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KLİNİK ÇALIŞMA  
RESEARCH ARTICLE

# The role of interventional pulmonology in endobronchial metastasis of renal cell carcinoma

Deniz DOĞAN<sup>1</sup>  
Demet TURAN<sup>2</sup>  
Mehmet Akif ÖZGÜL<sup>2</sup>  
Erdoğan ÇETİNKAYA<sup>2</sup>

<sup>1</sup> Department of Chest Diseases, University of Health Science, Gulhane Training and Research Hospital, Ankara, Turkey

<sup>1</sup> Sağlık Bilimleri Üniversitesi, Gülhane Eğitim ve Araştırma Hastanesi, Göğüs Hastalıkları Bölümü, Ankara, Türkiye

<sup>2</sup> Department of Chest Diseases, University of Health Science, Yedikule Chest Diseases and Chest Surgery Training and Research Hospital, Istanbul, Turkey

<sup>2</sup> Sağlık Bilimleri Üniversitesi, Yedikule Göğüs Hastalıkları ve Göğüs Cerrahisi Eğitim ve Araştırma Hastanesi, Göğüs Hastalıkları Bölümü, İstanbul, Türkiye

## ABSTRACT

### The role of interventional pulmonology in endobronchial metastasis of renal cell carcinoma

**Introduction:** Although metastasis of extrapulmonary solid organ malignant tumors to the lungs is very common, endobronchial metastases are very rare. The most common extrapulmonary tumors that make endobronchial metastases are breast, kidney and colorectal carcinomas.

**Materials and Methods:** In this study, we retrospectively examined the data of eleven renal cell carcinoma patients who underwent endobronchial metastases in an eight-year period.

**Results:** Ten of the patients were male and the mean age was  $55 \pm 1$  (41-71) years. The most common symptom was cough (45.5%, n= 5), on the other hand 18.2% (n= 2) of the patients had no complaints. Right bronchial system, left bronchial system and tracheal distribution rates of endobronchial lesions were 45.5% (n= 5), 63.6% (n= 7) and 27.3% (n= 3) respectively. The mean time from diagnosis of primary renal cell carcinoma to endobronchial metastases was  $47.5 \pm 32$  (5.2-100.5) months. A total of twenty two interventional procedures were performed. All except one patient underwent endobronchial treatment. Argon plasma coagulation was most commonly used as the endobronchial metastases option (n= 10, 100%). The mechanical resection (n= 6, 60%), laser (n= 5, 50%), cryoextraction (n= 5, 50%) and cryotherapy (n= 4, 40%) methods were used other than argon plasma coagulation. The mean survival time was  $19.4 \pm 15.7$  (3.2-40.5) months after endobronchial metastases and  $54.0 \pm 40.4$  (8.7-107.6) months after renal cell carcinoma diagnosis.

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### Yazışma Adresi (Address for Correspondence)

Dr. Deniz DOĞAN  
Sağlık Bilimleri Üniversitesi, Gülhane Eğitim ve Araştırma Hastanesi, Göğüs Hastalıkları Bölümü, ANKARA - TÜRKİYE  
e-mail: dr\_denizz@yahoo.com

**Conclusion:** Extrathoracic malignancy that most metastasis to the airways is renal cell carcinoma. Endobronchial treatment procedures for endobronchial metastasis of renal cell carcinoma can be performed with low complication rates.

**Key words:** Renal cell carcinoma; metastasis; endobronchial metastasis; endobronchial treatment

## ÖZ

### Renal hücreli karsinomun endobronşiyal metastazında girişimsel pulmonolojinin yeri

**Giriş:** Akciğer dışı solid organ tümörlerinin akciğerlere metastazı oldukça sık olmasına rağmen, endobronşiyal metastazları son derece nadirdir. En sık endobronşiyal metastaz yapan akciğer dışı tümörler meme, böbrek ve kolorektal karsinomlardır.

**Materyal ve Metod:** Biz bu çalışmada, sekiz yıllık bir dönemde endobronşiyal metastaz yapmış 11 renal hücreli karsinom hastasının verilerini retrospektif olarak inceledik.

**Bulgular:** Hastaların 10'u erkek ve ortalama yaşları  $55 \pm 1$  (41-71) yıl idi. En sık başvuru şikayeti öksürük (%45.5, n= 5) olan hastaların %18.2 (n= 2)'sinde herhangi bir şikayet yoktu. Endobronşiyal lezyonların sağ bronşiyal sistem, sol bronşiyal sistem ve trakeadaki dağılım oranları sırasıyla %45.5 (n= 5), %63.6 (n= 7) ve %27.3 (n= 3) idi. Primer renal hücreli karsinom tanısından endobronşiyal metastaza kadar geçen ortalama süre  $47.5 \pm 32$  (5.2-100.5) aydı. Toplam 22 girişimsel işlem yapıldı. Hastalardan birisi dışında hepsine endobronşiyal tedavi uygulandı. Endobronşiyal tedavide en sık argon plazma koagülasyon (n= 10, %100) kullanıldı. Argon plazma koagülasyon dışında mekanik rezeksiyon (n= 6, %60), lazer (n= 5, %50), kriyoekstraksiyon (n= 5, %50) ve kriyoterapi (n= 4, %40) kullanıldı. Ortalama sağkalım süresi, endobronşiyal metastazdan sonra  $19.4 \pm 15.7$  (3.2-40.5) ay, renal hücreli karsinom tanısından sonra ise  $54.0 \pm 40.4$  (8.7-107.6) aydı.

**Sonuç:** Hava yollarına en sık metastaz yapan akciğer dışı malignite renal hücreli karsinomdur. Renal hücreli karsinomun endobronşiyal metastazı için endobronşiyal tedavi işlemleri düşük komplikasyon oranları ile yapılabilir.

**Anahtar kelimeler:** Renal hücreli karsinom; metastaz; endobronşiyal metastaz; endobronşiyal tedavi

## INTRODUCTION

Endobronchial metastasis (EBM) is very rare, although pulmonary metastasis is very common in extrapulmonary solid organ malignancies. EBM frequency ranges from 2 to 28% (1,2). The most common cancers that cause EBM are breast, kidney and colorectal carcinomas (3-5). 20-30% of patients with renal cell carcinoma (RCC) have metastases at diagnosis and the most common distant metastatic site is lung parenchyma (6-8). At the same time, RCC is the most common extra-thoracic tumor metastasizing to the central airway (1). Despite being the most common tumor with EBM, there are no large series in the literature and they are generally referred to as case reports. Currently, there is still no elaborate treatment for RCC tumors with EBM. In this study, we aimed to determine the general characteristics, endobronchial therapy (EBT) options and survival times of RCC patients with EBM.

## MATERIALS and METHODS

Eleven patients with RCC who underwent EBM between January 2009 and December 2016 in a tertiary education and research hospital interventional bronchology unit were retrospectively screened. The demographic features such as age and sex of the patients, and the presence of primary RCC were recorded. Distribution of endobronchial (EB) lesions

in the bronchial system and airway stenosis rates, applied EBT methods/frequency, complications due to treatment, and average life expectancy after EBT were analyzed. Airway stenosis due to EB lesion is classified in three groups. 1) Mild stenosis ( $\leq 50\%$  stenosis), 2) Moderate stenosis (51%-70% stenosis), 3) Severe stenosis ( $\geq 71\%$  stenosis). Rigid bronchoscopic procedures (Karl Storz, Germany) were performed under general (total intravenous anesthesia) anesthesia. General anesthesia induction was achieved with midazolam 0.05-0.1 mg/kg, propofol (maximum dose 1000 mg), remifentanyl (maximum dose 2 mg) and rocuronium (maximum dose 50 mg) considering the patient's condition. We did not encounter any side-effects or complications due to anesthesia. Approval for the study was granted by the Scientific Board Committee of Yedikule Chest Diseases and Chest Surgery Training and Research Hospital (08.10.2018).

## RESULTS

Eleven patients (10 male, 1 female) with EB metastasis of RCC were underwent interventional rigid bronchoscopic procedures. The mean age of the patients was  $55 \pm 1$  (41-71) years. Of 11 patients nine were known to have RCC prior to EBT (metachronous cases), and in the remaining two patients EB tumoral lesion was detected as an initial finding without any extrapulmo-

nary tumor (anachronous cases). The time from the detection of primary RCC to the occurrence of EBM was  $47.5 \pm 32$  (5.2-100.5) months in the whole population. The most common symptom of the patients was cough (45.5%, n= 5). Other symptoms were dyspnea (36.4%, n= 4), hemoptysis (27.3%, n= 3) and chest pain (9.1%, n= 1) and the rate of patients without any symptoms was 18.2% (n= 2). Of total 11 patients one had mild, one had moderate and nine had severe airway stenosis. We couldn't reach the initial RCC diagnosis in the of nine patients who were known to have RCC prior to EBT diagnosis. One of these patients applied to our clinic with right total atelectasis. His interventional rigid bronchoscopy revealed a right EB lesion that was totally obstructed the right main bronchus. He was thought to be not eligible for EBT and the procedure was terminated after getting forceps biopsies. The histopathological examination of these biopsies formerly revealed RCC metastasis. This patient died 11 days after the biopsy because of severe respiratory failure due to the progression of the primary disease. Only demographic data of this patient was used in this study. The demographic characteristics, treatment modalities and survival rates of all patients are summarized in Table 1. A total of 22 invasive rigid bronchoscopic procedures were performed. In all cases, interventional procedures were performed by rigid bronchoscopy under IV total anesthesia and the number of interventional procedures per case was  $2.0 \pm 1.1$ . In five of 11 patients, only one session was performed, while in six, multiple interventional procedures were needed. Patients who developed early metastasis frequently underwent one session while patients with late metastasis underwent multiple sessions. Both general ( $47.9 \pm 5$  vs.  $57 \pm 4$  months) and post-EBM survival ( $14.6 \pm 2$  vs.  $18.2 \pm 1$ ) were shorter in the patients that required multiple sessions of interventional EBT procedures. In 90.9% of the patients (n= 10), the level of bronchial stenosis was severe. EBT was performed all except one patient. Argon plasma coagulation (APC), laser, cryoextraction, and mechanical resection methods were used as EBT procedures. In four patients cryotherapy was used to the residual tissue after EBT (Table 2). The most common method was APC and was used in all patients. The most common method after APC was mechanical resection and was used in 60% of patients. Two patients underwent stenting after EBT. One patient with a tracheal lesion had a flat silicone stent, another patient with a left main bronchus lesion had a silicone Y stent. Both patients who

had stents were treated with EBT for four times. A patient was stuck with a Y stent for the first time after 6.5 months with a relapse. Approximately five months later, migraine and mucostasis complications were seen, but there was no need to remove the stent. The other patient underwent tracheal plain silicone stent implantation in the second session and about four months later the patient's own stent was removed. Complications were seen in four patients due to perioperative endobronchial treatment. These were necessity of follow-up in intensive care unit due to arrhythmia in one patient, prolonged hemorrhage in one patient and prolonged intubation in two patients. Endobronchial treatment was associated with no mortality in the early period. EB lesions were observed in 45.5% (n= 5) of the right bronchial system and 63.6% (n= 7) of the left bronchial system, and 27.3% (n= 3) of the trachea were observed (Table 3). One patient with tracheal involvement had tracheal and right main bronchus involvement, one patient had trachea, right main bronchus and left main bronchus involvement, and only the last patient had tracheal involvement. The mean duration of metachronous tumors in these three patients was  $55.5 \pm 40$  (30.8-100.5) months. The mean survival time after EBM was  $19.4 \pm 15.7$  (3.2-40.5) months and the mean life span of the whole population after RCC diagnosis (RCC diagnosis-ex) was  $54.0 \pm 40.4$  (8.7-107.6) months.

## DISCUSSION

Lung is the most common metastatic cite of RCC. It is also a non-thoracic solid tumor that most commonly metastasizes to the EB system. In the literature, there is a lack of published reports regarding the endobronchial metastases of the RCC. Most of them are generally case reports or limited series of cases (9-16). Metastases to the endobronchial system of RCC are often seen as metachronous cases (11). In our study, 82% of our patients (9 out of 11 patients) were diagnosed as primary RCC before EBM. Our two patients were first presented with endobronchial findings (anachronous cases). In the literature, the duration from the primary diagnosis of extra pulmonary tumors to the development of the EBM was reported at rates ranging from 36 months to 136 months, while there is not enough data on RCC (4,9,11,17,18). Literature data often include case reports and publications in the form of systemic review. Alessandro et al. (11) evaluated the data of 174 EBM patients retrospectively during the 18-year period and reported the average time from primary diagnosis to EBM in patients with

**Table 1.** Patients characteristics.

Case no	Age/Sex	Location	No. of treatments	APC	Laser	Cryotherapy	Cryoextraction	MR	Stent	Interval (month)	Survival-1 (month)	Survival-2 (month)
1	56/M	Left upper lobe bronchus	1	+	-	-	-	-	-	63.87	101.1	37.23
2	68/M	Left main bronchus	1	+	+	+	+	+	-	Not known	Not known	40.5
3*	71/M	Right main bronchus	1	-	-	-	-	-	-	Not known	Not known	-
4	65/M	Left main bronchus	4	+++	-	+	-	+	+	0**	16.43	16.43
5	41/M	Trachea	4	++	-	-	-	+	+	100.5	107.57	7.07
6	54/M	Intermedier bronchus	1	+	-	-	-	-	-	5.17	8.67	3.50
7	43/M	Left main and left upper lobe bronchus	2	+	+	-	-	+	-	28.47	68.14	39.67
8	50/M	Trachea and right main bronchus	1	+	+	+	+	-	-	30.8	34.03	3.26
9	45/F	Left main bronchus	2	++	+	-	+	-	-	68.43	96.86	28.43
10	55/M	Trachea, right and left main bronchus	3	++	+++	++	+	+	-	35.1	43.40	8.30
11	57/M	Right main bronchus	2	++	-	-	+	+	-	0**	9.53	9.53
Mean	55 ± 1		2.0 ± 1.1	1.45 ± 0.8	0.63 ± 0.9	0.45 ± 0.7	0.45 ± 0.5	0.54 ± 0.5		47.5 ± 32	54.0 ± 40.4	19.4 ± 15.7

\* Case 3 was not suitable for endobronchial therapy, we therefore only used its demographic data's.  
 \*\* Patients diagnosed with renal cell carcinoma by endobronchial biopsy (anachronous cases).  
 Interval: Interval between diagnosis of renal cell carcinoma and endobronchial metastasis.  
 Survival-1: Interval between diagnosis of renal cell carcinoma and mortality.  
 Survival-2: Interval between endobronchial metastasis and mortality.  
 APC: Argon plasma coagulation, MR: Mechanical resection.

**Table 2.** Techniques of endobronchial therapy

Bronchoscopic therapy	Number of patients (%)
APC	10 (100)
Mechanical resection	6 (60)
Laser	5 (50)
Cryoextraction	5 (50)
Cryotherapy	4 (40)

APC: Argon plasma coagulation.

renal carcinoma as 82 (17.47-147.27) months. Sorensen reported the duration of EBM of 34 kidney-derived tumors as 35 (0-114) months after English literature scan from 1962 to 2002 (17). In our patient population, the mean time from primary RCC to EBM was  $47.5 \pm 32$  (5.2-100.5) months. In our study, endobronchial lesions were mostly found in the left bronchial system. The rates of left bronchial system, right bronchial system and tracheal involvement were 63.6% (n= 7), 45.5% (n= 5) and 27.3% (n= 3) respectively. In the literature, we could not reach any data on the distribution of RCC metastases in the endobronchial system. However, when looking at the endobronchial metastases of extrapulmonary solid malignancies, Sorensen found that both bronchial systems were equally held (41% vs. 41%), Kiryu et al. reported right bronchial involvement by 80% (4,17). Tracheal metastasis of extrapulmonary solid tumors are seen in about 4% (17). In a systematic review Madariaga et al. searched the published English literature between 1978 to 2017 (10). They found that the most common extra-thoracic primary tumors were colon and kidney. The authors reported that the RCC had the longest metachronous tumor development time with an average of 90.0 (48.0-204.0) months in this study. Tracheal involvement was observed in three patients in our patient population. The mean duration of onset of metachronous tumors in these patients was  $55.5 \pm 40$  (30.8-100.5) months. In the absence of

tracheal involvement, this time was shorter and the average was  $41.5 \pm 30$  (5.2-68.4). Five and ten year survival rates of RCC after curative resection of pulmonary metastasis are 40% and 33%, respectively (19). Metastasectomy is the most prominent treatment method in selected cases because the mean survival time is as short as 10 months in cases of untreated metastatic RCC (20). However, there is no accepted treatment option for endobronchial metastases of RCC. Different EBT techniques have been applied in endobronchial RCC metastases in the literature including laser therapy, cryotherapy and electro-surgery snaring. In cases with tumor-induced bronchial obstruction, these treatment modalities are not curative but provide excellent palliation and a positive contribution to the survival of EBTs (13,14,16,21-25). These treatment approaches are often chosen and present as a viable option in cases with bronchial tumor obstruction. All of our patients underwent rigid bronchoscopy under IV total anesthesia and the mean number of interventional procedures per procedure was  $2.0 \pm 1.1$ . Except one patient who was not eligible for endobronchial therapy, the entire study population underwent EBT. The most common used EBT procedure was APC. The other options for locating and characterizing the EB tumors were laser, cryoextraction cryotherapy, and mechanical resection. In our study, overall survival ( $47.9 \pm 5$  vs.  $57 \pm 4$  months) and survival after EBT ( $14.6 \pm 2$  vs.  $18.2 \pm 1$  months) were shorter in patients requiring multiple sessions of intervention for EBT. This can be explained by the necessity of multiple endoscopic interventions due to excessive tumor volume or the tumor aggressivity. In this regard it is known that tumor volume is negatively correlated with life expectancy (26). Because of endobronchial tumor stenosis caused by extrapulmonary malignancies, stent applications for palliation can also be performed. This method is frequently applied for strictures due to esophagus and thyroid cancers (27-31). Because of the close proximity of the

**Table 3.** Location of endobronchial metastases diagnosed by bronchoscopy with biopsy in 11 patients

Locations	Number of patients (%)	
Trachea	3	
Right	Main bronchus	4
	Intermedier bronchus Intermedier bronchus	1
Left	Main bronchus	5
	Upper lobe bronchus	2

esophagus and thyroid malignancies, airway invasion can be seen more frequently. In addition, literature refers stent applications for colorectal, hepatocellular and breast cancers with EBM (32-34). Migration, formation of granulation tissue, mucostasis and fistula development are the most frequent complications in stent applications and care must be taken in terms of these complications (35). Stent applications may be performed after resection in RCC metastases. In our patient population, two patients underwent stent implantation. Approximately five months after stent insertion, complications of thrombosis and mucostasis were observed in the first patient, but no stent removal was required. The other patient had no complication, but four months later the stent was removed due to the request of the patient. The incidence of invasive bronchoscopic treatment varies from 1.6 to 11.0% in the literature, and the mortality rates due to treatment are reported to be 0.8 to 3.0% (36). These general complications include massive hemorrhage, endobronchial burns (in hot methods), failure in sufficient airway opening, asphyxia, tracheoesophageal fistula, mediastinal emphysema, pneumothorax, transient desaturation, chest pain, bronchospasm, atelectasis, airway laser, bronchial rupture, cardiac arrhythmia. In our patient population, there were only four complications associated with endobronchial treatment during the perioperative period. These were arrhythmia in one patient, prolonged hemorrhage in one patient, and need of extended intensive care unit due to prolonged intubation in two patients. No perioperative mortality was observed secondary to endobronchial treatment. In the literature, there are various literature data on the mean survival of non-small cell lung tumors after EBM. In general, although it depends on the biological behavior of the primary tumour, the mean survival time is usually short (37). Sorensen, in his study scanning English Medical Sources between 1962 and 2002, reported a median survival time of 204 patients as 15.2 (0-150) months after EBM (17). Similarly, in his series of 16 patients, Kiryu et al. reported the survival time as 15.5 months (4). A total of 43 diseases were present in a more current series, Lee et al. (9) reported mean survival after EBM as 16.1 (0-59) months (9). Although there is not enough data on survival time after EBM of kidney tumors in the literature, Heitmiller et al. reported that the RCC is associated with longer survival rates than other tumor metastases (38). In another study,

Sorensen evaluated the data of 204 metastatic disease for more than 40 years (17). In his study 34 patients had EB metastasis of RCC and their survival time after EBM diagnosis was 20 (0-150) months. In our study, mean survival was  $19.4 \pm 15.7$  (3.2-40.5) months after EBM. This value is consistent with Sørensen's data, and as mentioned above, is longer than the survival times of other tumor metastases. Therefore, given the current literature data and the findings in our study, the use of endobronchial treatments may be recommended in the presence of EBM due to RCC, if necessary in selected cases, including aggressive treatments. Because of the low complication rates of the EBT options, multiple interventional sessions are acceptable and safe with minimal additional complication rates. Although endobronchial treatments are not curative in most cases, endobronchial tumor tissue should be resected. We shouldn't hesitate to perform multiple sessions in this patient group.

The most important limitations of our study were the small sample size and the retrospective design. Although these limitations we achieved some invaluable results that would contribute to the literature. For future high volume prospective studies can strengthen and improve our results.

## CONCLUSION

In conclusion, these results suggest that the application of EBT methods may be used as a treatment approach in patients with EB metastasis of RCC, given the benefits of surgical resection of the metastatic lesions to be the best option in RCC patients. In the light of our results, we consider and recommend that EBT options can be performed with low complication rates and with an advantage of survival.

## CONFLICT of INTEREST

No conflict of interest declared by the authors.

## AUTHORSHIP CONTRIBUTIONS

Concept/Design: DD, EÇ

Analysis/Interpretation: DT, MAÖ

Data Acquisition: DT, MAÖ

Writing: DT, MAÖ

Critical Revision: All of authors.

Final Approval: All of authors.

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