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Transpulmonary Chemoembolization: A Novel Approach for the Treatment of Unresectable Lung Tumors

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This article describes the technique of transpulmonary chemoembolization for the palliative treatment of unresectable lung tumors. Early utilization of this method has resulted in reduction in tumor volume and alleviation of patient symptoms. After superselective catheterization, cytotoxic agents are administered, and the pulmonary arterial supply of the tumor is occluded by injection of microspheres and ethiodized oil. Emerging data suggest that this approach is well tolerated.
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The incidence of lung cancer has increased enormously in the last century,[1] and lung cancer is now one of the most common malignant diseases worldwide. In the United States, bronchogenic carcinoma is the second most common cancer for both men and women. In 2002, 169,400 new cases of bronchogenic carcinoma were diagnosed in the United States, and 154,900 people died of this disease, making bronchogenic carcinoma the leading cause of cancer-related death.[2]

Pulmonary metastases from primary tumors at other sites are also a major problem: between 20% and 30% of patients suffering from cancer develop pulmonary metastases.[3]

The prognosis for patients with bronchogenic carcinomas or pulmonary metastases is poor. In patients with stage I and II bronchogenic carcinoma, resection offers the best chance for long-term survival,[4-7] but only 25 to 30% of such tumors are resectable.[4-6] The mean survival duration after diagnosis is 12 months for patients with bronchogenic carcinomas and less than 1 year for patients with unresectable pulmonary metastases. Five-year survival rates are 10% for patients with bronchogenic carcinoma overall;[5] 23 to 50% for patients with bronchogenic carcinoma who undergo resection[4,8-10] and 1%[1] for patients with unresectable bronchogenic carcinomas. In patients who undergo resection of pulmonary metastases, the 5-year survival rate is 20 to 46%.[11-18]

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Standard Treatment Options for Bronchogenic Carcinoma and Pulmonary Metastases

Countless therapy regimens, including radiotherapy and chemotherapy,[1] have been tested as alternatives to tumor excision or as neoadjuvant therapy in patients with bronchogenic carcinoma or pulmonary metastases. Although such regimens have shown promising results[19] the overall response rates remain poor.[1] For combined chemotherapy, the overall response rates are 20 to 50%[20,21]; for single-agent therapy with doxorubicin, the overall response rate is 20 to 30%. The main limitation of these approaches has been the chemotherapy-associated toxicity when delivered via the intravenous route.[22]

Isolated Lung Perfusion

In the 1950s, isolated lung perfusion was developed as an experimental technique to improve the outcome in patients with pulmonary metastases from different tumors. The goal of isolated lung perfusion is to accomplish a closed circulation system by cannulation of pulmonary arteries and veins to allow injection into the lung of high-dose chemotherapy with minimal systemic toxicity.[23,24] This idea was reintroduced in the 1980s and tested as a potential alternative to systemic chemotherapy.[25,26] With isolated lung perfusion, it is possible to obtain drug concentrations near the tumor site twice as high as those achieved with systemic chemotherapy with only 25% of the systemic dose.[27] Several recent animal studies have reconfirmed that tumor drug concentrations and therapeutic efficacy are significantly higher[28,29] with isolated lung perfusion than with systemic chemotherapy.

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Despite these interesting results, isolated lung perfusion is not yet established clinically. The reasons for this may include the relative complexity and paucity of knowledge regarding the technical aspects of the procedure[30] combined with the limited number of robust human trials to date. The main limitation of isolated lung perfusion is that cannulation of pulmonary vessels is required, which necessitates either thoracotomy or other minimally invasive operative techniques[31] that cannot be repeated indefinitely. Furthermore, extracorporeal circulation is an integral part of these approaches.[32-34]

Transpulmonary Chemoembolization

An alternative to isolated lung perfusion is transpulmonary chemoembolization. Transpulmonary chemoembolization is performed percutaneously, obviating the need for more invasive procedures. In a CC 531 rat model, transpulmonary chemoembolization and isolated lung perfusion were both found to be equally superior to systemic chemotherapy in terms of response, and chemoembolization and isolated lung perfusion have shown similar results.[35] However, one of the most important benefits of transpulmonary chemoembolization over isolated lung perfusion is that transpulmonary chemoembolization can be repeated indefinitely, whereas isolated lung perfusion is most often a one-time therapy.[36]

Transpulmonary chemoembolization is a form of transarterial chemoembolization, which is an established treatment option for primary and secondary liver tumors.[37] Transpulmonary chemoembolization is applicable to the treatment of several unresectable lung lesions because of their supply via the pulmonary artery.[38] The purpose of transarterial chemoembolization is to block the vessels supplying a tumor by injecting chemotherapy simultaneously with embolic material. With this approach, the deposit time of the injected cytostatic drugs in the lesion is extended,[39] and an outflow into the periphery is avoided, thus reducing the incidence and the severity of the systemic side effects.

Anatomical Considerations

The blood supply of the lung is based on vasa publica, which belong to the functional circulation, and vasa privata, which are the nutritive vessels. The pulmonary arterial system provides blood to be oxygenated within the alveoli, and the superior and inferior pulmonary veins that deliver the oxygenated blood to the main circulation are part of the vasa publica. Vasa privata consist of the bronchial arteries, usually originating on the left-hand side from the thoracic aorta and on the right-hand side from the third and fourth intercostal arteries. Venous blood is applied to the azygos vein but also to the pulmonary veins via the bronchial veins.

As mentioned previously, several lung nodules are supplied by the pulmonary artery.[39] Others are fed by the bronchial arteries. Due to anastomoses between vessels originating from the bronchial arteries and the pulmonary artery these nodules can also be treated via the pulmonary artery.

One must be aware of the anastomoses between the bronchial arteries and the nutritive vascular supply of the spinal cord. Embolization via the bronchial arteries may result in serious complications such as paraplegia.

Indications and Contraindications

Indications

Transpulmonary chemoembolization should be performed only in patients who harbor histologically proven primary or secondary lung tumors, which were classified as unresectable and refractory to prior systemic therapy. Inclusion criteria are as follows: good performance status with a Karnofsky index >70%, and uncompromised lung function. At present, we have no limitations regarding tumor size, vascularity, or chest wall invasion.

Contraindications

Contraindications for the transpulmonary chemoembolization procedure include a Karnofsky status <70%, poor nutritional status, malignant pleural effusion, poor lung function (<60% of the normal vital capacity), serum creatinine level >2 mL/dL, hemoglobin level <14g/dL, white blood cell count (WBC) <3000 cells/mm^3, partial or complete thrombosis of the pulmonary artery, cardiovascular and/or respiratory failure, and overt arteriovenous shunting to the pulmonary venous circulation as seen angiographically. Additional contraindications for this procedure include coagulopathy (platelet count <5000/mm^3, prothrombin activity <50%) and renal insufficiency (serum creatinine >2 mg/dL [177 μmol/l]). Finally, the transpulmonary chemoembolization should not be performed in women who are pregnant or breast-feeding and in patients who suffer from a severe allergy to iodinated contrast media.

Preprocedure Workup

Before treatment, laboratory parameters, such as hemoglobin and creatinine levels, and platelet and white blood cell counts, are evaluated. Patients then undergo computed tomography of the chest to confirm the lesion to be treated (Fig. 1), to verify its location, and to have a baseline assessment of size necessary to evaluate changes in its measurements during the repetitive therapy sessions. Finally, pulmonary function tests are performed.

Technical Aspects of Transpulmonary Chemoembolization

The technique for transpulmonary chemoembolization is as follows: local inguinal anesthesia is induced, and depending on the affected side, a 5-French Headhunter catheter (Terumo, Frankfurt/Main, Germany; Fig. 2A) is placed via a 7-French sheath into the right or left pulmonary artery. Over a guidewire inserted into the segmental pulmonary artery of interest, the Headhunter catheter is advanced under fluoroscopic visualization, and an exchange length Amplatz superstiff guidewire (Boston Scientific, Stuttgart, Germany) is inserted for positioning a balloon catheter (diameter, 7 mm;

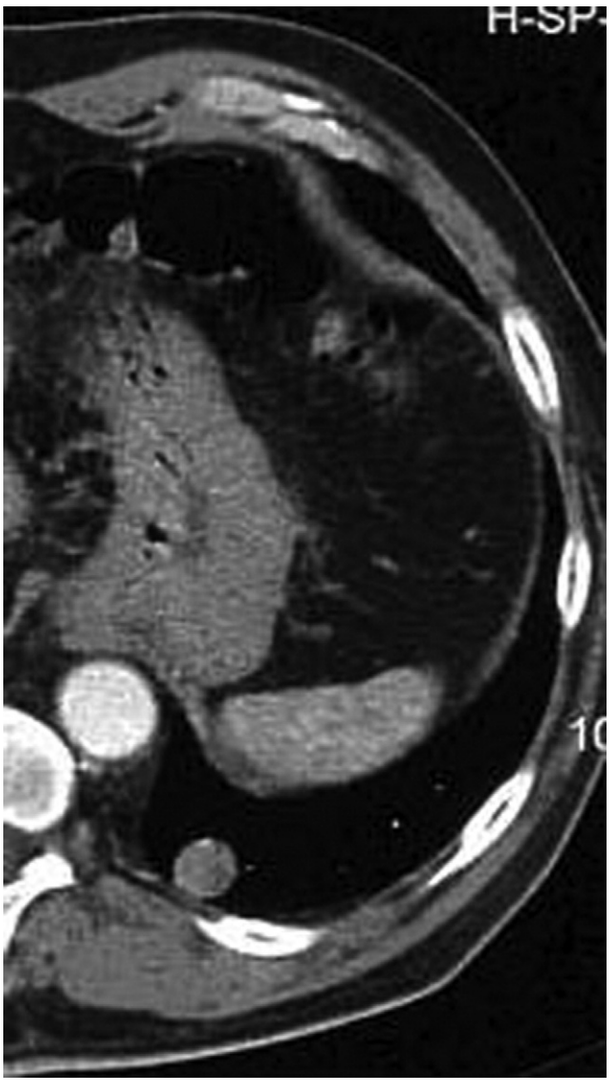

Figure 1 Baseline contrast-enhanced chest CT scan in a patient with a pulmonary metastasis verifies the presence of a lung nodule within the left lower lobe.

length, 110 mm; Fig. 2B) into the segmental pulmonary artery to be treated.

Unilateral pulmonary arteriography is then performed to assess tumor vascularity (Fig. 2C). To prevent shunts between the arterial and venous systems, the balloon catheter is inflated and the angiographic series repeated. At our institution, 5 mg/m^2 Mitomycin C (Medac, Hamburg, Germany) is drawn up in 50 mL of sodium chloride and then mixed with a maximum of 10 mL of iodized oil (Lipiodol; Guerbert, Sulzbach, Germany). After the emulsion is injected, 200 to 450 mg of microspheres (Spherex; Pharmacia and Upjohn, Erlangen, Germany; diameter: 45 μm) is administered under fluoroscopic control until blood flow ceases (Fig. 2D).

Potential Complications

Potential complications caused by the transpulmonary chemoembolization procedure are a "postembolization syndrome," which is characterized by pain, nausea, and fever. This complication can easily be managed by orally administered medications. Furthermore, lung infarction (Fig. 3) with secondary pneumonia, pleural effusion, and atelectases also may be seen but is rare. If the catheter is not advanced carefully into the pulmonary artery, a dissection of the vessel membrane might result. Last, when administering mitomycin C, the operator should be fully aware of its varied and serious multiorgan toxicities. Furthermore, mitomycin C might cause pulmonary fibrosis and some patients might develop allergic reactions to this medication.

Outcomes of Transpulmonary Chemoembolization

In 2005, a preliminary study examined transpulmonary chemoembolization with mitomycin C as an option for treatment of unresectable lung metastases in 23 patients.[40] All patients fulfilled the previously mentioned inclusion criteria for the procedure and had been previously treated with systemic chemotherapy without any response. In this study, 26 lung metastases were treated 2 to 4 times each at intervals of 2 and 4 weeks. A baseline noncontrast and contrast-enhanced chest CT scan was obtained before the transpulmonary chemoembolization procedure. After the procedure, additional chest CT scans (Fig. 4) were performed at 3-month intervals to enable the measurement of treated tumor sizes and to show their changes during treatment. Patient follow-up lasted between 6 and 12 months.

The study demonstrated that transpulmonary chemoembolization was easily accomplished, well tolerated, and associated with a low complication rate. All patients were discharged from the hospital on the same day of the procedure. Although patients demonstrated nonspecific symptoms such as fever and nausea, there were no major complications and the previously mentioned laboratory parameters were not affected.

In this study, 35% of patients had a response, 26% had unchanged tumor volume, and 39% experienced progressive disease. Response and progressive disease were defined according to the World Health Organization criteria: response was defined as a decrease in tumor volume of at least 25%, and progressive disease as an increase in tumor volume of at least 10%. Smaller changes in tumor volume were defined as stable disease. Response to treatment correlated positively with vascular supply—well-perfused metastases, such as metastases from leiomyosarcoma, renal cell carcinoma, and thyroid carcinoma, showed the most uptake of ethiodized oil and the largest reduction in tumor volume.

Transpulmonary Chemoembolization with Drug-Eluting Beads

Currently, treatment with drug-eluting beads[41] is being evaluated as an alternative to the present method of transpulmonary chemoembolization. These beads are mi-

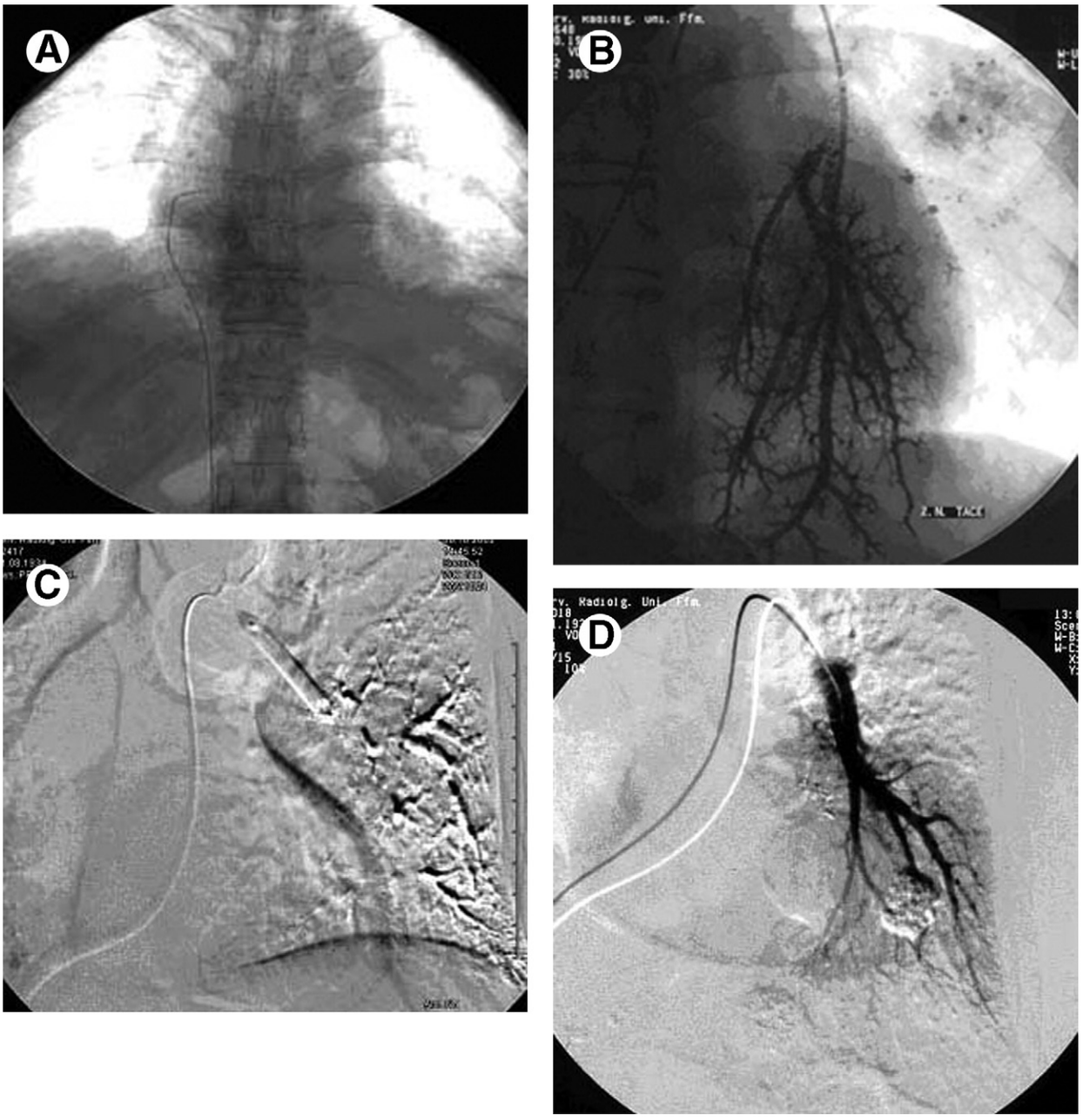

Figure 2 Transpulmonary chemoembolization procedure. (A) A Headhunter catheter is advanced from a right femoral vein approach into the vena cava inferior/right atrial junction via a 7F sheath. (B) The pulmonary artery to be treated is catheterized and angiographic series are performed to evaluate feeders and to detect any arteriovenous shunts (none seen). (C) A balloon catheter is used (diameter: 6-8 mm; length: 20-30 cm) for the administration of 5 to 10 mg of mitomycin C (in 50 mL of sodium chloride), 5 to 10 mL of lipiodol, and 300 mg of spherex until stasis is achieved. (D) Final pulmonary arteriogram shows uptake of chemoembolization agent and absence of vascularity within left lower lobe nodule.

crospheres consisting of starch that are loaded with cytostatic agents such as doxorubicin.[42] The expected advantages of embolization using beads include procedural simplification and a more controlled drug release over a longer period of time. Moreover, these beads could decrease systemic toxicity by reducing peak systemic plasma levels of the chemotherapeutic agent. Due to the prolonged exposure of the tumor to chemotherapeutic agents, better tumor response rates might be achieved.[43]

Transpulmonary Chemoembolization in Multimodality Therapy of Pulmonary Metastases and as a Single Therapy Option

Long-term survival rates in patients with pulmonary metastases who undergo resection are no higher than 46%[11-18];

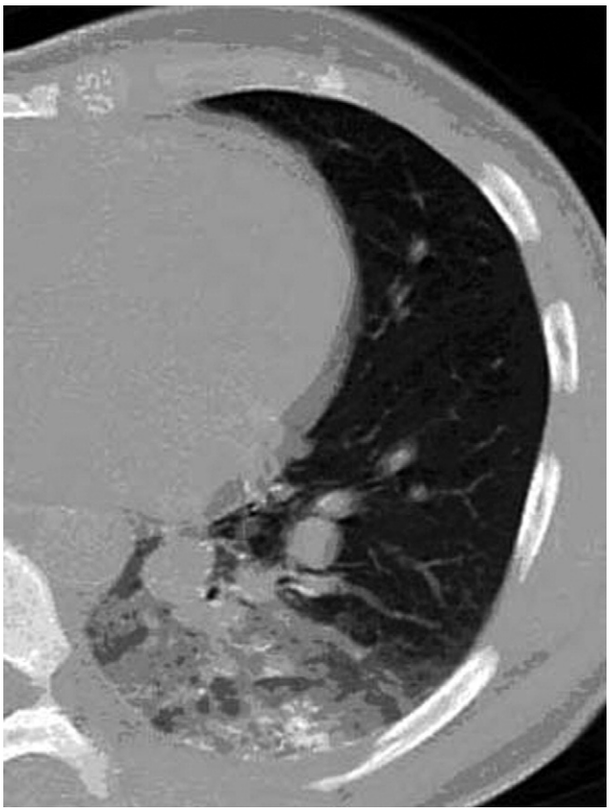

Figure 3 Noncontrast chest CT scan after first treatment shows uptake of ethiodized oil within left lower lobe nodule.

thus, treatment of pulmonary metastases remains a major clinical challenge. Application of systemic chemotherapy has shown promising short-term results, but long-term survival remains poor.[1] Therefore, improvements as they are offered by multimodality therapy regimens are necessary.[44] A significant survival advantage for patients treated with multimodality therapy was demonstrated in a recent study that compared multimodality therapy (including modified pharmacokinetic-modulating chemotherapy, radiotherapy, and radiofrequency ablation) with single-agent chemotherapy. For patients who underwent multimodality therapy, the 3-year survival rate was 87.5%; for those who received single-agent chemotherapy, the 3-year survival rate was 33.3%.[45]

Combined therapy with surgical ablation and chemotherapy could be another treatment option of pulmonary metastases.[46] In patients treated with such approaches, transpulmonary chemoembolization would be possible with all its advantages over systemic chemotherapy. However, only 30% of patients with pulmonary metastases are eligible for surgical therapy.[35] In the remaining patients, transpulmonary chemoembolization could be accomplished as a single-therapy option, with isolated lung perfusion reserved for patients already scheduled for metastasectomy[36] in whom a thoracotomy must be performed anyway. In our practice, thermal ablation as another therapy option is not performed before systemic chemotherapy or chemoembolization because of the risk of tumor seeding.

Limitations of Transpulmonary Chemoembolization

The number of transpulmonary chemoembolization-treated patients remains small, and studies to date have not included control groups, thereby limiting any definitive conclusions regarding its clinical integration. Compounding the problem, due to the synchronous application of mitomycin C and microspheres, no conclusions can be drawn about their relative contributions in the observed instances of tumor regression.

Conclusion

In summary, transpulmonary chemoembolization is a well-tolerated option in the treatment of lung cancer. Multidisciplinary efforts are needed to determine the additive benefit of

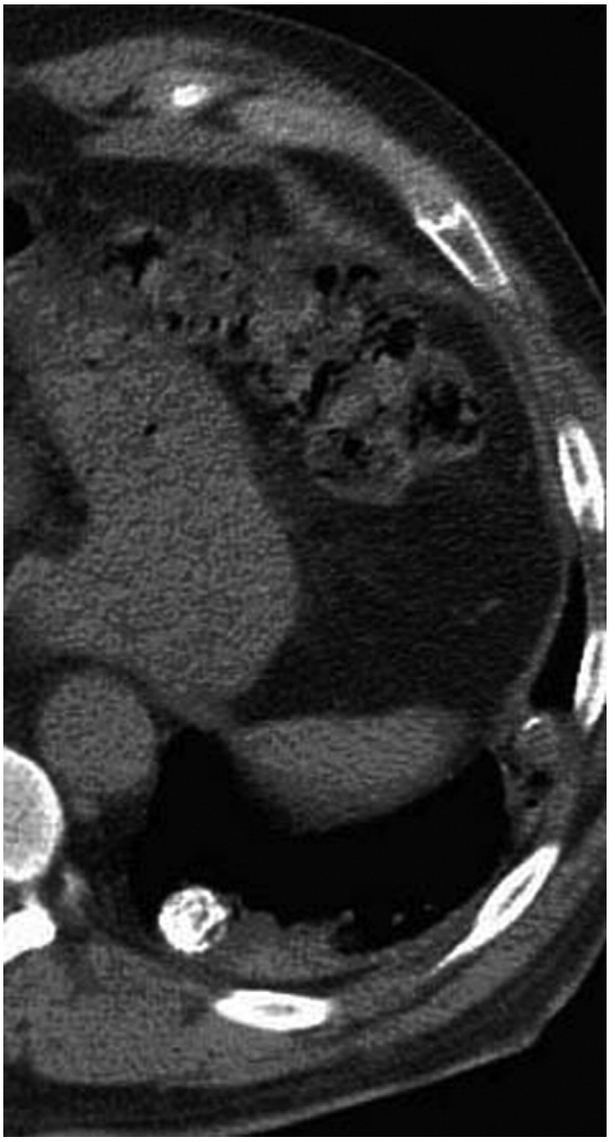

Figure 4 Noncontrast chest CT scan shows wedged-shaped abnormality consistent with pulmonary infarction of the left lung after chemoembolization.

this technique in the armamentarium of therapies currently available for the care of these patients.

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