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Published online before print
10.1148/radiol.2343032091
Radiology 2005; 234:917–922

Abbreviation:
TPCE = transpulmonary chemoembolization

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Authors stated no financial relationship to disclose.

Author contributions:
Guarantor of integrity of entire study, T.J.V.; study concepts and design, T.J.V., S.Z.; literature research, A.W.; clinical studies, T.J.V., S.Z.; experimental studies, A.W.; data acquisition, T.J.V., S.Z., A.W.; data analysis/interpretation, S.L., T.J.V.; statistical analysis, S.L., T.J.V.; manuscript definition of intellectual content, T.J.V.; manuscript editing, S.Z.; manuscript revision/review, S.Z., T.J.V.; manuscript preparation and final version approval, T.J.V., S.Z., A.W.

Treatment of Unresectable Lung Metastases with Transpulmonary Chemoembolization: Preliminary Experience[1]

Transpulmonary chemoembolization (TPCE) was evaluated as a new treatment for unresectable lung metastases. Institutional review board approval and patient consent were obtained. In 23 patients, 26 lung metastases of different origins were treated locally by using a transpulmonary approach. After femoral vein puncture, tumor-supplying pulmonary arteries were selectively explored, and 5–10 mg mitomycin C and 5–10 mL iodized oil and microsphere particles were applied with balloon protection. Diagnosis and follow-up (3-month intervals) were performed with unenhanced and contrast material–enhanced computed tomography (CT). Treatment was well tolerated in all patients, with no major side effects or complications. As indicated by using morphologic criteria, volume regression of embolized areas was achieved in eight patients, while stable disease was revealed at follow-up in six patients. In nine patients, progression of treated intrapulmonary metastases was recorded. TPCE could be a well-tolerated palliative treatment option in patients with pulmonary metastases.

The treatment of lung metastases of solid tumors is still a major problem, as many patients manifest extensive unresectable disease or pulmonary recurrence in the resected or contralateral side after complete resection (1,2). After surgery with a curative intention and a complete resection, a 5-year survival rate of only 29%–46% can be expected (3–6). The use of intravenous chemotherapy is primarily limited because of systemic toxicity and so far has not achieved a curative effect in patients with unresectable pulmonary metastases (7). As with neoadjuvant or palliative treatment of liver metastases, the regional application of cytotoxic agents might also be a method for improving the therapy of unresectable lung metastases. In an animal study, regional chemotherapy proved to be pharmacokinetically superior to systemic therapy of lung metastases (8). Lung metastases are supplied primarily from the arterial pulmonary circulation (9); thus, cytotoxic drugs can be delivered via the pulmonary arterial system.

The concept of isolated lung perfusion was developed by Weksler et al (8,10), and with this method the highest cytotoxic drug level in the lung with the lowest systemic concentration is achieved. However, isolated lung perfusion requires cannulation of the pulmonary arteries and veins; thus, an intervention has to be performed by means of thoracotomy. In contrast, chemoembolization of the lung can be performed percutaneously without thoracotomy. Experimental data for chemoembolization of the lung have proved in an animal model that chemoembolization was superior to intravenous chemotherapy in regard to tumor response and was comparable to isolated lung perfusion (11,12). Thus, the purpose of our preliminary study was to evaluate transpulmonary chemoembolization (TPCE) as a treatment for unresectable lung metastases.

Patient Data

Patient Age (y)/ Sex	Diagnosis of Primary Tumor	No. of Treatments	Tumor Volume (mL)		Course
			Pretreatment	After Final Treatment	
33/F	Leiomyosarcoma	4	14.6	6 (−58.9)	Response
44/M	Colorectal carcinoma	2	2.8	5.7 (+103.6)	Progressive disease
44/M	Adenocarcinoma of the lung	2	23.7	22.0	Stable disease
47/F	Squamous cell carcinoma of the tongue	4	13.9	13.4	Stable disease
54/F	Breast cancer	3	14.6	21.7 (+48.6)	Progressive disease
55/F	Carcinoid tumor	2	46.4	28.2 (−39.2)	Response
55/M	Adenocarcinoma of the lung	3	0.6 right/11.0 left	1.1 right (+83.3)/11.3 left	Progressive disease
59/M	Thyroid cancer	4	5.1	2.6 (−49.0)	Response
61/M	Esophageal carcinoma	3	8.3	12.2 (+47.0)	Progressive disease
61/M	Hepatocellular carcinoma	2	29.3	17.9 (−38.9)	Response
62/F	Cancer of unknown primary tumor	2	3.8	4.0	Stable disease
62/M	Renal cell carcinoma	2	5.4	1.7 (−68.5)	Response
63/M	Renal cell carcinoma	2	18.0	16.3	Stable disease
63/M	Colorectal carcinoma	4	1.1 left/1.2 left/ 1.7 left	2.6 left (+136.4)/10.4 left (+766.7)/4.4 left (+158.8)	Progressive disease
67/F	Cholangiocellular carcinoma	3	0.7	1.4 (+100)	Progressive disease
68/M	Leiomyosarcoma	3	4.9	2.2 (−55.1)	Response
69/F	Small cell carcinoma	3	4.4	3.9	Stable disease
74/M	Colorectal carcinoma	3	22.5	31.8 (+41.3)	Progressive disease
74/M	Mesothelioma	2	54.3	48.5	Stable disease
75/M	Hepatocellular carcinoma	2	3.5	1.2 (−65.7)	Response
79/M	Colorectal carcinoma	3	1.9	0.4 (−78.9)	Response
80/M	Colorectal carcinoma	3	5.8	19.8 (+241.4)	Progressive disease
83/F	Colorectal carcinoma	3	33.4	48.3 (+44.6)	Progressive disease

Note.—Data in parentheses are percentages of increase or decrease.

Materials and Methods

Patients

Our prospective study was approved by our institutional review board, and informed consent was obtained from all patients.

A total of 23 patients (eight women, 15 men; age range, 33–83 years; median age, 62 years) with unresectable lung metastases were treated between March 2001 and October 2003 with repetitive TPCE treatments, in keeping with the inclusion-exclusion criteria for our study protocol. The lung metastases were of different origins: colorectal carcinoma ($n = 6$), renal cell carcinoma ($n = 2$), leiomyosarcoma ($n = 2$), and other origins ($n = 13$; Table). In total, 26 metastases were treated, with a mean of 1.1 metastases (range, 1–3 metastases) per patient.

The indication for TPCE was presence of unresectable lung metastases that showed no response to systemic chemotherapy as seen at contrast material–enhanced computed tomography (CT). The criterion for unresectability was multisegmental unilateral or bilateral involvement. The patients had no clinical symptoms and, in particular, had no restriction in lung function. The target metastases ranged in volume from 0.6 to 54.3 mL, and the mean volume of the metastases was 12.8 mL. No histologic proof was obtained in the treated tumors; verification of lung metastases was achieved by observation of an increase in the size of lung nodules on follow-up CT scans. Treatment with TPCE was limited to patients with no extrapulmonary spread. Contraindications to our TPCE protocol were poor performance status (Karnofsky status, <70%), nutritional impairment, neoplastic pleural effusion, poor lung function, and renal failure (serum creatinine level, >2 mg/dL [177 μmol/L]). Partial or complete thrombosis of the pulmonary artery was a further exclusion criterion for the procedure, as was cardiovascular or respiratory failure. To ensure adequate treatment compliance, the patients had to be mentally alert.

In all cases, the primary cancer had been treated with complete surgical resection without residual tumor.

Technique

Our approach is based on a technique used to treat primary and secondary liver tumors (13).

After local anesthesia was induced, a 7-F sheath was inserted into the right femoral vein. Depending on the site of the tumor, a 5-F headhunter catheter (Terumo, Frankfurt/Main, Germany) was inserted into the right or left pulmonary artery by one author (T.J.V.) with more than 15 years' experience in interventional techniques. After angiographic evaluation of the unilateral pulmonary arterial system, performed with use of a manual injection of 10 mL of contrast medium, a hydrophilic guidewire (Terumo) was placed into the segmental pulmonary artery, and the headhunter catheter was advanced. Subsequently, an Amplatz superstiff guidewire (Boston Scientific, Stuttgart, Germany) was inserted, and a balloon catheter (diameter, 7 mm; length, 110 mm) was placed into the selected segmental pulmonary artery. Although the stiff guidewire was considered to cause a greater risk in the procedure, it was preferred to achieve a precise positioning of the balloon catheter in the segmental branches of the pulmonary arterial system. Depending on size, location, and arterial supply of the arteries, the tip of the catheter was advanced further into subsegmental pulmonary arteries with use of the guidewire.

Angiographic series were performed by injecting contrast material after the catheter was blocked to exclude early arteriovenous shunting to pulmonary veins. Mitomycin C (5 mg/m^2; Medac, Hamburg, Germany), which was used as the chemotherapeutic agent, and iodized oil (a maximum of 10 mL; Lipiodol; Guerbet, Sulzbach, Germany) were injected, followed by an injection of 200–450 mg of microspheres (Spherex; Pharmacia and Upjohn, Erlangen, Germany). The embo-

lization suspension was injected slowly under fluoroscopic guidance until stasis of the blood flow was observed.

Only one lung segment was treated in a single chemoembolization session. For all patients, treatment was repeated up to a maximum of four sessions. The number of treatments ranged from two to four treatments per patient, with a mean of 2.8 treatments per patient. For each patient, sessions were separated by at least 2 weeks and by as many as 4 weeks. This allowed patients to recover from treatment.

Follow-up

We evaluated the patients by means of clinical examination (T.J.V., S.Z.) and a questionnaire that was adapted to this type of intervention. The questionnaire contained questions about coughing, chest pain, shortness of breath, fever, and the need for pain medicine. In accordance with the definition of complications established by the Society of Interventional Radiology (14), specific complications were classified as major or minor. Major complications were defined as those that, if left untreated, might threaten a patient's life, lead to substantial morbidity and disability, or result in hospital admission or a substantially lengthened hospital stay. All other complications were considered minor.

Before each treatment, specific laboratory values were monitored. These included white blood cell count, blood platelet count, hemoglobin level, bilirubin level, creatinine level, alanine aminotransferase and aspartate aminotransferase levels, cholinesterase level, and coagulation values.

Both nonenhanced and contrast-enhanced CT were performed 24–48 hours after the intervention and every 3 months thereafter. CT was performed by using a four–detector row spiral CT scanner (Somatom Plus 4 VZ; Siemens Medical Solutions, Erlangen, Germany) with a collimation of 4 × 2.5 mm (four detectors with 2.5-mm section thickness) and a section thickness of 5 mm. The reconstructed sagittal images had a section thickness of 2.5 mm and an increment of 1.25 mm. All images were compared with the previous ones, as well as with the CT scans obtained before TPCE, to assess any changes in size of the treated metastases. The follow-up period lasted at least 6 months and as many as 24 months. Analysis of the CT scans was performed by one of the authors (T.J.V.).

To evaluate treatment success, response was defined in our study as achievement of a volume decrease of at least 25% in the targeted metastasis during the complete course of treatment. Stable disease was defined as no relevant change in size, while progressive disease was defined as an increase in size of 10% or more in a targeted metastasis during TPCE.

Volume measurement was performed by using the transverse CT images to evaluate the largest cross-sectional diameter as the length and the perpendicular diameter as the width. The craniocaudal diameter was measured on reconstructed sagittal images. Tumor volume was calculated on the basis of the evaluated diameters on the transverse images by using the ellipsoidal volume formula: volume = length × width × height × 0.523.

The percentage of iodized oil enhancement was defined as low for less than 25%, as moderate for 25%–50%, and as high for more than 50% retention of iodized oil. The enhancement in the metastasis was measured by evaluating the increase in attenuation caused by iodized oil. For the determination of the degree of iodized oil enhancement, only unenhanced CT images were used.

Results

The mean volume of the metastases was 12.8 mL, with a range of 0.6–54.3 mL. In all treated patients (n = 23, Table), TPCE procedures were performed in the absence of contraindications to the procedure, with an average of 2.8 (range, 2–4) TPCE procedures performed per patient. Technically, repeated TPCE was successfully performed in all patients. After TPCE, none of the evaluated blood parameters was significantly affected. In general, the patients tolerated the TPCE procedure well. No fatal or major complications related to this step of treatment were observed. Three patients showed minor complications as follows: One patient experienced coughing fits, and two patients had a slight elevation in temperature. These symptoms responded to treatment with oral medication. All patients were discharged on the same day after TPCE treatment. There was no procedure-related mortality.

The scans obtained during TPCE treatment showed a moderate to high enhancement with iodized oil in 30% of the embolized metastases (Fig 1) and a low to moderate enhancement with iodized oil in 70% of the embolized metastases (Fig 2).

The maximum uptake was observed in patients with lung metastases of thyroid carcinoma, leiomyosarcoma, renal cell carcinoma, or carcinoid tumor. Morphologic findings at CT included the presence of small regional infarctions in the treated areas.

The CT scans obtained after the final course of TPCE demonstrated a decrease in the size of the treated metastases in eight patients; a mean decrease in tumor volume of 56.8% (6.36 mL), with a range of 38.90%–78.94%, was found as a response to treatment.

In the other patients, imaging after TPCE revealed stable disease in six patients and progressive disease in nine patients; the mean increase in volume of the targeted metastases was 147.9% (4.74 mL), with a range of 41.30%–766.67%.

The group in which metastases were responsive to treatment consisted of patients with leiomyosarcoma (n = 2), hepatocellular carcinoma (n = 2), carcinoid tumor (n = 1), thyroideal carinoma (n = 1), colorectal carcinoma (n = 1), and renal cell carcinoma (n = 1). Five patients in this group had a high percentage of uptake of iodized oil (leiomyosarcoma, n = 2; thyroideal carcinoma, n = 1; renal cell carcinoma, n = 1; and carcinoid tumor, n = 1), and three patients had a moderate uptake of iodized oil (colorectal carcinoma, n = 1; hepatocellular carcinoma, n = 2).

Discussion

The treatment of lung metastases is still a major challenge in modern oncology and includes surgical techniques, systemic chemotherapy, and now also thermoablative procedures such as radiofrequency ablation (15). In the case of metastatic colorectal cancer, multiple sites of metastases do not represent a contraindication for surgery if a complete resection is possible (16). In the small group of patients eligible for surgical therapy, 5-year survival rates of 21%–44% for pulmonary resections of metastases can be achieved (17). Neoadjuvant and adjuvant chemotherapy regimes are aimed at improving resectability and postoperative prognosis. Despite systemic chemotherapy, however, many patients will develop recurring disease. Because of its toxicity, the application of systemic chemotherapy is limited (7). Isolated lung perfusion has proved to be highly effective in animal and clinical models with pulmonary metastases with

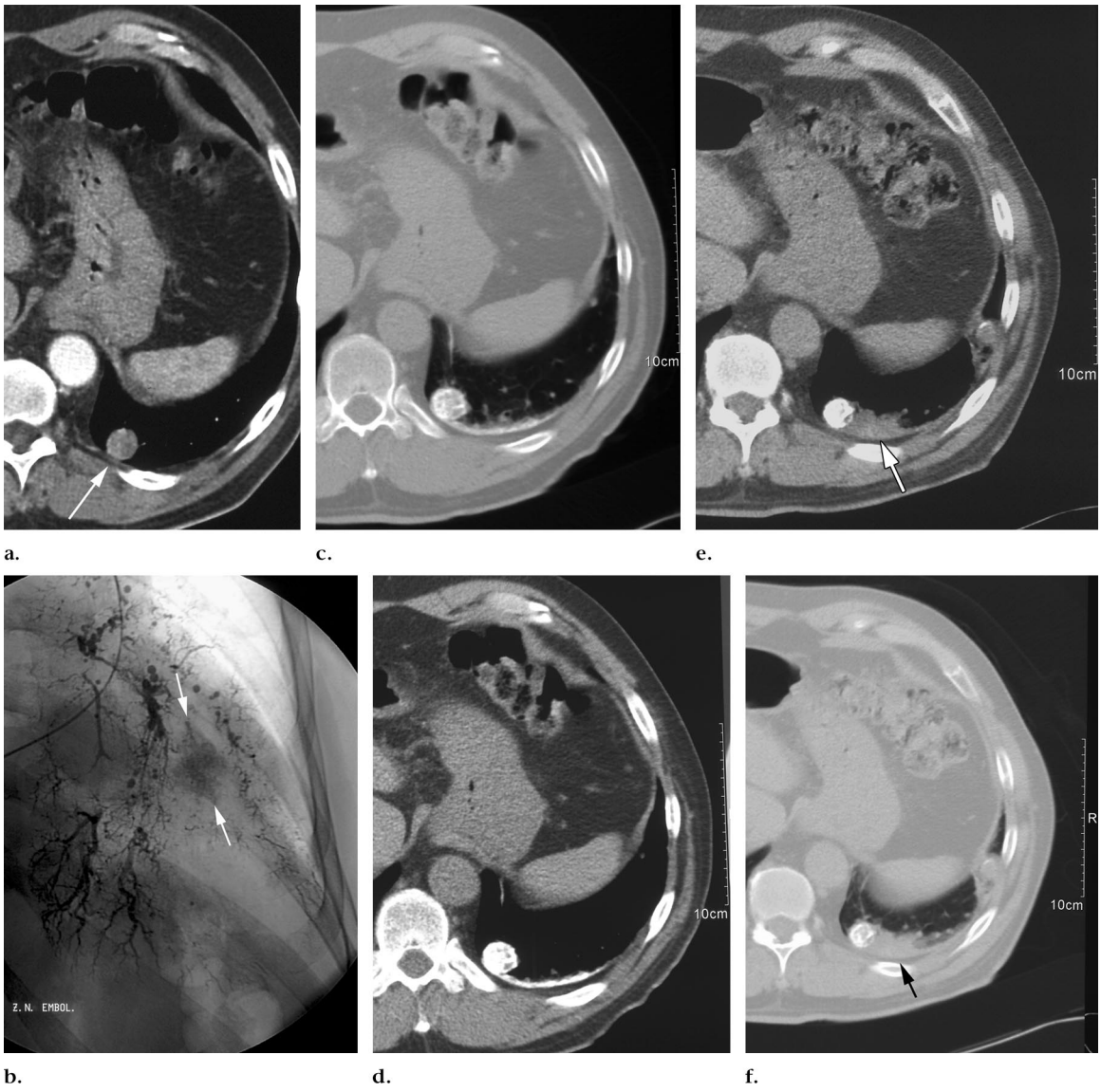

Figure 1. Images in a 68-year-old patient with a lung metastasis of a leiomyosarcoma of the left calf. A high degree of iodized oil enhancement and quantitatively measurable response to treatment were verified. **(a)** Transverse pretreatment CT scan with verification of leiomyosarcoma metastasis (arrow) in the left lower lobe. **(b)** Final angiogram after first course of TPCE of the left tumor-supplying pulmonary arteries with stasis of iodized oil in the vessels and an increased opacity of the tumor (arrows). **(c, d)** Unenhanced transverse CT scans after first course of TPCE show a high degree of iodized oil enhancement in the metastasis. **(e, f)** Unenhanced transverse follow-up CT scans 1 month after the first course of TPCE. A quantitative tumor volume reduction from 4.9 to 2.5 mL was documented. Note the small adjacent lung infarction verified as an area with lung consolidation (arrow).

a quantitative survival advantage, but the procedure has the clear disadvantage of the need for thoracotomy (8,9,18). Few reports exist about radiofrequency thermal ablation of lung metastases (19,20), and the method has to be further evaluated for the treatment of unresectable lung metastases.

As has been successfully implemented for the neoadjuvant or palliative treatment of liver metastases, local chemotherapy could be a promising approach in the treatment of unresectable lung metastases. Schneider et al (11,12) performed a study to compare isolated lung perfusion, systemic chemotherapy, and chemoembolization of the lung in a CC531 animal model by using carboplatin as a chemotherapeutic agent for all applications. Their data showed that chemoembolization was more effective than was intravenous chemotherapy and resulted in no serious toxicity. Its effectiveness was comparable with that of isolated lung perfusion but was less stressful for a possible clinical application. At histologic examination, those authors showed that the area of tumor necrosis was the largest in the chemoembolization group. Isolated lung perfusion achieved the highest cytotoxic concentration of the lung in the metastatic lung nodules with the lowest systemic concentration. In contrast to our presented chemoembolization protocol, isolated lung perfusion requires cannulation of the pulmonary artery and vein, which is an intervention that is only possible with thoracotomy (9,11,19). This is the reason why the pro-

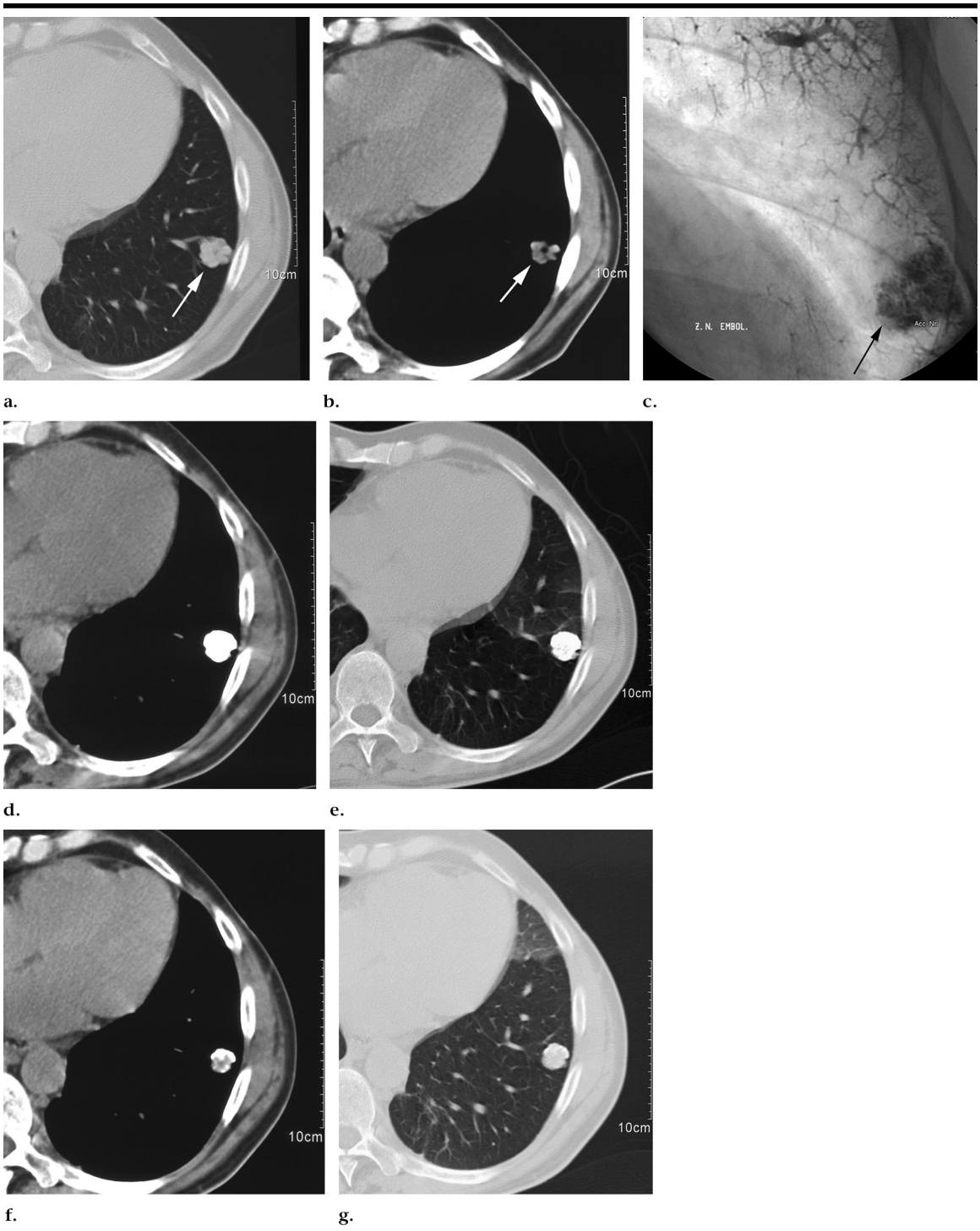

Figure 2. Images in a 59-year-old patient with metastasis of a thyroid carcinoma. A high degree of iodized oil enhancement and quantitatively measurable response to treatment were verified. **(a, b)** Transverse unenhanced pretreatment CT scans with verification of thyroid carcinoma metastasis (arrow) in the left lower lobe. **(c)** Angiogram after TPCE of lung metastasis (arrow) in the left lower lobe. **(d, e)** Transverse unenhanced CT scans show a very high degree of iodized oil enhancement after first course of TPCE. **(f, g)** Unenhanced transverse CT scans after fourth course of TPCE with a volume reduction of the metastasis from 5.1 to 2.6 mL and reduced iodized oil enhancement of 50%.

cedure is stressful for patients and cannot be repeated extensively.

In our opinion, the advantage of the presented method is that it can be performed percutaneously with use of an endovascular catheter. The following factors possibly influenced the outcome of our study: first, the balloon protection used to prevent flow of embolic material into the main pulmonary artery and thereafter into segmental pulmonary arteries and possible arteriovenous shunts;

second, the superselective application of the chemotherapy drug; third, the use of iodized oil, which has been shown to act as a carrier for cytotoxic agents (21); and fourth, the use of microspheres to delay the elimination of the cytotoxic drug.

The main limitations of the study were the relatively small study group, the lack of a control group, and, because of these two points, missing information about the clinical effectiveness of the treatment in terms of a survival advantage of the treated group. Another point is that because we used mitomycin C and microspheres together, we cannot evaluate the single contribution of either the microspheres or the mitomycin C to the tumor shrinkage, as it might be that the ischemia caused by embolization of the microspheres could be the single reason for tumor shrinkage. Indications for the use of TPCE are the local control of lung metastases and thus prevention from progress without any major side effects, as could be expected with systemic chemotherapy. Another indication of TPCE could be the devascularization of lung metastases before intrapulmonary thermal ablations, thus providing a neoadjuvant protocol. In addition, it has to be discussed that, from an oncologic point of view, the palliative indication for such a treatment might be limited owing to the missing clinical symptoms in patients with lung metastases. In summary, the present data prove that TPCE could be a well-tolerated palliative treatment option in patients with lung metastases; however, further studies are needed to evaluate the clinical value and specify the indications of TPCE.

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