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ORIGINAL PAPER

Yttrium-90 radioembolization treatment for unresectable hepatocellular carcinoma: a single-centre prognostic factors analysis

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Abstract The aim of this study was to evaluate the efficacy and the safety of Y90 radioembolization (Y90-RE) in patients with unresectable hepatocellular carcinoma (HCC) analysing our results and correlating them with independent prognostic factors for overall survival (OS) and for complications. Forty-three patients with advanced inoperable HCC including those with multiple bilobar lesions or portal vein thrombosis (PVT) treated with Y90-RE were reviewed. Treatment efficacy and safety were evaluated. Survival was calculated by the Kaplan–Meier method. Univariate analyses were performed for identifying potential prognostic factors. Radiologic response was evaluated with the modified Response Evaluation Criteria in Solid Tumours (mRECIST) criteria. Clinical toxicities were prospectively recorded. Median overall progression-free survival and OS were 27.7 and 16.8 months, respectively. Longer median OS was revealed in those without PVT ($p = 0.0241$) and those whose pre-treatment haemoglobin values was higher ($p = 0.0471$). According with mRECIST criteria, we observed a disease control rate of 69.2 and 61.9% at 3- and 6-month follow-up, respectively. Complications developed in 28 patients (65.1%), among which grade 2–3 events were reported in 17 patients. We noted that activity administered dose presented a correlation with intra-procedural toxicity ($p = 0.039259$) while common hepatic artery use as release site was associated with a most frequent presentation of remote adverse events. Y90-RE is an alternative treatment with a promising outcome for poor-risk advanced inoperable HCC. PVT and pre-treatment haemoglobin values can be predictors of efficacy. Activity administered dose and arterial release site can be predictors of safety.

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Introduction

Hepatocellular carcinoma (HCC) is the second most common cause of cancer-related deaths worldwide with rapidly growing incidence rates in the USA and Europe [1, 2].

Altogether, the general prognosis of HCC continues to be poor with overall survival (OS) rate at 5 years ranged from 24 to 41% [3]. Surgical resection and liver transplantation remain the most effective treatment options for small and oligo-nodular (five or fewer intra-hepatic lesions) HCCs [4]. However, surgical approach is only feasible in 9–27% of the HCC patients, as the most patients get diagnosed at advanced stages or the poor hepatic condition in setting of underlying chronic liver disease limits any surgery [1]. Furthermore, the shortage of organ donors and high costs of the whole transplantation process limits the application of this treatment option, raising demands for novel treatment strategies of early-stage HCC [5].

Therefore, a majority of the patients with unresectable HCC are referred for image-guided locoregional embolotherapy including catheter-based intra-arterial therapies techniques, such as transarterial embolization (TAE), conventional transarterial chemoembolization (TACE), drug-eluting bead TACE (DEB-TACE) and yttrium-90 radioembolization (Y90-RE). The main benefit of these therapies is explained by the preferentially arterial blood supply of liver tumours, which allows to deliver the anticancer therapy directly to the tumour feeding artery while sparing the healthy hepatic tissue mainly supplied by the portal vein [6].

Y90-RE is a catheter-based therapy that delivers internal radiation to tumours. Y90-microspheres are administered via percutaneously placed catheters to the hepatic arterial system to treat patients with HCC and metastatic cancer to the liver. Unlike other current therapies for the treatment of unresectable liver tumours, Y90-RE is much less often associated with toxicities such as abdominal pain, fever, nausea and vomiting [7, 8].

The rationale for Y90-RE for hepatic tumours comes from the anatomic and physiological aspects of these tumours that can be exploited for the delivery of a therapeutic agent. Hepatic tumours derive at least 90% of their blood supply from the hepatic artery, and liver parenchyma obtains 70–80% of its blood supply from the portal vein [9–11]. This differential pattern of vascular perfusion provides an intrinsic advantage for hepatic arterial regional therapies delivered selectively to liver tumours while minimizing potential compromise to normal liver function [12].

The administration of Y90 represents a true radioembolization, combining the benefits of internal radiation therapy, as well as the embolic effect of the Y90-microspheres [6, 13].

Our experience on Y90-RE as an emerging alternative, mostly applied for niche indications such as HCC with portal vein invasion, will be discussed focusing on the analysis of prognostic factors for overall survival (OS) and for complications.

Materials and methods

Patient selection

Patients with advanced HCC treated with Y90-RE between October 2009 and August 2015 were reviewed.

Eligibility for Y90-RE was determined by a multidisciplinary team including hepatologists, surgeons, medical oncologists, interventional radiologists, nuclear medicine physicians and radiotherapist on the basis of disease stage, Eastern Cooperative Oncology Group (ECOG) performance status = 0–2, serum total bilirubin $\leq$2 mg/dL and ability to undergo angiography.

All patients were investigated with computed tomography (CT) or magnetic resonance imaging (MRI) study to detect the specific features of neoplasm, such as localization, number of nodules, portal vein thrombosis (PVT) and extrahepatic metastasis.

Moreover, serum haematology, renal and liver biochemistry, α-fetoprotein (AFP) response, clotting profile and virology were reviewed for each patient.

Procedure details

1 or 2 weeks before the radioembolization treatment, each patient underwent a liver angiography to delineate the course of hepatic arteries and identify any aberrant and collateral feeding vessels; the angiographic study was followed by injection of technetium-99 m macroaggregated albumin (mTc99-MAA) into the hepatic artery for the determination of the mTc99 uptake by cancerous and healthy liver's tissue (in order to calculate the tumour–normal liver ratio) and the percentage of lung shunting by single-photon emission CT/CT scan. Those who had tumour–normal liver ratio 2.0 or percentage of lung shunting >20% were excluded from subsequent radioembolization to avoid suboptimal treatment outcomes and unfavourable toxicities. Prescription of activity of Y90-

microspheres was based on body surface area model as previously described [14], and for each patient, the nuclear medicine physician calculated the administered activity dose (GBq), the lesion dose (Gy), the liver dose (Gy) and lung dose (Gy) aiming at a radiation dose <200 Gy to the tumour and <80 Gy to the normal liver.

All treatments were performed with Y90-microspheres (SIR-spheres; SIRTEX Medical, Sydney, Australia).

If necessary, prophylactic embolization of gastroduodenal, gastric and/or other extrahepatic arteries was performed to prevent undesirable delivery of microspheres into these vessels.

Injection of Y90-microspheres was performed from hepatic artery or from one of the principal hepatic branches on the basis of the lesions distribution.

Patients were discharged the day after the procedure.

Serial blood tests were performed once a month for 1 year. Imaging follow-up was performed with contrast-enhanced (ce)CT scan after 1–3 and 6 months from the date of Y90-RE procedure for monitoring treatment efficacy and identifying potential complications.

Data analysis

Progression-free survival (PFS) was estimated from the date of Y90-RE to the date of radiologic sign of progression or death from any cause, while overall survival (OS) was calculated from the date of Y90-RE procedure to the date of death from any cause.

The Kaplan–Meier method was used to calculate median OS and PFS.

The modified Response Evaluation Criteria in Solid Tumours (mRECIST) [15] was used to evaluate tumour response follow-up ceCT scan.

Concerning tumour response, we considered follow-up ceCT of 1, 2, 3 and 6 months in order to make the cohort of follow-up CTs as large as possible.

Cox proportional hazards model was used to compare the survival among several variables summarized in Table 1.

Fisher's test was used to compare the treatment response and the procedure-related side effects among the variables described in the Procedure Details.

Finally, Mann–Whitney *U* test was used to compare radiation-induced liver disease (RILD) with variables specifically related to the liver.

Treatment-related toxicity was classified according to the latest version of the National Cancer Institute Common Terminology Criteria for Adverse Events [16].

Complications were divided in three categories: intra-procedural (occurred during the procedure), peri-procedural (occurred within the discharge) and late complications (occurred after the discharge).

A p value of less than 0.05 was considered statistically significant with confidence interval of 95%.

Results

Patient population

From October 2009 to August 2015, 48 patients with advanced HCC were proposed for Y90-RE treatment by the multidisciplinary team. Three patients were subsequently excluded from Y90-RE due to pulmonary shunt fraction >20 and 1 patient due to high bilirubin level; finally, 1 patient refused the procedure. This rendered 43 patients (mean age of 65.8 years; male-to-female 37:6).

The characteristics of all patients are shown in Table 2.

The most common aetiologies of liver disease were hepatitis C virus (HCV)-related cirrhosis and alcoholic liver disease. Biopsy was performed in 27.9% of cases. Most patients had multifocal (79.06%) and bilobar disease (62.79%).

Twenty patients (46.5%) had received prior therapy including TACE (30%), RFA (5%), RFA combined with TACE (50%) and tumour resection ± RFA (10%).

PVT was noted in 6 patients (13.95%).

The median prescribed dose was 1.18 ± 0.47 GBq. Prophylactic radioembolization of gastroduodenal artery (GDA) was performed in 29 patients (67.5%).

The features of treatments are summarized in Table 3.

Treatment response

Follow-up assessments of treatment response were conducted at 1, 3 and 6 months after the procedure using mRECIST criteria, and the results are reported in Table 4.

1-month follow-up ceCT was available for 33 patients: 6 of them had local response including 3 patients with complete response and an additional 15 patients had stable disease, resulting in a disease control rate of 63.6% (21/33 patients).

3-month follow-up ceCT was available for 21 patients: 10 patients had local response including 5 patients with complete response and an additional 3 patients had stable disease, resulting in a disease control rate of 61.9% (13/21 patients).

6-month follow-up ceCT was available for 13 patients: 7 patients had local response including 5 patients with complete response and an additional 2 patients had stable disease, resulting in a disease control rate of 69.2% (9/13 patients).

In conclusion, 5 patients had complete response lasting for 6 months.

Table 1 Variables considered for OS and PFS analyses

Patient related	Tumour related	Treatment related
Age and sex	Number of lesions	Dose at lesion, liver and lung
Cause of HCC	Portal vein thrombosis	Prophylactic embolization of gastroenteric arteries
Recent treatments	α-Fetoprotein levels	Site of microsphere release and side effects
Presence and stage of cirrhosis with Child–Pugh score		Both intra- and peri-procedurally and long term
Biochemical findings (*bilirubin, GOT, GPT, cholinesterase, albumin, creatine*)		
Haematological findings (*INR, haemoglobin, white cell and platelet counts*)		

HCC hepatocellular carcinoma

Response rate was statistically significant higher in patients with higher activity administered dose ($p = 0.02$).

Survival

The median OS starting from the treatment was 27.7 months (SE = 3.044, 95% CI 15.75–27.68 months), and median PFS was 16.8 months (SE = 2.873, 95% CI 11.13–22.39 months) (Figs. 1, 2).

Longer median OS was seen in those without PVT ($p = 0.0241$; $R = 2.0835$) and those with higher pre-treatment haemoglobin (HBG) values ($p = 0.0471$; $R = -0.3397$).

Patients with number of tumour lesions <3 definitely derived longer median OS ($p = 0.0155$; $R = 1.6520$) than patients with number of tumour lesions ≥3.

Finally, the absence of prophylactic radioembolization was the variable significantly related to PFS ($p = 0.0241$; $R = -1.2357$).

Clinical complications and toxicity

Complications developed in 28 patients (65.1%), among which grade 2–3 events were noted in 17 patients.

The complications are summarized in Table 5.

The statistical analysis showed that activity administered dose presents a correlation with intra-procedural toxicity ($p = 0.039259$) while common hepatic artery use as release site is associated with a most frequent presentation of remote adverse events ($p = 0.039$).

Moreover, the presence of radiation-induced liver disease is correlated with high liver estimated dose ($p = 0.0495$), high pre-treatment GTP levels ($p = 0.0128$) and the presence of PVT ($p = 0.0247$).

Discussion

In the last decade, Y90-RE has emerged as a viable option for locoregional treatment of unresectable HCC associated or not with PVT.

Although Y90-RE has not been endorsed by the American Association for the Study of Liver Diseases (AASLD) or European Association for the Study of the Liver (EASL), due to lack of prospective randomized studies accumulating evidence has proved its efficacy and prolongation of survival in patients with advanced HCC.

However, several recent studies have reported that Y90-RE is a safe procedure with a strong antitumour efficacy and a high degree of tumour necrosis (36–70%) on histopathology [17–19].

Our current study results in terms of OS (SE = 3.044, 95% CI 15.75–27.68 months) are consistent with the published literature regarding Y90-RE in HCC. Salem et al. reported an OS of 17.2 months in Child–Pugh A disease [20], Hilgard et al. achieved a median OS of 16.4 months in 108 patients (47% BCLC B; 51% BCLC C) with lobar-directed Y90 [21] and Sangro et al. [22] reported a median OS of 16.9 months in BCLC B patients who were poor candidates for TACE (bilobar disease or >5 tumours).

Recent Rognoni et al. metanalysis [23] suggests that median OS in patients receiving Y90-RE for intermediate–advanced HCC falls in the range of 12–24 months; halved to 6–12 months should PVT be present.

Our results show a longer median OS in patients without PVT ($p = 0.0241$; $R = 2.0835$), and it agreed with those in previous studies that PVT is an unfavourable prognostic group even after Y90-RE [20].

Today, Y90-RE candidates are patients with intermediate-stage disease who poorly meet the criteria for cTACE and, most commonly, patients with PVT or progressive disease after cTACE. Y90-RE is technically considered safer than cTACE due to its non-embolic approach, particularly in patients with PVT [24], who present a higher risk to develop liver ischaemia since the affected lobe is predominantly perfused via the hepatic artery.

The prospective phase II study reported by Mazzaferro et al. [25] reveals less than 10% severe adverse events for Y90-RE in patients with PVT, while hyperbilirubinemia and clinical liver failure were found in 30 and 37% of

Table 2 Patients characteristics

Characteristics patients	Number/mean value (%)	Standard deviation (SD)
Number of patients	48	
Patients excluded	5	
Age	65.8	±9.78
Sex: M; F	37 (86.04%); 6 (13.95%)	
Child–Pugh class		
A	37 (86.04%)	
B	4 (9.30%)	
C	2 (4.65%)	
BCLC stage		
A1	1 (2.32%)	
A4	4 (9.30%)	
B	32 (74.42%)	
C	6 (13.95%)	
CLIP stage		
0	1 (2.32%)	
1	31 (72.09%)	
2	8 (18.60%)	
3	2 (4.65%)	
4	1 (2.32%)	
α-Fetoprotein		
≥400	38 (88.37%)	
<400	5 (11.63%)	
Portal vein thrombosis		
Presence	6 (13.95%)	
Absence	37 (86.05%)	
Liver lobes involved		
One	16 (37.21%)	
Both	27 (62.79%)	
Number of hepatic lesions		
≥3	34 (79.06%)	
<3	9 (20.93%)	
Extrahepatic metastasis		
Present	1 (2.32%)	
Absent	42 (97.67%)	
Portal vein thrombosis		
Present	6 (13.95%)	
Absent	37 (86.05%)	
Prior therapy		
Resection	1	
Chemoembolization	6	
RFA	1	
Chemoembolization + ablation	10	
Resection + chemoembolization + radiofrequency ablation	2	23
None		
Aetiology factors		
HBV	5 (11.63%)	
HCV	20 (46.51%)	
HCV + HBV	1 (2.32%)	

Table 2 continued

Characteristics patients	Number/mean value (%)	Standard deviation (SD)
Alcol	8 (18.60%)	
Alcol + HCV	4 (9.30%)	
Unknown	5 (11.63%)	
Cirrhosis		
Yes	36 (83.72%)	
No	7 (16.28%)	
Comorbidity		
IDDM	8 (18.60%)	
NIDDM	6 (13.95%)	
HIV	1 (2.32%)	
Dyslipidemia	5 (11.63%)	
Others	25 (58.14%)	
Diagnosis		
Biopsy	12 (27.9%)	
Imaging	31 (72.09%)	
Lab tests pre-treatment		
HB	13.1	±1.57
WBC	5.20	±1.91
PLT	127.20	±70.20
INR	1.13	±0.099
Bilirubin TOT	1.34	±0.73
Bilirubin DIR	0.37	±0.28
Bilirubin IND	0.97	±0.51
Aspartate aminotransferase	71.19	±51.56
Alanine aminotransferase	69.37	±59.84
Cholinesterase	4.46	±2.14
Albumin	3.62	±0.46
Creatinine	1.52	±4.14
Lab tests post-treatment 3 months (8 patients)		
HBG	12.14	±2.24
WBC	43.36	±334.45
PLT	62.96	±62.95
INR	1.3	±0.33
Bilirubin TOT	4.37	±6.12
Bilirubin DIR	1.97	±3.94
Bilirubin IND	2.31	±2.41
Aspartate aminotransferase	147.83	±388.74
Alanine aminotransferase	94.20	±240.884
Cholinesterase	5.14	±3.58
Albumin	3.24	±0.59
Creatinine	1.17	±0.72

RFA radiofrequency ablation, *HBV* hepatitis B virus, *HCV* hepatitis C virus, *HBG* haemoglobin, *WBC* white blood cell, *PLT* platelet counts

patients, respectively. Patients with PVT invading the right or left portal vein or its segmental branches had a median OS of 17 after Y90-RE; patients with main PVT had a 9-month OS [25].

An OS between 3.2 and 10 months was observed in those with PVT as compared to 15.3–16.4 months in those without PVT in other studies [21, 26, 27]. Moreover, patients who had branched first-order PVT survived longer

Table 3 Median dose and treatment characteristics

Treatment characteristics	Media ± SD or *n*° (%)
Activity administered dose	1.18 ± 0.47
Estimate tumour dose	287.02 ± 680.42
Estimate liver dose	29.37 ± 7.03
Estimate lung dose	3.21 ± 2.09
Pulmonary shunt	5.5 ± 3.17%
Scintigraphy gastroenteric uptake	
Yes	4 (9.1%)
No	40 (90.9%)
Prophylactic embolization	
No	14 (32.55%)
Yes	29 (67.44%)
Position of microspheres released	
Common hepatic artery	13 (30.23%)
Right hepatic artery	24 (55.81%)
Left hepatic artery	3 (6.98%)
Right hepatic artery and left hepatic artery	3 (6.98%)
Lobe treated	
Right	22 (51.16%)
Left	3 (6.98%)
Right and left	18 (41.86%)

Table 4 Tumour response evaluated with mRECIST

	Complete response	Partial response	Stable disease	Progressive disease
1 month (33 patients)	3 (9.1%)	3 (9.1%)	15 (45.45%)	12 (36.3%)
3 months (21 patients)	5 (23.8%)	5 (23.8%)	3 (14.2%)	8 (38.1%)
6 months (13 patients)	5 (38.5%)	2 (15.4%)	2 (15.4%)	4 (30.8%)

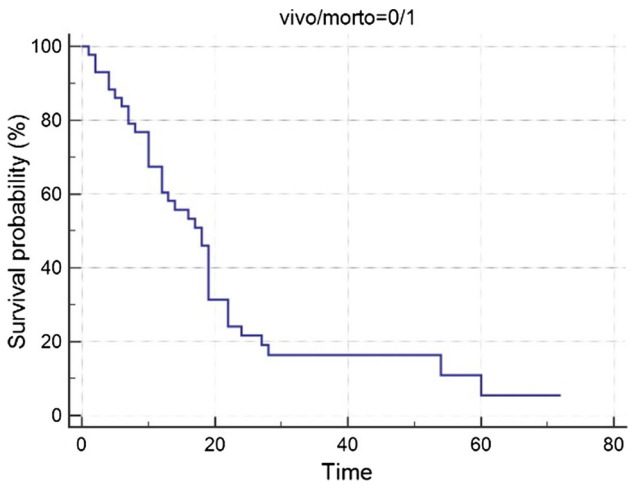

Fig. 1 Overall survival from treatment

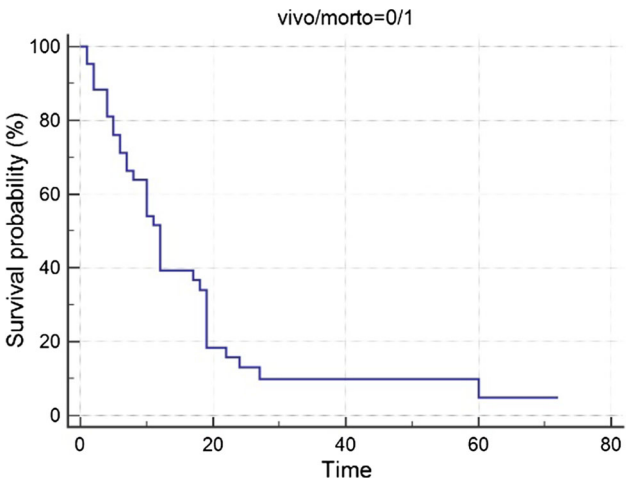

Fig. 2 Progression-free survival

(6.5–16.6 months) than those who had main PVT (4.4–7.5 months) [28].

A recent systematic review by Fidelman and Kerlan [24] concluded that the median OS was between 3.2 and 13 months for HCC patients with PVT who underwent Y90-RE, which was significantly longer for patients with underlying Child–Pugh A than ones with Child–Pugh B liver disease.

Our data showed that the number of individual intra-hepatic tumours was identified as significant risk factors by

Table 5 Clinical complications

Categories	Number of patients	($n°$) type of complications
Intra-procedural	4 (9.30%)	2 hypertensive peak
		1 vagal crisis
		1 dissection of a branch of right hepatic artery
Peri-procedural	15 (34.88%)	5 nausea
		8 abdominal pain
		1 headache
		1 fever
Late complications	9 (20.93%)	3 radiation-induced liver disease
		1 radiation chronic gastritis
		1 pleural–peritoneal effusion
		1 cholecystitis
		1 ascitic failure
		1 hepatorenal syndrome
		1 digestive haemorrhage from varices rupture

univariate analysis. Although there are no specific studies in the literature of this correlation, it is easy to understand that smaller number of HCC lesions corresponds to a better OS ($p = 0.0155$; $R = 1.6520$) than patients with higher number of HCC lesions.

In our study, higher pre-treatment HBG values corresponded to a longer median OS ($p = 0.0471$; $R = -0.3397$). In terms of survival, only limited data on the HBG level in HCC have been published [29, 30]. The prevalence of anaemia among patients with HCC is, as in other cases of cancer, higher than in the healthy population and it may be associated with a number of reasons; the pathogenesis of cancer-associated anaemia including nutritional deficiency, haemolysis, blood loss and infiltration of the bone marrow by tumour cells was postulated to be one of the common causes [31]. Similarly, chronic liver injury can result in anaemia in patients with HCC [32].

Several studies showed that increased HBG levels are associated with improved treatment outcomes [33, 34].

In addition to its effects on clinical outcomes, anaemia has a significant and meaningful impact on quality of life (QOL). Effective management of anaemia has resulted in marked improvements in energy level, ability to do daily activities and overall QOL scores in several studies [35–40]. These effects on QOL were seen when the final HBG levels were increased from 1.8 to 2.0 g/dl over baseline levels of 9.2–9.5 g/dl [36–39]. These studies support the idea that HBG levels should be increased to at least 11 g/dl for effective management of anaemia. Detailed analyses confirmed that the greatest increase in QOL scores is seen as the HBG increases to 11–12 g/dl [41].

To our knowledge, there has been no thorough analysis of the prognostic potential of HBG levels in HCC patients and our study suggests, for the first time in the literature, that correcting low levels of HBG before treatment could improve not only the QOL but also the OS of patients treated by Y90-RE.

The absence of prophylactic GDA radioembolization was another variable significantly related to the survival in our population. The choice to perform prophylactic radioembolization of extrahepatic vessels is largely operator-dependent and varies considerably across institutions; however, many experienced high-volume centres have moved away from routine prophylactic radioembolization of the GDA, suggesting coil embolization of non-target vessels should be no longer routinely recommended [42].

Minimizing the risk of gastrointestinal ulceration after Y90-RE requires complete angiographic mapping of the hepatic arterial anatomy and identification of hepaticoenteric anastomotic vessels [43]. However, radioembolization of these vessels introduces new risks such as arterial dissection, coil migration, recanalization and visceral ischaemia [44]. Recently, Borggreve et al. performed a prospectively randomized trial comparing the incidence of gastrointestinal complications after Y90-RE in 456 patients who underwent radioembolization of at least 1 hepaticoenteric anastomotic vessel with 781 patients who had no embolization and they did not find any significant difference in gastrointestinal complications and they concluded that it is advisable to limit hepaticoenteric collateral vessel embolization to vessels distal or close to the site of microsphere injection [45].

In another recent study, Ward et al. evaluated the safety of Y90-RE without prophylactic radioembolization of the GDA in 62 patients undergoing treatment for liver dominant metastatic disease. No signs or symptoms of gastric or duodenal ulceration were observed in the follow-up, leading to the conclusion that Y90-RE without embolization of the GDA can be performed safely.

Our opinion, based upon the data obtained, it is in line with this recent literature. In particular, we think that in cases of less extensive HCC lesions a more selective embolization is sufficient. In these patients, it is reasonable to expect a better response to treatment and a better prognosis with only selective embolization, avoiding GDA radioembolization.

Evaluation of the treatment response after radioembolization is a key component for the management of patients with HCC [46]. The survival-based end points traditionally used in clinical studies have largely been replaced by objective radiologic responses, which have been widely used and accepted as surrogate end points. In addition, surrogate markers for therapeutic efficacy such as OS and PFS equally rely on imaging methodologies to identify patients with disease recurrence or progression.

Anatomic biomarkers represent the veteran technique and have been routinely used to evaluate tumour response, but no universally accepted standard method or imaging criteria exists [47, 48]. As such, the Response Evaluation Criteria in Solid Tumours (RECIST) system is one of the radiologic markers that have been widely accepted in the evaluation of tumour response to systemic chemotherapy [49, 50]. However, most embolotherapy techniques, included Y90-RE, induce tumour ischaemia/infarction which leads to tissue necrosis without immediate effects on the tumour size [51].

The inability of RECIST to assess post-embolotherapy tumour response prompted development of a biologically more suitable approach [15, 52, 53]. More recently, modified RECIST (mRECIST) proposed to adopt a single long-axis measurement of enhancing tumour tissue [15]. Both the current one- and two-dimensional measurement methods are limited by high inter- and intra-observer variability [54–57].

Our follow-up assessments of treatment response were conducted at 1 month (disease control rate of 63.6%), at 3 months (disease control rate of 61.9%) and, finally, at 6 months (disease control rate of 62.9%) after the treatment using mRECIST criteria.

However, tumour response usually represents only a surrogate end point, whereas OS, which is universally considered the primary outcome in oncological studies [58, 59], was consistently assessed in our study, whereas treatment responders definitely enjoyed a longer median survival (27.7 months starting from the treatment) and also a longer PFS (16.8 months), essentially comparable with the long-term results of a previously reported prospective single-centre study by Salem et al. [60] who reported PFS of 7.7 and 4.5 months after radioembolization in patients with Child–Pugh class A and B status and PVT, respectively.

In a more recent study, Lee et al. [61] reviewed 30 patients with advanced inoperable HCC and they reported a PFS of 3.3 months and an OS of 13.2 months.

Since treatment for patients with unresectable HCC is essentially palliative, it is crucial to offer them effective treatment with minimal toxicity.

In 2008, Kulik et al. [28] established the safety profile of Y90-RE for the first time, demonstrating the safety and tolerability of Y90-RE in HCC patients both with and without PVT. They showed that there were no differences in bilirubin toxicities when the patients were stratified based on PVT status. Two years later, Hilgard et al. [28] confirmed Kulik's findings in a prospective single-centre observational study designed to validate safety and anti-tumour effect of Y90-RE in advanced stage HCC. The most frequent adverse events on this study were transient fatigue and abdominal pain.

El Fouly et al. [62] showed that Y90-RE was better tolerated than TACE, required less hospitalization and necessitated fewer treatment sessions.

Toxicity profiles in our study were also comparable to other reported studies [63, 64] Complications developed in 65.1% of patients. The most common side effects were peri-procedural complications consist of abdominal pain or nausea and, less commonly, headache and fever. It has been attributed to an idiosyncratic reaction, often to resin microspheres [65].

Concerning other systemic side effects were reported also 2 cases of hyperintensive peak and 1 case of vagal crisis classified among intra-procedural complications.

A case of dissection of a branch of right hepatic artery was included in our intra-procedural complications classification. Systemic chemotherapeutic agents may render blood vessels fragile. Hence, vascular adverse events may occur more often following systemic chemotherapy for secondary liver tumours and biologic agents have been widely known to cause vascular adverse events during arteriography [66]. Arterial dissection, vasoconstriction and poor vascular flow have been reported in the literature [67], suggesting that careful selection and manipulation of microcatheters and wires are mandatory in this kind of treatment. The correlation between the appearance of complications and the location of microspheres administration was also statistically significant in our studio: more proximal catheter was place, more complications occurred. This is because the more proximal the catheter, the farther it is from the lesion, and therefore, the treatment will be less selective.

Among late complications, our results showed that the presence of radiation-induced liver disease was related to high liver estimated dose, high pre-treatment GTP levels and the presence of PVT. Three of our patients developed an hepatic adverse events (1 ascites, 1 hepatorenal syndrome and 1 cholecystitis). The incidence of hepatic adverse events in the literature is highly variable as a result of diverse patient selection, duration of patient follow-up to

assess for toxicities and definitions for grading toxicities [68]. The presence of underlying cirrhosis further complicates this picture, as the natural history of cirrhosis progression may be confounded with liver toxicity from Y90-RE, especially in patients with Child–Pugh class B and C disease [66]. Radiation-induced cholecystitis is a well-known adverse event when infusion is performed proximal to cystic artery and occurs in as many as 2% of cases [66]. Several studies have assessed the impact of prophylactic embolization (e.g. gelatine, coils) of the cystic artery, but a decrease in the rate of cholecystitis has not been observed with these manoeuvres [69]. Biliary adverse events from embolization have been reported, but are relatively uncommon compared with other intra-arterial therapies, likely because of the minimally embolic effect of embolization [70].

Two patients developed gastrointestinal radiation injury (1 chronic gastritis and 1 digestive haemorrhage from varices rupture) which is a well-recognized side effect in more than 10% of patients due to the inadvertent delivery of microspheres to the GDA and less commonly short gastric arteries [61]. Meticulous and slow injection of microspheres may reduce the chance of backflow to the GDA and other small arteries supplying the stomach and duodenum. Prophylactic embolization and prophylactic use of proton pump inhibitors may also be helpful [71].

The present study has the following limitations. First, the series is composed of few patients. Retrospective design, which has the associated issues of potential selection bias, was another limitation. Analyses of clinical toxicities are excepted because there were prospectively recorded.

Third, the follow-up is dishomogeneous (1-month follow-up was available for 33 patients, 3-month follow-up was available for 21 patients and 6-month follow-up was available only for 13 patients).

Conclusion

Altogether, our results are consistent with the literature and with reports indicated that Y90-RE could be potentially useful for treatment of HCC, especially in patients with locally advanced tumour, which may be associated with concurrent PVT or not, and may present with preserved or impaired liver function (Child–Pugh A vs. B). Notably, the present results require further confirmation by prospective investigations in multicentre clinical trials.

Compliance with ethical standards

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

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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