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Ana Judite Martins dos Santos Pinto da Silva

Imaging patterns of hepatocellular carcinoma and response to Yttrium 90

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Mestrado Integrado em Medicina

Área: Cirurgia Geral

Trabalho efetuado sob a Orientação de:
Mestre Carlos Alberto Sousa Soares
E sob a Coorientação de:
Mestre Renato José Barroso Bessa de Melo

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FMUP FACULDADE DE MEDICINA UNIVERSIDADE DO PORTO
UNIDADE CURRICULAR PROJETO DE OPÇÃO DISSERTAÇÃO / MONOGRAFIA

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Cirurgia Geral

TÍTULO DISSERTAÇÃO/MONOGRAFIA

Imaging patterns of hepatocellular carcinoma and response to Yttrium 90

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Aos meus pais, José Davide Silva e Ana Maria Silva

Ao meu irmão, Davide

À minha avó e tia Kika

Ao Miguel e à Laura

Imaging patterns of hepatocellular carcinoma and response to Yttrium 90

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ABSTRACT

Purpose. **Hepatocellular carcinoma (HCC) exhibits a variable response to Yttrium 90 (^{90}Y) radioembolization. Imaging response assessment criteria in transarterial therapies appear to display an imperfect correlation with survival. We sought to evaluate whether specific imaging patterns of HCC at presentation may predict tumor response. Additionally, we assessed specific tumor features and their relation with overall survival (OS) and progression-free survival (PFS).**

Methods. **A retrospective cohort of 16 patients with HCC diagnosis selected for ^{90}Y radioembolization was reviewed. Computed tomography (CT) images before and after treatment were assessed for specific tumor features. Tumor response was graded according to mRECIST, EASL and Choi criteria. HCC characteristics associated with OS and PFS were documented.**

Results. **Sixteen patients were included in the study, with a median follow-up of 26.2 months. The median overall and post-radioembolization survival was 37.5 months and 22.6 months respectively. Tumor size (p 0.046) and number of tumor nodules (p 0.029) recorded at baseline significantly changed with radioembolization. No complete imagiological responders were recorded according to any criteria. Both mRECIST and EASL criteria reported a majority of stable disease (61.5% and 53.8%, respectively). Choi response criteria classified most patients as responders (69.2%). Radiologic tumor response according to imaging assessment criteria exhibited no relation with patient survival.**

Conclusions. **HCC imaging features at presentation may predict tumor response to radioembolization. Prospective trials with larger cohorts are necessary in order to confirm and further extend the assessment of radioembolization response and related predictors and to determine tumor characteristics related to PFS and OS.**

KEYWORDS: Hepatocellular carcinoma; Yttrium 90; Radioembolization; mRECIST; Choi criteria; EASL

1. Introduction

Liver cancer positions as the sixth most prevalent neoplasm globally. Poor prognosis at presentation places it as the third leading cause of cancer-related mortality, accountable for 696,000 deaths annually. [1]

Treatment management of hepatocellular carcinoma (HCC) includes potentially curative, palliative, and symptomatic approaches. [2] Only ten percent of HCC patients will be eligible for curative therapies [3] , thus, targeted therapies have been emerging. [4] Recently, Yttrium 90 (^{90}Y)

microspheres were approved for liver cancer [5, 6] and acknowledged as a treatment option for HCC in selected cases [7-10].

Indications for ^{90}Y radioembolization continue to expand [8, 11, 12] due to its feasibility in the presence of portal vein thrombosis[13, 14] and favorable safety profile in the cirrhotic liver with evidence of preserved liver function[15]. Still, consensual selection criteria for radioembolization in HCC are yet to be established.

This transarterial therapy associates a marginal embolic effect and cytotoxicity of radiation, frequently inducing necrosis without significant tumor size variation. [16] Therefore, response assessment criteria which rely on tumor size shrinkage solely to state response to treatment may be inadequate. [17, 18]

HCC response to radioembolization with ^{90}Y occurs in varying degrees with most series reporting response rates of twenty five to fifty percent. [19] Disparity in the magnitude of tumor response may reflect differences in tumor imaging patterns prior to ^{90}Y therapy.

Imaging response has shown the ability to predict survival benefit following locoregional therapies. [20] Still, radioembolization impact on survival varies widely with a reported median overall survival of 12.8 months. Median time-to-progression ranges from 7.9-10.0 months and from 11.8-15.5 months for patients without portal vein invasion. [20, 21].

The aim of our study was to recognize specific imaging patterns of HCC at presentation that may predict tumor response to ^{90}Y radioembolization. Futhermore, we sought to investigate the relation of tumor response predictors with progression-free-survival (PFS) and overall survival (OS).

2. Patients and Methods

2.1. Patient selection

This retrospective review included sixteen patients with hepatocellular carcinoma submitted to ^{90}Y radioembolization at Centro Hospitalar de São João, EPE. of Porto, Portugal from 2010 to 2013.

Inclusion criteria consisted of: 1) diagnosis of hepatocellular carcinoma according to EASL-EORTC practice guidelines criteria [22] and 2) radioembolization treatment using ^{90}Y glass microspheres.

2.2. Clinical characteristics

Clinical data collected comprised age, gender, etiology of HCC, total bilirubin (mg/dl), albumin (g/L), ALT (U/L), creatinine (mg/dL) and alpha-fetoprotein (ng/mL) levels, Child Pugh status and evidence of cirrhosis. Supplementary data included target liver region, target liver volume and number of radioembolization treatments.

2.3. ^{90}Y Glass Microspheres radioembolization

Prior to ^{90}Y injection, a digital substraction angiography was obtained for vascular anatomy documentation and hepatofugal vessels were coil-embolized. Simultaneously, a hepatic arterial perfusion scintigraphy with SPECT-CT images using technetium-99m labeled macroaggregated albumin (MAA-Tc-99m) was also performed to simulate the microspheres distribution and identify potential pulmonary or extra-hepatic abdominal shunting. Patients with a pulmonary shunt determining lung exposure superior to 30 Gy per treatment, or cumulative lung exposure superior to 50 Gy, were excluded.

Radioembolization treatment was executed by percutaneous transarterial injection of glass microperes loaded with ^{90}Y (TheraSphere®, MDS Nordion, Ottawa, Ontario, Canada), through the hepatic artery.glass microperes loaded with ^{90}Y, through the hepatic artery.

Radiation dose was individually determined for each patient according to liver volumetric calculation. Median calculated radiation dose was 126.5 GBq (range, 114.0–151.0).

Bremsstrahlung scans obtained post- radioembolization procedure verified the adequate distribution of the ^{90}Y microspheres to the tumor lesions.

2.4. Computed Tomography Assessment

Abdominal triphasic computed tomography (CT) scans of the liver were obtained at two distinct time points, baseline and post-radioembolization.

A radiologist who was blind to the patient outcome reviewed all CT images for the following tumor features (1) number of lesions; (2) bidimensional tumor size; (3) median tumor attenuation (density in Hounsfield units [HU]); (4) tumor margins (well or poorly defined); (5) arterial enhancement (hyperenhancing or hypoenhancing); (6) tumor enhancement pattern (homogenous or heterogeneous); (7) extent of tumor necrosis (≤50%; or >50%).

Images were also reviewed for the presence of portal venous thrombosis, ascites and pathological lymph nodes.

2.5. Statistical Analysis and Response Assessment

Tumor response to radioembolization was evaluated according to mRECIST [23], EASL[24] and Choi[25] imaging response assessment criteria.

Categorical variables were reported as number (%) and measured data was reported as median (range, minimum to maximum).

Differences in baseline tumor features and after ^{90}Y radioembolization were compared using Fisher exact test (categorical variables) and Wilcoxon sign test (continuous variables).

Survival among strata was recorded using Kaplan-Meier curves and compared through a log-rank test.

The primary endpoint was PFS described as the time, measured in months, from radioembolization treatment until CT documentation of disease progression. The secondary endpoint was OS, defined as time between HCC diagnosis and date of death.

All statistical analysis was executed with SPSS 22.0 software (SPSS Inc., Chicago, Illinois, USA) and statistical significance was determined at a p value of < 0.05.

3. Results

Patients included in the study were predominantly male (75.0%) with a median age of 63.5 years (range 54 – 74 years). The most frequent etiologies were HBV infection and alcohol consumption (25.0%). The majority of patients exhibited liver cirrhosis (81.2%) and had Child-Pugh stage A liver dysfunction (68.8%).

Eleven patients were submitted to one radioembolization session while five patients were submitted to 2 sessions.

Four patients were subjected to multimodality therapy, two patients received transarterial chemoembolization prior to radioembolization and two patients were submitted to hepatic resection after radioembolization.

Median follow-up was 26.18 months (range 10-60 months), with a total of 9 death events recorded. The median overall and post-radioembolization survival was 37.5 months (CI, 24.7-50.2) and 22.6 months (CI, 17.2-28.1), respectively.

Table 1 summarizes the clinicopathological features of the patients submitted to radioembolization.

Most patients (53.8%) had less than 5 tumor nodules, even though a considerable number of patients had multifocal disease, with two cases of innumerable tumor lesions.

Of the 16 patients with HCC diagnosis proposed to ^{90}Y radioembolization treatment, 13 had adequate pre and post RE imaging and three patients were excluded for lack of follow-up imaging.

The median baseline target lesion longest axis was 66.0 mm (15.0-99.0 mm), and median tumor attenuation was 84.0 HU (0-133 HU). Most tumors presented a heterogenous hyperenhancing pattern (92.3%), less than 50% tumor necrosis (92.3%) and poorly defined margins (69.2%).

The median hepatopulmonary shunt fraction estimated by MAA-Tc-99m scintigraphy before radioembolization was 7.1% and the median target liver volume was 834.0. Median ^{90}Y activity of microspheres administered to the patient was 2.3 GBq (range, 1.2–3.6).

No complete imagiological responders were recorded according to any criteria. Both mRECIST and EASL criteria reported a majority of stable disease (61.5% and 53.8%,

respectively). Partial response was documented according to mRECIST and EASL in 3 and 1 patients, respectively. Choi response criteria classified most patients as responders (69.2%).

The comparison of the imaging features of the follow-up CT scan obtained a median of 2.6 months after treatment to the baseline CT scan are summarized in table 2. This analysis demonstrated significant difference in pre and post-radioembolization tumor size (p 0.046) and number of lesions (p 0.029), as well as a trend towards lower tumor attenuation (p 0.092) following radioembolization.

The median survival, as previously refered, was 37.5 months (95% CI, 24.7-50.2) and was not significantly altered by patient's clinical status, age, gender or etiology of HCC.

There were no clinical characteristics or tumor features linked with improved median survival. Overall survival was diminished in patients with Child-Pugh B liver dysfunction(18.0 months), and bilirubin levels superior to 1.5 mg/dl (27.6 months) compared to those with Child-Pugh status A (60.0 months) and bilirubin level inferior to 1.5 mg/dl (44.8 months), although, it did not reach statistical significance (p 0.381 and 0.285 respectively).

Survival according to baseline characteristics is displayed in Table 3.

4. Discussion

Response assessment criteria for HCC seem to underestimate tumor response when applied to selective transarterial therapies such as radioembolization. Thus, investigation on alternative response criteria addressing these limitations is starting to emerge [26]. Choi criteria, initially designed for evaluation of treatment response of GIST to imatinib mesylate, was proposed as an appropriate predictor of HCC response to ^{90}Y radioembolization [27]

In this study, we present the radiologic tumor features linked with response.This analysis might help support the recognition, at presentation, of HCC patients with predictable benefit from ^{90}Y radioembolization.

Our investigation of the imaging features related with radioembolization concluded both tumor size (p 0.046) and number of lesions (p 0.029) significantly decreased with treatment, establishing the importance of monitoring these parameters. Previous clinical studies corroborate the finding of radioembolization´s ability to diminish tumor burden among patients with HCC [28].

In our perspective, other tumor features, such as tumor attenuation, the presence of ascites and presence of PVT should be addressed in future studies considering that our results showed differences, though, these were not statistically significant.

Mean overall survival was not considerably altered by patient's age, gender or etiology of HCC recommending that these factors should not be applied as selection criteria.

Mean overall survival was related to Child-Pugh status and bilirubin level, though the results were not statistically significant.

The evaluation of response criteria relation with survival or PFS did not reveal significant results with any of the response criteria assessed.

Our study is limited by its retrospective design and reduced number of patients. Additionally, CT scanning assessment could have been inconsistent due to subjectivity in interpretation and technical discrepancies. Variation in the follow up CT time after radioembolization treatment mirrors standard clinical practice circumstances.

In summary, tumor features of HCC at presentation in association with patient clinical status may predict response to radioembolization. Prospective trials with larger cohorts are necessary in order to confirm and further extend the assessment of radioembolization response and related predictors and to determine tumor characteristics related to PFS and OS.

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Table 1. Patient and Tumor Characteristics at Baseline and Radioembolization Parameters*

Characteristics	Values
Age, median (range)	63.5 (54 to 74)
Gender, no. (%)	
Male	12 (75.0)
Female	4 (25.0)
Etiology, no. (%)	
HBV	4 (25.0)
HCV	3 (18.7)
HBV+HCV	1 (6.3)
Alcohol	4 (25.0)
HCV+alcohol	1 (6.3)
Hemocromatosis	1 (6.3)
Not determined	2 (12.5)
Child-Pugh, no. (%)	
A	11 (68,8)
B	5 (31.2)
Albumin (g/L), median (range)	35.5 (30.6 to 43.2)
Alpha-Phetoprotein (ng/mL), median (range)	21.5 (2.9 to 2554.0)
ALT (U/L), median (range)	61.0 (28.0 to 145.0)
Creatinine (mg/dL), median (range)	0.9 (0.5 to 10.6)
Total billirubin (mg/dL), median (range)	0.8 (0.4 to 2.4)
Presence of cirrhosis, no. (%)	13 (81.2)
Number of treatments, no. (%)	
1	11 (68.8)
2	5 (31.2)
Y^{90} Activity administered, GBq, median (range)	2.3 (1.2 to 3.6)
Target Liver Volume, cc, median (range)	834.0 (360.0 to 1381.9)
Hepatopulmonary shunt fraction, median (range)	7.1 (1.9 to 21.9)

Abbreviations: HBV, hepatitis B virus; HCV, hepatitis C virus; ALT, alanine aminotransferase

*N=16

Table 2. Comparison of Tumor Characteristics at Baseline and Post-Radioembolization*

Characteristics	Baseline	Post-Radioembolization	p Value[∞]
Number of lesions[+], median (range)	3 (1 to 11)	4 (1 to 11)	0.313
Tumor nodules, no. (%) < 5 > 5	 7 (53.8) 6 (46.2)	 7 (53.8) 6 (46.2)	 0.029
Tumor size, longest axis, mm, median (range)	66.0 (15.0 to 99.0)	56.0 (19.0 to 121.0)	0.073
Tumor size, perpendicular axis, mm, median (range)	54.0 (15.0 to 89.0)	44.0 (15.0 to 92.0)	0.046
Tumor attenuation, HU, median (range)	84.0 (0 to 133.0)	78.0 (0 to 127.0)	0.092
Vascularity pattern, no. (%) Hyper Hypo	 12 (92.3) 1 (7.7)	 10 (76.9) 3 (23.1)	 0.231
Necrosis, no. (%) < 50% > 50%	 12 (92.3) 1 (7.7)	 10 (76.9) 3 (23.1)	 0.231
Presence of ascites, no. (%)	1 (7.7)	1 (7.7)	0.077
Presence of PVT, no. (%)	10 (76.9)	12 (92.3)	0.231

Abbreviations: PVT, portal vein thrombosis

*N=13, [+] Two patients with innumerable lesions, [∞] Fisher exact and Wilcoxon rank test

Table 3. Survival by Baseline Characteristic*

Characteristics	**Mean Survival** (95% confidence interval)	**p Value**
All	37.5 (24.7,50.2)	NA
Age, years < 65 > 65	36.9 (7.4,51.6) 27.0 (NA)	0.921
Gender Male Female	36.8 (20.5,53.1) 27.5(3.9,19.8)	0.799
Etiology HBV HCV Alcohol Other	 18.5 (17.8,19.2) 28.7 (26.3,31.0) 26.5 (9.2,43.8) 50.8 (28.0,73.6)	0.542
Child-Pugh A B	40.6 (25.5,55.7) 23.3 (12.8,33.9))	0.381
Albumin (g/L) ≤ 35 > 35	44.7(26.4, 63.1) 24.2 (15.9,32.4)	0.095
AFP (ng/mL) ≤ 400 > 400	41.9 (26.9,57.1) 29.5 (26.6,32.4)	0.603
ALT (U/L) ≤ median > median	30.7 (21.3,40.1) 37.3 (22.6,52.1)	0.903
Total billirubin (mg/dL) ≤ 1.5 > 1.5	27.6 (3.9,19.9) 44.8 (26.4,63.1)	0.285
Number of treatments 1 2	36.6 (19.9,53.4) 30.4 (22.2,38.6)	0.815

Abbreviations: ALT, alanine aminotransferase; AFP, alpha-fetoprotein; NA, not applicable

*N=16

Table 4. Survival by Imaging features at baseline*

Characteristics	Mean Survival (95% confidence interval)	p Value
Tumor burden ≤ 5 > 5	 32.6 (16.7,48.6) 31.1 (22.2,39.9)	0.447
Tumor size, longest axis ≤ median > median	 38.2 (18.4,58.0) 27.4 (23.3,31.6)	0.783
Tumor margins Well Poor defined	 37.1 (20.8,53.2) 27.0 (3.1,33.0)	0.857
Tumor attenuation, HU ≤ median > median	 26.2 (21.0,31.5) 42.3 (19.7,64.9)	0.447
Presence of PVT Yes No	 28.0 (20.0,36.0) 35.6 (21.4,49.8)	0.697
Presence of Ascites Yes No	 31.0 (NA) 39.0 (24.7,53.3)	0.867
Tumor enhancement Hypervascular Hypovascular	 41.9 (26.9,57.1) 29.5 (26.6,32.4)	0.603

Abbreviations: ALT, alanine aminotransferase; AFP, alpha-fetoprotein; PVT, portal vein thrombosis; NA, not applicable

*N=16

Table 4. Survival by Response Criteria

Response	mRECIST	EASL	Choi
	No.(%)		
PR	3 (23.1)	1 (7.7)	
Stable	5 (38.5)	7 (53.8)	NA
Progression	5 (38.5)	5 (31.3)	
Response	NA		9 (69.2)
No response			4 (30.8)
p Value	0.765	0.428	0.930

Abbreviations: PR, parcial response; NA, not applicable

AGRADECIMENTOS

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  Cartwright J (2007) Big stars have weather too. IOP Publishing PhysicsWeb. http://physicsweb.org/articles/news/11/6/16/1. Accessed 26 June 2007

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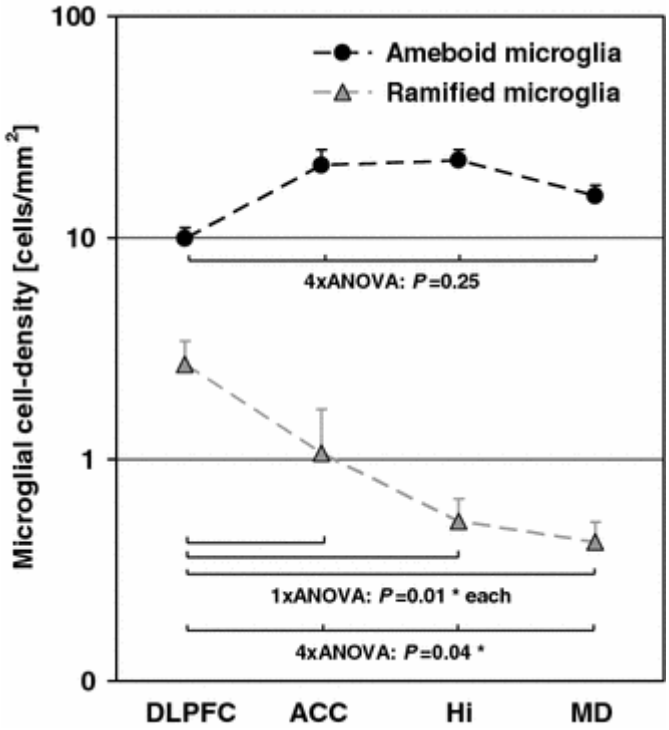

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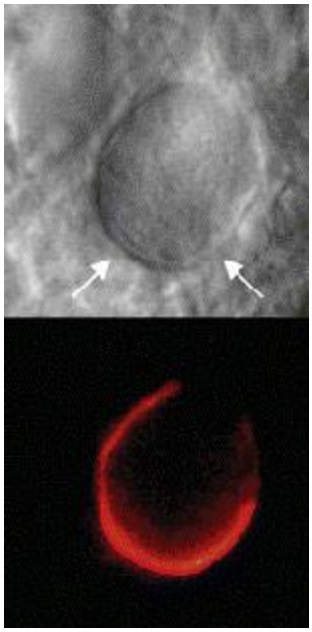

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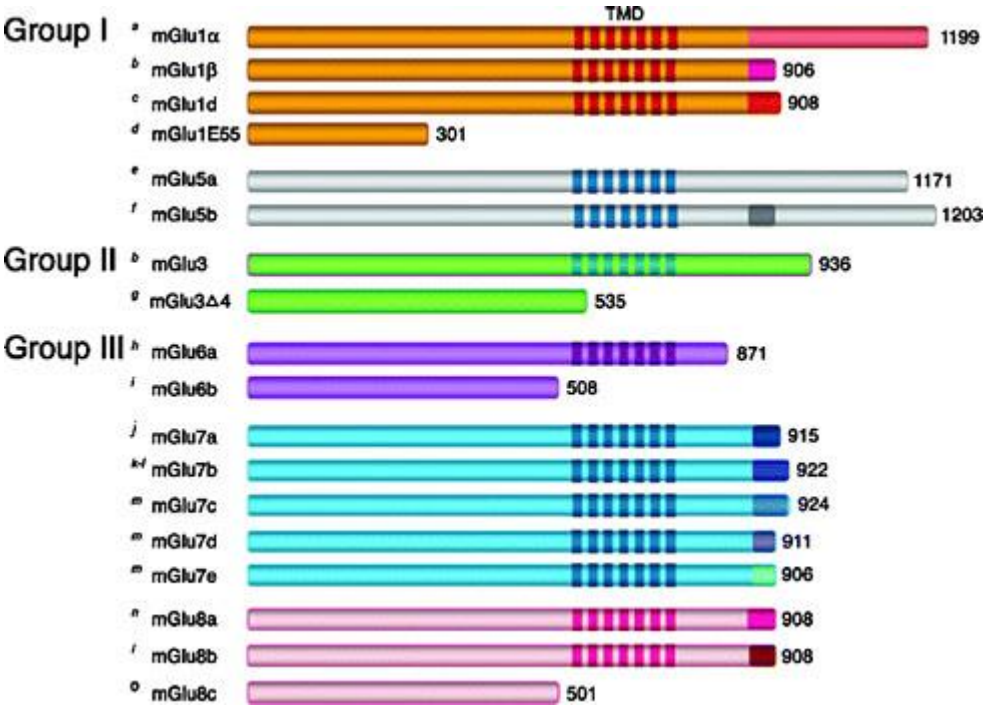

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