

LUNG METASTATIC DISEASE: SURGICAL RESECTION AND LOCOREGIONAL CHEMOTHERAPY

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Abstract

Currently, surgical resection remains the gold standard for resectable lung metastases. Prognostic factors are histology, complete resection, number of metastases and disease-free interval. However, there is a high rate of recurrent disease in the thorax, even if systemic chemotherapy is applied. Because the latter is limited in dose due to systemic toxicity, new treatment options are being developed to selectively deliver high-dose chemotherapy into the lung, reducing systemic toxicity. Isolated lung perfusion (ILuP), similar to isolated limb perfusion, is an experimental surgical technique to deliver high-dose chemotherapy into the lung without systemic exposure. Biological response modifiers like tumour necrosis factor can also be administered. ILuP results in significantly higher concentration of chemotherapy in the target organ compared to systemic chemotherapy, together with a survival benefit in experimental models of pulmonary metastases. Several phase I studies have shown that ILuP is technically feasible with low morbidity and low impact on the patient's pulmonary function. However, the utility of this technique is limited because it is an invasive technique. Other techniques to selectively deliver high-dose locoregional chemotherapy are embolic trapping (chemo-embolization), selective pulmonary artery perfusion (SPAP) without control of the venous effluent and the minimally invasive lung suffusion technique. This review will discuss surgical resection of lung metastases and address several techniques developed to deliver high doses of chemotherapy into the lung, as well as the current progress in experimental and clinical studies.

Key words: Lung metastases, prognosis, surgery, chemotherapy, combined modality treatment, lung perfusion, chemo-embolisation

INTRODUCTION

Surgical resection is a widely accepted procedure for patients with lung metastases. However, due to local and distant recurrences, the reported 5-year overall survival rates are only 30-50%. In a large retrospective study evaluating 5206 resections of lung metastases, the International Registry of Lung Metastases, the main prognostic factors were histological type and complete resection (1). When analyzing survival data, patients with one metastasis and a disease-free interval of more than 3 years had the best survival (1). Even after complete surgical resection of the lung metastases a very high intrathoracic recurrence rate of 50-60% was found for some histologic tumour types (1). Reoperation in these patients is still feasible but is limited by the remaining pulmonary reserve, often resulting in functionally inoperable patients (2, 3).

Systemic chemotherapy is utilized to prevent recurrent disease, intrathoracic as well as extrathoracic. However, the maximum dose of intravenous (IV) chemotherapy is limited due to systemic side effects. This resulted in the development of new treatment modalities for locoregional chemotherapy. Isolated liver and limb perfusion gave rise to a similar technique for the lung named isolated lung perfusion (ILuP). ILuP has the advantage of delivering a high dose of a chemotherapeutic agent selectively into the lung while the venous effluent is diverted. This technique is however invasive, which gave rise to the development of selective pulmonary artery perfusion (SPAP). This is an endovascular and thus less invasive technique which can be useful for chemotherapeutic agents with a high initial uptake in the lung parenchyma. During SPAP a balloon catheter is introduced into the pulmonary artery and the chemotherapy is delivered into the lung

at a determined rate. Once chemotherapy is given, the balloon is inflated which results in a blood flow stop within the pulmonary artery (=blood flow occlusion or BFO). This flow block increases the uptake of drug by the lung without a washout of the drug into the systemic circulation, since no control of the venous effluent is present with this technique, in contrast to ILuP. Another locoregional technique is lung suffusion which uses video-assisted thoracoscopic surgery (VATS) to isolate the pulmonary veins and a balloon catheter like in SPAP is brought up into the pulmonary artery. Next, the balloon within the pulmonary artery is inflated and the pulmonary vein snares are tightened. In this way the lung is isolated from the circulation. Subsequently, blood from the pulmonary artery is aspirated to create volume for the chemotherapy to be injected so it can dwell in the lung. At the end of the procedure lung circulation is restored.

Non-surgical means of delivering a high dose of locoregional therapy are also investigated and include chemo-embolisation, a technique which uses particles loaded with drugs that are trapped inside the lung pulmonary circulation.

This review will discuss surgical resection for lung metastases, followed by the rationale and history behind ILuP and SPAP. Afterwards, experimental studies to deliver locoregional chemotherapy in the lung are reviewed. Finally, a summary is given of the clinical studies performed with ILuP as well as other techniques to deliver high local concentration of chemotherapy into the lung.

Surgical resection for lung metastases

Both the lung and the liver are common sites for malignant spread, with the lungs as the most common site of extranodal involvement. This is probably due to the fact that these two organs filter the entire circulation. The patients with untreated pulmonary metastases have a very poor prognosis with a 5-year overall survival rate of only 5% or even less. Systemic chemotherapy often fails in achieving a curative result in the majority of cases and radiotherapy only plays a palliative role in most cases.

Although only supported by retrospective trials, surgical resection of pulmonary metastases yields a clear survival benefit. The patients need to be carefully selected according to general guidelines before undergoing lung metastasectomy (2, 4). These criteria include achievable complete resection, controlled or controllable primary tumour and extrapulmonary sites, low operative risk and no other treatment options available to achieve the same chance of cure or superior palliation.

There is however an ongoing discussion for patients undergoing surgical resection of lung metastases regarding the type of preoperative imaging, lymph node status, the optimal surgical approach, the accepted maximum number of resectable lesions, and the role of adjuvant therapy and/or re-operation for recurrent disease.

Radiographic diagnosis and preoperative imaging

Computed tomography (CT) is the standard imaging modality for both detection and preoperative imaging. With the rise of the fast high-resolution CT (HRCT), it is now possible to detect pulmonary nodules as small as 3 mm, which however results in a loss of sensitivity. Both conventional CT and HRCT have a sensitivity of 100% regarding nodules of 10 mm or higher (5). When the nodule size is smaller than 6 mm, the sensitivity of conventional CT drops to 63% and HRCT between 48-69% (5, 6). Another way to increase detection is decreasing the slice thickness. Reducing the slice thickness from 5 mm to 3 mm results in a significant increase in the detection of lesions (7). It could be postulated that the identification of more lesions would limit the usefulness of bimanual lung palpation during operation, but with the decrease in sensitivity with smaller lesions, palpation may detect lesions missed by preoperative CT. It should also be noted that a pulmonary lesion found in a patient with a history of cancer could also represent a second primary tumour requiring different treatment.

Because lesions are found earlier and some of those may be benign, more studies have investigated the tumour volume doubling time. In sarcoma patients for example, small lesions on the lung CT may well be benign. For lesions smaller than 5 mm a follow-up CT scan is indicated after 2 months to evaluate tumour growth. When the lesion starts growing, it is more likely that this represents malignant disease (8). If the nodule in sarcoma patients remains 5 mm or smaller, further follow-up is needed. If the nodule remains under the 5 mm after 6 months of follow-up, the chance is very high that this is a benign lesion (8).

In the preoperative staging of cancer patients, positron emission tomography or PET scan has become a widely used tool. It has an overall sensitivity of 67.5% in detection of pulmonary metastases (9). For lesions larger than 10 mm, the sensitivity is even 87.8%. However, this technique has a very low sensitivity of 29% for lesions smaller than 10 mm (9). When looking at the histological type of the metastases, there is also a difference in detection. In 93% of the lesions of

squamous cell carcinoma a positive identification was made with PET scan whereas this was only 44% for sarcoma patients (9). This suggests that although PET scan is very useful in the detection of extrathoracic disease, it should not be used alone to select patients for surgery but rather in combination with chest CT (9).

Pulmonary and mediastinal lymph node status

The need for lymph node sampling and/or involvement remains controversial with pulmonary metastases. Lymph node dissection during pulmonary metastasectomy is highly variable between surgeons and institutions and nodal involvement is not always reported in published series. In the International Registry of Lung Metastases only 4.6% of the patients underwent lymph node dissection (1). In a large study of 708 lung metastasectomies, nodal dissection was performed in 65% of the patients and in a recent survey obtained from the members of the European Society of Thoracic Surgeons (ESTS), only 55% of the surgeons perform mediastinal lymph node sampling during pulmonary metastasectomy whereas 33% perform no sampling or lymph node dissection at all (10, 11). No clear evidence exists about whether nodal dissection influences survival but it certainly provides a better intraoperative staging, which may determine adjuvant treatment. In a study of 245 patients, a systematic lymph node dissection was performed during lung metastasectomy for metastases from colorectal carcinoma, renal cell carcinoma and sarcoma (12). This study found more nodal involvement in patients with renal cell carcinoma and colorectal carcinoma than sarcoma lung metastases, 42.4%, 31.3% and 20.3% respectively. The presence of positive intrathoracic lymph nodes resulted in a worse prognosis with a median survival of 64 months for patients without nodal involvement, whereas for patients with hilar and mediastinal nodal disease, median survival was 33 and 21 months, respectively (12). This is supported by several other studies showing a decreased survival when hilar or mediastinal lymph nodes are involved (13-16). Complete mediastinal nodal dissection prolongs surgical time by a median time of only 15 minutes and does not result in increased morbidity and hospital stay, as shown in a prospective study of the American College of Surgeons Oncology Group (ACOSOG) in patients with early-stage lung cancer undergoing major pulmonary resections (17). Because of the low negative impact of the action itself, this implies that a systematic nodal dissection needs to be performed during lung metastasectomy to provide a better intraoperative staging. Also, it will result in more consistency in the

reports of patients undergoing lung metastasectomy making it easier to compare different studies.

The surgical approach

For the surgical treatment of lung metastases there are 4 different approaches, 3 open and 1 thoracoscopic, all having their advantages and disadvantages. The first one is a median sternotomy resulting in exposure of both lungs but it may be difficult to palpate and resect lesions in the left lower lobe (18). The second is a clamshell incision, bilateral anterior thoracotomy in the 4th intercostal space connected by a transverse sternotomy, which provides a panoramic view of mediastinum and both lungs including good exposure of both hili and left lower lobe in comparison to median sternotomy alone. The major disadvantage of this technique is the higher postoperative morbidity. The third is a lateral thoracotomy (classical posterolateral or anterolateral muscle-sparing). This technique allows a very good exposure of unilateral parenchymal or hilar lesions. Both types of thoracotomy are performed through the 4th or 5th intercostal space. In the muscle-sparing anterolateral approach the serratus anterior or latissimus dorsi muscles are preserved, reducing postoperative muscle pain. If bilateral disease is present, a bilateral thoracotomy or a staged unilateral thoracotomy can be performed. Because lung metastases are a systemic disease, one may argue that when lesions are found on one side, there is a high probability there are also metastases on the other side, although not visible on preoperative imaging. In a study comparing bilateral thoracotomy for bilateral and unilateral thoracotomy for unilateral lung metastases, there was no difference in overall survival between these two groups (19). This suggests that there is no need to perform a bilateral approach for unilateral disease and a contralateral approach can be performed when lung metastases are found on that side on radiographic follow-up (19).

Thoracoscopic resection (VATS) is a minimally invasive surgical approach. It is primarily used for diagnostic purposes but more and more surgeons use it to perform oncologic resections (20, 21). The major advantage of VATS is the lower morbidity, shorter hospital stay and decreased intrathoracic adhesions, improving the feasibility of reoperation compared to open procedures (22). Early studies showed that VATS was inferior to open thoracotomy because of the loss of tactile sensation and subsequently missing lesions that did not show up on preoperative imaging (23). However, with the improvement of preoperative imaging, more recent studies indicate that VATS might result in similar

survival compared to thoracotomy in selected patient groups (21, 24-26). These studies were performed in patients with 1 or 2 small peripherally located lesions which are easily accessible with VATS. New techniques have been developed, making it possible to mark the lesion with a hook wire or dye, allowing resection of deeper lesions with VATS (27, 28). Very small lesions can still be missed on CT scan and subsequently during VATS. There is, however, no evidence that resection of a very small nodule between 1 to 3 mm, that is not detected on CT scan and which is found by bimanual manipulation, improves survival. Micrometastases that are missed during the initial procedure can be resected when they become detectable during follow-up without affecting survival (19).

So far, no randomized trials have been published that evaluate long-term survival after open surgery compared to VATS. At the present time VATS may be considered a valid approach for diagnosis as well as treatment of pulmonary metastases if there is only a single metastasis which is peripherally located. If there are any discrepancies between the preoperative imaging and the peroperative findings or uncertainty about the surgical margins, conversion to a thoracotomy is advised to perform the resection.

Repeated resection and extended resections for pulmonary metastases

In selected patients repeated resection of pulmonary metastases may be beneficial. In a study of Jaklitsch et al. 54 patients underwent 2-6 sequential thoracic metastasectomies for different primary tumours (29). This study showed that overall survival for patients who underwent repeated complete resection was better compared to patients with unresectable recurrent disease and was unrelated to the number of previous metastasectomies. Depending on the primary tumour, repeat complete metastasectomy results in improved survival (vide infra). A surgeon should keep in mind to the possibility of performing a complete resection with the excision of as little healthy lung tissue as possible but without compromising the principles of oncologic resection. The remaining lung volume will determine whether the patient is able to undergo a subsequent resection. Because most pulmonary metastases are situated in the periphery of the lungs, they can be usually be excised by a non-anatomical wedge excision, whereas anatomical resection is essential for primary lung cancer. However, if the lung nodule is situated more closely to the hilum or it grows into extrapulmonary tissue, an extended resection is required.

These resections range from segmentectomy to en bloc resection of the metastases with the invaded structures. Complete resection with negative margins is the essential key during lung metastasectomy. If this can be achieved in order to obtain long-term survival and, a 5-year overall survival between 16-25% is reported (30, 31). These studies as well as others show an acceptable postoperative mortality and morbidity, justifying extended resections in selected cases of patients with lung metastases (1, 30-33).

Alternative techniques for preserving lung parenchyma

Radiofrequency ablation (RFA), stereotactic body radiation therapy (SBRT), laser-assisted resections, microwave ablation and cryoablation are techniques used to preserve lung parenchyma, allowing the patient to undergo repeated procedures or treat patients that are unable to undergo extended resections.

The group of Rolle et al. investigated laser resection of lung metastases with a 1318-nm Nd: YAG laser during a surgical procedure performed in 328 patients (34, 35). They found an improved survival for patients with complete resection compared to incomplete resection, and in 9% of their patients complete resection of 20 or more lung metastases per patient was achieved, which is often not possible with stapler resection because of insufficient lung parenchyma (35). These results suggest that laser resection of lung metastases can be a good alternative compared to stapler resections, especially in patients with multiple lung metastases, because of the reduced parenchymal loss allowing increased complete resection rates, which may increase survival (35).

SBRT is a technique that allows high doses of radiotherapy to be given to a very selective area, allowing targeting of lung nodules without damaging large areas of normal lung tissue around it as with normal radiotherapy. This technique was initially used for patients that were inoperable but more studies appeared using it for patients with both operable and inoperable lung metastases of all kinds of primary tumours (36-39). It has shown to be a safe and effective treatment, which may prolong survival and improve local control in selected cases (36-39).

RFA is a percutaneous technique which can be used in high risk patients or patients that are medically inoperable. A probe is inserted under CT guidance into the lesion with thermoablation of the lesion. Microwave ablation and cryoablation are similar techniques which were found to be effective in the treatment of lung malignancies (40, 41). A downside of these tech-

niques is local recurrences, especially if the tumour is close to large blood vessels or other possible heat sinks, resulting in insufficient treatment in that area. However, microwave ablation and cryoablation are supposed to be less influenced by these heat sinks. When performing SBRT, RFA, microwave ablation or cryoablation, no histological confirmation of malignancy is present, there is no lymph node sampling and no precise tumour staging. This results in an unclear selection of patients for adjuvant therapy. Palpation of the lung to ensure that no additional lesions are present is not possible with these percutaneous techniques. Although they may improve survival and palliation, their use in operable patients remains controversial (42). No randomized studies exist directly comparing these techniques with classical surgical resection. Because there is no clear definition of complete resection with these techniques, their use should presently be limited to inoperable patients until randomized evidence becomes available resulting in more general guidelines.

Lung metastasectomy for different histological tumours

1. Breast cancer and testicular cancer

Chemotherapy is the primary treatment option for patients with lung metastases from breast cancer, testicular tumours and germ cell cancer (43-46). Metastatic disease of breast cancer responds very well to systemic chemotherapy and/or antihormonal therapy, resulting in an unclear role for surgical resection. Some studies report no benefit in overall survival for patients undergoing complete metastasectomy for breast cancer compared to systemic chemotherapy or to patients undergoing an incomplete resection, whereas others do find a survival benefit (47-51). However, in selected cases, with a DFI of more than 36 months and complete resection, a long disease-free and overall survival period may be obtained (52, 53). However, not all lung nodules are metastatic lesions. Rena et al. (54) showed that, in 50% of the patients with a history of breast cancer and a newly diagnosed lung nodule, primary lung cancer was found. Complete surgical resection needs to be performed in this patient group in order to have histological confirmation and a real chance of cure when a primary lung cancer is found (53, 54). Another study showed that there is a reasonable chance that the hormonal receptor status of the primary tumour is different from the lung metastases, warranting histological evidence to plan further treatment (50). In conclusion, although most studies do not find a survival benefit, surgical resection of

lung metastases from breast cancer is warranted in selected cases if complete resection can be achieved, if there is suspicion of primary lung cancer and to plan further treatment depending on the hormonal receptor status of the metastases.

Surgical resection of lung metastases as well as resection of lymph nodes has an adjuvant role after chemotherapy in patients with testicular cancer. Resection of the lung metastases may direct further treatment. If histology only confirms necrosis, fibrosis or teratoma, there is no indication for further treatment. However, if viable tumour cells are found, the patient requires additional chemotherapy. With the current multimodality strategy, a 5-year survival rate of up to 82% can be achieved (55). Multiple metastases, elevated tumour marker levels of alpha-fetoprotein or chorionic gonadotropin, or viable cells in the resected metastases after chemotherapy, negatively influence overall survival (12, 45, 46, 56). However, if needed, repeat resections should be performed (45).

2. Colorectal cancer

Of all patients with a history of colorectal cancer, around 10-20% will develop lung metastases, but only 2% will have metastases confined to the lung without extrathoracic disease (57, 58). In a literature review of reports of more than 40 patients from 1995 up to 2006, an overall 5-year survival ranging between 38.3% and 63.7% was found (59). Positive hilar or mediastinal lymph nodes or elevated carcinoembryonic antigen negatively influence survival (59-63). It is suggested that obtaining R0 resection is important to achieve long-term survival and that patients with only one lung nodule tend to have a better survival than patients with more metastases (59). Half of the patients with colorectal disease will develop liver metastases (64). In selected cases, resection of both pulmonary as well as hepatic lesions may result in a good long-term survival (65, 66). Some reports show no difference in survival between patients with synchronous and metachronous liver and lung metastases (67, 68). However, some studies found a decreased survival if synchronous liver and lung metastases were present (69-71). Neeff et al. showed a decreased survival in patients having primary lung metastases and subsequently liver metastases, whereas the study of Zabaleta et al. found that patients with lung metastases and a history of liver metastases have a decreased survival (69, 71). Shiono et al. underlined the importance of tumour biology on survival (72). They investigated histopathological variables such as bronchial, vascular and lymphatic invasion. Patients without any of the investigated variables had a 5-year overall survival of 93.3% (27). In conclu-

sion, in selected patients, surgical resection and even repeated resection, should be undertaken if complete resection of colorectal lung metastases is achievable. So far, the benefit of surgical resection of colorectal metastases on survival is claimed by retrospective and non-randomized trials only. Recently, the PulMiCC trial has begun (73). This randomized study aims to examine whether or not surgical resection of colorectal lung metastases influences survival as well as looking at other factors like quality of life after surgery. Hopefully this study will shed more light on surgical resection for lung metastases from colorectal cancer.

3. Head and Neck tumours

Head and neck tumours are a large group of various epithelial tumours like squamous cell carcinoma, glandular cystic carcinoma and adenoid cystic carcinoma. They metastasize to local lymph nodes and subsequently to more distant organs, mostly to the lung (74-76). The 5-year overall survival after pulmonary metastasectomy varies between 20.9% and 59% (75, 77-81). The survival varies depending on the histological type of the tumour, with the best survival for patients with adenoid cystic carcinoma and the worst for the squamous cell carcinoma (78). Reported positive prognostic factors are long DFI and complete resection, negative ones are a DFI of less than 12 months and mediastinal lymph node invasion. Just as in breast cancer, it is important to distinguish between primary lung cancer and a metastasis, certainly for squamous cell carcinoma, because the risk factors are mostly the same as for primary lung cancer. For this reason an aggressive approach with surgical resection of a single lung lesion in a patient with a history of squamous cell carcinoma is warranted. For the other types of head and neck cancer the benefit of surgical resection is less clear because of the small number of series published (76). The general consensus is that surgical excision is advocated if the patient meets the standard inclusion criteria for surgical resection.

4. Hepatocellular carcinoma

The lungs are the most common extrahepatic site for metastases (82). Because the therapy for HCC is benefitting from improved local control due to liver resection, RFA, liver transplantation and other methods, the resection of lung metastases from HCC has been increasingly reported during the last decade with encouraging results (83, 84). The reported 5-year overall survival after lung metastasectomy is 36% (84). A DFI of more than 12 months and serum alpha-fetoprotein lower than 500 ng/mL are required to undergo pulmonary metastasectomy. Even after liver transplantation, surgical resection of lung metastases can be performed (85).

5. Malignant melanoma

Malignant melanoma is able to disseminate widely in the body. This results in a very small number of patients with isolated pulmonary metastases who are eligible for surgical resection. For this reason, excision remains controversial. As soon as there is distant disease in patients with melanoma, the median survival is around 6 months with a 5-year survival of less than 5% (86, 87). However, when isolated pulmonary metastases are present, resection may give rise to an overall 5-year survival of up to 38% (88-92). In a recent study, resectable lung metastases smaller than 2 cm had a positive effect on survival, even in patients who had undergone previous complete resection of extrathoracic disease (92). These studies show that carefully selected patients with completely resectable lung metastases, even with resectable extrapulmonary disease, should be eligible to undergo a simultaneous or staged resection, which might result in prolonged survival.

6. Osteosarcoma

At the time of diagnosis of osteosarcoma, 10-20% of patients already have pulmonary lesions and up to 70% will develop lung metastases (93-96). It is essential to control the thoracic disease because failing to do so will result in a worse prognosis (43). When complete resection can be achieved, even repetitively, a long 5-year survival can be obtained of up to 43% (96-98). In most studies, complete resection is a very strong prognostic factor. The data published about other factors like DFI, number and size of metastases, and age are conflicting, making it difficult to define their prognostic influence. Neo-adjuvant chemotherapy before surgical resection of lung metastases might result in a positive effect on survival, especially if there is a histological response. If patients are treated with chemotherapy alone the outcome is very poor, suggesting that patients with lung metastases from osteosarcoma need a multimodality treatment, of which complete surgical resection is the most important factor (99).

7. Renal cell carcinoma

Around 25-30% of the patients with renal cell carcinoma (RCC) will develop metastatic disease and the lung is the most common site for these metastases (100, 101). Complete resection of lung metastases from RCC results in a 5-year overall survival rate between 31 and 53% whereas incomplete resection results in only 22% (102-106). Prognostic factors include complete resection, the number of metastases (<5 nodules), hilar or mediastinal lymph node metastases and long DFI. If complete resection can be achieved, repeated resection is supported. With a

10-year overall survival of 42%, complete metastasectomy remains the best treatment option for resectable lung metastases from RCC (107).

8. Soft tissue sarcoma

The group of the soft tissue sarcoma (STS) is very heterogeneous with over 50 malignant subtypes (108). The lung is the most common site of metastases from STS, occurring in 20% of the patients. The reported 5-year overall survival after complete resection of these metastases varies between 18 and 43% (109-114). All these studies indicate complete surgical resection as the most significant prognostic factor. Other factors found by some studies but not supported by others, are the number of lung nodules and thoracic lymph node metastases. However, a short DFI and sarcoma type seem to be prognostic in most studies. Patients with a short DFI have a worse prognosis. The same holds true for Ewing sarcoma, liposarcoma, and peripheral nerve sarcoma, in contrast to other histological types such as malignant fibrous histiocytoma, rhabdomyosarcoma, and synovial sarcoma (110, 113, 115). When complete resection can be achieved, repeated resections are indicated because survival data for STS after chemotherapy remain disappointing compared to osteosarcoma because STS is less sensitive to chemotherapy. Therefore, complete surgical resection, and even repeated resection, are the best treatment options for selected patients with STS to achieve long term survival.

International registry of lung metastases

The largest retrospective multicenter study of lung metastasectomy published so far is performed by Pastorino et al. with data of 5026 patients operated between 1991 and 1995 (1). They included patients with lung metastases from epithelial tumours (43%), sarcomas (42%), germ cell tumours (7%), melanomas (6%), and other types (2%). Eighty-eight percent of the patients had complete surgical resection of these lung metastases, with an overall mortality of 1.0%. This study reported a median survival time (MST) of 35 months for patients with complete resection compared to a MST of 15 months for patients with

incomplete resection. After a second metastasectomy for recurrent disease, a 5-year overall survival rate of 44% was obtained. Data of the patient group that underwent complete surgical resection were put in a multivariate analysis which showed that primary tumour type, disease-free interval and number of lung metastases were significant prognostic factors (1). With these factors they could define 4 different prognostic groups (Table 1) with a significant difference in survival. Depending on the primary tumour histology, they discovered that patients who underwent complete surgical resection had a very high intra thoracic recurrence rate. For epithelial tumours, 44% of the patients developed intrathoracic recurrences while this rate was even 66% for the patients with metastatic disease from sarcoma (1). Similar data were reported from our own institution (116). It is suggested that this high recurrence rate is due to micrometastases that are not picked up during the initial work-up and procedure, and partially due to the inability of systemic chemotherapy to reach a sufficiently high dose to eliminate micrometastases. Although reoperation of these new metastases is feasible and may improve survival, it is limited by the remaining lung volume of the patient. For this reason an improved local control at the time of the initial resection may be obtained by a combined modality treatment including surgery and locoregional chemotherapy. The locoregional methods to selectively deliver a high dose of chemotherapy to the lung will be further discussed in this review.

The blood supply of the tumour

The blood supply of the tumour is very important for the effect of the treatment. Several experimental, autopsy and clinical studies have evaluated the blood vessel distribution of primary lung tumours and lung metastases. Already in 1967 Miller et al. (117) concluded that most metastases receive their blood supply from the pulmonary artery. Milne et al. (118) showed in 1976 that primary lung tumours receive their primary blood supply from the bronchial arteries, whereas lung metastases are predominantly vascularised by the pulmonary artery. In 48% of all lung metastases

Table 1. The prognostic groups according to the International Registry published by Pastorino et al. (1)

	Resection	Risk factors	Characteristics	MST (mos.)
Group I	Complete	No	Single metastasis and DFI >35 mos.	61
Group II	Complete	1	DFI >36 mos. or multiple metastases	34
Group III	Complete	2	DFI <36 mos. and multiple metastases	24
Group IV	Incomplete, unresectable	/	/	14

MST: median survival time; mos: months; DFI: disease free survival time

the pulmonary artery was the only supply, in 16% this was the bronchial artery and in 36% there was a dual vascularisation (118). These studies were supported by Mochizuki et al. who used first-pass dynamic CT imaging for solitary pulmonary nodules and concluded that the pulmonary circulation supplies a significant portion of pulmonary metastatic tumour vasculature but that primary bronchogenic carcinoma is predominantly supplied by the bronchial arteries (119). Therefore the pulmonary artery is the preferred route to deliver chemotherapy to lung metastases, whereas the bronchial arteries are the desired route for primary bronchogenic carcinoma.

The rationale behind high-dose locoregional therapy

During the last decades, there knowledge of cell survivability pathways, drug resistance and genetics has increased. The poor results of patients undergoing lung metastasectomy for certain tumour types followed by chemotherapy is probably because of the drug resistance of these cells for the chemotherapeutic agent and the already mentioned inability of these chemotherapeutic agents to reach an effective drug concentration in the tumour mass itself, also known as first order targeting (120, 121). This means that, in addition to surgery, a more effective delivery system needs to be developed to introduce drugs inside the lung together with better chemotherapeutic agents. The biophysical methods resulting in increased drug targeting in the lung parenchyma include embolic trapping or chemo-embolisation, selective pulmonary artery perfusion (SPAP) without control of the venous effluent, lung suffusion and isolated lung perfusion (ILuP) in which the lung circulation is completely separated from the systemic circulation (121). These are all promising techniques that can be used for the treatment of lung metastases of tumours that do not respond well to systemic chemotherapy (121).

Isolated lung perfusion

History

The first to report a method of pulmonary perfusion was Creech in 1959 (122). He performed a perfusion of both lungs simultaneously with divided circuits for the systemic and pulmonary circulation. In 1968, a co-worker of the paper of 1959 named Krentz, commented on this report that 1 of the 4 patients had a major clinical response to the perfusion; however 2 others died shortly after perfusion. This was the first clinical report of lung perfusion for the treatment of cancer (123). This technique remained dormant until

1983, when Johnston et al. demonstrated that ILuP was a reproducible and safe technique (124). In this report he used a dog model to determine the dosage of doxorubicin. He observed no systemic toxicity and found that the local toxicity of ILuP was closely related to the drug uptake in the lung and the drug concentration in the perfusate (124). The dose-dependent relations were also supported by Baciewicz et al. who found similar toxicity at lower concentrations of doxorubicin, but with the use of mild hyperthermic perfusate, which may result in an increased uptake of the drug into the lung tissue (125). Johnston also refined simultaneous bilateral perfusion as lung metastases may present bilaterally (126). With these good results, the interest in ILuP has awoken again.

Technique

As mentioned above, Creech was the first to report pulmonary perfusion in patients (122, 123). In order to perfuse two lungs simultaneously, two extracorporeal systems are needed. In most recent clinical phase I studies, one-sided lung perfusions are performed because these studies are designed to evaluate dose-limiting toxicity (DLT) and maximal tolerated dose (MTD). If the perfusion would be performed bilaterally and pulmonary toxicity and oedema occurred, this would result in a hazardous situation. So, in case of bilateral lung metastatic disease, staged procedures are currently preferred.

In general, a thoracotomy is performed with subsequent cannulating of the pulmonary artery and both pulmonary veins (Figure 1). After installing a perfusion circuit, the vessels are centrally clamped resulting in a closed circuit and the agent is injected into the perfusion circuit. In addition, the lung is ventilated during

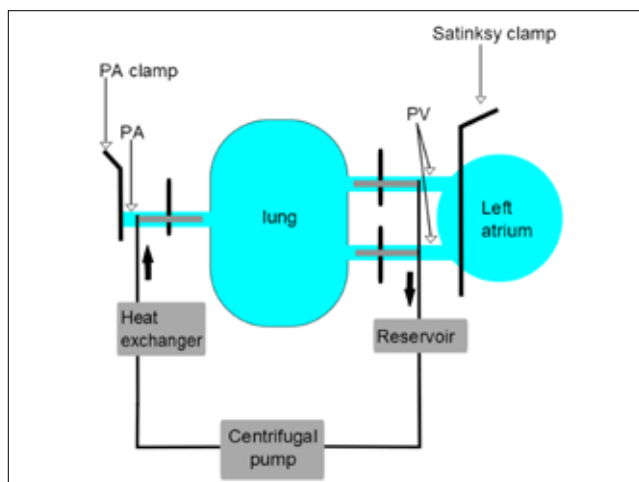


Figure 1. Isolated lung perfusion
PA: pulmonary artery; PV: Pulmonary vein

perfusion to allow a homogeneous distribution of drug throughout the lung. The bronchus is gently snared to block the bronchial arterial circulation. It may be beneficial to use hyperthermic perfusion to increase drug uptake in the lung parenchyma. The technique that has been applied in our phase 1 trial for ILuP with melphalan is described in more detail (127). We prefer to resect metastatic disease after isolated lung perfusion but we mark all metastases and any suspicious nodules before the start of the perfusion because possible lung oedema after the perfusion may render identification of very small lesions difficult or impossible. In this way, it is easier to obtain a homogeneous distribution of drug throughout the procedure as well as prevent any bleeding on the resection sites with subsequent loss of chemotherapeutic agent from the perfusion circuit because of the systemic heparinization. This is in contrast to the study of Schröder et al. who performed the metastasectomy before perfusion, although his precise motivation is not mentioned (128).

Experimental studies of ILuP

In 1993, experimental research with ILuP got a boost by the development of a rat model of ILuP published by Weksler et al. from Memorial Sloan-Kettering Hospital in New York (129). Rats only have one lobe on the left side which can easily be isolated and perfused when performing a thoracotomy. With this new model, several chemotherapeutic drugs and biological agents could be investigated in tumour models and some were found to be effective in the treatment of lung metastases of primary carcinomas or sarcomas (121). At our own institution, the model of Weksler was modified by important changes of intubation technique, anaesthesia and approach for catheterisation of the pulmonary vessels, which resulted in a faster and safer procedure (130). The experimental studies of ILuP are summarised in Table 2.

1. Doxorubicin:

Doxorubicin belongs to the anthracycline antibiotics group with a proven activity against several solid tumours like breast and oesophageal carcinoma, as well as osteosarcoma, soft-tissue sarcoma and non-Hodgkin's lymphoma (131). In a Fisher rat model of methylcholanthrene-induced sarcoma lung metastases, ILuP with doxorubicin was an effective and safe method, and superior to IV doxorubicin (132, 133). The lung tissue levels of doxorubicin were 20-fold higher compared to IV doxorubicin, were well tolerated by the animals and did not result in the cardiac and haematologic toxicities which were found after IV doxorubicin (132). After performing ILuP with doxorubicin, there

was an eradication of macroscopic and microscopic sarcoma lung metastases, whereas the sham perfused lungs had massive tumour growth (134). To improve the activity of doxorubicin, several additional techniques or drugs were tested such as buthionine sulfoximine, P-glycoprotein modulators like cyclosporine, liposomal-encapsulated doxorubicin and intraoperative low dose photodynamic therapy (135-142). These additional techniques had various effects on the drug uptake, as seen in Table 2. Mürdter et al. (143) performed an ex vivo lung perfusion with doxorubicin on resected human lungs after a pneumonectomy, resulting in an excellent model for preclinical evaluation.

2. Gemcitabine

ILuP with gemcitabine showed to be effective in prolonging survival in a rodent model with pulmonary adenocarcinoma metastases compared to IV treatment (144). The combination of melphalan with gemcitabine resulted in a beneficial effect prolonging survival even more compared to single-therapy with gemcitabine in the same model (145).

3. 5-Fluorodeoxyuridine (FUDR)

FUDR is very active against metastases from colorectal carcinoma. This drug was investigated in a dimethylhydrazine-induced carcinoma model, showing a significant decrease of the number of tumour nodules after ILuP with FUDR (146). The use of this drug is however hampered by its dose-limiting toxicity.

4. Cisplatin

Cisplatin has been investigated in several pig models. Significantly higher lung tissue concentrations were obtained compared to systemic treatment or pulmonary artery blood flow occlusion (147, 148). Kaneda et al. (149) showed that ILuP with cisplatin was pharmacokinetically superior to IV treatment in a rodent model. When digitonin is added, the uptake is even more enhanced as shown in a rodent model (150). Also the use of hypertensive chemotherapy is investigated (151). Before starting the ILuP, endothelin was injected into the pulmonary artery resulting in vasoconstriction. In a sarcoma bearing rodent model there was limited pulmonary toxicity and an increased uptake in the lung metastases (151). There was a significant reduction of tumour volume and even 20% treatment response in a rodent model with sarcoma lung metastases after ILuP with cisplatin compared to sham ILuP (152).

5. Tumour necrosis factor alpha (TNF- α)

TNF- α has a high anti-tumour potential when delivered in a high dose during the ILuP procedure, as confirmed by Weksler (153). After perfusion, about 5 times less tumour was observed compared to the unperfused lung in this rodent model with sarcoma lung metastases. However, when used in combination

Table 2. The experimental studies of Isolated lung perfusion			
Author	Drug	Model	Effect comment
Weksler (132)	Doxorubicin	Rat	Effective against sarcoma mets
Abolhoda (133)	Doxorubicin	Rat	Effective against sarcoma mets
Port (135)	Doxorubicin + BSO	Rat	More effective than doxorubicin alone
Krueger (168)	Doxorubicin	Pig	High lung levels, heterogeneous distribution
Kuemmerle (136)	Doxorubicin + P-glycoprotein modulator	Rat	No additional effect on sarcoma mets compared to doxorubicin alone
Yan (141)	Liposomal doxorubicin	Rat	Better distribution ratio but lower overall concentration in lung parenchyma compared to I LuP with doxorubicin alone
Cheng (142)	Liposomal doxorubicin + low dose photodynamic therapy	Rat	Improved uptake in tumour tissue in comparison to liposomal doxorubicin alone but no higher overall concentration in lung parenchyma compared to I LuP with doxorubicin alone
Mürdter (143)	Doxorubicin	Ex vivo human lung perfusion	Preclinical pharmacokinetic studies
Van Putte (144)	Gemcitabine	Rat	Effective against adenocarcinoma mets
Van Putte (145)	Gemcitabine + melphalan	Rat	More effective than gemcitabine or melphalan alone against adenocarcinoma mets
Ng (146)	FUDR	Rat	Effective against carcinoma mets
Ratto (147)	Cisplatin	Pig	High lung levels obtained
Kaneda (149)	Cisplatin	Rat	High lung levels obtained
Tanaka (150)	Cisplatin + digitonin	Rat	Higher lung levels than cisplatin alone
Matsuoka (151)	Cisplatin + endothelin	Rat	Increased uptake in sarcoma mets compared to cisplatin alone
Li (152)	Cisplatin	Rat	Effective against sarcoma mets
Weksler (153)	TNF- α	Rat	Effective against sarcoma mets
Hendriks (154)	Melphalan + TNF- α	Rat	No additional effect of TNF-
Schrump (155)	Paclitaxel	Sheep	High lung levels obtained
Nawata (156)	Melphalan	Rat	Effective against sarcoma mets
Den Hengst (157)	Melphalan	Rat	High lung levels obtained, effective against sarcoma mets
Hendriks (154)	Melphalan	Rat	Effective against adenocarcinoma mets
Van der Elst (159)	Melphalan	Pig	Safe pharmacokinetic profile for I LuP

Mets: metastases, BSO: buthionine sulfoximine, I LuP: isolated lung perfusion, FUDR: 5-fluorodeoxyuridine, TNF- α : Tumour necrosis factor alpha

with melphalan, TNF- α showed no additional benefit in a rodent model of adenocarcinoma lung metastases (154). The lack of effect is probably due to the tumour characteristics used in this rat model.

6. Paclitaxel

Paclitaxel has been investigated in a sheep model with retrograde hyperthermic I LuP for 90 minutes (155). In this study, no pulmonary toxicity was observed and significantly higher lung tissue concentrations were achieved compared to IV treatment.

7. Melphalan

Melphalan has been used for many years for isolated limb perfusion. Therefore, melphalan is also investigated in the setting of I LuP for both carcinoma and sarcoma lung metastases. Nawata et al. showed in 1996 that melphalan was effective in eliminating sarco-

ma lung metastases in a rodent model, but no survival data were published (156). This effect was confirmed by a study from our own institution in a rodent model with metastatic rhabdomyosarcoma. In this study, I LuP with melphalan was able to reach a much higher concentration in the lung parenchyma, eliminate more tumour nodules and improve survival compared to IV melphalan (157). In the studies performed by Hendriks et al, I LuP with melphalan resulted in a significant reduction of the number of lung nodules in a carcinoma bearing rodent model (154). Improved survival was also observed when compared to IV treatment (158). The combination therapy of melphalan with TNF- α and with gemcitabine was also tested. As mentioned above, TNF- α had no additional benefit, but the combination of melphalan with gemcitabine resulted

in a superior result compared to single therapy with one of these two drugs in the treatment of colorectal carcinoma lung metastases (145). This is the first and only reported study showing the additional effects of two chemotherapeutic agents in the setting of ILuP and it is a promising tool for future phase I clinical studies. The pharmacokinetic properties of ILuP with melphalan have also been investigated in a pig model, demonstrating its feasibility, safety and the absence of any systemic toxicity (159).

Recent clinical studies of ILuP

Most chemotherapeutic drugs that were tested in animal studies with good results were followed by a clinical phase I trial. It is very difficult to extrapolate the data found in those animal studies into a clinical study. These phase I trials are needed to evaluate the feasibility of ILuP for resectable or non-resectable lung metastases and to determine the dose limiting toxicity (DLT) and maximum tolerated dose (MTD). Because these studies use incremental doses, MTD is defined as one dose below the DLT. Table 3 summarizes the clinical studies performed from 1995 until now.

1. Doxorubicin

After the insights gained from their experimental studies, the group of Johnston performed a pilot clinical trial of ILuP. In this trial, 4 patients were included with unresectable metastatic sarcoma of the lung and 4 patients with diffuse bronchoalveolar carcinoma (160). From these 8 patients, 6 were perfused with doxorubicin and 2 with cisplatin (see section cisplatin below). In this study, 3 patients underwent single lung perfusion whereas 5 underwent total lung perfusion. The perfusion time was between 40-60 minutes with normothermic conditions except for 1 patient who underwent perfusion with moderate hyperthermia of

40°C. During this study there were no intraoperative complications. One patient developed pneumonia followed by sternal dehiscence. All patients died of progressive disease 23-151 days after perfusion without any clinical response to the treatment. However, this study clearly demonstrated that ILuP was well tolerated and reproducible, with minimal systemic leakage even with the higher perfusion doses (160). In 2000, a study with a phase I protocol was published by Burt et al. (161) In this study, 8 patients with inoperable lung metastases from a sarcoma underwent single lung perfusion with doxorubicin. During ILuP a good separation between the perfusion and systemic circuit was observed with minimal systemic levels while a high concentration of doxorubicin was found in the lung parenchyma. However, the concentration in the tumour was lower than in the normal lung tissue. In this study, an important chemical pneumonitis developed in a patient with a dose of 80 mg/m² and the MTD was defined at 40 mg/m². There were no perioperative deaths but there was also no partial or complete response. There was a significant decrease in forced expiratory volume in 1 second (FEV₁) and a trend towards a decrease in diffusion capacity in the 7 patients that underwent treatment with the MTD (161).

In 2002, Putnam et al. (162) reported a phase I trial of single lung perfusion with doxorubicin in 16 patients with unresectable sarcoma lung metastases. They also obtained a good separation of the perfusion circuit from the systemic circulation. After perfusion, 2 patients developed grade 4 lung toxicity after a dose of 75 mg/m², resulting in a MTD at 60 mg/m² of doxorubicin. In this study there was an overall operative mortality of 19%. One patient died due to a paradoxical tumour embolus, one due to pneumonia 3 weeks postoperatively and 1 because of drug-related

Table 3. Clinical studies of isolated lung perfusion from 1995 on

Year	Author	Ref.	Drug	N	Lung temperature (°C)	Perfusion time (min)	Resectable lung metastases	MTD
1995	Johnston	(160)	Doxorubicin/Cisplatin	6/2	NA	45-60	No	NA
1996	Pass	(163)	TNF- α and γ -interferon	15	38-39.5	90	No	6 mg
1996	Ratto	(148)	Cisplatin	6	37	60	Yes	200 mg/m ^{2a}
2000	Burt	(161)	Doxorubicin	8	37	20	No	40 mg/m ²
2002	Putnam	(162)	Doxorubicin	16	37	NA	No	60 mg/m ²
2002	Schröder	(128)	Cisplatin	4	41	21-40	Both	70 mg/m ^{2a}
2004	Hendriks	(127)	Melphalan	16 ^b	37, 42	30	Yes	45mg - 42°C
2007	Grootenboers ^c	(164)	Melphalan	7 ^d	37, 42	30	Yes	45mg - 37°C ^c

n: number of patients; min: minutes; MTD: maximum tolerated dose; NA: Not available; TNF- α : Tumour necrosis factor alpha; Ref.: reference
^aFixed dose, ^b21 procedures (5 bilateral), ^cThe extension trial of the study of Hendriks (127), the safe MTD was found to be 45 mg at 37 °C (see text) ^d8 procedures (1 bilateral)

lung injury. Only 1 major response occurred and the reported median survival in this study was 19 months. During the follow-up early morbidity was noted in 3 patients: a prolonged chest tube drainage, an air leak longer than 7 days, and a grade 4 lung toxicity.

2. Cisplatin

As mentioned above, the group of Johnston performed a clinical trial of I LuP with doxorubicin and cisplatin. Two of the 8 patients were treated with cisplatin with a total lung perfusion after installing a systemic cardiopulmonary bypass (160). One patient, with metastatic chondrosarcoma, underwent I LuP for 60 minutes with a dose of 20 µg/mL cisplatin with moderate hyperthermia whereas the other patient, with diffuse bronchioloalveolar carcinoma, was perfused for 50 minutes with a dose of 14 µg/mL under normothermic conditions. One patient developed pneumonia followed by empyema 4 days later, requiring reintubation, and this patient died 81 days after perfusion (160).

In 1996, Ratto et al. (148) used the combination of I LuP with cisplatin and metastasectomy of lung metastases from soft tissue sarcomas. The major endpoints of this study were feasibility, toxicity and distribution of cisplatin in the normal and tumour tissue. Because they used a fixed dose of cisplatin of 200 mg/m² with a perfusion time of 60 minutes, the DLT could not be determined. Perfusion temperature ranged from 37 to 37.5°C. During this study, no patient died during or after the procedure but 2 patients developed interstitial and alveolar lung oedema after 2 days, requiring prolonged respiratory support for 1 patient. The concentration of cisplatin in the lung exceeded more than 40 times the systemic plasma concentration and no systemic toxicity was noticed. No difference was found in the concentration of cisplatin in the normal and tumour tissue and there was no histological damage of the lung specimens. After the perfusion there was a decline in FEV₁ and carbon monoxide diffusion capacity measured at 10 and 30 days postoperatively but after 1 year there was improvement when reassessed in 2 patients (148).

Schröder et al. (128) published a pilot study in 2002 including 2 patients with unilateral and 2 patients with bilateral sarcoma lung metastases, which were confined to a lobe or entire lung. First a metastasectomy was performed followed by I LuP with cisplatin under hyperthermic (41°C) conditions. The patients included had at least 4 previous surgical metastasectomies, controlled primary site, and no other effective treatment options. Cisplatin was perfused at a fixed dose of 70 mg/m² for 30 minutes. There was a good separation of the perfusion circuit from the systemic circula-

tion with low systemic cisplatin plasma levels and no drug-related systemic toxicity during perfusion. After perfusion, all patients developed non-cardiogenic lung oedema. After a mean follow-up of 12 months, 3 patients were still alive and disease-free while 1 patient died of cerebral metastases after 13 months without any evidence of local recurrence in the lung at autopsy (128).

The above mentioned reports of I LuP with cisplatin differed profoundly. For instance, Johnston's group only included unresectable metastases whereas Ratto and Schröder investigated two different patient groups: resectable lung metastases and patients without any other treatment option left. Ratto used 3 times greater cisplatin concentration compared to Schröder without any additional histological damage (128, 148, 160). These variations make it very hard to draw any conclusions, especially on the reported survival data.

3. Tumour necrosis factor alpha (TNF- α) and γ -interferon

The effect of TNF- α and γ -interferon when used during I LuP was investigated by Pass et al. (163). This is the only clinical study performed until now with TNF- α . In total, 20 patients were included but 5 did not receive any lung perfusion. In the remaining 15 patients, 10 right-sided and 6 left sided perfusions were performed as 1 patient underwent staged bilateral perfusion. Primary tumours were colon adenocarcinoma, renal cell carcinoma, adenoid cystic carcinoma, Ewing's sarcoma and soft-tissue sarcoma. The perfusion was performed under mild hyperthermic conditions for 90 minutes with increasing doses of TNF- and γ -interferon. There were no perioperative deaths and there were no significant changes in cardiac output or systemic blood pressure. During follow-up, 3 patients had a short-term partial response but unfortunately, had progressive disease after 6-9 months (163).

4. Melphalan

Until now only one phase I study was performed regarding I LuP with melphalan for determining the MTD (127). This study included 16 patients that underwent a total of 21 procedures for resectable lung metastases, 11 unilateral and 5 bilateral staged procedures. There were no technical difficulties and no systemic toxicity was encountered. Operative mortality was 0%. The MTD was determined at 45 mg melphalan for a perfusion temperature of 42°C. In an extension trial following this study, which included an additional 7 patients (8 procedures) an increased toxicity was found when perfusing at 42°C, resulting in an adjustment to a safe MTD of 45 mg melphalan at 37°C (164). In the pharma-

cokinetic studies of this trial, a significant correlation was found between the perfused melphalan doses, the perfusate area under the concentration-time curve and the lung tissue melphalan concentration (165). In contrast, no correlation was found between the melphalan dose and the melphalan concentration in the tumour tissue. The peak concentration was 250 times higher and the area under the curve of melphalan was 10 times higher compared to the concentration within the systemic circulation. Recently, the long-term follow-up of this trial was reported (166). After a median follow-up of 62 months, 6 out of 23 patients were alive and free of recurrent disease, while one patient died due to a non-malignant cause. Sixteen patients developed recurrent disease, of whom 11 died. Five of the 16 patients developed recurrent disease in the perfused lung, 3 in the perfused lung only and 2 with locoregional metastases. The overall 5-year survival rate was $54.8 \pm 10.6\%$ with a disease-free median survival time of 19 months (95% confidence interval: 4-34). Since this is a phase I study with different dose levels, the survival data need to be interpreted carefully and cannot be generalised. Long-term lung functional data showed that both lung function and diffusion capacity initially dropped 1 month after perfusion, after which a slight improvement was noted. Long-term radiographic follow-up with chest-CT showed no long-term toxicity from ILuP (166).

Selective pulmonary artery perfusion

As mentioned above SPAP with BFO is an endovascular technique in which a balloon catheter is passed from the femoral vein into the pulmonary artery (Figure 2). Subsequently, a chemotherapeutic agent is injected and a balloon is inflated, allowing the chemotherapeutic agent to slowly diffuse into the lung tissue but no control of the venous effluent is present. Advantages include its percutaneous nature avoiding a thoracotomy which is necessary for ILuP, and its potential for repetitive application.

The reported experimental studies are displayed in Table 4. Several studies investigated this endovascular technique with doxorubicin in a pig model and found the same pharmacokinetic advantages as ILuP but with lower systemic concentrations compared to IV treatment (167, 168). With a tracer study, Demmy et al. proved that 75% of the tracer would remain in the lung after 30 min of indwelling time (169). In a pig study of SPAP, Brown et al. found a 6.9 times higher concentration of cisplatin in the lung tissue compared to IV treatment (170). SPAP with gemcitabine was shown to be effective and resulted in a high initial uptake in the lung parenchyma in a rodent model, with complete saturation of the lung after 20 minutes. Levels obtained were significantly higher than after systemic treatment (171). Further research of SPAP with BFO in a pig model with gemcitabine, carboplatin or the combination of both showed a significantly improved drug uptake in the lung compared to IV treatment, and the mediastinal lymph node concentrations were comparable with IV treatment or even higher for SPAP with carboplatin (172).

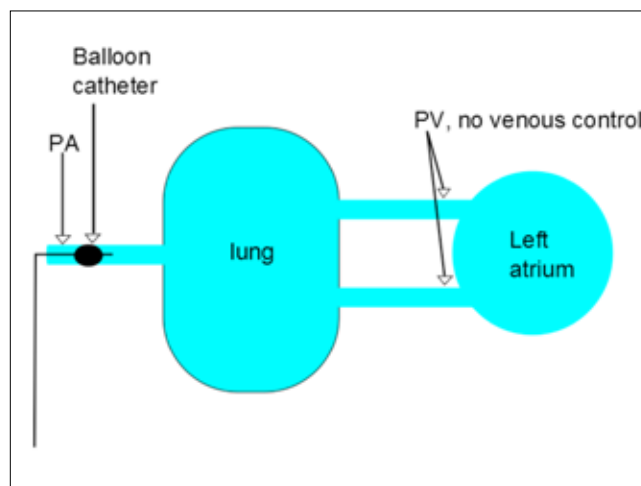


Figure 2. Selective pulmonary artery perfusion
PA: pulmonary artery; PV: Pulmonary vein

Table 4. The experimental studies of selective pulmonary artery perfusion with blood flow occlusion

Author	Drug	Model	Effect comment
Furrer (167)	Doxorubicin	Pig	Similar lung levels as ILuP
Krueger (168)	Doxorubicin	Pig	Similar lung levels as ILuP
Demmy (169)	-	Dog	High tracer uptake in the lung
Brown (170)	Cisplatin	Pig	High lung levels obtained
Van Putte (171)	Gemcitabine	Rat	High uptake in lung tissue
Van Putte (172)	Gemcitabine, carboplatin or both	Pig	High lung levels obtained, comparable to higher concentration in mediastinal lymph nodes compared to IV treatment
Den Hengst (157)	Melphalan	Rat	Equally effective against sarcoma mets as ILuP

ILuP: isolated lung perfusion; IV: intravenous; mets: metastases

SPAP with BFO was shown to be equally effective as ILuP in the treatment of sarcoma lung metastases in a rodent model with melphalan (157). In this study, SPAP resulted in the same levels of melphalan in the lung parenchyma as ILuP, which were significantly higher than following IV treatment. Systemic levels were equal to IV treatment. SPAP with melphalan was equally effective as ILuP in reducing the number of lung nodules as well as prolonging survival (157). So far, no clinical studies have been reported on SPAP with BFO.

Chemo-embolisation (embolic trapping)

Embolic trapping is the use of microspheres loaded with chemotherapy which are blocked in the lung parenchyma and release the chemotherapy locally (Figure 3). The experimental and clinical studies are displayed in Table 5.

Schneider et al. (173) described this technique using starch microspheres with carboplatin in a rat model. This study showed that embolisation was reversible without any early toxicity. Baylatry et al. (174) showed in a sheep model that drug eluting beads loaded with irinotecan resulted in lower systemic exposure compared to direct injection of irinotecan into the pulmonary artery. In a rat model of adenocarcinoma lung metastases, chemo-embolisation was compared with ILuP and IV treatment with carboplatin (175). Chemo-embolisation and ILuP resulted in significantly higher lung parenchymal concentrations compared to IV treatment. However, the tumour concentration of carboplatin was significantly higher for the chemo-embolisation group compared to the ILuP group (175). This same group also investigated the use of carboplatin-loaded starch microspheres in a pig model to evaluate safety before utilizing it in clinical studies. There were only mild hemodynamic acute effects and no long-term toxicity was found 6 months after treatment, rendering this technique feasible in humans (176). Vogl et al. (177)

used chemo-embolisation with palliative intention in 52 patients with unresectable lung metastases from 2001-2005. The tumour-feeding pulmonary arteries were selectively injected with lipiodol, mitomycin C and Spherex microspheres under the guidance of a pulmonary artery balloon catheter. Patients received repetitive treatment ranging from 2 to 10 sessions. Treatment was well tolerated without any major side effects or complications. Partial response was found in 16 cases, stable disease in 11 and progressive in 25 cases (177). No follow-up studies have as yet been reported regarding this technique.

Other locoregional techniques

Lung suffusion is a technique combining SPAP with BFO and video-assisted thoracic surgery (VATS). In this technique, a balloon catheter is introduced in the femoral vein and brought up into the pulmonary artery (Figure 4). After installing single-lung ventilation a VATS procedure is used for isolation of the pulmonary veins. The balloon catheter is inflated and the pulmonary veins are snared, which isolates the

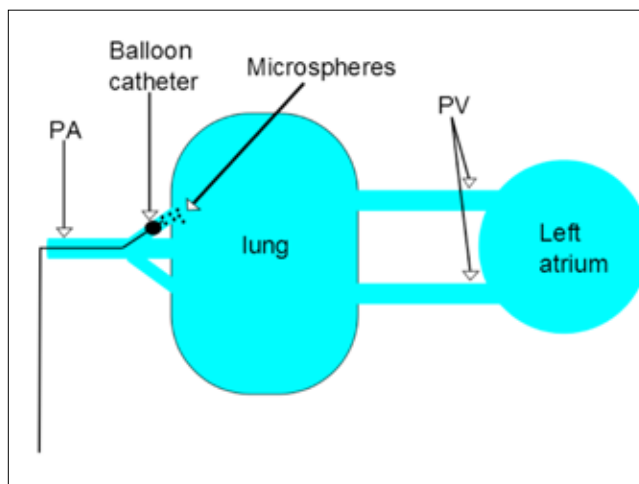


Figure 3. Chemo-embolisation
PA: pulmonary artery; PV: Pulmonary vein

Auhor	Drug	Model	Effect comment
Schneider (173)	Carboplatin + microspheres	Rat	Equally effective as ILuP
Baylatry (174)	Irinotecan + drug eluting beads	Sheep	Lower systemic exposure
Pohlen (175)	Carboplatin + microspheres	Rat	Equal lung parenchyma concentrations as ILuP; Higher tumour concentration as ILuP
Pohlen (176)	Carboplatin + microspheres	Pig	Safe pharmacokinetic profile
Vogl (177)	Lipiodol, mitomycin C and Spherex microspheres	Human, unresectable lung metastases	2-10 treatments/patient; 52 patients; 16 partial response; 11 stable disease; well tolerated

ILuP: isolated lung perfusion

lung from the systemic circulation except for inflow from the bronchial arteries. Blood from the pulmonary artery is withdrawn to create volume for injection of the chemotherapeutic agent. The lung is inflated and the drug is injected. After 30 minutes of indwelling time under pulmonary artery guidance, the snares are released and the balloon is deflated. The group of Demmy et al. (178) reported a clinical trial in 2009 with 4 patients with stage IV non-small cell lung cancer receiving suffusion treatment with cisplatin followed by systemic chemotherapy. There was a reported reduction of 14-96% of the tumour volume, with no pulmonary toxicity and a mild reduction of overall diffusion capacity (178). No further studies were reported by this group.

In 2005 Jinbo et al. (179) described a hybrid technique in a canine model with an endovascular part similar to SPAP and lung suffusion, but with a VATS guided introduction of a pulmonary vein catheter through the left auricular appendage (Figure 5). A closed circuit could be achieved with minimal systemic leakage, resulting in the same pharmacokinetic profile as ILuP. No clinical data have been reported so far.

Future developments and conclusion

With the extensive research carried out around ILuP, this technique has proven to be safe, well tolerated and reproducible. ILuP results in a significantly higher drug level in the pulmonary metastases without systemic exposure, preventing systemic toxicity. All this offers a valid clinical model for further investigation of a combined treatment of surgery and chemotherapy for patients with lung metastases. Until now, only phase I studies have been published on ILuP performed in a heterogeneous group of patients, defining the MTD of the drugs studied. However, to further determine the effect of ILuP on local recurrence, long-term toxicity, lung function and survival, phase II and III trials are needed. A phase II study is currently running at our institution in collaboration with 3 centres in the Netherlands (Leiden, Nieuwegein, Rotterdam) investigating ILuP with 45 mg melphalan at 37°C for the treatment of patients with resectable lung metastases from colorectal adenocarcinoma, soft tissue sarcoma and osteosarcoma. The aim of this trial is to include 100 patients and to study progression-free survival and overall survival as well as lung function and pharmacokinetic data.

With the results obtained from ILuP studies, more and more investigators are trying to find an alternative and less invasive technique. SPAP with BFO and chemo-embolisation are techniques that require only a percutaneously inserted pulmonary catheter, mak-

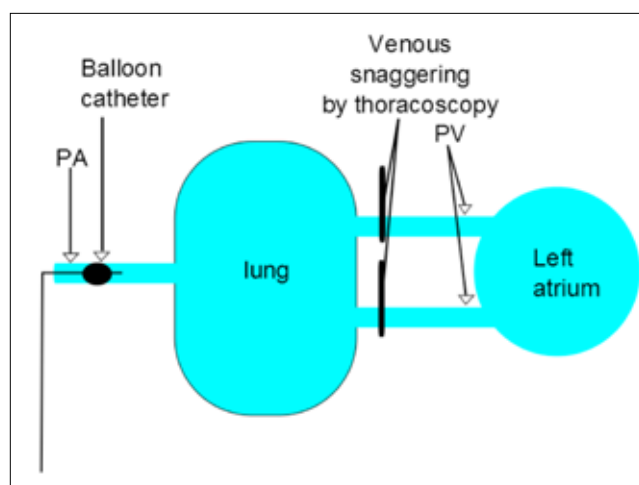


Figure 4. Lung suffusion

PA: pulmonary artery; PV: Pulmonary vein

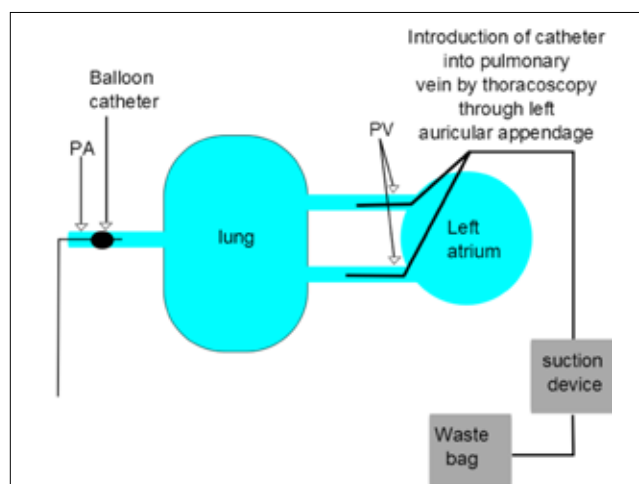


Figure 5. Hybrid technique

PA: pulmonary artery; PV: Pulmonary vein

ing repeated application possible. These less invasive techniques can be used for induction or adjuvant treatment, not only for lung metastases but also for primary bronchogenic carcinoma.

Hopefully, these new technical developments in locoregional high-dose chemotherapy together with surgical resection will result in a better outcome for our patients with lung metastases.

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