Diagnostic Yield and Bleeding Complications Associated With Bronchoscopic Biopsy of Endobronchial Carcinoid Tumors

Yang Gao, MD,† Teng Moua, MD,† David E. Midthun, MD,† John J. Mullon, MD,† Paul A. Decker, MS,‡ and Jay H. Ryu, MD†*

Background: **Bronchial carcinoid often appears hypervascular on bronchoscopic visualization and may be associated with hemoptysis. The diagnostic yield and bleeding complications associated with bronchoscopic biopsy of bronchial carcinoid tumors remain unclear.**

Materials and Methods: **Patients with bronchial carcinoid tumors that were bronchoscopically visualized and biopsied at our tertiary referral medical center, over an 8-year period from 2010 to 2017, were retrospectively identified and reviewed to assess diagnostic yield and bleeding complications. Correlations with patient characteristics and carcinoid tumor features were analyzed.**

Results: **Forty-nine patients were included (57% female). Tumors were predominantly (71%) located in proximal airways (mainstem and lobar bronchi). Bronchoscopic biopsy was diagnostic in 45 patients (92%). Thirteen patients (27%) experienced moderate (n = 12, 25%) or severe (n = 1, 2%) bleeding. Among these, 6 tumors (46%) had a vascular appearance and 4 patients (31%) had experienced recent hemoptysis. However, neither vascularity nor hemoptysis was associated with bleeding at biopsy ($P = 0.68$ and 0.73, respectively). Carcinoid tumors were classified as typical in 79% and atypical in 21% with no difference in diagnostic yield or bleeding risk ($P = 0.28$ and 0.92, respectively). Tumor size was also not associated with increased diagnostic yield or bleeding risk ($P = 0.54$ and 0.39, respectively).**

Conclusion: **Bronchoscopic biopsy of endobronchial carcinoid is associated with a high diagnostic yield and severe bleeding is rarely encountered. Diagnostic yield and bleeding seemed independent of vascular tumor appearance or history of recent hemoptysis.**

Key Words: bronchial carcinoid, bronchoscopic biopsy, bleeding complication, diagnostic yield

(*J Bronchol Intervent Pulmonol* 2020;27:184–189)

Received for publication June 4, 2019; accepted November 22, 2019.

From the *Division of Pulmonary Medicine, Guang'anmen Hospital, China Academy of Chinese Medical Sciences, Beijing, China; †Division of Pulmonary and Critical Care Medicine; and ‡Department of Health Sciences, Mayo Clinic, Rochester, MN.

Disclosure: There is no conflict of interest or other disclosures.

Reprints: Jay H. Ryu, MD, Division of Pulmonary and Critical Care Medicine, Gonda 18 South, Mayo Clinic, 200 First St. SW, Rochester, MN 55905 (e-mail: ryu.jay@mayo.edu).

DOI: 10.1097/LBR.0000000000000639

Carcinoids belong in the spectrum of neuroendocrine tumors and are encountered most commonly in the gastrointestinal tract, but may also be seen in the lung, ovary, thymus, kidney, thyroid, or other sites.[1] When occurring in the lung, the majority arise in the proximal airways. Pulmonary carcinoid tumors are rare and account for 1% to 2% of adult lung malignancies.[2]

Although pulmonary carcinoid tumors are often visualized by bronchoscopy, bronchoscopic biopsy raises concern for bleeding complications because of their vascular appearance. The majority of studies pertaining to pulmonary carcinoid tumors are surgical case series without detailed analysis of bronchoscopic data. Reported incidence of moderate to severe hemorrhage associated with bronchoscopic biopsy of carcinoid tumors has been as high as 52%.[3] On the other hand, some studies have reported bronchoscopic biopsy of carcinoid tumors to be relatively safe.[4–6]

Our study objective was to analyze the diagnostic yield and bleeding complications of bronchoscopic biopsy in patients with bronchial carcinoids in the current era. In addition, we sought to correlate diagnostic and bleeding rates with patient and tumor characteristics.

MATERIALS AND METHODS

Using a computer-assisted search of the medical records, we identified all patients with biopsy-proven bronchial carcinoid tumors at our tertiary referral medical center, over a period of 8 years from 2010 to 2017. Of 115 patients identified, 66 whose tumors were not visible on bronchoscopy or did not undergo bronchoscopic assessment at our medical center were excluded. All bronchoscopic procedures were performed in the operating room except for 2 (4%) which were performed in the outpatient bronchoscopy suite. Six patients underwent rigid bronchoscopy under general anesthesia, whereas the remaining 43 patients underwent flexible fiberoptic bronchoscopy under monitored anesthesia care with endotracheal tube placement. Bronchoscopists

TABLE 1. Classification of Bleeding During Bronchoscopy

No bleeding	Traces of blood with no need for continuous suctioning. Bleeding stopped spontaneously
Mild bleeding	Continued suctioning of blood from the airways. Bleeding stopped spontaneously
Moderate bleeding	Use of cold saline and or epinephrine to stop bleeding. Intubation of the biopsied segment with the bronchoscope into the wedge position
Severe bleeding	Placement of bronchial blocker or balloon catheter, applying fibrin sealant. Fluid resuscitation, blood transfusion, admission to critical care unit, or death

Adapted from British Thoracic Society Bronchoscopy Guideline.[7] Adaptations are themselves works protected by copyright. So in order to publish this adaptation, authorization must be obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.

were either interventional-certified or advanced diagnostic bronchoscopists.

We extracted data including age, sex, race, smoking status, hemoptysis history before diagnosis, tumor location, tumor appearance (vascularity), tumor size (assessed from surgically resected specimen), bronchoscopic biopsy technique, specimen description, histopathologic findings, procedure-associated bleeding complications, interventions necessary to manage bleeding, and patient outcomes (procedure-related hospitalization or mortality) from the medical records. Tumor vascularity or hypervascular appearance was defined as a "hyperemic" appearance with "visible surface blood vessels," as described by the performing bronchoscopist in the procedure note. Severity of bleeding associated with bronchoscopic biopsy was classified by the type of clinical intervention necessary to stop the bleeding and stabilize the patient (Table 1).[7] We categorized carcinoid tumors as typical or atypical based on the 2004 World Health Organization criteria as described in the original diagnostic histopathologic reports.[8] Tumor location was categorized as central or peripheral, with central tumors arising from the mainstem or lobar bronchi, and peripheral tumors located distally to this; none arose from the trachea.

Statistical Analysis

Categorical variables such as sex, race, tumor vascularity, and histologic subtype are presented as counts or proportions and compared using χ^2. Continuous variables such as age and tumor size were compared using Kruskal-Wallis test. *P*-values <0.05 were considered statistically significant. An analysis was performed using R version 3.4.2 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Forty-nine patients were included in the final analysis [28 women (57%) and 21 men (43%)] (Table 2). The median age was 55 years (interquartile range: 38 to 66); 7 (15%) were active smokers, and 13 (28%) were former smokers. Seventeen patients (35%) had hemoptysis during the 12 months before procedure.

Endobronchial biopsies consisted of 26 forceps biopsies, 6 electrocautery loop snares, 6 cryobiopsies, 14 endobronchial needle aspirations, and 6 rigid bronchoscopies with the intention of complete resection (9 patients underwent combined biopsy modalities in 1 procedure). Debulking was performed in 6 patients who underwent rigid bronchoscopy and 4 additional patients during flexible fiberoptic bronchoscopy.

Tumor appearance on bronchoscopy was described as hypervascular in 25 patients (51%). Thirty-five patients (71%) had centrally located tumors (mainstem and lobar bronchi) whereas 14 (29%) were located in segmental or subsegmental bronchi. Median tumor size at resection was 2.2 cm (interquartile range: 1.6 to 3.6). Among 43 patients with assessed histologic differentiation, 34 (79%) were typical and 9 (21%) were atypical carcinoid tumors; 6 patients did not have definitive resection at our institution to determine final classification.

Bronchoscopic biopsy was diagnostic of carcinoid in 45 (92%) patients (Table 2). No presenting tumor characteristics including location, appearance (vascularity), size or histologic type correlated with diagnostic yield. Among the 4 that were nondiagnostic on bronchoscopic biopsy, sampling techniques included 2 endobronchial needle aspirations and 2 forceps biopsies. Subsequent carcinoid diagnosis was confirmed on surgical resection for all 4 patients.

Thirteen (27%) patients experienced moderate to severe bleeding at the time of bronchoscopic sampling. Only 1 patient (2%) experienced severe bleeding and required an intensive care unit (ICU) stay. There were no procedure-related deaths (Table 3). These 13 bleeding complications were caused by 7 endobronchial forceps biopsies, 3 electrocautery loop snares, 4 cryobiopsies (resulted in the case of severe bleeding from attempted debulking of an obstructing tumor), and 3 endobronchial needle aspirations (4 patients had combined biopsy modalities). Three of 4 patients experiencing moderate to severe bleeding with the use of the

TABLE 2. Patient Characteristics and Diagnostic Yield

Characteristics	All Patients (N = 49), n (%)	Diagnostic Yield, n (%)		*P*
		Diagnostic (n = 45)	Nondiagnostic (n = 4)	
Age (y), median (IQR)	55.5 (38-66)	56.8 (41-66)	46.5 (33.25-59.5)	0.465
Sex				0.175
Male	21 (43)	18 (40)	3 (75)	
Female	28 (57)	27 (60)	1 (25)	
Race				0.868
Caucasian	46 (94)	42 (93)	4 (100)	
African American	1 (2)	1 (2)	0 (0)	
Other	2 (4)	2 (5)	0 (0)	
Smoking				0.639
N-missing data	2	2	0	
Current	7 (15)	7 (16)	0 (0)	
Former	13 (28)	12 (28)	1 (25)	
Never	27 (57)	24 (56)	3 (75)	
Tumor hypervascularity				0.277
Yes	25 (51)	24 (53)	1 (25)	
No	24 (49)	21 (47)	3 (75)	
Tumor size (cm), median (IQR)	2.2 (1.6-3.6)	2.2 (1.6-3.6)	2.8 (2.2-3.6)	0.538
Histologic type				0.280
N-missing data	6	6	0	
Atypical	9 (21)	9 (23)	0 (0)	
Typical	34 (79)	30 (77)	4 (100)	
Tumor location				0.187
Central	35 (71)	31 (69)	4 (100)	
Peripheral	14 (29)	14 (31)	0	

P-value: comparison between diagnostic and nondiagnostic groups.
IQR indicates interquartile range.

cryoprobe underwent tumor debulking and the remaining patient had thrombocytopenia (55×10^9/L) related to chronic hepatitis C virus infection.

Recent hemoptysis and hypervascular-appearing tumors were described in 31% (n = 4) and 46% (n = 6), respectively among those patients experiencing moderate to severe bleeding; neither were significantly different compared with patients with none or mild bleeding ($P = 0.73$ and 0.68, respectively). Although mean tumor size (3.1 ± 2.2 cm) was greater in patients with moderate or severe bleeding, the difference was not significant ($P = 0.39$). Other clinical features were similar to those with mild or no bleeding, including central versus peripheral airway location (77% vs. 69%, respectively) and typical versus atypical carcinoid histology (78% vs. 79%, respectively).

DISCUSSION AND CONCLUSIONS

In our study, bronchoscopic biopsy of endobronchial carcinoid tumors was associated with a high diagnostic yield (92%) and acceptable bleeding risk. Most patients had none to only mild bleeding which ceased spontaneously. Interventions for postbiopsy bleeding were needed in 27% of cases and only 1 patient (2%) experienced severe bleeding resulting in ICU stay without transfusion; there was no procedure-related mortality. No presenting clinical-related or tumor-related characteristics, including tumor vascularity or recent history of hemoptysis, correlated with increased bleeding risk. However, we acknowledge that our study is likely underpowered to detect important difference in the factors associated with bleeding. We were also unable to identify clinical-related or tumor-related characteristics that correlated with diagnostic yield.

The diagnostic yield for bronchoscopic biopsy in our study compares favorably to prior studies with reported diagnostic rates ranging from 48% to 100% (Table 4).[3–6,9–14] This broad range of diagnostic rates is explained, in part, by selection bias, including ours, which were all retrospectively compiled. Patients who underwent bronchoscopy but did not undergo bronchoscopic biopsy for various reasons would have been excluded from analysis. In addition, our study included only bronchoscopically visible endobronchial carcinoid tumors, where in recent years nonvisible pulmonary carcinoid tumors may be located and accessed using newer technologies such as endobronchial ultrasound.[19]

In general, diagnostic flexible bronchoscopy is considered a safe procedure with low incidence of

TABLE 3. Patient Characteristics and Bleeding Complication

Characteristics	All Patients (N = 49), n (%)	Bleeding, n (%)		*P*
		No or Mild (n = 36)	Moderate to Severe (n = 13)	
Age, median (IQR)	55.5 (38-66)	54.5 (37.75-69.75)	60 (49-63)	0.830
Sex				0.709
Female	28 (57)	20 (56)	8 (62)	
Male	21 (43)	16 (44)	5 (38)	
Race				0.562
Caucasian	46 (94)	33 (92)	13 (100)	
African American	1 (2)	1 (3)	0 (0)	
Other	2 (4)	2 (5)	0 (0)	
Smoking status				0.491
N-missing data	2	2	0	
Current	7 (15)	6 (18)	1 (8)	
Former	13 (28)	8 (23)	5 (38)	
Never	27 (57)	20 (59)	7 (54)	
Hemoptysis prior 12 mo				0.819
Yes	17 (35)	13 (36)	4 (31)	
No	32 (65)	23 (64)	9 (69)	
Vascular appearance				0.750
Yes	25 (51)	19 (53)	6 (46)	
No	24 (49)	17 (47)	7 (54)	
Tumor size (cm), median (IQR)	2.2 (1.6-3.6)	2.2 (1.5-3.2)	2.2 (1.8-4.0)	0.382
Histologic type				0.915
N-missing data	6	2	4	
Atypical	9 (21)	7 (21)	2 (22)	
Typical	34 (79)	27 (79)	7 (78)	
Tumor location				0.609
Central	35 (71)	25 (69)	10 (77)	
Peripheral	14 (29)	11 (31)	3 (23)	

P-value: comparison between NM (no or mild) group and MS (moderate or severe) group.
IQR indicates interquartile range.

significant bleeding ranging from 0.2% to 5.0%.[20–25] For the carcinoid patients in our cohort, by contrast, the incidence of moderate to severe bleeding was higher, although no or minimal bleeding was evident for the majority. The reported bleeding incidence in carcinoid patients undergoing bronchoscopic biopsy vary significantly, ranging from 0% to 52%, in part, due to divergent criteria in defining bleeding severity and differing biopsy techniques (Table 4).[3–6,9–17] For example, some studies reporting absence of bleeding complications only accounted for "significant" or "appreciable" hemorrhage without defining their

TABLE 4. Summary of Prior Studies in the Literature

References	Year	No. Patients With Bronchoscopic Biopsy	Diagnostic Yield (%)	Overall Bleeding Incidence (%)
Todd et al[9]	1980	35	NR	17
Hurt and Bates[10]	1984	61	NR	3
McCaughan et al[11]	1985	25	96	12
Rea et al[5]	1989	27	59	0
Conley et al[12]	1992	7	100	43
Schreurs et al[13]	1992	64	81	NR
Fink et al[6]	2001	87	83	0
Filosso et al[4]	2002	47	60	0
Schrevens et al[14]	2004	67	48	NR
Thomas et al[3]	2008	23	92	52
Machuca[15]	2010	89	83	0
Zhong[16]	2012	100	70	0
Correia Sda[17]	2014	41	76	NR
Dixon[18]	2016	35	66	6

NR indicates not reported.

criteria.[4–6] The hypervascular appearance of carcinoid tumors in combination with history of recent hemoptysis may cause hesitation in performing bronchoscopic biopsies in such patients. However, our study suggests moderate to severe bleeding requiring specific intervention is not common. Most moderate to severe bleeding if occurred was immediately controlled, with only 1 patient requiring ICU level monitoring post-procedure and with no long-term sequelae.

In general, fine needle aspiration is believed to be safe and less traumatic.[19,20,26] In our cohort, it seemed to be associated with lower yields (2 nondiagnostic in 4, 50%) compared with other bronchoscopic biopsy techniques (forceps: 91%, cryo:100%) allowing larger samples. Cryobiopsy of endobronchial lesions yields larger biopsy specimens and provides better diagnostic yield compared with traditional forceps biopsy, both for assessing benign and malignant disease, but may increase bleeding risk.[27–30] However, some authors argue the cold probe may exert a vasoconstrictive effect leading to decreased bleeding.[31,32] In our cohort, 67% of patients undergoing cryobiopsy experienced moderate (n = 3) to severe bleeding (n = 1), although diagnostic yield was 100%.

Our study cohort of patients with endobronchial carcinoid tumors shared similar clinical and epidemiologic features to those generally attributed to patients with bronchopulmonary carcinoid tumors. These features include a mean age at diagnosis in the sixth decade of life, a slight prevalence in females over males, and high proportion of centrally located tumors, all of which are consistent with previous studies.[4,6,14,18,33] To the best of our knowledge, this is the first study to explore potential correlations between diagnostic and bleeding rates with patient and tumor characteristics in those undergoing bronchoscopic biopsy for endobronchial carcinoids.

There are several limitations of our study. First, a retrospective approach with limited sample size may introduce selection and information bias, with missing or incomplete data and inability to establish causation. Second, our samples do not represent the total population of pulmonary carcinoid patients, with diagnostic yield applicable only to those endobronchially visible at bronchoscopy. Although not common in clinical practice, the scenario of endobronchial carcinoid adds insights into procedurally related complications and yield in diagnostic management plans.

In conclusion, bronchoscopic biopsy of endobronchial carcinoid tumors is associated with high diagnostic yield and serious bleeding complications are rare. Hypervascular appearance or prior history of hemoptysis does not seem to predict higher risk of bleeding from bronchoscopic biopsy of carcinoid tumors.

REFERENCES

1. Kunz PL. Carcinoid and neuroendocrine tumors: building on success. *J Clin Oncol*. 2015;16:1855–1863.
2. Dasari A, Shen C, Halperin D, et al. Trends in the incidence, prevalence, and survival outcomes in patients with neuroendocrine tumors in the United States. *JAMA Oncol*. 2017;3:1335–1342.
3. Thomas R, Christopher DJ, Balamugesh T, et al. Clinico-pathologic study of pulmonary carcinoid tumours: a retrospective analysis and review of literature. *Respir Med*. 2008;102:1611–1614.
4. Filosso PL, Rena O, Donati G, et al. Bronchial carcinoid tumors: surgical management and long-term outcome. *J Thorac Cardiovasc Surg*. 2002;123:303–309.
5. Rea F, Binda R, Spreafico G, et al. Bronchial carcinoids: a review of 60 patients. *Ann Thorac Surg*. 1989;47:412–414.
6. Fink G, Krelbaum T, Yellin A, et al. Pulmonary carcinoid: presentation, diagnosis, and outcome in 142 cases in Israel and review of 640 cases from the literature. *Chest*. 2001;119:1647–1651.
7. Du Rand IA, Blaikley J, Booton R, et al. British Thoracic Society guideline for diagnostic flexible bronchoscopy in adults: accredited by NICE. *Thorax*. 2013;68 (Suppl 1):i1–i44.
8. Travis WD, et al. World Health Organization., International Agency for Research on Cancer. *Pathology and Genetics of Tumours of the Lung, Pleura, Thymus and Heart*. Lyon, Oxford: IARC Press, Oxford University Press; 2004.
9. Todd TR, Cooper JD, Weissberg D, et al. Bronchial carcinoid tumors: twenty years' experience. *J Thorac Cardiovasc Surg*. 1980;79:532–536.
10. Hurt R, Bates M. Carcinoid tumours of the bronchus: a 33 year experience. *Thorax*. 1984;39:617–623.
11. McCaughan BC, Martini N, Bains MS. Bronchial carcinoids. Review of 124 cases. *J Thorac Cardiovasc Surg*. 1985;89:8–17.
12. Conley YD, Cafoncelli AR, Khan JH, et al. Bronchial carcinoid tumor: experience over 20 years. *Am Surg*. 1992;58:670–672.
13. Schreurs AJ, Westermann CJ, van den Bosch JM, et al. A twenty-five-year follow-up of ninety-three resected typical carcinoid tumors of the lung. *J Thorac Cardiovasc Surg*. 1992;104:1470–1475.
14. Schrevens L, Vansteenkiste J, Deneffe G, et al. Clinical-radiological presentation and outcome of surgically treated pulmonary carcinoid tumours: a long-term single institution experience. *Lung Cancer*. 2004;43:39–45.
15. Machuca TN, Cardoso PF, Camargo SM, et al. Surgical treatment of bronchial carcinoid tumors: a single-center experience. *Lung Cancer*. 2010;70:158–162.
16. Zhong CX, Yao F, Zhao H, et al. Long-term outcomes of surgical treatment for pulmonary carcinoid tumors: 20 years' experience with 131 patients. *Chin Med J (Engl)*. 2012;125:3022–3026.
17. Correia Sda S, Pinto C, Bernardo J. Pulmonary carcinoid: analysis of a single institutional experience and prognostic factors. *Acta Med Port*. 2014;27:749–754.

18. Dixon RK, Britt EJ, Netzer GA, et al. Ten-year single center experience of pulmonary carcinoid tumors and diagnostic yield of bronchoscopic biopsy. *Lung*. 2016;194:905–910.
19. Varela-Lema L, Fernandez-Villar A, Ruano-Ravina A. Effectiveness and safety of endobronchial ultrasound-transbronchial needle aspiration: a systematic review. *Eur Respir J*. 2009;33:1156–1164.
20. Eapen GA, Shah AM, Lei X, et al. Complications, consequences, and practice patterns of endobronchial ultrasound-guided transbronchial needle aspiration: results of the AQuIRE registry. *Chest*. 2013;143:1044–1053.
21. Pue CA, Pacht ER. Complications of fiberoptic bronchoscopy at a university hospital. *Chest*. 1995;107:430–432.
22. Milman N, Faurschou P, Munch EP, et al. Transbronchial lung biopsy through the fibre optic bronchoscope. Results and complications in 452 examinations. *Respir Med*. 1994;88:749–753.
23. Facciolongo N, Patelli M, Gasparini S, et al. Incidence of complications in bronchoscopy. Multicentre prospective study of 20,986 bronchoscopies. *Monaldi Arch Chest Dis*. 2009;71:8–14.
24. Cordasco EM Jr, Mehta AC, Ahmad M. Bronchoscopically induced bleeding. A summary of nine years' Cleveland clinic experience and review of the literature. *Chest*. 1991;100:1141–1147.
25. Zhou GW, Zhang W, Dong YC, et al. Flexible bronchoscopy-induced massive bleeding: a 12-year multicentre retrospective cohort study. *Respirology*. 2016;21:927–931.
26. Bernasconi M, Koegelenberg CFN, Koutsokera A, et al. Iatrogenic bleeding during flexible bronchoscopy: risk factors, prophylactic measures and management. *ERJ Open Res*. 2017;3:00084–2016.
27. Aktas Z, Gunay E, Hoca NT, et al. Endobronchial cryobiopsy or forceps biopsy for lung cancer diagnosis. *Ann Thorac Med*. 2010;5:242–246.
28. Schumann C, Hetzel J, Babiak AJ, et al. Cryoprobe biopsy increases the diagnostic yield in endobronchial tumor lesions. *J Thorac Cardiovasc Surg*. 2010;140:417–421.
29. Hetzel J, Eberhardt R, Herth FJ, et al. Cryobiopsy increases the diagnostic yield of endobronchial biopsy: a multicentre trial. *Eur Respir J*. 2012;39:685–690.
30. Johannson KA, Marcoux VS, Ronksley PE, et al. Diagnostic yield and complications of transbronchial lung cryobiopsy for interstitial lung disease. A systematic review and metaanalysis. *Ann Am Thorac Soc*. 2016;13:1828–1838.
31. Boyd M, Sahebazamani M, Ie S, et al. The safety of cryobiopsy in diagnosing carcinoid tumors. *J Bronchology Interv Pulmonol*. 2014;21:234–236.
32. Pajares V, Puzo C, Castillo D, et al. Diagnostic yield of transbronchial cryobiopsy in interstitial lung disease: a randomized trial. *Respirology*. 2014;19:900–906.
33. Caplin ME, Baudin E, Ferolla P, et al. Pulmonary neuroendocrine (carcinoid) tumors: European Neuroendocrine Tumor Society expert consensus and recommendations for best practice for typical and atypical pulmonary carcinoids. *Ann Oncol*. 2015;26:1604–1620.