Review Article

Endoscopic treatment for lung cancer in medically inoperable patients

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Abstract: Due to the increasing incidence of abnormal pulmonary lesions, there has been a growing demand for local treatment options for lung malignancies. For medically-inoperable patients with underlying comorbidities, transbronchial endoscopic treatment has a vital role. Transbronchial therapy for lung tumors has a favorable strategy as it avoids pleural punctures. Recent advancements in navigation and confirmation technologies have significantly improved the accuracy of tool placement, enabling the treatment of centrally-located tumors, and also peripheral lung tumors, with high efficiency. Here, we present an overview of the evolution and recent advancements in transbronchial local treatments for lung malignancies, including radiofrequency ablation (RFA), microwave ablation (MWA), vapor ablation, cryoablation, photodynamic therapy (PDT), brachytherapy, and pulsed electric field (PEF)-based therapy. We also discuss critical factors contributing to the success of the transbronchial treatment, including localization and anesthesia strategies. Additionally, in recent years, it has been reported that some ablative treatments may activate the immune system by the release of tumor-associated antigens from damaged cancer cells, resulting in additional anti-tumor effects. This paper discusses the evidence regarding these additive effects on ablative therapies. The field of endoscopic treatments for peripheral lung malignancy remains relatively underexplored, with limited publications available. The paper concludes by summarizing the prospects for future developments in this area.

Keywords: Bronchoscopy; lung cancer; ablation

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Introduction

Surgical resection stands as the most effective treatment for patients with early-stage lung cancer (1). However, eligibility for surgical resection is constrained, ranging from 38% to 83% for early-stage lung cancer patients, primarily due to prevailing comorbidities, age-related considerations, and performance status (2-5). For these patients, as well as those with medically inoperable conditions, several guidelines recommend stereotactic body radiotherapy (6). However, the indication of stereotactic body radiotherapy remains controversial in some populations; for instance, the presence of interstitial lung disease (ILD) or the proximity of vital mediastinal structures such as major blood vessels and the heart, may increase potential risks associated with radiotherapy.

Alternative ablation technologies, such as radiofrequency ablation (RFA), microwave ablation (MWA), cryoablation, photodynamic therapy (PDT), brachytherapy, and pulsed electric field (PEF)-based therapy, are promising treatments for lung malignancies. Particularly for peripheral lung tumors, these technologies have been predominantly

employed percutaneously under image guidance. Computed tomography (CT) and cone-beam CT (CBCT) guidance are currently the most robust methods for localizing the tumor and probe tip during transthoracic procedures. Employing the transthoracic technique may provide an advantage in stabilizing the probe position through the cumulative resistance from penetrating the skin, chest muscle, and lung parenchyma. However, the transthoracic approach is associated with high complication rates, including pneumothorax, hemothorax, and pleural effusion. To address these complications of the transthoracic approach, transbronchial ablation strategies are being developed and evaluated. The transbronchial approach carries a lower risk of pneumothorax, as the treatment probe does not pass through the pleura.

In this review, we present a comprehensive overview of the historical evolution and recent advancements in transbronchial treatments for lung malignancies. This will also include a review of critical factors contributing to the success of the transbronchial approach, including localization and anesthesia strategies.

Endoscopic treatment

Thermal ablation

Since the early 2000s, attempts to employ thermal ablation techniques for lung tumors have followed the success seen in hepatocellular carcinoma. Initially, RFA marked the initiation of local ablation therapy for lung tumors, followed by MWA (7). These thermal ablation strategies were predominantly performed using a transthoracic approach under image guidance, initially. While transthoracic RFA/MWA has proven to be a secure and effective procedure, the majority of complications are pleural-related arising from the transthoracic and transpleural puncture (8).

Transthoracic RFA has more comprehensive body of evidence regarding complications. A review of published literature in 2013 reported that the most common complication is pneumothorax resulting from electrode insertion, with reported frequencies ranging from 8% to 49%, and approximately 10% of patients requiring a chest tube insertion (9). In comparison; in a large retrospective single-center study with 108 transthoracic MWA cases, pneumothorax occurred in 32%, and chest tube insertions were required in 19% of the cases. This study reported one fatal incident complicated with intraprocedural respiratory arrest due to an expanding pneumothorax (10). Hemothorax is another life-threatening and potentially fatal complication of transthoracic ablations. A case report documented massive intraparenchymal hemorrhage and hemothorax during RFA requiring intubation and admission to intensive care unit (11). Unfortunately, this patient died of pulmonary aspiration on Day 23 post-ablation. Another paper detailed a case with significant hemothorax, requiring transfusion and thoracotomy (10). Another important complication of transthoracic ablation is needle-tract seeding of viable cancer cells. Although the incidence of needle-tract seeding is rare (0.3–0.7%) (12,13), it must be carefully considered when aiming to cure lung cancer.

While the current clinical experience in this field is limited, it is worth noting that transbronchial ablation therapy for lung tumors has a favorable profile as it avoids pleural punctures. Beyond this, transbronchial ablation also offers the advantages of reducing the risk of needle-tract seeding and accessing challenging lung regions that are less accessible through the transthoracic approach. Such regions include those shielded by the scapula, or located near the lung apex and mediastinal pleura. Recent advancements in image-guided technologies have increased interest in transbronchial ablation.

RFA

RFA employs alternating high-frequency current to generate heat around a needle electrode, coagulating cancer tissue and inducing necrosis while minimizing injury to surrounding normal tissues. To increase the thermal necrotic area, various strategies have been integrated into RFA system algorithms and catheter tip functions (14).

An internally-cooled electrode has been developed for bronchoscopic RFA. Internal cooling involves circulating chilled water through the electrode (without entering the tissue), preventing local charring around the uninsulated electrode tip and enabling a longer current flow duration. This prolonged current flow leads to a greater volume of local tissue coagulation. Tsushima *et al.* introduced an internally-cooled RFA device with 1.7-mm diameter that fits bronchoscopy working channels. In an animal model, they observed improved ablation efficiency compared to non-cooled RFA (15). Koizumi *et al.*, also from the same group, conducted a prospective single-center study using bronchoscopic internally-cooled RFA in 20 inoperable patients with 23 non-small cell lung cancer (NSCLC) (T1-2aN0M0) in 2015 (16). Prior to ablation, they confirmed the RFA electrode's location with intra-operative CT scans. The disease-control rate was 83% and the median

progression-free survival was 35 months, with manageable complications.

Another type of RFA electrode is the wet-electrode (also known as a perfusion-electrode), which infused saline (either isotonic or hypertonic) into the tissue adjacent to the electrode. This increases tissue conductivity, resulting in higher current flow and a larger coagulated area. Steinfort *et al.* conducted an ablate-and-resect study in 2023 to assess the safety of a hypertonic saline-irrigated RFA catheter with an occlusion balloon (17). They included 11 patients with stage I NSCLC located in the outer two-thirds of the lung. The position of the electrode was confirmed using CBCT before ablation. In the first patient, heated saline dispersion occurred due to cough, resulted in sustained hypoxia requiring intensive care unit admission. However, in other patients, no severe adverse events were observed.

MWA

MWA is based on the utilization of oscillating electromagnetic fields to generate heat. This technology is primarily explained by the dipole rotation theory: when subjected to an oscillating electric field, water molecules are dipole and undergo forced rotate and continuous realignment. This process increases their kinetic energy, thereby elevating the tissue temperature (18,19).

In 2013, Ferguson *et al.* initially reported bronchoscopic MWA using a gas-cooling system in porcine models, demonstrating feasibility (20). Chan *et al.* reported a retrospective study of image-guided transbronchial MWA for lung nodules in a single institution in 2021 (21). Thirty lung nodules were treated with a mean maximal diameter of 15.1 mm (range, 7 to 29 mm) via transbronchial MWA, with 73% of the nodules situated in the peripheral-third of the lung field. Their procedure in a hybrid operating room was incorporated with several technologies, including CBCT at baseline, after positioning the catheter pre-MWA, and post-MWA, electromagnetic navigation bronchoscopy (ENB) to navigate the MWA catheter to the target (± fluoroscopy), and the transbronchial access tool for accessing targets without a bronchus sign. Complications included pain (13.3%), pneumothorax requiring chest tube insertion (6.7%), post-ablation reactions (6.7%), hemoptysis (3.3%) and pleural effusion (3.3%). After a median follow-up of one year, none of the nodules displayed evidence of progression. Xie *et al.* conducted a prospective study in 2018 using water-cooled MWA for thirteen inoperable patients with fourteen peripheral lung cancer targets (22). The MWA probe was placed under the guidance of radial probe endobronchial ultrasound (RP-EBUS), ENB, and fluoroscopy. Complete ablation, defined as stability or a decrease in the size of the ablation zone without enhancement in CT and/or hypermetabolism on a positron emission tomography scan, was achieved in 79% of cases. The 2-year local control rate was 71%, and the median progression-free survival was 33 months. In 2021, Bao *et al.* reported a pilot study aimed at treating ground glass nodules by transbronchial MWA (23). Fifteen patients underwent ENB-guided MWA, with ten of them having multiple lesions and undergoing simultaneous surgical resection. Ablation effectiveness, confirmed with CT scans within the first postoperative week, was observed in 73% of cases. Four patients experienced mild complications, including pneumothorax, hemoptysis, and pulmonary infection. Pritchett *et al.* reported a larger prospective multi-center study using image-guided transbronchial MWA for stage I lung cancer in 2023 (24). They enrolled 40 patients who were medically inoperable or declined surgery for peripheral lung tumors with a maximum diameter less than 2 cm. MWA was performed under augmented fluoroscopy guidance, with the tip location confirmed by CBCT pre- and post-ablation. Technical success was achieved in all patients, and no evidence of local recurrence was observed during the 12-month follow-up. Two serious adverse events occurred within 30 days, including an exacerbation of chronic obstructive pulmonary disease requiring admission and a sudden death of unknown cause.

RFA *vs.* MWA

Both transbronchial RFA and MWA have demonstrated feasibility in the treatment of peripheral lung tumors using recent image-guided technologies. While no direct clinical comparisons between transbronchial RFA and MWA exist, MWA has recently been gaining interest due to the theoretical advantages over RFA. Unlike RFA, which generates heat through resistive heating when electrical current passes through ionic tissue, MWA enables direct heating of the tissue volume around the probe tip, resulting in homogenous and rapid heating. This feature theoretically enhances its ablation performance. The heat sink effect can limit the effectiveness of ablative techniques when tumors are in the proximity to blood vessels, leading to a cooling effect (25). MWA is less susceptible to the heat sink effect compared to RFA due to its rapid heating (26,27). Additionally, aerated lung tissue can hinder the effectiveness of RFA due to the low electrical conductivity (28,29), while MWA is less affected by this.

Vapor ablation

Bronchoscopic thermal vapor ablation (BTVA) is an emerging technique with potential applications in the treatment for lung cancer. A disposable vapor catheter is inserted into the targeted lung subsegment through a bronchoscope's working channel, and heated water vapor is delivered through the catheter. Initially developed as an endoscopic lung volume reduction technique for severe emphysema, BTVA reduces the volume of emphysematous segments by inducing a local inflammatory response through vapor exposure (30). In 2015, Henne *et al.* demonstrated the safety and potential effectiveness of BTVA for treating lung tumors in porcine models (31). Subsequently, the same group demonstrated the potential efficacy of BTVA for treating lung tumors using fresh explanted human lungs with primary and secondary cancer lesions, showing the uniformity of segmental ablation that did not extend beyond fissures (32). The first human application of BTVA in lung cancer treatment was conducted in an ablate-and-resect study in 2018 (33). Among five patients, one exhibited microscopically complete necrosis of the entire tumor, with a median interval of 5 days (range, 4 to 5 days) between ablation and resection. One patient experienced pleuritic chest pain requiring oral opioids post-procedure. Conceptually, BTVA has a potential to treat lung cancer. However, further clinical evidence is required to conclusively establish its efficacy.

Cryoablation

In contrast to RFA, MWA, and BTVA, cryoablation (also known as cryotherapy) applies hypothermal effects on target tissue rather than heat energy. Cryoablation involves passing cryogenic liquid gas through a cryoablation probe. The expansion of the pressurised gas generates a rapid drop in temperature based on the Joule-Thomson effect (34). Multiple freeze-thaw cycles are used to induce cellular necrosis. The mechanisms of cryoablation involve both immediate effects, such as cell membrane disruption through cellular crystallization and dehydration due to osmolality change in the extracellular space, and delayed effects, including ischemia from microthrombi formation (34,35).

Currently, cryoablation is most commonly used in the treatment of liver, kidney, lung, prostate, and breast cancers. For lung cancer treatment, a CT-guided transthoracic approach is performed, with its feasibility and efficacy demonstrated in multiple studies (36-39). Recent prospective multicenter trials have reported favorable local control outcomes for metastatic lung tumor treated with transthoracic cryoablation. The SOLSTICE study, involving 224 lung metastases in 128 patients, showed a local control rate of 85% at 1 year and 77% at 2 years (40). The ECLIPSE study, comprising 60 lung metastases in 40 patients, demonstrated a local control rate of 88% at 3 years and 79% at 5 years (41). However, similar to RFA and MWA, transthoracic approach in cryoablation is associated with a high complication rate of pneumothorax and bronchopleural fistula. Sänger *et al.* reported the safety of transthoracic cryoablation for 39 stage IA NSCLC patients in a retrospective single-center study; they observed complications within the first 90 days post-ablation, including pneumothorax in 21% and 55%, pneumothorax requiring chest tube insertion in 18% and 45%, and bronchopleural fistula in 7% and 9%, in patient with and without ILD, respectively (42). No acute exacerbation of ILD or deaths occurred within 90 days.

To mitigate complications in lung tumor cryoablation, there is ongoing research for delivering cryoablation by a transbronchial approach, as opposed to a transthoracic one. Zheng *et al.* conducted a pilot study of transbronchial cryoablation using a novel flexible cryoprobe in an *in-vivo* porcine model in 2022 (43). The cryoprobe, with a 2.2-mm tip, is compatible with a therapeutic bronchoscope. They demonstrated the feasibility of transbronchial cryoablation with histopathological assessment. Currently, no published clinical studies describe the use of a transbronchial cryoablation as a curative treatment of peripheral lung tumors.

In transbronchial cryoablation, a key challenge arises from the limited ablation volume associated with current flexible cryoprobes, which are less effective than rigid transthoracic probes due to the smaller diameter (44). Tumors located adjacent to the bronchus pose a particular challenge, necessitating a larger ablation volume to encapsulate the entire tumor, given that flexible cryoprobes are delivered through an airway. Furthermore, enhancing the flexibility of cryoprobes is essential for improved access to the peripheral lung area, particularly in the apices.

Table 1 summarizes the selected outcomes and complications of thermal ablation for lung malignancies.

PDT

PDT is performed as a definitive treatment for early-stage lung cancer, employing a unique biopharmaceutical approach leveraging an injectable photosensitizer and

Table 1 Selected outcomes and complications for different treatment modalities in lung malignancies

First author (reference)	Year	Study type	Approach	Modality	Number of patients	Number of targets		Diameter, mm	Follow-up period, months	Local control rate, % (time point)	Complication rate						
						Total	Primary lung cancer/ metastasis/others				Pneumothorax		Bronchopleural fistula	Pleural effusion		Hemothorax	Mortality
											Total	Chest tube placement		Total	Chest tube placement		
Simon (45)	2007	R	TT	RFA	153	189	116/73/0	–	20.5 (mean)	Tumor ≤30 mm: 83% (1 y), 64% (2 y), 57% (3 y), 47% (4 y), 47% (5 y); tumor >30 mm: 45% (1 y), 25% (2 y), 25% (3 y), 25% (4 y), 25% (5 y)	28.4%	9.8%					3.9%
Choe (46)	2009	R	TT	RFA	65	67	67/0/0	44 (mean)	20.5 (mean)	–	7.5%	1.5%	1.5%			1.5%	0.0%
				Cryo		9	9/0/0	21 (mean)		–	11.1%	0.0%	0.0%			0.0%	0.0%
Pennathur (47)	2009	R	TT	RFA	100	104	75/29/0	–	17 (mean)	65% (overall)		59.0%			3.0%		1.0%
Okuma (48)	2010	R	TT	RFA	72	138	12/126/0	21 (mean)	14 (mean)	Primary lung cancer: 38% (1 y), 0% (2 y, 3 y)	34.8%	2.2%		10.1%			1.4%
Hiraki (49)	2010	R	TT	RFA	105	252	35/217/0	14 (mean)	15.9 (mean)	97% (6 m), 86% (12 m), 81% (18 m), 76% (24 m)							
Hiraki (50)	2011	R	TT	RFA	50	52	52/0/0	21 (mean)	37 (median)	69% (overall)		1.9%	1.9%	1.9%	1.9%		0.0%
Kashima (51)	2011	R	TT	RFA	420	1,000	–	18 (mean)	22.1 (mean)		46.1%	1.6%	0.4%			0.1%	0.4%
Huang (52)	2011	R	TT	RFA	329	329	237/92/0	23 (mean)	24 (median)	70% (overall)	19.1%					3.0%	0.6%
Ambrogi (53)	2011	P	TT	RFA	57	59	59/0/0	26 (mean)	47 (mean)	77% (overall)	11.3%	5.0%		3.8%			0.0%
Kodama (54)	2012	R	TT	RFA	44	51	51/0/0	17 (mean)	28.6 (mean)	95% (1 y), 86% (3 y), 57% (5 y)	34.5%	25.5%	0.0%	5.5%	0.0%	0.0%	0.0%
Garetto (55)	2014	R	TT	RFA	81	100	30/70/0	23 (mean)	23 (mean)	79% (overall)	14.0%	6.0%		6.0%		2.0%	0.0%
Dupuy (56)	2015	P	TT	RFA	51	51	51/0/0	21 (median)	24 m in 71% of patients	69% (1 y), 60% (2 y)		5.9%	0.0%		2.0%		0.0%
Koizumi (16)	2015	R	TB	RFA	20	23	23/0/0	24 (median)	–	83% (overall)	0.0%		0.0%	0.0%		0.0%	0.0%
Steinfort (17)	2023	P	TB	RFA	8	8	8/0/0	25 (mean)	5–12 days (range)	–	12.5%	12.5%	0.0%	0.0%		0.0%	0.0%
Lu (57)	2012	R	TT	MWA	69	93	56/37/0	22 (mean)	36 m in all patients	78% (overall)	18.8%	1.4%				2.9%	0.0%
Vogl (58)	2013	R	TT	MWA	57	91	30/61/0	–	10.2 (mean)	67% (overall)							
Yang (59)	2014	R	TT	MWA	47	47	47/0/0	49% of lesions ≤35 mm	30 (median)	96% (1 y), 64% (3 y), 48% (5 y)	63.8%	10.6%	2.1%	34.0%	6.4%		0.0%
Carrafiello (60)	2014	R	TT	MWA	24	26	14/11/1	31 (mean)	9.9 (mean)	71% (overall)	37.5%	0.0%	0.0%	4.2%	0.0%	0.0%	0.0%
Zheng (61)	2016	R	TT	MWA	183	183	138/45/0	34 (mean)	34.5 (median)	82% (1 y), 76% (2 y), 74% (3 y), 74% (4 y)		15.8%			3.3%		0.0%
Ko (62)	2016	R	TT	MWA	15	32	–	14 (mean)	14.9 (mean)	84% (overall)	37.5%	3.1%					0.0%
Healey (10)	2017	R	TT	MWA	108	108	82/24/2	30 (mean)	14.1 (median)	75% (1 y), 59% (2 y), 40% (40 m)	32.4%	3.7%	2.8%			0.9%	1.9%
Zhong (63)	2017	R	TT	MWA	113	113	113/0/0	31 (median)	22.1 (mean)	84% (overall)	10.6%	10.6%		8.0%			0.0%
Tsakok (64)	2019	R	TT	MWA	52	61	61/0/0	24 (mean)	12 (median)	93% (overall)	29.1%	21.8%		21.8%			0.0%
Chan (21)	2021	R	TB	MWA	25	30	14/1/15	15 (mean)	11.5 (median)	100% (6 m)	6.7%	6.7%	0.0%			0.0%	0.0%
Bao (23)	2021	P	TB	MWA	15	15	15/0/0	All lesions ≤30 mm, 53% of lesions ≤10 mm	–	–	6.7%	6.7%	0.0%	0.0%		0.0%	0.0%
Xie (22)	2022	P	TB	MWA	13	14	14/0/0	20 (mean)	33 (median)	71% (2 y)	10.5%	10.5%	0.0%	0.0%		0.0%	0.0%
Pritchett (24)	2023	P	TB	MWA	10	11	11/0/0	14 (median)	12 m in all patients	100% (1 y)	0.0%	0.0%	0.0%	0.0%		0.0%	20.0%
Yamauchi (37)	2012	R	TT	Cryo	22	34	34/0/0	14 (mean)	29 (mean)	97% (overall)	28.0%	4.0%		32.0%			0.0%
Bang (65)	2012	R	TT	Cryo	13	20	0/20/0	26 (mean)	11 (median)	90% (overall)							7.7%
Callstrom (40)	2020	P	TT	Cryo	128	224	0/224/0	10 (mean)	12 m in 90% of patients, 24 m in 77% of patients	85% (1 y), 77% (2 y)		26.0%	0.0%				0.0%
de Baère (41)	2021	P	TT	Cryo	40	60	0/60/0	14 (mean)	36 m in 83% of patients, 60 m in 60% of patients	88% (3 y), 79% (5 y)	6.3%	4.2%					0.0%

R, retrospective study; P, prospective study; TT, transthoracic approach; TB, transbronchial approach; RFA, radiofrequency ablation; Cryo, cryoablation; MWA, microwave ablation; y, year; m, month.

laser light of specific wavelengths. When exposed to the laser, photosensitizers induce the production of reactive oxygen species, leading to cell death through necrosis or apoptosis (66). The photosensitizer, administered prior to laser irradiation, accumulates in cancer tissue. This mechanism by which the agent accumulates in the tumor has been explained by the enhanced permeability and retention (EPR) effect resulting from abnormal vascular characteristics around cancer tissue. This effect allows the photosensitizer to preferentially leak into tumor tissue through the permeable tumor vasculature, where it is retained due to reduced lymphatic drainage (67,68). Additionally, a new mechanism has also become clear related to nano-sized agents; nanoparticles can actively transfer into tumors through endothelial cells (69). However, relying solely on the EPR effect results in only a modest increase in the photosensitizer concentration within the tumor, approximately two-fold higher than in normal tissues. To enhance the efficiency and the safety of PDT, photosensitizers with nanoforms or the ability to bind specifically to cancer cells has been developed (70). Conjugation of active nanocarrier systems with biomolecules like ligands and antibodies enhances their specificity for targeting tumor cells (71).

Transbronchial PDT is performed as a minimally invasive treatment for centrally located early-stage NSCLC and advanced NSCLC causing airway obstruction. In a literature review by Moghissi *et al.* in 2003, involving 523 patients with early-stage lung cancer, transbronchial PDT treatment achieved a >70% complete response rate. Furthermore, for carcinoma *in situ*, the 5-year survival rate reached 90%, excluding deaths unrelated to cancer from the analysis (72).

Over the past two decades, PDT has expanded to treat peripheral early-stage lung tumors in several clinical studies. In 2004, Okunaka *et al.* reported a case series of transthoracic interstitial PDT for non-surgical candidates with relapsed primary NSCLC after radical radiotherapy or metastatic lung tumors (73). A needle with a catheter was placed under CT guidance, and subsequently the needle was replaced with a PDT probe. Porfimer sodium was used as a photosensitizer. Seven out of nine patients achieved a partial response, and two had stable disease post-PDT. Recently, transbronchial PDT has been attempted for peripheral NSCLC. In 2018, Chen *et al.* conducted a pilot study of transbronchial PDT with porfimer sodium in three patients with primary adenocarcinoma and metastatic lung cancer under ENB guidance and CBCT confirmation (74). An 8-mm lung adenocarcinoma achieved a complete response, while 20- and 36-mm metastatic lung nodules from colon cancer showed a partial response. In 2020, Usuda *et al.* reported a multi-center single-arm study for transbronchial PDT using talaporfin sodium as a photosensitizer for seven patients with peripheral stage IA NSCLC (75). They used RP-EBUS to confirm the target's location and a guide sheath to maintain the same position near the target, where a laser probe was introduced. Four patients achieved a complete response and three patients had stable disease at 3-month and 1-year assessments. Bansal *et al.* summarized and reported two phase 1 studies of transbronchial PDT using porfimer sodium for peripheral NSCLC in 2023 (76). RP-EBUS was used to confirm the location of the targeted lesion before the placement of the PDT probe. Among the five tumors not surgically resected after PDT, one showed a complete response, three exhibited stable disease, and one had progressive disease after 6 months. In ten tumors that were resected after PDT, only one squamous cell carcinoma, resected 32 days after PDT, demonstrated a tumor response. In contrast, other tumors resected 12–18 days after PDT did not show any tumor radiological response, but pathological assessment revealed a mean percent tumor cell necrosis of 22% in the resected lung tissue. *Table 2* depicts previous PDT studies for peripheral lung tumors (73-78).

An important adverse event associated with PDT is the potential for photosensitivity, which can persist in patients for up to 4–6 weeks following injection (79), with incident rate of 5–41% (80). Patients should be counselled to avoid sunlight exposure during this period.

One of the limitations of PDT in treating lung cancer is the penetration depth, particularly in transbronchial PDT. Scattering is one of the primary attenuation factors for limiting penetration depth when light is absorbed by tissue. A long excitation wavelength is desirable because the scattering intensity decreases significantly with wavelength (81). Generally, the expected penetration depth of the laser light into human mucous tissue is less than 10 mm (81). However, a study using mice xenograft tumors irradiated with near-infrared phototherapeutic window demonstrated that PDT was effective at a tissue depth of 20 mm (82). Another contributor to penetration depth is the beam size. Monte Carlo simulations indicated a ten-fold increase in the penetration depth by expanding the beam diameter from 0.5 to 3 mm (83,84). Overcoming the challenge of penetration depth in transbronchial PDT is expected through the adoption of photosensitizers activated by longer wavelengths. Additionally, the development of a

Table 2 Photodynamic therapy studies for peripheral lung cancer

First author (reference)	Year	Approach	Photosensitizer	Number of patients	Tumor size	Tumor response, n					Complications
					Mean, mm	CR	PR	SD	PD	Time point	
Okunaka (73)	2004	Transthoracic	Porfimer sodium	9	36	0	7	2	0	–	2 pneumothorax (1 chest tube placement)
Chen (74)	2018	Transbronchial	Porfimer sodium	3	21	1	2	0	0	At 3 months	1 photosensitivity
Usuda (75)	2020	Transbronchial	Talaporfin sodium	7	16	4	0	3	0	At 1 year	1 photosensitivity
Allison (77)	2022	Transbronchial	Porfimer sodium	1	28	1	0	0	0	–	1 photosensitivity
Allison (78)	2022	Transbronchial	Porfimer sodium	1	18	1	0	0	0	–	none
Bansal (76)	2023	Transbronchial	Porfimer sodium	5 in non-resection study	17	1	0	4	0	At 3 months	8 photosensitivity
						1	0	3	1	At 6 months	
				10 in resection study	23	The mean percent tumor cell necrosis, 22%. One patient showed no residual tumor					

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

laser probe capable of broader irradiation and facilitation of delivery through bronchoscopy is anticipated to enhance the effectiveness of the procedure.

Brachytherapy

Brachytherapy is a technique that precisely places radioactive isotopes via a catheter, either within or adjacent to the tumor. In the case of lung cancer, radioactive seeds are delivered either transthoracically or transbronchially. Currently, 3D-treatment planning is calculated based on tumor volume and radiographic data after catheter placement.

Endobronchial brachytherapy has proven effective for lung cancer confined to the endobronchial lumen without extrabronchial invasion. In 2011, Aumont-le Guilcher *et al.* conducted a large retrospective study to assess the feasibility of endobronchial brachytherapy using Iridium-192, involving 226 patients with contraindications to surgery and external beam radiation therapy (85). The majority of tumors were squamous cell carcinoma and at T1 stage. A complete endoscopic response rate was 94% at 3 months. The overall 2- and 5-year survival rates were 57% and 29%, respectively, while the cancer-specific 2- and 5-year survival were 81% and 56%, respectively. In another large study of endobronchial brachytherapy using Iridium-192 by Soror *et al.* in 2019, 126 patients with isolated endobronchial tumor recurrence after surgery or radiochemotherapy were retrospectively reviewed (86). The 3-month complete local response was 87%, with 5-year disease-free survival and overall survival were 41%, and 24%, respectively.

A combination of brachytherapy and external beam radiation therapy has been proposed as an alternative to surgery for endobronchial carcinomas. Kawamura *et al.* reported a case series including 16 radiographically occult early endobronchial cancers in 13 patients (87). Ten lesions in ten patients were treated with a combination of endobronchial brachytherapy and external beam radiation therapy, achieving a 2-year local control rate of 89% compared 80% with brachytherapy alone.

Combining brachytherapy with other therapeutic modalities may be feasible for selected patients with lung cancer. In 2004, Freitag *et al.* conducted a study involving 32 patients with bulky endobronchial NSCLC tumors (10–60 mm along the bronchus) who received a combination of PDT and endobronchial brachytherapy (88). Six weeks after PDT, brachytherapy was performed with five fractions of 4 Gy at weekly intervals, resulting in a complete response in 75% of patients (24/32), which was confirmed with negative histological results from biopsy; 81% of patients (26/32) were free of residual tumor and local recurrence at a mean follow-up of 24 months.

Transbronchial brachytherapy for peripheral lung cancer was reported by Kobayashi *et al.* in a case series in 2000 (89). The brachytherapy catheter location was confirmed with prior barium marking or a CT scan. One patient who received a total of 24 Gy in three fractions at 7-day intervals showed stable disease at the 18-month assessment, while another patient who received 15 Gy in a single fraction experienced a 75% decrease in tumor size in 10 months. In 2006, Harms *et al.* also reported a case in which transbronchial brachytherapy for peripheral NSCLC was performed under ENB guidance (90). This resulted in a durable partial response on CT follow-up at 12 months and repeated biopsies were negative for malignancy.

However, it is important to note that complications associated with transbronchial brachytherapy for central airways are not negligible. Aumont-le Guilcher *et al.* reported that the most common late complication was radiation bronchitis, occurring in 19.5% of cases after a mean interval of 10 months (85). Bronchial stenosis and bronchial wall necrosis occurred in 9.5% and 3.5% of cases, respectively. Notably, fatal complications occurred in 5.8% patients (4.4% from hemoptysis, 0.9% from necrosis of the bronchial wall, and 0.4% from radiation stenosis). Soror *et al.* also reported that 12.7% of patients died from massive uncontrollable hemoptysis post brachytherapy (86). For reference, among the complications of external beam radiotherapy for malignant airway obstruction, esophagitis is frequently observed. The reported incidence of any grade esophagitis ranged from 6% to 50%, while grade 2 esophagitis was reported at 0–13% (91-93). Instances of fatal hemoptysis after external beam radiotherapy for palliative purposes are rare.

PEF-based therapy

PEF is a unique nonthermal ablative modality. PEF utilized a short and strong electrical field generated around a catheter. The induced transmembrane voltage creates microscopic pores in cell membranes and increases membrane permeability. Specifically, the method used to induce cell membrane disruption leading to permanent loss of cell integrity is called irreversible electroporation (IRE) (94). IRE offers theoretical benefit as it is not affected by the heat sink effect caused by surrounding blood flow, unlike thermal ablation modalities. Clinical trials assessing the efficacy of IRE have mainly focused on liver, pancreas, and kidney malignancies (95,96). In 2011, Thomson *et al.* conducted a single-center prospective non-randomized cohort study of IRE for various cancers including six lesions of primary lung cancer or metastatic lung cancer in four patients (96). However, none of the patients exhibited a tumor response following CT-guided IRE. In 2015, a larger prospective multi-center phase 2 trial of CT-guided transthoracic IRE was conducted for lung malignancies, which included 23 patients (97). The study was terminated prematurely as the expected efficacy was not met at interim analysis. Although 7 (30%) patients achieved complete remission, the overall local control rate was 39%.

PEF encompasses several different technologies, such as IRE, tumor-treating fields, and nano-pulse stimulation, which vary based on the properties of the shape of electric pulses, pulse durations, and electric field amplitude (94). New PEF technologies are being explored for transbronchial approaches for lung malignancies. Currently, clinical studies using a biphasic monopolar PEF system (the Aliya™ system, Galvanize Therapeutics, Redwood City, CA, USA) are ongoing (NCT04732520, NCT04773275, NCT05890872).

Anti-tumor immune response induced by local treatment

Tumor regression outside of the locally treated region is called the abscopal effect, firstly described in radiation therapy (98). Tumor antigens released following local therapy are taken up by antigen-presenting cells, such as dendritic cells, which then migrate to the tumor-draining lymph nodes and prime $CD8^+$ T cells to differentiate into cytotoxic T cells. This leads to migration to tumor sites and the killing of tumor cells (99). The abscopal effect has been observed not only in radiotherapy but also in the local treatment modalities described above in this review.

Immunogenic changes following thermal ablation techniques, such as RFA, MWA, and cryoablation, have been investigated across various malignancies, including lung cancer. Early investigations have revealed the abscopal effect subsequent to thermal ablation, accompanied by upregulation of immune cells in the peripheral blood (100-102). PD-1 expression in tumor-infiltrating $CD4^+$ and $CD8^+$ lymphocytes, along with an increased expression of programmed death-ligand 1 (PD-L1) in resected tumors, was observed post-RFA in colorectal cancer (103). Infiltration of natural killer cells and macrophages increased in tumors following thermal ablation (104,105). Recently, there has been increasing interest in the synergistic effect of thermal ablation in combination with immune checkpoint inhibitors. A synergistic anti-tumor effect of cryoablation

and intratumoral interleukin (IL)-12 injection combined with immunotherapy was shown using murine subcutaneous cancer models (106). In a retrospective study including 64 patients with stage IIIB or IV NSCLC, patients treated with cryoablation combined with nivolumab exhibited a significant increase in the number of immune effector cells, including total $CD4^+$ and $CD8^+$ T cells and natural killer cells, as well as improved short-term efficacy compared to a group treated only with cryoablation. Like thermal ablation, non-thermal ablation including PDT and PEF also reports additional effects on immune responses. In a study investigating chlorin e6-mediated PDT combined with anti-PD-L1 therapy, mice inoculated with lung cancer cell lines exhibited significantly improved survival compared to those under naïve conditions or monotherapy (107). Similar synergistic effect of PDT combined with immune checkpoint therapy have been observed in glioma (108), breast cancer (107), colorectal cancer (109), and melanoma (110). Similar to PDT, animal experiments have suggested that PEF promotes the release of tumor-associated antigens from cancer cells, triggering a tumor-specific immune response and resulting in the abscopal effect (111). An ablate-and-resect clinical study for NSCLC stage IA2-IB treated with PEF demonstrated the formation of tertiary lymphoid structures within the tumor, suggesting that PEF enhanced immune activity (112). Moreover, a synergistic anti-tumor effect of PEF has been observed when combined with anti-PD-1 immune checkpoint inhibitor in a mouse model (113,114).

Local treatment modalities have the potential to show the abscopal effect or synergistic effects combined with immune checkpoint inhibitors. However, one of the current issues is difficulties in predicting which patient benefits from immune effects following ablative treatment. Several post-treatment biomarkers were reported as potential to predict immune response. Circulating immune cells in peripheral blood, including $CD4^+$ T cells (115), $CD8^+$ T cells (115), and dendritic cells (116), were increased after thermal ablation therapy, and regulatory T cells in peripheral blood might be a negative indicator of effective immune responses post-RFA for lung cancer (101). Cytokines and soluble factors, including IL-2 (117), IL-6 (118), IL-10 (118), IFN-γ (117), and heat shock proteins (119), were reported to be increased in patients undergoing thermal ablation. Although pre-treatment biomarkers to predict the efficiency of ablative therapy are warranted to select appropriate patients, such definitive markers are yet to be identified so far.

Localization and confirmation technologies

As previously mentioned, certain modalities have been developed for the treatment of lung tumors located in peripheral area using a transbronchial approach due to the reduced risk of pleural-related complications compared to a transthoracic approach. Precise probe placement is crucial for the treatment of peripheral lung tumors, and is achieved with two distinct components: 'navigation' and 'confirmation'.

Commercially-available navigation modalities include virtual bronchoscopic navigation, ENB, and augmented fluoroscopy. These technologies assist in guiding the insertion of the bronchoscope and the probe into the appropriate bronchus more efficiently. However, it is important to note that selecting the correct bronchus does not necessarily ensure optimal positioning of the probe tip (120). This precision becomes particularly significant when using preprocedural CT images for guidance, as it requires consideration of 'CT-to-body divergence' (121). Factors like atelectasis and instrumentation can distort the regional parenchyma, leading to a discrepancy between the expected target location and the actual target location. The I-LOCATE trial conducted by Sagar *et al.* revealed a high incidence of atelectasis during bronchoscopy under general anesthesia (122). This study demonstrated that 89% of patients experienced atelectasis in at least one lung segment within a median time of 33 minutes from the anesthesia induction. Notably, a higher body mass index and a longer time between the anesthesia induction and the atelectasis survey were identified as significant risk factors for the incidence of atelectasis. Given the relatively common occurrence of atelectasis during general anesthesia, it is essential to confirm the position of navigated tools relative to the target using other modalities. Two commonly used options for 'confirmation' in clinical practice are RP-EBUS and CBCT. In the context of local ablation therapy, CBCT offers an advantage over RP-EBUS as it allows for the conformation of probe position relative to the target and surrounding tissues. This capability enables a more precise calculation of both the potential efficacy and safety of the ablation zone.

Anesthesia management during endoscopic treatment

Anesthesia strategy plays a critical role in preventing atelectasis during transbronchial treatments. The Ventilatory Strategy to Prevent Atelectasis (VESPA) was

assessed in a randomized controlled study by Salahuddin and colleagues (123). In this study, the control group was intubated with a laryngeal airway mask and maintained at zero positive end-expiratory pressure (PEEP), while the VESPA group was intubated with an endotracheal tube, followed by recruitment maneuvers and subsequent maintenance at a PEEP level of 8 to 10 cmH_2O. Chest CT imaging was conducted for all patients, and the scans were reviewed by a blinded chest radiologist to confirm the presence of atelectasis. Atelectasis was observed within 20–30 minutes after artificial airway insertion in 84% of the control group compared to 29% in the VESPA group. Bhadra and colleagues introduced a Lung Navigation Ventilation Protocol (LNVP) as an optimized anesthesia protocol for diagnostic bronchoscopy under general anesthesia to mitigate atelectasis and minimize unnecessary respiratory motions (124,125). Under the LNVP, patients were intubated with an endotracheal tube using total intravenous anesthesia technique and neuromuscular blocking agents for paralysis. Recruitment maneuvers were performed with 30 cmH_2O over 30 seconds or 40 cmH_2O over 40 seconds, and patients received higher PEEP based on the lung tumor location. During the acquisition of CBCT images to confirm the biopsy tool's location, breath-holding was implemented, maintaining airway pressure at a plateau using an adjustable pressure-limiting valve. In a retrospective single center study, the LNVP protocol was compared to a conventional ventilation protocol, which involved intermittent or continuous mechanical ventilation with 0 or 5 cmH_2O PEEP (124). Atelectasis was less frequently observed in CT images of the LNVP group (16–36%) compared to the conventional group (64–68%). Blinded readers analyzing CT images concluded that one or two lesions were obscured by atelectasis in the LNVP group (n=25), while nine lesions were obscured in the conventional group (n=25).

For peripheral lung tumor treatment, it is essential to employ dedicated ventilation strategies as described above to mitigate atelectasis. Additionally, precise placement and fine adjustment of treatment tools are necessary to ensure the treatment of malignant lesions with adequate margins while avoiding unnecessary injury to surrounding vital structures. Effective communication between the proceduralist and anesthesiologist is vital for treatment success.

Future direction of endoscopic treatment

The future direction of endoscopic treatment is shaped by ongoing advancements aimed at safer and more efficient lung malignancy management, particularly in peripheral lung areas. Various novel imaging technologies are used for precise placement of the tool tip in clinical practice, including ENB, augmented fluoroscopy, and CBCT. Additionally, the integration of recent robotic technology enhances reachability of bronchoscopic tools into the periphery (126). De Leon *et al.* assessed the safety of bronchoscopic MWA using the NEUWAVE™ system (NeuWave Medical, Inc., Madison, WI, USA) in conjunction with a robotic bronchoscope (the MONARCH™ platform, Auris Health, Redwood City, CA, USA) in swine lungs, observing no complications over a 30-day period (127). A prospective, multi-center, single-arm clinical study is currently underway, focusing on transbronchial MWA using the NEUWAVE™ guided by the MONARCH™ platform for oligometastatic lung tumors (NCT05299606).

In considering the future clinical applications of endoscopic treatment, a more in-depth discussion of its indications is warranted. Several studies have noted cases with multiple lung nodules, all treated using the ablation modality. Although many papers lack detailed discussions on lung function and the rationale behind choosing ablative therapy, it is conceivable that ablative therapy was selected in cases where surgical resection for multiple locations may pose challenges to postoperative lung function. Patients with multiple rather than singular lung tumors may tend to undergo local ablation treatment, potentially yielding benefits. Additionally, the presence of underlying lung disease is also a crucial aspect to consider when transbronchial treatment is indicated. For example, radiation therapy for ILD is often avoided due to the risk of exacerbation. Whether ablative treatment modalities like RFA/MWA/cryoablation/PDT are safe for such cases still lacks sufficient evidence. A previous systematic review compared the treatment for lung cancer in ILD patients with stereotactic body radiotherapy and RFA, summarizing treatment-related ILD-specific toxicity at 5.7% (7/122) for stereotactic body radiotherapy and a lower 2.4% (1/42) for RFA (128). A single-center retrospective study compiling 42 sessions of transthoracic ablative therapy for lung cancer in ILD patients reported major adverse events at 0% (0/11) for RFA, 20% (2/10) for MWA, and 19% (4/21) for cryoablation (129). Given the limited evidence on the safety of ablation therapy regarding underlying lung diseases such as ILD, chronic obstructive pulmonary disease, and asthma, conclusive findings are yet to be established, emphasizing the need for ongoing case accumulation.

Another noteworthy trend in endoscopic treatment for malignancy involved leveraging ablation techniques to stimulate immune responses. As described previously, recent evidence has highlighted the potential for enhancing anti-tumor immune responses following local treatments. Ongoing studies are assessing the synergistic treatment effects of those modalities when combined with immune checkpoint inhibitors.

Conclusions

There has been a rise in demand of local treatment for lung malignancies due to the growing incidence of abnormal pulmonary lesions. For medically-inoperable patients with underlying comorbidities, the transbronchial approach has emerged as a pivotal option. Recent advancements in navigation and confirmation technologies have significantly improved the accuracy of tool placement, enabling the treatment of not only centrally-located tumors but also peripheral lung tumors with high efficiency. Moreover, there has been a growing interest in the anti-tumor immune response induced by local treatments recently. This has the potential to enhance anti-tumor effects and ensure long-term effectiveness. Clinical studies are needed to assess the potential clinical benefits from the additive immunologic effect.

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Footnote

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