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Transpulmonary chemoembolization (TPCE) as a treatment for unresectable lung metastases

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Abstract To evaluate tumor response after treating unresectable lung metastases with transpulmonary chemoembolization (TPCE) in palliative intention. From 2001 to 2005, 52 patients (mean: 59.8 years; 32 males/20 females) suffering from 106 unresectable lung metastases (mean:6 metastases/patient; range,1–21) were treated with 2–10 TPCE-sessions (mean: 3.3 sessions/patient). Metastases originated from primaries, including colorectal carcinoma (n=20), breast cancer (n=6), renal cellular carcinoma (n=5), thyroid cancer (n=4), cholangiocellular carcinoma (n=2), leiomyosarcoma (n=2), and others (n=13). Tumor-feeding pulmonary arteries were selectively probed after puncturing the femoral vein, and administering 10 ml lipiodol, mitomycin C, and microspheres (Spherex) each via balloon catheter over pulmonary approach. During therapy, follow-up was accomplished at 4-week intervals using unenhanced and contrast-enhanced CT. After sequential therapy, follow-up was performed every 3 months for a period of 6 months up to 2.25 years. All patients tolerated the treatments well without major side effects or complications. In 24% (n=13) moderate to high lipiodol uptake was found, while 75% (n=39) of the tumors showed a low uptake. According to the RECIST criteria, "partial response" was achieved in 16 cases, "stable disease" in 11 cases, and "progressive disease" in 25 cases [mean survival: 17 months/median: 21.1 months (Kaplan-Meyer)]. According to these findings, TPCE is a well-tolerated procedure for palliative treatment of unresectable lung metastases.

Keywords Chemoembolization · Lung metastases · Palliative treatment

Introduction

Pulmonary metastases are a challenge in community health and occur in patients with cancers of different origins. Between 20% and 30% of patients afflicted with cancer develop pulmonary metastases [1]. Mean survival after diagnosis of unresectable lung metastases is less than 1 year. In patients with lung metastases who undergo pulmonary resection, a 5-year survival rate of 20–46% [2–8] has been reported. Although systemic chemotherapy has shown promising results [6, 9], the overall response rate remained poor [10] with 20% to 30% for doxorubicin and 20% to 50% for combined chemotherapy [9, 11, 12]. Furthermore, intravenous chemotherapy has a number of disagreeable side effects, which is a limiting factor [13]. An alternative to systemic chemotherapy might be isolated lung perfusion (ILuP), which is an experimental clinical technique to improve treatment results in the therapy of pulmonary metastases from certain solid tumors [14]. This method was developed at the end of the 1950s and experienced a renaissance at the beginning of the 1980s [15]. It permits a selective delivery of high-dosed chemotherapy into the lungs while keeping systemic toxicity low [13, 16, 17]. With this procedure cytostatic drug concentrations were doubled compared to systemic application, but only with a quarter of the dosage [18]. This corresponds

with findings of various animal studies that report tumor levels [13, 19] and efficacy [20] to be significantly higher after ILuP when compared to systemic application. Between 2001 and 2003, ILuP was conducted in 16 patients, which showed that this method was feasible in humans [21]. This is also supported by several findings [19, 22], but despite positive results in humans, ILuP is not used clinically today. Reasons for this are the complexity of this method and insufficient knowledge regarding technical necessities of the procedure [23] as well as limited human trials. Another disadvantage of ILuP is its dependence on cannulation of pulmonary vessels achieved either by minimal invasive operative and catheter technology [24] or via thoracotomy. Thus, it cannot be repeated extensively. Moreover, it requires extracorporeal cardiovascular circulation [25–27]. TPCEs can be performed percutaneously and thus substitute invasive schemes. In 2002 a survey was published that compared intravenous application with ILuP and chemoembolization in a rat model. Chemoembolization turned out to be superior to i.v. therapy and equal to ILuP as far as efficacy was concerned [28]. A preliminary study evaluating TPCE as a treatment in lung metastases presented noticeable findings, namely, a reduction of tumor volume in about 33% of cases [29]. The aim of this study is to evaluate these results and to analyze a larger quantity of treated patients.

Materials and methods

In the period between March 2001 and May 2005, 52 patients suffering from 106 unresectable lung metastases (mean: 6 metastases per patient: range, 1–21) were treated with transpulmonary chemoembolization (TPCE) after obtaining approval from our Institutional Review Board and informed consent from all patients. The study was designed in a prospective manner, and the treatment was in accordance with the inclusion and exclusion criteria established in our study protocol. Part of these data was already evaluated in 2005 [29]. The current data, however, convey a larger patient material with a prolonged follow-up period. Unresectable metastases were defined as multisegmental uni- or bilateral affected areas (≥T3), without mediastinal lymph nodes being affected (≥N1). The presented procedure was exclusively performed in metastases that did not respond to the treatment of systemic chemotherapy or radiation and which were consequently classified as uncurable.

A total of 106 unresectable lung metastases were treated in 52 patients (32 males, 20 females) with a mean age of 59.8 years (range, 33 to 83 years).

Forty-six patients had a mean of six metastases (range, 1 to 21), and six patients had multiple metastases (>21) of different origins: colorectal carcinoma (n=20), breast cancer (n=6), renal cellular carcinoma (n=5), thyroid cancer (n=4), cholangiocellular carcinoma (n=2), leiomyosarcoma (n=2), and others (n=13). Mean tumor volume before treatment was 28.28 ml (range, 0.1 ml to 295.1 ml).

Clinically, all the patients had a satisfactory performance status (Karnofski index >70). They had adequate treatment compliance, and the pulmonary function was not restricted. All patients underwent pulmonary function tests in order to assess pulmonary function. Patients with either a Karnofski status <70% or respiratory, cardiovascular, or renal dysfunction (serum creatinine >2 mg%), or partial or complete thrombosis of the pulmonary arteries, were excluded.

Technique

TPCE was accomplished in only one lung lobe per session. In 4-week intervals treatment was repeated between two and ten times with a mean of 3.3 per patient. For patients with multilobar affection, all affected lobes with all the metastases were treated successfully. Subsequent to regional anesthesia with 1% mepivacin via a 7-F sheath, which was inserted into the right femoral vein, a 5-F headhunter catheter (Terumo, Frankfurt am Main, Germany) was placed either into the right or left pulmonary artery. An angiographic survey of the arterial system was performed by injecting 20 ml of contrast material, and the relevant segmental pulmonary artery was probed by a headhunter catheter. In connection with this procedure a balloon catheter (diameter: 7 mm, length: 110 mm) was positioned into the segmental pulmonary artery. Depending on the size, location, and arterial supply, the tip of the catheter was advanced farther into the subsegmental pulmonary arteries using a guidewire. In order to detect arteriovenous shuntings as early as possible, the catheter was blocked and contrast-enhanced angiographic series were performed. The embolization suspension consisted of 5 mg/m^2 mitomycin (Medac, Hamburg, Germany) as the cytostatic agent and a maximum of 10 ml lipiodol (Guerbert, Sulzbach, Germany) followed by an injection of 200 – 450 mg of microspheres (Spherex, Pharmacia and Upjohn, Erlangen, Germany) for vessel occlusion. This suspension was injected carefully under fluoroscopic guidance (mean lipiodol amount: 9.13 ml; range, 6.5 - 10.0 ml; standard error: 0.95; mean mitomycin amount: 8.75 ml; range 7.0 – 10.0 ml; standard error: 0.96) until stasis of the blood flow was achieved.

Prior to any treatment, specific laboratory parameters were controlled, such as hemoglobin, creatinine and bilirubin levels, leukocyte and thrombocyte numbers as well as blood clotting.

At 24 to 48 h before initial treatment, non-enhanced and enhanced computed tomographies were performed, which were repeated every month. After the sequential therapy, follow-up was performed every 3 months for a period of 6 months up to 2.25 years. For that purpose, a four-row multidetector spiral CT (Somatom Plus 4 VZ, Siemens

Medical Solutions, Erlangen, Germany) was used. All patients were examined with 4×2.5-mm collimation and a slice thickness of 5 mm. In order to recognize any alteration in the tumor volumes, all images were compared to previous ones as well as to CT scans taken before treatment with TPCE.

Tumor volume was calculated using the ellipsoid formula:

$$Volume = length \times width \times height \times \pi/6$$

Therefore, in axial CT scans at a lung window 2,000/-500 the maximum cross-sectional diameter with the help of an electronic calliper was determined as length and the perpendicular diameter as width. Height was estimated by the number and thickness of the slices on which the tumor was visible.

According to our study protocol, response was defined as a reduction in tumor size of at least 25% after the last treatment. Insignificant changes in volume were defined as stable disease and an increase in size of more than 10% as progressive disease. Lipiodol enhancement was quantified by measuring an increase of Houndsfield units (HU) in the treated lesions, which was evaluated in unenhanced CT images only. Houndsfield units from 75 to 125 were defined as "low," 125 to 250 as "moderate," and more than 250 as "high."

Prior to treatment, patients were physically examined and their health was analyzed by means of a standardized questionnaire including the following information: dyspnea, chest pain, cough, pyrexia and analgetic demand. In accordance with the complication definitions established by the Society of Cardiovascular and Interventional Radiology (SCVIR), complications were categorized as minor and major. Minor complications were those that required no therapy and involved no sequelae but may have required an overnight hospital stay for observation. Major complications were those that required therapy with hospitalization and those that involved permanent adverse events including death [30].

Results

In total, 106 metastases (mean: 6 metastases/patient; range, 1–21) were treated with a mean volume of 28.28 ml (range, 0.1 ml to 295.1 ml). The procedure was performed in absence of contraindications in all patients with an average of 3.3 sessions per patient (range, 2 to 10).

Overall, treatment was well tolerated without any major complications or even TPCE-associated mortality. Aforementioned laboratory parameters were not significantly influenced. Three patients developed minor side effects with an increase in blood parameters. They showed a slight leukocytosis (mean leukocyte account: 11,660.66 leukocytes; range, 11,300 – 12,200) with mild fever (mean temperature: 38.3°C; range, 37.9 – 39.2°C) and coughing. These symptoms responded well to orally administered medication. The majority of the patients (n=49; 94.2%) were discharged from hospital the same day.

High or moderate lipiodol enhancement was observed in 25% (high: 6, moderate: 7) of the treated tumors. Tumors with a maximum of lipiodol uptake were 50% of the metastases of thyroid carcinoma (two high, two low enhancement), leimyosarcoma (one high, one moderate enhancement), 50% of the metastases of renal cellular carcinoma (two high, two low enhancement) and 100% of the metastases of carcinoid (one high enhancement). A moderate enhancement was observed in 3 of 17 colorectal carcinomas (17.6%), 1 of 6 breast carcinomas (16.6%), and 1 of 2 cholangiocellular carcinomas (50%). All other metastases presented with a low amount of lipiodol uptake.

Sixteen patients (30.7%) responded to transpulmonary chemoembolization with a mean decrease in tumor volume of 56.38% (range, 38.18%-95.74%) (Figs. 1, 2). In 7 patients (13.5%) stable disease was documented, and in 29 patients (55.8%) progressive disease with a mean increase in tumor volume of 139.52% (range, 12.55%-766.67%) was recorded. Mean time to progression was 5.5 months (range, 1–67 months).

Survival was calculated according to the Kaplan-Meier method with a mean of 17 months for all patients (95% confidence interval 13.7–20.2 months). Median survival time of all lesions was 21.1 months (95% confidence interval 4.2 - 38 months) (Table 1).

Discussion

Treatment of pulmonary metastases is still an enormous challenge today. As already emphasized, long-term survival has been reported in only 46% of treated patients [2–8, 31], and systemic chemotherapy did not meet the expectations [9–11]. For this reason, multimodality therapy regimes have been postulated [32]. In 2005 a retrospective study comparing multimodality therapy [including modified pharmacokinetic modulating chemotherapy (PMC), radiation and RFA] vs. single chemotherapy was published, showing a significant survival advantage for patients treated with multimodality therapy: the 3-year survival rate of patients in the multimodality group was 87.5% vs. 33.3% in the chemotherapy group [33]. Isolated lung perfusion (ILuP) turned out to be superior to systemic chemotherapy in animal studies [19, 20], but requires thoracotomy, which is stressful for the patients and which is therefore the reason why this method cannot be repeated extensively. Moreover, extracorporal circulation is required [28]. TPCE of the lung offers the advantages of ILuP over systemic chemotherapy [19, 20], but without the above-mentioned disadvantages. Moreover, a survey published in 2007 showed TPCE to be even superior to ILuP in terms of

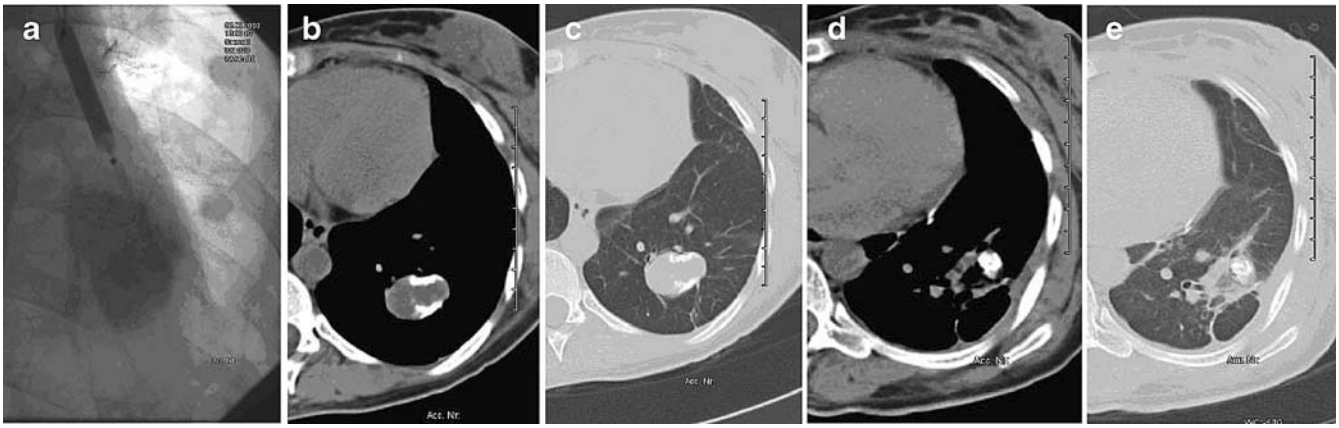

Fig. 1 A 33-year-old female patient suffering from oligonodular lung metastases of a leiomyosarcoma in the left lung. Verification of a moderate degree of lipiodol uptake and a measurable response to treatment (partial response). **a** Final angiogram after the first course of TPCE of the left tumor-supplying pulmonary arteries with stasis of lipiodol in the vessels and an increased opacity of the tumor. **b** Unenhanced axial CT scan after first course of TPCE. Documentation of a moderate peripheral lipiodol uptake in the metastasis (soft tissue kernel). **c** Unenhanced axial CT scan after first course of TPCE. Documentation of a moderate peripheral lipiodol uptake in the metastasis (lung window kernel). **d** CT scan 2 months after the first course of treatment. High lipiodol uptake and measurable response to treatment. A volume reduction from 14.6 ml to 6 ml has been achieved (soft tissue kernel). **e** CT scan 2 months after the first course of treatment. High lipiodol uptake and the measurable response to treatment. A volume reduction from 14.6 ml to 6 ml has been achieved (lung window kernel)

lipiodol uptake in a rat model [1]. This means that TPCE of the lung could be a promising component in a multimodality therapy concept.

As an alternative to multimodality therapy, a combination of surgical ablation and chemotherapy is discussed [8, 34]. The macroscopic parts could be resected by surgery, while the residual microscopic components could be destroyed by chemotherapy [8]. In those cases regional chemotherapy instead of systemic chemotherapy with all its side effects should be considered.

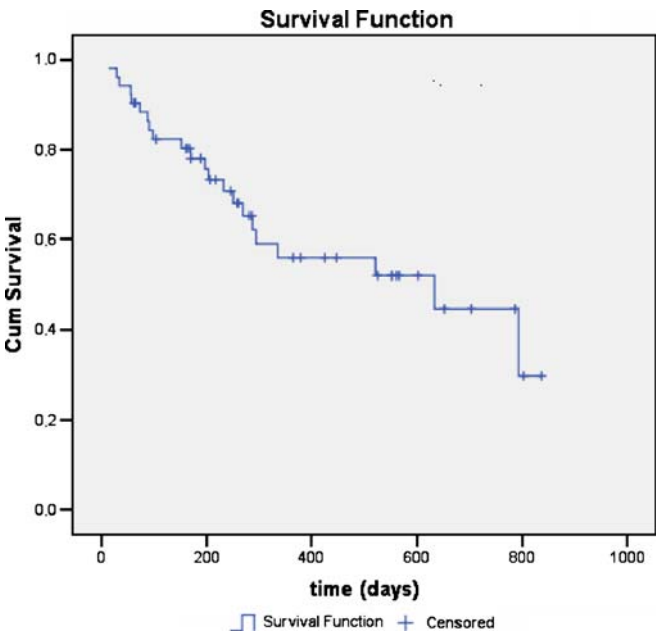

Fig. 2 Survival curve

The findings of this survey might have been affected by the following: A balloon catheter was used in order to detect arteriovenous shuntings, which provides the opportunity to discontinue the procedure. Furthermore, an outflow of the embolization solution into the pulmonary artery is avoided by this catheter. Besides, medication was administered superselectively. Moreover, lipiodol was used as a drug carrier [35], and microspheres (Spherex) were used for vascular occlusion.

Our data show that TPCE using mitomycin followed by embolization agents such as lipiodol and microspheres is a well-tolerated treatment method for patients with unresectable lung metastases. Our study is limited due to the small number of treated patients, the inhomogeneous patient material, the variety of previous therapies, and the missing control group. A further limitation is that mitomycin and microspheres were administered simultaneously. Thus, no conclusions can be drawn whether the ischemia achieved by the application of microspheres was the only reason for tumor regression. Another point is that the lipiodol uptake, which was measured in the lesions, might not be correlating with the amount of mitomycin C in the lesion, which is presumed in our study protocol. Therefore, no conclusion can be drawn about the real amount of cytostatic drugs in the lesions.

Interestingly, the lowest response rates were observed in patients with lung metastases of colorectal carcinoma most likely because of the chosen chemotherapeutic agent mitomycin. Mitomycin was used because of the study protocol and the fact that the study team had more experience with this drug than with any other drug. Here new studies using drug concentrations with irinotecan or oxaliplatin should be considered. The results obtained in

Table 1 All tumors

Age	Sex	Diagnosis	Number of treatments	Total volume of all lesions before treatment [ml]	Total volume of all lesions after treatment [ml]	Outcome
44	Male	Colorectal carcinoma	2	3.8	5.7	Progress
68	Male	Leiomyosarcoma	3	4.9	2.2	Partial response
59	Male	Thyroid carcinoma	4	5.1	2.6	Partial response
49	Female	Thyroid carcinoma	5	1.9	2.4	Progress
62	Female	Metastases of unknown primary	3	3.8	4	Stable
61	Male	Esophageal carcinoma	3	8.3	12.2	Progress
80	Male	Colorectal carcinoma	3	5.8	19.8	Progress
67	Female	Cholangiocellular carcinoma	3	0.7	1.4	Progress
79	Male	Colorectal carcinoma	3	1.9	0.4	Partial response
75	Male	Hepatocellular carcinoma	2	3.5	1.2	Partial response
62	Male	Renal cell carcinoma	2	3.3	1.7	Partial response
74	Male	Colorectal carcinoma	3	22.5	33.5	Progress
55	Female	Carcinoid	2	46.4	28.2	Partial response
60	Male	Gastric cancer	5	295.1	146.1	Partial response
78	Male	Colorectal carcinoma	3	162.2	189.5	Stable
63	Male	Renal cell carcinoma	3	29	39.9	Progress
53	Male	Cholangiocellular carcinoma	2	0.1	0.8	Progress
62	Male	Colorectal carcinoma	4	44.1	52.4	Stable
54	Female	Uterine sarcoma	3	14.6	21.7	Progress
58	Male	Melanoma	4	40.9	88.5	Progress
47	Female	Squamous cell carcinoma of the tongue	5	13.9	8.7	Partial response
63	Male	Renal cell carcinoma	2	18	16.3	Stable
63	Male	Colorectal carcinoma	4	1.1	2.6	Progress
83	Female	Colorectal carcinoma	3	33.4	48.3	Progress
68	Female	Colorectal carcinoma	2	28.1	94.7	Progress
64	Female	Metastases of unknown primary	3	0.1	0.1	Stable
55	Male	Colorectal carcinoma	2	140.5	181.3	Progress
54	Male	Colorectal carcinoma	9	39.3	219	Progress
33	Female	Leiomyosarcoma	3	14.6	6	Partial response
61	Male	Hepatocellular carcinoma	2	29.3	17.9	Partial response
65	Male	Pancreatic carcinoma	2	0.2	0.1	Stable
68	Male	Colorectal carcinoma	3	0.2	0.4	Progress
42	Male	Renal cell carcinoma	3	6.3	9.3	Progress
40	Female	Thyroid carcinoma	3	1.2	0.4	Partial response
52	Male	Colorectal carcinoma	2	12.22	15.41	Progress
56	Male	Colorectal carcinoma	2	5.77	5.77	Stable
61	Female	Breast cancer	5	29.25	11.52	Partial response
34	Female	Thyroid carcinoma	3	5.02	5.65	Stable
58	Female	Breast cancer	3	2.93	5.58	Progress
68	Female	Colorectal carcinoma	3	6.5	33.14	Progress
67	Female	Breast cancer	3	8.57	4.24	Partial response
37	Male	Colorectal carcinoma	2	167.74	376.1	Progress
61	Female	Breast cancer	2	3.51	2.24	Partial response
54	Male	Renal cell carcinoma	6	48.72	108.45	Progress

Table1 (continued)

Age	Sex	Diagnosis	Number of treatments	Total volume of all lesions before treatment [ml]	Total volume of all lesions after treatment [ml]	Outcome
63	Male	Colorectal carcinoma	6	9.05	29.51	Progress
71	Male	Colorectal carcinoma		0.08	0.11	Progress
70	Female	Colorectal carcinoma	2	152.51	189.96	Progress
63	Female	Breast cancer	3	1.53	0.25	Partial response
35	Male	Parathyroideal carcinoma	2	1.41	0.06	Partial response
64	Male	Colorectal carcinoma	3	3.27	3.8	Stable
64	Female	Breast cancer	3	59.62	49.46	Stable
61	Male	Metastases of unknown primary	2	2.04	1.94	Stable

hypervascular cancers such as thyroid, renal cell or hepatocelluar carcinoma prove the hypothesis of the major impact of the lipiodol uptake and its tumoricidal influence on the tumor matrix. Also the positive results in patients with underlying histologies of breast cancer should be proven in further studies.

We treated only one lung lobe per session in order to guarantee a sufficient pulmonary reserve after the treatment. Therefore, only a maximum of all lesions of one lung lobe was treated, which means in cases of multiple lesions with more than one lung lobe being affected, the remaining lesions were left untouched during that session. In further studies it has to be evaluated how many lung lobes can be treated simultaneously without affecting pulmonary capacity.

On the other hand, with this method even a larger number of lesions can be treated than with other ablating procedures such as RFA. It is still too early to say whether RFA could be replaced with TPCE in the future. However, the additional advantage of TPCE over ablating procedures with no risk of pneumothorax is obvious, although judging pneumothorax a complication is discussed heavily among experts. Furthermore, healthy lung tissue is preserved due to the fact that a safety distance as postulated for ablation procedures is not required for TPCE.

In summary, TPCE can be considered to be a well-tolerated treatment method in patients with lung metastases showing no response to conventional oncological therapies.

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