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RESEARCH ARTICLE

EFFICACY OF TRANS-ARTERIAL RADIO EMBOLIZATION WITH YATTRIUM-90 FOR HEPATIC MALIGNANCIES

Salem Ali Salem Al Obaiyah[1], Tariq A Munshy[2], Noha Husain Guzaiz[3], Mohammed Hamad Mohammed Al Mutarid[1] and Bandar Salem Al Alhindi[4]

1. Interventional Radiology Fellow, King Abdullah Medical City, Makkah, Saudi Arabi.
2. Consultant Interventional Radiologist, King Abdullah Medical City, Makkah, Saudi Arabia.
3. Consultant Vascular and Interventional Radiologist, Medical Imaging Department, King Abdullah Medical City, Makkah, Saudi Arabia.
4. Assiststantprofessor of Interventional Radiology, Bisha University, Saudi Arabia.

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Abstract

Objective: to assess the efficacy of trans-arterial radio embolization with yattrium-90 for end-stage unresectablehepato-cellular carcinoma HCC.

Methods: End stage HCC patients who were treated with TARE between May 2019 and January 2023 at King Abdullah Medical City in Makkah, Saudi Arabia, were enrolled in this retrospective cohort study. TARE was performed with resin (SIR-Spheres®) loaded with Yttrium-90 microspheres (SIR-Spheres). 3 and 6 months after the completion of TARE, patients underwent a contrast-enhanced CT or MRI to evaluate their treatment responses, after which imaging follow-up was performed at 2- or 3-weeks intervals.All statistical analyses were performed using the Statistical Package for Social Sciences (SPSS version 25.0; IBM, Armonk, NY, USA).

Results:The study included 29 patients. Among them (65.5%) were Males. Interval decrease in size was found in (27.6%), Interval increase in size was observed in (24.1%). furthermore, the tumor was Stable in size in (48.3%).LR-TR Viable was found in (61.9%), LR-TR Nonviable was observed in (19%). Also LR-TR Equivocal was in (19%).

Conclusion:TARE is safe and effective in the treatment of unresectable HCC, as it has a safer toxicity profile than chemoembolization, longer time-to-progression, greater ability to downsize and/or bridge patients to liver transplant, and utility in tumor complicated by portal vein thrombosis. TARE can also serve as an alternative to ablation and chemotherapy.

Introduction:-

Hepatocellular carcinoma (HCC) is worldwide the sixth most common cancer overall and fourth most common cause of cancer-related mortality. (1) (HCC) is a primary tumor of the liver and constitutes more than 90% of the primary tumor of the liver. Hepatocellular carcinoma occurs in approximately 85% of patients diagnosed with

Corresponding Author:- Salem Ali Salem Al Obaiyah
Address:- Interventional Radiology Fellow, King Abdullah Medical City, Makkah, Saudi Arabi.

cirrhosis. Significant risk factors for hepatocellular carcinoma include viral hepatitis (hepatitis B and hepatitis C), alcoholic liver disease, and non-alcoholic liver steatohepatitis/non-alcoholic fatty liver disease. Several therapies have been developed for treating patients with this aggressive malignancy. Broadly divided into surgery, locoablative therapy, transcatheter therapy, radiation therapy, and systemic therapy, these therapies can be used alone or in combination; planned in a single or in multiple sessions; and performed with curative, downstaging, bridge, debulking, or palliative intent. (2)

Transarterialradioembolization (TARE) or selective internal radiation therapy (SIRT) is a transcatheter intra-arterial procedure performed by the interventional radiologist for the treatment of primary and secondary hepatic cancers. Microspheres impregnated with the radioisotope yttrium-90 (Y90, ^{90}Y) are selectively delivered through the hepatic vasculature to the target tumor(s). Selective intra-arterial injection of these microspheres allows for the safe administration of high radiation doses to the tumor. TARE is safe and effective in the treatment of unresectable HCC, as it has a safer toxicity profile than chemoembolization, longer time-to-progression, greater ability to downsize and/or bridge patients to liver transplant, and utility in tumor complicated by portal vein thrombosis. TARE can also serve as an alternative to ablation and chemotherapy. (3)

Assessing treatment response after therapy is essential for determining prognosis and informing future management. Computed tomography (CT) and magnetic resonance imaging (MRI) play critical roles for assessing treatment response of hepatocellular carcinoma (HCC) after locoregional therapy. (4) Interpretation is challenging because posttreatment imaging findings depend on the type of treatment, magnitude of treatment response, time interval after treatment, and other factors. To help radiologists interpret and report treatment response in a clear, simple, and standardized manner, the Liver Imaging Reporting and Data System (LI-RADS) has developed a Treatment Response (LR-TR) algorithm. (5) Introduced in 2017, the system provides criteria to categorize response of HCC to locoregional treatment (e.g., chemical ablation, energy-based ablation, transcatheter therapy, and radiation therapy). LR-TR categories include:

1. Nonevaluable, this category is assigned when the treatment response cannot be evaluated due to poor image quality or inadequate technique (e.g., failure to obtain the required phases). (6)
2. Nonviable, the nonviable category should be assigned to treated lesions with no perceived enhancement or demonstrating only expected posttreatment enhancement patterns. The latter may depend on the applied locoregional treatment used and the time interval after treatment. (7)
3. Equivocal, this category is applied to treated observations that cannot be confidently categorized as viable or nonviable due to overlapping enhancement features in the absence of technical or patient-related limitations. (8)
4. Viable, the viable category should be assigned to treated observations with nodular, masslike, or thick irregular regions of arterial phase hyperenhancement (APHE), washout appearance, or enhancement similar to pretreatment tumor. These features indicate the presence of viable tumor cells with high certainty. This is valid for all locoregional treatments with the exception of radiation therapy as discussed further. (9)

The main objective of this study is to assess the efficacy of trans-arterial radio embolization with yattrium-90 for end-stage unresectablehepato-cellular carcinoma HCC.

Materials and Methods:-

End stage HCC patients who were treated with TARE between May 2019 and January 2023 at King Abdullah Medical City in Makkah, Saudi Arabia, were enrolled in this retrospective cohort study. The inclusion criteria were patients with clinical or histological diagnosis of end stage HCC according to HCC guidelines. The exclusion criteria were as follows: (1) age < 19 years, (2) decompensated liver cirrhosis; (3) other HCC stages than end stage; (4) patients outside hospital records.

The study protocol adhered to the ethical guidelines of Declaration of Helsinki and was approved by the institutional review board of King Abdullah Medical City in Makkah. Informed consent was not required because of the retrospective study design.

TARE was performed with resin (SIR-Spheres®) loaded with Yttrium-90 microspheres (SIR-Spheres). The dose was determined from the planning angiogram and prepared in the nuclear medicine department according to the manufacturer’s preparation guide.

Approximately 3 and 6 months after the completion of TARE, patients underwent a contrast-enhanced CT or MRI to evaluate their treatment responses, after which imaging follow-up was performed at 2- or 3-weeks intervals.

For target lesions, the tumor response was defined as a complete response (CR), indicated by the complete disappearance of viable lesions, or as a partial response (PR), defined as at least a 30% decrease in the sum of diameters of viable target lesions, taking as reference the baseline sum of the diameters of target lesions. Progressive disease (PD) was defined as an increase of at least 20% in the sum of the diameters of viable target lesions, taking as reference the smallest sum of the diameters of viable target lesions recorded since treatment started. Stable disease was any case that did not qualify for either PR or PD. Objective response was defined as the proportion of participants whose best overall response is either CR or PR. Disease control was defined as the proportion of participants whose best overall response is CR, PR or SD. Responders were defined as the sum of the patients who showed an objective response.

All statistical analyses were performed using the Statistical Package for Social Sciences (SPSS version 25.0; IBM, Armonk, NY, USA). Statistical significance was set at $p < 0.05$.Data are expressed as mean ± standard deviation, median (range) or n (%), as appropriate. Differences between continuous and categorical variables were examined for statistical significance using a student's t-test (or the Mann–Whitney test, as appropriate) and the chi-squared test (or Fisher's exact test, as appropriate). Paired related continuous variables were analyzed using a paired t-test (or Wilcoxon paired test, as appropriate).

Multivariate analysis was performed by adjusting for significant variables ($p < 0.05$) in the univariate analyses. The Cox proportional hazards model was used to perform multivariate analysis. For a multivariate analysis using composite variables, the constituent variables were not incorporated into the multivariate analysis to prevent statistical collinearity. The adjusted hazard ratio and 95% confidence interval were calculated for each selected risk factor.

Results:-

Table (1):- Socio-demographic characteristics of the studied patients (No=29).

Variables		Frequency (No.)	Percentage (%)
Age	Mean +SD 65.51+ 8.55		
	< 60 years	7	24.1
	≥ 60 years	22	75.9
Gender	Male	91	5656
	Female	91	5456

Table (1)shows socio-demographic characteristics of patients. The current study included 29 patients. Among them (65.5%) were Males . The mean +SD age of patients is 65.51+ 8.55. About (75.9%) of the studied patients were in age category of (≥ 60) years old.

Table(2):- Tumor characteristics among studied patients.

Variables	(No=29)(100%) (No.) (%)
Involved liver segment	
One segment	8 (27.6)
Two segments	8 (27.6)
Three segments	7 (24.1)
Four segments	5 (17.2)
Five segments	1 (3.4)
Multiplicity (tumor focality)	
Focal	14 (48.3)
Multifocal	15 (51.7)
Arterial supply	
Single	21 (72.4)
Dual	8 (27.6)
Tumor-related Thrombosis	
None	24(82.8)

Portal vein	2(6.9)
Left hepatic vein	1(3.4)
Intrahepatic IVC into right atrium	1(3.4)
Lt hepatic vein, IVC & right atrium	1(3.4)
Histopathological Type of hepatic tumor	
HCC	21(72.4)
Liver mets of colon cancer	4(13.8)
Liver mets of net tumor	2(6.9)
Hccfibrolammellar type	1(3.4)
Liver mets of carcinoid tumor	1(3.4)
Size (cm)	
Focal	
Mean +SD	8.54+ 4.19 (2-16)

Table (2) shows tumour characteristics among the studied patients. Equal percentage (27.6%) among patients with tumours involved in one segment and two segments of the liver and (24.1%) with tumours involved in three segments of the liver. As regards the multiplicity of the tumour, more than half of patients (51.7%) had multifocal tumours. A single arterial supply of tumour was observed in 72.4 percent of patients. Tumour-related thrombosis in the portal vein was observed in 6.9% of patients. Regarding Histo-pathological Type of hepatic tumourHepatocellular carcinoma was reported in 72.4 percent of the studied patients. The mean size of the tumour is 8.54+ 4.19 cm, with a range of 2–16 cm.

Table (3):- The subdivision of patients according to percentage of lung shunting detected.

Percentage of lung shunting	**Number of patients (%)**
< 5	10 (34.5)
5.1-10	10 (34.5)
10.1-15	7 (24.1)
15.1-20	1 (3.4)
>20	1 (3.4)

Table (3)shows the subdivision of the included 29 patients according to percentage of Lung shunting (LS). LS percentage of < 5 was found in 34.5%, Also percentage of 5.1-10 was found in in 34.5%, percentage of 10.1-15 was found in 24.1%.

Table (4):- Tumor radiological response (CT/MRI) after 3-6 months.

Variables	**(No=29)(100%)**
	(No.) (%)
Follow up by CT or MRI after 3-6 months	
Interval decrease in size	8 (27.6)
Interval increase in size	7 (24.1)
Stable in size	14 (48.3)

Table (4) shows Tumor radiological response (CT/MRI) after 3-6 months follow up. Interval decrease in size was found in (27.6%), Interval increase in size was observed in (24.1%). furthermore, the tumor was Stable in size in (48.3%).

Table (5):- POST-TARE LI-RADS after 3-6 months of HCC follow-up.

Variables	**(No=21)(100%)**
	(No.) (%)
POST-TARE LI-RADS after 3-6 months	
LR-TR Nonviable	4 (19)
LR-TR Viable	13 (61.9)
LR-TR Equivocal	4 (19)

Table (5) shows Tumor radiological response (POST-TARE LI- RADS) after 3-6 months follow up. LR-TR Viable was found in (61.9%), LR-TR Nonviable was observed in (19%).Also LR-TR Equivocal was in (19%).

Table (6):- Tumor response after 3-6 months (CT/MRI) follow up in relation to patient and Tumor characteristics.

Variables	**Interval decrease in size**	**Interval increase in size**	**Stable in size**	**P-value**
	(No.8) (27.6%)	**(No.7) (24.1%)**	**(No.14)(48.3%)**	
Age				
< 60 years	1 (3.4)	3 (10.3)	3 (10.3)	.370*
≥ 60 years	7 (24.1)	4 (13.8)	11 (37.9)	
Gender				
Male	6 (20.7)	3 (10.3)	10 (34.5)	.345*
Female	2 (6.9)	4 (13.8)	4(13.8)	
Involved liver segment				
One segment	5 (17.2)	1(3.4)	2 (6.9)	**.047***
Two segments	3 (10.3)	0	5 (17.2)	
Three segments	0	3 (10.3)	4 (13.8)	
Four segments	0	2 (6.9)	3 (10.3)	
Five segments	0	1 (3.4)	0	
Multiplicity (tumor focality)				
Focal	6 (20.7)	3 (10.3)	5 (17.2)	.196*
Multifocal	2 (6.9)	4 (13.8)	9 (31)	
Arterial supply				
Single	6 (20.7)	5 (17.2)	10 (34.5)	.982*
Dual	2(6.9)	2 (6.9)	4 (13.8)	
Tumor-related Thrombosis				
Present	0	4 (13.8)	1 (3.4)	**.005***
Absent	8 (27.6)	3 (10.3)	13 (44.8)	
Histopathological Type of hepatic tumor				
HCC	7 (24.1)	5 (17.2)	9 (31)	.240*
Liver METS of colon cancer	1 (3.4)	0	3(10.3)	
Liver METS of net tumor	0	0	2 (6.9)	
HCC fibrolammellar type	0	1 (3.4)	0	
Liver mets of carcinoid tumor	0	1 (3.4)	0	
Size (cm)				
Mean +SD	5.40+2.21	12.17+3.85	8.70+ 4.01	**.007****

*Chi Sequare test ** Kruskal Wallis Test

Table (6) According to CT/MRI follow-up after 2–6 months, it was observed that 10.3% and 6.9% out of 24.1% of the tumours were involved in three and four liver segments, respectively, among patients who were found to have an interval increase in the size of the tumour. There was tumour-related thrombosis in 13.8% out of 24.1% of patients who were found to have an interval increase in the size of the tumour, versus 3.4% out of 48.3% of patients who were found to have a stable increase in the size of the tumour. The mean size of the tumour in patients who were found to have an interval increase in size (12.17+3.85) was found to be higher than the size among patients with a decrease and stable tumour size. There is a statistically significant association between the involved liver segment, tumour-related thrombosis, the size of the tumour, and tumour response (p-value.05).

Table (7):- Tumor response after 3-6 months (POST-TARE LI-RADS) follow up in relation to patient and Tumor characteristics.

Variables	**LR-TR Equivocal**	**LR-TR Nonviable**	**LR-TR viable**	**P-value***
	(No.4) (19%)	**(No.4) (19%)**	**(No.13)(61.9%)**	
Age				
< 60 years	1 (4.8)	0	3 (14.3)	.557*
≥ 60 years	3 (14.3)	4 (19)	10(47.6)	
Gender				
Male	2 (9.5)	4 (19)	9 (42.9)	.282 *
Female	2 (9.5)	0	4 (19)	
Involved liver segment				
One segment	3 (14.3)	1 (4.8)	3 (14.3)	.445*
Two segments	1 (4.8)	2 (9.5)	4 (19)	
Three	0	0	3 (14.3)	
Four segments	0	1 (4.8)	3 (14.3)	
Multiplicity (tumor focality)				
Focal	4 (19)	2 (9.5)	6 (28.6)	.155*
Multifocal	0	2 (9.5)	7 (33.3)	
Arterial supply				
Single	3 (14.3)	3 (14.3)	9 (42.9)	.960*
Dual	1 (4.8)	1 (4.8)	4 (19)	
Tumor-related Thrombosis				
Present	0	0	4 (19)	.219*
Absent	4 (19)	4 (19)	9 (42.9)	
Size (cm)				
Mean +SD	6.18+2.99	3.90+1.273	10.39+4.043	**.004****

*Chi Square test ** Kruskal Wallis Test

Table (6) According to (POST-TARE LI-RADS) follow up after 2-6 months of 21 cases of HCC , It was observed that The mean size of tumor in patients whom were found to have LR-TR viable (10.39+4.043) was found to be higher than size among patients with LR-TR Equivocal and LR-TR Nonviable. There is statistically significant association between Size of tumor and Tumor response p-value <.05.

Discussion:-

TARE with 90Y microspheres is still being studied clinically for the treatment of advanced HCC. The importance of radioembolization as a safe and effective treatment for unresectable HCC, however, is being supported by a growing body of research that has been published in the recent few decades.

In our study we have found that tumor radiological response (CT/MRI) after 3-6 months follow up was that interval decrease in size was found in (27.6%) , Interval increase in size was observed in (24.1%) . furthermore the tumor was Stable in size in (48.3%) . On the other hand, another study (10) aimed to assess the efficacy of TARE with yattrium-90 in HCC revealed that TARE could be an effective and safe treatment option for patients with unresectable liver-dominant primary or metastatic cancer which is inconsistent with our results.

Regarding the tumor radiological response (POST-TARE LI-RADS) after 3-6 months follow up we have found that LR-TR Viable was found in (61.9 %), LR-TR Nonviable was observed in (19%), also LR-TR Equivocal was in

(19%). This means that there is a nodular, mass like, or thick irregular regions of arterial phase hyperenhancement (APHE), washout appearance, or enhancement similar to pretreatment tumor in most of the participants (61.9%). These features indicate the presence of viable tumor cells with high certainty and ineffective TARE, these results are inconsistent with that found in previous studies (11, 12).

Evidence of the efficacy and safety of TARE, including recent reports from both single-center and multicenter observational cohorts (13, 14, 15, 16) is accumulating in the literature. Although TARE with yttrium-90 integral to the matrix of glass microspheres is approved by the United States Food and Drug Administration for the treatment of HCC under a humanitarian device-exemption status, the AASLD, EASL, and European Organization for Research and Treatment of Cancer do not currently endorse TARE as a standard treatment for HCC, primarily due to the lack of randomized controlled trial data supporting the efficacy and safety of TARE compared with TACE. (17, 18).Typically, recent studies indicate that transarterialchemoembolization (TACE), transarterialradioembolization (TARE), and repetitive hepatic arterial infusion chemotherapy (HAIC) have achieved favorable outcomes in advanced HCC. However, many patients fail to respond to the transarterial treatment, even though the optimal technique is adopted (19), which is consistent with our results.A multi-institutional, retrospective study that looked at TARE preoperatively in 100 patients treated for HCC and intrahepatic metastases in 16 centres across Asia and Europe found a risk of 24% grade 3 and above complications in patients who received TARE and a 30% risk in the matched non-preoperative TARE group. Both groups experienced similar complications from liver failure (20).Two randomised trials comparing sorafenib with TARE, the SARAH (21) and SIRveNIB (22) trials, have examined the role of TARE in multifocal HCC. 360 patients from 11 Asian nations were included in the SIRveNIB trial, of whom 182 were randomly assigned to TARE and 178 to sorafenib (the standard of care chemotherapeutic pill for multifocal HCC) (23). The median overall survival was the same (8.8 months for the TARE group and 10 months for the sorafenib group). TARE had fewer adverse events of grade 3 or above that could be attributed.

A number of limitations apply to our study: First of all, this study had a retrospective design and only involved one centre. Because individuals with early-stage HCC were excluded, there may have been a selection bias. As a result, our findings cannot be applied to patients receiving bridge therapy before transplantation or surgery. Despite these drawbacks, this study emphasises the significance of meticulous patient selection prior to therapy. There is a need for additional research that focuses on examining safe dosimetry cutoff values in patients with cirrhosis and reduced liver function.

Conclusion:-

TARE is safe and effective in the treatment of unresectable HCC, as it has a safer toxicity profile than chemoembolization, longer time-to-progression, greater ability to downsize and/or bridge patients to liver transplant, and utility in tumor complicated by portal vein thrombosis. TARE can also serve as an alternative to ablation and chemotherapy. However, our results showed that TARE was ineffective in most of the studied population; 48.3% had stable tumor size response after 3-6 months follow up, and 61.9% were LR-TR Viable, this indicate the presence of viable tumor cells with high certainty and ineffective TARE.

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