



Regional lung chemotherapy techniques to enable or enhance minimally invasive lung surgery

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Abstract: Great strides occurred in the application of minimally invasive techniques for pulmonary lobectomy for almost all indications including advanced neoplasms. Novel treatments besides systemic chemotherapy might be useful to shrink large tumors to enable video-assisted thoracoscopic surgery (VATS) or to enhance treatments for patients with disseminated or otherwise unresectable disease. Several such regional treatments are under investigation and they include inhaled chemotherapy, direct tumor injection, chemoembolization, bronchial artery infusion (BAI), and pulmonary suffusion. These all have specific advantages and limitations depending on the tumor anatomy, physiology and location. Alternatively, VATS theoretically reduces morbidity for oligometastatic disease regional therapy patients who formerly required thoracotomy for vascular access. Promising experimental work with in-vivo pulmonary perfusion patterned on successful methods learned from lung allograft resuscitation is underway. Some of these strategies (alone or combined with standard therapy) are reproducible with existing clinical expertise and should be tested further in clinical trials. This in order to continue the progress toward reducing the morbidity of local control in patients with advanced malignancy, particularly those who are frail.

Keywords: Bronchial arteries; embolization therapeutic; minimally invasive surgical procedures; extracorporeal circulation

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Introduction

Because of the related technologies that thoracic surgeons use to care for their patients during and after surgery, it is not surprising that there is a long history of attempting regional lung chemotherapy for pulmonary malignancy. For instance, the pulmonary artery catheter made it possible to select one lung or another for study and Karakousis *et al.* used this in 1981 to target chemotherapy for sarcoma (1). The heart-lung machine provided the ability to recirculate and oxygenate the systemic circulation. Creech applied this to the lung similarly in 1959 (2). About 25 years later, investigators employed this methodology to perfuse human lung with chemotherapy clinically (3,4). Enthusiasm for such targeted methods described in this review was tempered by inconsistent or inadequate results and

relatively high technique-associated morbidities. These results have also been diminished by our relatively poor understanding of patient-specific tumor biology and host immune dynamics and, in some ways, mirrored some of the failures of promising systemic chemotherapy. Unlike systemic chemotherapy, clinical research for surgical targeted chemo was slowed by the relative expense of the operating room and the delivery technologies involved.

Over this same time that regional lung chemotherapy has struggled to make its mark, there has been steady improvement in the ability of surgeons to confront even advanced malignancy by minimally invasive techniques. Thus, overall video-assisted thoracoscopic surgery (VATS) lobectomy reliability rates have exceeded 90% signaling inclusion of advanced cancer patients who realize many of the benefits seen for earlier stage disease (5-7). There

may be additional benefits in that the better preservations of host performance and reductions in blood loss and opioid requirements enabled by less invasive surgery allow for fewer disruptions of essential systemic therapies and innate immune responses. Furthermore, local therapies like surgery or radiation should probably strive for even less toxicity as their relative anticipated benefits diminish inversely with cancer stage.

Some stage III tumors demonstrate promising partial responses with induction therapies to clinical situations that have enabled minimally invasive, rather than open, approaches. However, disease stability or progression that requires conversion or planned open thoracotomy keep VATS reliability short of 100%. The therapies described in this article could be of interest to surgeons striving to reach an even higher goal for their lung resection program by enabling even better primary tumor responses. Even more excitingly, the expansion of imaging, pharmacologic and perfusion technologies used by our colleagues in medicine, diagnostic and therapeutic radiology, cardiac surgery, lung transplantation, and others have created exciting opportunities for thoracic surgeons to help enhance current operations and even extend them to groups we have not been able to help, like stage IV patients. Newer immune-based therapies are aided by interventions directed selectively to the bulk of disease to generate an “abscopal” effect toward the rest of systemic disease (8).

This article will review contemporary methods (largely done as part of clinical trials) to achieve regional lung therapy and will briefly describe the aspects of the lung anatomy and physiology that make this a promising organ on which to expand such efforts. Broader and historical reviews on this topic by Mallick and others are available to the reader (9,10).

Pulmonary circulation

The minute cardiac output approximates the blood volume that is about 5 liters. The pulmonary component is about 10% of the blood volume yielding about 250 mL per lung that is targeted. The lung vasculature is a low pressure and high flow system with a rich, high-compliance network (30 mL/mmHg) that holds about a third of the blood volume and has the ability to easily distend and recruit unused capillary beds (11). Thus, the pulmonary resistance actually falls with increasing intravascular pressure.

The lung circulation (arteries and veins) and microcirculation (<50 μ M) create a complex sinusoidal

anatomy, the physiology of which has been difficult to study in a normal subject much less in the perturbed state of malignancy. Many factors can affect flow and perfusion such as gravity (e.g., West zones), airway closure or tethering open of small vessels, and cytokine-induced venous constriction (9).

Often ignored, because it contributes only about 1% of the pulmonary blood flow in non-pathologic states, is the bronchial artery component. This becomes important in pathologic states such as central lung tumors or bronchiectasis (up to 30% of cardiac output) or in situations where small contributions over time become problematic such as attempts to isolate the lung for regional lung chemotherapy (12). Unfortunately, the anatomy of the bronchial arteries is quite variable with half of patients having a single vessel on one side and two on the other (13). Typically, these 1.5–2 mm vessels arise from the anterior descending aorta at T5–6 level and terminate at the capillary level within the pulmonary circulation. Manipulating or perfusing them can be hazardous because of collateral vessels that feed unforgiving organs such as the spinal cord or esophagus. Other regional arteries spanning from the chest (e.g., internal thoracic) to the abdomen (e.g., left gastric) can supply the bronchial circulation as well.

With respect to injury, the lung is a delicate organ both anatomically and physiologically and this is the primary concern with interventions that target it. That stated, it has certain characteristics and tolerances that make it ideal for some of the methods described in this article. First, the high degree of vascular interconnectivity described above is useful for delivery of agents instilled into any of the vessel lumens. Next, the lung tolerates deflation for extended times without injury (14). Finally, the alveolar epithelium tolerates hypoxia quite well and lung can maintain its function reasonably well despite upregulation of pro-inflammatory cytokines (15,16).

Intravascular and airway techniques for localized delivery of chemotherapeutic agents

The methods used for lung regional therapy are classified broadly into single injection or single pass techniques and those that require an extracorporeal system to perfuse the organ from a reservoir containing the desired drug. Results from such clinical studies are difficult to interpret because patients go on to receive systemic or other local therapies such as surgery and radiation. In general, indications for localized therapy are broad and

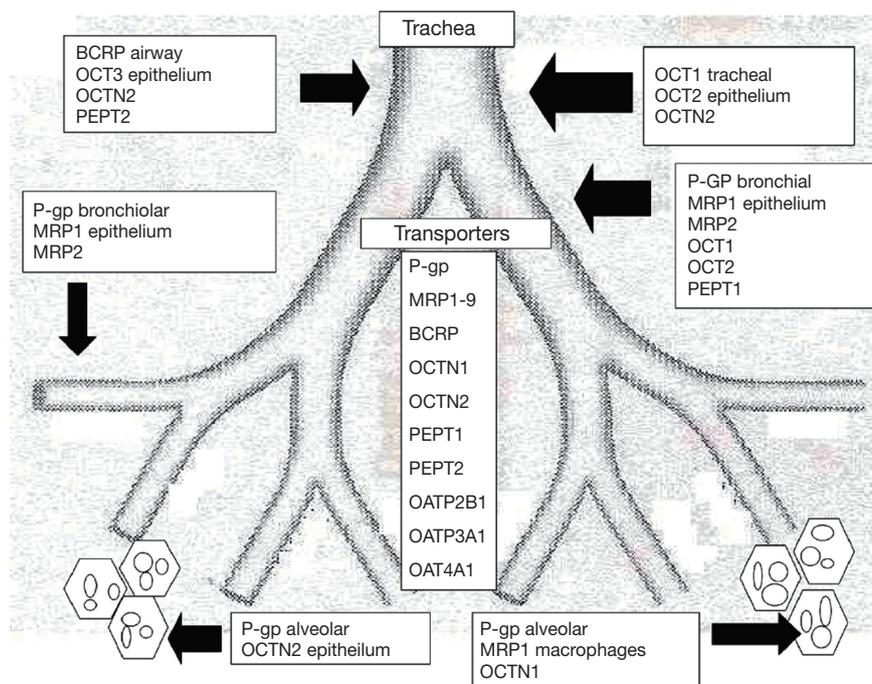


Figure 1 Diagram demonstrating differences in transporters for potential inhalation agent depending on the location in the airway (12).

generally require all or the majority of the measurable disease to exist in the targeted lung. Pregnancy, breast-feeding, allergy to the contrast media or desired agent are relative contraindications. Side effects or complications common to all the treatments are fevers, chest pains, cough, hemoptysis, vomiting, transient hypotension or other hemodynamic changes, and hematoma at the site of percutaneous puncture.

Single pass based methods

Inhaled and direct tumor injection

With up to 100 m² of epithelial surface area for absorption, it is understandable why the airways and alveoli would be promising areas for drug delivery. In addition, adding carbon dioxide to the aerosol increases deposition. The difficulty comes with preparing particles to be within a precise range of 1–3 μm to be able to reach the alveoli for deposition. This generally requires use of dry powder inhalers and nebulizers that generally deliver only about one-fourth of the agents to the lung and retain a similar amount within the devices (12). There is also the need for protective strategies for health-care personnel who might inhale these agents inadvertently.

There are differences in delivery based on whether the drugs are hydrophobic, hydrophilic, or engineered to have enhanced efficiency by nanotechnology. Some of these nanotechnology methods package drug by including linkage or incorporation into dozens of technologies that involve liposomes, microparticles, carbohydrates, polymers, bioadhesives, and cell-type targeting (12). In addition, the rate by which these strategies work depends on the location within the airway (*Figure 1*).

Human trials are limited but attempts were made with drugs like 5-FU, 9-nitro-camptothecin, carboplatin, cisplatin, doxorubicin, and gemcitabine (12). Respiratory inflammatory complications with reductions of PFTs >20% are the biggest problem with this strategy. In addition, one of the main barriers to its use for advanced tumors is the size limitation of the primary to be less than 5 cm. Therefore, while it is unlikely that this technology can shrink a large tumor to allow VATS, it was included in this article because of its potential to treat widespread smaller tumors or minimal residual disease. As the vascular methods described later, concomitant lung surgery also offers unique opportunities for selective and controlled lung ventilation to harness these technologies in ways not possible easily outside of the operating room.

Direct tumor injection using a transbronchial aspiration

needle is another airway-based method to augment the local effects of systemic chemotherapy. The desired drug is delivered on an ml-to-ml basis to tumor volume using the formula $\text{volume} = 0.5 \times \text{height} \times \text{width} \times \text{depth}$ using the maximal length in each dimension (17). Downstream injection leakage is monitored by mixing indigo carmine with the agent. Enhancing its practice has been the emergence of technologies such as endobronchial ultrasound to target involved lymph nodes and tumor and navigational bronchoscopy for more peripheral lesions. Bolus injection dispersion might be erratic based on the variations of intratumoral interstitial fluid pressure, hypoxia, vascular architecture, extracellular

matrix, and gross tumor structure (17). Some of the same methodologies to concentrate and enhance local delivery for inhaled drugs are adaptable to injected agents. Notably, downstream leaked drug that fails direct absorption may still be useful if taken up by surrounding alveoli and lymphatics (Figure 2). This technique may be less toxic than inhaled methods and has demonstrated a remarkable local airway regression that could simplify an open or VATS bronchoplastic procedure (Figure 3). However, because patients also received systemic therapy a precise attribution is not possible.

Arterial chemoembolization

Chemoembolization is a successful option for hepatic malignancies and is under study now for lung tumors. The technique begins by targeting the upstream segmental pulmonary artery branch similar to that used by Karakousis *et al.* who attempted to treat metastatic sarcoma without limiting antegrade flow (Figure 4). Once targeted, balloon occlusion interrupts inflow while chemotherapeutic agents like mitomycin C and flow arrestors like iodized oil and microspheres are delivered to the tumor (18). Before deflating the balloon, permanent artery occlusions using coils or other agents, as well as temporary degradable occlusion by starch or gelatin sponges prevent the drugs from washing away. About a third of patients experience tumor regression and there is interest in developing injectates that elute drug over a protracted time. Because there are potential distal bronchial artery collaterals from the pulmonary artery tree, paraplegia is a potential serious complication from this procedure.

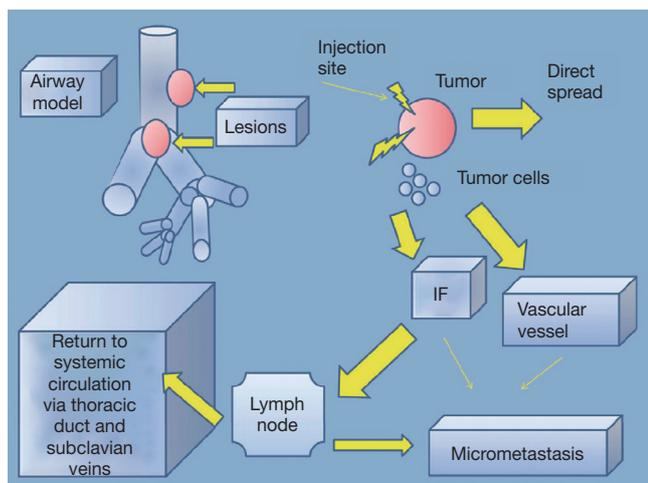


Figure 2 Diagram depicting the rationale behind direct tumor injection therapy including processing of drug after injection (17). IF, interstitial fluid.

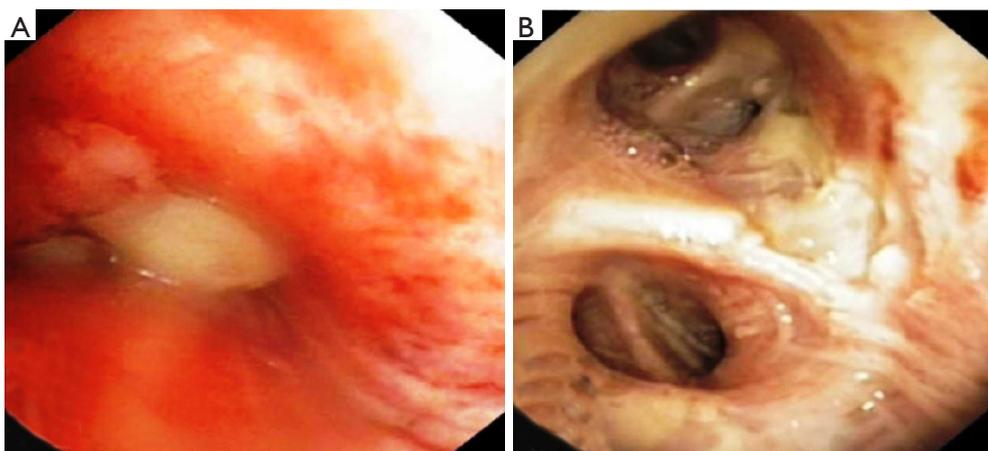


Figure 3 Photograph of bronchus with treatment effect after direct tumor injections and reduced carboplatin systemic therapy (17).

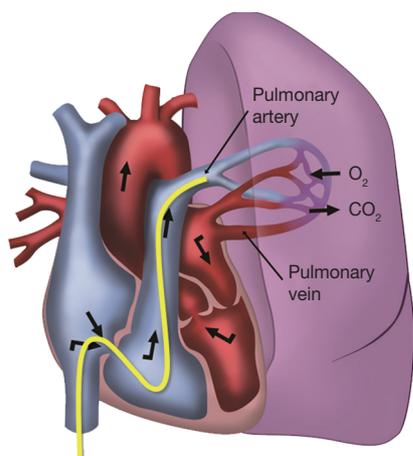


Figure 4 Schematic diagram of methodology for directed catheter therapy such as chemoembolization (9).

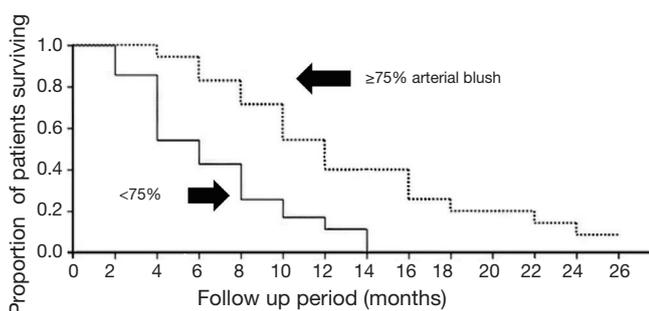


Figure 5 Survival curve for patients as categorized by degree of contrast blush during BAI therapy (21). BAI, bronchial artery infusion.

Bronchial artery infusion (BAI)

This method has developed especially well with the improved catheters available to interventional radiologists since its emergence over 50 years ago (19). Patients generally have multiple feeding bronchial arteries and about 25% have non-bronchial feeding vessels found by conventional angiographic techniques using superselective catheterization. Three-dimensional CT angiography was concordant with angiography in 70% of cases in 2013. Moreover, with better imaging technology, this rate will certainly improve (20). The best results occurred with multiple arterial infusions with combination agents (cisplatin, doxorubicin, and/or gemcitabine) where Nakanishi documented a 3% complete response and 50% partial response rate (21). In that work, cases that demonstrated high percentages (>75%) of total tumor

blush achieved the best response rates (Figure 5). Patients received at least two treatments and they were staged 2–4 weeks apart with care taken to limit contrast medium to protect kidney function. The chemo was pushed slowly by hand with the catheter at the origin of the feeding artery so as not to occlude it. Some cases had dramatic responses and appear to sufficient to render a patient resectable by VATS, if appropriate (Figure 6) (22). The downside of this technique is that it is resource intensive, requires a lot of interventional radiologist expertise, and suffers from the unusual, but devastating potential complications of spinal cord injury or damage to other organs perfused by these vessels.

Lung suffusion

As the more complicated perfusion techniques described below, suffusion involves control of the pulmonary artery and veins; however, it does not employ their puncture and direct cannulation. Surgeons accomplished this by VATS control of the pulmonary veins using techniques learned from lobectomy. After their dissection and mobilization, silicone tapes double looped the veins to create a snare effect. Inflow control and distal drug delivery is by a transfemoral approach using a balloon catheter of sufficient girth to occlude the proximal right or left pulmonary artery. Given the wide range of minimally invasive approaches to the left atrium for the purpose of transcatheter valve or electrophysiological interventions, it is likely that the veins will be isolated percutaneously in the future.

Once vessels are controlled, the sequence in Table 1 is carried out to isolate the circulation and deliver chemotherapy to the lung. Figures 7–9 demonstrates the isolation strategy. This work emulates the cardiac vascular phenomenon by which an arterial dose of an organ preservation solution will fill the sinusoidal bed of the entire heart despite coronary occlusions if the venous drainage is impeded. Based on preclinical work, 75% of the drug remains locked in the desired lung for 30 minutes and slowly permeates (suffuses) the tissue uniformly (23). Also, preclinical work demonstrated an ablative effect on lymph nodes draining the target lung. The maximal tolerated dose in a canine model was 25% of a systemic dose (24).

In clinical work, this technique was carried out successfully in 10 patients with a variety of pathologies including oligometastatic lung cancer and pulmonary metastases with an objective to determine the maximal tolerated dose in the normal tissue. One additional patient

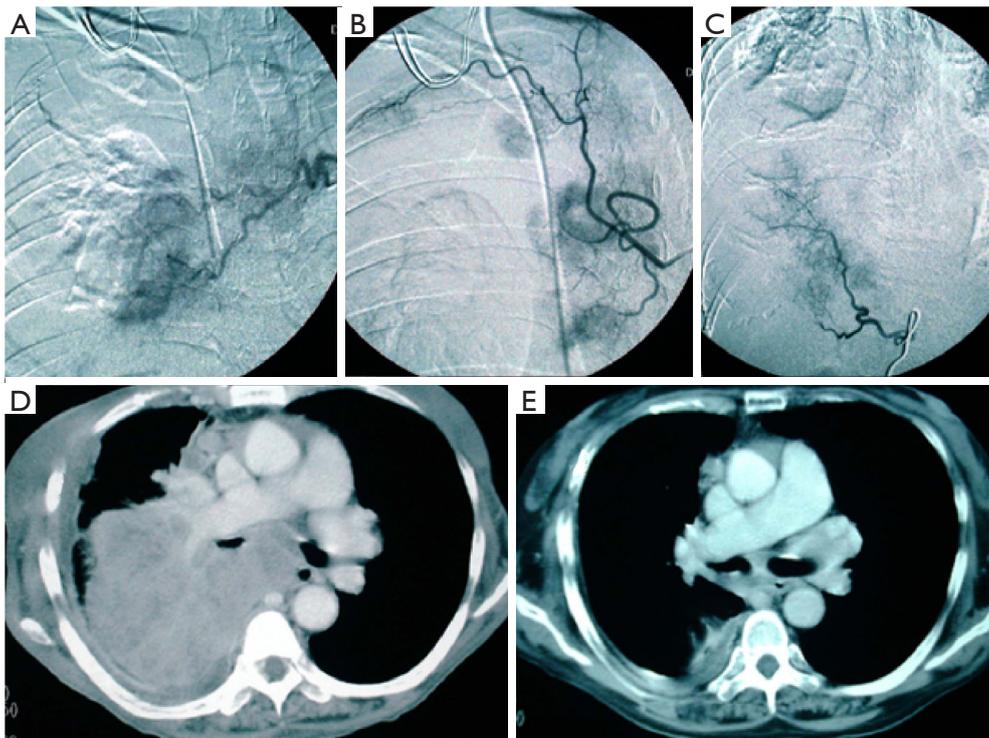


Figure 6 Bronchial artery contrast injections (A,B,C) in patient with large, inoperable tumor showing prominent blush. Dramatic improvement on CT imaging from (D) to (E) after chemo infusions (22).

Table 1 Lung suffusion sequence and equipment

Steps	Special equipment
Intubation and selective lung ventilation	Double lumen endotracheal tube
Decubitus positioning	Extra-long silicone vessel loops with ends sutured without tension within ports
VATS dissection using anterior port sites with pulmonary vein ensnaring	Sheath large enough for balloon occluder
Temporarily close ports and position supine	Fluoroscope equipment; deflectable tip wire; stiff and standard guidewires
Femoral venous catheterization	Low pressure occlusion balloon (Arndt™ 9 French-off label use)
Place PA occlude in target pulmonary artery	Hemostat for elastic tape snares
Occlude PA with air filled balloon and monitor PA pressure for rest of sequence	Technetium labeled macroaggregated albumin
Occlude pulmonary veins, cease target lung ventilation, and aspirate blood from PA as atelectasis develops and reinfuse systemically	Portable gamma camera
Ventilate lung to open vascular space then instill radionucleotide (optional, to document isolation) followed by desired drug in PA	
Suffusion dwell with continuous PA pressure monitoring and optional lung samples at end of treatment time	
Lung reperfusion by releasing vein snares and then deflating balloon	

PA, pulmonary artery; VATS, video-assisted thoracoscopic surgery.

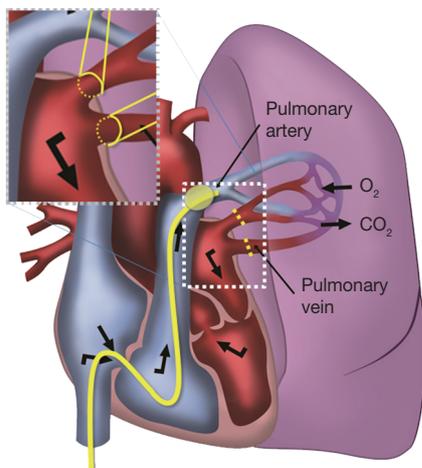


Figure 7 Schematic diagram of methodology for pulmonary suffusion (9).

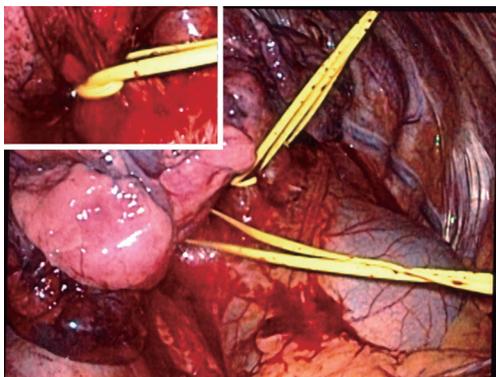


Figure 8 Intraoperative photo demonstrating use of silicone tapes to occlude pulmonary veins during pulmonary suffusion (9).

did not tolerate occlusion of the pulmonary vessels and did not receive the chemotherapy. So far, the patients (5% and 7.5% systemic) have experienced minimal low toxicity and have been discharged in 1–3 days to start additional therapies, if indicated, without delay (24). The dose level currently reached is 10% of a systemic dose. While not designed to determine outcomes, 7 patients had measurable disease after the suffusion. Of these, there was 1 complete response, 1 partial response, 1 stable disease (all difficult to distinguish from effect of sequential chemo) and, more importantly, 4 differential responses (suffused tissue stabilized or regressed while non-suffused metastases progressed).

The cost of the relatively expensive operating room environment needed to accomplish the suffusion if being



Figure 9 Setup for suffusion. C, femoral PA occlusion balloon; D, double lumen endotracheal tube for selective lung ventilation; F, fluoroscope showing PA catheter; I, C-arm imaging; V, vein occlusion using hemostats large enough to bridge skin edges to maintain tension on elastic silicone tapes (9).

done as a stand-alone procedure hampered its progress. It is relatively inexpensive if added onto an established operation like metastasectomy.

Recirculation based methods

Experimentally in small animal models, it is possible to emulate a recirculation-based system using a large quantity of perfusate and discarding it using a venotomy (25). In humans, this is not practical and generally, a recirculating perfusion system has been used. Unfortunately, some pulmonary toxicity has been attributed to these systems themselves in addition to the cytotoxic agents they contain. Recently, investigators harnessed gentler, more physiologic methods to perfuse donated lung organs *ex vivo* in order to resuscitate them (26). These same systems are being applied in promising preclinical work to eliminate the adverse effects of extracorporeal circulation on lung tissue.

Isolated lung perfusion (ILP)

Limb perfusion using a recirculating system is effective for tumors like melanoma and sarcoma (27). A typical system is demonstrated schematically in *Figure 10*. Other items that may be included in this circuit are a heat exchanger for warming the perfusate and a small reservoir to keep the prime volume low. An oxygenator is not needed because of the low metabolic needs of the lung and its ability to get oxygen by ventilation. Like BAI techniques, ILP was described over 50 years ago but was not attempted

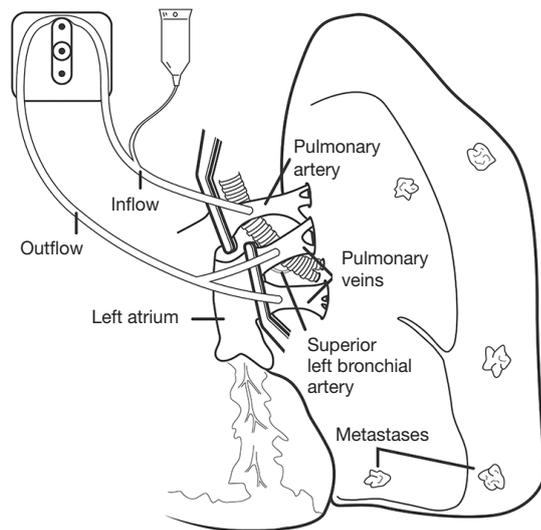


Figure 10 Simplified lung perfusion circuit with roller pump. Circuits may have different types of venous reservoirs and heat exchangers for thermotherapy to enhance drug effects (not shown) (9).

in humans until 1986 when it was associated with a high mortality (3). Since that time, six phase I trials averaging about 10 patients each have demonstrated much better safety but only modest evidence for tumor response (28-33). One of these trials had a long-term survival that was more promising which led to a multicenter Phase ILP trial of 50 patients with metastatic pulmonary sarcoma (12 with bilateral treatments) using 45 mg of melphalan in a 37 °C. perfusate for 30 minutes with a 5-minute washout (34,35). There was no operative mortality and a 57% overall 3-year survival. Like inhaled therapy, ILP resulted in a 20% reduction in pulmonary function. Although there was not a control group, investigators recommended further study based on favorable patient outcomes compared to historical results.

It is unclear whether an intended randomized Phase III trial for this technique of ILP will go forward. Because of the morbidity from the perfusion-driven cytokine and chemotherapeutic lung dysfunction and the thoracotomy required for cannulation in patients with advanced stages of cancer, a significant improvement in survival is required to increase its popularity. However, given improvements in catheter design, it is reasonable to believe that thoracoscopic ILP cannulation is possible and there has been preclinical work in this regard (36). Furthermore, many improvements in lung perfusion technology have occurred.

In vivo lung perfusion (IVLP)

Ex vivo perfusion, incorporating protective extracorporeal circulation features, actually improves the function of impaired donor lungs (26). This success logically leads investigators to bridge this same technology to avoid the previous problems with ILP lung injury caused more by the circuit biomaterials than the chemotherapy itself. Preclinical experiments (Figure 11) have been successful in prolonged lung perfusion with doxorubicin *in vivo* lasting 8 times longer (4 hours) than the typical 30-minute ILP used clinically (37). Previous experiments that showed that there was no decline in lung function from IVLP alone attributed this to the innovations listed in Table 2.

While no human trials for this strategy have been published yet, it is reasonable to expect that they are underway by the Toronto group that has made so many recent contributions to these and related technologies.

Technique selection and future trends

Changing normative practice in medicine can be a lengthy process even when there is evidence from well-designed randomized clinical trials. For patients with advanced malignancy where there are many competing technologies such as new targeted drugs directed to modulate patient-specific genomic finding that do not require invasive procedures, it is not surprising that many of the techniques described in this article have not had an increased popularity. However, technology to deliver targeted therapies has progressed nicely over the past decades and many patients will have an opportunity to benefit from them while simultaneously experiencing other diagnostic and staging procedures. This is provided their toxicity and invasiveness do not interfere with systemic therapies. Furthermore, it seems likely that they could be useful to prime local tumor responses as part of comprehensive immunotherapy treatment strategy.

The optimal technique for a patient will depend on the objective of local therapy (e.g., cytoreductive to reduce the toxicity of surgery or radiation, eradication of minimal residual disease, lymph node targeting, etc.) and the patient's tumor anatomy and host physiologic reserve. It seems likely that these novel therapies will combine with traditional ones and be selected based on availability of technology and human resources. For instance, advanced interventional radiology experience might drive a BAI program, interventional pulmonary medicine directs tumor

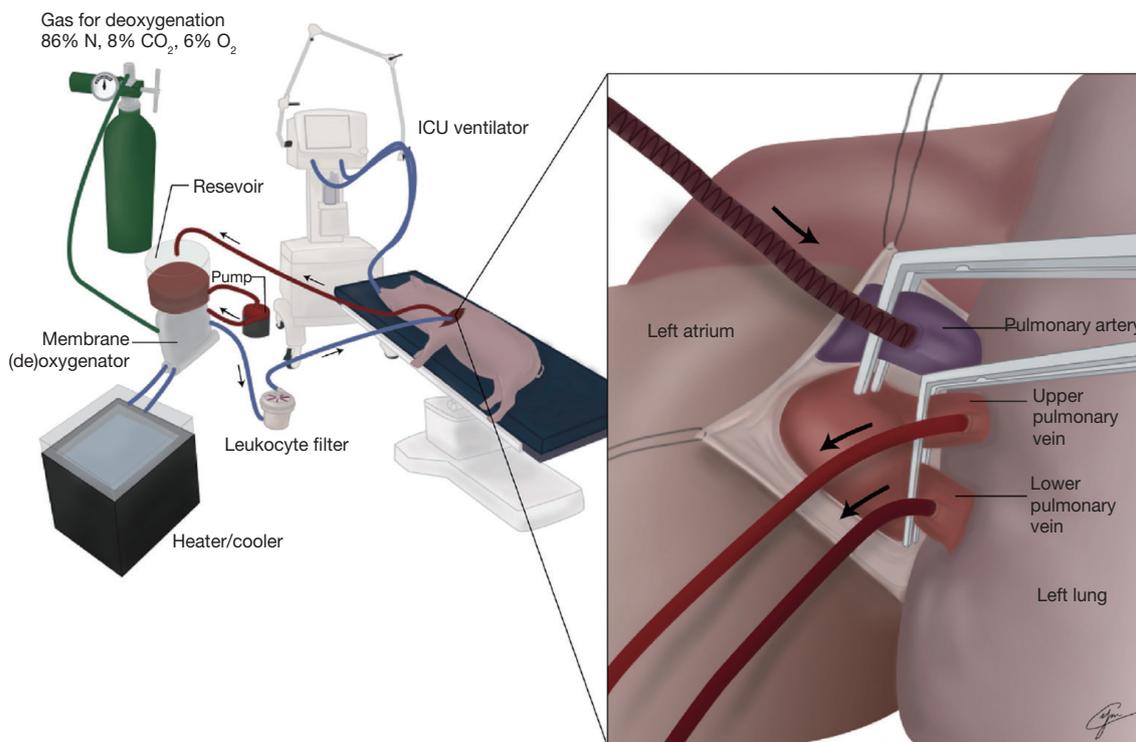


Figure 11 Experimental circuit employing more lung-protective technology adapted from methods to resuscitate damaged pulmonary allografts (37).

injection, and a lung transplant program *in vivo* perfusion. Table 3 lists the techniques described in this article and their relative strengths.

Future trends are likely to include less invasive ways of perfusing the desired portion of the lung using transeptal catheterization and incorporation of less injurious perfusion strategies as outlined in the *in vivo* perfusion section. Bronchial artery perfusion seems underutilized, especially for the 10% of patients whose lung tumors derive over 75% of their blood supply from systemic vessels. Better CT imaging advances will identify such patients more readily in the future. Enhanced targeting by navigational bronchoscopy or spin CT imaging in hybrid operating rooms will allow more directed tumor ablation after which anti-neoplastic therapy is administered to deal with minimal residual local disease beyond image resolution. Nanotechnology will continue to improve to allow better packaging of anti-tumor agents for increased delivery or long-term elution. It is also likely that successful aspects from other clinical regional programs such as heated intraperitoneal chemotherapy will be applied to lung tumors.

Conclusions

There has been a lot of interest in enhancing regional lung therapies to improve local control and possibly effect cure. Such treatments will continue to evolve and represent viable alternatives for patients with tumor biology too difficult to control or in whom frailty and comorbidities limit traditional options. Potential benefits of these therapies need to be weighed against the risks associated with their delivery. Inhaled agents are interesting but have respiratory toxicity and tumor size limitations. Direct injection of the tumor and involved lymph nodes with enhanced drugs will likely increase as enhanced and more accessible imaging enables more physician groups to participate. Vascular targeting of tumors is more complicated but avoids some toxicity of airway-based methods and has a better potential to treat large areas of the lung and draining lymphatics. Its future depends on simplifying and reducing the invasiveness the infusion or perfusion technologies associated with its use. Some of the treatments described might be useful for reducing the tumor size and invasion of structures difficult to resect surgically in order allow an R0 resection or enable

Table 2 Innovative aspects of IVLP

Aspect	Comment
Perfusate solution	Osmotic pressure (high dextran and albumin) designed for lung perfusion that clears pulmonary edema in injured lungs
Perfusion flow	Targeting 16% of cardiac output for left lung (450–500 mL/min) yields lower PA pressures (10–15 mmHg) than used previously. This resulted in lower hydrostatic pressure that drives lung edema but maintained uniform tissue distribution of perfusate
Left atrial pressure	Maintained at 3–5 mmHg. Previous perfusions ignored this which if too high causes backpressure and edema or if low injures the endothelium by repeatedly fluttering the microvasculature open and closed
Ventilation	Protective mechanical ventilator settings with lower tidal volumes
Perfusion pressure	Close as possible to physiologic levels (10–15 mmHg). Important to realize that this target is reached by focusing first on all the other aspects listed above as well as technical issues with cannula placement and monitoring equipment
Centrifugal pump	Less likely to have tubing spallation or spikes of pressure with circuit occlusion and therefore more protective on vasculature
Membrane gas exchanger	Provides physiologic CO ₂ levels to the lung needed for its protection

IVLP, in vivo lung perfusion.

Table 3 Advantages and disadvantages of non-inhalation lung regional chemotherapy techniques

Advantages	Disadvantages
Direct tumor injection	
Minimally invasive	Large tumor size can make uniform delivery difficult
Imaged based certainty that agent reaches targeted lesion	Other tumor characteristics such as intratumoral interstitial fluid pressure, hypoxia, vascular architecture, extracellular matrix, and gross tumor structure can adversely affect absorption
Locally leaked drug can reach target after being resorbed by lung tissue	
Chemoembolization	
Minimally invasive	Requires microspheres or other slow release preparation
Useful for slow release of drugs	Incorrect dosage or incorrect delivery possible
Pulmonary arterial anatomy accessible (ideal for peripheral tumors supplied largely by pulmonary arteries)	Less useful general organ therapy for minimal residual disease
BAI	
Minimally invasive	Bronchial artery cannulation can be difficult
Good for central tumors largely supplied by systemic arteries	Potential for collateral ischemic or embolic damage to spinal cord or other vital thoracic organs supplied by bronchial arteries
	Limited applicability for non-selective general organ therapy for minimal residual disease
Suffusion	
Less invasive VATS approach	Small risk of venous or arterial injury
Targets entire lung and draining lymphatics	Duration of therapy limited
Systemic drug leak less of concern	Heating target lung requires topical thermal therapy
ILP	
Sustained amplification of dose for extended periods to lung and draining lymphatics	Invasive, requires thoracotomy for vascular control and risk of vascular injury
Capable of heated therapy to augment drug effect	Perfusion reservoir risks systemic toxicity from leak (numerous collaterals)

BAI, bronchial artery infusion; ILP, Isolated lung perfusion.

a minimally invasive approach for patients too frail for thoracotomy.

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Footnote

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