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ORIGINAL ARTICLE

Correlation between radiological response after locoregional treatment and histopathological findings in patients undergoing liver transplant for hepatocarcinoma

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ABSTRACT

Background and Objectives: Liver Imaging Reporting and Data System treatment response (LR-TR) algorithm has been developed to evaluate response after locoregional treatment (LRT) in patients with hepatocellular carcinoma (HCC). The aim of the study was to corroborate if the post-treatment radiological findings described using LR-TR correspond to the final histopathological results, and survival in relation to different LR-TR groups in patients underwent LRT before liver transplantation (LT). **Methods**: A retrospective single-center study was performed. Data of patients undergoing LT and LRT due to HCC between January 2010 and December 2022 were collected. **Results**: Four hundred and four patients were transplanted, of which 103 (25.5%) had HCC. Ninety-seven patients (93.2%) received LRT. 53% of treated patients had a complete response on pathological examination. Re-evaluation imaging was performed in 88 patients. 59% were classified as non-viable LR-TR, 32.5% as viable LR-TR, and 8.5% as equivocal LR-TR. Regarding the correlation between the degree of tumor necrosis and the post-treatment LR-TR category, 37% of patients evaluated as viable LR-TR had a "complete response" compared to 62.9% with "no complete response". For those evaluated as non-viable LR-TR, 59.2% had a "complete response" compared to 40.8% with a "no complete response" ($P = 0.123$). There were no statistically significant differences in overall and disease-free survival between the viable LR-TR, non-viable LR-TR, and equivocal LR-TR groups ($P = 0.3484$ and $P = 0.4152$, respectively). **Conclusion**: We have not been able to establish whether radiological response correlates with anatomopathological outcomes, as well as survival in these groups. More prospective studies are needed to validate these findings.

Key words: liver transplantation, hepatocellular carcinoma, locoregional treatment, radiological response

INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common primary liver malignancy and the second-most common cause of cancer-related death worldwide.[1] Currently, patients with HCC have several therapeutic options available aimed at prolonging their survival, depending on the tumor stage, the patient's baseline condition, institutional preference, equipment availability, and expertise. Liver transplantation (LT) is known as the oncological treatment of choice for cirrhotic patients with early-stage HCC. Locoregional therapy (LRT) has

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been increasingly used for the treatment of HCC as a bridging therapy to liver transplantation in order to maintain criteria for transplantation by monitoring tumor burden, and to allow patients who do not meet transplant criteria to be considered (downstaging).[2]

Imaging plays an integral role in HCC treatment response assessment. Computed tomography (CT) and magnetic resonance imaging (MRI) are routinely used to assess treatment response following therapy. Detection of residual viable tumor and local recurrence after LRT, are critical for the timely retreatment of HCC, transplantation eligibility, and prediction of patients' prognosis after the subsequent hepatic transplantation.[3]

The Liver Imaging Reporting and Data System (LI-RADS) is a system of standardized imaging criteria developed for the evaluation of patients at risk of developing HCC. The 2017 version of LI-RADS introduced a treatment response (LI-RADS treatment response [LR-TR]) algorithm for the assessment of lesions that have been previously treated with local-regional therapies. Since treatment of HCC is on a lesion-by-lesion basis, often with different lesions treated with varying forms of LRT and therefore responding differently, a treatment response assessment system that takes this into account was needed, which is where the LR-TR algorithm becomes useful.[4]

However, there are currently no published data that evaluate the performance of the treatment response algorithm for predicting the degree of local-regional therapy induced necrosis in individual lesions.

The aim of the study was to corroborate whether the post-treatment radiological findings described using LR-TR algorithm align to the final histopathological outcomes ("complete response" *vs.* "not complete response") in patients who underwent LRT before liver transplantation. Additionally, the study aimed to assess overall and recurrence-free survival rates in relation to the different LR-TR categories.

MATERIAL AND METHODS

A retrospective study was conducted at a single tertiary referral University Hospital center between January 2010 and December 2022. The study included patients who underwent liver transplant for HCC and received LRT. Data on the transplants were collected in a prospective, anonymized database. Exclusion criteria included duplicate records, a diagnosis of another tumor type in the pathology report, or intraoperative or immediate postoperative death.

In our center, the diagnosis of suspected HCC is usually made through follow-up ultrasonography and alpha-fetoprotein (AFP) blood tests, which are periodically performed on cirrhotic patients. To confirm the diagnosis of HCC, a CT scan and/or liver MRI is performed.

The treatments used in our center were chemoembolization and radiofrequency. Radiofrequency was indicated for small (less than 15 mm) and single nodules, while chemoembolization was used for the rest of the patients. Imaging tests were performed one month after locoregional treatment, with repeat sessions for patients with suspected viable tumors.

The minimum post-transplant follow-up period was set at 36 months. The follow-up protocol included analytical controls with AFP and periodic imaging tests. We analyzed demographic, biochemical, and clinical data, as well as locoregional treatments prior to the transplant, reassessment imaging tests, anatomopathological and clinical follow-up data.

LR-TR criteria were used to asses radiological response, by establishing three categories: LR-TR Viable, LT-TR Nonviable and LT-TR Equivocal.[5] LR-TR Viable is assigned to enhancement patterns demonstrating persistent arterial phase hyperenhancement or enhancement that is similar to pre-treatment imaging characteristics. LR-TR Nonviable applies to lesions that demonstrate no enhancement on post-treatment imaging or demonstrate an expected treatment-specific enhancement pattern. LR-TR Equivocal is assigned to those treated observations that demonstrate enhancement atypical for treatment-specific expected enhancement pattern and not meeting criteria for definitely nonviable or definitely viable.

Statistical analysis

Quantitative variables were presented as mean and standard deviations or median and interquartile range, depending on their distribution. The Shapiro-Wilks test was used to assess the normality of each continuous variable. Categorical variables were presented using frequency tables and percentages.

Quantitative variables were compared using Student's *t*-test or Mann-Whitney *U* test, as appropriate. Categorical variables were compared using the chi-square test or Fisher's exact test. Overall and disease-free survival functions were estimated using the Kaplan-Meier method, and the long rank test was used to compare between groups. A P value of < 0.05 was considered statistically significant for all tests. The calculations were performed using the statistical program STATA vs 14. This study has been authorized by the Granada Research Ethics Committee.

RESULTS

Four hundred and four patients were transplanted, and 111 (27.5%) had hepatocellular carcinoma, all with underlying liver cirrhosis. Of these, eight patients were excluded from the study. One due to a duplicate history, one due to a cholangiocarcinoma in the explant, one due to intraoperative exitus secondary to hemodynamic failure, and five due to death in the immediate postoperative period. Of these, two were due to primary graft non-function, two due to acute hepatic artery thrombosis, and one due to abdominal sepsis.

Eighty-one patients (78.6%) and 22 patients (21.4%) were included for transplantation according to Milan criteria and extended criteria, respectively. The predominant sex was male (81%), with an average age of 58 ± 6 years. More than 90% of patients had a performance status of 0–1. There were no significative differences in pre-transplant comorbidities.

The most common etiopathogenic basis of liver cirrhosis was alcoholic, in 39.2% of patients, followed by HCV liver disease (35%), association of both in 7.5%, HBV liver disease (6%) or combined with alcohol (7.2%) and finally cryptogenic or autoimmune liver diseases in 5% of cases. 72.2% of patients had a Child A functional stage, 22.7% had a Child B stage, and only 5% of patients were Child C. The average MELD score was 12.8 ± 4 points. The average alpha-fetoprotein level was around 54 ng/mL.

There were 10% of re-interventions, mostly for bleeding (50%), one patient for hepatic artery thrombectomy, and a single liver retransplantation for primary graft dysfunction.

Patients were on the transplant waiting list for a mean of 183 ± 129 days. The median length of hospital stay was 27 ± 17 days, with a median ICU stay of 4 ± 3 days and a median follow-up of 51 months.

Ninety-seven patients (93.2%) received locoregional therapy prior to transplantation: 71 patients (73%) underwent chemoembolization, 13 patients (13.5%) underwent radiofrequency, and 13 (13.5%) underwent both. 53% of treated patients had a complete response (necrosis > 90%) on pathological examination.

Re-evaluation imaging was performed in 88 patients (90.7%). Of them, 8 (8.2%) underwent ultrasound, 68 (70.1%) underwent magnetic resonance imaging, and 12 (12.4%) underwent computed tomography. Of the 88 patients who were reevaluated, 59% were classified as non-viable LR-TR, 32.5% as viable LR-TR, and the remaining 8.5% as equivocal LR-TR.

Regarding the correlation between the degree of tumor necrosis and the post-treatment LR-TR category (Table 1), 37% of patients evaluated as viable LR-TR had a "complete response" compared to 62.9% with "no complete response". For those evaluated as non-viable LR-TR, 59.2% had a "complete response" compared to 40.8% with a "no complete response". And finally, 62.5%% of patients evaluated as equivocal LR-TR had a "complete response" compared to 37.5% with "no complete response" but these differences were not significant ($P = 0.123$).

Overall survival rates at 6-month, 1-year, 2-year and 4-year were 95%, 83.3%, 63.7% and 44.2%, respectively. There were no statistically significant differences in overall and recurrence-free survival between the viable LR-TR, non-viable LR-TR, and equivocal LR-TR groups ($P = 0.3484$ and $P = 0.4152$, respectively) (Figure 1).

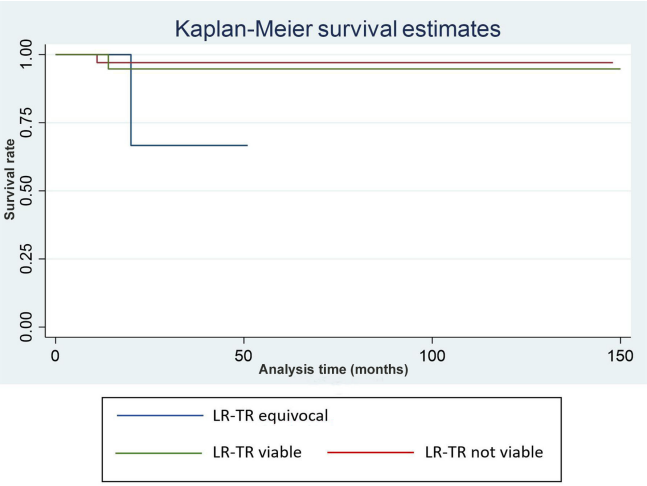

Figure 1. Disease-free survival among the three groups of LR-TR. LR-TR: Imaging Reporting and Data System Treatment Response.

DISCUSSION

With the increasing use of LRT for HCC treatment before liver transplantation, accurate assessment of treatment response is necessary for patient management and transplant allocation. Several systems have been described for standardized measurement and reporting of treatment response in solid tumors, such as the Response Evaluation Criteria in Solid Tumors (RECIST), the modified RECIST (mRECIST), the Choi criteria, and the modified Choi criteria.[4,5] These systems are intended for evaluating treatment response at the patient level. However, the LR-TR algorithm differs in that it focuses on assessing lesions rather than patients. This distinction is particularly important in the assessment of HCC, as patients may develop multiple lesions over time and require different local-regional therapies for maintaining transplant eligibility or disease

Table 1: Correlation between the degree of tumor necrosis and the LR-TR category

	LR-TR				
***n* (%)**	**Equivocal**	**Non-viable**	**Viable**	**Total**	**Fisher´s exact**
Complete response	5 (62.5)	30 (59.2)	11 (37)	46 (53)	0.123
No complete response	3 (37.5)	21 (40.8)	18 (62.9)	42 (46.9)	0.123
Total	8 (100)	51 (100)	29 (100)	88 (100)	0.123

LR-TR LI-RADS: Imaging Reporting and Data System Treatment Response.

control. Lesion response within a single organ can be heterogeneous, making it necessary to evaluate at the lesion-specific level. Therefore, the LR-TR system provides a comprehensive and useful approach for predicting treatment efficacy.[6] However, there is not enough published data comparing histopathology data and correlation with LR-TR categories.

Our results show that the 2017 version of the Liver Imaging Reporting and Data System (LI-RADS) Treatment Response (LR-TR) algorithm does not perform well in predicting complete necrosis and incomplete necrosis for lesions treated with embolization or radiofrequency that meet the criteria for either the LR-TR Nonviable or Viable categories. These results are likely due to the small sample size. While there are few studies evaluating this radiological-anatomopathological correlation, some studies do find it to be significant, as is the case in the article by Shropshire *et al.*[7]

One of the primary goals of standardized reporting systems like LI-RADS is to improve interreader agreement in reporting, which can be challenging when lesion categorization is subjective. In our study, a small number of lesions were classified as LR-TR Equivocal, with features of both the LR-TR Viable and Nonviable categories.[8] This reflects reader uncertainty in applying the criteria for these response categories and using the treatment response algorithm tiebreaking rule guidelines to choose the category with lower certainty. Although most LR-TR Equivocal lesions were found to be completely necrotic upon histopathologic examination, strict interpretation of the treatment response algorithm may have resulted in some incompletely necrotic lesions being reassigned to the LR-TR Viable category.

Our study has several limitations. It has a single-center retrospective design, and all patients were evaluated and treated in a tertiary transplant hospital, leading to biased patient selection that limits generalizability to non-transplant centers. The inclusion of different imaging modalities and locoregional treatments introduced heterogeneity. Additionally, the study period may be a limitation, as technical capabilities changed during that time.

In conclusion, this study aimed to evaluate the performance of the LR-TR algorithm in predicting treatment response and survival outcomes in patients who underwent LRT before liver transplantation. The results suggest that the LR-TR categories may not accurately reflect the degree of necrosis induced by local-regional therapy and may not be reliable predictors of survival. Further studies with larger sample sizes are needed to validate these findings and to develop more accurate assessment tools for treatment response in HCC patients.

DECLARATIONS

Author contributions

Mohamed Hassin Mohamed Chairi conducted the investigation and wrote the original draft. Ana Belén Vico Arias contributed to the methodology and formal analysis. Natalia Zambudio Carroll managed the software and data curation. María Trinidad Villegas Herrera provided the supervision. Jesús María Villar del Moral made the validation.

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Conflicts of interest

The authors declared no potential conflicts of interest.

Data sharing statement

No additional data is available.

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