Review

Isolated lung perfusion and related techniques for the treatment of pulmonary metastases

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Summary

Surgical resection is a widely accepted treatment for pulmonary metastases on the condition that a complete resection can be obtained. However, many patients will develop recurrent disease in the thorax despite the use of systemic chemotherapy, dosage of which is limited because of systemic toxicity. Similar to the basic principles of isolated limb and liver perfusion, isolated lung perfusion is an attractive and promising surgical technique for the delivery of high-dose chemotherapy with minimal systemic toxicity. The use of biological response modifiers, like tumour necrosis factor, is also feasible. Other related methods of delivering high-dose locoregional chemotherapy include embolic trapping (chemo-embolisation) and pulmonary artery infusion without control of the venous effluent.

Isolated lung perfusion has proven to be highly effective in experimental models of pulmonary metastases with a clear survival advantage. Lung levels of cytostatic drugs are significantly higher after isolated lung perfusion compared to intravenous therapy without systemic exposure. Phase I human studies have shown that isolated lung perfusion is technically feasible with low morbidity and without compromising the patient’s pulmonary function. Further clinical studies are necessary to determine its definitive effect on local recurrence, long-term toxicity, pulmonary function and survival.

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1. Introduction

Surgical resection of lung metastases is a widely accepted procedure but due to local and distant recurrences reported 5-year survival rates are only 30—40%. Main prognostic factors are histological type and complete resection. A better survival is reported in patients with a single metastasis and a disease-free survival of more than 3 years [1]. Reoperations are feasible but often patients become inoperable due to insufficient pulmonary reserve and new treatment modalities are looked for [2]. The maximal dose of intravenous chemotherapy is limited due to systemic side effects, mainly haematological. As isolated limb and liver perfusion, isolated lung perfusion (ILuP) has the advantage of selectively delivering an agent into the lung while diverting the venous effluent. Other techniques to deliver high-dose locoregional chemotherapy in the lung are also investigated and these include chemo-embolisation, embolic trapping of loaded particles in the pulmonary circulation, and pulmonary artery infusion where a cytostatic drug is injected in the pulmonary artery without control of the venous effluent. This is mostly performed with a balloon catheter inflated in the pulmonary artery, so-called blood flow occlusion. In this way, the pulmonary circulation is temporarily arrested to allow a better uptake of the injected drug in the lung parenchyma.

In this review surgical resection for lung metastases is discussed, followed by the rationale and history of ILuP. Afterwards, experimental studies of locoregional chemotherapy are reviewed. The specific technique of ILuP in patients is described followed by a summary of clinical studies performed until now with the intent to deliver high-dose chemotherapy to the lung parenchyma.
2. Surgery for pulmonary metastases

Due to their filtering capacity for the entire circulation, the lung and liver are common sites for malignant spread. Two distinct patterns of haematogenous metastases exist, the portal and caval type. The portal type mainly metastasises to the liver and the caval type to the lungs. Among patients with metastatic cancer, 20–30% will have secondary spread to the lung according to necropsy series.

In 1786, John Hunter reported the first case report in history of pulmonary metastases. The primary cancer was a malignant tumour of the femur and the patient died of widespread pulmonary deposits only 7 weeks after the leg was amputated. It took about 140 years before the first successful resection of a true pulmonary metastasis was performed by Divis [3]. A well-known case was reported by Barney and Churchill who removed a solitary lung mass by lobectomy, which proved to be a metastasis of a renal cell carcinoma [4]. The patient subsequently had a nephrectomy for the primary tumour and survived for over 20 years without any signs of recurrence.

Although no prospective randomised trials are available which demonstrate a survival benefit, surgical resection is a widely accepted treatment for pulmonary metastases. Retrospective studies are in favour of surgical resection for lung metastases. An aggressive approach in carefully selected patients is indicated after careful evaluation by an interdisciplinary oncological team consisting of oncologists, thoracic surgeons and radiotherapists.

The specific criteria for pulmonary metastasectomy as originally described by Ehrenhaft et al. nearly 50 years ago have changed little despite the availability of chemotherapy and radiation therapy as alternative therapeutic options [5]. These criteria include radical treatment of the primary tumour, absence of extrathoracic metastases and low operative risk. Complete resection can be performed and no alternative treatment is available. Ongoing discussions in the surgical treatment of pulmonary metastases focus on preoperative imaging of lung metastases, optimal surgical approaches including video-assisted thoracoscopic surgery (VATS), the role of adjuvant therapy, the maximum number of resectable lesions and re-operation for recurrences.

VATS is mostly indicated for diagnosis but can be utilised for definitive treatment when only one small peripheral lesion is present on chest CT [6,7]. In case of a surgical resection a systemic nodal dissection is advocated as for primary lung cancer [8]. Approximately 20% of patients will also have lymph node involvement, which heralds a poor prognosis [9].

Other than chemotherapy for pulmonary metastatic tumours of the testicle, breast cancer and germ cell cancer, surgical resection is still the primary treatment for metastatic disease if a complete resection is possible [10]. In germ cell tumours resection of lung metastases and lymph nodes has an adjuvant role after chemotherapy, to confirm complete pathological remission and remove mature teratoma that may cause obstructive symptoms [11]. In patients with prior breast cancer, resection of metastatic disease is a valid therapeutic option and offers a real chance of cure in case of a new primary lung cancer [12,13]. Patients who may benefit from pulmonary metastasectomy are those with various types of head and neck cancer, tumours of endocrine origin, colorectal cancer, renal cell cancer, and sarcoma [14–18]. An additional problem with these chemotherapy-resistant tumours is the high frequency of secondary pulmonary recurrences, probably due to micrometastases present in the lung at the time of pulmonary resection resulting in a high recurrence rate and low long-term survival [1,19].

Results of an International Registry of 5206 cases of lung metastasectomy operated from 1991 to 1995 were reported by Pastorino et al. [1]. This is the largest reported series on surgical resection of pulmonary metastases. Complete resection was possible in 88% of cases. Overall mortality was 1.0%. Mean follow-up was 46 months. In case of complete resection median survival time (MST) was 35 months and for incomplete resection only 15 months. Metastases to hilar or mediastinal lymph nodes were present in 5% of cases, indicating a poor prognosis. After second metastasectomy a 10-year survival rate of 29% was obtained.

A multivariate analysis was performed on patients who underwent a complete resection. Significant prognostic factors were primary tumour type, disease-free interval and number of metastases [1]. From these data four prognostic groups could be discerned which determine the prognosis of the patient (Table 1).

What are the technical limitations of thoracic surgery? Resection of pulmonary metastases by pneumonectomy or beyond pneumonectomy is exceptional. However, in carefully selected patients extensive resections might be successfully performed with an operative mortality less than 5% and a 5-year survival rate of 20% following complete resection [20]. In our own series reported in 2001, eight patients underwent a primary or completion pneumonectomy indicating the limit of our surgical possibilities [19]. These extensive operations may be offered to selected patients with isolated primary or recurrent pulmonary metastases, sufficient pulmonary reserve and prognostic favourable primary tumours as colorectal and renal cell carcinoma.

As shown by the International Registry and also in our own series, most patients who underwent resection of lung metastases from primary carcinomas or sarcomas will have recurrent disease inside the chest [1,19]. For this reason,
combined modality therapies including surgery and chemotherapy are currently evaluated to obtain a better local control and improve overall survival. Methods to deliver high-dose locoregional chemotherapy will be further discussed in this review.

3. High-dose locoregional chemotherapy: rationale and historical review

The poor results of surgical resection of pulmonary metastases from certain tumours combined with intravenous chemotherapy are probably due to genetic drug resistance and the inability to achieve effective drug concentrations within the tumour mass, so-called first order targeting [21,22]. This implies that better chemotherapeutic agents and more efficient drug delivery as an adjuvant to surgery, are needed. Specific biophysical methods to improve drug targeting in lung parenchyma include embolic trapping (chemo-embolisation), regional infusion in the pulmonary artery without control of the venous effluent, and ILuP in which the lung is completely separated from the systemic circulation [21].

These are all promising techniques for the treatment of tumours metastatic to the lungs, which do not respond to conventional systemic chemotherapy [22]. ILuP has the advantage of both selectively delivering an agent and diverting the venous effluent. This allows a drug to be delivered in a higher dose, while drug levels in critical organs that are relatively sensitive to the drug, are kept low enough to avoid severe complications. An additional advantage is the prevention or delay of loss of active drug through metabolism.

Creech was the first to report a method of pulmonary perfusion [23]. He perfused both lungs simultaneously with divided circuits for systemic and pulmonary circulations. Krementz, a co-author of the paper of 1959, commented in 1986 that four patients had undergone lung perfusion of which one experienced an impressive clinical response but two others died postoperatively. It was the first clinical report of lung perfusion for the treatment of cancer [24]. In 1983, Johnston put the basis for further clinical and experimental studies by showing ILuP to be a reproducible and safe technique [25,26]. He determined a dosage of adriamycin (doxorubicin) without apparent systemic toxicity in a dog model, without any control of the bronchial arterial circulation. This can be explained by experimental, autopsy and clinical studies, which show that a significant portion of both pulmonary and metastatic tumour vasculature is fed by the pulmonary circulation. On the other hand, bronchial artery infusion is the desired route in primary bronchogenic carcinoma. Milne also showed that primary lung tumours are predominantly vascularised by the bronchial arteries whereas in lung metastases, the pulmonary artery is predominant: 48% of all lung metastases receive their nutrition from the pulmonary artery only, 16% from bronchial arteries only, and 36% have a dual vascularisation [27]. Mochizuki et al. evaluated vascular supply pattern through first-pass dynamic CT in differentiating solitary pulmonary nodules [28]. Based on the final diagnosis, they concluded that a pulmonary artery pattern was a good indicator of metastatic lung tumours or inflammatory nodules in contrast with the aortic supply pattern, which was a better indicator of primary bronchogenic carcinoma.

Toxicity after ILuP, as documented by Johnston, was closely related to drug uptake in the lung and concentration of the drug in the perfusate [25]. Lactate dehydrogenase levels in perfusate and postperfusate serum indicating cell necrosis showed dose-dependent increases. These dose-dependent relations were also found by Baciewicz at a lower dose [29]. This could be explained by the use of mild hyperthermia (39 °C), which may increase doxorubicin uptake into the perfused lung tissue.

A second step forward was the development of a surgical procedure by Johnston that allowed both lungs to be perfused simultaneously. As lung metastases may present bilaterally, the advantage of total lung perfusion is obvious [30].

These initial reports stimulated further experimental research in ILuP and related methods to deliver high-dose chemotherapy to the lung parenchyma.

4. Experimental studies of high-dose locoregional chemotherapy

4.1. Isolated lung perfusion (ILuP)

Weksler and the group of Memorial Sloan-Kettering Hospital in New York developed a model of in vivo isolated single-lung perfusion in a rodent model to study the effects of locoregional therapy. In the rat there is only one lobe on the left side and their technique for ILuP involved cannulation of the single left pulmonary artery and vein through a thoracotomy incision (Fig. 1) [31].

Quite a lot of chemotherapeutic drugs and also biological agents have been found to be effective in experimental models of high-dose locoregional chemotherapy for the treatment of lung metastases originating from primary carcinomas or sarcomas [22]. These are summarised in Table 2.

Fig. 1. Microscopic view in the rat showing the single left pulmonary artery and vein which are encircled.
4.1.1. Doxorubicin

ILuP with doxorubicin in a methylcholanthrene-induced sarcoma model in the Fisher rat was found to be a safe and effective method, and superior to intravenous injection. With a perfusate drug concentration that was well tolerated by the animals, lung tissue doxorubicin levels were 20-fold higher than after intravenous injection [32]. In contrast, significant cardiac and haematologic toxicities were noted after intravenously administered doxorubicin. After ILuP a complete clearance of macroscopic and microscopic tumour was observed, whereas sham perfused lungs had massive tumour replacement [33]. Weksler also demonstrated that perfusate doxorubicin concentration and the duration of perfusion are the only factors determining the final lung concentration of doxorubicin [34]. To enhance anti-tumour activity of doxorubicin, the group of Memorial Sloan-Kettering investigated the use of buthionine sulfoximine (BSO) in their sarcoma-bearing animal model [35]. BSO inhibits the glutathione synthesis, which plays an important role in tumour resistance to chemotherapy and radiotherapy. Pretreatment of animals with BSO maximally depleted liver and tumour glutathione levels and was superior to intravenous doxorubicin and doxorubicin ILuP alone for the treatment of metastatic pulmonary sarcoma [35].

4.1.2. 5-Fluorodeoxyuridine (FUDR)

ILuP with FUDR was investigated in a dimethylhydrazine-induced carcinoma model in the BDIX rat. This agent is one of the most active chemotherapeutic drugs for treatment of metastases of colorectal adenocarcinoma, but its use is hampered by a dose-limiting toxicity [36]. A significant decrease in the number of tumour nodules was observed when lungs were perfused with FUDR.

4.1.3. Tumour necrosis factor alpha (TNF-α)

ILuP with the biological agent (TNF-α) was investigated by Weksler. He confirmed the anti-tumour potential of TNF-α when delivered in a high dose in ILuP procedures [37]. After perfusion with TNF in the sarcoma bearing rat model, approximately five times less tumour was exhibited compared to the unperfused lung.

4.1.4. Cisplatin

Most of the experimental work with cisplatin was performed by Ratto et al. [38]. Pig studies showed that ILuP resulted in higher lung tissue levels compared with pulmonary artery blood flow occlusion. The addition of digitonin enhanced the uptake of cisplatin in a rat model of ILuP [39].

4.1.5. Paclitaxel

The use of paclitaxel was evaluated by Schrump et al. in an experiment with sheep [40]. Paclitaxel was administrated by retrograde hyperthermic ILuP for 90 min with the use of a membrane oxygenator. No pulmonary toxicity was observed and systemic plasma levels after ILuP were far below the levels observed after intravenous therapy, showing that paclitaxel is not readily released from the lung parenchyma.

4.1.6. Melphalan

In our own laboratory of experimental surgery, techniques for intubation and anaesthesia were modified in the Wag/Rij rat and a new approach of catheterisation of the pulmonary vessels was developed with improved results (Fig. 1) [41]. Melphalan and TNF-α were extensively studied in this rat model of ILuP for pulmonary metastatic adenocarcinoma [42]. Significantly fewer lung nodules were found after ILuP with melphalan compared to intravenous treatment. TNF-α did not provide any additional effect [42]. Survival after ILuP with melphalan was studied in a rat model of unilateral metastatic pulmonary adenocarcinoma [43]. Median survival time of ILuP-treated animals was significantly longer compared to intravenous treatment.
Combining several chemotherapeutic drugs was feasible in the same experimental setting with melphalan and gemcitabine yielding the best survival results [44].

Pharmacokinetics of melphalan were further investigated in a pig model by van der Elst et al. demonstrating a safe pharmacokinetic profile without systemic toxicity [45].

4.2. Pulmonary artery infusion with blood flow occlusion

Furrer and colleagues investigated endovascular single-lung pulmonary artery infusion with blood flow occlusion (BFO) with doxorubicin in a pig model. This technique can be performed without thoracotomy using a percutaneously inserted balloon catheter, which represents a great advantage allowing repetitive application [46]. Pulmonary artery BFO was necessary to prevent rapid dilution of the injected drugs, and to improve contact with the lung parenchyma as shown in rat studies. Similar pharmacokinetic advantages as with ILuP were found while plasma drug levels were lower than after intravenous infusion [48].

Demmy et al. described a dog model of pulmonary artery infusion and demonstrated that 75% of tracer remained in the lung after 30 min dwell time [47].

In addition, gemcitabine was found to be an effective chemotherapeutic agent with a high initial uptake in lung parenchyma making it also a suitable drug for use in pulmonary artery infusion [48]. In a rat model, the lung was found to be saturated after 20 min with significantly higher lung levels compared to intravenous injection [48].

4.3. Chemo-embolisation (embolic trapping)

An original technique of chemo-embolisation with degradable starch microspheres was described by Schneider et al. [49]. In a rat model reversible embolisation could be demonstrated after pulmonary artery injection. Combination of these microspheres with carboplatin was feasible without early toxicity. This technique proved to be equally effective as ILuP.

4.4. Ex vivo human lung perfusion

Pharmacokinetic studies in rodents are difficult to extrapolate to human beings. To obtain a detailed pharmacologic analysis a model of ex vivo human lung perfusion was developed by Mürdter et al. [50]. Isolated lung perfusion is applied in resected lungs, which provide an excellent model for preclinical investigation (Fig. 2).

5. Technique of isolated lung perfusion in humans

As mentioned before, Creech was the first to report a method of pulmonary perfusion in patients [23,24,26]. In order to perfuse both lungs simultaneously, two extracorporeal systems were needed. In this way, the systemic and pulmonary circulation could be completely separated. In most recent clinical phase I studies unilateral ILuP was applied. As these are dose finding studies in patients designed to determine dose-limiting toxicity (DLT) and maximal tolerated dose (MTD), it would not be ethical to perfuse both lungs at the same time in order to avoid bilateral pulmonary toxicity and oedema. So, in case of bilateral lung metastases staged procedures are required. In any instance, careful discussion with the patient is necessary and written informed consent should be obtained.

In general, the pulmonary artery and both pulmonary veins are cannulated and connected to an extracorporeal circuit. After central clamping of the vessels the cytostatic drug is injected into the circuit. Hyperthermic perfusion may be used to improve drug uptake inside the lung parenchyma.

The technique of ILuP as performed in our phase I clinical trial is described in more detail [51]. An antero- or posterolateral thoracotomy is performed in a standard fashion. All suspicious nodules are carefully palpated and their anatomic localisation is documented before perfusion. In case no preoperative histologic diagnosis is present, a frozen section of one of the tumour nodules is performed to obtain pathological confirmation of metastatic disease. Next, the main pulmonary artery and both pulmonary veins are isolated. The pericardium is opened to gain proximal control of the pulmonary vessels. On the left side Botallo’s ligament may be divided to obtain sufficient length on the intrapericardial portion of the pulmonary artery. On the right side the interatrial groove can be dissected to put a Satinsky clamp more centrally on the left atrium. Purse-string sutures with polypropylene are inserted on the pulmonary artery and both pulmonary veins.

The patient is systemically anticoagulated to an activated clotting time of at least 200 s. The pulmonary artery and veins are cannulated by standard techniques (Fig. 3); the main bronchus is snared in order to occlude bronchial arterial blood flow. A perfusion circuit is used, consisting of a centrifugal pump, a heat exchanger, and special extracorporeal circuit tubings (Fig. 4). ILuP is carried out for a period of 30 min while the flow rate is calculated preoperatively but adjusted to the mean pulmonary artery pressure. After stabilisation of temperature and flow, and when there are no

Fig. 2. Ex vivo human lung perfusion in a resected lung to perform pharmacokinetic studies.
signs of systemic leakage, melphalan is injected into the perfusion circuit through the pulmonary artery line. During perfusion the lung is ventilated to obtain a homogeneous distribution of melphalan. After 30 min of perfusion, melphalan is washed out of the lung. At the end of the washing period, the cannulas are removed, the arteriotomy and the venotomies repaired and the clamps released, restoring blood flow to the lung. After correcting the activated clotting time, a complete metastasectomy is performed, usually by wedge excisions with the use of staplers.

Based on their experience with four patients, Schröder et al. recommended resecting the metastases before ILuP [52]. After ILuP they had difficulties in identifying metastatic nodules due to the oedematous lung tissue. In our experience, we prefer to identify and record all metastatic disease before cannulating the pulmonary artery and veins. Subsequently, ILuP is performed in order to have a homogeneous perfusion throughout the lung. In addition, less bleeding will occur at the sites of resection because heparin is corrected with protamine after the perfusion.

6. Recent clinical studies of high-dose locoregional chemotherapy

   In the clinical setting only phase I trials have been performed until now. Clinical studies on pulmonary artery infusion with blood flow occlusion are not yet available. Chemo-embolisation and ILuP are discussed separately.

6.1. Chemo-embolisation (embolic trapping)

   The technique of transpulmonary chemo-embolisation was recently applied by Vogl et al. in 23 patients with unresectable lung metastases [53]. Microspheres combined with mitomycin C were injected by a pulmonary artery catheter with balloon protection. There were no complications. Regression was observed in eight patients, stable disease in six and progressive disease in nine. Further phase I studies are necessary to determine the MTD and precise toxicity of this procedure.

6.2. Isolated lung perfusion (ILuP)

   The group of Johnston performed a pilot clinical trial of ILuP based on the insight gained in their previous experimental studies. The trial consisted of four patients with unresectable metastatic sarcoma to the lung and four patients with diffuse bronchioloalveolar carcinoma [54]. There were no intraoperative complications. No objective clinical responses were seen and all patients died of progressive disease 23–151 days after perfusion. However, this study demonstrated that the complex procedure of ILuP was well tolerated and reproducible [54].

   Most agents tested in laboratory settings were subsequently investigated in human phase I trials. As it is difficult to extrapolate results of animal studies into a clinical setting, most protocols in patients study the feasibility of ILuP in resectable or unresectable lung metastases, and determine DLT and MTD of the chemotherapeutic agent used in ILuP. Incremental doses are used and MTD is defined as one dose level below DLT. Clinical studies from 1995 on are summarised in Table 3 [51,52,54—61].

6.2.1. Doxorubicin

   In the pilot study by Johnston et al. four patients with pulmonary metastatic sarcoma and four patients with diffuse bronchioloalveolar carcinoma were treated with doxorubicin and cisplatin via ILuP [54]. Six patients were perfused with doxorubicin and two with cisplatin. The latter are discussed further under the heading cisplatin.

   Single left lung perfusion was performed in three patients and total lung perfusion in five patients. Perfusion time ranged from 45 to 60 min at ambient or normothermic temperatures, except for one patient who underwent perfusion at moderate hyperthermia of 40 °C.

   Pulmonary perfusate drug concentrations increased with higher doxorubicin dosages. Drug tissue levels also tended to increase with higher doses with only minimal systemic leakage.

   No intraoperative complications occurred but there was one postoperative complication. This patient developed pneumonia with subsequent sternal dehiscence. The pneu-
6.2.2. Tumour necrosis factor alpha (TNF-α)

The MTD in this study was defined at 40 mg/m² of doxorubicin given while systemic levels were minimal or undetectable. Concentrations of doxorubicin correlated with the dose inoperable lung metastases from sarcoma underwent single-lung perfusion with doxorubicin in a phase I protocol. Intrapulmonary concentrations of doxorubicin correlated with the dose given while systemic levels were minimal or undetectable. However, tumor levels were lower compared to lung levels. The MTD in this study was defined at 40 mg/m² of doxorubicin since an important chemical pneumonitis developed in one patient at a dose of 80 mg/m². On postoperative lung scanning no ventilation or perfusion was present at the perfused lung in this patient. No perioperative deaths were encountered. There were no partial or complete responses. One patient had stabilisation of disease in the perfused lung, whereas the lesions in the untreated lung progressed markedly. In the seven patients perfused with 40 mg/m² or less of doxorubicin, there was a significant decrease in the forced expiratory volume in 1 s and a trend toward a significant decrease in diffusing capacity [57].

Putnam et al. reported another phase I study of isolated single-lung perfusion with doxorubicin in 16 patients with unresectable pulmonary metastatic disease, also in sarcoma patients [58]. Systemic levels were minimal or undetectable while two patients developed a grade 4 pulmonary toxicity at a dose of 75 mg/m², therefore defining the MTD at 60 mg/m² of doxorubicin in this study. Overall operative mortality was 18.8%. One patient died of a paradoxical tumor embolus, one of drug-related lung injury, and one of pneumonia 3 weeks postoperatively. Early morbidity was noted in three patients and consisted of prolonged chest tube drainage more than 7 days, persistent air leak longer than 7 days and grade 4 lung injury. Late toxicity included a decrease in forced expiratory volume in 1 s, forced vital capacity, and a decrease in ventilation and perfusion in the treated lung. Only one major response occurred. Median survival time was 19.1 months in this study [58].

6.2.3. Cisplatin

In the study by Johnston et al. two patients were treated with cisplatin [54]. One patient with diffuse bronchioloalveolar carcinoma was treated with a dose of 14 μg/ml in normothermic conditions; the other patient with metastatic chondrosarcoma was given 20 μg/ml with moderate hyperthermia. In both of them total lung perfusion was done during cardiopulmonary bypass. Perfusion times were 50 and 60 min, respectively. Metastasectomy was not undertaken. One patient developed a pneumonia and subsequently empyema 4 days later. He required reintubation and died after 81 days [54].

Ratto et al. used the bimodality treatment of ILuP and resection in six patients with lung metastases from soft tissue sarcomas [56]. Major end-points were feasibility, toxicity, and distribution of cisplatin in normal and neoplastic tissues. Cisplatin was perfused at a fixed, high dose of 200 mg/m² for 60 min; so, DLT could not be determined in this study. Lung perfusion temperature ranged from 37 to 37.5 °C. Mean pulmonary artery pressure was kept below 35 mmHg. No patient died during or after the procedure. Two patients developed interstitial and alveolar lung oedema after 48 h, for which one patient required prolonged respiratory support. No systemic toxicity was noted. Total cisplatin concentration in the lung exceeded more than 40 times systemic plasma concentrations. There was no difference in

<table>
<thead>
<tr>
<th>Year</th>
<th>Author</th>
<th>Reference</th>
<th>Drug</th>
<th>Lung temperature (°C)</th>
<th>Perfusion time (min)</th>
<th>Resectable metastases</th>
<th>MTD</th>
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<tr>
<td>1995</td>
<td>Johnston [54]</td>
<td>Doxorubicin/cisplatin</td>
<td>8</td>
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<td>1996</td>
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<td>41</td>
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<td>2004</td>
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<td>Melphalan</td>
<td>16</td>
<td>37, 42</td>
<td>30</td>
<td>Yes</td>
<td>45 mg–42 °C</td>
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</table>

MTD: maximum tolerated dose, n: number of patients, min: minutes, NA: not available; TNF: tumour necrosis factor.
cisplatin lung and tumour concentration. No histological damage of lung specimens was observed. Decline in ventilatory function 10 or 30 days after the ILuP procedure was significant for forced vital capacity, forced expiratory volume in 1 s and carbon monoxide diffusion capacity, although reassessments in two patients after 12 months showed further improvement [56].

Schröder et al. conducted a pilot study in four patients with unilateral (n = 2) and bilateral (n = 2) sarcoma metastases confined to a lobe or entire lung [52]. Metastasectomy was performed, followed by ILuP with cisplatin at an in-flow temperature of 41 °C. Eligibility included at least four previous surgical metastasectomies, controlled primary site and no other effective treatment options in contrast to Ratto’s study [56]. Cisplatin was given at a fixed dose of only 70 mg/m² for about 30 min at 41 °C. Systemic cisplatin plasma levels were low. Throughout the ILuP there was no evidence of drug-related systemic toxicity. Postoperatively, all patients developed transient pulmonary toxicity presenting as non-cardiogenic lung oedema. After a mean follow-up of 12 months, three patients were alive and disease-free, and one patient died of cerebral metastases after 13 months without pulmonary recurrence at post-mortem examination.

It is difficult to make some general remarks based on so few studies with small groups of heterogeneous patients treated with cisplatin. Furthermore, above-mentioned investigations differed profoundly in some aspects. For instance, Johnston’s patients were not treated with metastasectomy and Schröder and Ratto were investigating two different groups of patients: those with resectable pulmonary metastases and those without any treatment options left, making any conclusions fragile, especially on survival data [52,54,56].

6.2.4. Melphalan

Regarding melphalan, only one phase I study was performed to determine the MTD in clinical ILuP [51]. In an initial study, 21 procedures were performed in 16 patients with resectable lung metastases. All procedures were performed without technical difficulties. Operative mortality was 0%, and no systemic toxicity was encountered. The MTD was found to be 45 mg at 42 °C. However, in an extension trial of this study more toxicity was observed with a perfusion temperature of 42 °C [59]. So, a safe MTD should be set at 45 mg of melphalan at 37 °C. Pharmacokinetic studies in this trial showed a significant correlation between perfused melphalan doses, perfusate area under the concentration–time curve and lung tissue melphalan concentrations [60,61]. However, there was no correlation between melphalan dose and tumour tissue concentrations. The peak concentration and area under the curve of melphalan were 250- and 10-fold higher than in the systemic circulation, respectively [60].

After a mean follow-up of 25 months, 8 out of 23 patients are alive and disease-free; 14 patients developed recurrent disease, of which 3 died [59]. One disease-free patient died of a non-malignant cause. However, as different dose levels were used in this phase I trial, survival data should be interpreted with caution and cannot be generalised.

7. High-dose locoregional chemotherapy: summary and future perspectives

After extensive experimental research performed in many laboratories over the world, ILuP has now become a mature clinical technique. In summary of the clinical studies, ILuP procedures are generally well tolerated, reproducible and significant drug levels are obtained in pulmonary metastases and lymph nodes without systemic toxicity, offering a valid clinical model for further investigation of combined chemotherapy and surgery in patients with pulmonary metastases [61]. At the present time, only phase I trials have been performed in heterogeneous groups of patients defining the MTD of the specific drug studied. Further phase II and III trials are necessary to determine the effect of ILuP on the rate of local recurrence, long-term toxicity, pulmonary function and survival.

Recently, we initiated a phase II trial together with two centres in the Netherlands including patients with resectable lung metastases from colorectal adenocarcinoma, soft tissue and osteosarcoma. ILuP is performed with 45 mg melphalan at 37 °C. Progression-free and overall survival will be studied as well as pharmacokinetic and lung function data.

To obtain a better international cooperation and exchange of experimental and clinical data a research group on ILuP was created within the European Association for Cardio-Thoracic Surgery with a yearly meeting during the annual congress.

Alternative strategies for ILuP are also developed. Experimental data on less invasive procedures as pulmonary artery infusion and chemo-embolisation are accumulating. These techniques can be applied by a percutaneously inserted pulmonary artery catheter making repetitive application possible. In this way, these promising techniques can be used as induction or adjuvant treatment, not only for lung metastases but also for primary bronchogenic carcinoma.

Hopefully in the near future, these new developments in locoregional high-dose chemotherapy combined with surgical resection will provide a better outcome in our patients treated for lung metastases.

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References


