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Effectiveness and Safety of Argon Plasma Coagulation in Patients with Haemoptysis Caused by an Endobronchial Malignancy

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Keywords
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Abstract
Introduction: Patients with central neoplasms and haemoptysis show low survival rates. Symptom control without recurrence 48 h after bronchoscopic interventions may improve the prognosis of these patients. Bronchoscopic argon plasma coagulation (APC) is a useful technique for endobronchial management of haemoptysis in patients with central malignancies. Nevertheless, limited data are available in the literature on its efficacy and safety and the main predictors of success are still unclear. ***Methods:*** An observational, prospective, single-centre cohort study was carried out to assess the efficacy (i.e., immediate bleeding cessation without recurrence during the following 48 h) of bronchoscopic APC in the treatment of patients with haemoptysis caused by endobronchial malignancies and the main predictors of success. ***Results:*** A total of 76 patients with median age 75 years (interquartile range: 65–79) were enrolled. 67 (88.2%) patients had bleeding cessation without recurrence 48 h after bronchoscopic APC. A low rate of non-serious adverse events (5.3%) was recorded and a low (7.6%) recurrence rate of haemoptysis at 3.5 months after the procedure was also shown. No clinical, demographic and endoscopic variables related to a successful procedure at 48 h were found. ***Conclusion:*** This study demonstrates that bronchoscopic APC is an effective procedure in the treatment of patients with haemoptysis caused by endobronchial malignancies, regardless of the clinical characteristics of the patients, the endoscopic and histological features of the neoplasm and the severity of the symptom. Furthermore, it shows a low rate of complications and long-term efficacy in bleeding control.

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Introduction

Malignancy is one of the most frequent causes of haemoptysis worldwide and the leading cause of mortality in patients complaining of this symptom [1–6]. Haemoptysis can occur more frequently in endobronchial than in peripheral cancers [1, 7–9]. Its occurrence in patients with central neoplasms is associated with a lower survival than in patients with peripheral lesions or in those with non-bleeding endobronchial cancers [10]. Haemoptysis control without any recurrences at 48 h following a bronchoscopic intervention improves survival in patients with mild bleeding and endobronchial malignancies [10].

Bronchoscopic argon plasma coagulation (APC), a non-contact form of electrocoagulation, is a useful technique to manage haemoptysis in patients with central malignancy [9–12]. However, scientific evidence on its efficacy, safety, and predictors of success is poor [10, 13, 14].

The aim of the study was to evaluate the effectiveness of bronchoscopic APC in patients with haemoptysis caused by an endobronchial malignancy in terms of immediate bleeding cessation without any recurrence at 48 h. Furthermore, safety profile and variables associated with success were evaluated.

Methods

Study Design

An observational, prospective, single-centre study was carried out in Italy after the approval of the Local Ethical Committee (protocol number: 2017/ST/296) and registration at ClinicalTrials.gov (identifier: NCT03983005). Written informed consent was signed by all recruited patients.

Patients and Interventions

From August 2018 to July 2023 adult (i.e., ≥18 years old), patients with haemoptysis caused by endobronchial malignancies (i.e., identifiable with flexible bronchoscopy), without coagulopathy or other medically correctable causes of bleeding, who needed endoscopic intervention with APC to stop the bleeding, were enrolled. Patients were deemed suitable for enrolment if able to tolerate bronchoscopy and to sign the written informed consent for the study participation.

Exclusion criteria were: patients with haemoptysis caused by endobronchial malignancies with coagulopathy or other medically correctable causes of bleeding; patients not able to tolerate bronchoscopy; patients with haemoptysis without identifiable endobronchial malignancies during flexible bronchoscopy; patients with pace-maker and/or automated implantable cardioverter-defibrillator; patients who refused/were not able to sign the informed consent for the study participation.

Blood volume was estimated by the enrolling physician based on patient description. Description of the prevalent endobronchial growth pattern was based on the scientific literature [15].

All procedures were performed with local anaesthesia and with conscious or deep sedation (flexible bronchoscopies) or general anaesthesia (rigid bronchoscopies). The bronchoscopes used were Olympus BF-UC180F, Pentax EB19-J10U, and Pentax EB-1970UK (flexible), and Efer-Dumon Series 3 (rigid). The choice of the instrument (flexible vs. rigid) was based on the severity of the symptom and on the site and the grade of bronchial obstruction.

APC was performed with VIO 200D APC 2 and ICC 200 APC 300 (Erbe Elektromedizin GmbH, Tübingen, Germany). Probes with an outer dimeter of 1.5 and 2.2 mm were employed.

Outcomes

The primary outcome was the percentage of patients with bleeding cessation without any recurrences at 48 h after bronchoscopic APC. Secondary outcomes were: incidence of adverse events following bronchoscopic APC; incidence of haemoptysis recurrences (number of relapses) at 3.5 months; number of patients alive at 3.5 months after the endoscopic intervention; demographic, clinical and endoscopic factors associated with bleeding cessation after the intervention (i.e., age, gender, ethnicity, smoking history, cancer type and stage, Eastern Cooperative Oncology Group-Performance Status (ECOG-PS), comorbidities, antithrombotic therapy, haemoglobin level, and platelet count; endoscopic growth pattern of malignancy; site of the bleeding lesion; current/former chemotherapy and radiation therapy, duration and severity of haemoptysis). Life-threatening haemoptysis was defined as any episode with an estimated blood loss >100 mL/24 h or which caused haemodynamic instability, or alteration of gas exchange and/or airway obstruction [16].

Statistical Analysis

An ad hoc electronic form was used to collect demographic, epidemiological, and clinical variables. Qualitative and quantitative variables were reported as absolute/relative frequencies and means (standard deviations) or medians (interquartile ranges, IQRs), depending on their parametric distribution. Logistic regression analysis was carried out to assess the relationship between demographic, epidemiological, and clinical variables and the outcomes of interest. A two-tailed p value <0.05 was considered statistically significant. The statistical software STATA version 17 (StatsCorp, College Station, TX, USA) was used to perform statistical analyses.

Results

A total of 76 (72.4% male) patients with a median (IQR) age of 75 (65–79) years were enrolled (Table 1). The median (IQR) estimated haemoptysis maximum volume (mL)/24 h was 17.5 (10–20) mL.

A life-threatening haemoptysis occurred in 3 patients (Table 2). The median (IQR) duration of the symptom was 13 (8.5–24.0) days. Before bronchoscopy, all patients

Table 1. Baseline demographic and clinical characteristic of the cohort

Demographic and clinical characteristics	*N*: 76
Males, *n* (%)	55 (72.4)
Median (IQR) age, years	75 (65–79)
Ethnicity, *n* (%)	
Caucasian	68 (89.5)
African	5 (6.6)
Asian	2 (2.6)
Hispanic	1 (1.3)
Mean (SD) BMI, kg/m^2	24.3 (3.4)
Smoking habit, *n* (%)	
No smoker	11 (14.5)
Current	21 (27.6)
Former	44 (57.9)
Mean (SD) pack/year	40.6 (20.7)
ECOG-PS (0–4), *n* (%)	
0	16 (21.1)
1	44 (57.9)
2	14 (18.4)
3	2 (2.6)
Blood tests	
Mean (SD) Hb, g/dL	11.9 (1.8)
Median (IQR) platelets, cells/mcl	248,500 (165,500–327000)
Median (IQR) creatinine, mg/dL	0.9 (0.8–1.1)
Comorbidities, *n* (%)	
Heart disease	22 (29.0)
Liver cirrhosis	3 (4.0)
Chronic obstructive pulmonary disease	28 (36.8)
Chronic kidney disease	6 (7.9)
Need for transfusion, *n* (%)	1 (1.3)
Antithrombotic therapies, *n* (%)	
Anticoagulant	9 (11.8)
Antiaggregant	19 (25.0)

BMI, body mass index; ECOG-PS, Eastern Cooperative Oncology Group-Performance Status; Hb, haemoglobin; SD, standard deviation.

were unsuccessfully treated with oral/intravenous tranexamic acid.

The majority (62/76, 81.6%) had a primary lung cancer, with the most incident histological pattern being squamous cell carcinoma (35/62, 56.4%). Most (71/76, 93.4%) underwent flexible bronchoscopy during spontaneous breathing, with an overall median time between specialistic referral and endoscopic examination of 2 days (Table 3).

Active bleeding or blood oozing was recorded for each endobronchial lesion. Flexible bronchoscopy in intubated patients and rigid bronchoscopy were employed in all the cases of life-threatening haemoptysis and/or in patients with partially occluding, non-removable, lesions of the main bronchi. Only APC was used to treat bleeding. Two patients with severe bleeding were treated under lateral decubitus previous bronchial saline instillation.

There was no intra-procedural deaths and a low rate of non-serious adverse events (5.3%) (Table 3). In case of relapse, oral tranexamic acid was prescribed before bronchoscopy, which was performed only in case of persistent bleeding after pharmacological therapy.

Proportion of patients with bleeding cessation without any haemoptysis recurrences at 48 h after

Table 2. Characterization of the symptom and neoplastic disease at the time of bronchoscopic intervention

Haemoptysis	
Median (IQR) estimated maximum volume, mL/24 h	17.5 (10–20)
Life-threatening haemoptysis, *n* (%)	3 (4.0)
Median (IQR) days between the last episode and clinical evaluation	1 (1–2)
Median (IQR) duration, days	13 (8.5–24.0)
Associated symptoms	
Cough, *n* (%)	66 (86.8)
Fever, *n* (%)	7 (9.2)
Dyspnoea, *n* (%)	15 (19.7)
Chest pain, *n* (%)	9 (11.8)
Neoplasia	
Metastatic disease, *n* (%)	14 (18.4)
Clear cell renal carcinoma	5 (35.8)
Mammary adenocarcinoma	4 (28.7)
Melanoma	1 (7.1)
Kaposi sarcoma	1 (7.1)
Undifferentiated pleomorphic sarcoma	1 (7.1)
Colorectal adenocarcinoma	1 (7.1)
Laryngeal squamous cell carcinoma	1 (7.1)
Lung cancer, *n* (%)	62 (81.6)
Squamous cell lung cancer	35 (56.5)
Adenocarcinoma	19 (30.6)
SCLC	6 (9.7)
Angiosarcoma	1 (1.6)
Bronchial carcinoid	1 (1.6)
Tumour stage, *n* (%)	
2	2 (2.6)
3	19 (25.0)
4	55 (72.4)
Median (IQR) days between endobronchial neoplasia diagnosis and onset of haemoptysis	61 (30–332.5)
Chemotherapy/immunotherapy/TKI, *n* (%)	
Ongoing	22 (29.3)
Previous	24 (32.0)
Never/not yet performed	29 (38.7)
Radiotherapy, *n* (%)	
Ongoing	–
Previous	9 (12.0)
Never performed	66 (88.0)

SCLC, small cell lung cancer; TKI, tyrosin kinase inhibitors.

bronchoscopic APC was 88.2% (67/76). Among those with a relapse, no one underwent a repeat bronchoscopy; 2 patients were successfully treated with oral tranexamic acid, whereas the remaining subjects had a mild, self-limiting episode (Table 4). One cancer-related death occurred 48 h after the procedure.

One month after APC exposure, 54/65 (83.1%) did not show any recurrence. One patient with a neoplastic infiltration of the main carina underwent a re-treatment with APC and a Y stent placement during rigid bronchoscopy due to a bleeding relapse associated to a lesion growth; the patient died 20 days after the second treatment for reasons not related to the procedure and the malignancy.

At 3.5 months 53/76 (69.7%) were alive. Recurrence was found in 7.6% (4/53).

At the end of the scheduled follow-up, the median number of haemoptysis recurrences was 1, with a median time-to-first-recurrence of 5 days. No variables were associated with a successful procedure at 48 h (Table 5).

Table 3. Endoscopic and procedural characteristics of the cohort

Bronchoscopy	
Type of bronchoscopy, *n* (%)	
Flexible bronchoscopy during spontaneous breathing	71 (93.4)
Flexible bronchoscopy in intubated patient	2 (2.6)
Rigid bronchoscopy	3 (4.0)
Median (IQR) days between pulmonology evaluation and bronchoscopy with APC	2 (1–5)
Outpatients, *n* (%)	49 (64.5)
Type of prevalent endobronchial growth, *n* (%)	
Exophytic	45 (59.2)
Submucosal/peribronchial	31 (40.8)
Site of the bleeding lesion, *n* (%)	
Right upper lobe	18 (23.7)
Right middle lobe	6 (7.9)
Right lower lobe	8 (10.5)
Left upper lobe	12 (15.8)
Left lower lobe	13 (17.1)
Trachea	1 (1.3)
Right main bronchus	2 (2.6)
Left main bronchus	15 (19.7)
Intermediate bronchus	1 (1.3)
Presence and severity of bronchial obstruction/lesion location in the bronchial tree, *n* (%)	
Fully obstructive/segmental or subsegmental	18 (23.7)
Partially obstructive/segmental or subsegmental	14 (18.4)
Fully obstructive/lobar	10 (13.2)
Partially obstructive/lobar	9 (11.8)
Mucosal infiltration without obstruction/lobar	7 (9.2)
Partial obstruction/main bronchi	2 (2.6)
Mucosal infiltration without obstruction/main bronchi	15 (19.7)
Mucosal infiltration without obstruction/trachea	1 (1.3)
Median (IQR) duration of the whole endoscopic procedure, min	16.5 (15–20)
Median (IQR) power, W	40 (30–40)
ICC 200 APC 300 median (IQR) flow, L/min	1 (0.8–1)
VIO 200D APC 2 flow, L/min	0.3–0.8
Adverse events, *n* (%)	
No AEs	72 (94.7)
Bleeding	1 (1.3)
Cardiac arrhythmia (atrial fibrillation)	1 (1.3)
Persistent cough	1 (1.3)
Oxygen desaturation	1 (1.3)

APC, argon plasma coagulation; AE, adverse event.

Discussion

This is the largest prospective study aimed at assessing the effectiveness of bronchoscopic APC in patients with haemoptysis caused by an endobronchial malignancy. A high effectiveness was proved, with bleeding cessation without any recurrences 48 h after the procedure in 88.2%. This is a crucial result since patients with an endobronchial bleeding related to malignancy show a decreased survival compared to those with no bleeding central cancers and with peripheral malignant lesions with or without haemoptysis [10]. Bleeding control

Table 4. Patients' outcomes at 48 h, 1 month, and 3.5 months after APC

	48 h	1 month	3.5 months
Patient outcome, *n* (%)[a]			
Lost to follow-up	–	0/76 (0)	4/76 (5.3)
Alive	75/76 (98.7)	65/76 (85.5)	53/76 (69.7)
Death	1/76 (1.3)	9/76 (11.8)	19/76 (25.0)
If death, *n* (%)			
Disease related	1/76 (1.3)	7/9 (75.0)	17/19 (90.9)
Unrelated to the procedure or pathology	–	2/9 (25.0)	2/19 (9.1)
Late adverse events related to the procedure, *n* (%)	–	–	–
Recurrences, *n* (%)[b]	9/76 (11.8)	11/65 (16.9)	4/53 (7.6)
Bronchoscopy for recurrence, *n* (%)[b]			
Not performed	9/9 (100.0)	8/11 (72.7)	3/4 (75.0)
Flexible bronchoscopy	–	2/11 (18.2)	1/4 (25.0)
Flexible bronchoscopy in intubated patient	–	–	–
Rigid bronchoscopy	–	1/11 (9.1)	–
Bleeding lesion at repeated bronchoscopy, *n* (%)	–	3/3 (100.0)	–
New therapeutic bronchoscopy with APC, *n* (%)	–	3/3 (100.0)	1/1 (100.0)
Efficacy of therapeutic bronchoscopy, *n* (%)	–	3/3 (100.0)	1/1 (100.0)
Pharmacological therapy for bleeding before bronchoscopy, *n* (%)			
No therapy	7/9 (77.8)	7/11 (63.6)	2/3 (66.7)
Oral tranexamic acid	2/9 (22.2)	4/11 (36.4)	1/3 (33.3)

[a]Cumulative. [b]Between timepoints.

without any recurrences at 48 h is associated with improved survival in these patients [10].

Bronchoscopy plays a key role in the management of patients with haemoptysis [16, 17]. It can assess upper airways and provide histopathological and microbiological samples from central and peripheral lung lesions [17–19]. Furthermore, it may be crucial to detect bleeding source, provide direct therapeutic interventions, and may help plan bronchial artery embolization [17, 19].

Bronchoscopic APC is suggested by international guidelines as an optional treatment for bleeding control in patients with central lung cancer [9, 12]. However, limited data on its performance, mostly based on retrospective studies, are available [10, 14, 17, 20].

The majority of our study patients, who had mild haemoptysis, were treated with flexible bronchoscopy during conscious sedation. The rate of complications was 5.3% and no serious adverse events were recorded; in particular, systemic gas embolism, which is the most severe complication of APC, was never recorded [21].

Furthermore, a long-term effectiveness associated with a low recurrence rate at 3.5 months (7.6%) was shown. Our findings are consistent with Morice et al. [13] who reported a 100% efficacy of the technique in 31 patients with endobronchial lesions who underwent APC for haemoptysis and 25 with airway obstruction and haemoptysis; most of the procedures were performed with flexible bronchoscopy. No recurrence after 90 days or complications were reported [11].

Reichle et al. [14] reported a 99% immediate efficacy in 45 patients with endobronchial bleeding lesions. However, most procedures were performed during rigid bronchoscopy and long-term outcomes were not reported [12]. More recently, Grosu et al. [10] showed a control without any recurrences at 48 h in 26 patients with central cancers with mild haemoptysis (88%). Adverse events and follow-up data were not reported [9].

We did not identify any demographic, clinical, and endoscopic variables associated with a successful procedure at 48 h thus confirming a high efficacy of the technique in all patients with haemoptysis. Our study has some limitations: the observational cohort and the role played by confounders can affect the internal validity of the primary and secondary outcomes. Furthermore, the methodological shortcomings of the relatively small sample size (the study was carried out during the COVID-19 pandemic), the single-centre design,

Table 5. Logistic regression analysis to assess the relationship between demographic, clinical, and endoscopic factors and bleeding cessation 48 h after the intervention

	OR (95% CI)	*p* value
Demographic characteristics		
Males	0.72 (0.14–3.79)	0.70
Age, years	0.98 (0.91–1.05)	0.50
BMI, kg/m^2	1.17 (0.93–1.48)	0.19
Smokers	1.84 (0.33–10.3)	0.49
ECOG-PS (0–4)		
0	–	–
1	0.88 (0.16–4.83)	0.88
2	–	–
3	–	–
Comorbidities		
Heart disease	0.79 (0.18–3.49)	0.76
Liver cirrhosis	–	–
Chronic obstructive pulmonary disease	1.19 (0.27–5.19)	0.83
Chronic kidney disease	–	–
Haematological parameters		
Hb, g/dL	1.01 (0.68–1.49)	0.95
Platelets <100,000	–	–
Antithrombotic therapy		
Anticoagulant	1.08 (0.12–9.85)	0.94
Antiaggregant	0.63 (0.14–2.80)	0.54
Haemoptysis		
Life-threatening haemoptysis	–	–
Duration		
<10 days	–	–
10–20 days	0.84 (0.14–5.04)	0.85
>20 days	0.56 (0.08–3.79)	0.55
Neoplasia		
Non small lung cancer versus small cell lung cancer	–	–
Metastatic versus primary lung cancer	–	–
Chemotherapy/Immunotherapy/TKI		
Ongoing	REF.	REF.
Previous	3.63 (0.35–37.8)	0.28
Never performed	0.76 (0.16–3.58)	0.73
Radiotherapy		
Ongoing	–	–
Previous	–	–
Never performed	–	–
Bronchoscopy		
Type of endobronchial growth		
Exophytic	–	–
Submucosal/peribronchial	0.51 (0.13–2.07)	0.34
Site of bleeding lesion		
Left lung versus right lung	2.55 (0.59–11.08)	0.21

BMI, body mass index; ECOG-PS, Eastern Cooperative Oncology Group-Performance Status; Hb, haemoglobin.

the consecutive enrolment could reduce the inference of the main findings. The lack of a control group is another potential limitation of the study.

In conclusion, our study demonstrates that bronchoscopic APC is a safe and effective procedure in the treatment of patients with haemoptysis caused by an endobronchial malignancy. It may be performed with flexible bronchoscopy on an outpatient basis, with a long-term efficacy in bleeding control regardless of the clinical characteristics of the patients, the endoscopic, and histological features of the neoplasm, as well as the severity of the symptom.

Statement of Ethics

Ethics Committee Milan Area 1; protocol number: 2017/ST/296. Written informed consent was obtained from participants to participate in the study.

Conflict of Interest Statement

None of the authors has conflict of interest to disclose.

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Author Contributions

Michele Mondoni: conceptualization, investigation, supervision, and writing – original draft; Andrea Baccelli: conceptualization, investigation, and writing – original draft; Momen M. Wahidi, Paolo Carlucci, Fausta Alfano, Rocco Francesco Rinaldo, Gabriele Guido,Carmelo Intravaia, Andrea Luciani, Paolo Busatto, Stefano Centanni, and Luca Alessandro Belmonte: investigation and writing – review and editing; Laura Saderi: formal analysis and writing – review and editing; Giovanni Sotgiu: investigation, formal analysis, methodology, supervision, and writing – original draft.

Data Availability Statement

All data generated or analysed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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