Isolated Lung Perfusion for Pulmonary Metastases

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KEYWORDS

• Isolated lung perfusion • Pulmonary metastasis • Pulmonary artery perfusion • Chemotherapy

KEY POINTS

- Isolated lung perfusion (ILP) for pulmonary metastasis allows the lung to be preferentially perfused with high doses of chemotherapy, avoiding the dose-limiting effects of systemic toxicity.
- ILP can be performed retrograde or antegrade, with hyperthermia, using a blood flow occlusion technique, or using delayed clamp release. Minimally invasive techniques may be used.
- Doxorubicin, 5-flurodeoxyuridine, tumor necrosis factor alpha, paclitaxel, melphalan, gemcitabine, and cisplatin have all been used in ILP for pulmonary metastases.
- Several small and large animal models have been developed showing safety and reproducibility of ILP.
- Several phase I clinical trials showed ILP to be feasible in patients with pulmonary metastases, but long-term outcomes and survival are mixed.

INTRODUCTION

The lung is the most common site of metastatic involvement for invasive cancer, largely because circulating tumor cells are filtered via the pulmonary capillary bed. The incidence of lung metastases varies with tumor type and time of diagnosis of the primary cancer. Some cancers, such as sarcomas, often metastasize to the lungs with 20% to 30% of patients with metastatic cancer experiencing secondary spread to the lung.[1] Lung metastases are treated commonly using surgical resection, a technique with 5-year survival rates of only 20% to 40%.[2] Many patients experience recurrent pulmonary disease from micrometastases unrecognized at the time of pulmonary resection. Although reoperation for recurrent pulmonary metastases is an option, many patients are poor surgical candidates owing to lack of adequate pulmonary reserve or poor functional status. When lung metastases are inoperable, most patients die within 1 year.[2] Intravenous (IV) chemotherapy, another common treatment option for cancer, is limited by systemic side effects and toxicity, failing to significantly prolong patient survival.[2] Poor results seem to be attributed to drug resistance within the tumor mass and inability to deliver effective drug concentrations owing to systemic side effects and toxicity associated with higher doses.[1]

Isolated lung perfusion (ILP) is a surgical technique developed to deliver high-dose chemotherapy to the lung, minimizing systemic exposure by selectively delivering agent though the pulmonary artery and selectively diverting venous effluent. ILP has the distinct advantage of delivering high-dose drug treatment to the lung while limiting exposure of sensitive critical organs, thus avoiding severe complications. In addition, ILP minimizes the impact of active drug loss from renal metabolism of the drugs.[1] The lung was identified as an ideal organ for isolated perfusion because of its symmetry, an exclusive arterial supply from the pulmonary artery, venous drainage into 2 pulmonary veins (PV), and tolerance for hyperthermic conditions without significantly impairing systemic function.[3–5]

First proposed in 1958 by Creech and colleagues[6] testing nitrogen mustard in different

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organs, ILP was developed originally to convert inoperable pulmonary metastases into resectable malignancies. Current usage of ILP is aimed to treat micrometastatic disease and improve first-order targeting.[7] Most research regarding ILP has focused on sarcoma and colorectal carcinoma pulmonary metastases. Notably, Johnston and associates[8] began research into ILP in 1983, investigating the toxicity and pharmacokinetics of doxorubicin in addition to the effect of hyperthermia on lung function and uptake of doxorubicin during ILP. Johnston and colleagues[8] described a staged bilateral isolated single lung and simultaneous bilateral lung perfusion in dogs and humans, providing initial data on the technique's safety and reproducibility. Other groups have described results using various chemotherapeutic drugs, including: doxorubicin, liposomal-encapsulated doxorubicin (Liporubicin), 5-flurodeoxyuridine (FUDR), tumor necrosis factor alpha (TNF-α), paclitaxel, melphalan, gemcitabine, combined use of gemcitabine and carboplatin, and cisplatin. Studies examined in this retrospective article include assay, cellular, rat, dog, pig, sheep, and human phase I models in evaluation of ILP as a feasible and reproducible surgical technique.

SURGICAL TECHNIQUE

The premise behind ILP for pulmonary metastasis is that the lung can be perfused preferentially with high doses of chemotherapy to the tumor while avoiding systemic toxicity. The lung is an ideal organ for this technique because it receives its arterial blood supply almost exclusively from the pulmonary artery (PA) and drains into the 2 PV.[5] This nearly eliminates systemic toxicity while providing targeted therapy for both macroscopic disease and microscopic disease.

The patient is anesthetized, a double-lumen endotracheal tube is placed, and the patient is placed in a lateral position. A Swan–Ganz catheter is placed by some surgeons in the PA contralateral to the lung being perfused. An anterolateral or posterolateral thoracotomy is made and, if a Swan–Ganz catheter was placed, the position of the catheter is confirmed with palpation and adjusted as necessary. The pleural cavity is inspected to rule out extrapulmonary disease. Next, a pericardiotomy is made and the posterior mediastinum is dissected, ligating or occluding all systemic–pulmonary collaterals.[9–13] Some surgeons place an occluder around the main bronchus for occlusion of bronchial arteries.[12,13] The main PA and superior and inferior PV are dissected free. The patient is then systemically heparinized before occlusion of the PA and PV with vascular clamps. Two polypropylene purse-string sutures are placed in the PA and PV. Next, the cannulas are inserted. The arterial cannulas are placed in the main PA or a branch of the PA and the venous cannulas are placed in the superior and/or inferior PV and connected to the extracorporeal circuit to drain into the venous reservoir.[9–13]

The extracorporeal circuit, which is similar to the heart–lung machine used in cardiac surgical procedures, consists of a centrifugal or roller pump, membrane oxygenator, and heat exchanger. The perfusion circuit is primed before starting ILP.

There are 2 basic perfusion techniques—a single pass (Fig. 1) and a recirculating blood circuit. The single pass removes the venous effluent after

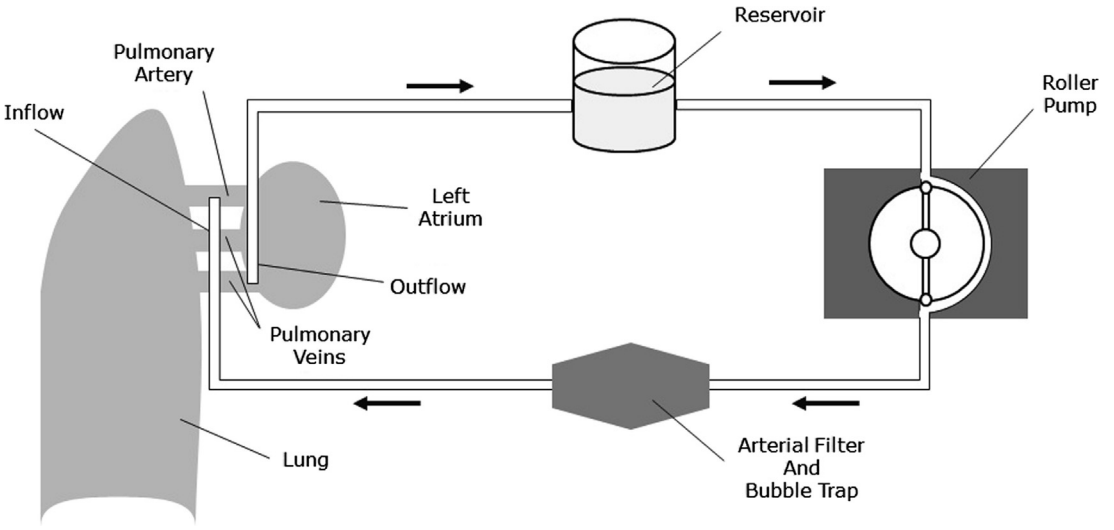

Fig. 1. Diagram of the perfusion circuit.