ACTA RADIOLÓGICA PORTUGUESA
January-April 2021|Vol 33 nº1|11-16

Original Article / Artigo Original

Hepatocellular Carcinoma and Treatment Response: A Retrospective Study in Patients Submitted to TACE

Carcinoma Hepatocelular e Resposta ao Tratamento: um Estudo Retrospectivo em Pacientes Submetidos a TACE

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Received: 17/07/2020
Accepted: 22/01/2021
Published: 30/04/2021

Abstract

Aim: The aim of the study is to establish predictors of tumor response in hepatocellular carcinoma (HCC) patients following Transarterial Chemoembolization (TACE), in order to improve patient selection.
Methods: This retrospective study included 47 patients with clinical diagnosis of HCC who underwent TACE between January of 2016 and December of 2017 in a tertiary hospital. The study time was defined between the last CT before the first TACE performed, and the CT/MRI performed after the procedure to evaluate tumor response. Population characteristics were recorded through clinical records, imaging and radiology reports. The diagnostic categories were also calculated according to the ACR LI-RADS® (Liver Imaging Reporting and Data System) and treatment response was assessed according to mRECIST (modified Response Evaluation Criteria In Solid Tumors) criteria.
Results: From 47 patients, 66,0% had early stage HCC (or BCLC-A in Barcelona Clinic Liver Cancer classification). Thirty-two patients (68,1%) achieved objective response, the sum of complete response (21,3%) and partial response (46,8%) given by mRECIST. Despite the BCLC-A category not being more frequent in patients with complete response after TACE, the subgroup of patients with small single lesions (<5cm) (P=0.012) and an inferior number of lesions (P=0.001), had a higher rate of complete response. No other variable showed significant differences in terms of tumor response.
Conclusion: Complete response was more frequent after TACE in patients with small single HCC and with an inferior number of HCCs.

Keywords

hepatocellular carcinoma; transarterial chemoembolization; mRECIST; radiologic response; LI-RADS

Resumo

Objetivo: O objetivo do estudo é estabelecer preditores de resposta tumoral no carcinoma hepatocelular (CHC) após a quimioembolização transarterial (TACE), de forma a melhorar a seleção de doentes.
Metodologia: Este estudo retrospetivo incluiu 47 doentes com diagnóstico clínico de CHC que realizaram TACE entre janeiro de 2016 e dezembro de 2017 num hospital terciário. O tempo de estudo foi definido entre a última TC antes da primeira TACE efetuada, e a realização de TC/RM após o procedimento, para avaliação da resposta tumoral. As características da população foram registadas com recurso ao processo clínico, aos exames de imagem e aos relatórios radiológicos. Foram também calculadas as categorias de diagnóstico segundo o ACR LI-RADS® (*Liver Imaging Reporting and Data System*) e definida a resposta ao tratamento de acordo com os critérios mRECIST (*modified Response Evaluation Criteria In Solid Tumors*).
Resultados: Dos 47 doentes, 66,0% pertenciam ao estadio precoce do CHC (ou BCLC-A na classificação *Barcelona Clinic Liver Cancer*). Trinta e dois doentes (68,1%) atingiram uma resposta objetiva, a soma das respostas completas (21,3%) e parciais (46,8%) dadas pelo mRECIST. Apesar da categoria BCLC-A não ser mais frequente nos doentes com resposta completa após a TACE, o subgrupo de doentes com lesões únicas e pequenas (<5cm) (P=0,012), bem como com um menor número de lesões (P=0,001) apresentou maior taxa de resposta completa. Nenhuma outra variável demonstrou diferenças significativas relativamente à resposta tumoral.
Conclusão: A resposta completa após TACE foi mais frequente em doentes com CHC único e de menores dimensões e em doentes com menor número de lesões.

Palavras-chave

Carcinoma hepatocelular; Quimioembolização transarterial; mRECIST; Resposta radiológica; LI-RADS.

Introduction

Transarterial chemoembolization (TACE) is currently used throughout BCLC stages. In patients with early hepatocellular carcinoma (HCC), when surgical resection or radiofrequency ablation (RFA) are unsuccessful/unfeasible or as a bridging therapy to maintain patients within the Milan Criteria for liver transplantation (LT). For intermediate HCC, transarterial chemoembolization (TACE) is the first-line treatment option. In patients with advanced HCC, TACE is used for palliative purposes.[1,2]
Treatment response to TACE is usually assessed with computed tomography (CT) or magnetic resonance (MR) using modified response evaluation criteria in

solid tumors (mRECIST) criteria. These criteria rely on the concept of viable tumor, defined as an arterial phase enhanced tumor tissue, and the definition of target lesions. A large systematic review[3] showed that only half of the patients submitted to TACE achieved objective response (OR) (including complete and partial response according to mRECIST, a finding that is correlated with improved prognosis after LT[3,4] and an increased overall survival.[5] As a result, not all patients will derive similar benefit from TACE, and a better management of resources should be done in order to improve patients' outcome.[6]

The aim of this study was to identify predictors of tumor response in HCC patients undergoing TACE in order to stratify patients into different prognostic groups, improving patient selection.

Methods

Patients and Study Design

The present retrospective study included patients with HCC diagnosis who underwent a TACE procedure from January 2016 to December 2017 at a single tertiary hospital. Only information regarding the first TACE treatment for each patient was considered.

Inclusion criteria: age of 18 years old or older, a clinical diagnosis of HCC, a pre-TACE CT and post-TACE imaging. Some patients had previous history of treated HCC. Patients with history of treated HCC were included if they had no imaging evidence of viable tumor in the treated lesions.

Sixty-six HCC patients were submitted to TACE, mostly as bridge therapy for liver transplantation or disease downstage. Sixteen patients were excluded because there was no available pre-TACE CT. One patient was excluded because of discordant pathological diagnosis other than HCC during follow-up (hepatocholangiocarcinoma). Two patients had a previous history of HCC treated with locoregional therapy and evidence of viable tumor. The final cohort included 47 patients.

HCC Diagnosis

All diagnoses were validated in multidisciplinary setting. In patients with chronic liver disease HCC was diagnosed based on typical imaging features (on CT or MRI). A percutaneous liver biopsy was performed for HCC diagnosis confirmation in three patients (one had no known risk factors, one did not fulfill imaging criteria for diagnosis, and one had a concomitant non-liver primary malignancy).

Clinical Variables

The following variables were collected from electronic clinical records: sex, age, etiology of liver disease/risk factors and pre-treatment levels of alfa-fetoprotein (AFP) and Child-Pugh (CP) class, along with tumor characteristics (number of nodules, distribution of locations, Barcelona Clinic Liver Cancer (BCLC) stage).

When categorizing patients risk factors, were considered for the multifactorial group patients with history of alcohol intake and bepatitis B virus (HBV) or hepatitis C virus (HCV) infections and patients with both HBV and HCV infections. The number of TACE sessions was recorded as well.

According to the size and number of lesions, new categoric variables were attributed: unifocal/multifocal disease, diameter of the largest lesion ≤5cm/>5cm, multifocal disease or large single lesion >5cm. The diameter of the largest lesion was also evaluated as a continuous variable. Tumor burden was assessed as the sum of all lesion's diameters.

Pre-TACE Imaging Variables

All patients were submitted to imaging exams before and after TACE. To reduce bias, the collected imaging variables were always taken from the last liver CT before treatment. All CT images were obtained at the same tertiary hospital using either a 16 or a 64-MDCT (multidetector CT), with a triphasic protocol after intravenous contrast administration. Liver imaging reporting and data system (LI-RADS) was retrospectively attributed to each nodule according to LI-RADS 2018 version[7] based on the information from imaging reports. For this, information on lesion size, non-rim arterial phase hyperenhancement, enhancing capsule, non-peripheral washout and threshold growth was collected. In cases where critical imaging information was lacking in imaging reports, the images were reviewed using the Hospital's PACS system (Sectra® IDS7 software) by a Radiologist with 5 years of experience on abdominal imaging. When the assignment of LI-RADS grade was unclear, a team consensus was asked.

Transarterial Chemoembolization

Drug-eluting embolics (DEE) TACE was performed by the same interventional radiology team (2 operators with at least 2 years of experience) after decision from a multidisciplinary tumor board. Vascular access was achieved through the common femoral artery. A 4-French Cobra or Simmons catheter (Tempo, Cordis®, Miami, Florida, USA) was used to catheterize the celiac trunk or anatomic variant to gain access to the hepatic arteries, which was achieved with a 2.7-French Progreat microcatheter (Terumo®, Tokyo, Japan). Diagnostic angiographic runs were obtained at the celiac trunk, proper hepatic and right/left hepatic arteries to define tumor arterial supply. DEE chemoembolization was performed after superselective catheterization of the tumor-feeding arteries, and 1 or 2 vials of LifePearl 200 μm microspheres (Terumo®, Tokyo, Japan), charged with 75 mg of doxorubicin each for a maximum dose of 150 mg per session, were administered until near-stasis was achieved, defined as stasis of contrast medium during 5 heartbeats. A final manual angiographic run was performed to confirm effective embolization.

Treatment Response Evaluation

All patients were submitted to imaging evaluation after the procedure, either with CT or MRI. We retrospectively evaluated treatment response through mRECIST criteria,[8] which was calculated based on the information from radiological reports. In cases where critical imaging information was lacking on imaging reports, the images were reviewed by the same Radiologist. When the assignment of mRECIST was unclear, a team consensus was reached.

We recurred to RECIST 1.1 when the mRECIST could not be applied, for instance in the presence of hypovascular lesions[9,10] which were present in three patients.

The group attaining objective response (OR), including complete response (CR) and partial response (PR) patients, was compared to the patients with stable disease (SD) or progressive disease (PD). Moreover, a different group

including only patients with CR was formed, and the remaining patients (PR, SD or PD) were grouped.

Statistical analysis

Statistical analysis was performed using SPSS 26.0 (IBM, Armonk, New York, United States of America). The distribution of continuous variables was reported as mean and standard deviation or median and interquartile range. Categorical variables were presented with absolute and relative frequencies. Continuous variables were compared using the independent sample t-test; categorical variables were compared using Pearson's Chi-square test. The level of significance was $p < 0.05$.

Ethics Review

The hospital Health and Ethics Committee approved the study and waived the informed consent requirement given its retrospective nature.

Results

The population consisted of 47 patients, 37 (78,7%) men and 10 (21,3%) women with a mean age of 62,19 ± 9,21 years. Overall, there was a median time of two months (66 days) between CT scan and TACE and a median of 1 month (33 days) until imaging reevaluation.

The most prevalent risk factor for chronic liver disease was alcohol intake (46,8%) followed by HCV (23,4%). In the multifactorial group, another 7 patients had an history of alcohol abuse, reinforcing it as the main risk factor in our population (Table 1).

Comparison between OR and SD, PD subgroup analysis

A total of 32 patients (68,1%) achieved OR after first TACE, including 21,3% having CR (n=10) and 46,8% with PR (n=22). The remaining 15 patients, 27,7% had SD (n=13) and 4,3% had PD (n=2). There were no statistically significant differences between the two subgroups (Table 2). Nevertheless, the patients attaining OR had a non-significant lower mean diameter of the largest HCC and a non-significant lower diameter of the sum of HCCs (p>0,05). (Fig.1)

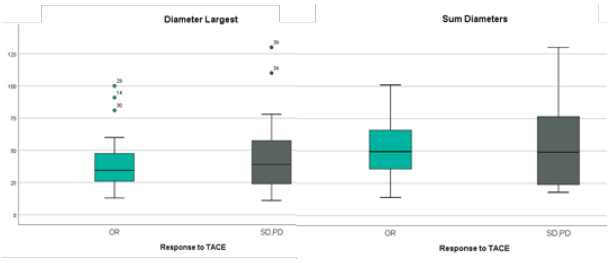

Figure 1 – Boxplots: Diameters in OR and SD, PD groups.

Comparison between CR and PR, SD, PD subgroup analysis

Table 3 shows the comparison between patients achieving CR and all other treatment responses. The groups were compared in terms of sex, age, CTP, AFP state. Ten patients (21,3%) achieved radiological complete response. CR was achieved in 2/22 patients with multifocal disease, 1/15 BCLC-B patients and 3/30 of patients with the diameter of the largest nodule superior to 5cm. CR rates were higher in patients with unifocal disease and single lesion <5cm (p=0,012). Patients with CR had less lesions (mean: 1,2) than patients with other treatment responses (mean: 2,05) (p=0,001). The patients with CR had a lower mean in largest lesion diameter (35,2mm) when compared to the others (44,3mm) (p=0,326). The same was observed in the sum of lesions diameters; patients achieving CR had a mean of 40,3mm compared to 57,1mm in the other group (p=0,084). (Fig.2)

Table 1 – Clinical, radiological and laboratory characteristics of the study population n (%)

Variable	All treated patients (n=47)
Demographics and Indications	
Male gender	37(78.7)
Age at TACE (yrs) [mean ± SD]	62.19±9.21
Child-Pugh class A/B	0(85.1)/7(14.9
HBV related chronic liver disease	1(2.1)
HCV related chronic liver disease	11(23.4)
Alcohol related chronic liver disease	22(46.8)
Multifactorial chronic liver disease	9(19.1)
NASH/ Hemochromatosis /Unknown	1(2.1)/1(2.1)/2(4.3)
Primary treatment other than TACE	2(4.3)
Combined treatment TACE+RFA	3(6.4)
Pre-TACE radiological evaluation	
Number of nodules [mean ± SD]	1.85±1.20
Single/Multiple	6(55.3)/21(44.7)
BCLC stage A/B/C	31(66.0)/15(31.9)/1(2.1)
Diameter of the largest nodule (mm) [mean ± SD]	42.36±25.69
Diameter of the largest nodule >5cm	12(25.5)
LI-RADS LR-3/LR-4/LR-5/LR-M	2(4.3)/9(19.1)/29(61.7)/7(14.9)
Pre-TACE laboratory evaluation	
AFP (ng/mL) [median (IQRs)]	10.1(3-23)
AFP elevated	24(60)
Post-TACE radiological evaluation	
Type of imaging technique (CT/MRI)	45(95.7)/2(4.3)
Treatment response	
CR	10(21.3)
PR	22(46.8)
SD	13(27.7)
PD	2(4.3)
Objective response	32(68.1)
Repeated TACE	29(61.7)

Data is expressed as mean standard deviation for continuous variables or median and interquartile variation in case of AFP. Categorical data is expressed as number of patients (percentage). TACE: Transarterial Chemoembolization; HBV: Hepatitis B virus; HCV: Hepatitis C virus; NASH: Non-alcoholic steatohepatitis; RFA: Radiofrequency Ablation; BCLC: Barcelona Clinic Liver Cancer; AFP: Alpha-fetoprotein; CT: Computed tomography; MRI: Magnetic resonance imaging; CR: Complete response; PR: Partial response; SD: Stable Disease; PD: Progressive disease.

Table 2 – Comparison between OR and SD,PD groups

	OR (n=32)	SD,PD (n=15)	P value
Sex:			0.884
Male	25 (78.1%)	12 (80.0%)	
Female	7 (21.9%)	3 (20.0%)	
BCLC§:			0.204
A	19 (61.3%)	12 (80.0%)	
B	12 (38.7%)	3 (20.0%)	
CTP:			0.121
A	29 (90.6%)	11 (73.3%)	
B	3 (9.4%)	4 (26.7%)	
AFP:			0.680
Normal	17 (53.1%)	7 (46.7%)	
Elevated	15 (46.9%)	8 (53.3%)	
Unifocal	15 (46.9%)	10 (66.7%)	0.205
Multifocal	17 (53.1%)	5 (33.3%)	
Multifocal or Large Single Lesion (>5cm):			0.708
Yes	21 (65.6%)	9 (60.0%)	
No	11 (34.4%)	6 (40.0%)	
Diameter Largest:			0.401
≤5cm	25 (78.1%)	10 (66.7%)	
>5cm	7 (21.9%)	5 (33.3%)	
LR-5:			0.419
Yes	21 (65.6%)	8 (53.3%)	
No	11 (34.4%)	7 (46.7%)	
LR-5/LR-M:			0.271
Yes	26 (81.2%)	10 (66.7%)	
No	6 (18.8%)	5 (33.3%)	
Number of lesions	1.94±1.1	1.73±1.4	0.589
Diameter Largest (mm)	39.3±20.5	48.8±34.2	0.244
Sum Diameters (mm)	52.0±22.6	56.9±36.1	0.635

Data is expressed as number of patients (percentage) for categorical variables and Pearson's qui-square. Continuous data is expressed as mean standard deviation. BCLC: Barcelona Clinic Liver Cancer; CTP: Child-Turcotte-Pugh score; AFP: Alpha-fetoprotein.
§Was excluded a patient with BCLC-C stage to enable the Chi-Square test, with a total of OR (n=31) and SD, PD (n=15).

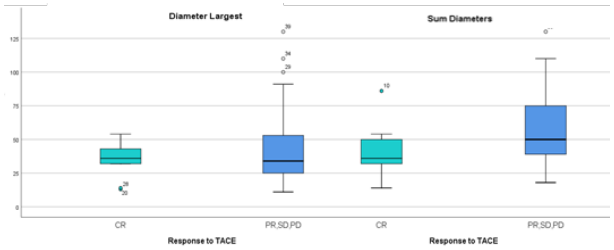

Figure 2 – Boxplots: Diameters in Complete Response and PR, SD and PD groups.

Discussion

The primary aim of this study was to establish factors associated with tumor response in HCC patients undergoing TACE. Our study population included 37 (78,7%) male patients which is in line with HCC epidemiology.[11] Most of the patients belong to CP class A (40/47), the least severe grade of chronic liver disease. From those 40 patients, 29 (72,5%) achieved OR. Good liver function, measured by CTP score has been previously associated with positive outcomes.[6,12,13] The results of our study revealed a statistically significant difference between CR after first TACE and "non-multifocal nor large single lesions", which could be simplified as small single lesions, setting this subset of patients within the BCLC A category as the ones

Table 3 – Comparison between Complete Response and all other Treatment Responses

	OR (n=10)	PR,SD,PD (n=37)	P value
Sex:			0.326
Male	9 (90.0%)	28 (75.7%)	
Female	1 (10.0%)	9 (24.3%)	
BCLC§:			0.085
A	9 (90.0%)	22 (61.1%)	
B	1 (10.0%)	14 (38.9%)	
CTP:			0.624
A	9 (90.0%)	31 (83.8%)	
B	1 (10.0%)	6 (16.2%)	
AFP:			0.177
Normal	7 (70.0%)	17 (45.9%)	
Elevated	3 (30.0%)	20 (54.1%)	
Unifocal	8 (80.0%)	17 (45.9%)	0.056
Multifocal	2 (20.0%)	20 (54.1%)	
Multifocal or Large Single Lesion (>5cm):			0.012*
Yes	3 (30.0%)	27 (73.0%)	
No	7 (70.0%)	10 (27.0%)	
Diameter Largest:			0.204
≤5cm	9 (90.0%)	26 (70.3%)	
>5cm	1 (10.0%)	11 (29.7%)	
LR-5:			0.180
Yes	8 (80.0%)	21 (56.8%)	
No	2 (20.0%)	16 (43.2%)	
LR-5/LR-M:			0.259
Yes	9 (90.0%)	27 (73.0%)	
No	1 (10.0%)	10 (27.0%)	
Number of lesions	1.2±0.42	2.05±1.27	0.001*
Diameter Largest (mm)	35.2±13.4	44.3±27.9	0.326
Sum Diameters (mm)	40.3±20.0	57.1±28.2	0.084

Data is expressed as number of patients (percentage) for categorical variables and Pearson's qui-square. Continuous data is expressed as mean standard deviation. BCLC: Barcelona Clinic Liver Cancer; CTP: Child-Turcotte-Pugh score; AFP: Alpha-fetoprotein. A 2-sided P value is considered significant when $P < 0.05$*
§Was excluded a patient with BCLC-C stage to enable the Chi-Square test, with a total of CR (n=10) and PR,SD,PD (n=36)

with most favorable outcome after TACE. Similarly, in a retrospective study with 168 patients Cerban et al. reported tumor size ≤4.5cm and single nodularity as predictive factors for CR.[1] Moreover, multifocal disease and tumor size were also correlated with a decrease in overall survival in several studies.[1,6,14,15]

Regarding large single lesions, a retrospective study including 1132 patients from Zhong et al. already showed that the overall survival in single tumors >8cm was comparable to BCLC-B HCC and it was proposed to assign these lesions to the intermediate-stage.[16] A difference in prognosis was also noticed by Cho et al. with large single lesions >5cm. Nonetheless, they recommended resection and not TACE as first-line treatment.[17,18] These results reinforce the need for adequate subcategorization within BCLC-A lesions, with a different strategy for large single lesions (>5cm) and multifocal disease within the BCLC-A stage, as it was recently proposed by our research group.[10]

Regarding multifocal lesions, their intricate vascularity is probably responsible for a higher rate of PR in these patients as it was stated to Cerban et al.[1] Similarly, Coletta et al. declared that nodules with 3-5cm are well vascularized and irrigated by a single artery, leading to TACE effectiveness[2] in the small single lesion group.

Regarding the comparison between OR and SD, PD the study failed to identify predictors of OR. Nevertheless, OR was observed in 80% of BCLC-B patients (with a higher rate of PR in these patients), a finding that supports its use as first-treatment within the BCLC algorithm. Not surprisingly the same was seen in patients with multifocal disease, as it is a prerequisite to stage B. OR was also present in 71,4% when the diameter of the largest nodule was ≤5cm, and these patients revealed a lower mean in the largest lesion diameter (39,3mm) comparing to the other group (48,8mm). Once again, this is in line with previous studies identifying tumor size ≤5cm as a favorable prognostic factor, also associated with positive survival outcomes.[6,13,19]

Alpha-fetoprotein levels were not significantly different between our study groups. We had a low frequency of patients with substantial elevation of AFP levels which might have decreased the power to detect its influence. However, and despite several studies showing AFP as a method for evaluating treatment response, there is still not a clear definition for AFP response and associated prognosis. Importantly, not all studies used the same cut-off for AFP. A previous study has shown that an AFP level (>25ng/mL) has been correlated with recurrence after CR(1). On a review Raoul et al. obtained an association between AFP levels ≤200ng/mL and positive survival outcomes(6). Yuen et al. showed that the patients with positive outcomes had a median AFP of 110ng/mL(20) and in O'Suilleabhain et al. an AFP <1000ng/ml was associated with an increase in 5-year survival rate.[21] Using a different approach, Sherman,[22] defined AFP response as a decrease in half of AFP's baseline, and supported its use as an auxiliary to image screening. It should be emphasized that imaging cannot be currently supplanted by tumor markers, as these have limitations and cannot be used in patients without a primary increase in AFP level.[22]

Considering the predictive value of imaging features other than size, including LI-RADS categorization, no significant association with OR or CR was found. One would expect that LI-RADS could be a predictor of objective or complete response since their classification depends on tumor size and vascularization. When the largest nodule belonged to LR-5 category, OR was obtained in 72,4% patients, but we found no difference between OR and SD, PD groups. It should be taken in account that LI-RADS criteria are dependent on imaging modality. Corwin et al. found category adjustment dependent of imaging modality with MRI assessment being more accurate and allowing for observations not noticed on CT with an important number of lesions suffering upgrade (99/228) and downgrade (22/228) which could, in turn, impact patient management.[23] Therefore, LI-RADS categories using CT should not be accounted when selecting patients for TACE, and further studies should be done using MRI criteria.

Our study has important limitations. Technical factors regarding the TACE technique should be taken in account, even though they are minimized by the use of a homogenous technique. The use of mRECIST criteria for treatment assessment is not without fault, as some limitations are recognized. These criteria are currently favored, as they are superior at identifying OR, but cannot be used in non-enhancing target lesions.[8,9,24] Evaluation by RECIST 1.1 takes into account the diameter of the whole lesion, and can underestimate tumor response, disregarding treatment induced necrosis that not necessarily results in tumor shrinkage.[25,26] Nonetheless, it fairly predicts prognosis in atypical lesions.[9]

The second aim of the study was to improve TACE patient selection. Even though overall survival or recurrence-free survival are the most relevant outcomes, treatment response is the most immediate outcome available, and is directly associated with patients' prognosis and overall survival.[26] Moreover, patients with CR after TACE have been associated with excellent posttransplant outcomes even when lesions initially exceeded Milan criteria.[27]

Other limitations to the study should be recognized. It is a retrospective, single-institution study with a small sample size. The retrospective study design itself might have resulted in selection bias, since it is highly dependable on clinical records and access to the CT's and TACE imaging and reports. There were also some larger intervals between evaluations - CT/MRI pre and post-TACE - than what is recommended in the guidelines, and a time gap between patients' first TACE making their assessments non-consecutive. Our statistically significant findings were done based on a small cohort of patients who attained CR, an extreme response when compared with the spectrum of treatment responses. Additionally, the patients were only studied for treatment response after the first TACE. However, if, CR is not achieved, patients can be considered for retreatment.

In conclusion, our study found a higher rate of complete response to TACE for small single HCCs, and fewer HCCs. Further studies with larger cohorts are required to validate the divergency in treatment response among patients in early stage and to acknowledge if BCLC-A multifocal or large HCCs behave more similarly to BCLC-B HCC.

Ethical disclosures / Divulgações Éticas

Conflicts of interest: The authors have no conflicts of interest to declare.

Conflitos de interesse: Os autores declaram não possuir conflitos de interesse.

Financing Support: This work has not received any contribution, grant or scholarship.

Suporte financeiro: O presente trabalho não foi suportado por nenhum subsídio ou bolsa.

Confidentiality of data: The authors declare that they have followed the protocols of their work center on the publication of data from patients.

Confidencialidade dos dados: Os autores declaram ter seguido os protocolos do seu centro de trabalho acerca da publicação dos dados de doentes.

Protection of human and animal subjects: The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Protecção de pessoas e animais: Os autores declaram que os procedimentos seguidos estavam de acordo com os regulamentos estabelecidos pelos responsáveis da Comissão de Investigação Clínica e Ética e de acordo com a Declaração de Helsínquia da Associação Médica Mundial.

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