Treatment of Pulmonary Carcinoid Tumors With Bronchoscopic Cryotherapy

A 28-Year Single-center Experience

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Background: **Pulmonary carcinoids are rare tumors originating from neuroendocrine cells in the lungs. Because of their potentially infiltrative nature, surgical resection remains the treatment of choice. However, not all patients with technically resectable disease will be able to undergo surgery, primarily because of poor lung function or medical co-morbidities. Centrally located, intraluminal tumors have been reported to be amenable to bronchoscopic treatment. We specifically examined the role of cryotherapy in the treatment of bronchial carcinoid tumors.**

Methods: **Sixty-three patients (52.38% female) who underwent a combined total of 243 cryotherapy procedures for treatment of bronchial carcinoid between 1992 and 2020 in our institution were included in the study. Following discussion in multidisciplinary meetings, patients were considered for first-line cryotherapy when lung resection was deemed not possible or when they had rejected surgery.**

Results: **Cryotherapy resulted in complete remission in 21 (33.33%) patients with maximum tumor diameter less than 20 mm (mean: 11.08 mm, 95% confidence interval: 8.76-13.40), and allowed 22 (34.92%) patients with larger lesions (mean: 24.04 mm, 95% confidence interval: 18.78-29.30) to proceed with parenchymal sparing resections. Marked symptomatic relief ($P < 0.001$) was reported by 58 (92.06%) patients. The median follow-up was 33 months (range: 0 to 243 mo). One (1.59%) patient was diagnosed with recurrence in a contralateral lobe 3 years after surgery and was treated with radiofrequency ablation.**

Conclusions: **In the absence of a definitive randomized controlled trial comparing bronchoscopic treatment with surgical resection, we provide evidence on the safety and efficacy of cryotherapy and encourage wider adoption of this inexpensive and minimally invasive technique for treatment of bronchial carcinoids.**

Key Words: carcinoid, neuroendocrine tumors, endobronchial tumors, cryotherapy

(*J Bronchol Intervent Pulmonol* 2022;29:71–82)

BACKGROUND

Pulmonary carcinoids are commonly identified as slow-growing, solitary, polypoid tumors within major bronchi. They can often times lead to hemoptysis, because of their highly vascular stroma, or give rise to symptoms related to airway obstruction and postobstructive pneumonia.[1] Typical carcinoids (TCs) have less than 2 mitotic figures per 2 mm^2 (or per 10 hpf) and no necrosis, while atypical carcinoids (ACs) exhibit increased mitotic activity (2 to 10 mitoses per 2 mm^2) and/or foci of necrosis.[2] Classification is highly important for therapeutic and prognostic purposes; ACs have 20% chance of distant spread and 35% chance of lymph node involvement and are associated with poorer overall survival.[3–5] Additional features of adverse prognostic significance are female sex, large tumor size, invasion into adjacent lung and lymph vessel invasion.[6–9]

Surgical resection is the gold standard of treatment, yet not all patients with technically resectable tumors will be able to undergo surgery at the time of presentation, either because of poor lung function or concomitant medical co-morbidities.[10] Lung preserving resections may be performed in selected patients; however, the correct origin of the tumor will need to be identified first.[11] Patients with small, centrally located,

Received for publication December 18, 2020; accepted June 15, 2021.
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N.A., V.A.: Conception and design. P.P., N.M., J.F., E.B., V.A., and N.A.: Administrative support. P.P., N.M., J.F., E.B., V.A., and N.A.: Provision of study materials or patients. P.P.: Collection and assembly of data. P.P., N.M.: Data analysis and interpretation. P.P., N.M., J.F., E.B., V.A., and N.A.: Manuscript writing. P.P., N.M., J.F., E.B., V.A., and N.A.: Final approval of manuscript.
Disclosure: There is no conflict of interest or other disclosures.
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DOI: 10.1097/LBR.0000000000000791

intraluminal pulmonary carcinoids, with no evidence of distant spread, may respond very well to endobronchial treatment while those with larger lesions and/or evidence of extraluminal growth can receive endobronchial therapy primarily to ease symptomatic distress and limit progression of the disease.[12,13]

Cryotherapy accomplishes pathologic tissue destruction by exploiting the biological response of living tissues to extremely low temperatures; cryosensitivity of a tissue depends on its intracellular water content and vascularity, with cartilaginous (bronchial) tissue known to be cryoresistant whereas, mucosal based vascular tumors (carcinoids), and granulation tissue, are cryosensitive.[14] A liquefied gas (cryogen) is allowed to flow and expand through a restricted nozzle at the tip of a cryoprobe, causing a Joule-Thomson effect. The loss of energy from the cryogen during expansion causes drop in temperature to the surrounding local tissues, thus leading to freezing of free extracellular and intracellular molecular water, and consequent cellular destruction. Cryotherapy has been described as a safe and effective adjunct to endobronchial resection for TC tumors and, unlike other proposed treatments, it has not been associated with bronchial stenosis or other long-term complications.[15]

This retrospective, observational study, aimed to uniquely examine the role of cryotherapy as first-line treatment for bronchial carcinoid tumors. Our analysis shows how cryotherapy in selected patients can result in definitive management or be part of a cytoreductive strategy in preparation for parenchymal sparing surgery. We provide supplementary evidence on the safety and efficacy of this technique to encourage wider adoption.

METHODS

Study Population

Sixty-three patients who underwent a combined total of 243 cryotherapy procedures for treatment of bronchial carcinoid between 1992 and 2020 in our institution have been included in the study. All patients had been diagnosed with endobronchial carcinoid tumors and before deciding on their management strategy they were discussed in a multidisciplinary meeting. Patients were considered for first-line cryotherapy when lung resection was deemed not possible, either because of poor pulmonary function or medical co-morbidities, or when they had rejected surgery. Written consent was obtained before every procedure.

Cryotherapy Procedure

Patients received cryotherapy under general anesthesia and muscle relaxation. The procedure was routinely performed using flexible bronchoscopy through a Negus rigid bronchoscope with jet ventilation. Alternatively, flexible bronchoscopy was performed through an endotracheal single-lumen tube or laryngeal mask airway.

With the lesion in direct vision, the distal tip of the probe was placed on or within the tumor bulk and cryotherapy was applied typically for 4 minutes, with the number of applications depending upon the size, site and macroscopic characteristics of the lesion. During the initial procedure, tumor biopsy was taken for histologic confirmation, either by means of cryoextraction (achieved by rapid withdrawal of the cryoprobe after freezing part of the lesion for ~3 s or until evidence of visible freezing) or with the use of biopsy forceps, depending on individual operator's clinical judgment and/or preference. In general, we advocate the use of cryoprobe extraction over biopsy forceps, because it reduces the risk of yielding small specimen samples with severe crush artefacts in which mitotic count may be difficult to evaluate.[16–18] Intraoperative bleeding occurring at the tumor site was controlled with boluses of 10 ml of adrenaline 1:100,000 solution and/or use of the cryoprobe at the bleeding point.

Repeat bronchoscopy was normally scheduled within 4 to 6 weeks, to observe response to cryotherapy and reassess resectability. Further repeat procedures were performed as indicated, with tumor cryodebulking undertaken for cytoreduction and cryorecanalization undertaken for symptomatic relief. Postoperative prescription of antibiotics was tailored to individual patient's symptoms and signs of infection.

Data Collection and Analysis

For this retrospective analysis, data were collected from archived research material, prospectively populated patient databases, operative logbooks, and patients' medical records. Categorical data are presented as n (%). Numeric data, depending on their distribution, are presented as mean [95% confidence interval (CI)] or median (total range).

Tumor size was calculated from radiographic findings on initial assessment. The maximum diameter of the tumor has been used, as volumetric data were not available. Because patients would not normally undergo repeat scans

between procedures, we selected to use bronchoscopic and histopathologic findings to estimate size reduction after cryotherapy; for patients with no visible tumor and negative histology specimens, the final tumor size was considered 0 mm. Two-tailed *t* test was used to analyze tumor size before and after cryotherapy; rejection of the null hypothesis at the level of 5% has been adopted.

Degree of airway obstruction was defined as lobar segments found occluded at presentation, or lobar segments at risk of occlusion by the tumor if no form of treatment was provided. Segments were considered "free from obstruction" when complete response to treatment was achieved, "at risk" when only partial response was achieved and "unrecoverably lost" either after surgery or when attempts for cryorecanalization had failed. Differences in symptomatology and degree of airway obstruction before and after treatment were calculated using the Wilcoxon paired-signed ranks test.

Cases with insufficient data, including 2 patients lost on follow-up, were excluded from statistical analyses. All computations were performed using Microsoft Excel (Microsoft Office 365 suite).

RESULTS

Patient Characteristics

Sixty-three patients (52.38% female), diagnosed with carcinoid tumor at a median age of 48 years (range: 17 to 88), received first-line cryotherapy when considered inoperable (69.84%) or if they had refused surgery (7.93%) (Table 1). Fifteen (23.80%) patients had significant cardiac (ischemic heart disease, heart failure, and valve abnormalities), respiratory (emphysema, asthma, and chronic obstructive pulmonary disease) or other (renal failure and cerebral event) medical comorbidities. Twenty (31.65%) patients were diagnosed with tumor in a mainstem bronchus or the bronchus intermedius and had baseline pulmonary function which would not allow for lung resection with a curative oncological outcome to be performed. Twenty-one (33.33%) patients were given cryotherapy with an intent to reduce the size of the tumor and help identify its limits, to be considered for parenchymal sparing procedures.

TABLE 1. Patient Characteristics on Admission

Patient Characteristics	Number of Patients (%)
Number of patients	63 (100)
Sex	
Male	30 (47.62)
Female	33 (52.38)
Presenting symptoms	
Cough	33 (52.38)
Haemoptysis	12 (19.04)
Breathlessness (resting and/or exertional)	33 (52.38)
Wheezing	5 (7.93)
Chest pain	15 (23.81)
Obstructive pneumonia/recurrent infections	16 (25.40)
Incidental	4 (6.35)
Other (ie, weight loss, anorexia, hoarse voice)	6 (9.52)
Diagnosis	
Atypical carcinoid	5 (7.93)
Typical carcinoid	58 (92.06)
Lymph node involvement	
Mediastinal (cN2)	2 (3.17)
Hilar (cN1)	1 (1.59)
No involvement (cN0)	60 (95.02)
Tumor location (imaging, bronchoscopy)	
Main bronchus	20 (31.75)
Bronchus Intermedius	15 (23.81)
Lobar bronchus (±lobar orifice)	28 (44.44)
Initial management with cryotherapy	
To avoid pneumonectomy	16 (25.40)
To avoid bilobectomy	4 (6.34)
To identify origin of the tumor	13 (20.63)
To reduce tumor size	8 (12.70)
To reduce operative risk (Jehova's witness)	1 (1.59)
Patient's preference	5 (7.93)
Unfit (medical co-morbidities, poor lung function)	15 (23.80)
No obvious tumor after excisional biopsy	1 (1.59)

Safe and Effective Symptomatic Relief

Cough (52.38%) and shortness of breath (52.38%) were the most commonly reported symptoms on admission, followed by recent or recurrent infections (25.40%), chest pain (23.81%), and hemoptysis (19.04%). Tumor was incidentally diagnosed in four asymptomatic patients (6.35%); 2 had been undergoing investigations for other medical conditions and 2 had been on surveillance following unrelated surgery. The median number of cryotherapy applications performed for each patient was 3 (range: 1 to 18) and the median interval between repeat procedures was 35 days (range: 6 to 3556). Bronchoscopic cryotherapy resulted in marked symptomatic relief in 58 (92.06%) patients who had undergone 3 or less cryoablation procedures ($P < 0.001$).

For patients alive in July 2020, the median follow-up has been 33 months (range: 0 to 243 mo). No immediate or late postprocedural complications had occurred from bronchoscopic cryotherapy; all patients were discharged home on the same day after their procedure and none

required re-admission, either in our institution or at their local hospitals. Cough with expectoration of blood-stained sputum was reported, especially in patients with highly vascular lesions and/or airway obstruction, but this typically resolved in 3 to 5 days after the procedure.

Outcomes in Distinct Patient Cohorts

Complete Tumor Removal with Cryotherapy Alone

Eighteen patients (28.57%) diagnosed with TCs, 5 of which in a mainstem bronchus, 2 in the bronchus intermedius and 11 in a lobar bronchus, had complete tumor remission with cryotherapy alone (Table 2). By the end of their treatment, patients had either no visible lesions to biopsy (Fig. 1) or negative histopathologic confirmation. Patients remained on follow-up, either at our institution (median: 28 mo; range: 1 to 243) or at their local hospital, and underwent routine repeat investigations in the form of check bronchoscopies and/or thoracic imaging.

Endobronchial local disease recurrence was suspected in 2 (3.17%) patients at 4 and 10 years following initial treatment; both patients attended further cryoablation sessions, however histology samples obtained on subsequent treatments had resulted negative. Two (3.17%) patients with suspected extraluminal local recurrence on Gallium Dotate positron emission tomography/computed tomography were investigated with endobronchial ultrasound biopsy which resulted negative. One (1.59%) patient with bronchoscopic evidence of extrinsic compression and negative histology remains under surveillance 15 months after treatment.

One (1.59%) patient who underwent a series of repeat cryoprocedures for TC currently has metaplastic bone in the area of the ablated tumor (Fig. 2) but remains asymptomatic. While intralesional dystrophic calcifications can be seen in up to 30% of TCs, exaggerated osseous metaplasia or complete ossification is a rather unusual finding (10%), scarcely reported in the literature.[19] It is believed that the ability of pulmonary carcinoids to acquire an osseous phenotype plays a role in permitting tumor cells to seed and survive in bony environments.[20]

Three deaths have been recorded in this group and were all unrelated to carcinoid.

Cryotherapy Followed by Surgical Resection But With No Residual Tumor Found

Three (4.76%) patients with TC and suspected residual disease after cryotherapy eventually underwent surgery but there was no evidence of tumor in the final histology specimens (Table 2). Of those, 2 underwent limited bronchial resection, 1 of the left secondary carina (Fig. 3) and 1 in the bronchus intermedius, and 1 underwent anatomical right lower lobectomy.

TABLE 2. Cryotherapy Outcomes in Distinct Patient Cohorts

Outcome	n	Maximum Tumor Diameter before Treatment (Median)	Number of Cryoablations (Median)	Follow-up (Months, Median)	Deaths	Time from First Treatment to Death (mo) and age at Time of Death (y)	Cause of Death Related to Carcinoid?
Complete tumor removal with cryotherapy alone	18	10.5 mm (range: 3-19)	4 (range: 2-18)	28 (range: 1-243)	3	28 m (83 y/o)	No
						61 m (59 y/o)	No
						188 m (85 y/o)	No
Cryotherapy followed by surgical resection but with no residual tumor found	3	12.5 mm (range: 10-15)	4 (range: 2-5)	84 (range: 32-88)	0	NA	NA
						272 m (45 y/o)	No
Cryotherapy followed by lung resection ± bronchoplasty for residual tumor	32	24 mm (range: 8-60)	2 (range: 1-8)	28 (range: 2-200)	2	42 m (78 y/o)	No
Cryotherapy followed by further nonsurgical treatment for residual disease	4	Insufficient data	3-4 (range: 2-4)	8 (range: 3-27)	4	4 m (58 y/o)	Yes
						8 m (63 y/o)	Yes
						19 m (66 y/o)	Yes
						38 m (65 y/o)	No data
Cryotherapy followed by no further treatment, despite residual tumor	4	19 mm (range: 19-28)	4-5 (range: 1-17)	47 (range: 0-81)	1	30 m (80 y/o)	No
Cryotherapy—ongoing treatment	2	14.5 mm (range: 11-18)	5-6 (range: 4-7)	9 (range: 2-15)	0	NA	NA

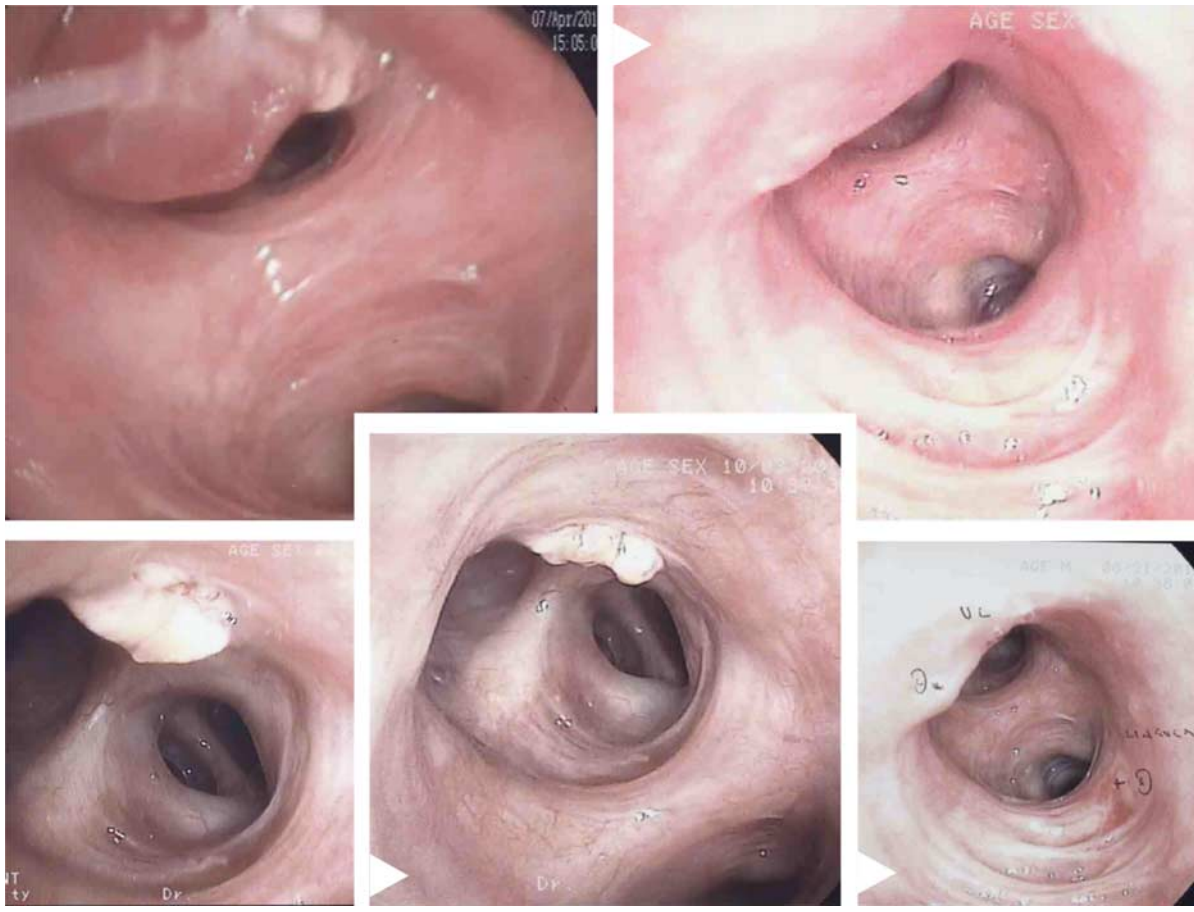

FIGURE 1. Bronchial carcinoid tumor with no atypical features in the orifice of the left upper lobe bronchus (top left), with complete remission following 8 cryotherapy procedures (bottom right). *a+*

FIGURE 2. A metaplastic bone can be seen in the orifice of the middle lobe bronchus, where a typical carcinoid tumor had been treated before with 18 cryotherapy procedures. *a+*

Cryotherapy Followed by Lung Resection ± Bronchoplasty for Residual Tumor

Thirty-two (50.79%) patients with incomplete or transient tumor regression after cryotherapy proceeded to have surgery (median time from first cryoablation to surgery was 83 d; range: 6 to 1013 d) (Table 2). Two patients had been diagnosed with AC and 30 had TC. Successful reduction of tumor size was achieved in 29 of 32 patients and 22 eventually underwent bronchoplastic/sleeve parenchymal sparing procedures. None of the patients required a more extensive resection than would have been undertaken at presentation and 13 patients ultimately required lesser procedures, with 9 pneumonectomies and 4 bilobectomies avoided; serial applications of cryotherapy in lesions appearing to be largely involving a main airway resulted to reduction of tumor size and correct identification of its limits, thus allowing resection margins to be more accurately defined when performing parenchymal sparing procedures.

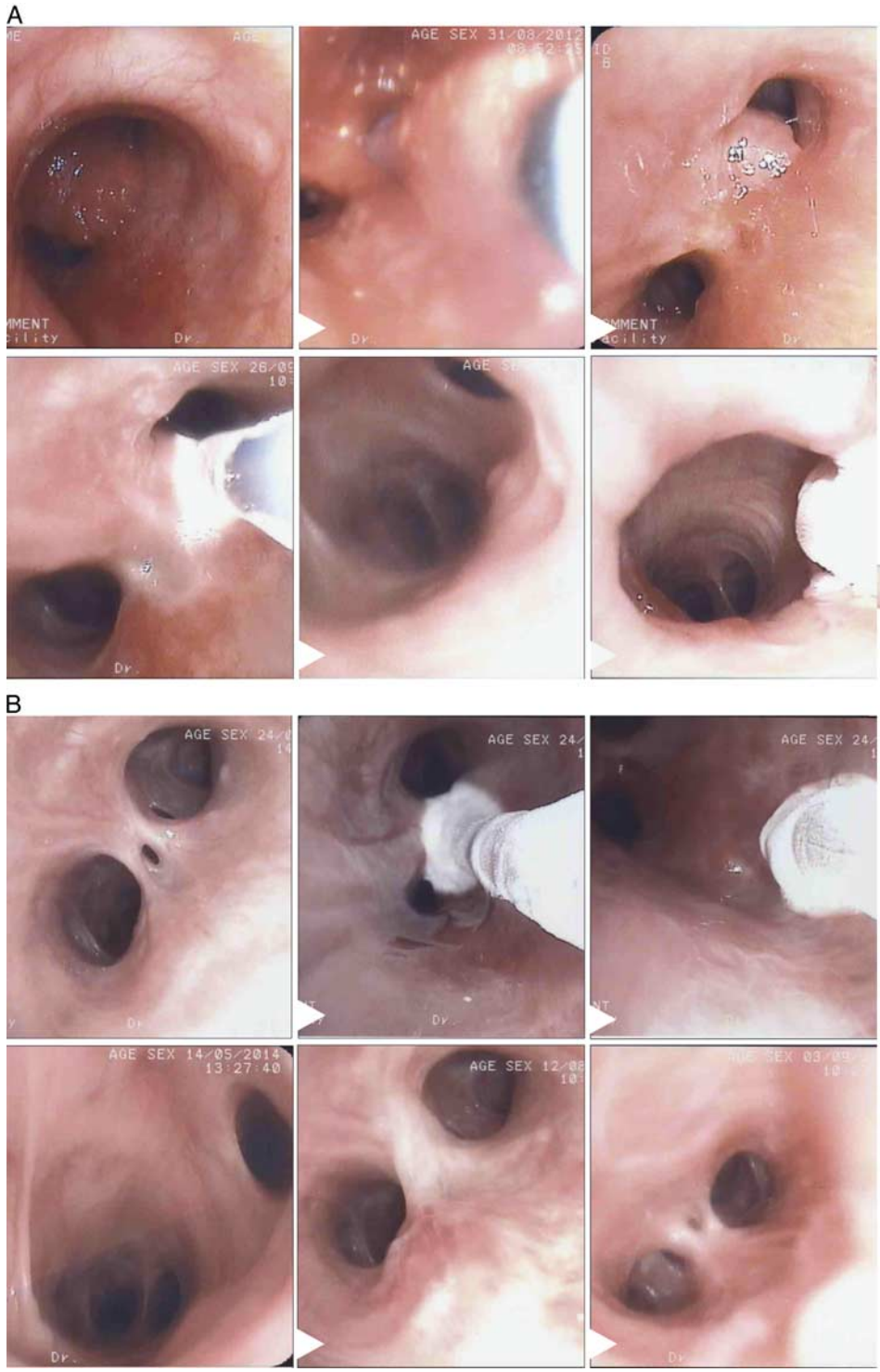

FIGURE 3. A, Typical carcinoid tumor involving the left secondary carina treated with cryotherapy. B, Successful remission after 4 cryoablations; the patient further underwent resection of the left secondary carina with no evidence of tumor in the resected specimen. *a+*

Only 1 of 32 surgical resections was performed with video-assisted thoracoscopic surgery (Fig. 4), and the rest were performed through standard posterolateral thoracotomy. For the patient undergoing thoracoscopic resection there was sufficient evidence preoperatively that a clear

bronchial margin could be obtained with the use of an automatic stapling device, while for all other cases thorough inspection of an open airway was deemed necessary to ensure complete resection.

One patient with suspected cN2 involvement was downgraded to pN1 after surgery and another patient with radiologic cN1 diagnosis was found to have negative nodes (pN0) on final histology. Two patients with no previous suspicion of nodal disease were unexpectedly found to have nodal involvement from histologic specimens obtained intraoperatively; one patient was diagnosed with pN2 disease and the other with pN1. There had been only a single case of postoperative complication; 1 patient was diagnosed with bronchial stenosis after left sleeve upper lobectomy and required balloon dilatations.

On final histologic report, 4 of the surgical patients were reported to have positive microscopic margins; 1 after bronchoplastic right lower bilobectomy (bronchial resection margin), 1 after middle lobectomy (bronchial resection margin), 1 after bronchoplastic middle lobectomy (vascular resection margin), and 1 after sleeve left upper lobectomy (bronchial resection margin). Of those, 1 patient was referred to a neuroendocrine unit after surgery for further assessment and management, 1 patient was found to have carcinoid in the left eye 1 year after surgery and was treated with radiotherapy, 1 patient had distal tumor recurrence (carcinoid with no atypical features) in a contralateral lobe 3 years after surgery and was treated with radiofrequency ablation, and 1 patient continued to have routine follow-up at his local hospital. All 4 patients are alive, with no further evidence of disease recurrence on surveillance (median: 9 y; range: 5 to 16).

Two deaths which had been recorded in the surgical group were not related to carcinoid.

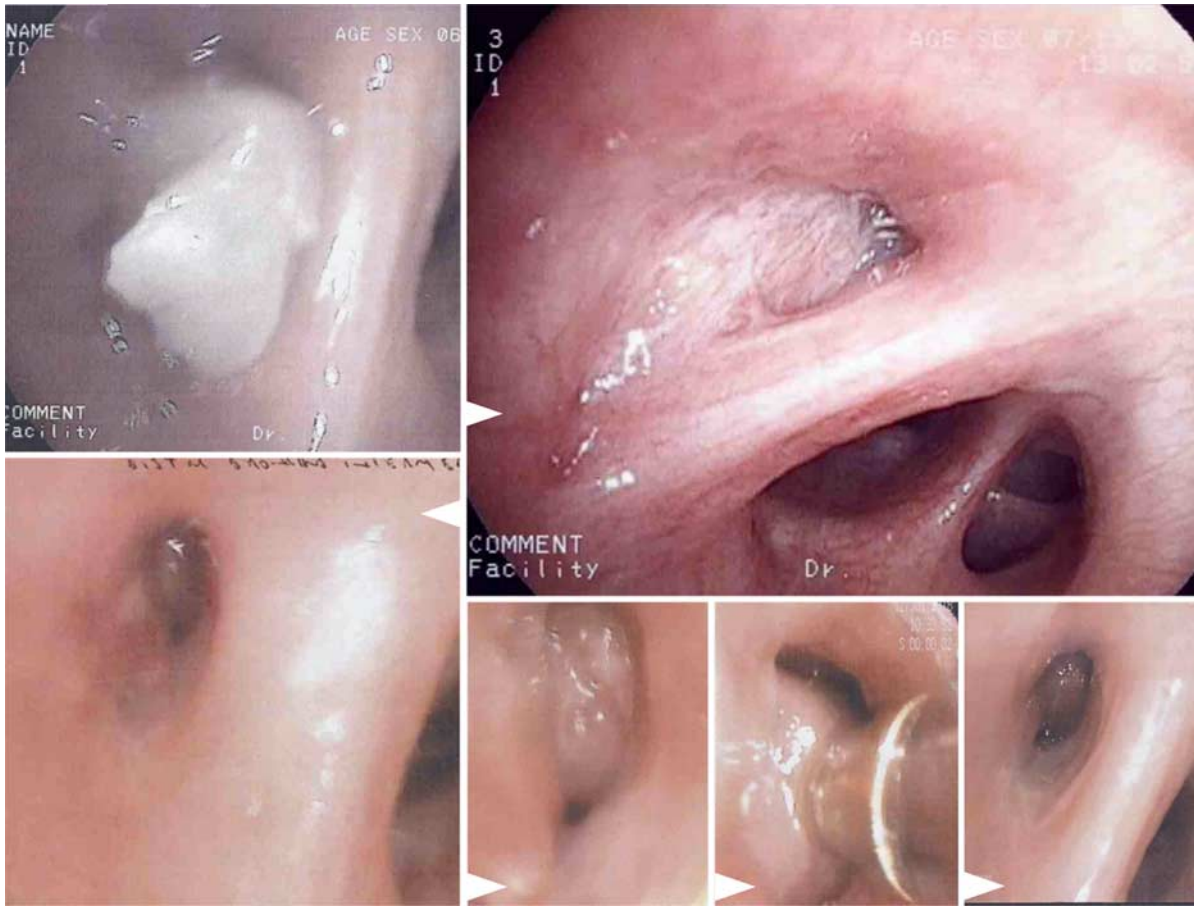

FIGURE 4. Typical carcinoid tumor in the orifice of the middle lobe bronchus (top left). After 6 cryotherapy procedures the tumor had significantly reduced in size and its origin was identified in the medial segmental bronchus (bottom right). The patient underwent video-assisted thoracoscopic middle lobectomy with clear resection margins on final histology. a+

Cryotherapy Followed by Further Nonsurgical Treatment for Residual Disease

Four patients (6.35%) with residual disease after cryotherapy were deemed inoperable; 1 continued to receive palliative cryotherapy and 3 were treated further with radiotherapy and/or brachytherapy (Table 2). There were no survivors in this group; lung cancer (AC) had been reported as a cause of death for 3 of these patients while data for the cause of death for the other patient, diagnosed with TC, were insufficient.

Cryotherapy Followed by no Further Treatment, Despite Residual Tumor

Significant reduction of tumor size with marked improvement of symptoms was achieved in 4 (6.35%) other patients with TC (Table 2). Despite evidence of residual disease, no further cryotherapy, or any other therapy, was provided. One patient was deemed unfit because of episodes of severe hypoxemia at induction of general anesthesia and 1 declined further treatment. For the remaining 2 patients, relevant information could not be retrieved because they stopped attending routine follow-ups. Only 1 death was recorded in this group and it had been unrelated to carcinoid.

Cryotherapy—Ongoing Treatment

Two (3.17%) patients diagnosed with TC receive ongoing treatment with no conclusive outcome (Table 2). The tumor in one of the patients has not exhibited the desired response after 7 cryoablations and the patient has now consented to surgery at a higher risk, because of medical co-morbidities. The other patient, a 70-year-old female diagnosed with tumor in the bronchus intermedius, has so far responded extremely well to 4 cryoablations with no residual tumor seen on bronchoscopy and no evidence of microscopic disease on repeat biopsy from the previous tumor site; the patient will be followed-up further with bronchoscopy and repeat imaging before considering complete remission.

Specific Outcomes for Size and Degree of Airway Obstruction

The average maximum tumor diameter before cryotherapy for all patients was 19.31 mm, 95% CI: 15.63-22.99 and the median number of sublobar segments obstructed or compromised by tumor was 7 (range: 2 to 10). The average maximum tumor diameter after cryotherapy was found to be significantly smaller at 12.87 mm, 95% CI: 8.25-17.48 ($P = 0.04$) while the median number of sublobar segments irreversibly lost, either as a result of a surgery or because of insufficient response to nonsurgical treatment, was reduced to 3 (range: 0 to 8) ($P < 0.001$).

Patients with complete tumor resolution after cryotherapy had tumors with maximum diameter less than 20 mm (median: 10.5 mm, range: 3 to 19). Those who eventually underwent surgical resection had tumors with significantly greater average maximum diameter compared with the those who required only cryotherapy (mean: 24.04 mm, 95% CI: 18.78-29.30 vs. mean: 11.08 mm, 95% CI: 8.76-13.40) ($P = 0.002$).

DISCUSSION

Existing Evidence in the Literature for Bronchoscopic Treatments

Even though cryotherapy has been reported to be safe and effective in managing a variety of tracheobronchial disorders, there is no sufficient evidence in the literature to support its routine use for bronchial carcinoids.[21–26] An extensive review of 43 studies concerning surgical management and 9 studies related to endobronchial treatment found that tumor location and tumor diameter could notably influence the selection of an optimal treatment strategy in patients with more favorable prognosis, however, the quality of the available evidence is low and prospective trials are needed.[27] A randomized trial could provide more accurate and definitive evidence, but the rarity of the disease, its limited recurrence rates and prolonged periods required for follow-up would make one incredibly challenging to design.

Current Adoption and Our Approach

Endobronchial treatment for carcinoid has not been made widely accessible to patients so far, not only because of lack of evidence but also because of concerns for intraoperative bleeding.[28] In our institution the procedure is routinely performed by thoracic surgeons and our unit is well equipped to provide urgent management in case of an adverse event. Response to treatment, resectability and operative risks are assessed by a single team which allows for uninterrupted, timely management.

We favor the use of cryotherapy over Nd: YAG laser, despite evidence also supporting photoresection, to prevent complications such as airway perforation, air embolism, fistula formation, necrosis, and scarring, which have been reported with laser procedures.[29–31]

We recognize the limited (5 mm) spectrum cryotherapy has, compared with laser, and to overcome this we offer cryodebulking and re-intervention at 6 to 8 weeks. We have selected to repeat cryoablations at nearly monthly intervals for visible residual tumors and maintain yearly follow-ups after completion of cryorecanalization procedures. Evidence in the literature shows that airway restenosis for endobronchial tumors can occur within 2 months to 4 years after recanalization procedures, with restenosis rates ranging from 24% to 28%.[32,33]

Lessons Learned Over the Years

As a high-volume tertiary cardiothoracic center, we have extensive surgical experience in management of thoracic tumors. Patients referred to our center for management of carcinoid are primarily offered surgical resection, as per published guidelines.[34] During the early years examined in the study, patients had been offered cryotherapy with a mainly palliative intention and with the possibility of improving the prospect of a surgical resection; the potential for a curative outcome was not an a priori factor at the onset of endobronchial treatment.

For patients diagnosed with TC, encouraging results from our own experience and other case studies generates interest and optimism in the possibility that cryotherapy could be curative for a subgroup of patients, especially those with purely intraluminal lesions measuring less than 20 mm.[12,35] Even though it can be argued that it may not be sufficient to rely on endobronchial biopsies to exclude the possibility of residual microscopic disease, it is important to emphasize that all biopsies had been performed by experienced bronchoscopists who could accurately identify the previous site of the tumor. Complete resolution is also supported by the negative histopathologic findings in patients who underwent subsequent resections, for tumors previously treated with cryotherapy.

For patients with larger tumors, or evidence of extraluminal growth, a cytoreductive strategy was applied in preparation for surgery, allowing those previously considered inoperable to undergo curative procedures. As per common surgical practice, the bronchial resection line had to be defined by the tumor existent margin. In larger lesions, where obstructive phenomena can lead to formation of granulation tissue, it was not always possible to correctly identify the limits of the tumor within the airway at the time of presentation. In some cases, the intraluminal component of the lesion was large enough to misleadingly appear to be arising from a wider area of the airway when it was in fact only in contact with its surface and the tumor origin was evidently found to be considerably smaller. Preoperative cryotherapy resulted in successful elimination of granulation tissue and reduction of tumor size, allowing more accurate assessment of the tumor's exact bronchial margin (as shown in Fig. 4), thus facilitating parenchymal sparing resections. During the later years of the study, this cytoreductive approach has been extended to surgical candidates with localized central disease and no evidence of nodal involvement or distant spread, fit enough to undergo extensive resections, in order to avoid unnecessary loss in lung function. The addition of initial bronchoscopic cryotherapy treatments did not affect surgical outcomes and our long-term results are in keeping with similar reports in the literature.[11,36–38]

Patients diagnosed with AC fit enough to undergo general anesthesia and lung resection proceeded to have surgery at earliest possible, while patients unfit for surgery continued to receive cryotherapy to achieve symptomatic relief and disease control. Cryotherapy alone or in combination with other nonsurgical treatments helped in alleviating symptoms but failed to provide a curative outcome to three inoperable patients with AC, while surgery provided the desired curative outcome to the two patients fit enough to undergo lung resection. We consider the role of cryotherapy in the management of AC to be strictly palliative with no potential for curative result; patients diagnosed with AC tumors should be surgically managed, whenever possible.

Management Algorithm

On the basis of these results, we continue to offer first-line cryotherapy with curative intent to patients with TC less than or equal to 20 mm and no evidence of nodal involvement or distant spread (Fig. 5). Patients with maximum tumor diameter greater than 20 mm are informed about the current lack of evidence to support successful management with cryotherapy alone and are advised to proceed with surgical resection, when medically fit.

Patients with suspected nodal disease are also prioritized for surgery to allow accurate staging. Taking into consideration the unexpected finding of nodal involvement in 2 surgical patients with no previous suspicion of nodal disease, and

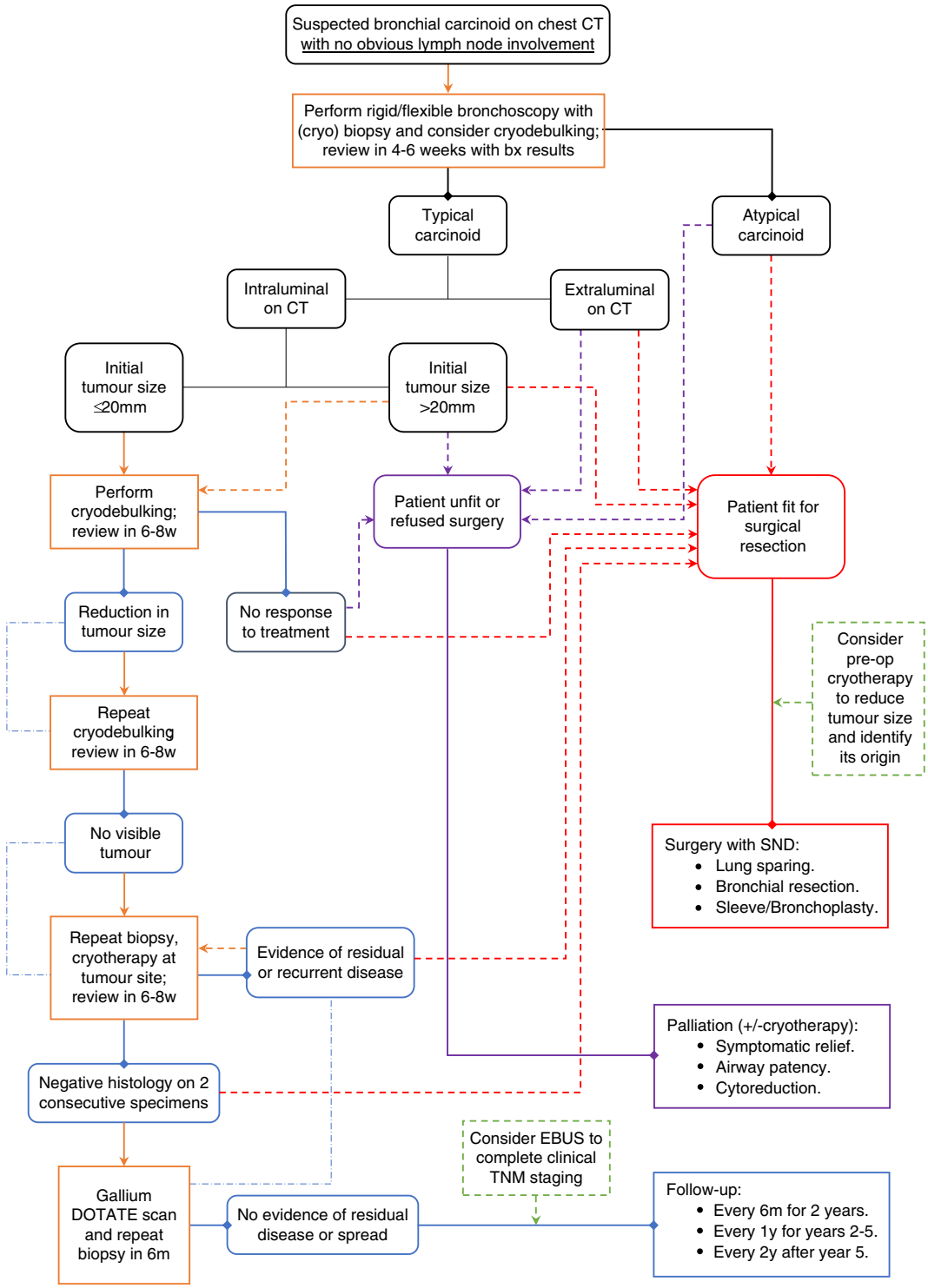

FIGURE 5. Management algorithm for patients with suspected bronchial carcinoid with no obvious lymph node involvement on radiographic findings. CT indicates computed tomography; EBUS, endobronchial ultrasound.

evidence in the literature suggesting nodal upstaging up to 13% for TC, we now offer endobronchial ultrasound lymph node biopsies to all patients with TC managed with cryotherapy alone. It is important, however, to note that, even though lymph node disease has been associated with worse survival for TC greater than 20 mm, survival for TC patients with

lesions less than or equal to 20 mm is not significantly affected by lymph node involvement.[5]

Prospective Data Collection

We are currently developing a protocol for a prospective study which will recruit surgical patients with central TC tumors to undergo up to 4 cryoablation procedures before proceeding with pulmonary resection. A detailed assessment of tumor location, size and appearances, before, during and after treatment will be undertaken. This information, in combination with the final examination of the histopathologic specimens, will allow us to precisely evaluate the possible utility of cryotherapy for effective cytoreduction and its potential for permitting surgical excisions with narrower resection margins, in instances when a main airway is suspected to be involved pretreatment.

Limitations of This Study

Our study is limited by its retrospective design and moderate sample size; it is not a randomized controlled trial and is based on a single-center experience. The approach to performing the procedure is comparable among consultants and surgical trainees within our department but neither universal nor standardized. Patients considered for first-line cryotherapy were not screened against previously devised criteria but were individually assessed and discussed in dedicated multidisciplinary meetings. A significant number of patients included in the study underwent cryotherapy procedures primarily with a palliative intent and they were characterized by variability in fitness levels, pulmonary function, and medical co-morbidities at the time of their presentation. Assessment of nodal involvement was not routinely undertaken for patients managed with a nonsurgical technique. Some patients had difficulty attending our clinics after completion of their treatment and were discharged to their referring physicians for long-term follow-up.

CONCLUSIONS

We recognize that there are currently no sufficient data to support a curative outcome when bronchoscopic treatment is applied to patients with pulmonary carcinoids. The results presented in our study as well as other published reports are encouraging, but further research is warranted. Cryotherapy can be performed in high-oxygen settings, is well tolerated by the patients and rarely results to complications. With our years-long experience, we wish to underline the palliative benefits of the procedure and highlight its curative potential in carefully selected cohorts. In the absence of a definitive randomized controlled trial comparing bronchoscopic treatment with surgical resection, we provide evidence on the safety and efficacy of cryotherapy and encourage wider adoption of this inexpensive and minimally invasive technique for treatment of bronchial carcinoids, especially at a time when advancement of bronchoscopic navigational techniques will allow more patients in the future to undergo diagnostic and therapeutic procedures without being subjected to the risks involved with percutaneous interventions.

ACKNOWLEDGMENTS

The authors thank Julie Beeson, Advanced Nurse Practitioner, Maria Kalliopi Konstantinidou, Clinical Fellow in Cardiothoracic surgery, and the department of Histopathology at Royal Brompton and Harefield NHS Trust, for their valuable contribution in data collection. The authors also would like to acknowledge Consultant Thoracic Surgeons Alan Rees, William Fountain, Dimitrios Kyparissopoulos, and Niall McGonigle for performing a number of the cryotherapy procedures included in this study. The authors are also immensely grateful to Omar Maiwand, Consultant Thoracic Surgeon who pioneered endobronchial cryotherapy at the Department of Thoracic Surgery at Harefield Hospital and trained generations of Thoracic Surgeons on its use.

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