0.5). The mean age was found as 43.57±14.07 (23-68) years. One patient had ankylosing spondylitis and one had chronic obstructive pulmonary disease as comorbidity. Other patients had no comorbidity. Eight patients were active smokers (57.1%).

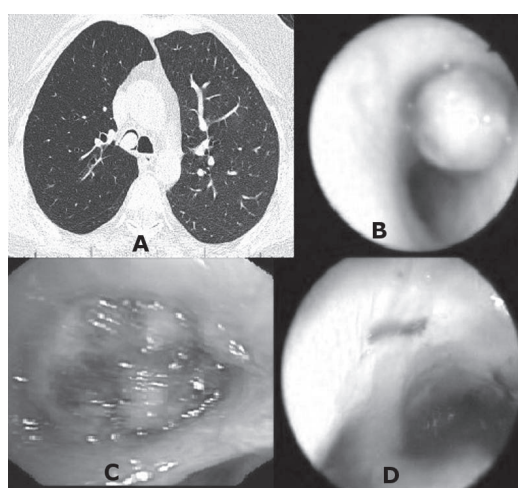
The mean time between onset of the symptoms and diagnosis was found as 15.25±20.95 (0.5-60) months. In the medical history, four patients had pneumonia and the other four asthma diagnosis; these patients were subsequently diagnosed with typical carcinoid tumors (Table 1).

The lesions were found in the right bronchial system in eight patients, in the left bronchial system in five patients, and in trachea in one patient (Table 1).

Eleven patients received endobronchial treatment in a single session. The procedure was performed in 2 sessions in two patients and 3 sessions in one patient. The reason of the need for the second session was prolongation of the procedure in one of two patients, who required the second session. In

the other patient, copious purulent secretion was observed in distal part of the lesion, therefore the procedure was discontinued and subsequently completed after antibiotic therapy. There was ankylosing spondylitis as comorbidity in the patient who required excision in three sessions and because oxygen desaturation was developed in the first session, the process was discontinued. Necrotic tissue developed due to the first session, it was removed in the second session and bronchoscopic excision was completed in the third session.

Radiologic and bronchoscopic images of the case samples are given in Figure 1.



**Figure 1.** In pulmonary tomography (A) lesion obstructing the right main bronchus nearly complete, polypoid lesion in the right main bronchus on bronchoscopy (B), view of the lesion treated with argon plasma coagulation (C) and subsequently obtained full lumen patency (D) are observed (Çetinkaya E., 2013)

**Table 1. Demographic and clinic characteristics of 14 patients with typical carcinoid tumors**

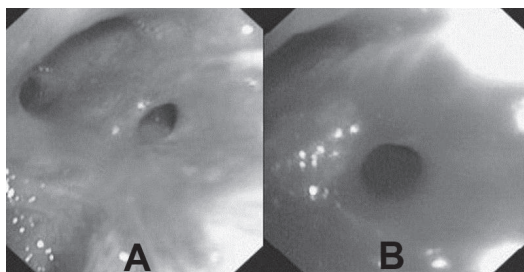
Patient no (gender)	Age	Symptom Duration	Symptom	Lesion location	Complication during procedure	Complication during follow-up	Follow-up duration
1 (Male)	35	12	Hemoptysis Coughing Dyspnea*	Right main bronchus	-	-	68
2 (Male)	64	12	Coughing Dyspnea	Lingula	-	-	30
3 (Male)	47	4	Syncope Fever†	Right upper lobe	Hemorrhage	-	67
4 (Male)	46	6	Hemoptysis	Distal trachea	-	-	34
5 (Female)	39	60	Dyspnea*	Left main bronchus	-	-	45
6 (Male)	40	0.5	Coughing Shortness of breath	Right upper lobe	Hypoxia	Stenosis in the treatment area	44
7 (Male)	68	1	Hemoptysis	Right lower lobe bronchus	-	-	31
8 (Female)	57	36	Dyspnea*	Right Main Bronchus	-	-	22
9 (Male)	23	60	Dyspnea*	Right main ronchus	-	-	18
10 (Female)	29	1	Coughing Fever†	Left upper lobe	Ventricular extrasystole	-	23
11 (Female)	28	5	Sore throat†	Left upper lobe	-	-	38
12 (Female)	47	8	Coughing Dyspnea	Left main bronchus	-	-	10
13 (Female)	30	5	Chest pain Fever†	Right middle lobe	Ventricular extrasystole	Stenosis in the treatment area	10
14 (Male)	57	3	Chest pain	Right intermediary bronchus	-	-	8

\*patients examined with shortness of breath and received inhaler therapy with the diagnosis of asthma; †patients presented with nonspecific symptoms such as syncope fever and sore throat, and diagnosed with pneumonia

Four patients developed a complication during endobronchial treatment. Among these patients, ventricular extrasystole, which did not disrupt hemodynamics during cryotherapy, was observed in two and hemorrhage which was controlled with local adrenaline in one patient. Only in one patient, bronchoscopy procedure was terminated due to hypoxia and completed in the third session.

Mean number of  $5.69 \pm 3.35$  (2-12) bronchoscopy procedures was performed in the patients during the diagnosis, treatment and follow-up. The mean follow-up duration was  $32.0 \pm 19.22$  (8-68) months. None of the patients developed recurrence during this follow-up duration.

In the long-term, follow-up following endobronchial treatment, two patients developed procedure related complications. Two patients developed about 50% stenosis in the excision area (Figure 2). Cryotherapy was sufficient in one and balloon dilatation in the other patient for this stenotic area. One patient developed granulation tissue in endobronchial treatment site, which was treated with cryotherapy and no recurrence was observed (Table 1).



**Figure 2.** Bronchoscopic appearance of the web-like stenosis developed in the opening of posterior segment of the right upper lobe after endobronchial treatment (A), and patency obtained after balloon dilatation (B) (Çetinkaya E., 2011)

## DISCUSSION

Typical carcinoids are accounted for 90% of pulmonary carcinoid tumors (5). Typical carcinoids have been reported to be seen in adults at about 45 years old (12). There are studies reporting an equal gender distribution, although a recent study with a large patient series has reported slightly higher incidence of typical carcinoid tumors in women (12,13). In our series, mean age was consistent with the literature, while no statistically significant difference was observed between female and male patients. We think that this inconsistency in gender distribution might be a result of the relatively small number of our patients.

In atypical carcinoids, regional lymph node involvement is seen in about 50% and distant metastasis in 25% (14), whereas in typical carcinoid tumors this rate is 10-15% for regional lymph node involvement and 3-5% for distant metastasis (14). Associated with this situation, 5-year survival varies between 61% and 88% in atypical carcinoid tumors, while it is higher than 90% in typical carcinoid tumors (15). Therefore, attention should be paid when making a choice between bronchoscopic excision and surgical excision. It has been reported that, persons with the histopathologically definite diagnosis of typical carcinoid tumors, without any finding of extra luminal spread, bronchoscopically well observable and with central localization proper for intervention might be eligible candidates for bronchoscopic excision (16). Similarly, in our case series, several criteria were taken into consideration when making the decision for bronchoscopic excision including all the cases being typical carcinoid tumors, the lesions being located in the airways, distal of the lesion clearly visualized and no local or distal metastases observed.

It is known that hemorrhage, pneumothorax and hypoxia may be developed during interventional bronchoscopy (17). It was reported in a series of 74 cases that burn in the bronchus occurred in one patient as a result of the use of Nd:YAG laser when the patient was inhaling 100% oxygen during bronchoscopic excision (6). In their total 245 bronchoscopic excision series with 175 carcinoid tumors, Cavaliere et al. reported one exitus due to hemorrhage (16). In our series, the procedure was terminated in one patient due to hypoxia and the excision was completed in total 3 bronchoscopy sessions. No other major complication, which would require discontinuation of the procedure or threat for patient's life, was observed.

Cömert et al. endobronchially performed electrocautery, cryotherapy and/or APC in 6 patients with typical carcinoid tumors (18) and they repeated the procedure 3 times in 3 patients, two times in 2 patients and 6 times in one patient. The reason for repeated interventions was recurrence observed in early bronchoscopic controls. Cryotherapy was applied after electrocautery or APC to the origin of the tumor (18). Neyman et al. applied 20 procedures in total 25 patients and performed Nd-Yag laser in a single session in 21,



and multiple sessions in four patients; 16 of 25 patients were endobronchially treated with laser, while the treatment was completed with surgery in nine patients because the tumor was located in the distal bronchial system and full cleaning could not be obtained with bronchoscope (6). In a series of 18 cases, Bertolotti et al. applied cryotherapy to the tumor implantation site (19). Cavaliere et al. included 150 patients with typical carcinoid tumor, performing bronchoscopic laser and mechanic excision in 38 patients (16). Karasulu et al. performed endobronchial treatment with rigid bronchoscopy and additionally APC in two patients with typical carcinoid tumor having polypoid growth (20). In our study, the most commonly used two tools were APC and cryotherapy followed by lower rates of electrocautery, laser and mechanic debulking. Eleven patients received endobronchial treatment in a single session, while three patients received 2 or 3 sessions of treatment. The reason of repeated session was copious purulent secretion in one patient, hypoxia in one patient and prolonged procedure in one patient. In our study, we did not follow a strict method and utilized multiple adjunct methods according to the clinical condition of the patients, bronchial characteristics of the tumors and the developments during the procedure.

In a bronchoscopic excision series of 245 benign lesions, more than 50% stenosis developed after the procedure was seen in two patients (16). In the other series, stenosis was reported in two of 25 patients in long term followed up and treated with balloon dilatation (6). In long-term follow-up of our patients, stenosis about 50% was seen in two patients that did not cause a significant complaint. One of these patients underwent balloon dilatation once and stenosis did not show recurrence. In the other patient, local intervention was made with cryotherapy two times and although full patency could not be provided, the pa-

tient had no clinically significant symptom. Our results are consistent with the literature reporting that although rare complications such as stenosis that can be easily intervened, they might be developed in long term with bronchoscopic excision. Most of the recurrences occur within the first 10 years in typical carcinoid tumors, while recurrences may be seen within the first 5 years in atypical carcinoid tumors (21). There is no consensus on how long cases of neuroendocrine tumors should be followed-up after treatment. In general, there are publications stating that 7-year follow-up is sufficient (22). It is noticed that performed endobronchial treatment in 18 patients with typical carcinoid tumor and reported local recurrence was found only in one patient at 55-month follow-up (19). However, recurrence was not observed in 35 patients who applied curative excision with a follow-up duration between 1 and 198 months in other case series (16). In our 14-case series, despite the mean follow-up duration was 32 month (8-68), no recurrence was observed.

Our study has some limitations including retrospective design, being single center, not being a randomized controlled study and relatively short follow-up duration. However, data of patients who have ideal conditions recommended for bronchoscopic excision and the follow-up duration of 32 months make this study valuable.

Endobronchial treatment is a safe and successful treatment method in well selected typical carcinoid tumor cases that are centrally located, having no radiologically suspected local or distant metastasis, not located on the bronchi with a wide base and distal visible on bronchoscopy.

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## TRANSPARENCY DECLARATIONS

Competing interests: none to declare.

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