Endobronchial high-intensity ultrasound for thermal therapy of pulmonary malignancies: simulations with patient-specific lung models

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ABSTRACT

Objective: This study investigates the feasibility of endobronchial ultrasound applicators for thermal ablation of lung tumors using acoustic and biothermal simulations.

Methods: Endobronchial ultrasound applicators with planar (10 mm width) or tubular transducers (6 mm outer diameter (OD)) encapsulated by expandable coupling balloons (10 mm OD) are considered for treating tumors from within major airways; smaller catheter-based applicators with tubular transducers (1.7–4 mm OD) and coupling balloons (2.5–5 mm OD) are considered within deep lung airways. Parametric studies were applied to evaluate transducer configurations, tumor size and location, effects of acoustic reflection and absorption at tumor-lung parenchyma interfaces, and the utility of lung flooding for enhancing accessibility. Patient-specific anatomical lung models, with various geometries and locations of tumors, were developed for further evaluation of device performance and treatment strategies. Temperature and thermal dose distributions were calculated and reported.

Results: Large endobronchial applicators with planar or tubular transducers (3–7 MHz, 5 min) can thermally ablate tumors attached to major bronchi at up to 3 cm depth, where reflection and attenuation of normal lung localize tumor heating; with lung flooding, endobronchial applicators can ablate ~2 cm diameter tumors with up to ~2 cm separation from the bronchial wall, without significant heating of intervening tissue. Smaller catheter-based tubular applicators can ablate tumors up to 2–3 cm in diameter from deep lung airways (5–9 MHz, 5 min).

Conclusion: Simulations demonstrate the feasibility of endobronchial ultrasound applicators to deliver thermal coagulation of 2–3 cm diameter tumors adjacent to or accessible from major and deep lung airways.

Introduction

Lung and bronchial cancers are the leading cause of cancer-related death worldwide, and in 2018 accounted for an estimated 234,030 new cases and 154,050 deaths in the United States [1], and ~2.09 million new cases and 1.76 million deaths worldwide [2]. The standard treatment option for early-stage non-small cell lung cancer (NSCLC) and most types of lung metastases is surgical resection, however, approximately 15–30% of patients are ineligible for surgery due to factors such as aging, poor cardiopulmonary function, or medical comorbidities related with smoking [3–5]. Image-guided stereotactic body radiation therapy and/or chemotherapy are also considered for non-surgical cases and treatment of advanced disease [6–8]. As an alternative to the above treatment approaches, thermal ablation with recently introduced technology provides a minimally invasive approach for treating patients not suitable for surgical resection or traditional therapies [9–11].

Percutaneous radiofrequency ablation (RFA) and microwave ablation (MWA) devices delivered under CT guidance are two widely developed technologies applied for high-temperature thermal ablation for lung cancer treatment, and have demonstrated potential for treating tumor sizes smaller than 3 cm diameter with reported advantages including improvements to local control and survival [3,12–14]. The percutaneous treatment of primary and metastatic disease may be contraindicated and/or less effective for large tumors located near major airways and blood vessels of the upper and central lung, with suitability often determined on a case-by-case basis [13,15–17]. Pneumothorax is a common complication of both RFA and MWA, and is often associated with percutaneous placement, needle trajectory, or adjustment of device positioning and orientation under CT imaging [13,18–20]. As an alternative to percutaneous needle-based ablation, endobronchial ultrasound imaging and fiberoptic bronchoscopy can be used to guide transbronchial insertion or intraluminal placement of RFA devices and cryotherapy applicators for treatment of tumors directly accessible from the bronchi [21–23]. Endobronchial ablation with these approaches can provide debulking for locally advanced tumors adjacent to and obstructing major airways, with reduced interventions and possibly lower pneumothorax rates compared to percutaneous ablation [24–26].
High-intensity ultrasound is a promising technology that applies minimally invasive approaches to treat tumors with precise spatial control of energy deposition and large ablation volumes possible. As one of the least invasive and most precise delivery platforms of ablation therapy, extracorporeal high-intensity focused ultrasound (HIFU) coupled with MRI or ultrasound real-time imaging and monitoring can deliver acoustic energy from outside the body to cause tumor coagulation in liver, kidney, pancreas, bone, or the brain, among others [27–29]. Alternatively, endocavity and catheter-based ultrasound (CBUS) devices via percutaneous and intraluminal approaches within the body can deliver thermal therapy directly adjacent to or within target lumens and tissues not easily accessible by extracorporeal systems [30]. With the guidance of MRI and ultrasound, endocavity HIFU and CBUS have been investigated for treatment of a variety of sites and indications, such as transurethral thermal treatment of prostate cancer and benign prostatic hypertrophy (BPH) [31–33], and endoluminal thermal therapy of esophageal, biliary tract, and pancreatic cancer [34–36].

Although extracorporeal HIFU has many advantages over other energy modalities, its applicability for treating lung tumors is complicated by limited acoustic access into the thoracic cavity, organ movement, and the high acoustic attenuation and reflections of acoustic energy due to the impedance mismatch of air-filled lung parenchyma with adjacent tissues [37]. Recent in silico and in vivo investigations have demonstrated that lung flooding through infusing saline into air-filled lung may be used during HIFU procedures as a means to reduce local attenuation and reflection of acoustic energy within lung parenchyma, potentially allowing for more effective acoustic energy transmission and targeting of lung tumors [37–40], although organ movement, focusing through the ribs, and need for reduction of typical HIFU treatment durations remain as challenges [30,38]. Given the limitations of other energy modalities and difficulties of treating lung with extracorporeal HIFU, there is motivation to explore endobronchial CBUS applicators as a more direct way to treat pulmonary tumors located adjacent to or accessible from the airways. Potential advantages of this minimally invasive approach include minimized requirement of lung flooding relative to extracorporeal HIFU and more precise and conformal ablative capability relative to other ablation modalities, which may reduce treatment durations and complications such as pneumothorax. Further, the reflections and acoustic attenuation of normal lung parenchyma may provide for preferential acoustic energy deposition and heating in tumors encaising or attached to a bronchial wall.

The purpose of our study is to apply acoustic and biothermal simulations to determine the feasibility and potential performance advantages of endobronchial ultrasound applicators to thermally coagulate pulmonary tumors adjacent to or accessible from lung airways. Parametric studies and 3D patient-specific lung model simulations were performed to investigate various applicator design features and anatomical conditions, including with or without lung flooding, with performance described by calculated temperature and thermal dose distributions.

**Materials and methods**

**Endoluminal ultrasound applicator**

The generalized schema of the proposed endobronchial ultrasound applicators and treatment delivery (Figure 1) includes large diameter endoluminal applicators (~10 mm outer diameter (OD)) with integrated planar or tubular ultrasound transducers for therapy delivery from within major bronchi, and smaller diameter applicators (~2–5 mm OD) with tubular transducers for use within small bronchi of deep lung regions. The specific design features of the endobronchial ultrasound applicators modeled in this work are shown in Figure 2, with designs varying according to intended positioning either within the primary and secondary bronchi of major lung airways or small bronchi within
deep lung. Each prospective applicator contains a single planar ultrasound transducer (10 mm width, 20 mm length, 1–9 MHz) or tubular transducer (1.7–6 mm OD, 10–20 mm length depending on sites, 3–9 MHz, 120–360° active sector), with transducer assembly integrated within an inflatable endobronchial water cooling/coupling balloon (2.5–10 mm OD, 15–30 mm length depending on sites, inflated once deployed), positioned at the distal end of a flexible delivery catheter. Cooling water circulation (15°C deployed), positioned at the distal end of a flexible delivery catheter. Cooling water circulation (15°C) was applied on the outer applicator surface to represent water cooling within the endobronchial balloon:

\[ n \cdot k \nabla T = h(T_\infty - T) \]

where \( n \) is the outward normal vector, the convective heat transfer coefficient \( h \) is 1000 W m⁻³ K⁻¹ and cooling water temperature \( T_\infty \) is set as 15°C [56].

**Parametric studies**

Parametric studies using analytical approximations for acoustic intensity fields and simplified geometric models were performed to investigate a broad range of applicator design features including transducer geometry, operating frequency and driving surface intensity, as well as the influence of anatomical variation such as tumor size, tumor-airway separation distance, and impact of varying degrees of lung inflation or flooding on the thermal performance of the endobronchial applicators. 2D models using either a rectangular geometry for planar transducer applicators or axis-symmetrical cylindrical geometry for tubular transducer applicators models

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**Table 1.** Thermal and acoustic properties of tissues used in the parametric study and patient specific simulations.

| Tissue type       | Speed (m/s) | Density (kg/m³) | Attenuation (Np/m) | Specific heat (J/kg/K) | Thermal conductivity (W/m/K) | Perfusion rate (kg/m³s) |
|-------------------|-------------|-----------------|--------------------|------------------------|----------------------------|-------------------------|
| Bronchial wall/bronchi\(^a\) | 1603        | 1100            | 25\(^f\)           | 3568                   | 0.49                       | 4.6                     |
|                   | (48)        | (48)            | (47)               | (48)                   | (48)                       | (53)                    |
| Tumor             | 1605        | 1135            | 5.01\(^f\)         | 3795                   | 0.51                       | 7                      |
|                   | (40)        | (40)            | (40)               | (51)                   | (47)                       | (53)                    |
| Flooded lung      | 1550        | 1030            | 1.38\(^f\)         | 3886                   | 0.52                       | 7.30                    |
|                   | (40)        | (40)            | (40)               | (48)                   | (47)                       | (54)                    |
| Higher inflated lung | 916        | 400             | 220\(^f\)          | 3886                   | 0.39                       | 2.83                    |
|                   | (49)        | (49)            | (49)               | (48)                   | (47)                       | (54)                    |
| Lower inflated lung | 1218       | 700             | 96.7\(^f\)         | 3886                   | 0.39                       | 4.96                    |
|                   | (49)        | (49)            | (49)               | (48)                   | (47)                       | (54)                    |

\(^a\)The attenuation coefficient of bronchial wall was approximated by weighted average of attenuation values of soft tissue (50% muscle) and cartilage (50%) in this study.

\(^b\)\( f \) is the frequency of ultrasound applicator in unit of MHz.

\(^c\)Perfusion rates were reduced to 0 kg/m³s over 52°C (55).
were created. Two types of heterogeneous tissue computational domains, as shown in Figure 3, were adopted for this study, using the acoustic and thermal parameters of Table 1: Model A of a tumor directly attached to the bronchial wall, and surrounded with either high or low inflated lung parenchyma (Figure 3(a)); Model B of a tumor at distance away from the bronchial wall, and surrounded with saline-infused flooded lung (Figure 3(b)). To reduce the computational cost and complexity in these parametric simulations, the acoustic energy produced by the transducers was approximated to follow fully-developed plane wave propagation with normal incidence angles at tissue interfaces [57]. Lung parenchyma tissue was modeled as lower inflated lung and higher inflated lung representing different air inflation levels of lung tissues with different densities and speeds of sound, or as flooded lung, with corresponding acoustic properties applied (Table 1). Constant speed of sound and impedance of lung tissue with frequency is assumed. Detailed descriptions of the analytical expressions used for modeling the acoustic intensity distributions and energy deposition, incorporating reflections and transmission at the tumor-lung interface, are described in Section 1 and Equations (S1)–(S6) of the Supplemental materials. Models A and B were used to investigate distinct prospective cases, including targeting of tumors attached or adjacent to major bronchi (major airways) and tumors adjacent to small diameter tertiary bronchi (deep lung). Different applicator configurations, tumor sizes and distances from the bronchial wall were incorporated as summarized in Table 2. Specifically, bronchial wall thickness was set at 1.5 mm at major bronchi and 0.75 mm at tertiary bronchi, and lumen diameters were set as 10 mm at major airways and 2.5–5 mm at smaller airways, based on measurements extracted from multi-detector CT imaging [58]. Tumor sizes in terms of radial depth extent were set as 1–3 cm at major airways and 0.5–1.5 cm at smaller airways with normal air-filled lung parenchyma (Model A, Figure 3(a)), and 2 cm at major airways and 1 cm at smaller airways with saline flooding lung parenchyma (Model B, Figure 3(b)). Acoustic power deposition profiles were calculated using Equations (S1)–(S6) in Supplemental materials, and imported into COMSOL Multiphysics 5.3 (COMSOL Inc., Burlington, MA) for thermal simulations. In the models described in Table 2, the absorption coefficient for all tissues is assumed to be equal to the corresponding attenuation coefficient, with all scattered energy locally absorbed. Some studies have suggested that the absorption coefficient (\(a_l\)) of the inflated lung parenchyma might be significantly less than the attenuation coefficient (\(\mu_l\)) due to its highly scattering properties [59–61]. As such, additional parametric studies using the geometry of Model A were performed to investigate the influence of lower absorption coefficient in lung tissue, as described in section 2 of the supplemental materials. Acoustic surface intensities of the transducers were iteratively adjusted to

![Figure 3](image.png)

**Figure 3.** 2D parametric simulation models with attaching (Model A) and adjacent but not attaching tumors (Model B) to the bronchial wall: transducer types (planar, 360° active tubular applicators), tumor sizes (0.5–3 cm, as denoted by yellow arrowed bar) and lung environments (lower and higher inflated lung, flooded lung) were varied to represent different treatment sites and conditions, as listed in Table 2.

**Table 2.** Endobronchial ultrasound applicator configurations and tumor location with dimensions investigated within parametric studies, for tumors attached and unattached to the bronchial wall, and with and without lung flooding.

| Model | Applicator type | Dimensions (balloon OD/ transducer width (W) & length (L)) | Frequency range (MHz) | BWa thickness (mm) | Tumor depth extent (cm) | B-T gapb (cm) | Lung background |
|-------|----------------|-----------------------------------------------------------|----------------------|-------------------|------------------------|-------------|----------------|
| A     | Planar         | W: 10 mm; L:20 mm                                         | 3–9                  | 1.5               | 1–3                    | 0           | Inflated lung  |
| A     | Tubular        | OD:10 mm; L:20 mm                                         | 3–9                  | 1.5               | 1–3                    | 0           | Inflated lung  |
| A     | Tubular        | OD:5 mm; L:10 mm                                          | 4–9                  | 0.75              | 0.5–1.5                | 0           | Inflated lung  |
| A     | Tubular        | OD: 2.5 mm; L:10 mm                                       | 4–9                  | 0.75              | 0.5–1.5                | 0           | Inflated lung  |
| B     | Planar         | W: 10 mm; L:20 mm                                         | 1–9                  | 1.5               | 2                      | 1–2         | Flooded lung   |
| B     | Tubular        | OD:10 mm; L:20 mm                                         | 3–9                  | 1.5               | 2                      | 1–2         | Flooded lung   |
| B     | Tubular        | OD:5 mm; L:10 mm                                          | 4–9                  | 0.75              | 0.5–1                  | 0.5–1       | Flooded lung   |
| B     | Tubular        | OD: 2.5 mm; L:10 mm                                       | 4–9                  | 0.75              | 0.5–1                  | 0.5–1       | Flooded lung   |

\(^{a}\)BW: bronchial wall.  
\(^{b}\)B-T gap: bronchi-tumor gap, 0 denotes the tumor is attached to outer bronchial wall.
achieve a maximum temperature of 75 °C within a 5 min sonication time. The resulting temperature profiles central to the transducer surface were analyzed to evaluate the performance of the endobronchial applicators. The minimum and maximum penetration depths were defined as the proximal and distal depths of the 52 °C temperature contour from the inner bronchial wall, corresponding to approximately 240 EM43 °C thermal dose margins. The ablative margin was defined as the distance that the 52 °C temperature contour exceeded the target tumor boundary in the depth direction.

**Patient-specific studies**

To evaluate the feasibility and performance of the endobronchial ultrasound applicators for thermal therapy of lung and bronchial cancer in a more realistic and complex anatomical setting, a total of five distinct tumor models within an anatomical lung airway model were generated, as shown in Figure 4. The lung airway structure with at least 2 mm lumen diameter of bronchi was segmented from the CT images of an adult patient with lung cancer using an airway segmentation algorithm developed by Nardelli et al. [62], within the open source software platform 3D slicer (www.slicer.org). A total of five tumors between 1 and 3 cm diameter were segmented using iSeg (Zurich MedTech AG, Zurich, Switzerland) and were placed at different sites to represent a range of patient cases. The details of tumor locations, sizes and lung background conditions are summarized in Table 3. Using select applicator configurations from the parametric studies, as summarized in Table 3, acoustic simulations to calculate acoustic intensity distributions in the heterogeneous tissue computational domains were performed using a 3D full-wave FDTD acoustic solver (P-ACOUSTIC) within Sim4Life, based upon the linear acoustic pressure wave and with adaptive rectilinear meshes. The acoustic simulation voxel size varies with the frequencies of the endobronchial ultrasound applicator to \( \lambda/10 \) (\( \lambda \) is the acoustic wavelength) for a convergent solution. An implicit time dependent FDTD thermal solver (P-THERMAL, T-CEM43) with maximum time step of 15 s was utilized to determine temporal 3D temperature and thermal dose profiles. The maximum thermal simulation voxel size was set as 0.25 mm. Convergence tests were performed for each model to ensure all grid sizes were fine enough for stable acoustic and thermal solutions. The transient temperature and thermal dose distributions for applicator configurations within each patient model were analyzed to obtain maximum temperature penetration and sparing of the bronchial wall, lethal thermal damage volumes, and penetration depth.

**Results**

**Parametric studies: tumors attaching to bronchi**

The resultant minimum and maximum penetration depths of the 52 °C contour for the parametric studies of Model A are summarized in Figures 5 and 6 for sites of major airways and deep lung, respectively. At major airways, an endobronchial planar applicator (10 mm \( \times \) 20 mm, 1.2–3.4 W/cm² acoustic intensity) was used to attach tumors to the outer bronchial wall, resulting in a target tumor boundary of 2 cm diameter. For deep lung, a 360° active tubular applicator was used to attach tumors to the inner bronchial wall, resulting in a target tumor boundary of 2 cm diameter. The results indicate that the endobronchial ultrasound applicators are capable of achieving high temperatures within the target tumor boundary, with minimal penetration into the bronchial wall.

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**Table 3. Details of anatomical lung and tumor models and applicator configurations for patient-specific simulation studies.**

| Anatomical model # | Transducer type | Dimensions (balloon OD; transducer OD (or W) × L) | Frequency (MHz) | Tumor sites & diameter | B-T gapa (cm) | ISATAb (W/cm²) | Lung conditions |
|--------------------|----------------|-----------------------------------------------|-----------------|------------------------|---------------|----------------|----------------|
| 1                  | 120° sectored tubular | Balloon OD: 10 mm; OD × L: 6 mm × 20 mm | 6              | Major airways, 1 cm    | 0       | 9              | Higher inflated lung |
| 2                  | Planar          | Balloon OD: 10 mm; W × L: 10 mm × 20 mm    | 5              | Major airways, 3 cm    | 0       | 4.5             | Lower inflated lung |
| 3                  | Planar          | Balloon OD: 10 mm; W × L: 10 mm × 20 mm    | 3              | Major airways, 2 cm    | 2       | 7.5             | Flooded lung |
| 4                  | 150° sectored tubular | Balloon OD: 2.5 mm; OD × L: 1.2 mm × 10 mm | 7              | Deep lung, 2 cm        | 0.5     | 30              | Flooded lung |
| 5                  | 360° active tubular | Balloon OD: 2.5 mm; OD × L: 1.7 mm × 10 mm | 7              | Deep lung, 2 cm        | 0       | 12.5            | Lower inflated lung |

\( ^a \text{B-T Gap: Bronchi-tumor gap, 0 denotes the tumor is attached to the outer bronchial wall.} \)

\( ^b \text{ISATA: Acoustic spatial average, temporal average surface intensity of the transducer in unit of W/cm².} \)
surface intensities, Figure 5, top row) can coagulate beyond the distal boundary of 3 cm tumors with an ablative margin of 4.1–6.8 mm at the frequency range of 3–5 MHz, but may result in sparing of the proximal tumor boundary and incomplete coagulation of the tumor. The proximal tumor sparing is more significant when treating smaller tumors (<2 cm in depth) at frequencies below 6 MHz. Complete coagulation along depth was achieved with appropriate selection of frequency ranges: 5 MHz for 3 cm tumor, 6–8 MHz for 2 cm tumor and 9 MHz for 1 cm tumor. In contrast, tubular applicators (6 mm transducer OD, 20 mm length, 10 mm balloon OD, 6.4–20.1 W/cm² acoustic surface intensities, 3–9 MHz, Figure 5, bottom row) in major airways could coagulate smaller tumors (1 cm in radial depth) with approximately 2.5–5.5 mm ablative distal margin extending into lung beyond the tumor and proximal coverage extending 1.0–1.2 mm into the bronchial wall with 1.5 mm thickness, varying with frequency and lung inflation levels. For larger tumors of 2–3 cm, coagulation depth was limited to 10.4–15.4 mm deep from the inner bronchial wall for 4–9 MHz, resulting in sparing of the distal tumor and tumor–lung boundary. For deep lung cases accessible by smaller diameter tubular applicators (2–4 mm
transducer OD, 10 mm length, 2.5–5 mm balloon OD, 8.6–29.3 W/cm² acoustic surface intensities, 4–9 MHz, Figure 6), applicators could ablate up to the 1.5 cm tumor at frequencies between 4 and 6 MHz, with 2.3–5.0 mm distal ablative margin and up to 0.5 mm sparing of proximal tumor boundary. At 7–9 MHz, ablation penetration to the distal tumor boundary was limited to smaller tumors (<1 cm in radial depth), with almost no sparing of bronchial wall. For both tumor sites with either a planar or tubular transducer, lung inflation level slightly affected the penetration depths at lower frequency range (4–6 MHz), however it had little influence at higher frequency range (7–9 MHz). Results for the parametric analysis of various values of the absorption coefficient ranging from $\mu_l$ to 0.1$\mu_l$ in relation to the attenuation coefficient are described in supplemental materials (Section 2, Figure S1) in brief, as the absorption is decreased, heating of the proximal and distal tumor margins is increased.

**Parametric study: tumors unattached to bronchi**

The parametric studies of Model B with tumors adjacent to but unattached with the bronchial wall, as shown in Figure 3(b), were performed to include saline flooding of lung in both sites of major airways and deep lung, and the minimum and maximum penetration depths are summarized in Figure 7. At major airways, an endobronchial planar applicator (10 mm × 20 mm, 3.6–9.7 W/cm²) at lower frequency (1–3 MHz) could produce a 2–2.5 cm long coagulation zone in depth which can cover the 2 cm tumor with up to 4 mm margin while sparing at least 2 cm of normal intervening flooded lung; in contrast, at higher frequency (>3 MHz), penetration to the outer boundary of the tumor was not achievable for tumors either 1 cm or 2 cm from the bronchial wall, and intervening flooded lung was not spared. In comparison, the tubular applicator (10 mm balloon OD, 7.8–17.5 W/cm², 3–9 MHz, Figure 7, top row) was not effective at targeting the whole tumor, with maximum penetration of 20.3 mm (8.8 mm within the 2 cm tumor) for tumors 1 cm from the bronchial wall, and almost no ablation coverage of tumors 2 cm from the wall.

In deep lung, both endobronchial tubular ultrasound applicator (2–4 mm transducer OD, 10 mm length, 2.5–5 mm balloon OD, 14.7–38 W/cm², 4–9 MHz, Figure 7, bottom row) configurations demonstrated deeper penetration at lower frequency (4–5 MHz), but not enough to cover the distal tumor boundary. For tumors with 5 mm separation from the bronchial wall, the maximum penetrations at 4–9 MHz were 10.6–15.0 mm from the inner bronchial wall. Tumor coverage decreased when it was located further (~10 mm) from the bronchial wall: at least 1.4–6 mm of the tumor depth was sub-ablative for the 5 mm balloon OD applicator, and no ablative coverage of the tumor was produced for the 2.5 mm balloon OD applicator.

**Patient-specific simulations-tumors accessible from major airways**

Acoustic and biothermal simulations on anatomical models with tumors located adjacent to major airways (Models 1–3, Figure 4) utilized optimal frequencies and applied power ranges identified in the parametric studies (Table 3). The temperature and thermal dose distributions at the end of 5 min ablations for two distinct tumor targets attached to the major bronchi, using a sectored tubular or planar transducer applicator, are shown in Figures 8 and 9(a,b), respectively. An endobronchial sectored tubular applicator (6 mm

![Figure 7. Parametric study of lung flooding: penetration depths (52 °C margin) across frequency of ultrasound applicators with planar (10 mm × 20 mm, red line) or tubular transducers (10 mm balloon OD, blue line) for major airways placement, for treatment of a 2 cm lung tumor located 10 mm (top left) and 20 mm (top right) away from the outer bronchial wall (top row); comparison of deep lung endobronchial tubular ultrasound applicators (5 mm balloon OD, green line and 2.5 mm balloon OD, magenta line) for treatment of a 1 cm lung tumor located 5 mm (bottom left) and 10 mm (bottom right) away from the outer bronchial wall (bottom row). The ablation zone extends between min-depth and max-depth, as depicted. BW – bronchial wall. Min-depths of the tubular applicator with 5 mm balloon OD were overlapped by min-depth of the 2.5 mm balloon OD tubular applicator.](image-url)
Figure 8. Temperature and thermal dose distributions of patient-specific Model 1 on the coronal (a, b) and axial plane (c, d) after 300 s sonication with an endobronchial ultrasound tubular applicator (6 mm transducer OD × 10 mm length, 10 mm balloon OD, 6 MHz, 9 W/cm², 120° active zone), as applied to deliver thermal coagulation to the tumor (~1 cm in depth) attached to major airways. Temperature contours of 45 °C, 50 °C, and 60 °C are shown in (a) and (c), and thermal dose contours of 30 EM₄°C and 240 EM₄°C are shown in (b) and (d). US: ultrasound.

Figure 9. Temperature and thermal dose distributions along the coronal plane obtained after 300 s sonication using endobronchial planar applicators in (a, b) Model 2 representing treatment of a tumor directly attached to the bronchial wall with lower inflated lung, and (c, d) Model 3 representing a tumor separated by 2 cm from the bronchial wall with lung flooding. Two different applicator configurations were applied: 5 MHz, 4.5 W/cm² for model 2; 3 MHz, 7.5 W/cm² for Model 3. Temperature contours of 45 °C, 50 °C, 60 °C, and 70 °C are shown in (a) and (c), and thermal dose contours of 30 EM₄°C and 240 EM₄°C are shown in (b) and (d). US: ultrasound.
transducer OD, 20 mm length, 6 MHz, 9 W/cm², 120° active zone) located within the major bronchi, shown in Figure 8, demonstrated heating penetration above 52°C along 1 cm (in depth) for a tumor attaching to the bronchial wall. Thermal dose contours of 240 EM₄³°C covered ~87% of the target tumor volume within 5 min ablation, with up to 4 mm ablative margin in both coronal and axial planes. While not shown, it should be noted that transducer dimensions (length and/or active sector angle) could be adjusted to increase volumetric coverage. An endobronchial planar applicator (10 mm width × 20 mm length, 5 MHz, 4.5 W/cm²) shown in Figure 9(ab) demonstrated deep ablative penetration of larger tumors (~3 cm in depth) while providing some sparing of the bronchial wall (~0.7 mm from the inner bronchial wall). The ablation margin was approximately 5 mm in depth beyond the tumor, demonstrating isolation of tumor heating with inflated lung conditions. When the tumor was not attached to bronchial wall (Model 3) as shown in Figure 9(cd), flooded lung was simulated as a means to increase acoustic energy propagation. The endobronchial planar applicator (10 mm × 20 mm, 3 MHz, 7.5 W/cm²) could ablate the target tumor (up to 5 mm ablation margin) located at least 2 cm away from the major bronchi while sparing the whole bronchial wall and preserving most normal (flooded) lung tissue between the outer bronchial wall and the tumor.

**Patient-specific simulations: tumors accessible from deep lung**

Simulations on two anatomical models with tumors located in deep lung adjacent to tertiary bronchi (Models 4 and 5, Figure 4) were performed for small diameter tubular applicators, and the temperature and thermal dose distributions calculated as shown in Figures 10 and 11. Two tubular applicators (2 mm transducer OD × 10 mm length, 7 MHz, 30 W/cm², 150° active sector for Model 4 in Figure 10 and 1.7 mm transducer OD × 10 mm length, 7 MHz, 12.5 W/cm², 360° active sector for Model 5 in Figure 11) were positioned within the tertiary bronchi, and the balloon OD was initially set to 2.5 mm and fitted to conform to the actual bronchi diameter as obtained directly from CT segmentation. For the case of Model 4 shown in Figure 10, the 2 cm tumor was not attached to the small diameter tertiary bronchi, and thus flooded lung was simulated to provide acoustic energy access. In this scenario, the endobronchial sectored tubular applicator could penetrate 1.5 cm radial depth within the 2 cm tumor, thus only coagulating 54.5% of the tumor volume over 240 EM₄³°C with at least 0.6 cm distal tumor depth at sub-lethal thermal exposures (<50°C and <30 EM₄³°C). For Model 5, where the ~2 cm diameter tumor was fully attached and encasing the tertiary bronchi, as shown in Figure 11, the selected endobronchial tubular applicator with 360° active zone demonstrated coagulation (>52°C and >240 EM₄³°C of 85.4% of the tumor volume coverage and 3–5 mm margin, as shown in the dose coverage of 240 EM₄³°C contour. The axial extent of the thermal damage closely followed the length of the ultrasound transducer, and although not shown it can be inferred that sequential repositioning of the applicator or selecting a longer transducer could improve the volume coverage.

**Discussion**

This study investigated prospective design features and delivery strategies for endobronchial ultrasound applicators...
through acoustic and biothermal simulations on 2D parametric and 3D anatomical models, as a minimally invasive method for thermal ablation of pulmonary tumors accessible from central major or deep lung bronchial passages. Simulations demonstrate that through appropriate selection of the transducer configurations and sonication settings, tumors that are attached to and accessible via major airways can be ablated at up to 3 cm depth from the bronchial wall, while tumors adjacent to or encapsulating smaller deep lung airways can be ablated at up to 1.5 cm radial depth. Simulations also show that lung flooding, as proposed for use with extracorporeal HIFU, can provide improved acoustic energy propagation from endobronchial ultrasound devices to enhance ablation of tumors closely adjacent to but separated from accessible lung airways.

For cases of tumors attached to the airway, the acoustic impedance mismatch and high attenuation of the normal lung parenchyma at the distal tumor boundary can help to isolate ultrasound energy within the tumor and enhance heating at the tissue interface. Normal inflated lung tissue has a complex structure with inhomogeneous acoustic properties and variable air content or inflation levels during respiration [61,63,64], which affects and limits ultrasound propagation. A previous study demonstrated acoustic impedance of lung ranged from 0.1 Mrayl of fully inflated lung to 1.4 Mrayl of deflated or fully collapsed lung, with some studies also demonstrating frequency-dependent lung speed of sound and soft tissue-lung reflection coefficients [49,61,65,66]. To simplify the modeling in this study, speed of sound and impedance were not varied with frequency, and two inflation levels of normal lung were considered to bracket the expected range of variation in acoustic properties.

For both lung inflation levels, significantly higher acoustic attenuation values (Table 1) and substantial impedance mismatching (0.37–0.85 Mrayl in the inflated lungs, versus 1.82 Mrayl in the target tumor) were used compared to the values used for tumor and other adjacent soft tissues. Thus, for cases of lung tumors directly attached or enveloping the bronchial wall, a large portion of the acoustic energy (∼13–43% acoustic intensity, at normal incidence) was reflected from the tumor-inflated lung interface, while transmitted energy into the lung was steeply attenuated with depth, thus, constraining energy deposition and heating to within the tumor and a narrow boundary within inflated lung. Further, the high absorption coefficient used for lung results in high preferential heating at the distal tumor-lung interface, which for specific combinations of transducer geometry, frequency, and tumor size, can be so dominant that in tandem with the maximum temperature set-point employed herein (∼75 °C), corresponding simulations resulted in sub-ablative coverage of the proximal tumor region (Figures 5 and 6). The present study also investigated the potential impact of lower absorption compared to attenuation through parametric studies described in supplemental materials, with results shown in Figure S1 demonstrating that as absorption decreases (coefficients ranging from $\mu_a$ to 0.1$\mu_a$), the effective extent of ablation is shifted toward the proximal boundary of the tumor, and can result in more uniform heating and ablation coverage through the tumor depth, while possibly decreasing the distal ablative margin. Although not explicitly shown in the present study, more thorough tumor heating and larger margins than the 3–5 mm attained here can be achieved by using greater applied powers/intensities and higher maximum temperature set-points, and/or longer treatment durations.

**Figure 11.** Temperature and thermal dose distributions for patient-specific Model 5 along the axial (a and b) and coronal planes (c and d) after 300 s sonication with an endobronchial tubular applicator (1.7 mm transducer OD × 10 mm, 360° active zone, 7 MHz, 12.5 W/cm²). The 2 cm diameter tumor volume is encompassing and adjacent to the tertiary bronchial airway, surrounding with higher inflated lung. Temperature contours of 45 °C, 50 °C, and 60 °C are shown in (a) and (c), and dose contours of 300EM43 °C and 240EM43 °C are shown in (b) and (d). US: ultrasound.
This study also investigated the potential impact of utilizing lung flooding to enhance acoustic energy access for thermal ablation of lung lesions in close proximity but not directly attaching to lung airways. Saline-infused lung flooding, which was recently investigated for lung sonography enhancement and extracorporeal HIFU lung tumor ablation [37,38,40], has been demonstrated to reduce the acoustic impedance mismatch between normal lung and tumor, and significantly reduce the attenuation of normal lung tissue. Parametric studies and patient-specific simulations of endobronchial applicators herein have demonstrated that lung flooding may enhance ultrasound energy propagation through lung parenchyma to allow localized heating within a target tumor up to 2 cm separation distance from major airways, without excessive thermal damage to normal flooded lung tissue (Figures 7, and 9(c,d)), and with a similar margin of 3–5 mm compared to extracorporeal HIFU reported in previous studies [39]. Simulations demonstrate selective heating of tumor targets over intervening flooded lung tissue using planar transducer configurations, which is a result of the higher (~3.5×) attenuation/absorption coefficients in tumor over flooded lung. However, as shown in parametric studies (Figure 7) and Model 4 (Figure 10), the utility of lung flooding might be of limited utility for applicators with tubular transducer configurations, as the radial intensity falloff inherent to tubular transducer sources, not the tissue attenuation, limits energy penetration (<1.5 cm) and increases heating of normal tissues between the bronchial wall and the tumor.

This study provides preliminary guidance for continued development of endobronchial ultrasound devices for treatment of central and peripheral lung tumors. Simulation results indicate that larger endobronchial applicators with selected planar transducer configurations (10 mm × 20 mm, 3–7 MHz) and coupled encapsulating balloons may be suitable for coagulating large tumors extending 2–3 cm in depth from and attaching to the major bronchi (Figures 5 and 9(a,b)), or for targeting closely adjacent tumors up to 2 cm in size and less than ~2 cm separation from the major bronchi through lung flooding (Figures 7 and 9(c,d)). For larger partially circumferential tumors, the device may need to be rotated and/or translated sequentially to fully cover the entire tumor volume. Sectored tubular transducers (10 mm balloon OD, 7–9 MHz) may be suitable for treating smaller tumors (<2 cm in depth) attached to and partially encapsulating major bronchi efficiently (Figures 5 and 8), with a pre-set appropriate active sector angle and minimal repositioning. The proposed endobronchial ultrasound approach, with positioning within and integrated cooling of the inner bronchus, could provide better protection of central airways and major vessels compared to contemporary percutaneous RF or microwave ablation approaches, which require physical penetration through the lung parenchyma and have associated risk of thermal damage on the central airways, bronchial disruption or pneumothorax [19,20]. Simulations also indicate that compact applicator configurations with miniature tubular transducers (1.7–4 mm OD) and expandable balloons (2.5–5 mm OD) may be capable of coagulating tumors at up to 1.5 cm radial depth attaching to the tertiary bronchi (Figures 6 and 11), or adjacent tumors at up to 1.5 cm radial depth and up to 0.5 mm separation from the tertiary bronchi with lung flooding (Figures 7 and 10). These ultrasound applicator constructs, which could incorporate flexible catheter assemblies as small as 1–4 mm OD [30,67,68], could be combined with endobronchial navigational techniques, such as fluoroscopy, optical sensing, or electromagnetic navigation bronchoscopy [22,69–72], to navigate for placement adjacent to peripheral lesions that are <3 cm in diameter and not easily accessible to percutaneous devices [73,74].

While this preliminary work forms the basis of determining feasibility and indications of the potential advantages of this endobronchial ultrasound ablation approach, several simplifications and approximations were incorporated into the simulations. To minimize the computational cost and complexity, simplified plane-wave propagation expressions and tissue model geometries and interfaces were employed in the parametric study as described Equations (S1)–(S6) in Supplemental materials. Despite these simplifications, the parametric simulations generated similar maximum temperatures (75 °C versus 75–80 °C) and ablative margins (both with 3–5 mm) with the patient anatomic simulations, which incorporated more sophisticated acoustic modeling methods and complex tumor and tissue geometries. Additionally, the patient-specific models developed herein only incorporated lung bronchi with diameter >2 mm, and did not include major blood vessels and vasculature, which would act as local heat sinks to reduce the target temperatures and modulate temperature distributions, depending on their proximity to the applicator and target tumor [75,76]. Considerations of extended clinically relevant structures (e.g., ribs, blood vessels, major nerves or heart) or additional patient-specific anatomical geometries may provide further insights into device design and treatment strategies. Furthermore, only solid tumors with uniform acoustic and thermal properties were modeled to broadly represent nodular NSCLC or metastatic disease. In practice, the tumor may be more diffuse or infiltrating, and tumor composition and heterogeneity may be significantly different depending on the exact type of disease or metastasis present. For example, necrotic tumors may have lower attenuation and blood perfusion, whereas tumors such as pulmonary metastases of osteosarcomas may have areas of higher attenuation around calcifications and heterogeneous blood flow, variations which would significantly affect acoustic propagation and thermal distributions. Slight variation in tumor tissue properties from the nominal values employed herein are not expected to significantly alter results for tumors attached to the airways, due to the thermal dominance of the tumor-inflated lung boundary, but may be more impactful in flooded lung conditions where preferential tumor heating relies on its higher attenuation and absorption relative to flooded lung. In consideration of future work to enhance modeling accuracy, additional measurements of the acoustic and thermal properties of human lung and tumors/metastases could be quantified and incorporated, including dynamic changes to thermal properties [77], as well as to speed of sound and density...
Future work may also focus on specific device development, applying more detailed theoretical analyses of design and treatment delivery strategies, along with experimental device fabrication and testing on the bench and studies in lung tissue in vivo.

Toward completion of device development and implementation, we envision deep lung catheter-based ultrasound devices (~2 mm OD) deployed through the working channel of a flexible bronchoscope, and positioned at the target site under real-time steering and guidance using CT-based electromagnetic navigation methods typical of radial endobronchial ultrasonography in peripheral lung [78]. The ultrasound ablation can be performed once the water-coupling balloon is inflated, and at completion the device can be deflated and withdrawn. Similarly, flexible or rigid video bronchoscopes with larger bores can facilitate placement of larger ultrasound devices (5–10 mm OD) in the larger upper airways, following similar techniques currently applied for interventions ablating obstructing tumors in the trachea and bronchus. These procedures could be via trans-nasal or oral bronchoscopic introduction, while under procedural sedation or general anesthesia, following approaches common to interventional pulmonology [78]. Post-ablation monitoring and evaluation could be performed using CT, PET, and/or MRI based imaging techniques [79].

Conclusion

In summary, theoretical simulations were performed to evaluate the feasibility and prospective performance characteristics of endobronchial ultrasound for thermal treatment of lung tumors directly attached to or closely adjacent to bronchi. Various sizes of endobronchial ultrasound applicators were proposed, with larger device configurations integrating planar or tubular transducers and 10–12 mm OD expandable cooling balloons demonstrated as capable of thermally coagulating ~3 cm diameter tumors adjacent to major airways. Smaller diameter endobronchial devices (2.5–5 mm balloon OD), have potential to thermally coagulate up to 2–3 cm diameter tumors within deep lung with 3–5 mm margin. Lung flooding was also shown to enhance acoustic access to and enable ablation of tumors in close proximity (up to 2 cm away) but not attached to the airways.

Disclosure statement

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