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ORIGINAL ARTICLE

The evaluation of DLCO changes in patients with relatively higher lung shunt fractions receiving TARE

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Abstract

Objective Transarterial radioembolization (TARE) with Yttrium-90 (^{90}Y) labeled microspheres is an effective locoregional treatment option for patients with primary and metastatic liver cancer. However, TARE is also associated with radiation-induced lung injury due to hepatopulmonary shunting. If a large proportion of the injected radionuclide microspheres (more than 15%) is shunted, a rare but lethal complication may develop: radiation-induced pneumonitis (RP). Diffusion capacity of the lungs for carbon monoxide (DLCO) is a valuable test to assess lung function and a decrease in DLCO may indicate an impairment in gas exchange caused by the lung injury. Some previous researches have been reported the most consistent changes in pulmonary function tests after external beam radiotherapy are recorded with DLCO. This study aimed to examine the changes in DLCO after TARE with glass microspheres in newly treated and retreated patients with relatively higher lung shunt fractions.

Methods We prospectively analyzed forty consecutive patients with liver malignancies who underwent lobar or superselective TARE with ^{90}Y glass microspheres. DLCO tests were performed at baseline and on days 15, 30, and 60 after the treatment. All patients were followed up clinically and radiologically for the development of RP.

Results A statistically significant decrease was found in the DLCO after the first treatment (81.4 ± 13.66 vs. 75.25 ± 13.22, $p = 0.003$). The frequency of the patients with impaired DLCO at baseline was significantly increased after the first treatment (37.5 vs 57.5% $p < 0.05$). In the retreated group ($n = 8$), neither the DLCO (71.5 ± 10.82 vs. 67.50 ± 11.24, $p = 0.115$) nor the frequency of patients with impaired DLCO (25 vs 25%, $p = 1$) did not significantly change. Also, the change in DLCO values did not significantly correlate with lung shunt fraction, administered radiation dose, and absorbed lung dose after the first and second treatments ($p > 0.05$ for all). None of the patients developed RP.

Conclusion Our study showed that a significant reduction in DLCO after TARE may occur in patients with relatively higher lung shunt fractions. Further studies with larger sample sizes are needed to better investigate the changes in DLCO in patients with high lung shunt fractions.

Keywords Transarterial radioembolization (TARE) · Lung carbon monoxide diffusion capacity (DLCO) · Lung shunt fraction · Radiation pneumonitis (RP)

Introduction

In the last 10 years, transarterial radioembolization (TARE), using Yttrium-90 (^{90}Y) labeled microspheres which are infused through the hepatic arteries has arisen for locoregional treatment of inoperable primary or metastatic liver tumors [1, 2]. However, a significant amount of ^{90}Y-labeled microspheres may shunt to the lungs. If a large proportion of the injected radionuclide microspheres (more than 15%) is shunted, a rare but lethal complication may develop: radiation-induced pneumonitis (RP) [3]. Technetium-99 m-labeled macro-aggregated

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albumin hepatic arterial perfusion scintigraphy (^{99m}Tc-MAA HAPS) is a standard pre-treatment procedure that is used to evaluate the possible shunts to the lung. Therefore, TARE is relatively contraindicated if this scan suggests a hepatopulmonary shunt which would lead to radiation exposure of the lungs greater than 30 or 50 Gy, in a single treatment or multiple treatments, respectively [4].

The single-breath carbon monoxide diffusing capacity of the lung (DLCO) is an important pulmonary function test that provides valuable information about the ability of the lungs to transfer the gas in inhaled air to the red blood cells in pulmonary capillaries [5]. In some articles, it has been reported that DLCO may show the presence of limited gas exchange reserve caused by the potential toxicity of chemo-radiotherapy [6–8]. Additionally, some previous researches have been reported the most consistent changes in pulmonary function tests after external beam radiotherapy (RT) are recorded with DLCO [9, 10].

There are some research articles on the relation between the percent change in DLCO and RP. Guerra et al. studied the relationship between the percent change in DLCO and RP after external RT [11]. These authors concluded that patients with higher percent reductions in DLCO were more likely to have high-grade RP. The literature includes little information about the degree of radiation-related changes in DLCO after TARE. Ones et al. examined the effect of internal radiation exposure on the lungs in patients who underwent TARE; in this research, none of the patients developed RP during the follow-up period and no changes in DLCO have been observed [12]. In a recent paper by the same authors, a case with a fatal outcome was reported and it was also concluded that a decline in DLCO could be a valuable parameter for follow-up in patients receiving TARE [13]. Since RP was not detected in the former study, it was emphasized that the degree of lung injury was not severe in their cohort. Compared with previous cohorts, it has been also indicated that a significantly lower level of radiation exposure, possibly explaining the lack of statistically significant results.

The relationship between the percent reductions in DLCO and the severity of RP developing after TARE may still prove to be clinically significant, especially with high lung shunt fractions. Therefore, we here aimed to examine the change in DLCO after TARE with glass microspheres in newly treated and retreated patients with relatively higher lung shunt fractions.

Materials and methods

We prospectively analyzed forty consecutive patients with a variety of malignancies involving the liver and underwent TARE with ^{90}Y glass microspheres from February 2019 to January 2020. This study was performed with local institutional review board approval (dated November 2019; No: 09.2019.931).

Patient selection

Patients over the age of 18 with an Eastern Cooperative Oncology Group score of ≤ 2 and having a life expectancy of > 3 months were included in this study. Exclusion criteria were:

1) inadequate liver function (malignancy-associated ascites, serum albumin level < 3.0 g/dL, and total bilirubin level > 2.0 mg/dL);
2) unamenable ^{90}Y microspheres flow to the extrahepatic organs and;
3) non-cooperative patients for the respiratory function test.

TARE planning and treatment procedure

All patients underwent lobar or super-selective treatment with ^{90}Y glass microspheres (Therasphere, MDS Nordion, Canada). Prior to the administration of ^{90}Y microspheres, all patients were evaluated with a diagnostic angiogram and pretreatment coil embolization was performed to prevent non-target shunting of the microspheres to the extrahepatic vessels such as gastroduodenal, right gastric, and pancreaticoduodenal arteries, if necessary. ^{99m}Tc-MAA HAPS imaging was performed 1–2 weeks before treatment for the estimation of lung shunt fraction according to the European Association of Nuclear Medicine (EANM) guidelines [4]. Patients having a shunt of more than 20% were not eligible for ^{90}Y therapy. The administered treatment doses were decreased by 20 and 40%, for liver-lung shunting of 11–15% and 16–20%, respectively, to reduce the possibility of RP [4]. The administered treatment dose was calculated with the empirical method proposed for TheraSphere which encompasses the lung shunt fraction, perfused target volume, desired dose, anticipated residual waste, and time zone variance. Post-therapy ^{90}Y Bremsstrahlung SPECT/CT imaging was performed to assess the hepatic uptake pattern of the glass microspheres and to determine the extrahepatic shunts [4].

Calculation of lung shunt fraction

The lung shunt fraction was determined by 99mTc-MAA planar gamma camera imaging and tolerance doses of the lungs were calculated with this method during treatment planning as recommended in the EANM guideline [4]. Regions of interests were drawn around both lungs and liver on anterior and posterior planar images and the geometric mean of lung and liver counts were calculated. The lung

shunt fraction was obtained by dividing the geometric mean of the lung count by the geometric mean of the sum of the lung and liver count.

Dosimetry procedure

In this study, the absorbed doses were calculated with a dosimetry software, Simplicit90Y (Mirada Medical Ltd, Oxford, UK), that co-registers all the scans and creates personalized multi-compartment models using three-dimensional dosimetry data at a voxel-level. Registration, segmentation, and dose calculation were the three main processes in the dosimetry analysis [14]. At the first step, contrast-enhanced CT and/or MRI, PET/CT (Discovery ST PET/CT scanner, GE Healthcare, Milwaukee, WI, USA), ^{99m}Tc-MAA HAPS, and post-therapy ^{90}Y Bremsstrahlung SPECT/CT (Siemens Symbia TruePoint; Siemens Medical Solutions, USA) images were transferred to Simplicit90Y dosimetry software platform. Registration was performed using data from diagnostic contrast-enhanced CT and/or MRI with post-therapy ^{90}Y Bremsstrahlung SPECT/CT. To ensure accuracy, registration was examined and adjusted to fit the anatomical structures. The volume of interest (VOI) segmentation process involved segmenting whole liver, whole liver normal tissue, perfused tissue, perfused normal tissue, perfused tumor, and perfused viable tumor. The perfused tissue was the target hepatic volume that included normal liver parenchyma and tumoral lesion. The adaptive thresholding method was used to define the perfused tissue volume from functional imaging [15]. Perfused normal liver volume was defined as the perfused tissue volume minus the tumoral volume. The necrotic component of the tumoral lesions was drawn with the assistance of contrast-enhanced CT or MRI and/or PET/CT images obtained before the treatment. Viable tumor volume was calculated automatically by subtracting the necrotic volume from the tumor volume. The administered treatment dose and the lung shunt fraction were then entered into the Simplicit90Y software. The absorbed dose for each VOI (whole liver normal tissue, tumor, viable tumor, perfused volume, perfused normal tissue, and lungs) was calculated separately according to the administered activity.

DLCO and assessment of lung toxicity

DLCO tests were performed at baseline; and on days 15, 30, and 60 after the treatment. The results of pulmonary function tests utilizing a whole-body plethysmograph (Collins GS II, Collins, Braintree, MA, USA) were used to calculate DLCO [16]. For the analysis, the maximum of the post-treatment values were chosen. Results were compared with reference values based on race, height, age, and gender. The equipment's technical specifications and test performance technique both fulfilled the American Thoracic Society's requirements. DLCO was measured using the single-breath technique by two or more attempts, and to meet the American Thoracic Society's standards, values fewer than 5% were used. The hemoglobin value obtained within 24 h of the test was used to adjust the DLCO. An impaired DLCO value was accepted as ≤ 80 mmol/min/kPa. A decline in DLCO is expressed as a percentage reduction from the pre-treatment value (i.e., the percentage decrease in DLCO $= (1 - \text{post/pre}) \times 100$).

Radiation Therapy Oncology Group's toxicity criteria and the European Organization for Research and Treatment of Cancer Late Radiation Morbidity Scoring Scheme were used to evaluate the RP and lung toxicity [17]. All patients were followed up for symptoms for at least one year after TARE and underwent PET/CT imaging for evaluating the response to ^{90}Y therapy approximately 75 days after the treatment. CT images of the PET scans were also used to predict RP. In patients who received a repeated treatment, PET/CT images obtained approximately 5 months after the first treatment particularly focused on the identification of RP.

Statistical analysis

Statistical Package for Social Sciences (SPSS) version 25 was used for the analysis of data (SPSS Inc., Chicago/IL, USA). Data are presented as mean ± standard deviation or number (percentage), where appropriate. Hypothesis testing and graphical techniques were used to determine normality. The significance of the difference in DLCO values before and after the treatments was investigated using a paired samples t-test. The McNemar test was used to compare baseline and after treatment frequency. Based on the distribution, the correlations with changes in DLCO values were examined using Spearman's or Pearson's correlation tests. Statistical significance was defined as a p value of less than 0.05.

Results

Demographic and clinical information of all patients and retreated patients are summarized in Table 1. Three fourth of the patients were male, and hepatocellular carcinoma was the most common indication for treatment in both groups.

The DLCO values were significantly decreased after the first treatment (81.4 mmol/min/kPa ± 13.66 vs. 75.25 mmol/min/kPa ± 13.23, $p = 0.003$). In the retreated group ($n = 8$), DLCO values did not significantly change (71.5 mmol/min/kPa ± 10.82 vs. 67.50 mmol/min/kPa ± 11.24, $p = 0.115$). In addition, after the first treatment, the frequency of the patients with impaired DLCO at baseline was significantly increased (37.5 vs 57.5% $p < 0.05$) but it did not significantly change (25 vs 25%, $p = 1$) after the second treatment.

On day 60 after the first and the second treatments, the change in DLCO values did not significantly correlate with lung shunt fraction ($r = -0.256$, $p = 0.111$; $r = -0.301$, $p = 0.468$, respectively), administered radiation dose ($r = 0.002$, $p = 0.990$; $r = 0.084$, $p = 0.844$, respectively), and absorbed lung dose ($r = -0.128$, $p = 0.433$; $r = -0.192$, $p = 0.649$, respectively) (Fig. 1).

The 20 patients in the first treatment and four in the retreated group with absorbed lung dose values above the median value were further evaluated and formed the "relatively much higher absorbed lung dose" group. In this subgroup, on day 60 after the first and second treatments, the change in DLCO values also did not significantly correlate with the absorbed lung dose ($r = -0,226$, $p = 0.337$; $r = -0.800$, $p = 0.200$, respectively).

During follow-up, none of the patients experienced RP. The statistical results are shown in Table 2.

Discussion

To the best of our knowledge, this is the second study to investigate the effect of dose exposure to the lungs in patients with relatively higher lung shunt fractions receiving TARE (Fig. 2). Unlike previous work, a significant reduction in the DLCO was found after the first TARE treatment. No

Table 1 Patient characteristics ($n = 40$)

All patients ($n = 40$)	
Age, year	60.37 ± 10.1
Male gender, *n* (%)	30 (75%)
Tumor type, *n* (%)	
Hepatocellular carcinoma	14 (35%)
Colon ca	11 (27.5%)
Gastric ca	4 (10%)
Others*	11 (27.5%)
Lung shunt fraction, % (first treatment)	8.2 ± 4.6 (2–20%)
Lung shunt fraction ≤ 4%	6 (15%)
Lung shunt fraction > 4%, ≤ 9%	21 (52.5%)
Lung shunt fraction > 9%, ≤ 14%	7 (17.5%)
Lung shunt fraction > 14%, ≤ 20%	6 (12.5%)
Administered radiation dose, Gbq (first treatment)	1.4 ± 1.3
Absorbed lung dose, Gy (first treatment)	5.9 ± 7
Whole liver normal tissue dose, Gy (first treatment)	22.3 ± 15.6
Tumor dose, Gy (first treatment)	111.7 ± 65.1
Patients receiving two treatments ($n = 8$)	
Age, year	65.9 ± 6.0
Male gender, *n* (%)	6 (75%)
Tumor type, *n* (%)	
Hepatocellular carcinoma	4 (50%)
Cholangiocellular ca	2 (25%)
Breast ca	1 (12.5%)
Rectal ca	1 (12.5%)
Lung shunt fraction, % (second treatment)	10.3 ± 4.7 (5–19%)
Lung shunt fraction ≤ 4%	–
Lung shunt fraction > 4%, ≤ 9%	4 (50%)
Lung shunt fraction > 9%, ≤ 14%	3 (37.5%)
Lung shunt fraction > 14%, ≤ 20%	1 (12.5%)
Administered radiation dose, GBq (second treatment)	1.3 ± 0.7
Absorbed lung dose, Gy (second treatment)	5.9 ± 4.1
Whole liver normal tissue dose (second treatment)	21.8 ± 12.7
Tumor dose, Gy (second treatment)	126.3 ± 76.8

Data are presented as mean ± SD unless otherwise stated; *Rectal ca ($n = 2$), gastric neuroendocrine tumor ($n = 1$), esophageal ca ($n = 1$), extrahepatic bile duct carcinoma ($n = 1$), cholangiocellular ca ($n = 3$), breast ca ($n = 1$), lung neuroencodcrine tumor ($n = 1$), gastric ca ($n = 1$)

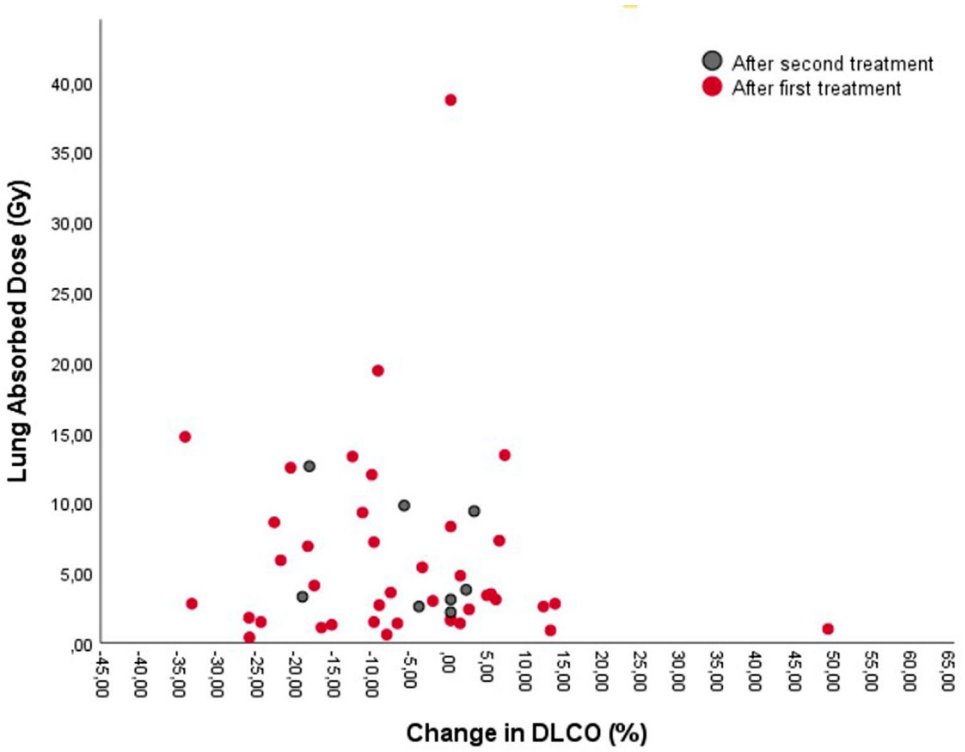

Fig. 1 Scatter plot of percent changes in diffusing capacity of the lung for carbon monoxide (DLCO) versus absorbed lung dose (Gy)

statistically significant difference in DLCO was observed after the second TARE procedure that applied to a limited number of cases. In addition to these results, no correlation was found between the change in DLCO and the lung shunt fraction, administered radiation dose, and absorbed lung dose. No clinical or radiologic findings of RP were detected during follow-up with these TARE treatments using glass microspheres.

The lungs are one of the most radiation-sensitive organs in the body, and the alveolocapillary complex is the most radiation-sensitive subunit of the lungs [18]. Damage to the alveolocapillary complex after RT causes disruption of intercellular connectivity, increased cellular permeability, and impaired physiological function [18, 19] Within days to weeks after radiation exposure, initial cytokine release is triggered. The first phase of cytokine release is usually observed within two weeks after radiation exposure, while the second phase begins 4–6 weeks after the first phase and it causes hypoperfusion and hypoxemia in the lungs [18–20]. Berg et al. published a study where the patients had RP with a decline in DLCO and FEV1 approximately 7–8% within 4–6 weeks following RT. This study reported that early decline in DLCO and FEV1 occurred before the radiological changes and symptoms and these parameters could predict the development of symptomatic RP [21]. In our study, a 35% decrease in DLCO value was observed after the first treatment in a patient with a 20% lung shunt fraction. However, RP did not develop clinically or radiologically in this patient like other cases during follow-up. In another study, Lierová et al. examined the changes in serum and lung tissue

Table 2 Changes in DLCO after treatments

	First treatment ($n=40$)	Second treatment ($n=8$)
Pre-treatment DLCO, mmol/(min/kPa)	81.4 ± 13.66	71.50 ± 10.82
Post-treatment DLCO, mmol/(min/kPa)	75.25 ± 13.23	67.50 ± 11.23
p for difference	0.003	0.115
% change in DLCO	− 6.51 ± 15.46	− 5.26 ± 8.96
Pre-treatment impaired DLCO, *n* (%)	15 (37.5%)	2 (25%)
Post-treatment impaired DLCO, *n* (%)	23 (57.5%)	2 (25%)
p for difference	0.039	1.00

Data presented as mean ± standard deviation or percentage as indicated

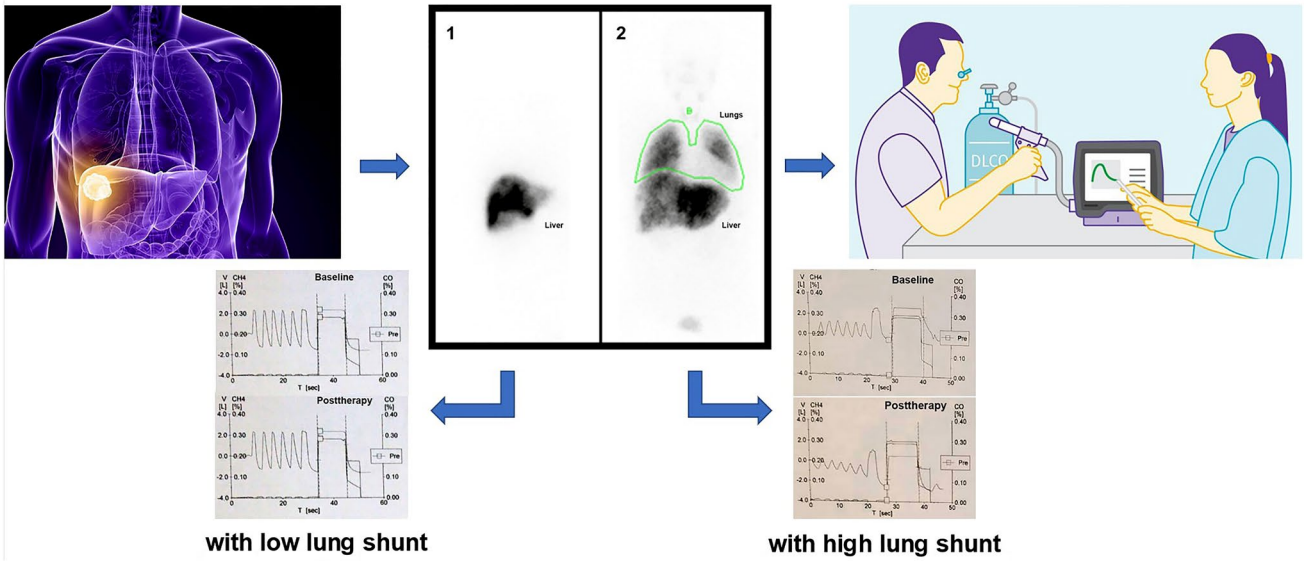

Fig. 2 Representative illustration of the main findings of our study

in the latent phase of lung injury in a mice experimental model and found a statistically significant increase in IL-6 and MCP-1 cytokines in hours and 7 to 21 days after the whole-body irradiation [22]. Significant neutrophil accumulation in the lungs, a characteristic feature of the latent phase of the radiation-induced lung injury, was also seen 21–30 days after irradiation in that study. Therefore, in our study, DLCO measurements were performed at 2, 4, and 8 weeks after TARE to detect the related changes.

TARE with ^{90}Y microspheres is a clinical treatment modality for patients with primary and metastatic liver cancer [23]. In this treatment modality, RP, is a long-term complication of non-target accumulation of the microspheres due to hepatopulmonary shunting, can cause fatal outcomes [24]. In 1995, Leung et al. published that five out of nine patients whose lung shunt fraction was greater than 13% developed RP and two of them died from respiratory failure after TARE [3] in another study in this regard, Ho et al. suggested that the post-treatment dose exposure of the lungs > 30 Gy in a single treatment or > 50 Gy from multiple treatments and lung shunt fraction greater than 20% increased the risk of RP [25]. However, Salem et al. reported a paper involving 403 patients who underwent TARE, of whom 58 of them received > 30 Gy cumulative lung dose and no patients developed RP during their follow-up [26]. In contrast, Dobrocky et al. presented that RP can develop even if the lung shunt fraction is low and in this case report, an asymptomatic patient who had an 11.5% lung shunt fraction developed RP as confirmed both by histopathological examination and imaging modalities [24]. Wright et al. also reported a case report where a symptomatic patient had RP within three weeks after the second TARE with ^{90}Y glass microspheres, and was treated with iv methylprednisolone and continued with oral prednisolone. In the next nine months after the steroid treatment, no clinical relapse or decline in pulmonary function was documented [27]. The relationship between DLCO decline and RP has been published by many researchers. Guerra et al. reported the correlation between percent change in DLCO and RP grade in patients who received external RT with or without chemotherapy [11]. In 2020, Aso et al. examined 16 patients who received concurrent chemoradiotherapy for lung cancer and developed varying degrees of RP [28]. They compared the FEV1 and DLCO values at baseline, in the third week, and in the second month after RT in this study. As a result, a statistically significant decrease in DLCO was observed in cases with high-grade RP and they emphasized that the decrease in DLCO value was the most sensitive marker for the early detection of RP after external RT.

Although there are publications in the literature reporting the relationship between external radiotherapy and DLCO, the change in DLCO values after TARE is limited to the study of Ones et al. published in 2017 with resin microspheres among 40 patients. In that study, none of the patients showed clinical or radiological signs of RP, and no significant change in DLCO was observed after the first and second treatments [12]. However, in our study performed with glass microspheres, a significant decrease in DLCO values after first TARE treatment draws attention. In addition, different from Ones et al.'s results, a significant increase in the number of cases with impaired DLCO after treatment (37.5 vs. 57.5%) was also detected in this study. Although there are differences in gastrointestinal and hepatobiliary complications after treatments

with glass and resin microspheres due to the discrepancies in their physical and activity properties, no difference has been reported between these two different radionuclide compounds in terms of pulmonary complications [29, 30]. Considering that similar administered treatment doses were applied in both studies (1.4 ± 1.3 Gy vs 1.6 ± 0.3 Gy), the different results between these two studies can be explained by the fact that the lung shunt fraction of the patients was higher in this study than the lung shunt fraction rates of the patients in the study of Ones et al.'s ($8.2\% \pm 4.6\%$ vs. $6.7 \pm 2.6\%$).

In this study, similar to the study of Ones et al., no statistically significant change was found in the mean DLCO value or the number of cases with impaired DLCO after the second treatment. This situation can be explained by the evaluation of small number of cases ($n = 8$) who received second TARE treatment in both studies. Also, no significant relationship was found between the changes in DLCO values obtained after the first and the second treatments and absorbed lung dose, the lung shunt fraction, and the administered radiation dose both in our study and in the study of Ones et al.. Therefore, more comprehensive studies are needed to better depict the possible relationship between the change in DLCO values after TARE and absorbed lung dose, lung shunt fraction, and the administered radiation dose.

This study had some limitations. Since no cases developed RP in this study, a cutoff value for the decline in DLCO could not be defined. Additionally, the lung shunt fraction is estimated by ^{99m}Tc-MAA planar gamma camera imaging as in standard clinical practice. For more accurate calculation, attenuation and scatter corrected tomographic SPECT/CT lung images could be used, but the authors preferred planar imaging as suggested in the last guideline and literature [4, 25, 26, 31]. This approach is reflected in the recent guideline and it has been emphasized that since tolerance doses for the lungs empirically established using planar imaging, lung doses must be primarily calculated with this method [4]. In addition, DLCO tests were performed up to 2 months after TARE in all patients, and late follow-up DLCO values were not available for the assessment of the long-term effect of RP.

The association between the decline in DLCO and the severity of RP developing after TARE may prove to be clinically important. If this assumed relationship proves to be valid, then it may be possible to identify potential candidates for RP using DLCO monitoring. The findings of this study suggest that there may be a significant reduction in DLCO in patients with relatively higher lung shunt fractions receiving TARE. Further studies with larger sample sizes are warranted to investigate DLCO changes with high lung shunt fractions.

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Data availability The datasets analyzed during the current study are available from the corresponding author on reasonable request.

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