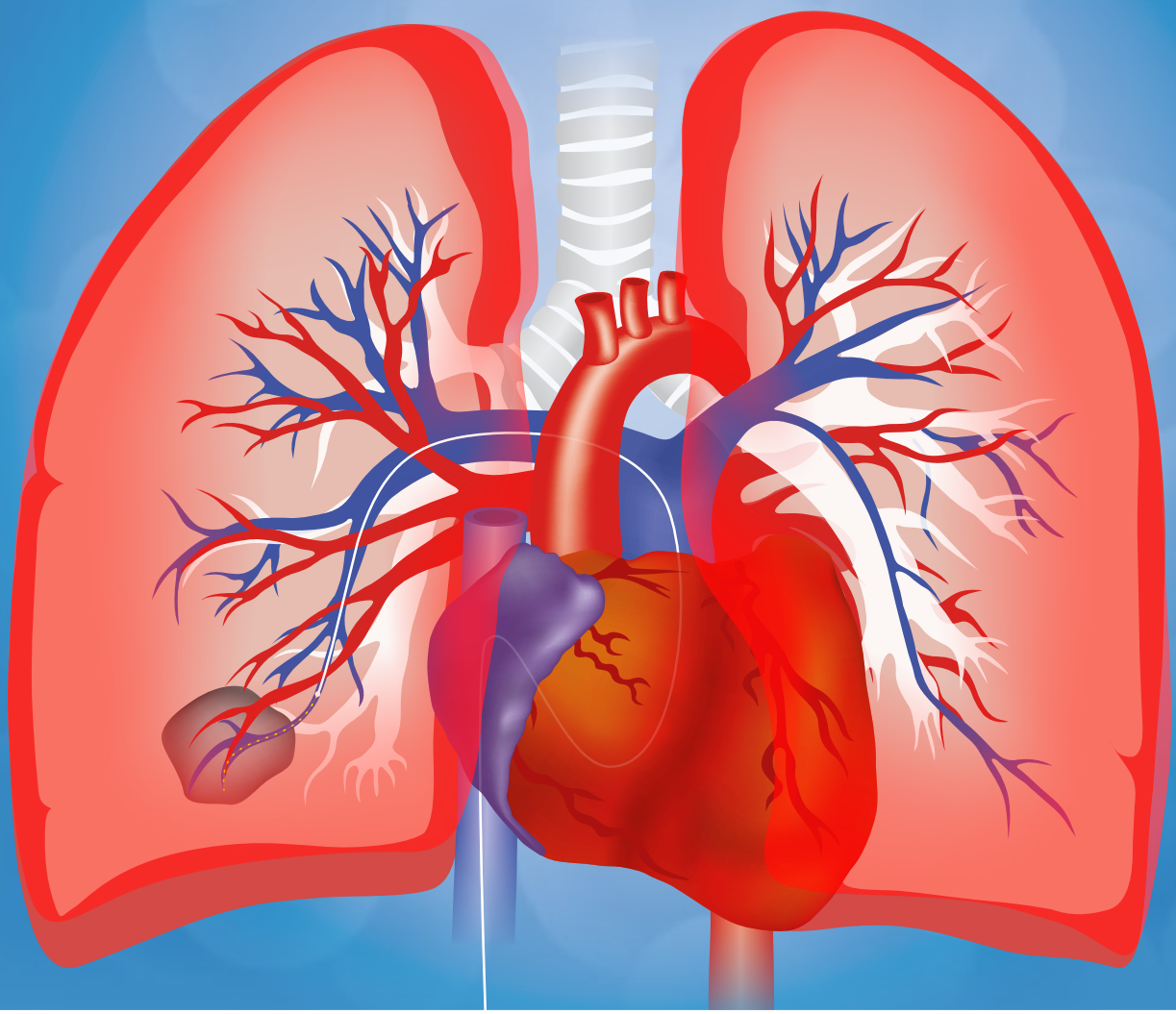
EmboCept® S

degradable starch microspheres

Indication: lung tumors

Transpulmonal chemoembolization (TPCE) with degradable starch microspheres (DSM)



The only degradable embolization agent for TPCE

Incidence and mortality

Since several decades lung cancer is the most often diagnosed cancer type worldwide with estimated 1.8 million new cases in 2012. Age-standardized incidence rates in men (34.2 cases per 100,000) are about three times higher as in women (13.6 cases per 100,000). At the same time, lung cancer is the most common cause of deaths among all cancer types with estimated 1.6 million deaths in 2012, which represents almost 20 % of all cancer deaths [1].

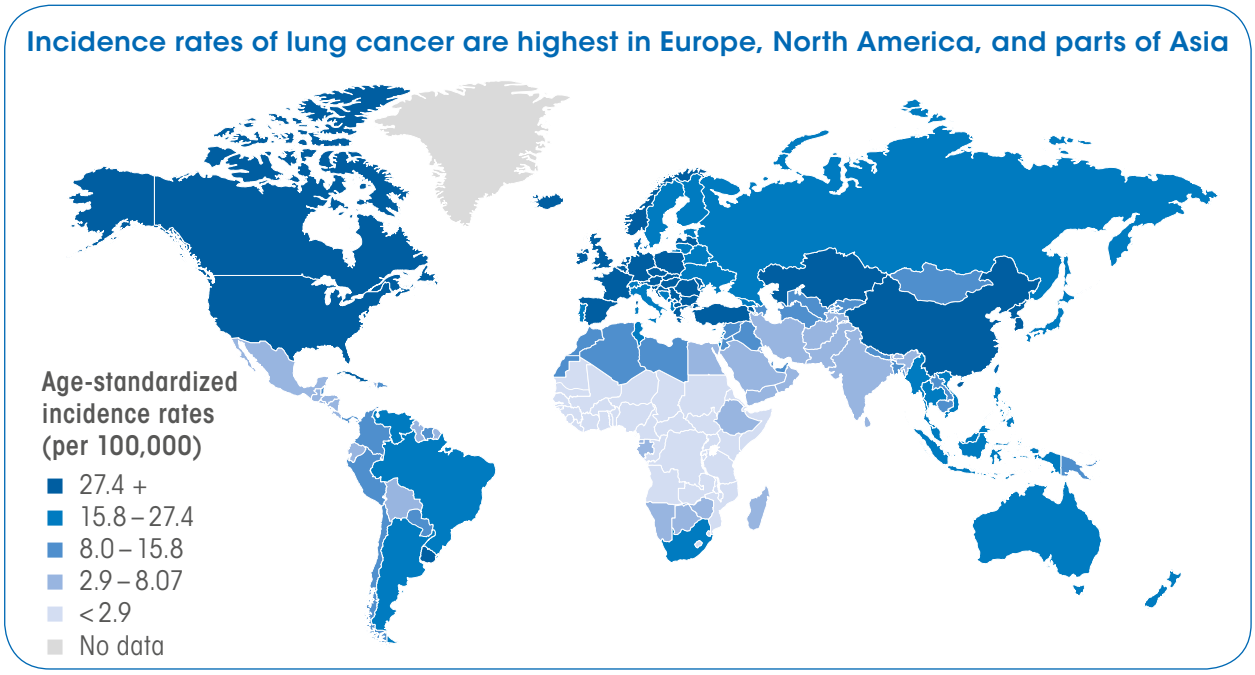


Figure 1: Global age-standardized incidence rates (per 100,000) of lung cancer (both sexes); modified from [2].

Types of lung tumors

Primary lung tumors are categorized according to cytologic differentiation into small or non-small cell lung cancer (SCLC and NSCLC, respectively), as therapeutic options for both types differ. The latter group is further subdivided according to histological and genetic parameters [3]. In addition, some primary tumors metastasize to lungs which are then called secondary lung tumors. The treatment of lung metastases depends on the primary tumor and is specified in the respective guideline.

Table 1: Frequency of different lung tumor types.

Primary lung tumors		Secondary lung tumors
SCLC	NSCLC	
~15 % of primary lung cancers [4]	~85 % of primary lung cancers [4] Classified according to histology into squamous carcinoma, adenocarcinoma, and large cell carcinoma [3]	Metastases of other primary tumor types, in particular: colon, kidney, breast, prostate, and oropharyngeal carcinoma or melanoma. 20 – 30 % of cancer patients develop metastases in the lung [5]

Treatment options

Depending on tumor type and stage a variety of surgical and non-surgical treatment options and algorithms exists for primary lung tumors. Lung metastases are likewise treated with surgical and non-surgical therapies, which also depends on size and position of the metastases and the pre-treatments of the primary tumor.

Therapies used to treat lung cancer:

- Surgery (lobectomy, video-assisted thoracoscopic surgery, limited resection, pneumonectomy)
- Ablation
- Chemotherapy including regional lung chemotherapy
- Radiotherapy
- Targeted therapy (e.g. patients with tyrosine kinase mutations)
- Immunotherapy

While surgery offers the best chances for long-term survival for patients with early stage tumors, only 25–30% of these tumors are resectable [5]. For unresectable lung tumors systemic chemotherapy, radiotherapy, targeted therapy, and local TPCE are the most remaining treatment options. Table 2 compares the outcome of TPCE, systemic chemotherapy, and targeted therapy as third- or further-line therapy.

Table 2: Comparison of treatment outcomes according to type of therapy in third- or further-line therapy of primary lung cancer.

	Transpulmonary chemoembolization (TPCE)** [6]	Systemic chemotherapy* [7]	Targeted therapy** [7]
RR	Mean 23.5 %	Median 11 % (range: 0 – 23 %)	EGFR inhibitors: Median 8.5 % (range: 0 – 50 %) VEGF inhibitors: Median 3 % (range: 0 – 12 %)
OS	Median 13.1 months (95 % CI: 10.7 – 15.6 months)	Median 10.25 months (range: 6.8–13.7 months)	EGFR inhibitors: Median 7.5 months (range: 5.2 – 10.8 months) VEGF inhibitors: Median 4.1 months (range: 6.1 – 9.25 months)

RR: response rate, OS: overall survival, CI: confidence interval,
* third-line,
** third- or further-line

Regional lung chemotherapy

A common problem of systemic chemotherapy is the low drug concentration at the tumor site preventing full efficacy potential of the drug. In addition, systemic chemotherapy is often accompanied by adverse events, which influence patients' quality of life. Regional lung chemotherapy is a therapeutic option that addresses both issues [8]:

- Increasing the concentration of chemotherapeutics and inducing ischemia within the tumor
- Accelerating tumor response by direct application at the tumor site
- Decreasing the risk for systemic adverse events

Different local-regional therapies can be used for targeted drug delivery in the lung [8]:

- Bronchial artery infusion (BAI): injection of single or multiple agents via insertion of a catheter into the bronchial artery
- Isolated lung perfusion: cannulation of pulmonary blood vessels to establish extra-corporeal circulation and deliver the active agent exclusively to the lung
- Lung suffusion: slow, diffuse permeation of the tissue by an injection during occlusion of arteries or veins
- Different techniques for chemoembolization:
  1. TPCE (via venous cannulation): occlusion of tumor supplying **pulmonary arteries** during local application of chemotherapeutic agents (figure 2)
  2. Transbronchial chemoembolization (via arterial cannulation): occlusion of tumor supplying **bronchial arteries** during local application of chemotherapeutic agents (figure 2)

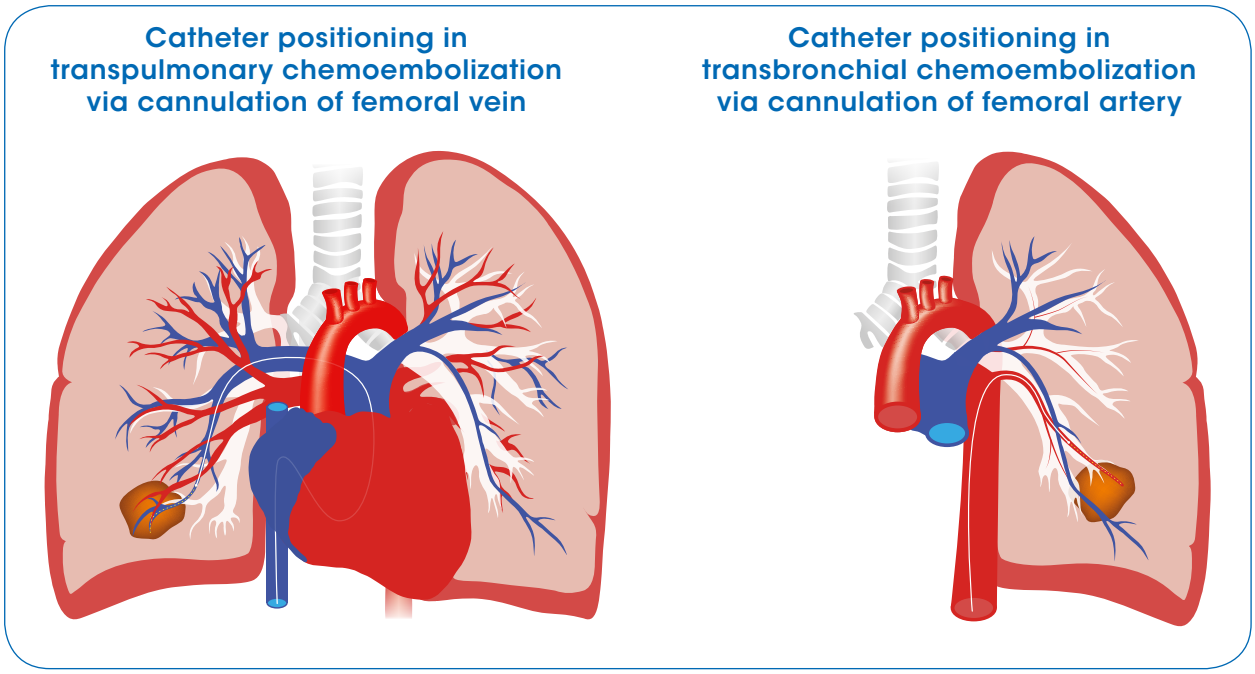


Figure 2: Illustration of the different catheter positioning in transpulmonary and transbronchial chemoembolization.

Rationale for TPCE

Although tumor resection offers the best prognosis for patients with stage I or II primary lung cancer, only 25–30% of these tumors are resectable [5]. For patients with unresectable lung tumors TPCE is a valuable treatment option. As compared to systemic chemotherapy, TPCE not only reduces systemic side effects and increases intratumoral chemotherapeutic concentrations via local application, but also **delays drug wash-out** by occluding tumor supplying blood vessels. In addition, the embolization causes tumor ischemia, leading to necrosis. In contrast to isolated lung perfusion, TPCE is a **percutaneous technique** without the need for thoracotomy. This allows **repeated application** of TPCE [6]. Furthermore, TPCE does not bear the risk of spinal ischemia [6].

TPCE technique

Patients that are in good general condition, without or with only minor cardiovascular co-morbidities, with sufficient lung function and a non-thrombosed *A. pulmonalis* are suitable for TPCE treatment.

TPCE step by step [9]:

1. Control of laboratory parameters (e. g. hemoglobin, creatinine, bilirubin, leukocytes, thrombocytes, and blood clotting), clinical status, and CT/MRI
2. Regional anesthesia by applying 1 % mepivacain via a 7F sheath inserted into the right femoral vein
3. Placement of a 5F headhunter catheter into the right or left pulmonary artery via transvenous access (figure 3)
4. Pulmonary angiography by injecting 20 ml of contrast medium to survey the arterial system
5. Optional: positioning of a balloon catheter (diameter: 6 – 8 mm, length: 100 – 300 mm) into the segmental pulmonary artery
6. Advancement of the catheter further into the subsegmental pulmonary arteries using a guidewire
7. Detection of arteriovenous shunts by blocking the catheter and performing a contrast-enhanced angiographic series. Termination of the procedure when arteriovenous shunts are detected
8. Careful injection of the chemotherapeutic agent mixed with DSM under fluoroscopic guidance until stasis of blood flow is achieved
9. Application of a pressure dressing upon removal of catheters
10. Post-interventional evaluation of laboratory parameters, clinical status, and CT/MRI
11. Repetition of treatment (at least 2 – 3 times) with intervals of four weeks

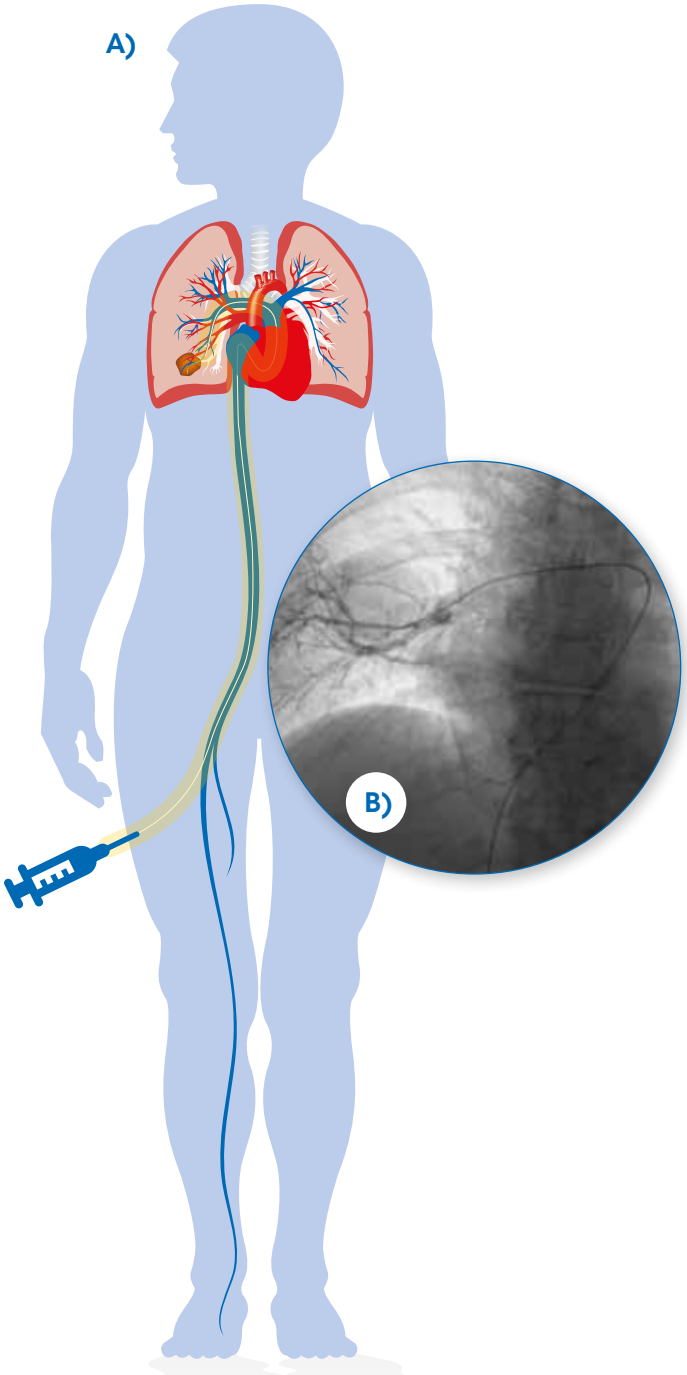


Figure 3: (A) Illustration of the TPCE technique depicting the positioning of the catheter via access through the right femoral vein into the pulmonary artery. (B) Angiography of a TPCE procedure (courtesy of T. Vogl).

Results of DSM-TPCE

Preclinical studies:

Preclinical studies utilizing different animal models demonstrated temporary arterial occlusion and tumor responses upon transpulmonary embolization with DSM without short- and long-term toxicities.

Temporary arterial occlusion in porcine models:

- Chemoembolization and subtotal occlusion of the entire arterial tree of the right pulmonary artery in a pig model followed by reperfusion within 25 – 40 minutes [10] (in humans 2h after DSM-TACE complete recovery of blood flow [11])

Angiographic demonstration of temporary pulmonary artery occlusion during transpulmonary embolisation with DSM

Figure 4: Angiography of temporary embolization in a porcine model. (A) Prior to embolization. (B) Complete stasis within the left pulmonal artery during embolization. (C) After embolization (courtesy of Dr. C. Meyer, „Bonner Interventionstage 2012").

➡ **DSM-TPCE is safe and reversible**

Safety profile in porcine models:

- An initial decrease of oxygen saturation from 100 % to maximally 80 % was restored five minutes after start of treatment [10] (figure 5)
- No significant effect on pulmonary arterial blood pressure and heart rate occurred [12]
- No early toxic effects such as edema or structural lung damage and no long-term toxicities like lung fibrosis or permanent perfusion obstruction were observed [10, 12]
- No non-target embolization to the brain was detected [12]

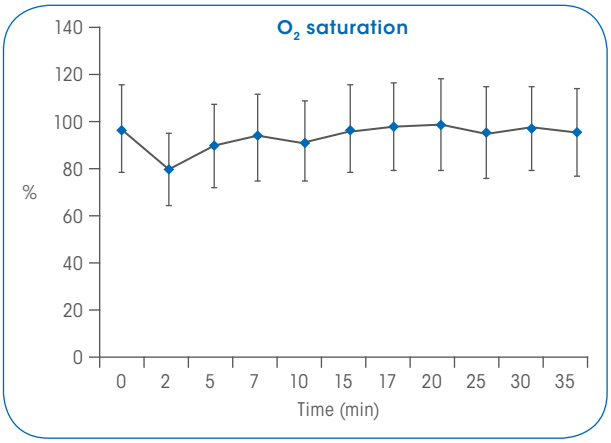


Figure 5: Oxygen saturation during and after DSM-TPCE in a porcine model; modified from [10].

➡ **DSM-TPCE is well tolerated because no toxic short- or long-term effects occur**

Tumor response in a solitary metastasis rat model:

- Intravenous therapy, isolated lung perfusion, and DSM-TPCE resulted in significantly less tumor growth (smaller tumor volume differences before and after treatment) as compared to control groups, which showed substantial tumor volume increases [13] (figure 6)
- DSM-TPCE resulted in significantly less tumor growth than intravenous therapy, despite using 66,7 % less carboplatin [13] (figure 6)
- Response to DSM-TPCE was comparable to isolated lung perfusion [13]
- Tumor volume was significantly smaller after DSM-TPCE than before treatment [13]

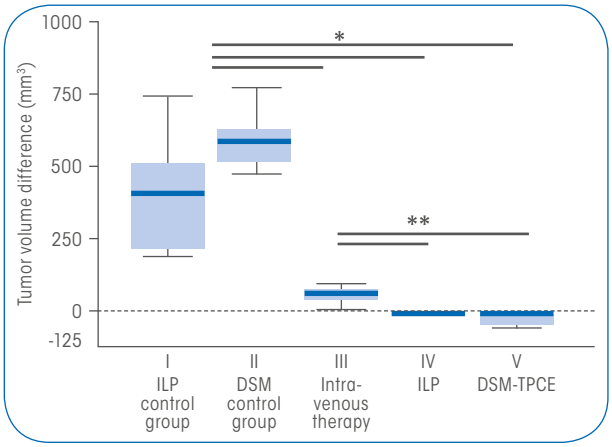


Figure 6: Tumor volume differences before and after treatment in a solitary metastasis rat model of CC531 adenocarcinoma. Rats in the isolated lung perfusion (ILP) and DSM control group both received treatment without chemotherapeutic agent. Intravenous therapy, ILP, and DSM-TPCE included application of carboplatin; modified from [13].
* P < 0.05 groups I and II vs groups III, IV, V;
** P < 0.05 group III vs groups IV and V.

➡ **DSM-TPCE results in reduction of tumor volume and is more effective than i. v. application**

Clinical studies:

Efficacy and safety data of preclinical studies could be confirmed in clinical trials in patients with primary lung cancer and lung metastases.

Efficacy:

Primary lung cancer:

- In a study with 17 patients with inoperable, chemo- and radiotherapy resistant primary lung tumors that were treated with 2 – 8 DSM-TPCE sessions, more than 60 % of patients achieved tumor volume reduction or stable disease. Mean time to progression was 2.4 months (range: 0.7 – 6.1 months) and median overall survival was 394 days (95 % CI: 320.6 – 476.3 days) [6] (figure 7 and 8, page 8)

Lung metastases:

- Two studies investigated tumor response to DSM-TPCE in patients with lung metastases of different origin. A preliminary study with 23 patients showed decreased tumor size of at least 25 % in eight patients with a mean volume reduction of 56.8 %, stable disease in six patients, and progressive disease in nine patients [14]. In a larger study including 52 patients that had 106 unresectable lung metastases of different origin and that were treated with 2 – 10 DSM-TPCE sessions, tumor responses or stable disease according to RECIST (response evaluation criteria in solid tumors) were observed in more than 50 % of patients. Mean time to progression was 5.5 months (range: 1 – 67 months) and median overall survival was 21.1 months (95 % CI: 4.2 – 38 months) [9] (figure 9 and 10, page 8)

- Evaluation of the achieved tumor response rates should consider that included patients had advanced stages of lung cancer or lung metastases and that overall response rates for systemic chemotherapy are 20–50 % for combination chemotherapy and 20–30 % for doxorubicin monotherapy indicating the difficulty of treating lung cancer [9]. Nevertheless, DSM-TPCE achieved tumor responses and stable disease in > 50 % of patients

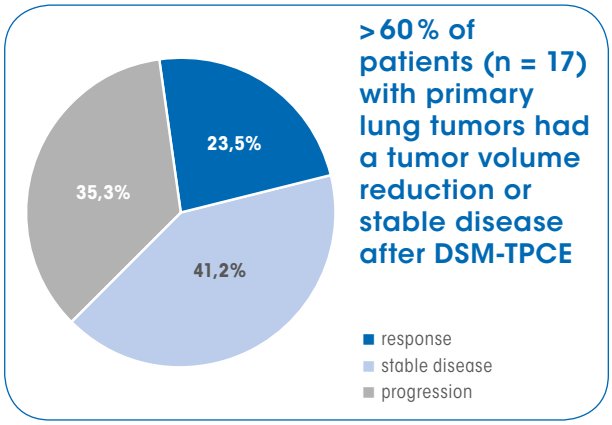


Figure 7: Tumor response according to the definition of the world health organization after DSM-TPCE in patients with primary lung cancer; modified from [6]. Response = volume reduction of > 25 %; stable disease = non-significant volume change; progression = volume increase of > 10 %.

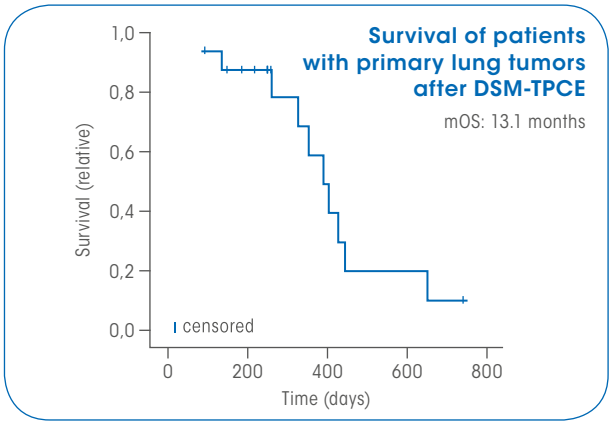


Figure 8: Survival curve of patients with primary lung tumors (n = 17) after DSM-TPCE; modified from [6]. mOS: median overall survival, CI: confidence intervall

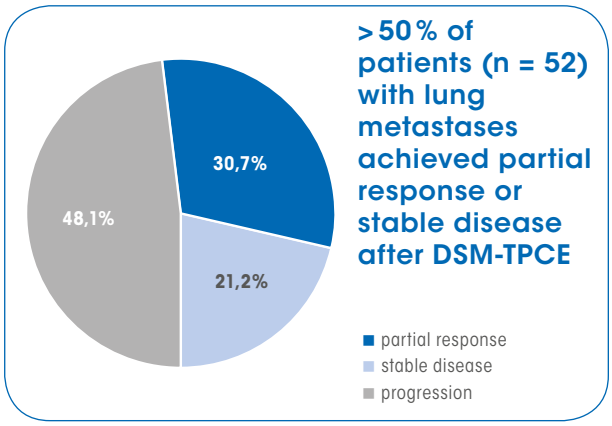


Figure 9: Tumor response according to RECIST after DSM-TPCE in patients with lung metastases of different origin; modified from [9].

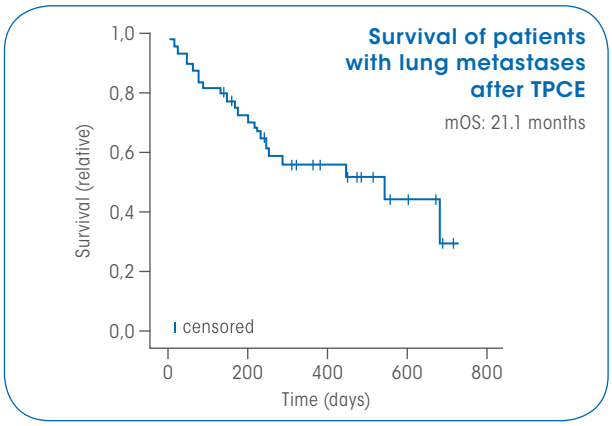


Figure 10: Survival curve of patients with lung metastases of different origin (n = 52) after DSM-TPCE; modified from [9]. mOS: median overall survival, CI: confidence intervall

➡ **DSM-TPCE results in tumor responses and stable disease in 50–60 % of patients with primary lung tumors and lung metastases**

Safety:

Treatment was well tolerated by patients with primary lung tumors and lung metastases without major complications. Minor complications (see table 3) were effectively treated with orally administered medication. For more information on contraindications and potential complications, please refer to the instructions for use of EmboCept® S [15].

Table 3: Minor complications in patients with primary and secondary lung tumors treated with TPCE.

Minor complications	Reference
Allergic reaction (to chemotherapeutics or contrast medium)	[16]
Transient flushing	[16]
Slight elevation in temperature	[6, 14]
Cough/coughing fits	[6, 14]
Increased blood parameters: slight leukocytosis with mild fever and coughing	[9]
Ischemic pain	[15]

➡ **TPCE is a well-tolerated treatment option for unresectable patients with lung tumors**

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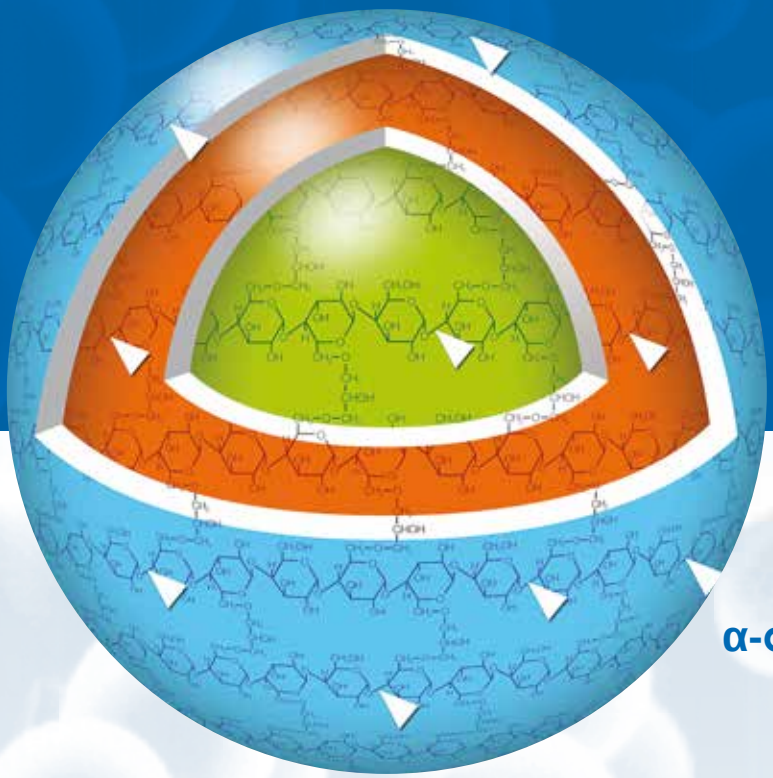
EmboCept® S

degradable starch microspheres

UNIVERSAL SHORT-TERM* EMBOLIC AGENT IN DSM-TPCE FOR LOCOREGIONAL TUMOR THERAPY.

***half-life 35 min[d]**



α-amylase

- higher intra-tumor concentration[a]
- short-term embolization[b,c]
- repeatable application[d]
- tumor volume reduction[e]
- no migration to the brain[e,f]
- easy handling compared to ILP[d]

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Non-clinical data

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Clinical data

e. Vogl TJ, Herzog C, Zangos S, et al. Transpulmonale Chemoembolisation (TPCE) als palliatives Behandlungskonzept bei primären Lungentumoren. Fortschr Röntgenstr 2007;179(03):300–7

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