Diffusion-weighted MRI of unresectable primary and secondary lung cancer: prediction of early response to transpulmonary chemoembolisation and transarterial chemoperfusion

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Aims and objectives

Lung cancer is the most common and highly lethal cancer worldwide with poor prognosis. About 75% of patients are diagnosed at advanced stage since there is no specific recognized symptom at early stage. The lung is also a common site for metastases of all kinds of cancer with the highest mortality rates.

TREATMENT OPTIONS

- **SURGERY** - Treatment is often challenging. Surgery alone is not the appropriate treatment for patients at terminal stage.
- **RADIATION THERAPY AND CHEMOTHERAPY** - Countless therapy regimens, including radiotherapy and chemotherapy have been tested as an alternatives to tumor excision or as neoadjuvant therapy in patients with bronchogenic carcinoma or pulmonary metastases. The main limitation of these approaches has been the chemotherapy-associated toxicity when delivered via the intravenous route.
- **TUMOR ABLATION THERAPY** - Ablative methods have shown to be effective, but the limits are often represented by the smaller and peripherally located tumors.
- **TRANSPULMONARY CHEMOEMBOLIZATION AND TRANSARTERIAL CHEMOPERFUSION** - The transpulmonary chemoembolization (TPCE) and transarterial chemoperfusion (TACP) are considered to be an alternative that allows the treatment of a larger number of tumors, with no risk of pneumothorax, and the treatment of centrally localized tumors. These two treatment options 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 [1, 2].

TREATMENT TECHNIQUE

**TPCE** - Subsequent to regional anaesthesia with 1% mepivacain (Mecain®; Actavis, Langenfeld, Germany), a 5-Fr pigtail catheter (Terumo, Frankfurt, Germany) was inserted into the right femoral vein in Seldinger's technique and placed into the pulmonary artery supplying the tumor. In case of chemoembolization, a locally applied chemotherapeutic agent is combined with an application of microspheres and ethiodized oil to occlude tumorous arteries, leading to necrotizing tumor tissue and prolonged drug persistence [3].

**TACP** - In cases of peripherally located tumors or tumors infiltrating the chest wall, transarterial chemoperfusion was preferred. For catheter positions in the descending aorta
or the internal thoracic artery, the catheter was inserted into the right femoral artery with a 5-Fr cobra catheter (Terumo). The catheter was placed in the thoracic aorta above the tumor feeding bronchial and intercostal arteries which were identified via DSA and C-arm CT [3].

**DWI MRI - THORACIC APPLICATION**

Diffusion-weighted imaging (DWI) enables differentiation of regions with high and low degrees of cellularity through the analysis of water molecule motion.

In lung imaging, DWI has been applied in the differential diagnosis of lung consolidations and neoplasms, based on the fact that the signal intensity is higher in viable tumour tissues than in less densely packed tissues, such as tumor necrosis or benign consolidations [4, 5, 6].

The evaluation of the data provided by DWI can be qualitative, semiquantitative and quantitative [7]:

1. **Qualitative evaluation** - involves visually assessing the relative signal intensity attenuation of images obtained at different b values and enables tissue characterization based on differences in water diffusion [8, 9].
2. **Semiquantitative evaluation** - using the signal intensity method for lung lesions and the spinal cord (LSR) in the differentiation of benign and malignant pulmonary lesions.
3. **Quantitative evaluation** - quantitative DWI analysis relies on ADC measurement. Several studies report utility and demonstrate its great importance in monitoring the treatment response of the tumors [10].

The aim of our study was to determine whether the change of apparent diffusion coefficient value after transpulmonary chemoembolization or transarterial chemoperfusion in a palliative intention could predict the early response in unresectable lung cancer and lung metastases, at the early stage of chemotherapy.
Methods and materials

STUDY DESIGN

The case selection was based on the inclusion and exclusion criteria as follows, and after discussing all the cases on Frankfurt lung cancer tumor board.

- **Inclusion criteria** - unresectable lung cancer and metastases, no response to systemic chemotherapy/radiation therapy, available follow-up imaging in 4 weeks interval after treatment, no restriction of pulmonary function, Karnofski index > 70
- **Exclusion criteria** - patients without MRI pre/post treatment, inadequate image quality, lesions < 1 cm, thrombosis of the pulmonary arteries, > 4 week MRI follow-up interval, declining to undergo follow-up CT

STUDY POPULATION

Overall 346 patients were scanned and treated in our institution between January 2012 and February 2016. For our final study cohort we included patients who:

- had a baseline CT and MRI scan
- underwent chemoembolization or chemoperfusion treatment within one week after baseline imaging examination
- had available subsequent post-treatment MRI performed within 4 weeks.

Finally 14 patients met our criteria (**Figure 1**). The tumors ADC value change was measured and compared.

Out of 14 patients, there were 4 patients with primary lung cancer and 10 patients who had lung metastases from different primaries (**Figure 2**).

MRI PROTOCOL

All MRI examinations were performed using a phased-array body coil and a 1.5-T system. Patients were examined in the supine position. The acquisition parameters of our institution’s standard chest MRI protocol are shown in the **Table 1**.

DW images were acquired using the respiratory gated single-shot echo-planar imaging sequence and array spatial sensitivity encoding technique with b values of 0 and 800s/mm².
**IMAGE ANALYSIS**

MR images were qualitatively reviewed by two radiologists in consensus with 4 and over 25 years of experience in chest imaging, blinded to the therapeutic response and other clinical data.

After the lesions were detected on T2-weighted and T1-weighted images the corresponding areas of diffusion restriction were identified on DWI and ADC maps. A manually traced ROIs were placed on ADC map and mean ADC values were extracted, for both pre- and post-treatment MRIs. In case of multiple lesions, only the largest lung lesion was included in the MR image analysis. Representative example is shown in Figure 3, where the upper row demonstrates the pre-treatment images and the lower row the post-treatment images.

**DATA ANALYSIS**

According to Response evaluation criteria in solid tumors (RECIST, version 1.1) the response to chemotherapy is classified as following: complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD). In our study, 4 patients showed Partial Response (PR) and 10 patients were classified with Stable Disease (SD). No patient belonged to complete response or progressive disease group.

For statistical analysis, unpaired t-test was performed in order to compare the change of ADC values in patients with PR and those with SD before and after the first treatment. A p-value < 0.05 was considered statistically significant.
Fig. 1: Case selection criteria.

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Fig. 2: Out of 14 patients enrolled in our study, there were 4 patients with primary lung cancer and 10 patients who had lung metastases from different primaries.

Table 1: The acquisition parameters of our institution’s standard chest MRI protocol.

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Fig. 3: Representative example: the upper row demonstrates the pre-treatment images and the lower row the post-treatment images. A manually traced ROIs were placed on ADC map and mean ADC values were extracted, for both pre- and post-treatment MRIs.

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Results

**STUDY POPULATION - DESCRIPTIVE STATISTICS**

All patients tolerated well the treatment and had no major complications. In Figure 4 we report all different types of lesions we treated in both response groups. Overall 9/14 (64%) patients were treated with TPCE and 5/14 (36%) with TACP without embolization (Figure 4).

**POST-THERAPY # ADC**

In our study we found that the change between the pre-treatment and the post-treatment mean ADC values (# ADC) was greater in patients who showed PR and this was at the statistically significant level (Figure 5). The results were independent from the type of lesion treated (primary lung cancer or lung metastases from different primaries).

**BASELINE ADC**

Additionally we also analyzed the pretreatment mean ADC values which showed no statistically significant difference between the PR and SD groups. This was to demonstrate, that at the baseline MRI, there was no important heterogeneity in terms of diffusion restriction among lesions in both groups (Figure 6).

**# ADC to differentiate SD vs PR**

When we used the change of ADC value for differentiating the PR group from the SD group, the best cut off value was 0.258, with the overall sensitivity and specificity of 100% and 80% respectively. The area under the receiver operator characteristic curve was 0.900 (Figure 7).

Representative example: a case of a 67-year-old woman with a left lung metastasis from breast cancer, who belonged to Partial Response group is demonstrated in Figure 8.
Fig. 4: We report all the different types of lesions we treated in both response groups. Overall 9/14 (64%) patients were treated with TPCE and 5/14 (36%) with TACP without embolization.

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**Fig. 5:** The change between the pre-treatment and the post-treatment mean ADC values (Δ ADC) was greater in patients who showed PR and this was at the statistically significant level.

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**Fig. 6:** The pretherapy mean ADC values showed no statistically significant difference between the PR and SD groups.

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**Fig. 7:** When we used the change of ADC value for differentiating the PR group from the SD group, the best cut off value was 0.258, with the overall sensitivity and specificity of 100% and 80% respectively.

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**Fig. 8:** A case of a 67-year-old woman with a left lung metastasis from breast cancer, who belonged to partial response group. On the T1 and T2 weighted images, the lesion is located quite peripherally, thus transarterial chemoperfusion treatment strategy was preferred. Corresponding areas of restricted diffusion were identified on DWI and ADC maps and subsequently manually traced ROIs were placed over the lesion in both pre-treatment and post-treatment ADC maps. Mean ADC values were extracted.

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Conclusion

Several studies have shown that DW imaging might represent a diagnostically useful tool for the characterization of pulmonary lesions.

Potential future applications of DWI in lung cancer include monitoring the treatment response after chemotherapy or radiation, discriminating post-therapeutic changes from residual tumors, and detecting recurrent cancer. Our preliminary data also suggest its promising role in monitoring early treatment response of different types of lung cancers after endovascular treatment. In our study this was assessed by the difference of ADC values in lesions before and after the first treatment.

The next step will be the combination of ADC values and other imaging parameters such as LSR and lesion dimension in order to further improve the prediction ability for treatment response.
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