Phase II Multicenter Clinical Trial of Pulmonary Metastasectomy and Isolated Lung Perfusion with Melphalan in Patients with Resectable Lung Metastases

Willem A. den Hengst, MD, Jeroen M.H. Hendriks, MD, PhD,* Bram Balduyck, MD, PhD,* Inez Rodrigus, MD, PhD,† Jan B. Vermorken, MD, PhD,‡ Filip Lardon, PhD,§ Michel I.M. Versteegh, MD,‖ Jerry Braun, MD,‖ Hans Gelderblom, MD, PhD,¶ Franz M.N.H. Schramel, MD, PhD,# Wim-Jan Van Boven, MD,** Bart P. Van Putte, MD, PhD,†† Özcan Birim, MD, PhD,‡‡ Alexander P.W.M. Maat, MD,‡‡ and Paul E.Y. Van Schil, MD, PhD**

Introduction: The 5-year overall survival rate of patients undergoing complete surgical resection of pulmonary metastases (PM) from colorectal cancer (CRC) and sarcoma remains low (20–50%). Local recurrence rate is high (48–66%). Isolated lung perfusion (ILuP) allows the delivery of high-dose locoregional chemotherapy with minimal systemic leakage to improve local control.

Methods: From 2006 to 2011, 50 patients, 28 male, median age 57 years (15–76), with PM from CRC ($n = 30$) or sarcoma ($n = 20$) were included in a phase II clinical trial conducted in four cardiothoracic surgical centers. In total, 62 ILuP procedures were performed, 12 bilaterally, with 45 mg of melphalan at 37°C, followed by resection of all palpable PM. Survival was calculated according to the Kaplan–Meier method.

Results: Operative mortality was 0%, and 90-day morbidity was mainly respiratory (grade 3: 42%, grade 4: 2%). After a median follow-up of 24 months (3–63 mo), 18 patients died, two without recurrence. Thirty patients had recurrent disease. Median time to local pulmonary progression was not reached. The 3-year overall survival and disease-free survival were 57% ± 9% and 36% ± 8%, respectively. Lung function data showed a decrease in forced expiratory volume in 1 second and diffusing capacity of the alveolocapillary membrane of 21.6% and 25.8% after 1 month, and 10.4% and 11.3% after 12 months, compared with preoperative values.

Conclusion: Compared with historical series of PM resection without ILuP, favorable results are obtained in terms of local control without long-term adverse effects. These data support the further investigation of ILuP as additional treatment in patients with resectable PM from CRC or sarcoma.

Key Words: Isolated lung perfusion, Local control, Lung metastases, Survival, Combined modality treatment.

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The 5-year overall survival (OS) of patients with pulmonary metastases (PM) from colorectal carcinoma (CRC) and sarcoma remained almost the same over the last 20 years, despite improvement in systemic chemotherapy and a better preoperative selection. This ranges for CRC between 39% and 68%[1–9] and for sarcoma between 22% and 50%.[1,9–14]

One of the reasons for this rather poor survival rate is the high rate of local recurrence in the operated lung, despite complete resection, which ranges between 43% and 66% as reported in a large retrospective study[1] and also in our own institution.[15] Recurrence is a significant problem because a number of patients will not tolerate a second operation, whereas those who can will have a further decline of their lung function parameters.[16,17] Systemic chemotherapy for PM is limited by its systemic side effects and does not result in permanent control or cure of these lesions.

Isolated lung perfusion (ILuP) is a surgical technique currently evaluated as an adjuvant treatment during thoracotomy to reduce the incidence of local pulmonary recurrence. With this technique, the lung is completely isolated from the systemic circulation by cannulating the pulmonary artery and veins. The lung is subsequently perfused with high-dose chemotherapy, with minimal systemic leakage.[18] It allows the chemotherapeutic agent to reach a much higher tissue concentration compared with systemic treatment,[19,20] exploiting the steep dose–response curve. This technique proved to be safe and reproducible.[18,21]

*Department of Thoracic and Vascular Surgery, Antwerp University Hospital, Edegem, Belgium; †Department of Cardiac Surgery, Antwerp University Hospital, Edegem, Belgium; ‡Department of Medical Oncology, Antwerp University Hospital, Edegem, Belgium; §Center for Oncological Research, University of Antwerp, Wilrijk, Belgium; ‖Department of Thoracic Surgery, Leiden University Medical Center, Leiden, the Netherlands; ¶Department of Clinical Oncology, Leiden University Medical Center, Leiden, the Netherlands; #Department of Pulmonary Medicine, St. Antonius Hospital, Nieuwegein, the Netherlands; **Department of Thoracic Surgery, Amsterdam Medical Center, Amsterdam, the Netherlands; ††Department of Thoracic Surgery, St. Antonius Hospital, Nieuwegein, the Netherlands; and ‡‡Department of Thoracic Surgery, Erasmus Medical Center, Rotterdam, the Netherlands.

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Address for correspondence: Paul E.Y. Van Schil, MD, PhD, Department of Thoracic and Vascular Surgery, Antwerp University Hospital, Wilrijkstraat 10, B-2650 Edegem, Antwerp, Belgium. E-mail: paul.van.schil@uza.be

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Melphalan is an alkylating agent. It has been used for decades in the treatment of melanoma with isolated limb perfusion.[22–24] However, it is also used in isolated limb perfusion for soft-tissue sarcoma,[25] in isolated liver perfusion for metastases of colorectal cancer,[26] and for hyperthermic intraperitoneal chemotherapy in the treatment of peritoneal carcinomatosis.[27] This makes melphalan one of the most extensively investigated chemotherapeutic agents for isolated organ perfusion, with a very well-known pharmacodynamic and pharmacokinetic profile. Because of its extensive use in isolated organ perfusion and because ILuP with melphalan yielded in an animal setting the highest efficacy for both PM of carcinoma[28] and sarcoma,[20] a clinical phase I trial was started in 2001.[21,29] In this clinical phase I trial, patients with resectable PM from a variety of cancers were treated with ILuP with melphalan followed by complete lung metastasectomy.[21,29] Patients were perfused with an increasing dose of melphalan under normothermic (37°C) or hyperthermic (42°C) conditions.[21,29] In this phase I clinical trial, followed by an extension trial, the maximum tolerated dose was set at 45 mg melphalan at a temperature of 37°C.[21,29] Recently, the long-term follow-up of this phase I trial has been reported showing no long-term pulmonary toxicity and a 5-year OS of 54.8%.[30]

Because of the results of this phase I clinical trial and the suggested feasibility of ILuP with melphalan for the improvement of local control in patients with resectable PM, a phase II clinical trial was started. This study presents the results of this multicenter phase II study of ILuP with 45 mg melphalan at 37°C for patients with resectable PM from CRC and sarcoma.

PATIENTS AND METHODS

From September 2006 until May 2011, a phase II clinical trial of ILuP with melphalan was conducted in four cardiothoracic centers in the Netherlands and Belgium: St. Antonius Hospital, Nieuwegein; Leiden University Medical Center, Leiden; Erasmus MC, Rotterdam, the Netherlands; and Antwerp University Hospital, Edegem, Belgium.

Study Protocol

The study protocol was approved by all four ethical committees of the different participating centers. Primary end-point of the study was time to progression (TTP) locally advance or metastatic. Secondary end-points were OS and pulmonary toxicity. For the inclusion and exclusion criteria, see Table 1.

Patients

A total of 50 patients with PM of osteosarcoma, soft-tissue sarcoma, or CRC were included in this study. A written informed consent was obtained from all patients.

Technique

The technique was the same as applied in our phase I clinical trial with melphalan and was reported in detail.[21] In short, patients underwent a thoracotomy. The PM were identified by bimanual palpation of the lung, and if no histological proof was present, a frozen section was performed to confirm the presence of metastatic disease. Possible other lesions were marked. Heparin was given to reach an activated clotting time of 200 seconds. The lung was isolated by cannulating the pulmonary artery and the two pulmonary veins with central clamping and snaring of the main bronchus to block the bronchial arterial circulation. This resulted in a closed circuit. Perfusion was performed with a centrifugal pump with the mean pulmonary artery pressure before clamping as maximum accepted pressure. Perfusion was performed at 37°C with 45 mg melphalan fixed dose for 30 minutes followed by a 5-minute washout. Afterward, the PM were resected followed by a systematic lymph node dissection. If bilateral disease was present, a staged bilateral thoracotomy took place within a period of 4–6 weeks. None of the patients received adjuvant systemic chemotherapy after the ILuP procedure.

TABLE 1. Inclusion and Exclusion Criteria

	Inclusion Criteria	Exclusion Criteria
1	Histologic, cytologic, or strong radiographic evidence of lung metastases from colorectal carcinoma, osteosarcoma, or soft-tissue sarcoma	Uncontrollable infectious disease
2	All metastatic diseases assessed by radiologic examination were resectable	Severe comorbidity
3	All metastatic diseases were confined to the lungs	Previous thoracotomy or pleuropulmonary diseases resulting in obliteration of the pleural space
4	Primary site has been radically treated and has no signs of recurrence	Pregnancy or lactation
5	Patients had adequate cardiac and pulmonary reserve to undergo a thoracotomy and metastasectomy	
6	No comorbid conditions are present that prevent an operation	
7	No more than 10 metastases are present in one lung	
8	No standard treatment options available, besides pulmonary metastasectomy	
9	Performance status ECOG 0–1	
10	Normal renal and liver function	
11	Adequate bone marrow reserve; absolute neutrophil count more than $2 \times 10E^9$/L and a platelet count of more than $150 \times 10E^9$/L	

ECOG, Eastern Cooperative Oncology Group.

Follow-Up

Postoperatively, the patients were evaluated by using the Cancer Therapy Evaluation Program, Common Terminology Criteria for Adverse Events (Version 3.0, DCTD, NCI, NIH, DHHS March 31, 2003[http://ctep.cancer.gov]). The first-year follow-up was done by the thoracic surgeon and referring physician at 1, 3, 6, 9, and 12 months. After 1 year, follow-up was left to the discretion of the referring physician.

Disease recurrence was evaluated by chest computed tomography (CT) at 3, 6, 9, and 12 months after the operation and thereafter according to local practice. Lung function was assessed by forced expiratory volume in 1 second, total lung capacity, diffusing capacity of the alveolocapillary membrane (DLCO), and vital capacity. These pulmonary function tests were determined at 0, 1, 3, 6, and 12 months to evaluate pulmonary toxicity. Follow-up time, OS, disease-free survival (DFS), and TTP were recorded. In this study, follow-up was determined by last contact with home physician or referring physician at the end of 2012, when a median follow-up of at least 2 years was achieved.

To evaluate local pulmonary control, local pulmonary progression-free survival (PPFS) and the time to local pulmonary progression (TTLPP) in the perfused lung were also recorded. TTLPP was the time period starting the day of the perfusion till the development of local pulmonary recurrence calculated for each perfused lung, and is purely a measure of local control and does not take into account extrapulmonary recurrences. For PPFS, local pulmonary recurrence was taken as event for each perfused lung.

Statistical Analysis

Mann–Whitney *U* test was used to evaluate differences between the CRC and sarcoma groups for patient characteristics age. Kaplan–Meier method was used to calculate OS, overall median survival time (MST), DFS, TTP, PPFS, and TTLPP. The log-rank test was used to determine the effect of number of metastases, length of disease-free interval (DFI = time between primary tumor and the diagnosis of metastases), and histology on OS and DFS, with p less than or equal to 0.05 for significance. Multivariate analysis was performed with Cox regression analysis. All survival data were reported with standard error or 95% confidence interval (CI).

RESULTS

Patient Characteristics

Patient characteristics are listed in Table 2. A total of 62 ILuPs, 12 bilaterally, were performed in 50 patients. Thirty had PM from CRC, of which n = 15 had rectal carcinoma as primary tumor. Twenty patients had sarcoma as primary tumor. Seven of these patients had osteosarcoma as primary tumor, of which one was a high-grade Paget's sarcoma. The other 13 sarcoma were as follows: n = 2 chondrosarcoma, n = 4 not otherwise specified sarcoma, n = 3 fibrosarcoma, n = 2 synovial sarcoma, and n = 2 leiomyosarcoma. All perfusions could be performed without technical difficulties, except for one were the centrifugal pump temporarily stopped due to low volume in the circuit, which was subsequently corrected.

TABLE 2. Characteristics of Patients Undergoing Isolated Lung Perfusion

	Overall	CRC	Sarcoma
Sex			
Male	28	17	11
Female	22	13	9
Age[a]	53 yr (18–76 yr)	59 yr (39–75 yr)	43 yr (18–76 y)
DFI			
≤36 mo	35	21	14
>36 mo	15	9	6
Preoperative chemotherapy or radiotherapy			
CT	16	14	2
RT	2	0	2
CT + RT	4	4	0
Other metastases treated			
Liver	12	12	0
Abdominal wall	2	2	0
Adnexal	1	1	0
Location of metastases			
Unilateral	30	18	12
Bilateral	20	12	8
Perfusion			
Unilateral	38	23	15
Bilateral	12	7	5
No. of metastases			
≤2	32	22	10
>2	18	8	10

[a]Mean age.
CRC, colorectal cancer; DFI, disease-free interval; CT, chemotherapy; RT, radiotherapy.

Fifteen patients (all CRC) were treated for other metastases before they underwent their treatment for PM with ILuP and metastasectomy; no sarcoma patients were treated for metastases on other locations.

A significant difference was found between the age of osteosarcoma patients and the age in the other groups, in which the osteosarcoma were younger ($p < 0.01$ for all groups).

The number of resected PM in one lung ranged from 1 to 10 with an overall mean of 2.7 and an overall median of 2. For CRC, it ranged from 1 to 8 with a mean of 2.1 (95% CI, 1.5–2.8) and a median of 1. For sarcoma, it ranged from 1 to 10 with a mean of 3.6 (95% CI, 2.2–5.0) and a median of 3. No statistical significant difference was found in the number of PM in one lung between CRC and sarcoma (p = 0.09).

The preoperative workup with conventional or helical chest CT scan of the 62 perfusions identified n = 28 with one PM, n = 14 with two PM, and n = 20 with more than two PM in one lung. On postoperative pathology report, six of the 28 with one PM, two of the 14 with two PM, and five of the 20 with more than two PM in one lung had more PM resected than preoperative identified by the radiographic investigations. So, in 21.0% of the interventions, more metastatic nodules were detected than suspected preoperatively.

In total, 20 patients had bilateral PM. Eight of these 20 patients underwent only a perfusion on one side (five

CRC, two synovial sarcoma, and one fibrosarcoma). Five of those eight patients underwent a regular thoracotomy with metastasectomy on the other side, whereas three did not because of development of progressive, unresectable disease after first ILuP (one CRC, one fibrosarcoma, and one synovial sarcoma).

After resection of multiple PM in one of the patients, one lesion considered to be a metastasis proved to be a T1 primary lung adenocarcinoma, which was completely resected. One patient was lost to follow-up 7 months after perfusion.

Mortality and Survival

Operative mortality was 0%. After a median follow-up of 24 months (3–63 mo), 18 patients died, two without radiographic evidence of recurrence. Cause of death was progressive disease in 16 patients, whereas the cause of death in the two patients that died without recurrence was unknown. The 3-year OS for all patients was 57% ± 9% (Fig. 1). The MST for all patients in this study was 44 months (95% CI, 30–58). The separate survival data for CRC and sarcoma are shown in Table 3.

Recurrent Disease and Disease-Free Survival

Thirty patients (60%) had recurrent disease. Most patients developed their initial progressive disease outside the perfused lung (23 patients; 77%), whereas only 23% had their initial recurrence in the perfused lung. Location of the first recurrence is depicted in Table 4. The 3-year DFS for all patients was 36% ± 8%. The median TTP for all patients was 16 months (95% CI, 7–25). During follow-up, a total of 11 patients developed recurrent disease inside the perfused lung of which one patient in both perfused lungs. The 3-year PPFS for all patients was 79% ± 6%, and median TTLPP was not reached. The separate DFS and TTLPP data for CRC and sarcoma are lined in Table 3.

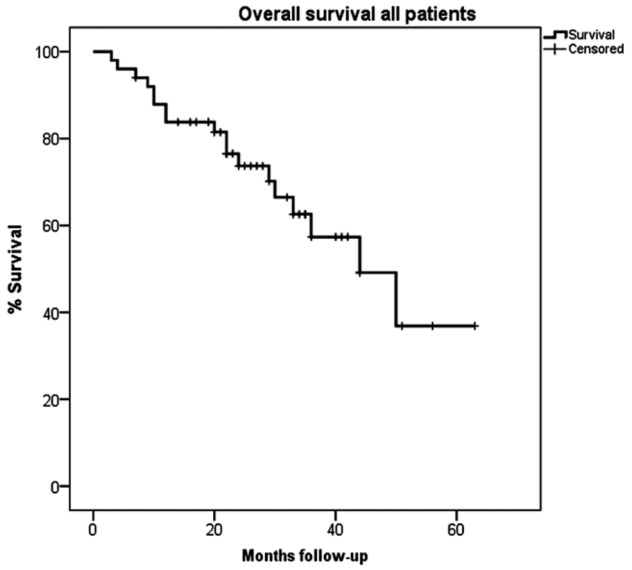

FIGURE 1. Kaplan–Meier overall survival curve for all patients.

Morbidity

In total, 19 patients, five bilateral perfusions, experienced a grade 3 ($n = 24$) or grade 4 toxicity ($n = 1$) during the first 90 postoperative days. This 90-day morbidity consisted of cardiac grade 3 ($n = 1$, 2%), respiratory grade 3 ($n = 21$, 42%) and grade 4 ($n = 1$, 2%), gastrointestinal grade 3 ($n = 1$, 2%), and bleeding grade 3 ($n = 1$, 2%).

Lung Function

Lung function data showed a decrease in vital capacity, total lung capacity, forced expiratory volume in 1 second, and diffusing capacity of the alveolocapillary membrane of 22.3%, 18.8%, 21.6%, and 25.8% after 1 month, and 7.9%, 11.1%, 10.4%, and 11.3% after 12 months, respectively, compared with preoperative values (Fig. 2).

Univariate Survival Analysis

Overall survival.

There was a significant better OS for patients with CRC metastases compared with sarcoma ($p < 0.01$). Gender did not influence OS ($p = 0.43$). No difference was found for patients with a DFI of more than 36 months compared with patients with a DFI less than or equal to 36 months ($p = 0.43$). Patients with less than or equal to two PM had a significant better OS ($p = 0.02$) compared with patients with more than two PM. No significant difference was found between patients with unilateral or bilateral PM ($p = 0.06$). The history of treated liver, abdominal wall, or adnexa metastases in patients with CRC PM did not influence OS after ILuP.

Disease-free survival.

The DFS was not different between patients with CRC metastases and sarcoma ($p = 0.15$). Female patients did it better compared with males ($p = 0.02$). A DFI of more than 36 months resulted in a better DFS compared with a DFI less than or equal to 36 months ($p = 0.01$). Patients with less than or equal to two PM had a significant better DFS compared with more than two PM ($p < 0.01$). No significant difference was found between patients with unilateral or bilateral PM ($p = 0.06$). The history of treated liver, abdominal wall, or adnexa metastases in patients with CRC lung metastases did not influence DFS after ILuP.

Multivariate Survival Analysis

Multivariate analysis was performed for OS and DFS with the following variables: gender, age, tumor type, DFI, and number of metastases in one lung.

Regarding OS, patients with sarcoma PM had a significant lower survival compared with CRC ($p < 0.01$) with a hazard ratio of 5.20 (95% CI, 1.69–15.95). Patients with more than 2 PM in one lung had a significant lower chance of survival in comparison to less than or equal to two PM in one lung ($p = 0.02$) with a hazard ratio of 4.85 (95% CI, 1.23–19.12). No other variables were found to be significant.

Regarding DFS, males had a lower DFS in comparison to females ($p = 0.03$) with a hazard ratio of 2.70 (95% CI, 1.08–6.77). Patients with more than two PM in one lung had a significant lower DFS in comparison to less than or equal to

TABLE 3. Survival Data According to Pathological Diagnosis

	3-Year OS	MST[a] (95% CI)	3-Year DFS	Median TTP[a] (95% CI)	3-Year PPFS	Median TTLPP[a] (95% CI)
All patients	57% ± 9%	44 (30–58)	36% ± 8%	16 (7–25)	79% ± 6%	NR
CRC	62% ± 13%	NR	41% ± 11%	21 (2–40)	72% ± 8%	NR
Sarcoma	48% ± 12%	30 (8–51)	27% ± 10%	8 (6–10)	90% ± 7%	44 (11–77)

[a]Months.

OS, overall survival; MST, median survival time; CI, confidence interval; DFS, disease-free survival; TTP, time to progression; PPFS, pulmonary progression-free survival; TTLPP, time to local pulmonary progression; CRC, colorectal cancer; NR, not reached.

TABLE 4. Location of First Recurrence

Location of Recurrence	Perfused Lung	Contralateral Lung	Liver	Brain	Primary Site	Multiple Sites	Other
No. of patients	7	10				3	4
% of total patients	14%	20%	6%	4%	2%	6%	8%
% of total recurrence	23%	33%	10%	7%	3%	10%	13%

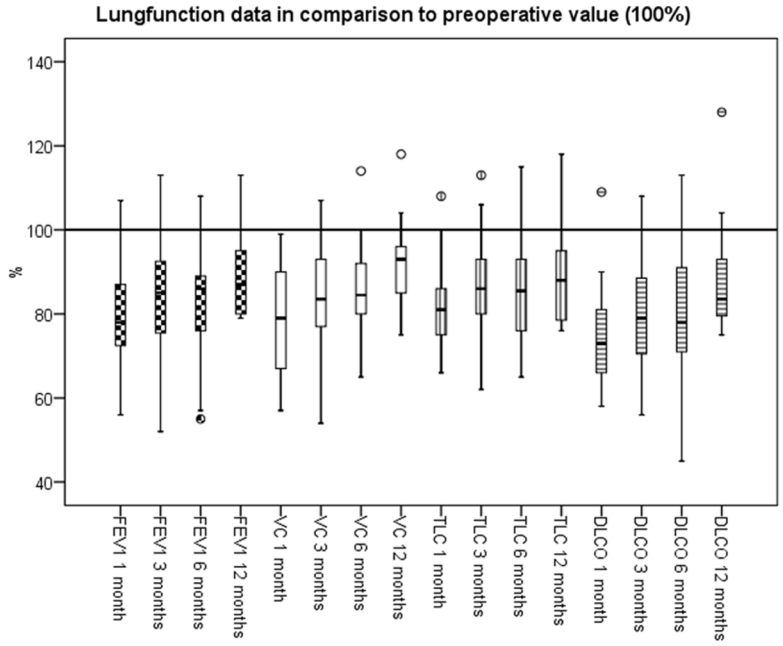

FIGURE 2. Postoperative lung function compared with the preoperative value (100%). VC, vital capacity; FEV1, forced expiratory volume in 1 second; DLCO, diffusing capacity of the alveolocapillary membrane; TLC, total lung capacity.

two PM in one lung ($p < 0.01$) with a hazard ratio of 3.64 (95% CI, 1.40–9.42). No other variables were significant.

DISCUSSION

This article reports the results of the first prospective multicenter phase II clinical trial treating patients with resectable PM from CRC and sarcoma with a lung metastasectomy combined with ILuP. This trial was organized because the phase I trial showed that the combination of a resection of PM through thoracotomy and ILuP was safe and feasible up to a dose of melphalan of 45 mg at a temperature of 37°C in all participating centers.[21,29]

One of the goals of this trial was the confirmation of the safety of this technique at the chosen dose of melphalan of 45 mg perfused at a temperature of 37°C and to evaluate local pulmonary control and DFS after thoracotomy with pulmonary metastasectomy combined with ILuP.

The 90-day morbidity in this study only showed well-known postoperative complications, which are also not uncommon after a routine thoracotomy with metastasectomy without ILuP, whereas we did not encounter any procedural mortality or excess morbidity compared with historical controls.[2,3,31,32] Therefore, the combination of a thoracotomy with ILuP suggests no increased risk in 90-day morbidity as compared with a metastasectomy without ILuP. In addition, two other parameters showed no additional negative effect of adding ILuP to a thoracotomy. First, the decrease in lung function stabilized in time and even slightly improved showing no long-term pulmonary toxicity of the ILuP procedure. These data are in line with the lung function data found in the initial phase I study.[30] Second, no difference in quality of life was found between

a standard thoracotomy with metastasectomy compared with thoracotomy with metastasectomy and ILuP.[33] These results confirm that the combination of ILuP with metastasectomy is a safe procedure.

This trial strongly suggests an additional positive effect of an ILuP procedure compared with a thoracotomy-only strategy because of the low percentage (only 23%) of local pulmonary recurrent disease. Numbers known from the current international literature are higher, 43% for CRC and 66% for sarcoma,[1] but this is also true for our own historical series, 50% and 56%, respectively.[15] There are only few studies that report PPFS or TTLPP with a PPFS of 3 years of 49%[8] and a TTLPP of 19.4 months,[2] both for CRC. In our study, the 3-year PPFS was 72% ± 8%, and the median TTLPP was not reached for CRC.

This is the first time that such a substantial improvement in local pulmonary control is demonstrated in an ILuP trial but has to be confirmed in subsequent trials, preferentially a randomized trial between thoracotomy only and thoracotomy with ILuP.

In the literature, the median TTP ranged from 13 to 26 months,[4,5,34] MST from 31 to 72 months,[4,5,34] 3-year OS from 56% to 78%,[5,35–37] and 3-year DFS from 28% to 44%[4,36] for CRC. For sarcoma, the median TTP ranged from 7 to 20 months,[12,38,39] MST from 19 to 64 months,[12–14,38–41] 3-year OS from 31% to 71%,[12–14,39,40,42,43] and 3-year DFS from 17% to 26%.[39,42] These results are comparable to our results. Despite the fact that the local pulmonary control was improved, the median TTP and DFS in our study were comparable but not better than the best reported in the literature. This emphasizes that there is also a need for improved systemic control as metastatic disease is not only a regional but also a systemic disease.

In this trial, the history of previous metastatic disease in the liver or intra-abdominal metastases from a CRC did not influence both OS and DFS after ILuP. This is confirmed in other studies.[44–46]

Although there was an extensive preoperative radiographic workup with conventional or high-resolution chest CT scan for every patient, the number of PM was underestimated in 21% ($n = 13$) of the procedures. This is supported by other reports, showing that even in 26% to 36% of the cases, the number of preoperative identified PM on conventional or high-resolution chest CT scan was lower than the number of PM found during the operation and found on pathological investigation.[47,48] These data, together with our results, suggests the need of manual palpation of the lung during lung metastasectomy to identify all PM.

Given the zero mortality, the low morbidity, and suggested improved local pulmonary control, an extension trial is now running to include another 50 patients for further confirmation of these positive findings. For this extension trial, four centers are participating in Belgium and the Netherlands. After completion, other chemotherapeutic drugs will be evaluated in the setting of ILuP to determine their efficacy compared with melphalan in patients with metastases from CRC and sarcoma tumors.

Because ILuP can only be performed once in every lung, other less invasive techniques are under investigation. The aim of these techniques is to be able to give multiple sessions of chemotherapy very selective to the lung to further enhance local pulmonary control. One of these techniques is selective pulmonary artery perfusion (SPAP).[49] With this technique, a balloon catheter is introduced into the femoral vein and brought up into the pulmonary artery, and a chemotherapeutic agent can be injected. To enhance the uptake, a balloon is insufflated (blood flow occlusion) which allows the chemotherapeutic agent to diffuse into the lung.[50] SPAP with melphalan is compared with ILuP with melphalan in a rodent model, showing similar results in lung tissue levels of melphalan and local control and OS.[20] Until now, no clinical studies using SPAP with blood flow occlusion are reported.

This study also has some limitations. There was not always control of the preoperative treatment patients received and the waiting period between the development of PM and the metastasectomy. Twenty patients received a wide variety of different chemotherapeutic treatments before they were included in our study. This was due to the fact that some patients were referred from peripheral centers. These different treatments could have had a negative impact on lung function, diffusion capacity, and physical status preoperatively.

CONCLUSION

In conclusion, this is the first report of a phase II clinical trial of ILuP used in combination with metastasectomy for patients with resectable PM from CRC and sarcoma. The results show an improved local pulmonary control without mortality and with the same morbidity as compared with previous literature on metastasectomy without ILuP. This is another incentive for the use of ILuP with metastasectomy in the treatment of patients with resectable PM. However, this needs to be confirmed in randomized trial comparing routine thoracotomy and metastasectomy with or without ILuP.

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