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Bronchoscopic Thermal Vapour Ablation for Localized Cancer Lesions of the Lung: A Clinical Feasibility Treat-and-Resect Study

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Keywords
Bronchoscopy · Catheter ablation · Ablation techniques · Lung cancer · Endobronchial ultrasound

Abstract
Background: Bronchoscopic thermal vapour ablation (BTVA) is an established and approved modality for minimally invasive lung volume reduction in severe emphysema. Preclinical data suggest potential for BTVA in minimally invasive ablation of lung cancer lesions. ***Objectives:*** The objective of this study is to establish the safety, feasibility, and ablative efficacy of BTVA for minimally invasive ablation of lung cancers. ***Methods:*** Single arm treat-and-resect clinical feasibility study of patients with biopsy-confirmed lung cancer. A novel BTVA for lung cancer (BTVA-C) system for minimally invasive treatment of peripheral pulmonary tumours was used to deliver 330 Cal thermal vapour energy via bronchoscopy to target lesion. Patients underwent planned lobectomy to complete oncologic care. Pre-surgical CT chest and post-resection histologic analysis were performed to evaluate ablative efficacy. ***Results:*** Six patients underwent BTVA-C, and 5 progressed to planned lobectomy. Median procedure duration was 12 min. No major procedure-related complications occurred. All 5 resected lesions were part-solid lung adenocarcinomas with median solid component size 1.32±0.36 cm. Large uniform ablation zones were seen in 4 patients where thermal dose exceeded 3 Cal/mL, with complete/near-complete necrosis of target lesions seen in 2 patients. Tumour positioned within ablation zones demonstrated necrosis in >99% of cross-sectional area examined. ***Conclusion:*** BTVA of lung tumours is feasible and well tolerated, with preliminary evidence suggesting high potential for effective ablation of tumours. Thermal injury is well demarcated, and uniform tissue necrosis is observed within ablation zones receiving sufficient thermal dose per volume of lung. Treatment of smaller volumes and ensuring adequate thermal dose may be important for ablative efficacy.

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Introduction

Surgical resection with lobectomy is currently the recommended therapy for management of localized (Stage I) non-small cell lung cancer (NSCLC) [1]; however, surgery is precluded in many patients by the presence of significant comorbidities or frailty [2]. Targeted ablation techniques may be used for such patients with curative intent and may be non-invasive (e.g., stereotactic ablative body radiotherapy) [3] or invasive (varied percutaneous techniques) [4, 5]. These techniques may be limited in many patients due to anatomic location of tumour or to clinical features such as multifocal disease, ground glass lesions, or underlying pulmonary disease (e.g., fibrosis) [6–8].

Bronchoscopic thermal vapour ablation (BTVA) is an established and approved modality for minimally invasive lung volume reduction in severe emphysema. Targeted delivery of thermal energy induces an inflammatory reaction within treated pulmonary segments resulting in fibrosis and shrinkage of the segment, and consequent lung volume reduction [9].

Subsequent modification of the emphysema treatment catheter allowed for delivery of thermal energy from a point beyond sub-segmental level. Greater energy delivery (per volume of lung) could be delivered and in an in vivo porcine model was shown to achieve a uniform field of necrosis which followed the sub-segmental anatomical boundary [10]. Subsequent ex vivo studies in human lungs demonstrated that with sufficient energy delivery, uniform ablation was achieved [11], indicating a potential role for BTVA in the minimally invasive treatment of lung cancer.

This study aimed to evaluate the safety and feasibility of a novel BTVA for lung cancer (BTVA-C) system for minimally invasive treatment of peripheral pulmonary tumours in this treat-and-resect study. Secondary end points regarding distribution of thermal injury and uniformity of necrosis following BTVA-C are also presented in detail to examine potential efficacy of the treatment.

Materials and Methods

Study Design and End Points

This prospective, single-arm, treat-and-resect study was conducted at a single tertiary centre (Royal Melbourne Hospital) in Victoria, Australia, between December 2018 and August 2019. Patients with microscopic proof of malignancy suitable for resection via lobectomy were considered for inclusion in the study. Lesions were required to be ≤20 mm and positioned within the outer third of the lung. Detailed inclusion and exclusion criteria are recorded in online suppl. File 1; for all online suppl. material, see www.karger.com/doi/10.1159/000514109.

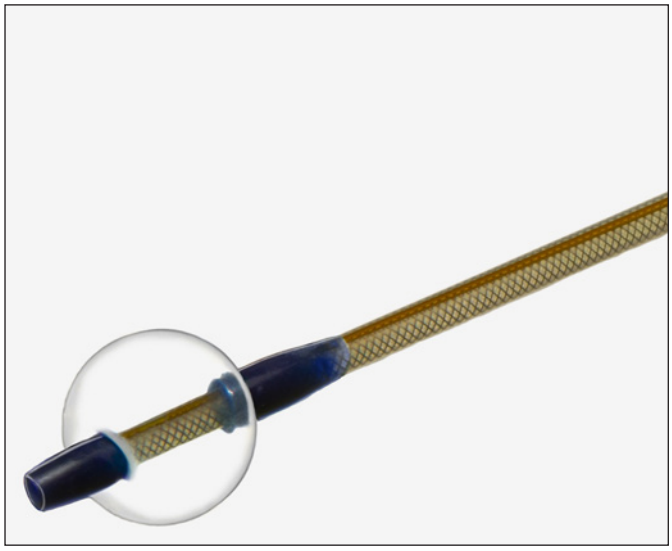

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Fig. 1. BTVA-C catheter with proximal occluding balloon inflated. The silicone compliant balloon at the distal end of the catheter shaft allows occlusion of up to 6 mm diameter lung airway during vapour treatment. BTVA-C, bronchoscopic thermal vapour ablation for lung cancer.

Pre-procedure planning of treatment was established based on analysis of the patient's diagnostic CT chest by commercially available quantitative pulmonary image analysis software – Apollo® Software (VIDA, Coralville, IA, USA) and by a commercially available virtual bronchoscopy navigation system – Archimedes® Planner (Broncus Medical Inc., San Jose, CA, USA). Details are presented in online suppl. File 2.

Bronchoscopic Thermal Vapour Ablation for Lung Cancer Device

The BTVA-C system is comprised of 3 components: (i) a sterile, disposable vapour delivery catheter (shown in Fig. 1), (ii) generator with attached handpiece, and (iii) water line kit. The generator consists of a graphic user interface to enter control parameters, an electronically controlled syringe pump for controlled delivery of sterile water to its handpiece, and a flow-based technology which creates resistive heating to convert sterile water into thermal vapour. The BTVA-C catheter is connected to the generator's handpiece and delivers the vapour to the patient. Sterile water is delivered via the water line kit to the handpiece where resistive heating converts sterile water into thermal vapour.

The catheter is a sterile, disposable, non-reusable device used to deliver vapour from the generator handpiece to the targeted airway. The catheter is very similar in design, construction, and use of the InterVapor catheter used for the treatment of emphysema.

Ablation Procedure and Post-Ablation Assessment

Procedures were performed under general anaesthesia. Bronchoscopic navigation to the target airway was performed using

Table 1. Demographics and radiologic features

	003	004	005	006	007
Age/sex	73 M	67 F	58 F	69 M	68 M
FEV1 (L, %predicted)	2.82 (98%)	1.58 (66)	1.47 (82)	2.41 (82)	1.82 (81)
Tumour size, mm					
Solid component	4×9	16×8	10×9	17×14	14×8
Overall size	24×16	27×23	12×11	18×16	40×25
Tumour visibility	Part-solid	Part-solid; mild spiculation	Part-solid; mild spiculation	Part-solid; dilated bronchi with bubble-like lucencies	Spiculated, part-solid
Pleural contact (Y/N)	N	Y	Y	Y	Y

standard videobronchoscopy (BF-P190, Olympus. Tokyo, Japan). Bronchoscopic navigation to target segment was aided by Archimedes planning software, as previously described [12]. Confirmation of position "on-target" with radial EBUS was confirmed where possible. Patients receiving "on-target" treatments received a single treatment in this safety/feasibility study. In patients where on-target treatment could not be confirmed with radial EBUS, 2 treatments were used to maximized likelihood that the tumour would be included within the treatment volume.

The BTVA-C system was programmed to deliver 330 calories per treatment of thermal energy over 8 s. Prophylactic broad-spectrum antibiotics were administered during the procedure (1 g amoxycillin IV). Following the procedure, participants were electively admitted overnight for routine observation following their BTVA-C procedures. Oral antibiotics (amoxycillin 1 g tds) was prescribed on discharge and continued until day of surgery.

Post-ablation CT chest was performed 1 day prior to plan surgical resection to visualize the area of localized inflammatory response (LIR) in relation to the original tumour location. Thoracoscopic lobectomy together with systematic nodal dissection was performed by a dedicated thoracic surgeon. All patients were followed until 30 days post-resection.

Pathologic Examination

Gross images with rulers were reviewed and gross measurements of parenchymal necrosis and tumour size were made. Size of ablation size was measured in the axial and lateral directions based on the gross pathological pictures (with scale) combined with the estimated slice depth. The axial and lateral measurements were aided by the histological examination to assure that structures and observations in the gross pathology pictures correlated to histological features.

Glass slides were reviewed using an Olympus BX41 microscope, and microscopic photographs were obtained with an Olympus DP27 camera and Olympus cellSens Entry software. Microscopic measurements were made using an eyepiece reticule for lesions confined to 1 glass slide or using a ruler after outlining areas of interest with a dotting pen and reconstructing the anatomy for lesions that bridged multiple glass slides. Pathologic review was performed blinded to any clinical information including diagnosis, imaging, treatment details, or surgical findings.

Parenchymal necrosis was identified as non-neoplastic lung that demonstrated pneumocyte and interstitial necrosis, often with accompanying haemorrhage. Tumour necrosis was identified as neoplastic tissue exhibiting cytoplasmic hyper-eosinophilia, loss of cellular borders, and nuclear changes of cell death (karryorhexis, karryolysis, or pyknosis); these changes were typically seen in both the malignant cells and tumour stroma. Viable tumour was identified as neoplastic tissue with intact cell borders, intact nuclear morphology, and healthy appearing stroma.

Results

Six patients provided informed consent and underwent BTVA-C. One patient, who received BTVA-C (2 treatments) to an 11 mm nodule in the superior segment left lower lobe, had previously undergone chemoradiotherapy for a right-sided stage III NSCLC and experienced significant radiation fibrosis. His BTVA-C was complicated by pleuritic chest pain, managed electively with intravenous antibiotics, resulting in an extra day admission in hospital. A brief inflammatory response was observed, with CRP and neutrophil count peaking at day 4 (220 mg/mL) and day 2 (16.8×10^9), respectively. At planned resection, he tolerated single-lung ventilation poorly, and planned anatomic resection was abandoned.

The remaining 5 patients who proceeded to surgical lobectomy of their tumours form the basis of this report and are presented in detail below. Radiologic details and treatment parameters are recorded in Table 1. Median size of solid component of tumour was 1.32±0.36 cm. Patient 2 reported moderate pleuritic chest pain requiring oral opioids on day 1 post-BTVA-C. This had resolved by the time of resection. No other procedure-related complications were reported (Table 2).

Patient 1

A 73-year-old male underwent 2 BTVA-C treatments at second-generation airway segment of apical RUL

Table 2. BTVA-C procedural findings and parameters

	003	004	005	006	007
Treatments, *n*	2	1	1	2	1
"On-target" treatment	Y	Y	Y	Y	Y
Distance from catheter to tumour, cm	2.8, 3.1	0.9	2.6	3.9, 3.6	3.9
Distance from catheter to pleura, cm	6.5, 7.0	5.5	3.6	4.8, 4.8	5.6
Bronchial segment^	Apical RUL (Rb1b)	Lateral RML (Rb4a)	Anterior RUL (Rb3a)	Apical RUL (Rb1b)	Apical RUL (Rb1c)
Generation*	2nd, 2nd	4th	3rd	5th, 5th	4th
Tumour position confirmed with radial EBUS	N	Y	Y	Y	Y
Treatment volume, mL	129, 128	28	55	33, 33	62
Procedural complications	Nil	Small right pleural effusion Pleuritic chest pain requiring oral opioids	Nil	Nil	Nil
Energy delivery					
Overall	660	243	330	660	330
Cal per mL	2.57	8.68	6	10	5.32[#]
Procedure duration	45	12	12	11	21
Interval BTVA-C to resection (days)	5	5	4	5	5

BTVA-C, bronchoscopic thermal vapour ablation for lung cancer. ^ Boyden classification of bronchial anatomy. * Describes generation # beyond segmental bronchus. [#] Small degree of back-leak of vapour noted, energy delivered to lung parenchymal likely to be lower than recorded.

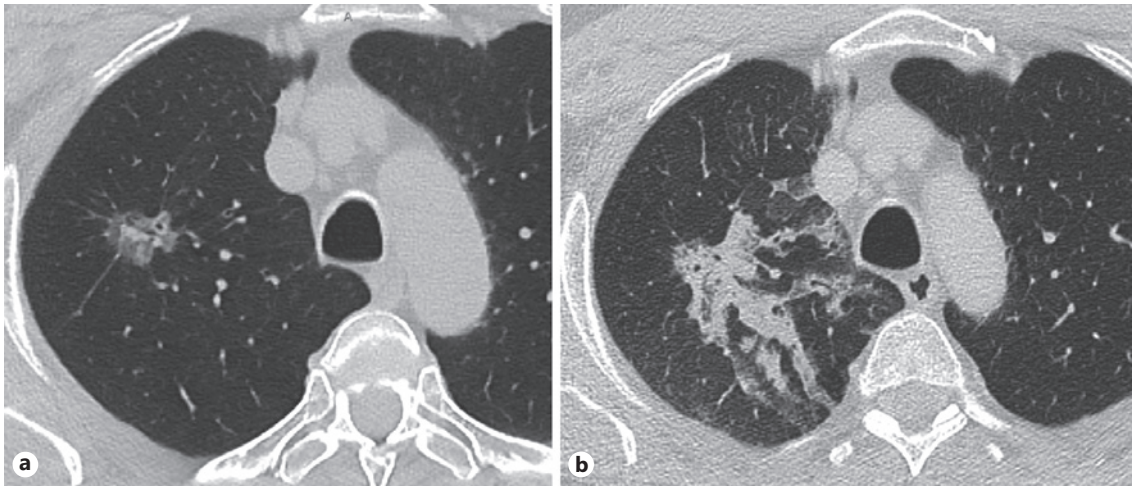

Fig. 2. Apical RUL part solid tumour. Imaging at baseline (**a**), imaging following BTVA-C demonstrates patchy bronchocentric non-contigious opacities indicating the distribution of LIR (**b**). BTVA-C, bronchoscopic thermal vapour ablation for lung cancer; LIR, localized inflammatory response.

(shown in Fig. 2). Total volume of treated lung parenchyma was 257 mL.

The pathologic findings in the resection specimen correlated with the radiologic findings. There was patchy parenchymal necrosis that appeared to correlate with bronchioalveolar units that did not completely envelop the tumour. The maximum tumour dimension pathologically was 2.5 cm, and approximately 69% of the tumour remained viable.

Assessment

BTVA-C safely delivered; however, delivery of thermal vapour proximal to planned segment resulted in a significantly larger treatment volume than planned, with

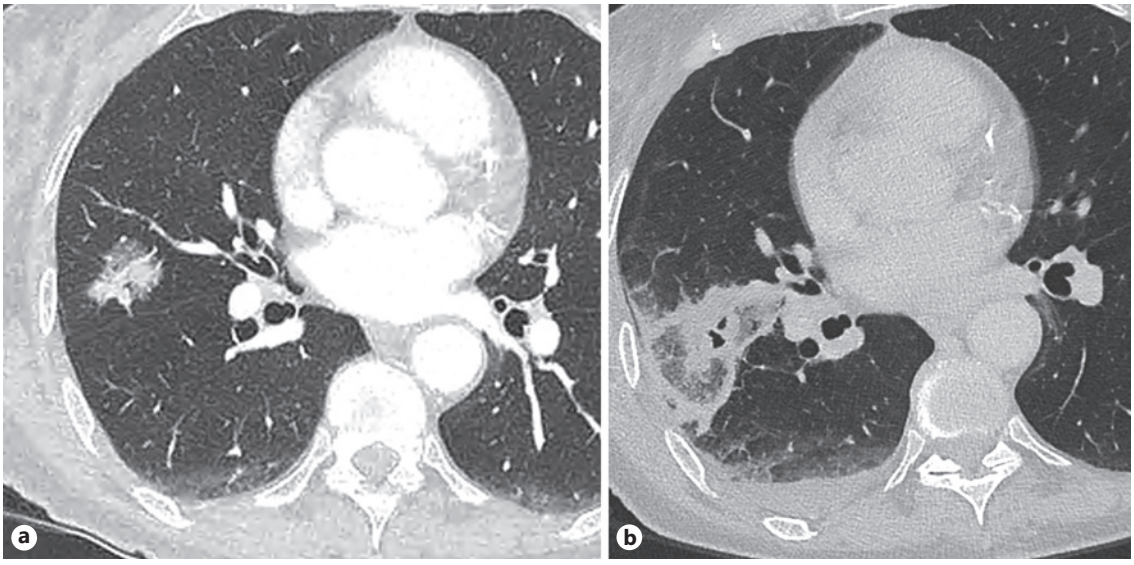

Fig. 3. a Lateral RML part solid tumour at baseline. Post-ablation imaging (**b**) demonstrates a wedge-shaped opacification totally encompassing the target lesion, with subtle cavitation of tumour evident. Thickening of the oblique fissure and a small right pleural effusion consistent with LIR. Dense opacity at periphery of treatment zone corresponded with areas of haemorrhagic necrosis seen histologically. Histologic examination demonstrated necrosis of 98% of tumour. LIR, localized inflammatory response.

consequent dilution of thermal dose and patchy and subablative injury within apical RUL segment.

Patient 2

A 67-year-old female underwent a single on-target BTVA-C treatment following confirmation of tumour position within Rb4a (shown in Fig. 3) by radial EBUS. The treatment catheter tip was positioned in the 4th generation airway of the lateral segment RML, just 9 mm from the tumour. Volume of treated lung parenchyma was 27 mL. Delivery of BTVA-C was auto-terminated at 6 s due to an internal generator safety switch.

Surgical resection was uncomplicated. Histologic examination of resected specimen (shown in Fig. 4) demonstrated a zone of parenchymal necrosis measuring 42 × 28 × 78 mm, comprising necrotic tumour (63%) and tumour demonstrating changes of expected necrosis (35.2%). A small portion of the tumour (1.8% of total tumour) was present outside the envelope of parenchymal necrosis and remained viable. The tumour within the envelope of parenchymal necrosis was necrotic with the exception of a microscopic focus of tumour in an area of pleural invasion.

Assessment

Successful delivery of BTVA-C with near-complete ablation of target achieved, despite truncation of BTVA-C delivery. Two small portions of viable tumour were identified just outside the ablation zone.

Patient 3

A 58-year-old female underwent a single on-target (confirmed by radial EBUS) treatment at 4th generation airway level within the anterior RUL segment (Rb3a) (shown in Fig. 5), with 55 mL of lung parenchyma treated. Catheter tip was 3.6 cm from proximal portion of tumour.

Surgical resection was uncomplicated. Examination of gross pathologic specimen demonstrated a wedge-shaped ablation zone incorporating the target lesion (shown in Fig. 6). Microscopic examination demonstrated complete necrosis of the entire tumour (100%).

Assessment

Successful delivery of BTVA-C with complete ablation (necrosis) of target lesion achieved.

Patient 4

A 69-year-old male received 2 on-target treatments in 5th generation airways of the apical RUL segmental bronchus (Rb1b) (shown in Fig. 7), treating a total parenchymal volume of 66 mL. On histologic evaluation, the tumour contained a prominent central scar along with a

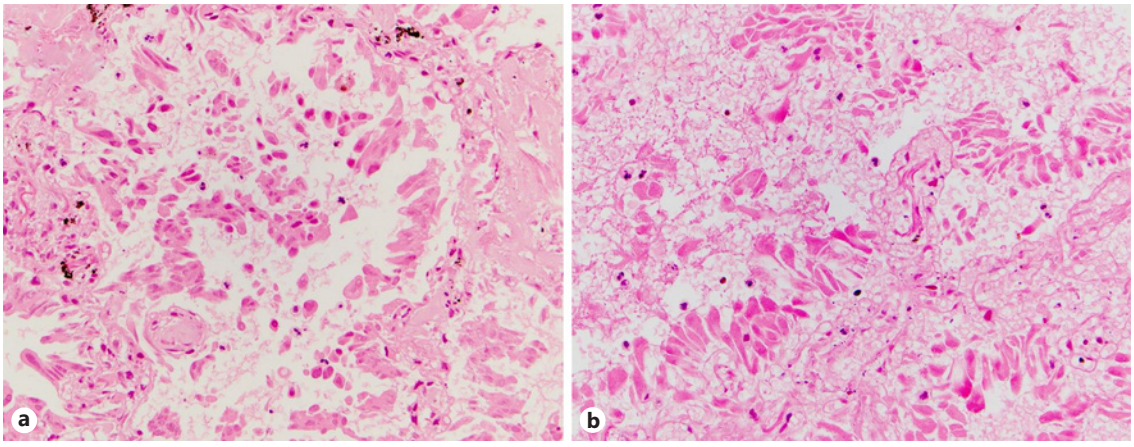

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Fig. 4. Representative histologic findings (haematoxylin and eosin ×40) from patient #3 demonstrating (**a**) "expected necrosis" – the cytoplasm of the cells is hypereosinophilic and glassy. The nuclei demonstrate early pyknosis and karyolysis. The cells have also become discohesive and sloughed from the underlying stroma, and complete tumour necrosis, with tumour with coagulation necrosis, hypereosinophilia, and nuclear loss evident (**b**).

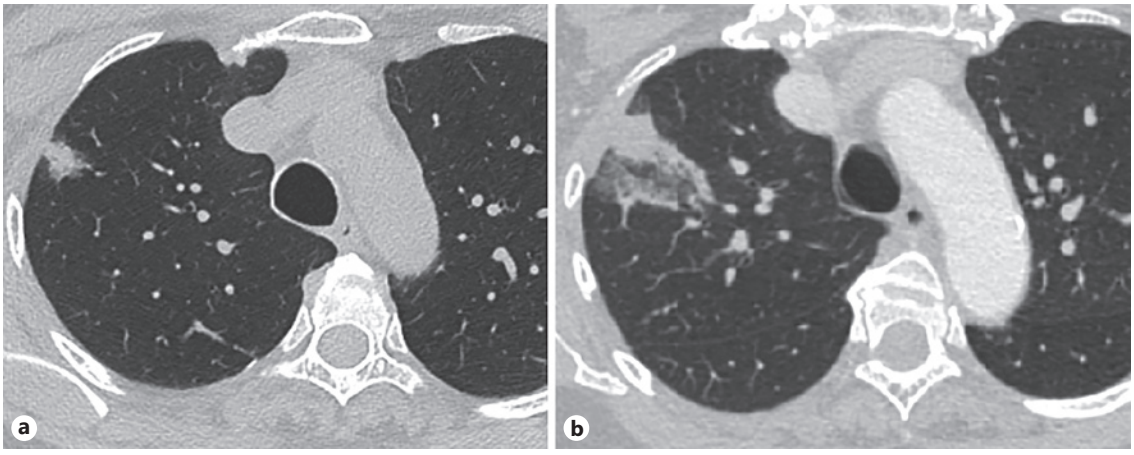

Fig. 5. a RUL tumour pre-ablation. **b** Post-ablation CT chest demonstrates incomplete wedge-shaped opacity with tumour positioned on border of zone of injury. Histologic examination demonstrated BTVA-C resulted in necrosis of the entire tumour specimen. BTVA-C, bronchoscopic thermal vapour ablation for lung cancer.

microscopic area of visceral pleural invasion deep to this scar that was within the envelope of parenchymal necrosis; the tumour within the pleura deep to the scar remained histologically viable. Histologic evaluation was also significant for an area of viable tumour outside of the zone of parenchymal necrosis. The remainder of the tumour demonstrated necrosis. Persistent air-leak was observed following lobectomy, which resolved spontaneously after 9 days.

Assessment

Approximately 14% of tumour remained viable at day 5 post-ablation. While 2 "on-target" treatments were successfully delivered, the anterior surface of the tumour was not within the ablation zone. The remainder of viable tumour was limited to a section of lung positioned between pleura and a small area of parenchymal scarring.

Patient 5

A 68-year-old male presented with synchronous primary tumours. Initial management was with lobectomy

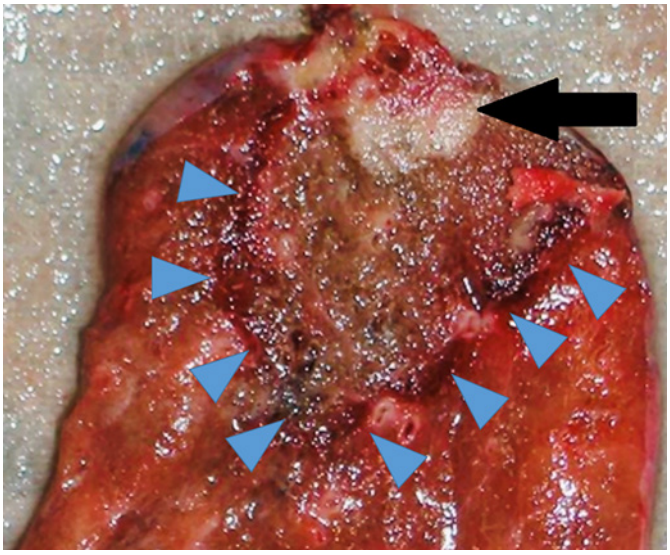

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Fig. 6. Resected RUL gross pathology findings (patient #3) demonstrating wedge-shaped ablation zone, incorporating the target lesion (arrow) surrounded by area of apparent haemorrhage (arrowheads). This area appeared microscopically as "expected" necrosis (shown in Fig. 5).

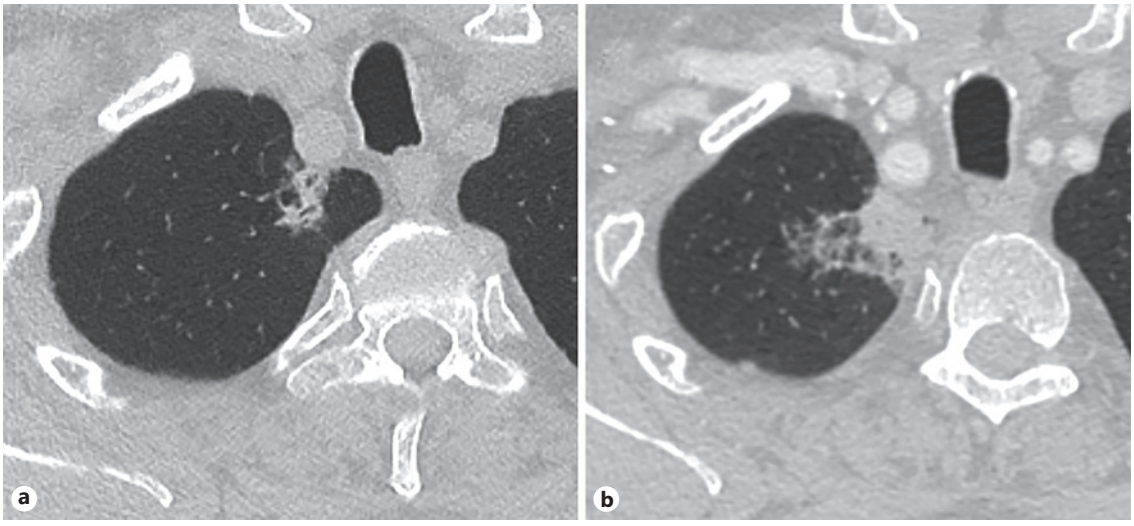

Fig. 7. a Pleurally based apical RUL tumour seen pre-ablation. **b** Post-ablation opacity encompassing target lesion with increased density of tumour observed. The most anterior aspect of the tumour was not located within the ablation zone, with this finding confirmed on histologic examination of the resection specimen.

for a 27 mm LUL tumour (T2 N1). Following recovery from this, the patient underwent BTVA-C to a Rb1c lesion (shown in Fig. 8), receiving 1 on-target treatment to a part-solid lesion with a 14 × 8mm solid component and 40 × 28 mm ground glass component.

Back-leakage of vapour was noted, with blanching of airway segments visible just proximal to the position of catheter balloon, potentially compromising the thermal dose to the target lesion. The catheter balloon was observed post-ablation to be fully inflated, suggesting mild proximal dislocation of the balloon during treatment as the cause for back-leakage of vapour.

Histologic examination revealed an adenocarcinoma with a central solid area and a peripheral lepidic area. A portion of this lepidic area was outside of the envelope of parenchymal necrosis and remained histologically viable. The solid area of the tumour contained dense desmoplastic stroma and was necrotic; this scarring did not appear to prevent tumour ablation.

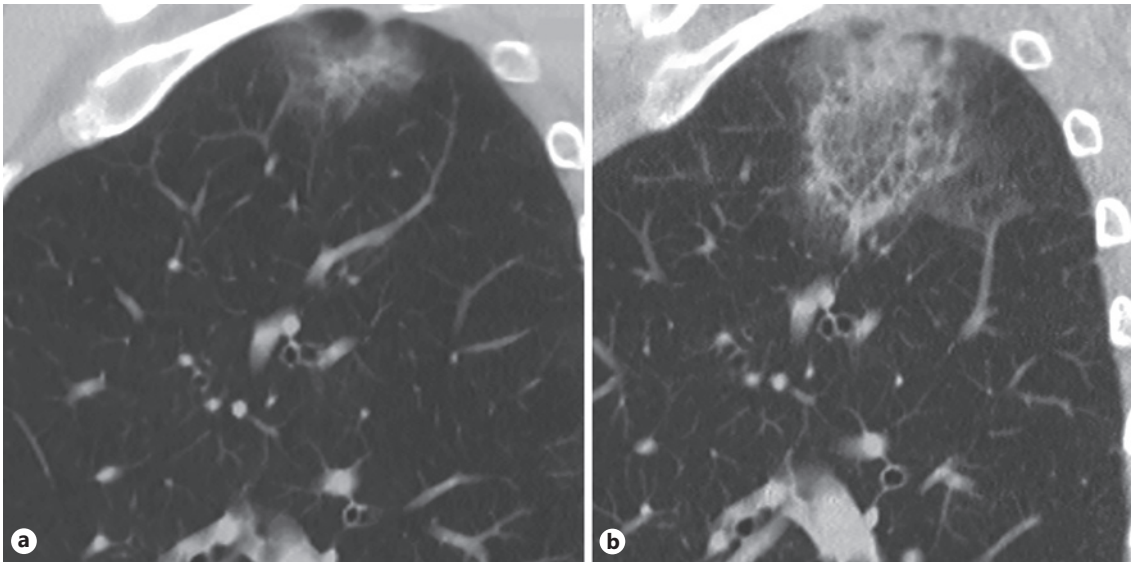

Fig. 8. a Sagittal CT image of RUL part-solid lesion in apical RUL. **b** Wedge-shaped opacity demarcates the post-ablation treatment zone.

Lobectomy was complicated by injury to the proximal right pulmonary artery. Immediate post-operative course was complicated by bleeding requiring return to theatre and subsequent admission to ICU. Support including ECMO was required; however, the patient was successfully weaned from ECMO and MV and discharged from ICU at day 20 post-surgery. He continues follow-up and remains at home and disease-free at 365 days.

Assessment

Despite 2 on-target treatments, viable tumour was located outside treatment zone suggesting need for improved methods for predicting treatment zone distribution.

Discussion

Our findings demonstrate the feasibility of BTVA for ablation of peripheral parenchymal cancers. Four patients with confirmation of "on-target" treatment by radial EBUS achieved large uniform ablation zones, even where a single treatment was delivered, provided thermal dose exceeded 3 Cal/mL. In 2 participants, BTVA-C achieved complete/near-complete necrosis (100 and 98%) of target lesions. Median procedure duration was just 12 min.

Safety also appears consistent with known safety profile of BTVA for treatment of emphysema. No infection, pneumothorax, or haemoptysis were reported within the short post-interventional observation period. Two patients experienced post-ablation chest pain, likely reflecting exuberant pleural inflammation secondary to thermal ablation, reflected in changes on CT chest (Fig. 3). This was not a noted complication of BTVA and possibly reflects the higher dose per treated volume received in these patients (50.6 cal/g, compared to 8.5 cal/g in emphysema therapy [9]). Importantly, these events were self-limiting. Major complications observed were assessed as not related to the treatment or device, instead reflecting the known complications of surgical lobectomy (persistent air leak is reported in 10% of patients following VATS lobectomy [13], major vascular injury in 3–8% [14, 15]).

Our findings indicate the potential for effective bronchoscopic ablation of peripheral tumours using readily available tools of radial EBUS and virtual bronchoscopy for treatment planning. The intervention was well tolerated with minor self-limiting complication observed in 1 patient who experienced pleuritic chest pain, associated with a small pleural effusion, suggesting pleural inflammation. This did not warrant intervention beyond oral analgesia and did not complicate surgery or post-operative recovery. Our findings are, therefore, reassuring regarding tolerability of the treatment in patients with compromised physiology. Radial EBUS is demonstrated safe even in patients with advanced COPD [16], and BTVA is established for use in patients with advanced emphysema [9], suggesting this technique will be feasible in patients

with compromised physiology, which is the group this modality is likely to be applied to.

Thermal doses used in this study are significantly lower than for BTVA for treatment of emphysema (target dose 330 Cal vs. average dose in STEP-UP study of 399 Cal [9]), though at higher concentrations (cal/mL). Ablation zones were well demarcated both on post-ablation CT chest and on histologic examination. Tumour positioned within ablation zones demonstrated necrosis in >99% of cross-sectional area examined. The only viable area within an ablation zone appeared to be in an area of pleural invasion deep to a central scar. Fibrosis and central scars in the other patients did not appear to diminish the efficacy of the vapour ablation. It may be that some combination of the pleural invasion, central scar, and distance from the ablation catheter led to this result. As this was the only patient with pleural invasion in this cohort, it will be important to evaluate areas of pleural invasion in future patients to determine whether pleural vessels exert a heat-sink effect, if pleural tissue is intrinsically heat-resistant, or if a large distance from catheter tip to pleura allows significant dissipation of thermal energy by the time vapour reaches the pleura, compromising ablative efficacy.

Persistence of viable tumour in resection specimens was most frequently noted outside the parenchymal ablation zone. Ensuring treatments fully encompass the target lesion will be important in future studies of this technique, either via more accurate targeting of treatments or use of multiple treatments. Intra-procedural imaging may also aid in ensuring target is fully encompassed in ablation zones [17].

Greater extent of tumour necrosis may have been observed within treatment zone with a longer interval from ablation to resection (median in this cohort 5 days). Cells receiving lower, but still lethal, thermal injury may have progressed to histologically evident necrotic cell death. Similarly, damage to blood vessels following thermal injury within and around the zone of parenchymal necrosis may produce delayed thrombosis and avascular/hypoxic death of tumour initially appearing viable. Further studies with longer ablation-to-resection intervals are required to address this finding.

From this limited experience, we identify some significant findings regarding the efficacy of BTVA-C. Treatment volume appears to be significant. If treatment volume is too large, thermal injury is limited to main airways and adjacent parenchyma. Reducing treatment volumes (likely through more distal delivery of BTVA-C) and ensuring sufficient energy per mL parenchyma are likely to be important in future work.

Surgical resection has remained standard of care for treatment of early stage NSCLC since the 1950s. Lobectomy is clearly preferred to sub-lobar resection, based on superior survival outcomes, however, may be problematic in patients with limited functional reserve. Perioperative mortality following lobectomy exceeds 1.5% and does not appear to be smaller following sub-lobar resection [18]. Stereotactic ablative body radiotherapy has proven efficacy, however, is limited in patients with underlying pulmonary disease (e.g., fibrosis) [7, 8], tumours positioned proximal to central airways [19], or previous radiation treatment.

Bronchoscopic ablation is likely to be significantly safer than current percutaneous techniques, which are associated with pneumothorax rates up to 60% [4] and intercostal drain requirement in up to 38% [5], which is clearly problematic for a modality likely to be applied in multiply comorbid patients. Haemorrhage, haemoptysis, and effusion are also frequently reported complications following percutaneous tumour ablation [20]. In physiologically frail patients, bronchoscopic ablation may allow diagnosis (using rapid on-site evaluation [21]), staging [22], and treatment to be completed in a single procedure. In addition to an improved safety profile, this is likely to be more cost-effective than existing modalities [23], especially in older patients who experience higher rates of morbidity and mortality following resection [24].

Numerous clinical studies are underway examining multiple novel devices for bronchoscopic tumour ablation, with a recently published review summarizing the published evidence for individual modalities [20]. Radiofrequency ablation and photodynamic therapy remain, prior to this study, the only modalities where bronchoscopic experience in ablation of peripheral tumours in clinical settings has been reported [20]. Studies examining bronchoscopically delivered microwave ablation, bronchoscopic laser interstitial thermal therapy, and cryoablation are limited to preclinical settings. All of these techniques require direct localization of target lesions to ensure accurate delivery of ablative energy, which may limit their utility.

In contrast, BTVA is an established technique with a known safety profile following its use in emphysema, and multiple treatments may be delivered within a single procedure [9]. This could be used to ensure treatment zones fully encompass a target lesion. BTVA-C may not necessitate bronchoscopic localization, as treatment need only be delivered via a "feeding" airway. Ablation zones are likely to be larger than achievable by localized ablative technologies. Additional treatments, perhaps following intra-procedural cone-beam CT imaging [17], may be possible, to ensure a margin around the tumour is achieved.

Future studies are required to optimize lesion targeting and to ensure tumours are encompassed by treatment zones. Efficacy for larger lesions should be established. "Dose" optimization will also be necessary, and establishing a safety profile in less physiologically robust patients will be required to allow this modality to proceed to definitive "treat-and-leave" studies. Intriguing translational research suggests that thermal ablation of NSCLC may up-regulate an antitumour immune response [25, 26], increasing responsiveness to immunotherapy which may also expand the application of BVTA-C, though this requires further study.

Conclusion

BTVA of lung tumours is feasible and well tolerated, with preliminary evidence suggesting high potential for effective ablation of tumours. Thermal injury is well demarcated, and uniform tissue necrosis is observed within ablation zones receiving sufficient thermal dose per volume of lung. Treatment of smaller volumes and ensuring adequate thermal dose may be important for ablative efficacy. Further studies are required to optimize targeting of BTVA-C as well as thermal dose and to establish the impact of intra-tumoural scarring and pleural contact on ablative efficacy of BTVA-C.

Statement of Ethics

This study received institutional review board approval (HREC/17/MH/422) with all participants providing written informed consent. This study was prospectively registered (NCT03198468).

Conflict of Interest Statement

Dr. Padera reports personal fees from Broncus Medical during the conduct of the study. The remaining authors have no conflicts to declare.

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Author Contributions

Study concept – A.V., M.R.M., and D.P.S. Study design – D.P.S., V.A., A.M., and R.P. Acquisition of data – D.P.S., P.A., K.R., L.B.I., and M.C. Analysis/interpretation of data – D.P.S., M.C., R.P., and K.R. Drafting of manuscript – D.P.S. and R.P. Revision of manuscript – M.C., K.R., P.A., L.B.I., M.R.M., and A.V.

References

1 Howington JA, Blum MG, Chang AC, Balekian AA, Murthy SC. Treatment of stage I and II non-small cell lung cancer: diagnosis and management of lung cancer, 3rd ed: American college of chest physicians evidence-based clinical practice guidelines. Chest. 2013;143(5 Suppl l):e278S–313S.

2 Dupuy DE. Treatment of medically inoperable non-small-cell lung cancer with stereotactic body radiation therapy versus image-guided tumor ablation: can interventional radiology compete? J Vasc Interv Radiol. 2013;24(8):1139–45.

3 Siva S, Ball D. Curing operable stage I non-small cell lung cancer with stereotactic ablative body radiotherapy: the force awakens. Oncologist. 2016;21(4):393–8.

4 Inoue M, Nakatsuka S, Jinzaki M. Cryoablation of early-stage primary lung cancer. Biomed Res Int. 2014;2014:521691.

5 Zhao ZR, Lau RWH, Ng CSH. Catheter-based alternative treatment for early-stage lung cancer with a high-risk for morbidity. J Thorac Dis. 2018;10(Suppl 16):S1864–70.

6 Sabath BF, Casal RF. Bronchoscopic ablation of peripheral lung tumors. J Thorac Dis. 2019;11(6):2628–38.

7 Bahig H, Filion E, Vu T, Chalaoui J, Lambert L, Roberge D, et al. Severe radiation pneumonitis after lung stereotactic ablative radiation therapy in patients with interstitial lung disease. Pract Radiat Oncol. 2016;6(5):367–74.

8 Chen H, Senan S, Nossent EJ, Boldt RG, Warner A, Palma DA, et al. Treatment-related toxicity in patients with early-stage non-small cell lung cancer and coexisting interstitial lung disease: a systematic review. Int J Radiat Oncol Biol Phys. 2017;98(3):622–31.

9 Herth FJ, Valipour A, Shah PL, Eberhardt R, Grah C, Egan J, et al. Segmental volume reduction using thermal vapour ablation in patients with severe emphysema: 6-month results of the multicentre, parallel-group, open-label, randomised controlled STEP-UP trial. Lancet Respir Med. 2016;4(3):185–93.

10 Henne E, Ferguson JS, Mest R, Herth FJ. Thermal vapor ablation for lung lesions in a porcine model. Respiration. 2015;90(2):146–54.

11 Ferguson JS, Henne E. Bronchoscopically delivered thermal vapor ablation of human lung lesions. J Bronchology Interv Pulmonol. 2019 Apr;26(2):108–13.

12 Herth FJ, Eberhardt R, Sterman D, Silvestri GA, Hoffmann H, Shah PL. Bronchoscopic transparenchymal nodule access (BTPNA): first in human trial of a novel procedure for sampling solitary pulmonary nodules. Thorax. 2015;70(4):326–32.

13 Zhao K, Mei J, Xia C, Hu B, Li H, Li W, et al. Prolonged air leak after video-assisted thoracic surgery lung cancer resection: risk factors and its effect on postoperative clinical recovery. J Thorac Dis. 2017;9(5):1219–25.

14 Louie BE. Catastrophes and complicated intraoperative events during robotic lung resection. J Vis Surg. 2017;3:52.

15 Liu L, Mei J, He J, Demmy TL, Gao S, Li S, et al. International interest group on bleeding during VLS. International expert consensus on the management of bleeding during VATS lung surgery. Ann Transl Med. 2019;7(23):712.

16 Georgiou HD, Taverner J, Irving LB, Steinfort DP. Safety and efficacy of radial EBUS for the investigation of peripheral pulmonary lesions in patients with advanced COPD. J Bronchology Interv Pulmonol. 2016;23(3):192–8.
17 Steinfort DP, Vrjlic I, Einsiedel P, Prasad J, Jennings B, Heinze S, et al. CT-fluoroscopic guidance for performance of targeted transbronchial cryobiopsy: a preliminary report. Respiration. 2018;96(5):472–9.
18 Altorki NK, Wang X, Wigle D, Gu L, Darling G, Ashrafi AS, et al. Perioperative mortality and morbidity after sublobar versus lobar resection for early-stage non-small-cell lung cancer: post-hoc analysis of an international, randomised, phase 3 trial (CALGB/Alliance 140503). Lancet Respir Med. 2018;6(12):915–24.
19 Chen H, Laba JM, Zayed S, Boldt RG, Palma DA, Louie AV. Safety and effectiveness of stereotactic ablative radiotherapy for ultra-central lung lesions: a systematic review. J Thorac Oncol. 2019;14(8):1332–42.
20 Steinfort DP, Herth FJF. Bronchoscopic treatments for early-stage peripheral lung cancer: are we ready for prime time? Respirology. 2020;25(9):944–52.
21 Steinfort DP, Leong TL, Laska IF, Beaty A, Tsui A, Irving LB. Diagnostic utility and accuracy of rapid on-site evaluation of bronchoscopic brushings. Eur Respir J. 2015;45(6):1653–60.
22 Leong TL, Loveland PM, Gorelik A, Irving L, Steinfort DP. Preoperative staging by EBUS in cN0/N1 lung cancer: systematic review and meta-analysis. J Bronchology Interv Pulmonol. 2019;26(3):155–65.
23 Smith BD, Jiang J, Chang JY, Welsh J, Likhacheva A, Buchholz TA, et al. Cost-effectiveness of stereotactic radiation, sublobar resection, and lobectomy for early non-small cell lung cancers in older adults. J Geriatr Oncol. 2015;6(4):324–31.
24 Vazirani J, Moraes J, Barnett S, Johnson DF, Knight S, Miller A, et al. Outcomes following resection of non-small cell lung cancer in octogenarians. ANZ J Surg. 2018;88(12):1322–7.
25 Rangamuwa K, Leong TL, Weeden C, Asselin-Labat ML, Bozinovski S, Christie M, et al. Thermal ablation in non-small cell lung cancer: a review of treatment modalities and the evidence for combination with immune checkpoint inhibitors. Transl Lung Cancer Res. 2020. [in press – accepted Nov 2020].
26 Rangamuwa K, Leong TL, Asselin-Labat ML, Bozinovski S, Christie M, John T, et al. Increase in tumour PD-L1 expression in NSCLC following thermal ablation is not related to systemic inflammatory response. Transl Lung Cancer Res. 2020. [in press – accepted Dec 2020].