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Hepatocellular Carcinoma and Treatment Response: A Retrospective Study in Patients submitted to Transarterial Chemoembolization

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Dissertação de candidatura ao grau de Mestre em Medicina
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DEDICATÓRIA

À minha mãe e às minhas irmãs, à minha pequena, grande, família, pelo apoio incondicional, pela exímia paciência e carinho, por serem os meus alicerces, por me transmitirem a força e energia para ultrapassar todos os obstáculos deste percurso, por contribuírem para a minha construção pessoal, por tudo…

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"Quisera eu olhar o passado,

Pelos rasgos de tempo sobre o negro,

A olhar o dia em que enganado,

Pensei que viveria para sempre"

-Balada da Despedida de Biomédicas 2020

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RESUMO

Introdução: O carcinoma hepatocelular (CHC) é uma causa importante de morbimortalidade em doentes com doença hepática crónica e as técnicas de imagem permitem o diagnóstico de CHC nestes doentes. A quimioembolização arterial (TACE) é um tratamento loco-regional cujas indicações têm vindo a crescer em doentes com CHC. Apesar de ser o tratamento preconizado em doentes no estadio intermédio da classificação BCLC (*Barcelona Clinic Liver Cancer*), pode ser realizada em todos os estadios do CHC. Os doentes submetidos a TACE são um grupo heterogéneo, e nem todos os doentes encontram o mesmo benefício neste tratamento. O objetivo do estudo é estabelecer biomarcadores de resposta tumoral após a TACE, de forma a contribuir para uma melhor seleção de doentes para este tratamento no contexto multidisciplinar.

Metodologia: Este estudo retrospetivo incluiu 47 doentes com diagnóstico clínico de CHC que realizaram TACE entre janeiro de 2016 e dezembro de 2017 no Centro Hospitalar Universitário do Porto. 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 disponíveis no PACS *(Picture Archiving and Communication System)* 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. Trinta e dois doentes (68,1%) atingiram uma resposta objetiva, a soma das respostas completas (21,3%) e parciais dadas pelo mRECIST. Apesar da categoria BCLC-A não se associar a resposta completa após a TACE, o subgrupo de doentes com lesões únicas e pequenas (<5cm) apresenta associação significativa (*P*=0,012*). O número de lesões também apresentou relação significativa com resposta completa (*P*=0,001*). Nenhuma outra variável demonstrou associação com a resposta tumoral.

Conclusão: A resposta completa foi associada a lesões únicas e pequenas (<5cm) e a tumores com um menor número de lesões. São necessários mais estudos com maiores coortes para validar a divergência encontrada na resposta ao tratamento entre doentes no estadio precoce e para identificar outros biomarcadores preditores.

Palavras-Chave: carcinoma hepatocelular; quimioembolização transarterial; mRECIST; resposta radiológica; LI-RADS

ABSTRACT

Background: Hepatocellular Carcinoma (HCC) is an important cause of morbidity and mortality in patients with chronic liver disease, and imaging techniques can accurately diagnose HCC in these patients. Transarterial Chemoembolization (TACE) is a locoregional treatment with growing indications in patients with HCC. Despite being the standard treatment for patients in the intermediate stage of BCLC (Barcelona Clinic Liver Cancer) staging system, it can be used throughout HCC stages. Patients undergoing TACE are a heterogeneous group, and not all patients encounter the same benefit in this treatment. The aim of the study is to establish tumor response biomarkers following TACE, in order to contribute to improvements in patient selection for this treatment in the multidisciplinary setting.

Methods: This retrospective study included 47 patients with clinical diagnose of HCC who performed TACE between January of 2016 and December of 2017 in *Centro Hospitalar Universitário do Porto.* 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 available at the PACS (Picture Archiving and Communication System), and image 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. Thirty-two patients (68,1%) achieved objective response, the sum of complete response (21,3%) and partial response given by mRECIST. Despite the BCLC-A category not being associated to complete response after TACE, the subgroup of patients with small single lesions (<5cm) presents significant association (P=0.012*). The number of lesions also presented significant association with complete response (P=0.001*). No other variable showed association with the tumor response.

Conclusion: Complete response was associated with small single lesions and with an inferior number of lesions. Further studies with larger cohorts are needed to validate the divergence found in treatment response among patients in the early stage and to identify other predictor biomarkers.

Key words: hepatocellular carcinoma; transarterial chemoembolization; mRECIST; radiologic response; LI-RADS

LIST OF ABBREVIATIONS:

AASLD: American Association for the Study of Liver Diseases
AFP: Alpha-fetoprotein
BCLC: Barcelona Clinic Liver Cancer
CEUS: Contrast-enhanced ultrasound
CR: Complete response
CT: Computed tomography
CTP: Child-Turcotte-Pugh score
DEE: Drug-eluting embolics
EASL: European Association for the Study of the Liver
HCC: Hepatocellular carcinoma
HBV: Hepatitis B virus
HCV: Hepatitis C virus
LI-RADS: Liver Imaging Reporting and Data System
LT: Liver transplantation
LR: LI-RADS category
LR-TR: LI-RADS Treatment Response
mRECIST: modified Response Evaluation Criteria in Solid Tumors
MRI: Magnetic resonance imaging
NASH: Non-alcoholic steatohepatitis
PD: Progressive disease
PR: Partial response
PVT: Portal vein thrombosis
RECIST: Response Evaluation Criteria in Solid Tumors
RFA: Radiofrequency ablation
SD: Stable disease
OR: Objective response
TACE: Transarterial chemoembolization

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BACKGROUND

The majority of primary liver cancers is accounted by Hepatocellular Carcinoma (HCC). Many of them develop in individuals with an underlying chronic liver disease, frequently associated with viral hepatitis (HVB or HVC) or alcohol abuse[1]. Worldwide, it is the sixth most common cancer and the fourth leading cause of cancer-related-death in 2018[2]. Moreover, the World Health Organization projects that in 2030 more than 1 million patients will die from liver cancer and that the numbers will continue increasing in 2045 and in 2060[3].

Regarding HCC diagnosis, contrast enhanced imaging has a crucial role, allowing diagnosis for patients with background chronic liver disease when hallmark imaging features are observed.[4] Liver Imaging Reporting and Data System (LI-RADS®) divides lesions according their likelihood of malignancy, and settles its classification based on lesion size and the evidence of hallmark traits of HCC: non-rim arterial phase hyperenhancement, enhancing capsule, non-peripheral washout and threshold growth[5]. Other ancillary features can also be considered for category adjustment. As for LI-RADS categories: LR-5 lesions possess diagnostic imaging criteria for HCC, with extremely high specificity, rendering unnecessary confirmatory biopsy[5,6]; LR-4 are defined as probable HCC[5]; LR-3 lesions typically require further imaging and follow-up as they have an intermediate probability of malignancy[7]; LR-2 and LR-1 lesions are probably benign or benign[5].

LR-M lesions are defined as definite or probable malignancy but not HCC specific, their characteristics are mostly based on intrahepatic cholangiocarcinoma, the most common liver neoplasm apart from HCC[5]. LR-M also allows LI-RADS a higher ability to distinguish atypical malignant lesions since LR-5 goal is to make the diagnose of HCC without false positives, at the cost of decreased sensibility[6]. This category will encompass a spectrum of malignant lesions including atypical HCC. An estimated 37% of LR-M lesions are HCC using LI-RADS 2014 and 2017 versions, that do not differ much from the current 2018 version[8].

Taking in account the tumor burden, the performance status (PS) and the Child-Turcotte-Pugh Score (CTP), the Barcelona Clinic Liver Cancer (BCLC), offers an algorithm that stratifies patients in different prognostic categories and some guidance for the treatment of HCC, supported by the European Association for the Study of the Liver (EASL) and the American Association for the Study of Liver Diseases (AASLD)[9-11]. (Fig.1)

Only a limited number of patients are qualified for curative treatments such as liver transplantation, liver resection or ablation therapy[9]. Many patients are diagnosed in BCLC-B or higher stage and are usually not amenable for these therapeutic modalities, which created a space for the development of transarterial chemoembolization (TACE) that is currently considered the standard treatment for

intermediate-stage (stage B) HCC. However, this stage alone comprises a wide and diverse spectrum regarding patient's tumor burden and liver function which translates in significant survival differences[12,13].

TACE is a locoregional therapy performed by interventional radiologists that can treat single or multiple nodules[14]. This procedure takes advantage of tumor vasculature being mainly supplied by the hepatic artery, in opposition to the portal vein who sustains the normal liver parenchyma[13]. Thus, the infusion of embolic material associated with a chemotherapeutic agent directly in the hepatic artery branch, responsible for tumor irrigation, causes ischemia and tumor necrosis, which is the physiology behind TACE[15].

This procedure is currently used throughout BCLC stages: in patients with early HCC, when surgical resection or radiofrequency ablation (RFA) are unsuccessful or unfeasible or to be used as a bridging therapy to maintain patients within the Milan Criteria while on waitlist for LT; as for intermediate HCC, TACE has a major role being the first-line treatment; in patients with advanced HCC, BCLC-C, TACE is used for palliative purposes[9,14,16]. In a recent study, Raoul *et al*. proposed an algorithm for the use of TACE in all HCC patients including combination therapy and TACE retreatment.[17]

Combination therapy is another viable option, TACE with RFA or microwave ablation has potential to improve treatment response in patients with unresectable HCC. Several studies provide evidence of increased tumor control and prolonged overall survival in HCC patients treated by TACE combined with RFA versus RFA in monotherapy[18].

There are some limitations to the use of TACE, it is contraindicated in case of severely decompensated liver disease (CTP class C), severe bleeding or coagulation disorder that are uncorrectable, complete portal vein obstruction, cachexia or multiple organ failure, expected survival under 3 months, leukopenia and thrombocytopenia due to chemotherapy toxicity and renal injury (creatinine >2 mg/dL or creatinine clearance rate <30 mL/min) due to contrast[18].

A large systemic review[19] showed that only half of the patients submitted to TACE achieved objective response (OR) after treatment (including complete and partial responders according to modified Response Evaluation Criteria in Solid Tumors (mRECIST)), a finding that is correlated with improved prognosis after Liver Transplantation (LT)[19,20] and an increased overall survival[21,22]. All in all, this advocates that not all patients will derive similar benefit from TACE, and a better management of resources should be done in order to improve patients' outcome[12].

The aim of this study was to establish the tumor response biomarkers in HCC patients undergoing transarterial chemoembolization, at a single university hospital, in the hope that the

findings could allow a stratification into different prognostic groups and improve selection of TACE as treatment modality.

METHODS

Patients and Study Design

The present study included consecutive patients, with the diagnosis of HCC who underwent a TACE procedure from January 2016 to December 2017 at the *Centro Hospitalar Universitário do Porto*. These patients were searched for their first TACE thus, this study focused on patients with first TACE between 2010 and 2017. The following inclusion criteria were considered: an age of 18 years old or older at the time of the first TACE, a clinical diagnosis of HCC by a multidisciplinary team, a CT pre-TACE and post-TACE imaging. Three patients were submitted to combined treatment with TACE and ablation. Some patients had previous history of treated HCC, but they were only included in this study if there was no imaging evidence of viable tumor (radiologic complete response). The eligibility criteria are summed in Table I.

Seventy-three patients with clinical diagnosis of HCC were submitted to TACE between January 2016 and December 2017. Sixteen patients were excluded because there was no access to a CT prior to their TACE, the CT was done in another Institution, or an MRI was the only type of exam pre-TACE. Four patients were excluded because of pathological diagnosis other than HCC during follow-up. Four patients were excluded due to technical difficulties that prevented adequate treatment with TACE. Two patients had a previous history of HCC treated with locoregional therapy and evidence of viable tumor. These patients were excluded from the analyses and the final cohort thus included 47 patients. (Fig. 2)

HCC Diagnosis

Hepatocellular carcinoma in patients with chronic liver disease was diagnosed based on typical imaging features (on Computed Tomography (CT) or Magnetic resonance imaging (MRI)) or histological findings. In patients with no risk factors, or who did not fulfill the imaging criteria for the diagnosis of HCC, a percutaneous liver biopsy was performed, as defined by the EASL and AASLD guidelines[23].

Clinical Variables

The following variables were collected through clinical information from patients' reports using the application *SClínico*: sex, age, etiology of liver disease/risk factors and preceding the treatment levels of alfa-fetoprotein (AFP) and Child-Pugh class along with other pre TACE tumor characteristics (number of nodules, distribution of locations, BCLC stage). Although focusing our study on the first TACE, the number of TACE sessions were 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. Were also made new variables considering the sum of all lesions diameters as a way to assess tumor burden and the sum of the diameters excluding LR-3 lesions (in order to include only lesions with higher suspicion index).

Pre-TACE Imaging Variables

All patients were submitted to imaging exams before and after TACE. In order to reduce bias, the collected imaging variables were always taken from the last liver CT before treatment, despite some patients also having pre-treatment liver MRI available. 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 reevaluation.

All CT images were obtained at the *Centro Hospitalar Universitário do Porto* using either a 16 or a 64-MDCT (multidetector CT), with a triphasic protocol after intravenous contrast administration.

LI-RADS was retrospectively attributed to each nodule according to LI-RADS 2018 version[5] based on the information from imaging reports using *SClínico*. For this, information on lesion size, non-rim arterial phase hyperenhancement, enhancing capsule, non-peripheral washout and threshold growth was collected. It was not always possible to assess the threshold growth, given the lack of previous exams for growth assessment. 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 (J.P.A.). When the assignment of LI-RADS grade was unclear a team consensus was asked.

Transarterial Chemoembolization

Drug-eluting embolics (DEE) TACE was performed at the *Centro Hospitalar Universitário do Porto* by an Interventional Radiology team after decision validation in the multidisciplinary discussion. Vascular access was achieved through the common femoral artery. A 4-French Cobra or Simmons catheter (Tempo, Cordis®, Miami, FL, 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 at the *Centro Hospitalar do Porto*, either with CT or MRI examinations. We retrospectively evaluated treatment response through mRECIST criteria, 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 (J.P.A.). When the assignment of mRECIST was unclear, a team consensus was asked.

These criteria rely on the concept of viable tumor, defined as an arterial phase enhanced tumor tissue. The longest diameter of the enhancing lesions was measured. We have selected 2 target lesions according to size[24].

Treatment response, as a product of the combined assessment of target, non-target and new lesions was classified into complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD)[25]:

i) CR – complete absence of arterial enhancement.
ii) PR – decrease in at least 30% of the sum of longest diameter of target lesions.
iii) PD – increase in at least 20% of the sum of the longest diameter of the target lesions, or the development of a new HCC lesion.
iv) SD – lesions not meeting criteria for either PR or PD.[24]

We recurred to RECIST 1.1 when the mRECIST could not be applied, for instance in the presence of atypical lesions[26,27] which were present in three patients.

Statistical Analysis

Statistical analysis was performed using SPSS 26.0 software (IBM, Armonk, NY, USA).

The distribution of continuous variables was reported as means and standard deviation or median and interquartile range. Categorical data were presented by absolute and relative frequencies. Continuous data were compared with the independent samples t test as for categorical data the comparison between two groups was determined by Pearson's Chi-square test.

A 2-sided p value <0.05 indicated statistical significance.

Ethics Review

Centro Hospitalar Universitário do Porto's Health and Ethics Committee approved the study and waived the informed consent requirement given its retrospective nature. The study also received the approval of the coordinator of the Department of Teaching, Training and Research and had the Hospital's Administration Council authorization.

RESULTS

The population consisted of 47 patients with 80 nodules, 37 (78,7%) men and 10 (21,3%) women with a mean age of 62,19 ± 9,21 years. The most prevalent risk factor for chronic liver disease was alcohol intake (46,8%) followed by Hepatitis C virus (23,4%). Forty patients were classified as Child-Pugh class A (85,1%), the remaining 7 were classified as class B. Concerning BCLC stage, 31 (66,0%) belonged to BCLC-A and 15 (31,9%) to the intermediate stage. The demographics, clinical and tumor characteristics are summarized in Table II. The treatment response according to chronic liver disease etiology is presented in Table III. In the multifactorial group were included patients with history of alcohol intake and HBV or HCV infections and patients with both HBV and HCV infections.

Comparison of OR by subgroup analysis

A total of 32 patients (68,1%) achieved OR, including 21,3% having CR (n=10) and 46,8% with PR (n=22). Meanwhile, 27,7% reached SD (n=13) and 4,3% had PD (n=2). The group attaining OR was designated as "responder" and the remaining group as "non-responder".

There were no statistical differences between the two groups. Even though, there were some tendencies towards OR: BCLC-B patients had a higher likelihood of achieving OR, 12 among 15 (80%) were responders; CTP score A with 29 out of 40 (72,5%) achieved OR; Multifocal disease patients 17 out of 22 (77,3%) were responders; when the diameter of the largest nodule was inferior or equal to 5 cm, 25 among 35 (71,4%) were objective responders, when this nodule belonged to LI-RADS 5 category it showed the same tendency with 21 out of 29 (72,4%).

The patients attaining OR revealed a lower mean in the largest lesion diameter, sum of lesions diameters and the sum of only LR-M, LR-5 and LR-4. However, there was no statistical significance. These data were displayed in boxplots for easier comprehension. (Fig.3-6)

The analysis is condensed in Table IV.

Comparison between CR and PR, SD, PD subgroup analysis

Only 10 patients (21,3%) achieved radiological complete response and were compared against all other treatment responses.

The groups were comparable in terms of sex, age, CTP, AFP state. Multifocal disease was mainly depicted as not achieving CR (90,9%) as well as BCLC-B patients (93,3%) and those with the diameter of the largest nodule superior to 5 cm (91,7%).

There was statistical significance in associating CR and non-multifocal nor large single lesion. That by the adjusted residual values sets the non-multifocal nor large single lesions group as a

contributing factor for CR (*P*=0,012*). Moreover, there was also a statistical difference between the mean number of lesions in the two groups (*P*=0,001*) associating an inferior number of lesions with CR.

The patients attaining CR revealed a lower mean in largest lesion diameter, sum of lesions diameters and the sum of only LR-M, LR-5 and LR-4. Nevertheless, no statistical significance was found. These data were displayed in boxplots for easier comprehension. (Fig.7-11)

The analysis is condensed in Table V.

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 conformity with the incidence of HCC in men surpassing women's[1].

The etiology of chronic liver disease was not implied as a relevant predictor of response. Our population had heterogeneous risk factors and liver disease etiology. There was only one patient with NASH who achieved PR and only one patient with hemochromatosis who achieved CR. We would need a larger cohort in order to evaluate the nature of liver disease as a predictor of objective response. NASH prevalence is increasing particularly in United States of America[2], and future studies might better acknowledge its influence in treatment response.

Most of the patients belong to CTP class A, 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 associated with positive outcomes[12,28,29].

The results of our study revealed a statistically significant association between CR after first TACE and non-multifocal nor large single lesion. Multifocal disease and tumor size are correlated with a decrease in overall survival in several studies[9,12,30,31]. Nonetheless, it is interesting to observe the predictor valuable of this variable and not of BCLC stage. This might be explained by a particularity in BCLC classification, which includes large single lesions in the BCLC-A stage. Despite the fact that: they are unresectable and also outside the Milan criteria, excluding the patient from upfront LT consideration; they still do not belong in the intermediate stage because it requires multifocal disease. Another difference between BCLC-A patients and our category of non-multifocal nor large single lesion are patients with up to 3 lesions all inferior to 3 cm, who are within the Milan Criteria and also integrate BCLC-A HCC. We had 9 patients with early stage HCC who achieved complete response; from those, 8 had unifocal disease and 7 were non-multifocal nor large single lesions. We came across this significant difference in response among BCLC-A HCC which leaves a question: Do multifocal and large single lesions within BCLC-A behave more similarly to BCLC-B patients? Should they be categorized differently?

Zhong *et al.* addressed the concerns on single large HCC. In a retrospective study including 1132 patients, it was identified that overall survival in single tumors >8cm was comparable to intermediate stage HCC and it was proposed to assign these lesions to stage B.[32] A difference in prognosis was also seen in Cho *et al.* with large single lesion HCC >5cm. Nonetheless, they recommended resection and not TACE as first-line treatment[33,34]. These results reinforce the need

for subcategorization of BCLC-A lesions, with a different strategy for single large lesions (>5cm) and multifocal disease within the BCLC-A stage, as it was recently proposed by our research group[27].

Almost half of the patients BCLC-A who achieved OR were complete responders (47,4%), the same could not be said of the BCLC-B patients that despite the tendency for accomplishing OR, in 12 out of 15 (80%), it was due to PR, the same rationale is behind multifocal disease. Cerban *et al.* stated that multinodular HCC has an intricate vascularity that can be the cause to the difference between CR and PR in these patients.[9] Similarly, Coletta *et al*. declared that nodules with 3-5 cm are well vascularized and account their irrigation to a single artery leading to TACE effectiveness[14] which correlates to the non-multifocal nor large single lesion group achievement of CR. When comparing this variable to multifocal disease, that was not a predictor of CR, the same question is posed: what distinguishes these two variables? The answer is the presence of large single lesions, that might behave more similarly to BCLC-B HCC. Despite not encountering statistical significance in multifocal lesions, the mean and standard deviation between the number of lesions was statistically different among the group who achieved CR and the group who did not. That occurred because in the CR group there were only 2 patients with multifocal disease, and both had only two lesions in opposition the other group included patients with up to six nodules.

As for the comparison between "responders" and "non-responders" the study failed to prove a predictor of OR which was one of its goals. However, it was observed that BCLC-B had a great OR rate, as 80% were "responders", a finding that is in agreement with BCLC algorithm. Not surprisingly the same was seen in patients with multifocal disease, as this is a prerequisite to intermediate stage.

When the diameter of the largest nodule was inferior or equal to 5 cm 71,4% were objective responders, they also revealed a lower median in the largest lesion diameter by 9,5mm. Tumor size ≤5 cm is associated with positive survival outcomes in several studies[12,29,35]. Cerban *et al.* in a retrospective study with 168 patients reported tumor size ≤4.5 cm and single nodularity as predictive factors for CR[9]. In our study, in spite of tumor size not achieving statistical significance we could detect a higher mean and median in the "non-responder" group specifically regarding the largest lesion diameter (Fig.4), the same findings were seen when considering the sum of lesions diameters according to treatment response (Fig.9-10).

Alpha-fetoprotein level (> 25 ng/mL) was correlated with recurrence after CR[9]. On a major review Raoul *et al.* gathered an association between AFP levels ≤200 ng/mL and positive survival outcomes[12], although not all studies used the same cut-off for AFP. In Yuen *et al.* study, the patients with positive outcomes had a median AFP of 110 ng/mL[36] and in O'Suilleabhain *et al.* an AFP below

1000 ng/ml was associated with an increase in 5-year survival rate[37]. Also, despite several studies implicating AFP as a method for evaluating treatment response, there is still not a clear definition for AFP response and associated prognosis. Sherman[38], defined AFP response as a decrease in half of AFP's baseline, and supported its use as an auxiliary to image screening. Should be emphasized that imaging cannot be supplanted by tumor markers, as it has limitations and cannot be used in patients without a primary increase in AFP level[38]. We had a low frequency of patients with substantial elevation of AFP levels which might have decreased the power to detect its influence.

Considering the predictive value of other imaging features, 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 response or complete response, particularly since their classification depends on tumor size and vascularization. When the largest nodule belonged to LI-RADS 5 category, OR was obtained in 72,4% patients, but we found no statistical significance among the responder and non-responder groups. It should be taken in account that LI-RADS criteria is dependent on imaging modality. In a study using LI-RADS version 2013.1, 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.[39] Because of the retrospective nature of Corwin *et al.* study, is important to notice that the number of patients involved was of 58 and 22 were proposed for MRI in order to characterize observations seen in CT, but we did not take in account MRI LI-RADS classification, as we intended to evaluate only the predictive value of CT imaging features. Therefore, LI-RADS categories using CT criteria should not be accounted when selecting patients for TACE, and further studies should be done using MRI criteria. Nevertheless, this raises an important question regarding the management of LR-3 lesions. In our study we had many patients with LR-3 lesions using CT criteria, which would not be treated if other imaging modalities were not done resulting in category upgrade. Therefore, further studies are needed in order to better define treatment response in these lesions.

Our study has some limitations. Our main goal was to assess treatment response after TACE, as the presence of OR is highly correlated with increased survival and the need of further treatment[40,41]. Nevertheless, objective guidelines on the timing of treatment response evaluation and preferred technique are still lacking. The most common time to assess treatment response with CT/MRI is between four to six weeks following TACE, either using CT or MRI[27,41].

Moreover, the use of mRECIST criteria is not without fault, as some limitations are recognized. These criteria are currently favored, as they are superior at identifying patients as responders, but

cannot be used in non-enhancing target lesions. Nevertheless, in our study we had only three cases in which there was a need to resort to RECIST 1.1 criteria[24,26,41]. 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[42,43]. Nevertheless, in atypical lesions, without arterial phase hyperenhancement, RECIST 1.1 is a good predictor of prognosis[26].

More recent criteria for treatment assessment have been proposed by the LI-RADS committee (LR-TR). The 2018 version also proposes criteria that are individualized for the locoregional therapy used and analyze each nodule separately. The four categories suggested are LR-TR Nonviable, LR-TR Equivocal, LR-TR Viable and LR-TR Nonevaluable. To define lesions as viable, LR-TR considers arterial phase hyperenhancement, washout appearance or enhancement similar to pre-treatment[5,15]. An evaluation that combined the mRECIST concept of viable tumor with the other factors that LI-RADS considers as viable tumor would be interesting, as this would probably improve accuracy in radiological treatment response evaluation.

The second aim of the study was to improve TACE selection. The pinnacle of all outcomes should be without a doubt the overall survival. Nonetheless, treatment response is the most immediate outcome available and has a direct impact on patients' prognosis and overall survival.[43] In this matter, TACE is already considered the best treatment option for intermediate stage HCC, as it extends overall survival in these patients[44,45]. Moreover, patients with CR after TACE have been associated with excellent posttransplant outcomes even when lesions initially exceeded Milan criteria[46].

There are other important limitations to the study. 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 the clinical practice indication. Moreover, there was 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 response evaluation. Additionally, the patients were only studied for treatment response after the first TACE, when not achieving CR patients could be considered for retreatment.

In conclusion, our study found an association between complete response, small single lesions and an inferior number of lesions. Nonetheless, 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 lesions behave more similarly to intermediate stage HCC. Moreover, other imaging biomarkers including MRI features and quantitative biomarkers should be included in future studies to assess their prognostic value, and further validation for treatment response evaluation should continue, as new imaging criteria arises.

APPENDIX

Table I. Eligibility criteria

Eligibility Criteria
Were Included patients with: HCC clinical diagnosis; ≥ 18 years old at the time of first TACE; Pre-TACE radiological evaluation by CT; Post-TACE reevaluation CT/ MRI. Patients with any BCLC stage were included if meeting the criteria. Patients with combination therapies were also included if meeting the criteria.
TACE did not had to be the first treatment if the prior achieved no imaging evidence of viable tumor.

HCC: Hepatocellular carcinoma; TACE: Transarterial Chemoembolization; CT: Computed tomography; MRI: Magnetic resonance imaging; BCLC: Barcelona Clinic Liver Cancer.

Table II. 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	40(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	26(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/PR/SD/PD	10(21,3)/22(46,8)/13(27,7)/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 III. Treatment Response according to chronic liver disease etiology

mRECIST/ RECIST	HBV	HCV	Alcohol consumption	Multifactorial	NASH	Hemochro matosis	Unknown
CR	0	0	5	4	0	1	0
PR	1	8	9	2	1	0	1
SD	0	2	7	3	0	0	1
PD	0	1	1	0	0	0	0
Total	1	11	22	9	1	1	2

Data is expressed as number of patients. HBV: Hepatitis B virus; HCV: Hepatitis C virus; NASH: Non-alcoholic steatohepatitis; CR: Complete response; PR: Partial response; SD: Stable Disease; PD: Progressive disease.

Table IV. Comparison between Responder and Non-Responder groups

	Responder (*n*=32)	Non-Responder (*n*=15)	*P* value
Sex:			0,884
Male	25 (78,1%)	12 (80,0%)	
Female	7 (21,9%)	3 (20,0%)	
BCLC:[a]			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
Sum Diameters LRM/LR5/LR4[b] (mm)	49,1±22,1	57,0±37,1	0,469

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]Was excluded a patient with BCLC-C stage to enable the Chi-Square test, with a total of Responders (*n*=31) and Non-responders (*n*=15).

[b]Were excluded patients' LR-3 lesions, with a total of Responders (*n*=31) and Non-responders (*n*=15) for this variable.

Table V. Comparison between Complete Response and all other Treatment Responses.

	CR (*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:[a]			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
Sum Diameters LRM/LR5/LR4[b] (mm)	42,4±19,9	53,8±28,8	0,270

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 $P < 0.05$*

[a]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)

[b]Were excluded patients' LR-3 lesions, with a total of CR (*n*=9) and PR,SD,PD (*n*=36) for this variable.

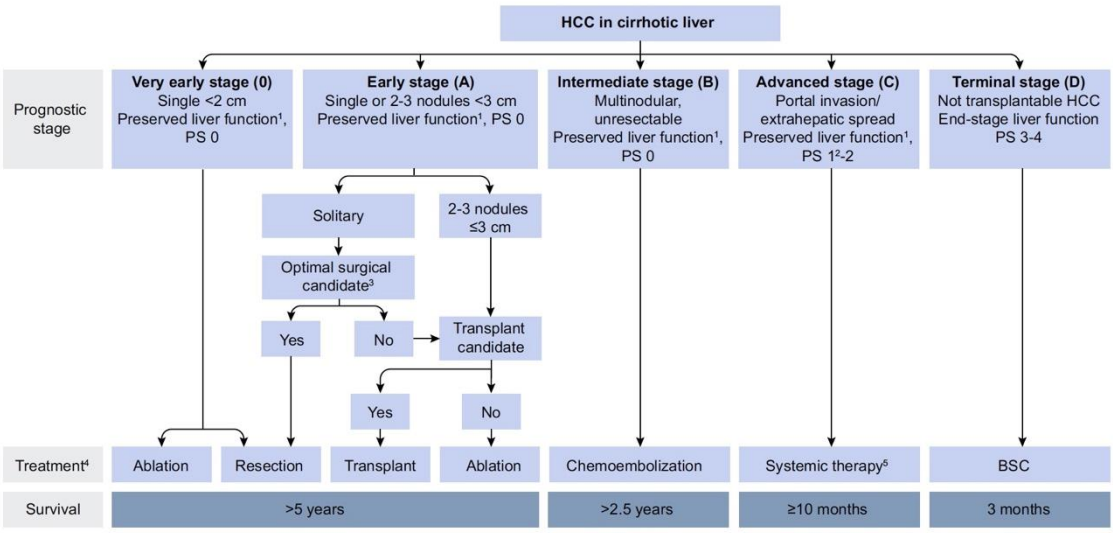

Figure 1. Algorithm for the management of HCC based on BCLC system proposed by EASL. Source: EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. *Journal of hepatology*, 2018.

[1]Preserved liver function describes Child-Turcotte-Pugh class A patients.
[2]PS: Eastern Cooperative Oncology Group Performance Status.

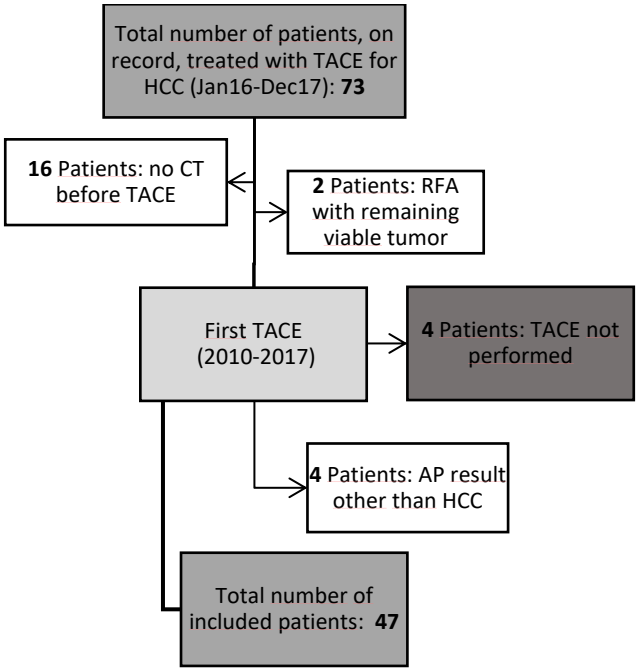

Figure 2. Patient selection criteria algorithm.

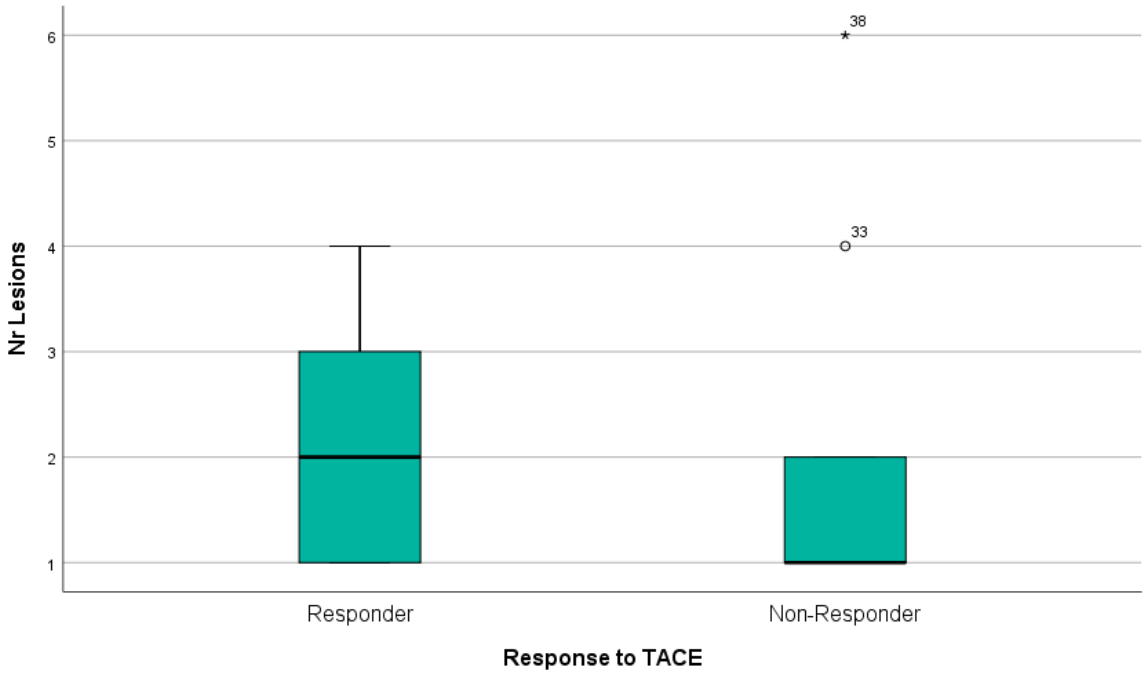

Figure 3. Boxplot showing the distribution of the number of lesions among "responders" and "non-responders" patients.

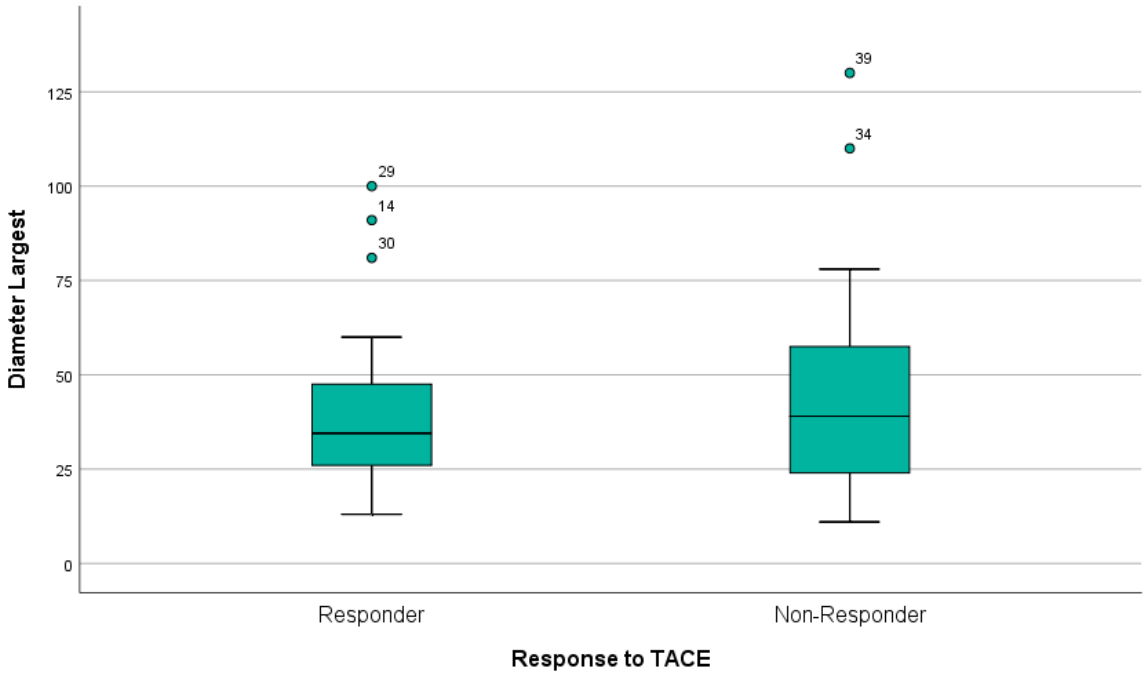

Figure 4. Boxplot showing the distribution of the diameter of the largest lesion among "responders" and "non-responders" patients.

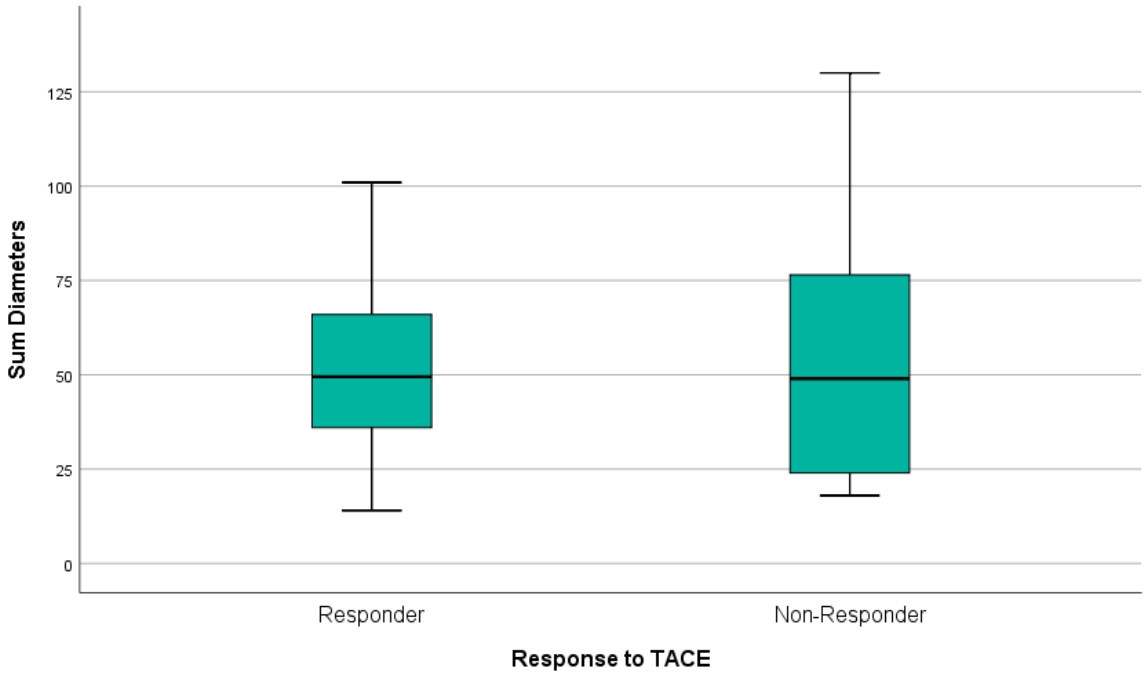

Figure 5. Boxplot showing the distribution of the sum of lesions diameters among "responders" and "non-responders" patients.

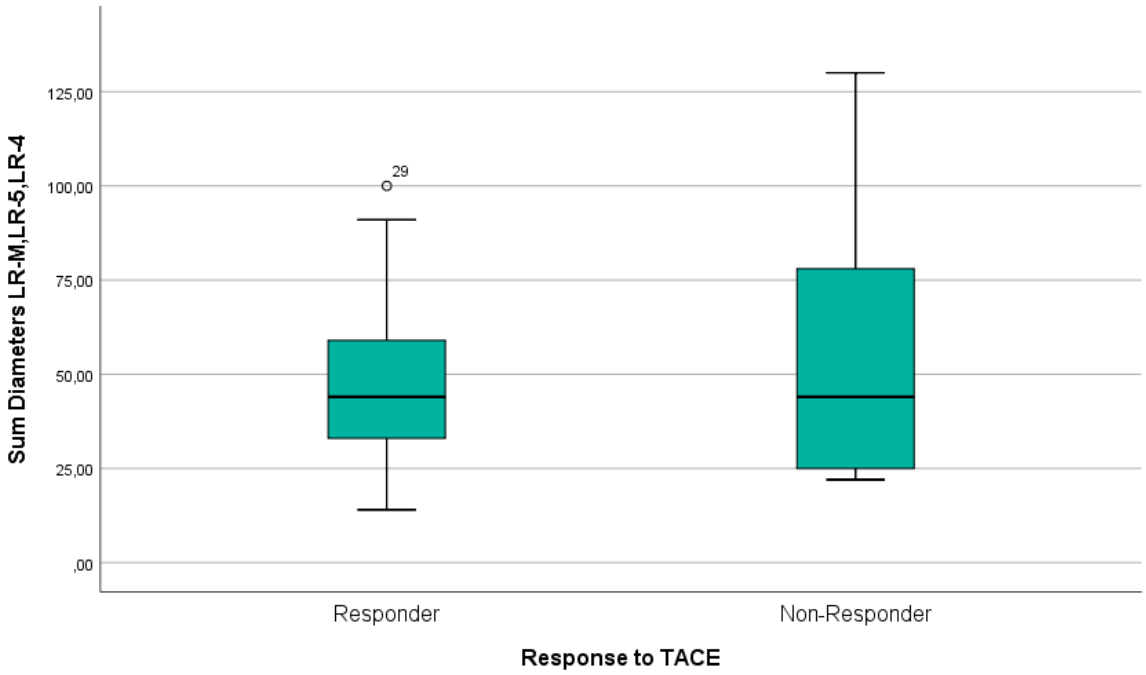

Figure 6. Boxplot showing the distribution of the sum of lesions diameters excluding LR-3 among "responders" and "non-responders" patients.

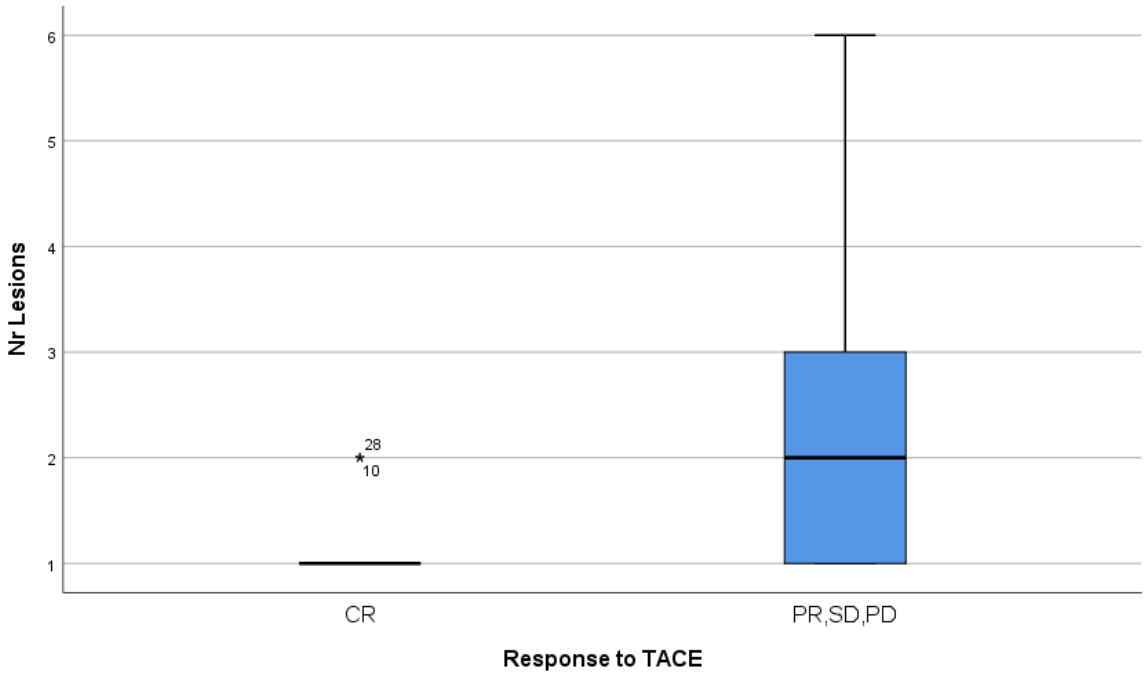

Figure 7. Boxplot showing the distribution of the number of lesions in patients with complete response compared to all other responses.

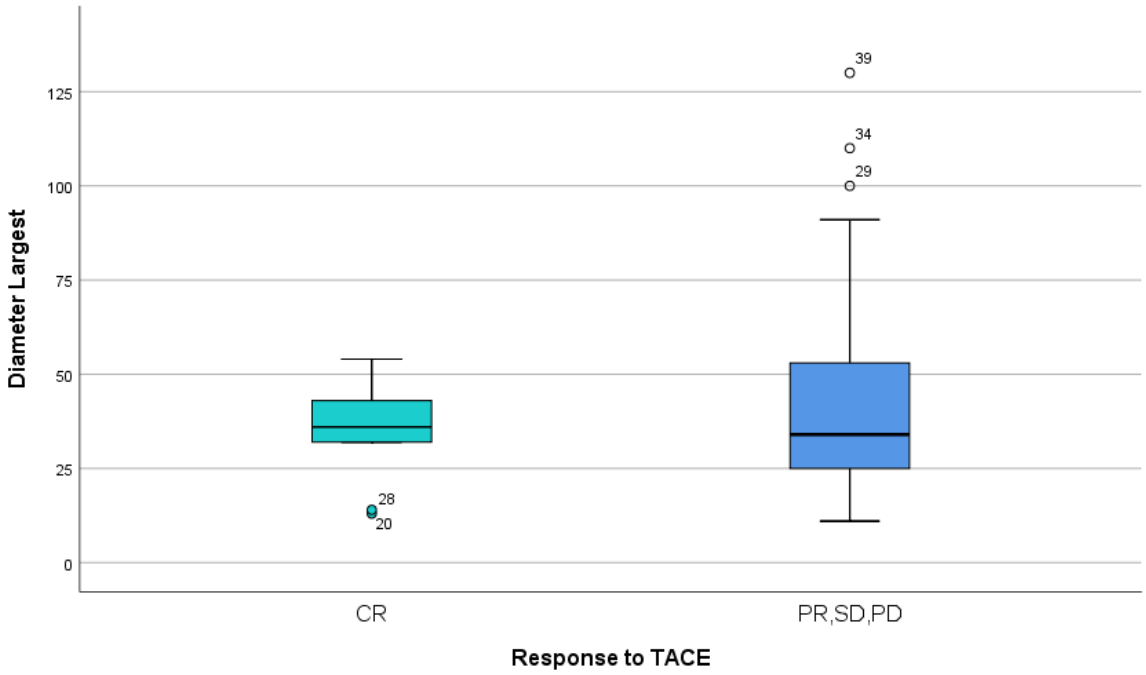

Figure 8. Boxplot showing the distribution of the diameter of the largest lesion in patients with complete response compared to all other responses.

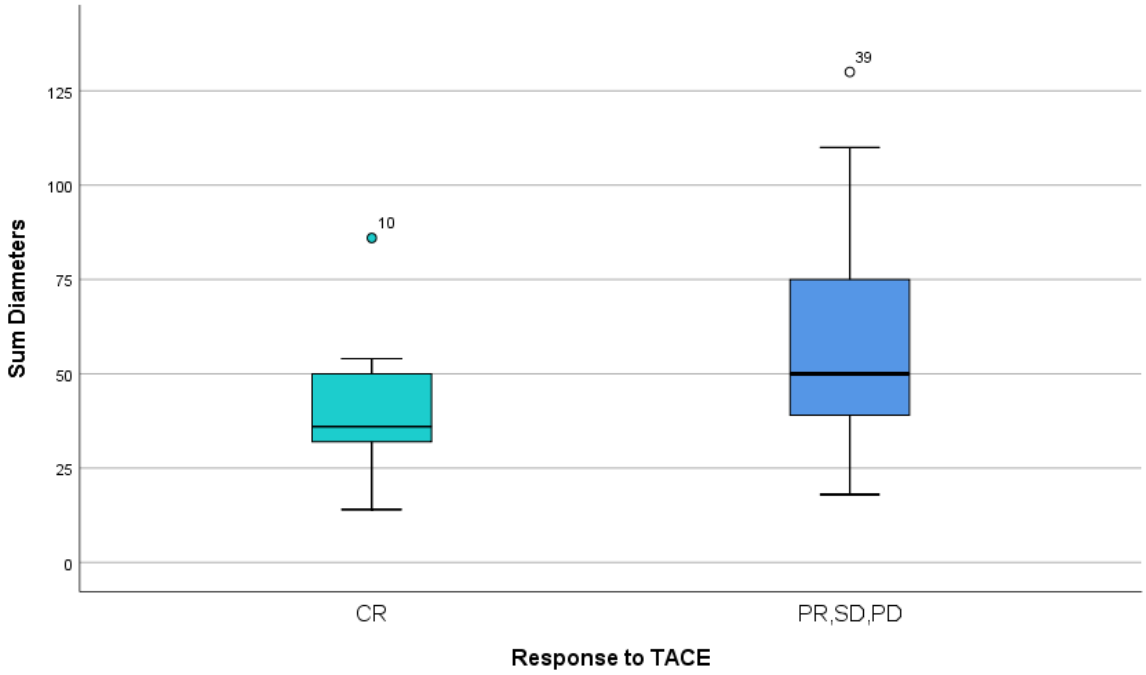

Figure 9. Boxplot showing the distribution of the sum of lesions diameters in patients with complete response compared to all other responses.

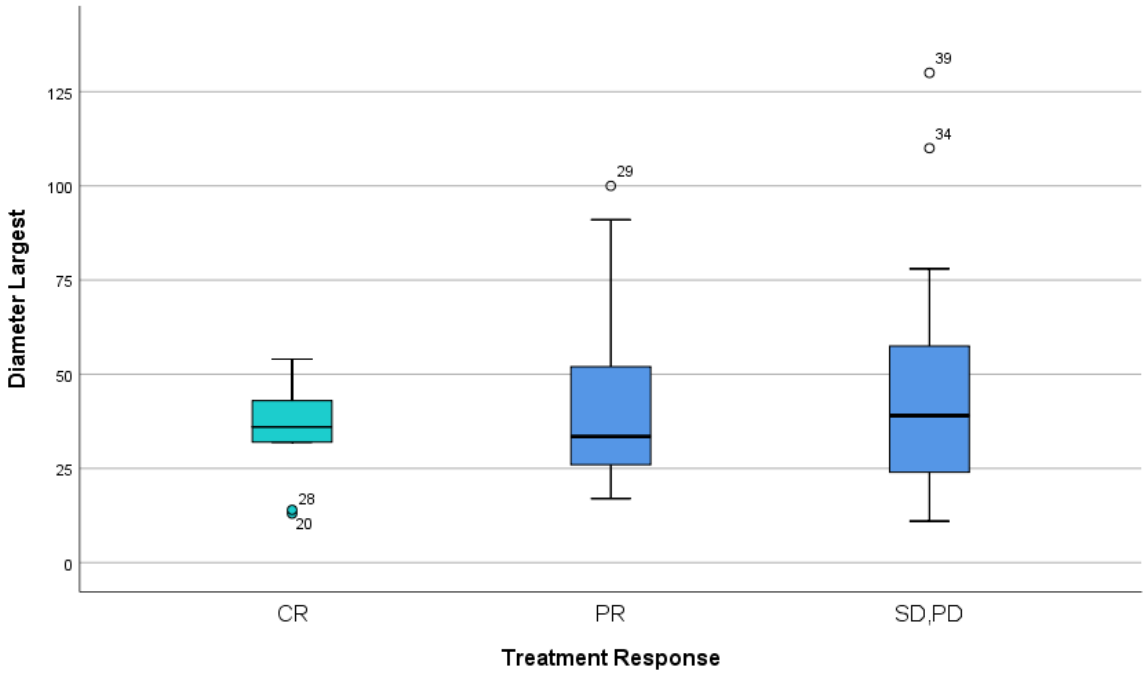

Figure 10. Boxplot showing the distribution of the sum of lesions diameters in patients with complete response compared to partial response and stable or progressive disease.

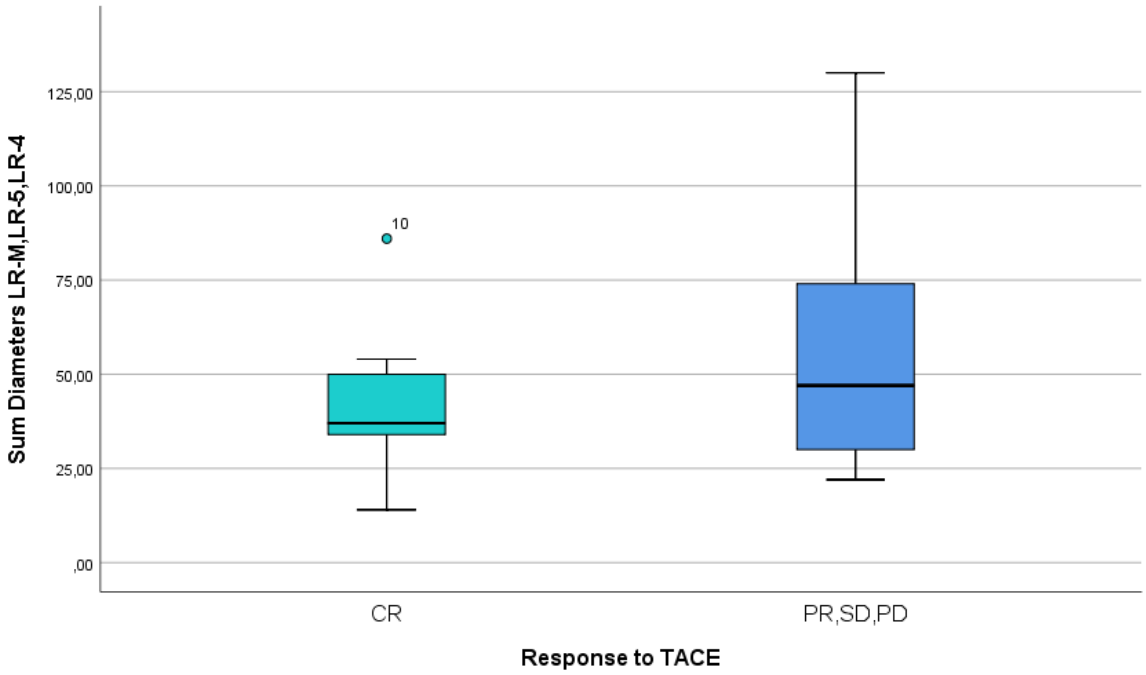

Figure 11. Boxplot showing the distribution of the sum of lesions diameters excluding LR-3 in patients with complete response compared to all other responses.

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