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INTERVENTIONAL

Transvenous pulmonary chemoembolization (TPCE) for palliative or neoadjuvant treatment of lung metastases

Thomas J. Vogl[1] · Ahmed I. A. Mekkawy[1,2] · Duaa B. Thabet[3] · Mostafa El-Sharkaway[2] · Hosam M. Kamel[2] · Moritz H. Albrecht[1] · Nagy N. N. Naguib[1,4] · Afaf Hassan[5]

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Abstract

Purpose To retrospectively evaluate tumor response, local tumor control, and patient survival after the treatment of pulmonary metastases using transpulmonary chemoembolization (TPCE) in palliative and neoadjuvant intent.

Materials and methods One hundred forty-three patients (mean age 56.7 ± 13.4 years) underwent repetitive TPCE (mean number of sessions 5.8 ± 2.9) between June 2005 and April 2017 for the treatment of unresectable lung metastases, not responding to systemic chemotherapy. Patients had predominant lung metastases with bilateral lung involvement in 80.4% of the cases. Regional delivery of the chemotherapeutic agents was performed through selective catheterization of the tumor-supplying pulmonary arteries with subsequent injection of iodized oil and microspheres. Patients, who underwent subsequent ablation ($n = 51$), either for all lesions (complete) or dominant lesions (incomplete), constituted the neoadjuvant group, and those who underwent TPCE alone represented the palliative treatment intent ($n = 92$). The response was assessed according to the revised Response Evaluation Criteria in Solid Tumors (RECIST).

Results Partial response was achieved in 11.9% ($n = 17$), stable disease in 66.4% ($n = 95$), and progressive disease in 21.7% ($n = 31$). The mean survival time and time to progression were 24.5 ± 1.7 and 7.5 ± 0.5 months, respectively. The mean survival time was shorter for the palliative group (19.7 ± 2), compared to the neoadjuvant group (30.1 ± 2.6 months). The use of TPCE alone or with incomplete ablation had a significantly increased hazard of death of 4.6- ($p = 0.002$) and 3.1-fold ($p = 0.027$), respectively, in comparison with TPCE with subsequent complete ablation.

Conclusion TPCE has the potential to improve local tumor control and to prolong survival with a neoadjuvant potential when combined with ablation therapy.

Key Points

- *Transpulmonary chemoembolization (TPCE) is a locoregional technique for delivering chemotherapy in higher intratumoral concentrations and with reduced systemic toxicity.*
- *TPCE can be an alternative treatment for patients with pulmonary metastases who failed prior systemic chemotherapy or with post-operative recurrence.*
- *The current retrospective study revealed that TPCE is a feasible treatment option for patients with unrespectable lung secondaries in both palliative and neoadjuvant intent and has the potential of improving local control and prolonging survival.*

Keywords Therapeutic chemoembolization · Lung neoplasms · Interventional radiology · Palliative care · Neoadjuvant therapy

Thomas J. Vogl and Ahmed Imam Abdelghany Mekkawy contributed equally to this work.

✉ Ahmed I. A. Mekkawy
time_dr@yahoo.com

[1] Institute of Diagnostic and Interventional Radiology, University Hospital Frankfurt, Johann Wolfgang Goethe University Frankfurt, Theodor-Stern-Kai 7, 60590 Frankfurt am Main, Germany

[2] Department of Diagnostic Radiology, South Egypt Cancer Institute, Assiut University, Asyut, Egypt

[3] Department of Chest Disease, Faculty of Medicine, Assiut University, Asyut, Egypt

[4] Department of Diagnostic and Interventional Radiology, Alexandria University, Alexandria, Egypt

[5] Department of Diagnostic Radiology, Faculty of Medicine, Assiut University, Asyut, Egypt

Abbreviations

Angio-CT	Computed tomography angiography
CT	Computed tomography
HR	Hazard ratio
ILP	Isolated lung perfusion
MDCT	Multidetector computed tomography
MRI	Magnetic resonance imaging
PD	Progressive disease
PR	Partial response
RECIST	Response Evaluation Criteria in Solid Tumors
SD	Stable disease
TPCE	Transpulmonary chemoembolization
TTP	Mean time to progression

Introduction

The lungs are the second most common site for metastatic involvement with an estimated cumulative incidence of 20–54% from extrathoracic malignancies [1] of which about 20% have isolated lung involvement [2]. Although surgical resection of lung metastases is still considered the best treatment option for patients with limited pulmonary metastases, only a minority of patients are indicated for it [3–5].

Systemic chemotherapy is an established treatment option with multiple therapeutic regimens tested as an alternative to tumor excision or as a neoadjuvant therapy [6, 7]. Nevertheless, the application of systemic chemotherapy delivered through an intravenous route is limited by its dose-related systemic toxicity and the development of drug resistance [8, 9]. Furthermore, systemic chemotherapy can only deliver low drug concentrations into the tumor microenvironment [10].

The regional chemotherapy has arisen to deliver higher concentrations into the target tissues while reducing systemic side effects [10]. In comparison to systematic therapy, the transarterial regional chemotherapy techniques have shown better response rates especially in organs with dual blood supply [11].

Isolated lung perfusion (ILP) is one of those techniques in which a closed circulation system for regional delivery of chemotherapy is established by cannulation of pulmonary arteries and veins [12]. This technique allowed a significantly higher intratumoral drug concentration in comparison to systemic chemotherapy [13].

Transarterial chemoembolization, which is an established technique for treatment of liver tumors [14], was suggested as a less invasive alternative to ILP that can be repeated more feasibly [15]. Due to the dominant supply of pulmonary metastases through pulmonary circulation, a transpulmonary route would be preferable [16].

In animal studies, transpulmonary chemoembolization (TPCE) exhibited effectiveness similar to ILP as well as equal superiority to systemic chemotherapy, even when one third of the dose was used [17]. In brief, TPCE is performed via super-selective catheterization of the tumor-supplying pulmonary arterial branches and blocking them by injecting cytotoxic drugs mixed with lipiodol and microspheres [18]. This approach prolongs the deposition time of the injected cytostatic drugs into the target tumor and minimizes its outflow into the circulation [17–19]. In addition, the ischemic effect induced by temporal embolization can provide an independent antitumor activity similar to that reported after hepatic artery embolization [20]. Generally, TPCE can be used as a single therapy to prevent tumor progression without the major side effects of systemic chemotherapy or as a neoadjuvant therapy before intrapulmonary thermal ablations [21, 22].

According to the aforementioned findings, the current study was suggested and aimed to evaluate tumor response, local tumor control, and patient survival after the treatment of unresectable lung metastases using TPCE in a palliative and neoadjuvant intent. It, also, aimed to consolidate the initial results of prior studies, by considering patients with more diverse lung involvements and using different combinations of chemotherapy.

Materials and methods

Study population

The current retrospective study was conducted after receiving Institutional Review Board approval. The electronic database of the radiology department—University Hospital Frankfurt—was searched to identify patients with known metastatic lung disease who underwent repetitive TPCE in the period between June 2005 and April 2017. The collected data included primary tumor site, treatment history, procedural technique, materials used, and the findings extracted from peri-procedural and follow-up imaging (including non-enhanced MRI and/or MDCT).

Inclusion criteria

Patients included were those with unresectable pulmonary metastases from extrathoracic primary tumors treated with TPCE and failed to properly respond to prior systemic chemotherapy or recurred after a curative resection or percutaneous ablation. Prerequisites for treatment were adequate performance status (Eastern Cooperative Oncology performance status of 2 or better), and adequate hematologic, hepatic, renal, and pulmonary functions. TPCE was performed as a last resort in an attempt to achieve disease control and life prolongation with minimal treatment burden. Patients with limited pulmonary involvement (mainly those with nodules ≤ 5 in number and ≤ 5 cm in size) had the opportunity to undergo subsequent ablation therapy. Informed consent was obtained from all patients before every treatment session. All included patients had routine follow-up imaging available. Moreover, patients with pulmonary metastases and treated extrathoracic metastatic sites were included.

Table 1 Patients characteristics

Variables	*n*	%
Age (mean, 56.7 years; median, 57.8; range, 11.5–86 years)		
Age subgroups (years)		
≤ 60	*n* = 76	53.1
> 60	*n* = 67	46.9
Gender		
Male (mean age, 59.5 ± 12.6 years)	*n* = 70	49
Female (mean age, 53.9 ± 13.7 years)	*n* = 73	51
Primary tumor site		
Colorectal Ca	*n* = 59	41.3
Breast Ca	*n* = 27	18.9
Sarcoma	*n* = 13	9.1
Renal cell Ca	*n* = 7	4.9
Miscellaneous	*n* = 37	25.9
Latency since initial diagnosis (months)		
≤ 36	*n* = 77	53.8
> 36	*n* = 63	44.1
Unknown	*n* = 3	2.1
Number of nodules: median 10 (1–more than 100)		
≤ 3	*n* = 34	23.8
4–15	*n* = 58	40.6
> 15	*n* = 51	35.7
Laterality of the nodules		
Unilateral	*n* = 28	19.6
Bilateral	*n* = 115	80.4
Type of metastasis		
Synchronous	*n* = 25	17.50
Metachronous	*n* = 88	61.50
Unknown	*n* = 30	21

Exclusion criteria

Pulmonary exclusion criteria were partial or complete thrombosis of the pulmonary artery, cardiovascular and/or respiratory failure, and overt arteriovenous shunting to the pulmonary venous circulation (either identified by pre-procedural angio-CT—when available—or during the procedure). Extrapulmonary exclusion criteria were severe anemia, leukopenia, and coagulopathy. Other contraindications included poor nutritional status, pregnancy, breastfeeding, and known allergy to iodinated contrast media.

Locoregional treatment technique

All treatments were outpatient procedures and were repeated in 4- to 6-week intervals. Patients with radiological progression for more than two successive sessions but still met the inclusion criteria were re-evaluated in the multidisciplinary tumor board to repeat the same treatment protocol. Patients with neoadjuvant intent were planned to receive three TPCE sessions before ablation.

Selection of the chemotherapeutic agent

The type, dose, and combination of the antineoplastic drugs were determined by discussion with the patient's oncologist in a multidisciplinary tumor board.

The used chemotherapeutic agents were mitomycin C 8 mg/m^2 (mito-medac®, Medac), gemcitabine 800 mg/m^2 (Gemcitabin HEXAL®, Hexal AG), cisplatin 35 mg/m^2 (Cisplatin Accord, Accord Healthcare Limited), and irinotecan 100 mg/m^2 (Irinotecan Aurobindo®, PUREN Pharma GmbH) in different combinations.

Until 2007, the patients were treated with a two-drug protocol consisting of mitomycin with either irinotecan or gemcitabine. From 2007, cisplatin was added to form a triple-drug protocol. Irinotecan-containing regimens were exclusively used in 42 of 59 cases of metastatic colorectal carcinoma. A small group of patients ($n = 9$) received other combinations according to their oncologists' recommendations.

Transpulmonary chemoembolization technique

After application of the local anesthesia, the pulmonary artery was reached through femoral venous access using a 5-French headhunter catheter under fluoroscopic gui dance.

After diagnostic pulmonary angiography, tumor-supplying pulmonary artery branches were either selectively or superselectively catheterized. Bolus injection of the chemotherapeutic agents was performed, followed by embolization with 5–10 ml of Lipiodol® (Guerbet) and 200–450 mg of degradable starch microspheres (200 μg) (EmboCept®, PharmaCept GmbH). The extent of embolization was determined by the treating interventionalist taking into consideration the depth and selectivity of catheterization. A near stasis of the antegrade flow in the feeding pulmonary arteries was strived. With bilateral lung involvement, the lung with the higher tumor burden was treated first and the other lung was treated in a successive session. Unenhanced computed tomography (CT) was then performed before discharge to verify lipiodol deposition and to exclude complications.

Imaging evaluation

Routine cross-sectional imaging evaluations, including MRI and/or MDCT, were performed before each treatment session, then monthly for 3 months after treatment cessation, and every 3 months thereafter.

Peri-interventional and post-treatment imaging data were retrospectively analyzed by two radiologists (8–30 years of experience) blinded to patient characteristics

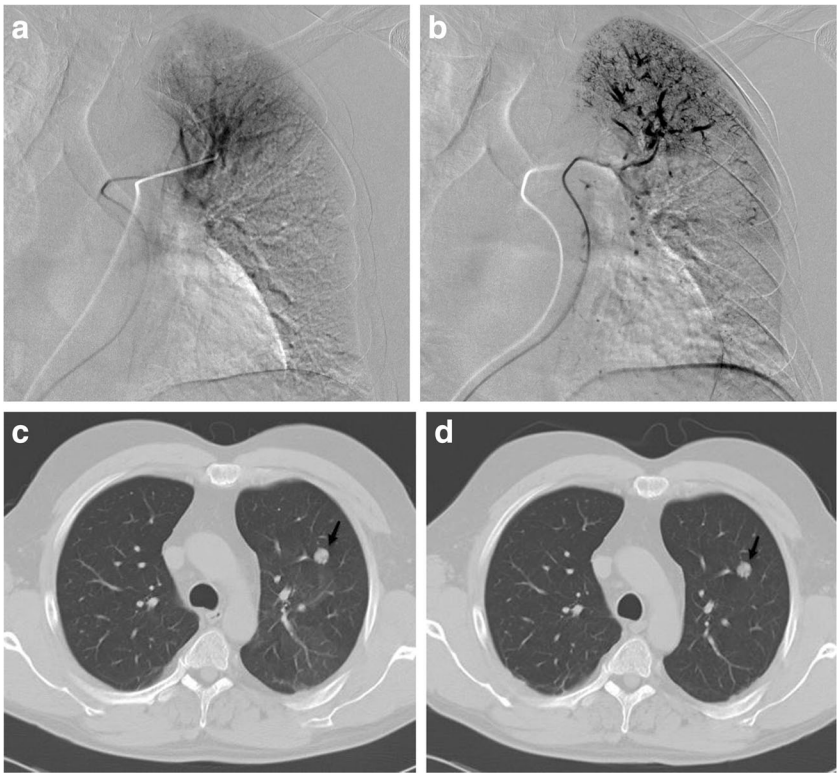

Fig. 1 A 42-year-old male patient with lung metastases of adenoid cystic carcinoma. The patient underwent four cycles of TPCE with a stable disease situation after 4 months of treatment. **a** Subtraction angiography immediately before embolization for verification of the catheter position and to exclude the presence of arteriovenous shunts. **b** Final angiogram after TPCE of the left upper-lobe tumor-supplying pulmonary arteries with stasis of lipiodol in the vessels. **c** Non-enhanced axial computed tomography (CT) of the lung after the first session of chemoembolization, demonstrating the treated left upper lesion (measuring 12.8 mm in longest diameter) with increased density of the surrounding lung parenchyma post-embolization. **d** Axial CT follow-up study 4 months after transpulmonary chemoembolization (TPCE), demonstrating a stable disease situation, now measuring 12.4 mm (arrow)

and other prognostic factors. The treatment response was evaluated according to the revised Response Evaluation Criteria in Solid Tumors (RECIST 1.1) [23]. Target lesions were preferentially selected to be representative of the tumor burden in both lungs and to allow reproducible measurements across successive treatment sessions.

Statistical analysis

The mean time to progression (TTP) and median survival time were calculated using the Kaplan–Meier estimator. Overall survival was estimated from the date of first TPCE. Whenever a patient retreated after tumor progression or tumor recurrence, survival time was determined in reference to the first treatment cycle. In univariate sense, the parameters considered were age, sex, primary tumor location, number of pulmonary nodules, laterality of involvement, number of treatment sessions, injected chemotherapeutic agents, and radiological response. Multivariate analysis was also performed to determine the independent prognostic factors using Cox proportional hazard model.

Patients who received any subsequent ablative therapy for target pulmonary nodules were included in the survival analysis but censored in local control evaluation, since the date of ablation. The same was applied to patients with incomplete follow-up data and those who were shifted to other lines of treatment. The statistical analysis was performed using SPSS v.21.0 (IBM Corp., Armonk, NY, USA). *P* value of 0.05 was considered the significant level.

Results

Baseline patient characteristics

This study included 143 patients (mean age 56.7 ± 13.4 years; 73 females and 70 males). Their characteristics are shown in Table 1.

Response to treatment

The 60-day post-interventional mortality was 0%. Technical success (catheterization of tumor-supplying pulmonary artery branches and injection of the therapeutic agents in territory of the target tumor) was achieved in 100% of cases.

Partial response (PR) was achieved in 11.9%, stable disease (SD) in 66.4%, and progressive disease (PD) in 21.7% (Figs. 1 and 2). The best treatment response of each individual patient is revealed in Fig. 3.

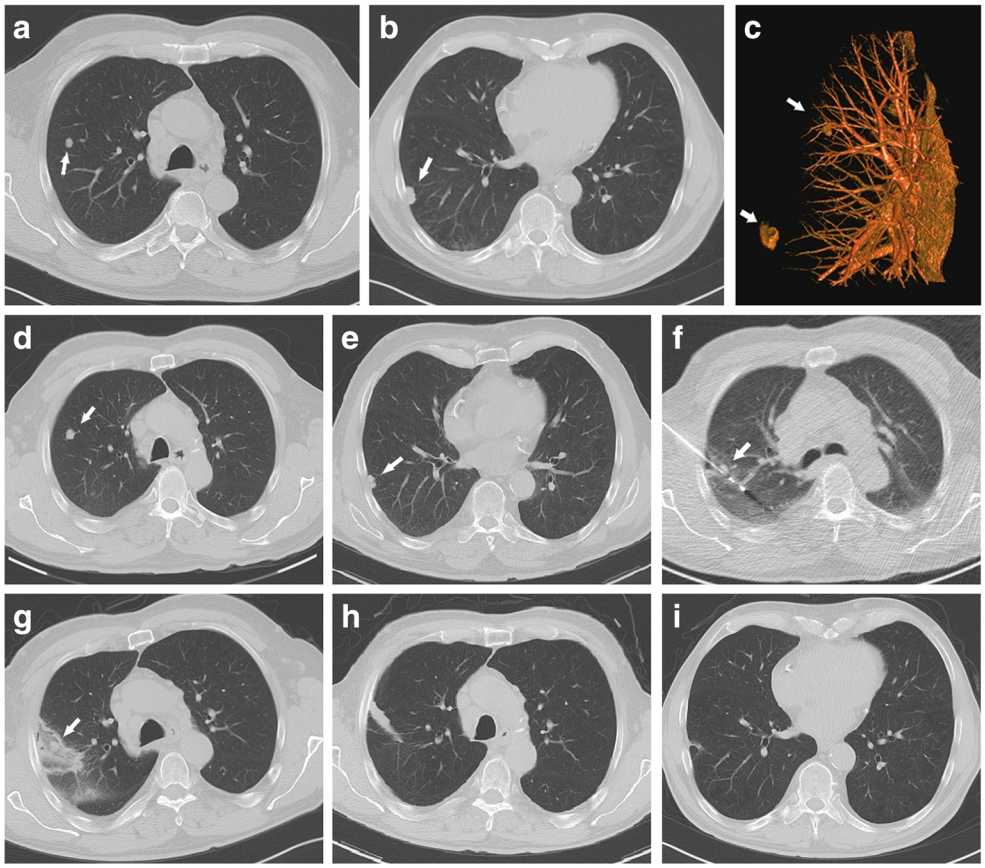

Fig. 2 A 70-year-old male patient with unilateral lung metastases ($n = 2$) of colorectal carcinoma. The patient underwent three cycles of TPCE followed by complete ablation of the two pulmonary nodules in two subsequent sessions. **a**, **b** Non-enhanced axial computed tomography (CT) of the lung after the first session of chemoembolization, demonstrating two right upper and lower lung lobes nodules measuring 10.6 and 19.4 mm in the longest diameter, respectively (arrows). **c** 3D reconstruction of a rotational angiogram done during the procedure demonstrating the position and blood supply of both right lung nodules and confirming their hyper vascular nature. **d**, **e** Axial CT follow-up study 3 months after transpulmonary chemoembolization (TPCE), demonstrating a stable disease situation with variable response of treated nodules, now measuring 12.6 and 15.7 mm, respectively (arrow). **f**, **g** Subsequent MW ablation of the right pulmonary nodules at segment 2, 3 months after the first TPCE session (arrows). The right pulmonary nodules at segment 9 was ablated a month thereafter (not demonstrated here). **h**, **i** Axial CT follow-up study during follow-up at 15 months, demonstrating A0 ablation of both treated nodules with no recurrent or residual masses

The median survival time in patients with PR, SD, and PD was 32.9, 20.3, and 9.9 months respectively ($p = 0.001$) (Table 2). In a pairwise comparison of the initial tumor response according to RECIST criteria, patients with PR or SD had a significantly better survival than those with PD.

Local control

The estimated TTP of the whole cohort averaged 7.5 ± 0.5 months. In univariate analysis, the type of primary tumor (Table 3), the time since initial diagnosis, and the time since diagnosis of metastases had a significant effect on local control. Patients presented for this treatment 36 months or more after initial diagnosis or more than 18 months from metastasizing had a statistically significant better local control ($p < 0.003$). Other factors including age, sex, number of nodules, laterality of involvement, type of metastasis (synchronous or metachronous), and used drug combination had no statistically significant effect.

Survival analysis

The mean survival time was estimated to be 24.3 ± 1.8 months with a median follow-up time of 9.8 months (1.3–51.1 months) across all treated patients.

Number of nodules and extent of lung involvement

The number of nodules exerted a significant effect on survival in univariate analysis with a longer survival in patients with three nodules or less in comparison to those with more than 15 nodules ($p = 0.008$) (Fig. 4). Also, patients with unilateral lung involvement had a significantly ($p = 0.001$) longer mean survival time of 38.2 ± 4.2 months in contrast to those with

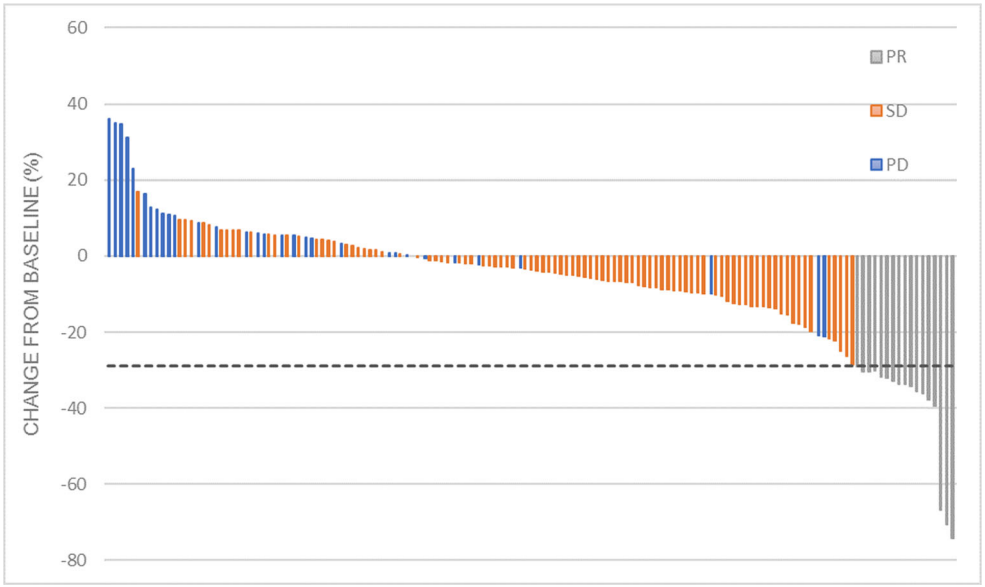

Fig. 3 The best treatment response of each individual patient, based on the maximal percentage of tumor reduction from the baseline SLD measurements, recorded through successive treatment sessions, or the minimum positive change if there is no reduction

bilateral involvement (21.6 ± 1.7 months). After excluding the complete ablation group, these two factors had no significant impact on survival. There was a tendency for a longer survival (42 ± 4.7 months) in patients with unilateral involvement, who underwent complete ablation ($n = 11$) in comparison to those with incomplete ablation ($n = 3$) or no ablation at all ($n = 14$) (28.6 ± 6.7 and 26.6 ± 8 months respectively), but the difference was not statistically significant.

Subsequent ablative therapy

The mean survival time of 19.7 ± 2 months in the palliative treatment group was significantly shorter than that of the neo-adjuvant group undergoing a subsequent ablation (30.1 ± 2.6 months) (Fig. 5).

Patients with complete ablation of all lung nodules had a significant survival advantage (median survival time of 46 ± 13 months) over those who underwent ablation of dominant nodules (incomplete ablation) or those who did not undergo any subsequent ablative therapy (23.5 ± 4.4 months, $p = 0.027$, and 15.7 ± 2.9 months, $p = 0.001$, respectively) (Table 4). There is no significant difference in the mean survival time between no ablation and incomplete ablation groups.

Type of primary tumor

There was a tendency of some tumors towards a statistically insignificant better survival (Table 5). The mean survival time of the two major contributing tumor pathologies, namely metastatic colorectal ($n = 59$) and breast cancers ($n = 27$), was 25 ± 2.4 and 31.5 ± 4.9 months, respectively.

All other evaluated factors, including age, sex, time interval since tumor diagnosis and since diagnosis of metastasis, type of metastasis (synchronous or metachronous), and the type of used chemotherapy, were not statistically significant ($p > 0.05$).

In a Cox model, patients who underwent either TPCE alone or with subsequent incomplete ablation had a higher hazard

Table 2 Mean survival time and time to progression according to the tumor response to treatment

Means for survival time and time to progression

RECIST	Mean survival time[a]				Mean time to progression[a]			
	Estimate	Std. error	95% confidence interval		Estimate	Std. error	95% confidence interval	
			Lower bound	Upper bound			Lower bound	Upper bound
PD ($n = 31$)	14.555	2.945	8.782	20.327	2.670	.167	2.342	2.997
SD ($n = 95$)	24.979	2.116	20.831	29.128	8.741	.782	7.208	10.274
PR ($n = 17$)	29.877	2.735	24.516	35.238	11.538	1.347	8.899	14.178
Overall	24.534	1.727	21.149	27.918	7.481	.547	6.409	8.553

[a] Estimation is limited to the largest survival time if it is censored

Table 3 Mean time to progression according to the type of the primary tumor

Major tumor groups ($n \geq 3$ patients)	Mean survival time[a]			
	Estimate	Std. error	95% confidence interval	
			Lower bound	Upper bound
Colorectal Ca ($n = 59$)	6.052	.532	5.010	7.094
Breast Ca ($n = 27$)	9.155	1.084	7.030	11.279
Sarcoma ($n = 13$)	6.054	1.273	3.559	8.548
Adenoid cystic Ca of H&N ($n = 4$)	15.533	3.800	8.085	22.981
Melanoma ($n = 4$)	3.450	.648	2.180	4.720
Renal cell Ca ($n = 7$)	6.800	2.919	1.079	12.521
Head and neck tumors ($n = 3$)	4.600	2.084	.516	8.684
Other GIT Ca ($n = 4$)	4.600	.636	3.353	5.847
Endometrial Ca ($n = 5$)	5.609	.820	4.003	7.215
Overall ($n = 126$)	7.506	.580	6.369	8.643

[a] Estimation is limited to the largest survival time if it is censored

ratio (HR) for death in comparison to those who underwent TPCE with subsequent ablation of all detectable lung metastases (HR = 4.6 and 3.1, respectively, $p < 0.05$). It was also noted that the patients who progressed within the first 5 months after treatment initiation had 3.9-fold increase in the death hazard when compared to patients with partial response ($p < 0.05$).

There were no major intervention-related complications reported in the archiving system of our department; this agrees with our assessment of the post-interventional imaging data.

Discussion

TPCE as a palliative and neoadjuvant treatment for patients with unresectable lung metastases was considered by many authors [18, 19, 21, 22, 24] to be a feasible and well-tolerated treatment option. Consequently, the results of the current study added more informative view in this concern with a new approach in data analyses.

The rationale of the current locoregional approach relies on many reports stating that the presence of malignant cells in the bloodstream does not seem to prevent long-term survival. Also, there is no sufficient evidence that metastases themselves can metastasize [25].

In the current patient population with unresectable lung metastases, who previously failed over multiple treatment options, the achieved 11.9% PR, 66.4% SD, and a mean TTP of 7.5 ± 0.5 months are really promising.

The tumor response rate in the present study, after converting the unidimensional measurements into volumetric data, was similar to that of Vogl et al [22]. However, we cannot support their assumption that most of the acquired

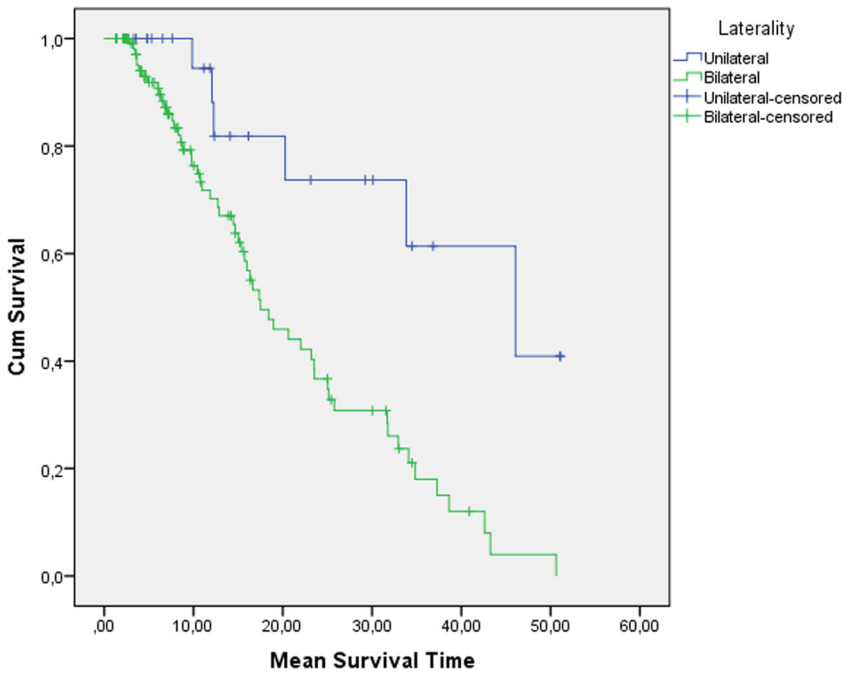

Fig. 4 Mean survival time according to the number of nodules identified

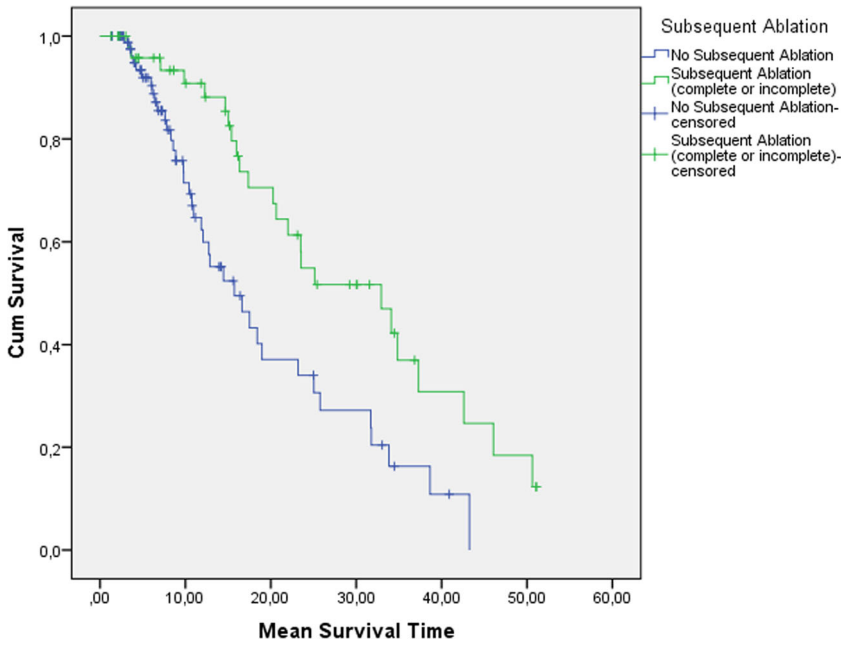

Fig. 5 Mean survival time according to the utilization of subsequent ablative therapy

effectiveness was due to embolization [22]. In their study, the median number of treated lesions was 6 nodules per patient (range 1–21), treated with 2–10 TPCE sessions (mean, 3.3 sessions/patient), while in the current study, a higher number of nodules were recorded (median,10 metastases/patient; range 1 to ≥ 100) and bilateral involvement was seen in 80.4% of patients. Moreover, contrary to Vogl et al who used single-agent chemotherapy (mitomycin C), in the current study multiple chemotherapeutic agents were utilized. Treatment continuation post-progression was allowed when it was clinically appropriate with a higher total number of treatment sessions/patient (mean, 5.8 ± 2.9 TPCE sessions/patient; range, 2–16). In accordance with RECIST guidelines [23], the rationale of treatment post-progression was that patient progression according to response evaluation criteria does not preclude the continuation of treatment as long as a substantial clinical benefit is expected [26].

In the current study, the estimated mean TTP exceeds that reported by Vogl et al (5.5 months; range, 1–67 months) [22]. However, this could be attributed to the different definition of progression in each study protocol. The achieved mean survival time of 19.7 months in patients treated with palliative intention and received TPCE alone is superior to that calculated by these latter authors (17 months; 95% confidence interval 13.7–20.2 months). This variability may be attributed to the use of combination chemotherapy and the allowance of treatment post-progression (mean, 1.9 ± 2.5 post-progression sessions/patient). Advantageously, much longer survival was achieved in the neoadjuvant group.

According to univariate analysis, the time since diagnosis and since metastasizing and the type of the primary tumor were significant factors affecting local tumor control. This can be explained by the slow growth rate of some tumors (e.g., adenoid cystic carcinoma) and tumor subtypes that could

Table 4 Mean and median survival times according to the subsequent ablative therapy

Means and medians for survival time								
EndAbla	Mean[a]				Median			
	Estimate	Std. error	95% confidence interval		Estimate	Std. error	95% confidence interval	
			Lower bound	Upper bound			Lower bound	Upper bound
No ablation	19.713	1.982	15.828	23.598	15.733	2.918	10.013	21.453
Incomplete ablation	26.108	2.940	20.346	31.870	23.533	4.445	14.822	32.245
Complete ablation	38.915	4.327	30.433	47.396	46.067	13.039	20.510	71.623
Overall	24.534	1.727	21.149	27.918	20.633	3.231	14.301	26.966

[a] Estimation is limited to the largest survival time if it is censored

Table 5 Mean and median survival times according to the type of the primary tumor

Means and medians for survival time								
Major tumor groups ($n \geq 3$ patients)	Mean[a]				Median			
	Estimate	Std. error	95% confidence interval		Estimate	Std. error	95% confidence interval	
			Lower bound	Upper bound			Lower bound	Upper bound
Colorectal Ca ($n = 59$)	25.076	2.437	20.299	29.853	25.033	4.361	16.486	33.580
Breast Ca ($n = 27$)	31.486	4.927	21.828	41.143	23.533	11.572	.853	46.214
Sarcoma ($n = 13$)	14.380	2.009	10.442	18.318	15.033	3.576	8.024	22.043
Melanoma ($n = 4$)	7.683	.672	6.367	9.000	6.733			
Renal cell Ca ($n = 7$)	16.060	4.368	7.498	24.621	14.667	2.981	8.824	20.509
Head and neck tumors ($n = 3$)	10.967	0.000	10.967	10.967	10.967			
Other GIT Ca ($n = 4$)	17.633	5.244	7.354	27.912	12.067	2.967	6.252	17.881
Endometrial Ca ($n = 5$)	26.267	6.695	13.144	39.389				
Overall ($n = 122$)	24.004	1.875	20.329	27.679	20.267	3.001	14.384	26.149

[a] Estimation is limited to the largest survival time if it is censored

still be eligible to undergo the current suggested treatment technique long time after initial diagnosis and consequently have an inherent longer median time to progression [27–29].

In the current study, number of nodules less than 3 and unilateral lung involvement were significant prognostic factors in univariate sense ($p = \leq 0.01$). However, in the case of patients with no ablation and incomplete ablation, both factors lost their initial significance. This finding could be attributed to the effect of background characteristics of those patients, in whom a complete ablation could be achieved. 93.8% of those patients had a number of nodules less than 3 whereas 68.8% of them had a unilateral lung involvement (Fig. 6).

Both primary tumor type and the used antineoplastic regimen had no significant effect on survival. This can be explained by the wide range of tumor pathologies included in the study and the fact that patients had a heterogeneous pre-interventional and post-progression therapeutic history which may have contributed to their overall survival.

As the main focus of the current study was to evaluate the effectiveness of TPCE, ablative therapy was represented in survival analysis as a single parameter. Complete ablation was defined as successful ablation of all pulmonary nodules, regardless of the ablation technique and the post-ablation follow-up [30]. Such ablation exhibited a significantly longer median survival time in

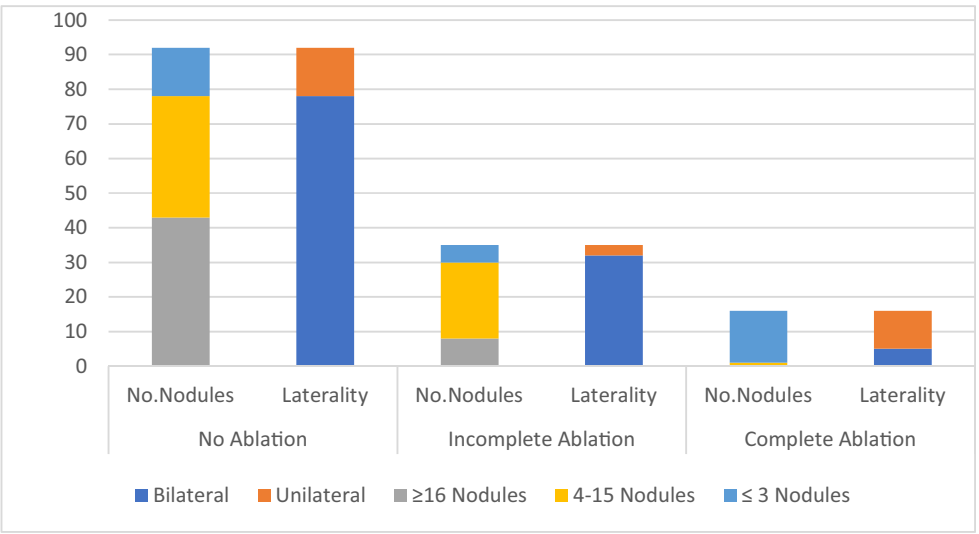

Fig. 6 Number of nodules and laterality of pulmonary involvement in the "no ablation," "incomplete ablation," and "complete ablation" groups presented as number of treated patients in each group

comparison to the incomplete ablation and no-ablation groups—an effect that could have been augmented by a selection bias.

While the role of combining chemotherapy with regional treatments, namely metastasectomy, in improving survival of patients with resectable lung malignancies is a matter of debate in literature [4, 29, 31, 32], it was shown that combining chemotherapy with local ablation, which is less invasive and more tolerable, had a significantly better survival than chemotherapy alone [33].

In addition, using a neoadjuvant systemic or regional chemotherapy before ablation can improve local control by eliminating micrometastasis and reducing the need for a larger safety margin [24, 34]. Furthermore, selective chemoembolization with consequential infarction and peri-nodular edema can reduce lung impedance and allow larger and more homogeneous ablation zones. This powerful rationale for multimodality treatment aims to improve local disease control [24], especially in more aggressive tumors, where a larger safety margin would be required [35].

Complete ablation being a highly significant or the only significant prognostic factor for survival has been consistently reported in literature [30, 36]. Unlike complete ablation, combining TPCE with incomplete ablation, when ablation of all tumor nodules could not be achieved, had no significant survival advantage over treatment with TPCE alone, either because of the rapid growth of untreated tumors or due to development of new lesions. This agrees with the present consensus against locoregional treatments when the control of all disease sites is not possible [3, 4, 30]. However, this approach of combining TPCE with palliative ablation may be indicated to control patient symptoms and to avoid possible complications [37, 38].

It is important to state that the current study had a number of limitations to be considered when interpreting the data beyond the retrospective study design. First, due to a large amount of missing data, the authors were unable to adjust for previous treatment history, date of metastasis, and treatments post-progression. In addition, there was no control group to determine the magnitude of survival benefit in comparison to best supportive care. Also, a detailed analysis of all ablation-related parameters was out of the scope of the current study.

In summary, TPCE is a feasible technique either alone or as a neoadjuvant treatment in combination with ablative therapy with the potential to improve local tumor control and to prolong survival. Therefore, our results encourage a more widespread use of this technique for the treatment of patients with unresectable lung metastases.

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Compliance with ethical standards

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Informed consent Written informed consent was not required for this study because of its retrospective nature.

Ethical approval Institutional Review Board approval was obtained.

Methodology
- Retrospective
- Observational
- Performed at one institution

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