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ONCOLOGY IMAGING

Factors affecting the response to Y-90 microsphere therapy in the cholangiocarcinoma patients

Mehmet Bozkurt[1] · Gonca Eldem[2] · Utku Burak Bozbulut[3] · Murat Fani Bozkurt[4] · Saadettin Kılıçkap[5] · Bora Peynircioğlu[2] · Barbaros Çil[6] · Eser Lay Ergün[4] · Bilge Volkan-Salanci[4]

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Abstract

Objective The aim of this study was to assess the early therapy response in patients with unresectable CCA who received Y-90 microsphere therapy for CCA and define the factors related to therapy response.

Materials and methods Data of 19 patients [extrahepatic (n: 6) and intrahepatic (*n*: 13)] who received 24 sessions of Y-90 microsphere therapy [glass (*n*: 13) and resin (*n*: 11)] were retrospectively evaluated. Tumor load, tumor size, therapy response evaluation by RECIST1.1 criteria (*n*: 13), tumor lesion glycolysis (TLG), metabolic tumor volume (MTV), and metabolic therapy responses were evaluated (*n*: 8) using PERCIST1.0 criteria.

Results No significant relation was found between therapy response and tumor localization, treated liver lobe, type of Y90 microspheres, the presence of previous therapies, perfusion pattern on hepatic artery perfusion scintigraphy, or patient demographics. The mean overall survival (OS) was 11.9 ± 2.3 months and was similar after both resin and glass Y90 microspheres; however, it was longer RECIST responders (*p*: 0.005). MTV and TLG values significantly decreased after therapy, and ΔMTV ($-45.4\% \pm 12.1$) was found to be positively correlated with OS. No statistical difference was found between iCCA and eCCA, in terms of OS and response to therapy. Although not quantitatively displayed, better-perfused areas on HAPS images had a better metabolic response and less perfused areas were prone to local recurrences.

Conclusions Both resin and glass microsphere therapy can be applied safely to iCCA and eCCA patients. Early therapy response can be evaluated with both RECIST and PERCIST criteria. Both anatomical and metabolic therapy response evaluations give complementary information.

Keywords Cholangiocellular carcinoma · Cholangiocarcinoma · PET-CT · Y-90 microsphere · Hepatic artery perfusion scintigraphy · RECIST · PERCIST

✉ Bilge Volkan-Salanci
bilgev@hacettepe.edu.tr

Mehmet Bozkurt
mehmetbozkurt@hotmail.com

Gonca Eldem
goncaeldem@gmail.com

Utku Burak Bozbulut
ubb_burak@hotmail.com

Murat Fani Bozkurt
fanibozkurt@gmail.com

Saadettin Kılıçkap
skilickap@yahoo.com

Bora Peynircioğlu
borapeynir@gmail.com

Barbaros Çil
barbaros@hacettepe.edu.tr

Eser Lay Ergün
eserergun2@gmail.com

[1] Department of Nuclear Medicine, Bakirkoy Dr.Sadi Konuk Training and Research Hospital, Istanbul, Turkey

[2] Department of Radiology, Faculty of Medicine, Hacettepe University, Ankara, Turkey

[3] Department of Medical Oncology, Osmaniye Public Hospital, Osmaniye, Turkey

[4] Department of Nuclear Medicine, Faculty of Medicine, Hacettepe University, 06100 Sıhhiye, Ankara, Turkey

[5] Department of Medical Oncology, Faculty of Medicine, Hacettepe University, Ankara, Turkey

[6] Department of Radiology, Koç University, Istanbul, Turkey

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Introduction

Cholangiocellular carcinoma (CCA) is a rare gastrointestinal tumor with a high mortality rate. Despite being the preferred treatment for non-metastatic, resectable CCAs, only a small proportion of patients are eligible for surgery. Recurrence is common after standard treatment of CCA. Local/regional treatment modalities such as transarterial Yttrium-90 (Y-90) microsphere therapy are important choices in patients who are unresponsive to standard chemotherapy and unsuitable for surgery [1]. Metabolic imaging with F18-fluorodeoxyglucose positron emission tomography–computed tomography (FDG PET-CT) is performed in addition to morphological imaging methods such as computed tomography (CT) and magnetic resonance imaging (MRI) for Y-90 microsphere therapy planning and for the evaluation of the therapy response [2]. When compared with anatomic imaging methods such as CT and MRI, FDG PET-CT provides data to differentiate disease progression from fibronecrotic tissues in evaluating early therapy response of the patients [3].

In this study, we retrospectively evaluated pre- and post-therapy CT, MRI, and FDG PET-CT images to assess the therapy response in patients with CCA who had undergone Y-90 microsphere therapy. Factors that might have an effect on therapy response were also evaluated.

Materials and methods

From January 2008 to November 2016, 19 patients with CCA, who had been admitted to Hacettepe University Department of Nuclear Medicine and received Y-90 microsphere therapy, were enrolled retrospectively. The Y-90 microspheres that were available at the hospital during patient admission were used, and none of the patients were directed for specific microsphere type. The medical records of patients were gathered via our hospital data collecting system with the approval of the local ethics committee (No: GO 16/758-16).

Patients who had liver transaminase levels less than 5 times of upper limits, total bilirubin levels less than 2 mg/dL, albumin levels at least 3.0 g/dL, and ECOG performance status 0-1 were accepted for Y-90 microsphere therapy planning. During planning angiography, 5 mCi/5 mL of Tc-99 m macroaggregated albumin (MAA) was administered through targeted lesions' hepatic artery. Hepatic artery perfusion scintigraphies (HAPS) were performed, and planar and single-photon emission computed tomography (SPECT) or SPECT-CT images were obtained. All the patients with a lung fraction of less than 20% and no evidence of extrahepatic leakage were present on HAPS. Y-90 microspheres were applied in the same position as the planning angiography of the selected hepatic artery branch. For this study, SPECT and SPECT-CT images of HAPS were achieved from the hospital PACS. Images were reevaluated, volume of interests (VOI) were drawn over the target lesions, and max and mean counts were defined as VOImax and VOImean. VOImax/VOImean values were also calculated in order to define lesion perfusion heterogeneity.

Y-90 resin microspheres (SIRspheres®, SirTeX Medical, Australia) at a dose calculated with the BSA formula [Activity: (BSA-0.2) tumor volume/total liver volume] as suggested in the prospectus. The resin microspheres were suspended in a sterile water solution (in 5% dextrose after 2015) and delivered under fluoroscopic imaging guidance with radiocontrast. The dose calculation of Y-90 activity was performed using the manufacturer's calculation table using liver volumes for Y-90 glass microspheres (TheraSphere®, MDS Nordion, Ottawa). The Bremsstrahlung images were reevaluated in order to confirm the placement of the Y-90 microspheres at the target lesion and to exclude extrahepatic leakage retrospectively.

FDG PET-CT images before and 12.2 ± 4.8 weeks [range 4.8-45.2] after the therapy and data of the 8 patients were reevaluated visually and semiquantitatively on Advanced Work Station 4.7 (GE Healthcare, Chicago, IL, USA).VOIs of target lesions of patients were drawn on pre- and post-therapy routine FDG PET-CT images. Care was taken to include the lesion completely in the transaxial, coronal, and sagittal views of the drawn VOIs. A total of 13 lesions were selected for therapy response assessment of six patients and eight therapy applications. The dimensions of the lesions, maximum standardized uptake values corrected by lean body mass (SUL peak) were calculated separately. Metabolic volumes of target liver tumors (metabolic tumor volume, MTV) were used in the bulk of the metabolic active part of the tumor through three-dimensional ROIs. The total lesion glycolysis (TLG) was calculated by multiplying the MTV of each lesion by the corresponding SUV mean of the lesion. The therapy response was evaluated for every treated lesion MTV and total lesion glycolysis (TLG), SUVmax, SUVmean, SULpeak, and SULmean values, ΔMTV, ΔTLG, ΔSULpeak, and ΔSULmean values were calculated from pre- and post-therapy FDG PET-CT images. The early metabolic response was calculated using PERCIST criteria 1.0.

The pre- and post-therapy CT (*n*: 11) and/or MRI (*n*: 5) images were reevaluated using RECIST 1.1 criteria in a total of 13 therapies by a radiology specialist. Tumor sizes and tumor load were measured from CT and MRI images.

Statistical analyses

IBM SPSS Statistics version 22.0 (Armonk, NY: IBM Corp.) was used to evaluate the data obtained in the study and the statistical significance limit was set at $p < 0.05$. Descriptive statistics were made by giving the mean ± standard deviation for the variables with a normal distribution. Median and cutoff values were given for the variables without normal distribution. Parameters calculated in the study were compared using nonparametric tests. Kruskal–Wallis analysis was performed in multiple groups as a nonparametric test. The relationship between the two parameters was assessed by the Spearman correlation coefficient. The relation between parameters according to Spearman's correlation coefficients. The correlation between MTV and TLG values, SUVmax and ΔMTV, ΔTLG, SULpeak, and SULmean values and ΔSULpeak, and ΔSULmean measured in FDG PET-CT images and the OS after therapy were evaluated by the Spearman correlation test. Survival outcome was assessed using the Kaplan–Meier method.

Results

The mean age of the patients was 55.6 ± 12.4 years [28–74]. Six patients were diagnosed as extrahepatic CCA (eCCA) (31.6%) and 13 (68.4%) as intrahepatic CCA (iCCA). The patients had undergone chemotherapy (*n*: 1, 5.3%), surgery (*n*: 6, 31.6%) and/or TACE (*n*: 2, 10.5%) before Y-90 microsphere therapy. Six patients received Y-90 microsphere therapy (31.6%) as the first-line treatment (Table 1). Age, tumor load, tumor size, SULpeak, and MTV and TLG values for iCCA and eCCA patients were not statistically different ($p > 0.05$).

A total of 24 Y-90 microsphere applications [glass: 13 (54.2%); resin: 11 (45.8%)] in 19 patients were included in the study. Patients' age, tumor size, tumor load, and OS after the Y-90 microsphere therapy were similar among resin and glass microspheres (Table 2). In 5 patients, a second microsphere therapy was administered at a mean time interval of 12.8 months ± 10.1 after the first treatment, either to the other lobe or to the same lobe due to disease progression. Y-90 administered activity was higher in patients who received glass microspheres (3.4 GBq ± 2.1) than those who received resin microspheres (1.0 GBq ± 0.3) to the right lobe (*p*: 0.03) [Table 3].

Table 1 Comparison of diagnoses of the patients, treated liver lobes, and Y-90 microsphere therapy line with microsphere types

		Resin (*n*)	Glass (*n*)	*p*
Pathology	ICC	7	9	0.772
	ECC	4	4	
Liver Lobe	Left	3	4	0.016*
	Right	8	3	
	Bilobar	0	6	
Y-90 microsphere therapy	1st line	3	6	0.622
	2nd line	3	3	
	3rd line	5	4	

*$p < 0.05$

Table 2 Effect of patient demographics on OS

	Microsphere	Mean ± SD	*p*
Age (years)	Resin	54.2 ± 9.3	0.642
	Glass	56.5 ± 13.0	
Size (mm)	Resin	79.6 ± 37.8	0.717
	Glass	72.6 ± 48.8	
Tumor Burden (%)	Resin	38.5 ± 17.7	0.983
	Glass	38.7 ± 15.5	
OS (days)	Resin	260.5 ± 161.0	0.638
	Glass	304.8 ± 285.4	

SD standard deviation

On follow-up, 14 patients deceased and 5 patients survived at the time of the analysis. The mean OS of all the patients was 11.9 months ± 2.3. There was no statistically significant difference between OS and the treated liver lobe (*p*: 0.275), type of the microspheres given (*p*: 0.638), or CCA type (*p*: 0.742). The mean OS (11.1 months ± 3.2) after microsphere treatment in patients who received the Y-90 therapy as the first line was not different than the patients who received Y-90 microsphere therapy as the second or third line (8.4 months ± 1.7, *p*: 0.471). Baseline SUVmean values were inversely correlated with OS (*p*: 0.033).

Total bilirubin levels of the patients were decreased after the 4th week of the therapy (*p*: 0.006). There was an increase in alkaline phosphatase (ALP) levels after the therapy. Serum gamma-glutamyltransferase (GGT) levels were also slightly elevated at the 8th week. We did not observe any serious side effects such as radiation-induced liver disease (RILD), pulmonary fibrosis, or gastrointestinal ulceration in our patients.

The mean tumor diameter measured was 75.3 mm ± 44.1, and the mean tumor load was 38.7% ± 15.8 at baseline. There was no statistically significant relationship between OS and tumor diameter (*p*: 0.52) or tumor load of the patients (*p*: 0.49). The therapy response with patient-based RECIST 1.1 and lesion-based RECIST analysis was not found to be associated with tumor diameter (*p*: 0.516 and *p*: 0.639, respectively) or tumor load (*p*: 0.642 and *p*: 0.945, respectively). RECIST was interpreted in 13 treatments: complete response (CR) was achieved in one patient (7.7%, OS: 22.3 months), partial response (PR) was shown in 2 patients (15.4%, OS: 17.9 months ± 14.4), 4 patients had

Table 3 Comparison of Y-90 microsphere doses and OS's with treated lobes and microspheres

Treated lobe	Microsphere	*N*	Mean dose (GBq) ± SD	$p^{‡}$	OS (months) ± SD	$p^{‡}$
Left lobe	Resin	3	0.8 ± 0.4	0.443	8.6 ± 6.2	0.532
	Glass	4	1.4 ± 1.2		5.5 ± 6.0	
Right lobe	Resin	8	1.1 ± 0.2	0.030*	8.5 ± 5.5	0.963
	Glass	3	2.0 ± 0.9		8.3 ± 12.2	

SD: standard deviation. GBq: giga Becquerel. $p^{‡}$: Kruskal–Wallis. $p^{‡}$: T test. *$p < 0.05$

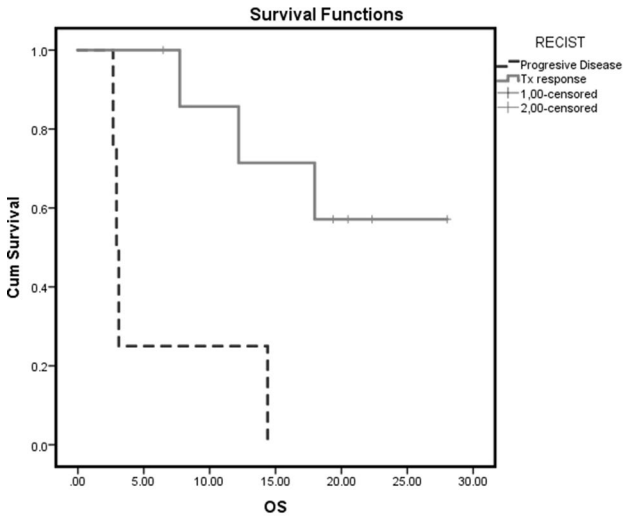

Fig. 1 Kaplan–Meier survival plot for RECIST therapy response. Progressive disease mean survival ± SD: 5.8 ± 2.9 months; therapy response mean survival ± SD: 21.4 ± 3.1 months (*p*: 0.005)

a stable disease (SD) (30.8%, OS: 11.3 months ± 5.9), and progressive disease (PD) was observed 6 patients (46.2%, OS: 10.3 months ± 8.3) [*p*: 0.356]. When the patients were grouped as responders (CR + PR + SD; 21.4 months ± 3.1) and non-responders (PD: 5.8 months ± 2.9), the mean OS of the patients after therapy was significantly longer in the responders (*p*: 0.005) (Fig. 1). The tumor load was also classified as low (≤ 25%) and high (> 25%) and there was no significant difference among therapy response (*p*: 0.217)

The HAPS images were compared visually with FDG PET images on the lesion basis for 13 lesions. The hyperperfused areas of the tumors had better therapy response on FDG PET (Figs. 2, 3). However, this finding was supported neither with HAPmax/VOImax nor HAPmean/VOImean values. A negative correlation was found between VOImean, a parameter showing mean perfusion and tumor size of the patients (*p*: 0.037) (Fig. 4). Extrahepatic CCA patients had higher VOImax and VOImean values when compared to iCCA patients (VOImax, *p*: 0.033; VOImean, *p*: 0.002).

The mean MTV value calculated from baseline FDG PET-CT images was 198.0 cm^3 ± 215.1; the mean TLG 1163.3 g ± 1538.0; and mean SUVmax was 8.3 ± 4.8. MTV and TLG values decreased significantly after microsphere therapy (*p*: 0.028 and *p*: 0.031, respectively) (Fig. 5). The differences were calculated as follows. ΔMTV was calculated as − 109.2 cm^3 ± 111.2, ΔTLG was found as − 616.8 g ± 689, and ΔSUVmax was measured as − 0.5 ± 3.3. No statistical difference was observed in SUVmax values after microsphere therapy (*p*: 0.327). There was no significant relationship between baseline MTV, TLG, or SUVmax values and the OS of the patients (*p*: 0.779, *p*: 0.955, and *p*: 0.102, respectively). There was a positive correlation between ΔMTV and OS of the patients (*p*: 0.032). However, ΔMTV and ΔTLG values were not different among the microsphere types (*p*: 0.881 and *p*: 0.655, respectively). In the visual analysis, the distribution pattern of FDG in lesions suggested that this pattern might be useful for the evaluation of therapy responses and predicting the sites for the local recurrence (Figs. 2,3, 4).

The early metabolic response was evaluated (*n*: 8, 42.1%) using PERCIST criteria 1.0 at a mean time of 2.8 months ± 2.8. Patients (*n*: 6) that had PR had a mean reduction of 45.4% ± 12.1 in their SULpeak uptake after treatment. Two patients had SD (mean SULmean reduction 7.0 ± 18.9). These patients had significantly higher survival rates when compared to the study group. There was no relation between metabolic response and tumor load, lesion size, dose applied (*p*: 0.2). OS of the patients with a partial metabolic response (15.2 months ± 10.7) were longer than the patients with SD (OS: 14.4 months ± 1.3); however, no statistical significance was found.

Discussion

CCA is the second most common primary liver malignancy [1]. In CCA, the percentage of patients who are eligible for surgery is limited and long-term survival expectancy is low, even after surgery [4]. Mean OS, which was 6 months with non-surgical treatments in patients who are not eligible for resection before the 2000s, increased to approximately 15 months after the introduction of liver-targeted therapies during the last decade [4]. Y-90 microsphere therapy is a relatively new treatment modality for CCA. The number of studies on Y-90 microsphere therapy of CCA and the

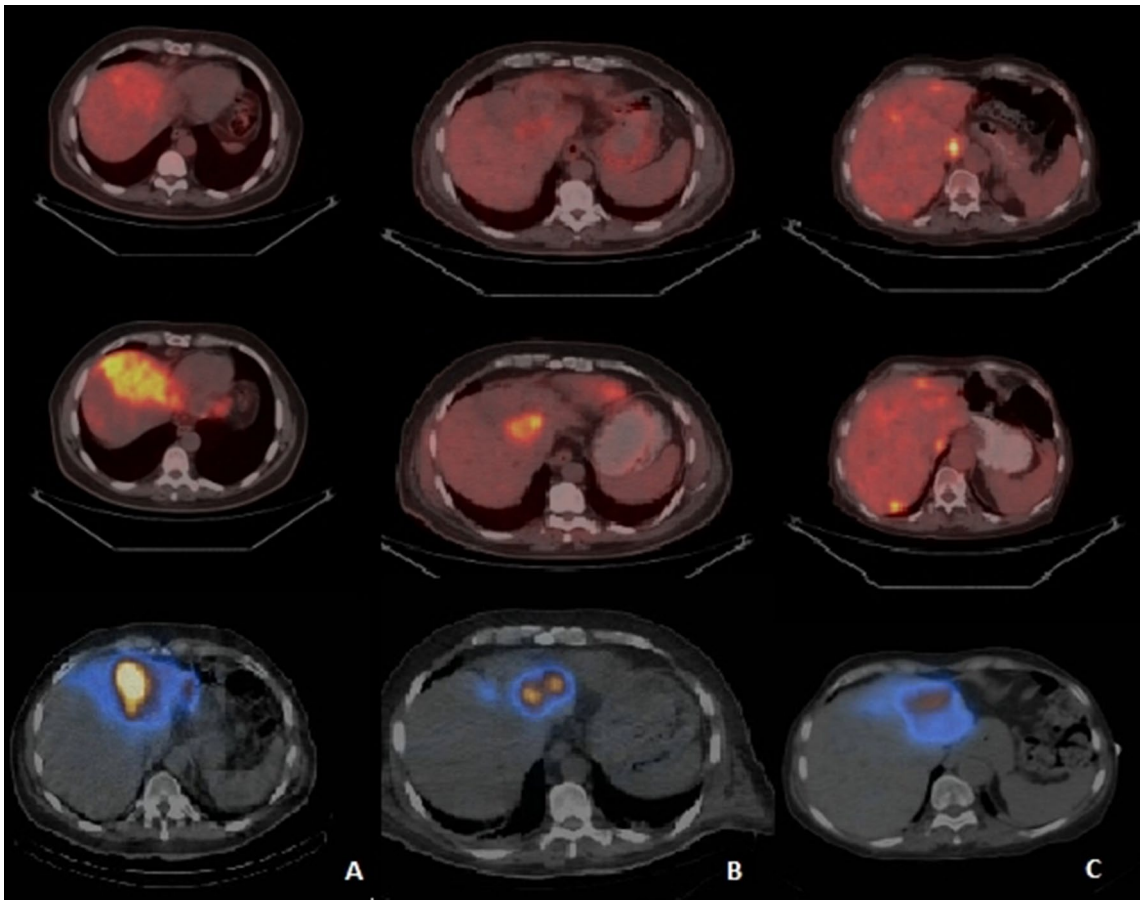

Fig. 2 Hepatic artery perfusion SPECT-CT images (bottom row) and pre-therapy (middle row) and post-therapy (top row) F-18 FDG PET-CT fusion images of three patients. Patients had a good metabolic response where the high Tc-99 m MAA uptake was present

number of patients in these studies were limited due to the low incidence of CCA.

In our study, HAPS, CT, MRI, and FDG PET-CT parameters were evaluated in patients with CCA who received both glass and resin Y-90 microsphere therapy and the relation of these parameters with OS and treatment response was investigated and the following findings and interpretations are presented.

No relation was found between therapy response and tumor localization, treated liver lobe, type of Y-90 microspheres used, presence of previous treatments, or patient demographics. This was an expected result because Y-90 microsphere therapy is a local therapy. Viable tumor lesion was defined, and Y-90 microspheres were given from feeding hepatic artery branches at the exact position to cover tumor perfusion. Applications were made independent of previous treatments.

Early therapy response (CR, PR, and SD) evaluated with anatomical imaging was correlated with the OS of the patients. However, we did not find a significant relationship with ΔSUVmax or ΔSULpeak. Haug et al. [5] evaluated the Y-90 microsphere therapy response using FDG PET parameters (SUVmax, SUVmean, and SUV2SD) in 26 patients and showed that the changes in these scores were significantly correlated with OS. The lack of correlation in our study is most probably due to the small number of patients that were evaluated with PET. FDG PET revealed early metabolic changes in therapy response, and when accompanied by a significant morphologic reduction in tumor dimensions, this results in a significant difference in OS.

Six of the patients (31.6%) included in our study were diagnosed with eCCA. No statistically significant difference was found between iCCA and eCCA, in terms of age, baseline imaging parameters, OS, and response to therapy. In the literature, the mean OS of the patients with iCCA was reported as 12-59 months [4]. In early-stage eCCA patients whose lesions can be surgically resected, OS after surgery was found to be 11-38 months [6]. The life expectancy of eCCA patients with liver metastasis presenting with residual disease or recurrence after chemotherapy and surgical treatment is fairly low (4–8 months) [7, 8]. In the study by Hoffmann et al., patients with iCCA and liver metastases of

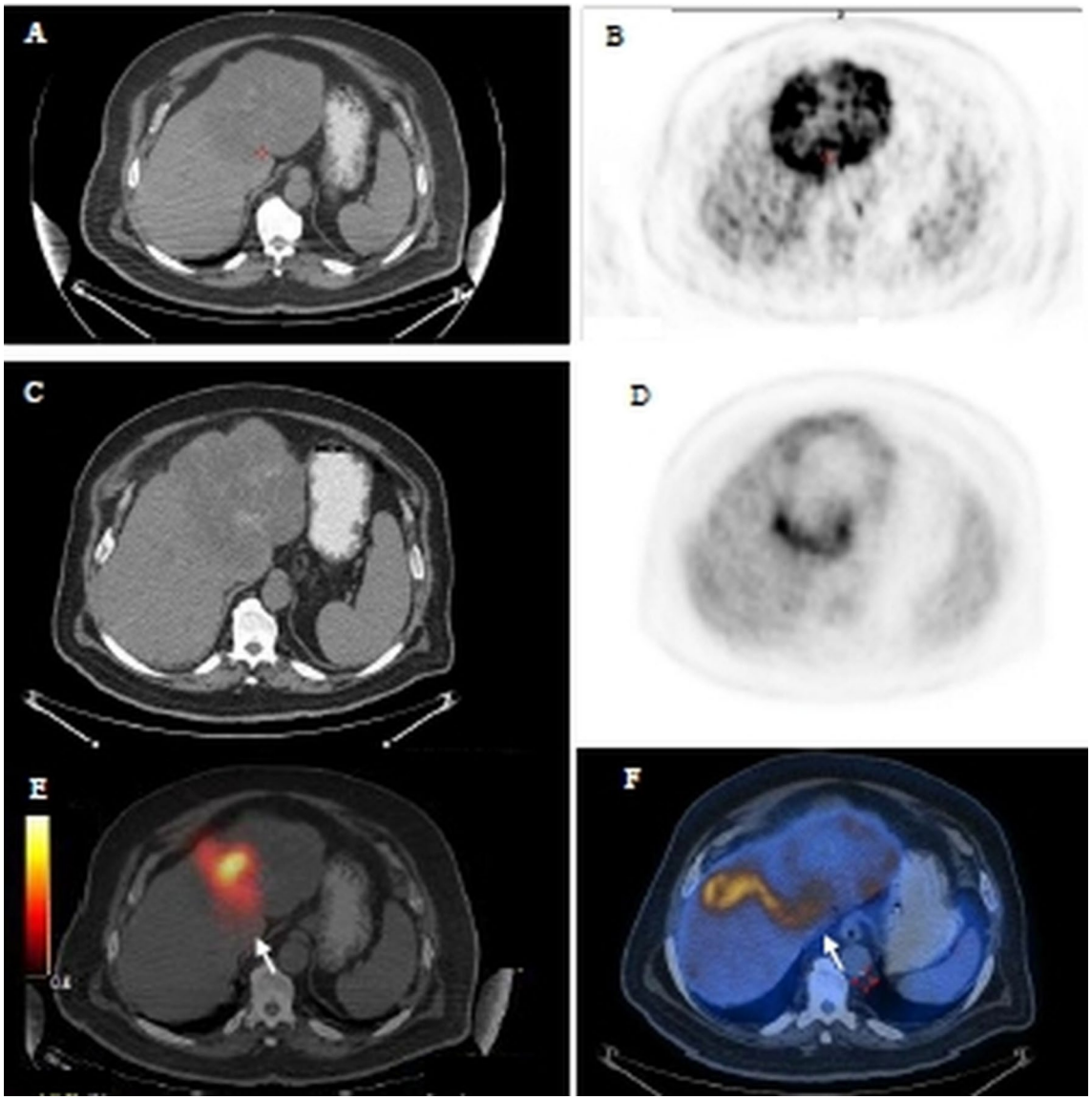

Fig. 3 Pre-therapy FDG PET (**a**, **b**), early (**c**, **d**), and late post-therapy FDG PET images (**e**) of a 70-year-old man diagnosed with iCCA. He was treated with Y-90 glass microspheres through the left hepatic artery in April 2013. There was a significant reduction in FDG uptake of the primary lesion after therapy, when the pre-therapy December 2012 FDG PET-CT images (**a**, **b**) were compared with post-therapy June 2013 FDG PET-CT images (C and D). Post-therapy FDG PET-CT of a patient showed a decrease in FDG uptake in the area where HAPS showed intense MAA uptake compared to the pre-therapy FDG PET-CT of the patient. Late post-therapy FDG PET-CT revealed progression to the right lobe of the liver (F, arrow) from the region where the MAA uptake was relatively low in the pre-therapy HAPS-CT fusion images of the patient (E, arrow). The patient died due to clinical progression 2.9 months after the therapy

chemorefractory CCA were reported to be included in the study; however, the percentage of the patients was not available [9]. In previous studies, which enrolled the patients who were treated with Y-90 microspheres for CCA, the distinction between eCCA and iCCA has not been denoted, to our knowledge. Probably, patients with eCCA may also have been included under the same group as iCCA, since their survival expectancy is low due to liver metastases. In our study group, since all the lesions, either primary or metastatic, were hepatic lesions and no significant difference was obtained between iCCA and eCCA, these lesions should be considered liver tumors of CCA for this local-specific type of treatment modality. Along with this opinion, our finding was concordant with the above-mentioned previous studies.

In our study, prior to Y-90 microsphere treatment, the patients underwent chemotherapy treatment (*n*: 1, 5.3%), surgery (*n*: 6, 31.6%), and/or TACE (*n*: 2, 10.5%). Y-90 microsphere treatment was applied as the first-line treatment in six (31.6%) of the patients. The OS of patients who received first-line microsphere therapy were statistically similar to

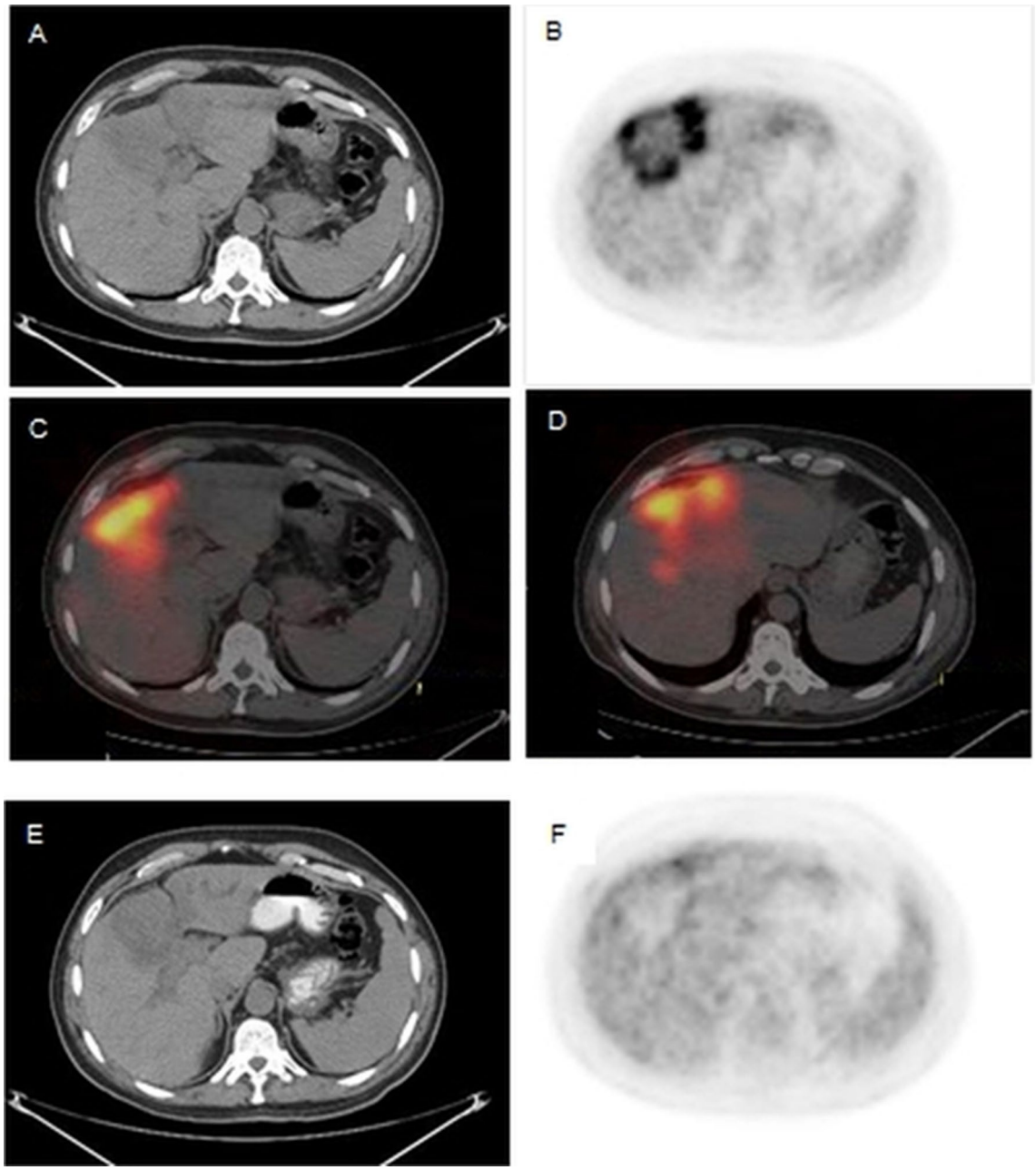

Fig. 4 Pre-therapy FDG PET (**a**, **b**), HAPS (**c**, **d**), and post-therapy FDG PET images of a 47 year-old-man, whose liver biopsy was diagnosed as iCCA. He received Y-90 microsphere therapy as first-line therapy. Pre-therapy FDG PET-CT revealed a mass that mainly involves the left lobe with maximum diameters of 7×5x9 cm (**a**, **b**). HAPS-CT fusion images showed a heterogeneous distribution of Tc-MAA in the liver mass (**c**, **d**). In February 2015, bilobar Y-90 glass microsphere therapy was administered to the patient. Partial therapy response was observed in post-therapy FDG PET-CT which was performed in March 2015 (**e**, **f**). In April 2016, due to the progression of the disease in the left liver lobe, the second dose of glass microsphere was given. The patient was still on follow-up, 28 months after the first microsphere therapy

second-/third-line microsphere therapy. In a prospective study of a total of 92 glass microsphere treatments in 46 patients with iCCA, it was reported that 35% of patients had previously received chemotherapy and 15% were administered other therapies targeting the liver [9]. In a retrospective study, it was reported that 79% of 33 iCCA patients had previously received chemotherapy, 37% had undergone surgery, and 18% had previous locoregional treatments such as RFA, TACE, and EBRT [9]. In another study, 25% of CCA patients who were treated with Y-90 microspheres, received microsphere therapy as initial treatment [10]. In the study of Haug et al., 24% of 26 iCCA patients were reported not

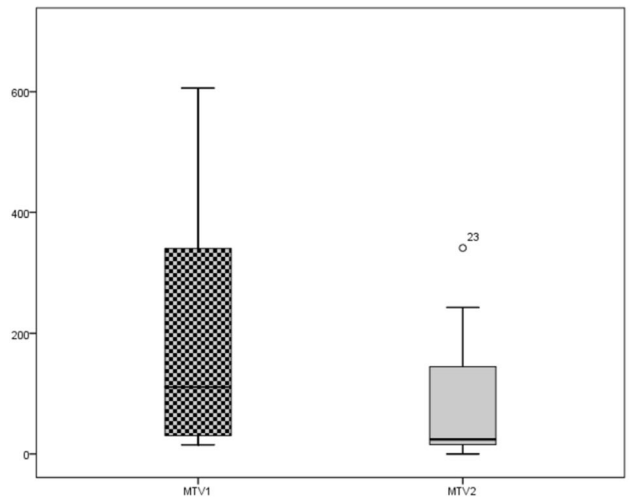

Fig. 5 Box-plot comparison of the MTV values in pre-therapy (MTV1) and post-therapy (MTV2) FDG PET-CT's of the patients (p: 0.028)

to receive systemic or locoregional therapy prior to Y-90 microsphere therapy [5]. The treatments administered before Y-90 microsphere therapy to the patients who were included in our study were similar to the treatments in literature. In a study, Y-90 microsphere therapy was recommended as the first-line treatment for iCCA patients with low tumor load (< 25%) [11]. Patients who have previously received chemotherapy or EBRT may have lower liver reserve due to liver toxicity of the drugs, which may lead to impaired liver function after treatment with microspheres [12, 13]. When given as first-line therapy, the patients are expected to be less likely to experience side effects. In addition, the previous administration of various treatments may be indicative of the presence of a treatment-resistant disease and may hinder the success of treatment. Moreover, although it is an invasive treatment procedure, it can be performed in outpatient. As our experience, the therapy is well tolerated by the patients when compared to systemic chemotherapy.

In our study, of the total 24 microsphere treatments given to 19 CCA patients, 13 were glass microspheres and 11 were resin microspheres. Although the patients received more radiation dose to right lobe with glass microspheres, there was no statistical difference in therapy response or OS between resin and glass microspheres. In the literature, previous studies used either resin or glass microspheres and this is the first study comparing the results of both types of microsphere treatments in CCA patients, to the best of our knowledge. Y-90 glass microspheres are expected to have a higher radiation dose, due to the structure of the microspheres [14]. In our study, there was no statistically significant difference between the doses given in the right lobe, left lobe, or bilobar in resin microspheres. The doses raised as the liver volume increased, and the highest dose was applied in the bilobar treatments. There was no statistically significant relationship between the treated liver lobe or microsphere type and the OS after treatment. The treatment efficacy seems to be similar with either type of microspheres in CCA. So, either microsphere type which is available at that time could be used when a hepatic tumor is targeted in a patient with CCA.

The mean OS of the patients in our study was 11.9 months. In a study with a similar group of patients as our study, the mean OS was found to be 11.5 months after microsphere treatment of chemorefractory 29 patients with iCCA [15]. In another study conducted in a similar group of patients, it was found that 12 out of 16 patients with iCCA who were treated with microspheres died with an average OS of 9.7 months [10]. Saxena et al. [16] reported that the mean OS was 9.3 months after treatment in 25 CCA patients. The meta-analyses of Boehm et al., which included eight studies published between 2003 and 2014, reported the mean OS of 127 patients with CCA to be 13.9 months after Y-90 microsphere treatment, which was consistent with the results of our study. In the study of Filippi et al., a mean OS of 18 patients with iCCA, 14 of whom had a single lobar tumor, was 14.8 months after microsphere treatment [17, 18]. Camacho et al. reported a mean OS of 16.3 months in a study that included 21 chemorefractory patients with CCA who had lower tumor burden (55.5% of the patients with tumor load < 25%) and smaller mean tumor size (6.6 cm) than in our study [19]. In the literature, the longest OS was reported to be 22 months in the study of Hoffman et al., which enrolled 33 patients with CCA after treatment, 75.8% of whom had low tumor load (< 25%) [9]. Different OS in studies may be related to the variability of tumor load or extension of the disease of the patients included in different studies. In addition, 50% of the patients received chemotherapy previously, all of the patients, who received microsphere as the second- or third-line therapy, were chemorefractory, mean tumor diameter was approximately 7.5 cm, and mean tumor load was 38.7% ± 15.8, in our study. The involvement of patients with a worse expectation of prognosis might lead to a shorter mean OS of the patients. Therefore, we advise discussing these particular groups of patients in a multidisciplinary meeting concerning the following issues. Finally, after all individual necessary examinations, history of previous treatments if available, determination of the disease status, the prediction of the degree of disease progression, patient survival, and optimization of the patient's expected rest life comfort should be taken into consideration while discussing the Y-90 microspheres therapy decision. In our opinion, if it is expected that the patient would have benefit, Y-90 microspheres could be chosen even as the first-line therapy in selected individual patients.

No correlation was found between the mean tumor size and OS of our patients. In addition, there was no correlation

between target lesion size and treatment response. A study which enrolled a total of 16 patients with iCCA reported a mean tumor size of 65.8 mm (12-120 mm), and Cox regression analysis showed FDG avidity, liver lesion size, liver tumor load, and radiologic response as predictors of OS after microsphere treatment [10]. In another study, which included 33 patients with iCCA or chemorefractory CCA, the percentage of patients with tumor load over 25% (26-50%) was 24.6%, and low tumor load was shown to be associated with longer survival time [5]. The small number of patients and retrospective nature of our study may be the reason for this finding.

HAPS is used for determining LSF's extrahepatic leakage and for predicting particle distribution within the tumor [20–24]. Heterogeneous involvement patterns in HAPS were found to be more frequent than homogeneous patterns for liver tumors with large size and necrotic centers when HAPS images prior to Y-90 microsphere treatments of 80 patients were investigated [25]. In a study that included 58 patients who received a Y-90 microsphere for liver metastasis from a colorectal tumor, it was reported that MAA uptakes of the tumors in the qualitative assessment of HAPS were not associated with CEA levels after one and 2 months of the therapy, treatment response that was evaluated by CT, or OS after the therapy [26]. MAA uptake in HAPS performed before the Y-90 treatment of liver metastases of colorectal tumors was not found to be associated with treatment response evaluated by MRI 6 weeks and 3 months after the treatment [27]. HAPS images and its relation to treatment response in CCA patients did not show a correlation between pre-treatment HAPS (mean tumor counts/mean liver counts) or MRI with OS [5]. However, in this study, ΔVol (2SD) was found to be associated with OS. Haug et al. classified HAPS images by calculating a ratio of tumor/liver and showed improved survival in hyperperfused patients [5]. But they did not quantify heterogeneous perfusion of the big tumor. In our study, HAPS parameters did not predict the overall response of the treatment as in the literature. However, as the size of the tumor increased, VOImean decreased, suggesting that the perfusion pattern in HAPS is more heterogeneous as the tumor size increases. Such perfusion heterogeneity of big tumors was also reported by our group [25]. Although not quantitatively displayed, we showed that on visual evaluation better-perfused areas on HAPS images had a better metabolic response on FDG PET images (Figs. 2, 3) and less perfused areas were prone to local recurrences (Fig. 4).

Serum bilirubin levels were significantly lower at the end of 4 weeks. Serum ALP and GGT levels of our patients showed a slight increase at the end of two months post-treatment when compared to the pre-treatment levels. Saxena et al. reported that grade III bilirubin and albumin toxicity was observed in 8% of the patients (2/25 patients) who were administered Y-90 resin microspheres [16]. In a study of Piana et al., which enrolled 81 patients treated with Y-90 microspheres for primary and metastatic liver tumors, ALP toxicity was reported in 7% of patients at 29-571 days after treatment [28]. Kennedy et al. reported 20.5% of grade 3 ALP increase in 1-40-month follow-up of a total of 208 patients from 7 centers, who received Y-90 microspheres for liver metastases of unresectable colorectal cancers [29]. In another study, which included 47 patients with primary and metastatic liver tumors treated with Y-90 microspheres, ALP toxicity was reported in 21% of the patients and GGT toxicity in 27% of them; however, no serious complication or RILD associated with treatment was reported [30]. Thus, the slight increase of liver enzyme levels and mild decrease at total bilirubin levels might be related to the physiological reaction following Y-90 microsphere treatment and seems to be an expected finding after the therapy.

When FDG PET-CT images were analyzed, MTV and TLG values in FDG PET-CT were decreased significantly as an early response to microsphere therapy. On the other hand, SUVmax values did not show a significant difference after therapy, which suggests MTV and TLG might be a better parameter to evaluate therapy response. Another finding of the study is that ΔMTV was positively correlated with the OS. In a study of Filippi et al., which enrolled 17 patients treated with Y-90 microspheres, patients with less than 50% difference in TLG had significantly lower survival and shorter time to progression (mean OS of 79.6 weeks ± 3.6 in patients with ΔTLG > 50% and 43.1 weeks ± 2.0 in patients with ΔTLG < 50%) [18]. Camacho et al. reported an OS of 21.7 months after treatment with microspheres in 9 CCA patients, and the PERCIST response of the target lesion was achieved in 77.7% of the patients and was associated with longer OS [19]. Our results, when interpreted with the literature, supported that change in MTV might be a good prognostic factor for survival.

In our study, of the patients whose treatment responses were evaluated with RECIST, any response rate (CR, PR, and SD: 53.8%) was PD (46.2%). There was no statistically significant relationship between RECIST and OS. However, when RECIST responses were grouped as responders and non-responders, the OS of the responders was longer than the non-responders. In a meta-analysis involving 127 iCCA patients who received Y-90 microsphere therapy, CR or PR was found in 27.4% of the patients [17]. In the study of Saxena et al., 24% had PR, 48% had SD, and 20% had PD, while no CR was shown with RECIST [16]. It seems that RECIST may predict therapy response; however, patient selection bias in between different centers may be responsible for different results in the literature.

In our study, although the number of patients seems to be limited, it should be considered that CCA is a rare tumor in the population. Therefore, the proportion of CCA patients who admitted to our university hospital, which is a

well-known and dedicated university hospital, is also less than the patients with other tumor types. It should also be noted that although the number of patients in the study is 19, the number of Y-90 microsphere therapy applications is higher (24 applications). Additionally, most publications in the literature concerning this rare type of tumor have a similar number of patients.

In conclusion, for the evaluation of the Y-90 microsphere therapy response in patients with CCA, both anatomical and functional imaging gave complementary information to each other. This study is the first which evaluates both the resin and glass microsphere therapy in iCCA and eCCA patients, and our results showed that both can be applied safely applied in this group of patients and had a similar therapeutic effect. We think that proper patient selection and evaluation of both tumor perfusion and metabolic characteristics before Y-90 microsphere therapy in a multidisciplinary session are important for the expectation of optimum Y-90 microsphere efficacy.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical standards All procedures performed in studies involving human participants were in accordance with the ethical standards of the local ethics committee (No: GO 16/758-16) and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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