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AIM: *Selective intraarterial radionuclide therapy (SIRT) with Yttrium-90 (Y-90) resin microspheres has been applied for hepatocellular carcinoma (HCC) lately. The aim of this study is to present our clinical experience of radiomicrosphere therapy in the treatment of unresectable HCC and determine the proper cases who could benefit from this therapy according to response results yielded by initial staging and control imaging modalities.*
METHODS: *We administered 43 Y-90 microsphere therapy to 34 patients with unresectable HCC (twice in 9 patients). Patients with histopathologically confirmed HCC having a life expectancy of ≥3 months; Child A-B, Okuda stage 1-2 and BCLC stage A-B-C classifications were included in the study. The patients were divided into two groups: Group A consisted of 29 patients who responded to Y-90 therapy (complete response, partial response and stable disease), Group B 5 of non-responders (progressive disease). Predefined parameters were evaluated for response to SIRT and compared between two groups.*
RESULTS: *We found a significant decrease in platelet and lymphocyte counts one month after therapy (p=0.02, p=0.01, respectively). On control imaging tests performed 3 months later, we observed complete response in 19% (n=6), partial response in 44% (n=15), stable disease in 25% (n=8) and progressive diease in 12% (n=5) of the patients. Mean overall survival (OS) was 19 (median value: 14) months.*
CONCLUSIONS: *Y-90 microsphere therapy is a safe and effective treatment option for the patients with unresectable HCC without any serious side effect. Mean tumor dose delivery and lack of bilobar disease seem the best predictors for treatment success.*

KEY WORDS: Selective intraarterial Radionuclide therapy, Yttrium-90, hepatocellular carcinoma

Introduction

The prognosis of hepatocellular carcinoma (HCC) is poor and overall 5-year survival is lesser than 20%. Advanced HCC patients usually survive less than 6 months without treatment [1]. Transarterial chemoembolization (TACE) is generally the treatment of choice for unresectable intermediate-stage HCC (Barcelona-Clinic Liver Cancer (BCLC) stage B) [2]. Sorafenib is an angiogenesis inhibitor available for systemic therapy to patients with unresectable HCC [3]. It is used in the treatment of patients with unresectable intermediate HCC who are not appropriate for TACE or showing progression despite locoregional therapies [1,4]. Although sorafenib provides an evident survival benefit in advanced HCC, its efficacy is limited with a median overall survival (OS) of less than 11 months and is associated with substantial side effects [5].

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Selective intraarterial radionuclide therapy (SIRT) with yttrium-90 (Y-90) resin microspheres has been applied for primary or metastatic inoperable liver tumors with successful results lately [6]. This procedure, also known as radioembolization (RE), selectively delivers a single high measurable targeted radiation dose to hepatic tumors via injection into the hepatic artery with minimum healthy liver exposure [6,7]. Y–90 labeled resin microspheres of an average size of 30-40 μm in diameter, considerably smaller than the particles of other liver-directed therapies such as TACE, makes it possible for the microspheres to lodge distally through the microvascular plexus of tumors [8,9]. Multicenter retrospective European study (ENRY) of Y-90 resin SIRT demonstrated a median OS of 12.8 months in patients with different tumor stages including advanced disease [10]. Many factors intrinsically effect the response to SIRT like patient demographics, severity of disease, performance status, previous treatment modalities and subsequent liver transplantation [11].
However, limited data are present about which of these parameters increase survival. The effects of a wide range of factors on survival after Y-90 resin SIRT and the tolerability of Y-90 resin in this heterogeneous population have not been evaluated in detail. The aim of this study is to present our clinical experience of radiomicrosphere therapy in the treatment of unresectable HCC and to determine the proper cases who could benefit from this therapy according response results yielded by initial staging and control imaging modalities with either PERCIST or RECISTcriteria.

Material and Methods

In this retrospective cohort study, we administered 43 Y-90 microsphere therapy to 34 patients with unresectable HCC between January 2008 and December 2016. HCC diagnosis was established histopathologically in 7 patients and radiologically in 27 patients. The therapy was administered twice in 9 patients (5/9 had bilobar treatment, 4/9 unilobar). HCC was decided to be unresectable according to Milan criteria (For a single tumor > 5 cm or multiple tumors (>3 foci) with a maximum diameter of 5 cm) [12]. Patients (18 years or older) with HCC having a life expectancy of ≥ 3 months; Child A-B, Okuda stage 1-2 and BCLC stage A-B-C classifications were included in the study. Cases having adequate hematologic, renal and hepatic function without extrahepatic disease or with additional limited extrahepatic metastases were enrolled. Concurrent malignancy, refractory ascites, cirrhosis, portal hypertension, main portal vein tumor involvement or main portal venous thrombosis were the exclusion criteria for the study. All the patients were treated by sorafenib before Y-90 therapy.
All patients had biochemical tests (hemogram and serologic markers). Pretreatment labaratory tests were hemogram, liver function tests (LFTs), tumor marker (alpha-fetoprotein (AFP)) and serologic markers. Prior surgical and medical therapies (including TACE and chemotherapy) were recorded. Eastern Cooperative Oncology Group (ECOG) performance status was assesed. The Child-Pugh, OKUDA and BCLC classifications were portrayed.
Pretreatment radiological evaluation consisted of contrast enhanced liver CT (CECT), magnetic resonance imaging (MRI) or FDG PET/CT. Pretreatment imaging modalities were performed to evaluate the location and extent of disease. They were also used to measure total liver volume, tumor volume in the target area and extrahepatic tumor burden. The extent of tumor involvement of the liver was classified as percentage of tumor/liver volume determined objectively on baseline CECT, MRI or FDG-PET/CT.
Pretreatment angiography with Tc-99m macroaggregated albumin (MAA) scintigraphy was suggested from all cases in order to determine hepatic arterial anatomy and decide eligibility for SIRT. Coil embolization was done if necessary at the same session. Tc-99m MAA SPECT/CT scan was performed after angiography to show gastrointestinal shunting. Lung shunt fraction (LSF) was calculated by planary imaging. The procedure was applied only if LSF was under 20% and radiation absorbed dose by the lungs do not exceed 30 Gy.
The appropriate activity of Y-90 resin to be administered for radioembolization was calculated according to body surface area model and dose control was made by partition method. Post-treatment PET/CT images were obtained at the same day to investigate technical success and predict treatment efficacy.
Post-treatment labaratory evalution included LFTs and complete blood count performed twice in a month to detect early complications. AFP was assayed 3 months after the treatment to assess response to therapy.
Post-treatment monitoring imaging with CECT, MRI or FDG PET/CT was performed 3 months after the therapy for evaluation of response and repeated at regular intervals. The response evaluation criteria in solid tumors (RECIST) and PET response criteria in solid tumors (PERCIST) were used to determine tumor response.
Predefined parameters evaluated for response to SIRT were sex, age, MAA shunting in percentage, existence of limited extrahepatic metastasis, liver tumor burden (the extent of tumor involvement in the liver), FDG uptake in tumor, SUVmax and SUL peak (peak SUL in a spherical 1-cm3 VOI is measured in the single hottest tumor) on baseline PET/CT, BCLC classification, tumor size (TS), total administered Y-90 dose, delivered tumor dose in Gy, presence of bilobar disease, previous treatment type, baseline (pretreatment) and post-treatment WBC - platelet count - AFP level, presence of complication after therapy. All patients were followed-up until death or for a maximum of 10 years. Overall survival (OS) was defined as the period until death or last follow-up. The patients were divided into two groups: Group A con-

sisted of 29 patients who responded to Y-90 therapy (complete response, partial response and stable disease), Group B 5 of non-responders (progressive disease).

Data were processed with SPSS (Statistical Package for Social Science) for Windows 15.0. Descriptive statistics were presented by number and percentage, mean with standard deviation or median value. Normalcy in sample distribution was measured with Kolmogorov-Smirnov test. Pearson's Chi-square test was used for categorical variables (sex, previous treatment type, presence of extrahepatic disease, BCLC classification, presence of FDG uptake on baseline FDG PET/CT, bilobar disease existence, presence of complication). Wilcoxon-Mann-Whitney test was performed for age, LSF, liver tumor burden, SUVmax and SUL peak on baseline FDG PET/CT, TS, total administered Y-90 activity, delivered tumor dose, normal liver parenchyma dose, lung dose and OS; Student's t test for pretreatment and post-treatment AFP, WBC, platelet and lymphocyte counts in the analyzes of continuous variables. p values of <0.05 were accepted as statistically significant. The study was approved by our institutional ethics committee (registration number is 18/72).

Predefined risk factors for developing radioembolization induced liver disease (REILD) were also studied. They were age, blood tests at baseline (WBC, platelet, lymphocyte counts, total bilirubin, AST, ALT, alkaline phosphatase, albumin, gamma glutamyl transferase levels), previous treatment type, liver tumor burden, treatment area, administered Y-90 activity (GBq), delivered tumor and non-tumoral liver doses in Gy and presence of FDG uptake on baseline FDG PET/CT.

Univariate analysis was performed first, to test the association with the occurrence of REILD. The nonparametric Mann–Whitney test was used for continuous variables and the Fisher exact test for categorical variables. Statistically significant variables (p<0.05) were then analyzed by multivariate binary logistic regression. The "enter" method was used for variable entry in the model. The Hosmer–Lemeshow test was used to check the goodness of fit. A 2-sided p-value of < 0,05 was considered statistically significant.

Results

A significant decrease in AFP or WBC was not observed in post-treatment laboratory evaluation following treatment. But we found a significant decrease in platelet and lymphocyte counts one month later (p=0.02, p=0.01, respectively). Serum AFP levels decreased in 21 cases, increased in 6 cases and didn't change in 7 cases at third-month monitorization after therapy. Pretreatment and post-treatment AFP levels; WBC, platelet and lymphocyte counts of the patients and their statistical comparison were represented in Table I.

There were 30 patients in Child-Pugh A and 4 in Child-Pugh B classification. 24 patients had OKUDA stage 1 and 10 OKUDA stage 2. Additionally to sorafenib, 5 cases were treated by surgery (2 left hepatectomy, 3 segmentectomy), 3 patients TACE and 3 patients chemotherapy before Y-90 therapy. 8/34 of the patients (24%) had limited extrahepatic metastases (5 lymph node, 2 lung, 1 pancreas). Y-90 microsphere therapy was applied to left lobe only in 5 cases, right lobe only in 17 cases and bilobar in 12 cases. All the categorical and continuous variables in responders (Group A) and non-responders (Group B), and their statistical comparison were given in Table II.

In 29/34 of the cases, FDG-PET/CT was performed before and 3 months after Y-90 therapy. 19/29 of these tumors had increased FDG uptake before therapy. We used PERCIST criteria to determine tumor response in these 19 cases. Since 10/29 of the tumors showed no FDG uptake, CECT or MRI was used to evaluate therapy response in these cases. In 5/34 of Y-90 therapies, only CECT or MRI was present in order to decide treatment response. We used RECIST criteria to determine tumor response in these 5 cases.

On control imaging tests performed 3 months later, we observed complete response in 19% (n=6), partial response in 44% (n=15), stable disease in 25% (n=8) and progressive diease in 12% (n=5) of the patients. 59% of the patients were dead until the study had been completed and mean OS time was 19 (median value (MV):14) months.

TABLE I - *Pretreatment and post-treatment AFP levels; WBC, platelet and lymphocyte counts of the patients and their statistical comparison.*

Variable	All patients (n=34)	p value
Mean pretreatment AFP (ng/ml)	1800 (MV:89.8)	0.1
Mean post-treatment(3-6 months) AFP (ng/ml)	3278 (MV:42.4)	
Mean pretreatment WBC (/mm^3)	7147 (MV:5785)	0.3
Mean post-treatment(15-30 days) WBC (/mm^3)	6749 (MV:5320)	
Mean pretreatment platelet count (/mm^3)	191000 (MV:186000)	0.02
Mean post-treatment (15-30 days) platelet count (/mm3)	160000 (MV:132500)	
Mean pretreatment lymphocyte count (/mm^3)	1700 (MV:1500)	0.01
Mean post-treatment (15-30 days) lymphocyte count (/mm^3)	1000 (MV:900)	

LSF: Lung shunt fraction, OS: Overall survival, MV: Median value, TACE: Transarterial chemoembolization, KT: chemotherapy, MV: Median value

Table II - *Categorical and continuous variables in responders (Group A) and non-responders (Group B) groups and the statistical comparison between two groups.*

Variable		Group A (n=29) Treatment response (+)	Group B (n=5) Treatment response (-)	p value
Sex	Male (n=29)	25	4	0.7
	Female (n=5)	4	1	
Mean age (years)		63.2 ± 9.8	67.4 ± 4.5	0.2
Mean LSF (%)		9.6 ± 6.1	8.1 ± 3.1	0.9
Previous treatments				
TACE (n=3)		3	-	0.6
KT (n=3)		2	1	
Surgery (n=5)		4	1	
None (n=23)		20	3	
Presence of extrahepatic disease				
(+) (n=8)		7	1	0.8
(-) (n=26)		22	4	
Mean liver tumor burden (%)		23 (MV:20)	40 (MV:35)	0.07
Presence of FDG uptake on baseline FDG PET/CT				
(+) (n=19)		14	5	0.07
(-) (n=10)		10	0	
Mean SUVmax on baseline FDG PET/CT		10.6 (MV:7.7)	8.3 (MV:7.6)	0.8
Mean SUL peak on baseline FDG PET/CT		8.5 (MV:5.7)	6.2 (MV:5.3)	0.6
BCLC classification				
Stage A (n=6)		6	0	0.06
Stage B (n=17)		14	3	
Stage C (n=11)		9	2	
Mean tumor size (mm)		68.5 (MV:50)	83.6 (MV:56)	0.4
Mean total delivered Y-90 activity (GBq)		1.5 ± 0.4	1.7 ± 0.4	0.1
Mean tumor dose (Gy)		239.2 (MV:196)	74.1 (MV:57.7)	0.04
Mean normal liver parenchyma dose (Gy)		27.9 ± 12.6	22.3 ± 8.7	0.4
Mean lung dose (Gy)		6.9 ± 3.8	6.3 ± 2.5	0.9
Bilobar disease				
Present (n=12)		7	5	0.004
None (n=22)		22	0	
Presence of complication				
(+) (n=7)		7	0	0.4
(-) (n=27)		22	5	
Mean OS (months)		44 (MV:14)	7 (MV:4)	0.1

LSF: Lung shunt fraction; OS: Overall survival; MV: Median value; TACE: Transarterial chemoembolization; KT: chemotherapy

Overall survivals of both groups were demonstrated by Kaplan-Meier graph (Fig. 1).

No significant complication was observed during the treatment or at early phase (two weeks) and the procedure was well-tolerated by all the patients. Two patients developed a treatment-associated gastroduodenal ulcer. REILD was seen in 5 cases 4-6 weeks after the therapy. Risk factors for REILD among patients receiving SIRT were given in Table III.

Discussion

There are many papers about Y-90 resin SIRT in HCC and liver-metastatic colorectal cancers proving the benefit of its administration to these patients. However, which factors predict response and which patients get the best use from this treatment are rarely concerned in them except a few ones. We organized our study over a design to fulfill this deficit. We examined previous pre-

Table III - *Risk Factors for REILD among patients receiving radioembolization*

Variables	Non-REILD (n=29)	REILD (n=5)	Univariate p	Multivariate p
Age, (years)	63 (13 - 80)	69 (54 - 83)	0.172	
Blood tests at baseline				
WBC count (/mm^3)	5870 (13 - 20000)	4420 (3700- 9700)	0.495	
Platelet count (/mm^3)	191000 (13 - 397000)	133000 (91000 - 253000)	0.511	
Lymphocyte count (/mm^3)	1.5 (13 - 6.5)	1.1 (0.8 - 1.5)	0.048	0.245
Total bilirubin (mg/dl)	0.8 (13 - 1.8)	1.4 (0.5 - 1.5)	0.068	
AST (IU/L)	40 (13 - 196)	78 (39 - 104)	0.020	0.241
ALT (IU/L)	30 (13 - 360)	41 (28 - 76)	0.273	
Alkaline phosphatase (IU/L)	120 (13 - 296)	167 (74 - 394)	0.181	
Albumin (g/dl)	3.7 (13 - 4.8)	3.6 (2.3 - 4.3)	0.575	
Gamma glutamyl transferase (IU/L)	113 (13 - 347)	232 (42 - 314)	0.061	
Previous treatments				
TACE (n=3)	3 (10.3%)	0 (0%)	0.611	
KT (n=3)	3 (10.3%)	0 (0%)	0.611	
Surgery (n=5)	5 (17.2%)	0 (0%)	0.427	
None (n=23)	23 (67.6%)	5(100%)	0.121	
Liver tumor burden (%)	22.7 (13 - 75)	23.8 (13.6 - 40.7)	0.865	
Treatment			0.635	
Bilobar	11 (37.9)	1 (20%)		
Unilobar	18 (62.1)	4 (80%)		
Administered avtivity (GBq)	1.5 (13 - 3.2)	1.29 (1.1 - 1.8)	0.074	
Estimated dose delivered to				
Tumor (Gy)	105.9 (13 - 681.7)	196 (55.76 - 262)	0.865	
Nontumoral liver (Gy)	24.8 (13 - 46.3)	50.4 (27.88 - 60)	0.016	0.170
Presence of FDG uptake on baseline FDG PET/CT	18 (75%)	1 (20%)	0.036	0.380

Data are presented as n (%) or median (range); TACE: Transarterial chemoembolization; KT: chemotherapy

defined variables adding some new parameters in unresectable HCC. Mantry et al stated that early stage disease presented by BCLC, treatment with other locoregional therapies, lack of bilobar disease, portal vein thrombosis, ascites and sorefenib treatment were independent risk factors in their study of 111 patients with unresectable HCC [1]. Sangro et al determined stage, performance status, normal liver parenchyma dose and tumor burden as prognostic parameters in European multicenter study of 325 patients with unresectable HCC [10]. Paprottka analyzed the pre-therapeutic characteristics of sex, age, tumor entity, hepatic tumor burden, extrahepatic disease and liver function in 389 patients with refractory liver-dominant tumors who received Y-90 radioembolization for predicting OS with univariate Cox regressi[13].

Extrahepatic disease, large tumor burden, high bilirubin levels (>1,9 mg/dL) and low cholinesterase levels (CHE <4.62 U/I) were pre-therapeutic risk factors at baseline for poor survival in the univariate analysis; tumor entity, tumor burden, extrahepatic disease and CHE were confirmed in the multivariate analysis as independent predictors of survival [13].

SIRT can be described as a form of liver-targeted brachytherapy. There are studies in literature that SIRT improves odds ratio rate in the liver. The addition of SIRT, using Y-90 resin microspheres, to standard first-line systemic chemotherapy in patients with liver-dominant metastatic colorectal cancer did not improve progression-free survival (PFS) at any site but significantly delayed progression in the liver [14]. Van Hazel et al showed that median 20.5-month liver PFS for patients treated with chemotherapy plus SIRT represents a substantial prolongation of local disease control compared with systemic chemotherapy alone (median 12.6 months) [7]. SIRT has been shown to increase also median OS in HCC [15]. Lee et al found median OS 13.2 months [15], Mantry et al 13.1 months 1, Sangro et al 12.8 months [10], Paprottka et al 356 days 1[3]. We found median OS 14 months in our study similar to previous ones.

Nearly half of the patients with metastatic tumors from colorectal cancer undergoing Y-90 radioembolization sub-

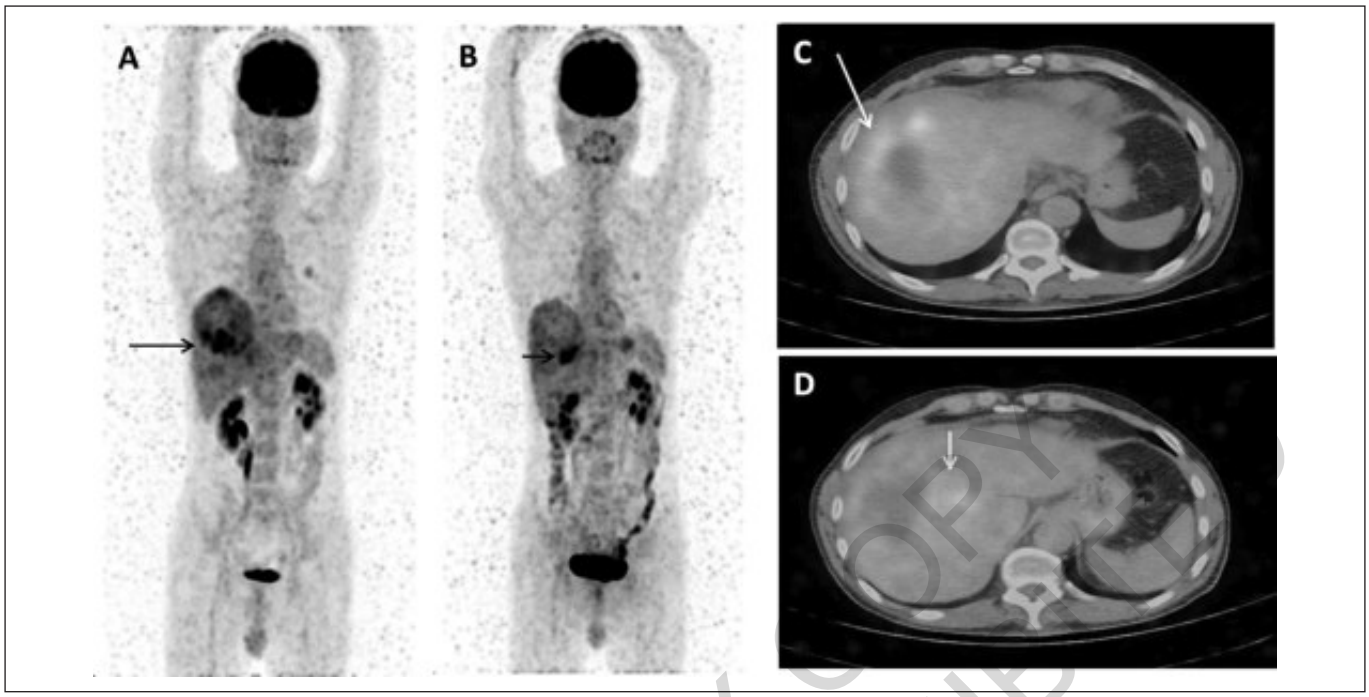

Fig. 1: Pre-therapy MIP (A), transaxial slice of FDG-PET/CT fusion (C), and post-therapy MIP (B), transaxial slice of FDG-PET/CT fusion (D) images of a 55 year old male patient with HCC. Long arrows indicate large hypodense solid lesion in upper right lobe of liver with central necrosis and increased FDG uptake (SUV max: 11.3). After 1.6 GBq Y-90 therapy (the dose absorbed by the tumor was 62.2 Gy), the size and metabolic activity of the lesion decreased (SUV max: 5.5) (short arrows) and the findings were evaluated in accordance with the partial response.

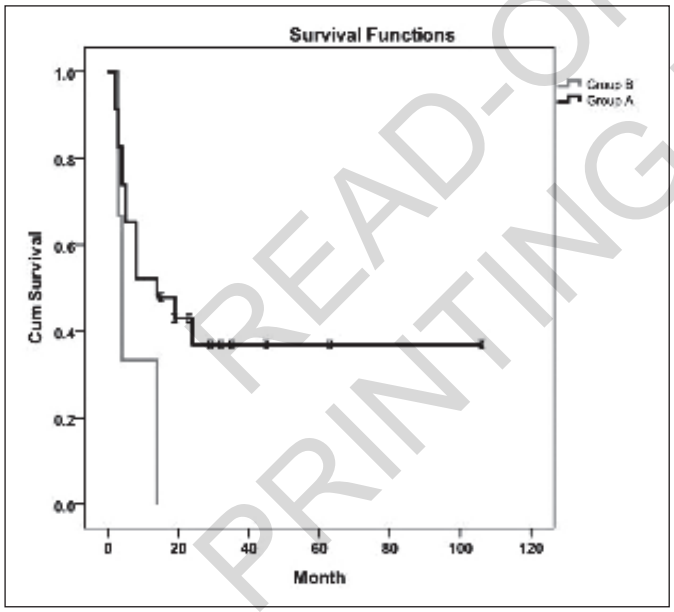

Fig. 2: Kaplan-Meier survival graph of responders (Group A) and nonresponders (Group B).

sequently receive additional alternative therapy 16. So it is crucial to recognize non-responders to SIRT and identify candidates for further systemic therapy or additional radioembolization at the beginning. FDG-PET/CT has gained wide clinical utility for identifying recurrence of malignancies and evaluation of therapy response (Fig. 2). HCC is not a typically FDG-avid tumor. FDG-PET/CT was not mandatory in SIRT treatment planning of our HCC patients. However, we performed it in patients who don't have CECT or MRI in order to predict prognosis and to detect extrahepatic spread. Additionally we used the PET/CT images for volumetric calculations. The value of PET imaging in patients with primary or metastatic liver tumors before and after Y-90 radioembolization was also indicated [17]. It is also feasible to obtain a single post-therapy FDG-PET for the same assessment which still can provide the needed prognostic information confirmed by the study of Obrzut et al [17]. In our study, FDG uptake is present in all cases of non-responders (Group B), while it is positive in 72% of responders (Group A).

However, there is not a statistically significant difference (p=0.07). But this is probably due to undersampling and presence of FDG uptake might be an independent variable if there were more patients in the study. Already, FDG uptake in HCC implies poor prognosis [18]. We assumpt from our findings that FDG-positivity can be considered a meaningful parameter for patient selection of SIRT. FDG uptake increases with tumor undifferentiation. We didn't find a relation between responder and nonresponders according to SUVmax and SUL peak values, although mean SUVmax and SUL peak are a little higher in group A.

Bilobar disease deteriorates treatment response and worsens prognosis. It was determined as a poor prognostic

risk factor by many authors [19]. Liver tumor burden is greater than 30% in all patients of non-responders (Group B), while it is under 30% in 80% of responders (Group A). When liver tumor burden increases, treatment response decreases. Mean tumor dose delivery and lack of bilobar disease seem the best predictors for treatment success according to our results. Tumor dose delivery is significantly lower in non-responders (Group B) (p=0.04) and all of the nonresponders have bilobar disease (p=0.004).

PVT is known as a strong negative prognostic factor in HCC. SIRT is a safe and effective treatment for HCC with PVT and is associated with prolonged survival and delayed tumor progression [20]. Although it is presenting as an initial manifestation in 10–40% of the patients with HCC, we had only 2 patients known with PVT. Since we could not get a statistical significant result, we didn't include them in the study. However, there was no treatment response in both patients. It is necessary to work with more patients with PVT in a larger patient group.

The selection of ^{90}Y activity is critical but imperfect that requires experience and knowledge of many factors including healthy liver reserve and LSF. Unfortunately, no single laboratory test is valid to measure liver health. Transaminases and bilirubin levels are major indicators of suitability of microsphere therapy. Dose calculations are a compromise between safety and maximizing efficacy. Since efficacy requires a high dose to the tumor, the ideal dose is the maximum dose that keeps healthy hepatic parenchymal exposure below 30 Gy [21]. There is probably a dose limit absorbed by the tumor from which it no longer responds.

This postulation comes to mind that all the patients should be delivered high doses for absolute cure. Unfortunately, we count dosing considering technical conditions depending on lung shunting and normal liver parenchyma which effect and limit delivery [19].

Major complications of SIRT generally result from irradiation of non-target tissue and include radiation-induced gastroduodenal ulcer and/or injury and radiation pneumonitis [22]. REILD is defined as irradiation of the non-tumoral liver parenchyma of the liver. Patients with REILD are usually characterized by jaundice with fatigue, anicteric ascites, increased abdominal girth, hepatomegaly, elevation of liver enzymes and usually occurring 1–2 months after RE. Treatment is largely supportive; severe cases may result in death [20].

We had 2 patients with gastroduodenal ulcer and a total of 5 REILD patients in only responder group. We did not have any patient with REILD in non-responder group. Since there is no histopathological confirmation could be possible, the diagnosis of REILD in our patient group was done according to clinical and laboratory findings.

The side effects of SIRT has been reported starting 1 week after treatment till 3 months after patient discharge. Adverse effects at one week after treatment occured in 21% of the patients, 41% at 3 months in the study of Mantry et al [1]; in 38% of the cases of Gabrielson et al at 3 months [19].

Y-90 therapy had fewer complications and higher life quality when compared with sorafenib treatment in the study of SARAH trial group conducted by Vilgrain et al [14]. Chow et al observed complications in 27% of the cases in their phase-III multicenter Asian clinical trial [23]. Our complication rate (20%) is a little lower than literature and there is no statistical difference between the responder and non-responder groups according to complications.

Identifying those patients with REILD risk prior to treatment is crucial. We aim to obtain the maximum therapeutic effect while keeping the healthy parenchymal dose as low as possible to prevent developing REILD. Although the absorbed dose in non-tumoral liver parenchyma has been low (28-60 Gy (MV:50.4)) in patients developed REILD, it is still significantly higher than the absorbed dose in patients without REILD (Table III). Besides that, pretreatment lymphocyte values were significantly lower and serum AST values were significantly higher in patients with REILD than those without REILD (p:0.02 and p:0.04, respectively). On the other hand, although it's not statistically significant, basal total bilirubin and gamma glutamyl transferase values were found to be higher in patients with REILD.

The presence of FDG avidity in pretreatment PET/CT in only 1 out of 5 patiens with REILD was found remarkable. It is well known that HCC tumors with FDG uptake are less differentiated.

Therefore, much more neovascularization in undifferentiated HCC tumors in comparison to well differentiated ones may be a limiting factor for radioactive microspheres deposition to the intact liver parenchyma preventing REILD development in follow up. Investigating this issue in more HCC cases with FDG involvement would be helpful. Due to the small number of our REILD patients, larger prospective studies are needed to clarify the role of FDG avidity in selection of patients with HCC to develope REILD after SIRT.

Our success of treatment is markedly higher than literature. 85% of the patients responded to SIRT. Complete remission was seen in 35% of the patients, stable disease in 34% and progressive disease in 31% according to the results of Paprottka et al [13]. Gabrielson et al. observed a three-month disease control rate of 52% in unresectable HCC [19].

Post-treatment platelet and lymphocyte counts decreased significantly according to pretreatment values. This may be taken into consideration for therapy suitability of the patient choice.

Our small patient number limits statistical power of the study. Our design will be a kernel model with new parameters for prospective future studies with much more patients.

Conclusions

According to our clinical experience, Y-90 microsphere therapy is a safe and effective treatment option for the patients with unresectable HCC without any serious side effect. Mean tumor dose delivery and lack of bilobar disease seem the best predictors for treatment success.

Acknowledgement

A part of this study was presented as oral presentation at the symposium held in Adana, Turkey at 10-12 February 2017, and it was published as an abstract in Journal of Gastrointestinal Cancer on June 20, 2017.

Riassunto

Scopo: La terapia selettiva con radionuclidi intraarteriosi (SIRT) con microsfere di resina di ittrio-90 (Y-90) è stata applicata recentemente per il carcinoma epatocellulare (HCC). Lo scopo di questo studio è presentare il nostro studio della terapia con radiomicrosfera nel trattamento dell'HCC non resecabile e determinare i casi appropriati che potrebbero trarre beneficio da questa terapia in base ai risultati di risposta forniti dallo stadio iniziale e dalle modalità di controllo per immagini.
Metodi: abbiamo somministrato 43 terapie con microsfere Y-90 a 34 pazienti con HCC non resecabile (due volte in 9 pazienti). I pazienti con HCC confermato dal punto di vista istopatologico con un'aspettativa di vita di ≥3 mesi; classificazioni Child AB, Classificazione Okuda 1-2 e stadiazione BCLC ABC sono state incluse nello studio. I pazienti sono stati divisi in due gruppi: il gruppo A era composto da 29 pazienti che hanno risposto alla terapia con Y-90 (risposta completa, risposta parziale e malattia stabile), il gruppo B 5 non davano nessuna risposta (malattia progressiva). I parametri predefiniti sono stati valutati per la risposta alla SIRT e confrontati tra i due gruppi.
Risultati: abbiamo riscontrato una significativa diminuzione del numero di piastrine e dei linfociti un mese dopo la terapia (p = 0,02, p = 0,01, rispettivamente). Nei test di controllo per immagini eseguiti 3 mesi dopo, abbiamo osservato una risposta completa nel 19% (n = 6), una risposta parziale nel 44% (n = 15), una malattia stabile nel 25% (n = 8) e una malattia progressiva nel 12% (n = 5) dei pazienti. La sopravvivenza globale media (OS) è stata di 19 (valore mediano: 14) mesi.
Conclusioni: la terapia con microsfere Y-90 è un'opzione di trattamento sicura ed efficace per i pazienti con HCC non resecabile senza alcun effetto collaterale grave.
Tumore di piccole dimensioni e mancanza di assenza di localizzazione bilobare sembrano le migliori condizioni per il successo del trattamento.

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