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Factors affecting tumor response to transarterial chemoembolization (TACE) therapy in patient with hepatocellular carcinoma (HCC)

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ABSTRACT

Hepatocellular carcinoma (HCC) is a major problem of global health.Transarterial chemoembolization (TACE) is the treatment of choice for unresectable HCC. The TACE is routinely conducted in major hospitals in Indonesia, however it rarely published. The use of modified response in evaluation criteria in solid tumors (mRECIST) was introduced as an accurate method of measuring tumor response in HCC. This study aimedto investigate the factorsaffecting tumor response to TACE therapy in HCC patients by using mRECIST. It was a retrospective cohort study conducted on 30 patients who successfully underwent the first TACE procedure in the Department of Radiology, Dr. Wahidin Sudirohusodo General Hospital, Makassar, Indonesia from January 2016 to August 2019. The multiphase abdominal computed tomography before and after as well as laboratory examination results before TACE were collected and analyzed. Chi-Square and Spearman-tests were used for the statistical analysis. A significant relationship between tumor location (p=0.016), number of tumor (p=0.001) and Child-Pugh score with tumor response to TACE therapy (p = 0.016) was observed. Solitary tumors tend to have a better therapeutic response, meanwhile, tumors located in the left lobe of patients with Child-Pugh B scores showed a decreased tumor response. Furthermore, no a significant relationship between age (p=0.920), sex (p=0.303), tumor size> 5 cm (p=0.082) and alpha-fetoprotein (AFP) levels (p=0.414) with tumor response was observed. In conclusion, TACE is preferably therapy for multinodular and unresectable HCC. Tumor response after TACE can be well assessed using mRECIST. The factorsaffecting tumor response to TACE therapy arenumber of tumor, location, and Child-Pugh score.

Keywords:
tumor response;
transarterial chemoembolization;
hepatocellular carcinoma;
mRECIST;
solid tumor;

ABSTRAK

Hepatocellular carcinoma (HCC) adalah masalah utama kesehatan global. *Transarterial chemoembolization* (TACE) adalah pengobatan pilihan untuk HCC yang tidak dapat dioperasi. TACE dilakukan rutin di rumah sakit utama di Indonesia, namun demikian jarang dipublikasikan. Penggunaan *modified response in evaluation criteria in solid tumors* (mRECIST) diperkenalkan sebagai metode yang akurat untuk mengukur respons tumor pada HCC. Penelitian ini bertujuan untuk mengkaji faktor-faktor yang mempengaruhi respon tumor terhadap terapi (TACE) pada pasien HCC menggunakan mRECIST. Ini merupakan penelitian kohort retrospektif terhadap 30 pasien yang telah menjalani TACE pertama di Bagain Radiologi RSUP Dr. Wahidin Sudirohusodo Makassar mulai bulan Januari 2016 sampai Agustus 2019. Hasil pemeriksaan *computed tomography* abdomen dengan kontras multifase sebelum dan sesudah serta hasil laboratorium sebelum TACE dikumpulkan dan dianalisis. Uji *Chi-Square* dan *Spearman* digunakan untuk analisis statistik. Terdapat hubungan bermakna antara lokasi tumor (p=0,016), jumlah tumor (p=0,001) dan skor *Child-Pugh* dengan respon tumor terhadap terapi TACE (p=0,016). Tumor soliter cenderung memiliki respon terapi lebih baik sementara tumor yang berlokasi di lobus kiri atau pasien dengan skor *Child-Pugh* B menunjukkan respon tumor yang menurun. Selanjutnya, tidak ada hubungan bermakna antara usia (p=0,920), jenis kelamin (p=0,303), ukuran tumor >5 cm (p=0,082) dan kadar *alpha-fetoprotein*/AFP (p=0,414) dengan respon tumor terhadap TACE. Dapat disimpulkan bahwa TACE merupakan terapi pilihan untuk penyakit HCC yang multinodular dan tidak dapat dioperasi. Respon tumor setelah TACE dapat dinilai dengan baik menggunakan mRECIST. Faktor-faktor yang mempengaruhi respons tumor terhadap TACE adalah jumlah tumor, lokasi, dan skor *Child-Pugh*.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is a major global health problem. Itranks sixth as the most diagnosed cancer and fourth as a cause of death from cancer worldwide.[1] The HCC is formed through the hepatocarcinogenesis process, in which the transformation of non-malignant liver cells into hepatocellular carcinoma gradually.[2] The molecular and cellular mechanisms underlying the change of cells that were not malignant to HCC are not yet fully understood[3] and the risk factors that thought to trigger HCC vary from region to region.[1]

In contrast to other liver tumors, HCCs almost exclusively is supplied by hepatic arteries. Uniquely, the liver has double vascularization with 75 to 80% portal vein components and 20 to 25% arterial components which allow eradication of the tumor through the feeding artery without disrupting the healthy part of the liver.[4]

Transarterial chemoembolization (TACE) is the treatment of choice for unresectable HCC.[5] Currently, TACE is a standard of care for HCC patients who belong to the BCLC stage B group, which has large or multinodular tumors with relatively proper liver function (child-pugh A or B).There is no evidence of vascular invasion or extrahepatic spread and performance status that is still active (ECOG PS 0-1).[6]

The TACE procedure requires injected embolic agent directly into the tumor feeding artery to isolate the tumor from its primary source of nutrition. This action causes ischemic necrosis of the targeted tumor.[7] After TACE, tumor response usually assessed to see the effectiveness of therapy. Previously the response in evaluation criteria in solid tumors (RECIST) method was used to evaluate tumor response. Recently, the use of modified response in evaluation criteria in solid tumors (mRECIST), a modification of the RECIST method, was introduced as a more accurate method of measuring tumor response in HCC.[8]

Previous studies have linked tumor responses to factors that are considered to play a role or are part of the development of HCC disease. Tumor location and tumor size have broadly recognized as a significant predictive factor of response for TACE.[7,9]Other studies have linked tumor responses with demographic factors, Child-Pugh scores, even with alpha-fetoprotein (AFP) levels, a serum marker of liver malignancy that judged to be sufficiently pathognomonic for an HCC.[10-11]

TACE practices is rarely published even though this procedure is routinely conducted in major hospitals. TACEis one of the therapies of choice in unresectable HCC in Indonesia. Therefore, before performing this procedure, the physician needs to predict whether the TACE would be useful, particularly while considering other therapeutic modalities. This study aimed to investigate the factors that can influence tumor response to TACE therapy in HCC patients.

MATERIALS AND METHODS

Patients

Thirty-two HCC patients who had successfully undergone the first TACE procedure at Dr. Wahidin Sudirohusodo General Hospital, Makassar from January 2016 to August 2019 were selected in this study. The inclusion criteria were all patients diagnosed with HCC from multiphase abdominal CT scan results, who were not candidates for resection. Two of them were excluded due tounderwent other therapies before. Of the 30 patients, tumor response wereassessed based on radiological and laboratory supportive results.

TACE procedure

TACE procedure was carried out through the femoral artery approach with fluoroscopic guidance and a co-

axial catheter system to incorporate local doses of chemotherapy agents and concentrated directly into feeding vessels of the tumor. This procedure was followed by embolization using temporary particle material.

TACE was preceded by injection of doxorubicin and lipiodol, which have mixed into a homogeneous emulsion. The dose of doxorubicin adjusted according to the size of the tumor. The emulsion mixture wasthen injected until static in second or third orde of the right or left hepatic arteries. Emulsion injection was followed by a dose of a mix of embolic agents and water-soluble contrast media to maintain the drug in the tumor and to provide an embolic effect. The embolic agent used for this procedure wasgel foam particles. Gel foam was used to induce or increase ischemic tumor necrosis and prevent drug wash-out, thereby maintaining high local concentrations.

The procedure performed on large HCCs was partial TACE, aimed to prevent the full effects of necrosis, which can affect the liver function overall. Therefore, the TACE procedure at our institution was planned to carried out in stages with controlled drug dosages.

Evaluation of tumor response

Tumor response assessment wasconducted using the mRECIST (FIGURE1). The assessment was carried out from the multiphase abdominal CT, which performed four weeks after initial treatment. According to mRECIST, the overall tumor response was determined based on the target and non-target lesion response, and also the presence of a new lesion.[8]

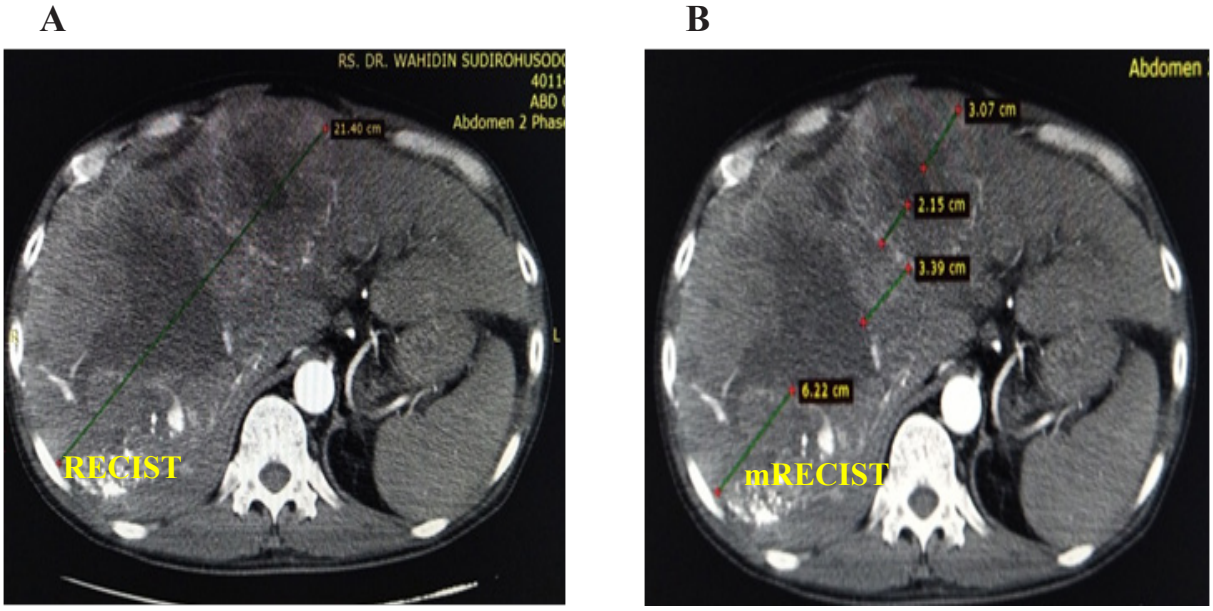

FIGURE 1. Assessment of target lesions on the axial cut of multiphase abdominal CT using RECIST vs. mRECIST method. A. The total diameter of target lesions obtained from the sum of the longest tumor axis. B. The total diameter was obtained from the sum of the longest tumor axis outside the area of necrosis

Target lesions response

Target lesions werethe primary lesion detected in the liver with typical enhancement in the arterial phase and wash-out in the venous phase. Target lesions must be measurable (> 1 cm) in at least one dimension. In multiple HCCs, the two largest of target lesions were chosen to represent the tumor size. The measurement results of target lesions were stated in four categories,

namely1) complete response (CR) if loss of intratumoral artery warming in all target lesions;2) partial response (PR) if there is a reduction in the total tumor diameter>30%; 3) progressive disease (PD) if an increase in overall tumor diameter> 20%; 4) stable disease (SD) ifall cases that cannot be grouped into PR or PD.

Non-target lesions response

All other lesions besides the target lesions were identified as a non-target lesion. Measurement of non-target lesions wasnot required, but their presence and absence werenoted during the follow-up. Disappearance of intratumoral enhancement of non-target lesions was noted as a complete response. Persistence in intratumoral enhancement of non-target lesions indicated a stable disease (FIGURE 2). The presence of one or more non-target lesions identified as a progressive disease.

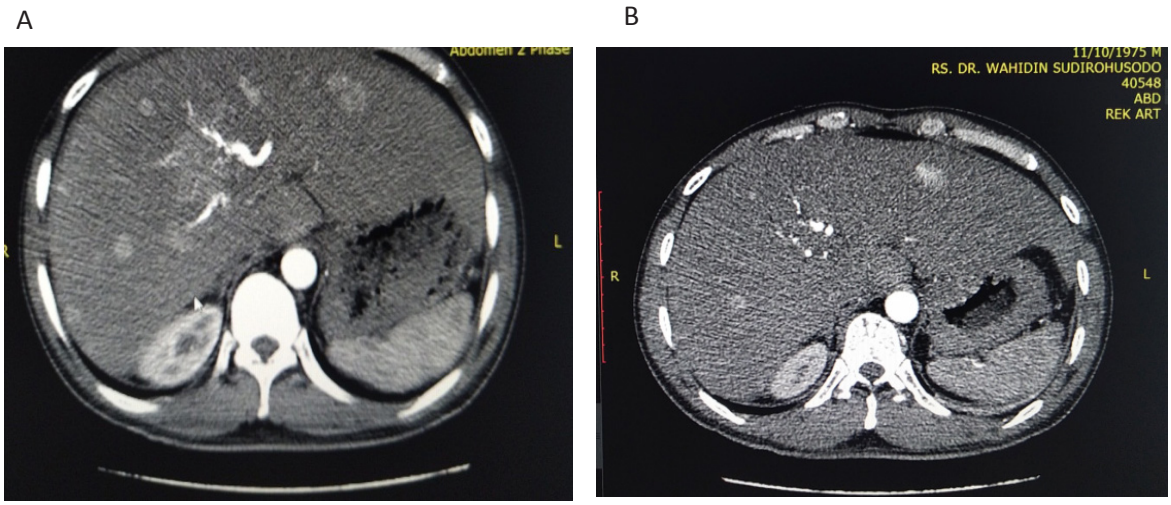

FIGURE 2. A. An axial cut of multiphase abdominal CT shows several small lesions in the liver with intratumoral enhancement in the arterial phase which identified as non-target lesions. The main tumor was on another cut of the image. B. One month after undergoing TACE therapy, in the same cut as the previous picture, lipiodol retention was seen in the branches of the right hepatic artery with a reduction in the number of lesions. Persistent intratumoral enhancement was seen in several non-target lesions. This finding identified as an incomplete response or stable disease of non-target lesions.

All lesions that werenot measurable on CT identified as non-target lesions.[8] Some of the findings that suggest a non-target lesion including a) portal venous thrombosis; b) porta hepatic lymph node. Lymph nodes detected in the hepatic port can considered malignant if the shortest axis of the lymph node is> 20 mm; c) pleural effusion and ascites.

New lesion

The presence of new focal lesions that enhancing in the arterial phase and wash-out in the venous phase must be identified as new HCC lesion.

The overall tumor response

The overall tumor response wasa combination of target lesions response, non-target lesions response, and the presence of new lesions (TABLE 1). If the target and non-target lesions were complete response (CR) without any new lesion found, then the overall response was complete. If one of them (target or non-target) was a partial or stable response without any new lesion, then the overall response was partial response

(PR). If both were stable without any new lesion, then the overall response was stable disease (SD). However, if one of them was progressive or there was a new lesion found, then the overall response was progressive disease (PD).

Statistical analysis

Informations were analyzed bivariate. Age, sex, location of primer tumors, number of tumors, largest tumor size, child-pugh score, and AFP levels were associated with tumor response after TACE. The Chi-Square and Spearman statistical tests were performed to evaluate the correlation between variables. The significance of statistical analysis was considered significant if the p value <0.05.

TABLE 1. Tumor response assessment in mRECIST

Target lesions	Non-target lesions	New lesion	Tumor response
Complete response	Complete response	(-)	Complete response
Complete response	Stable disease	(-)	Partial response
Partial response	Complete/stable	(-)	Partial response
Stable disease	Complete/stable	(-)	Stable disease
Progressive disease	Any response	(+) or (-)	Progressive disease
Any response	Progressive disease	(+)	Progressive disease
Any response	Any response	(+)	Progressive disease

RESULTS

Demographic and tumor characteristics

The result showed of the 30 patients involved in this studyaged varyfrom 41to 74 years with a mean of 55.06 ± 10.33 years. 90% of patients were male, and 83.3% had a primary tumor in the right lobe. 93.3% of patients had multiple tumors, and the tumor size varied between 6.6to 19.4 cm with a mean of 12.16 ± 3.17 cm. 83.3% of patients had a Child-Pugh class A score, and 63.3% had AFP levels>400 IU/mL. The baselines characteristicof patients are presented in TABLE 2.

TABLE 2. Baselines characteristic

Characteristics	n(%)	Mean± SD
Age (years old)		55.06±10.33
Sex		
• Male	27(90)	
• Female	3 (10)	
Main tumor location		
• Right lobe	25(83.3)	
• Left lobe	5 (16.7)	
Number of tumor		
• Single	2(6.7)	
• Multiple	28 (93.3)	
Maximum tumor size (cm)		12.16±3.17
Child-Pughscore		
• Class A	25(83.3)	
• Class B	5 (16.7)	
AFP levels		
• <400 IU/mL	11(36.7)	
• >400 IU/mL	19 (63.3)	

Factors associated with tumor response

Among the 30 patients, none achieve the CR, 10 % were PR, 73.3 % were SD, and 16.7 % were PD according to mRECIST criteria. A significant higher PR rate was observed in solitary tumors than those with multiple tumors (100% vs. 3.6 %; p=0.001). A significant higher PD rate was observed in left lobe tumors than thosein right lobe tumors (60% vs. 8%; p=0.016), and in Child-Pugh score B compared to child-pugh score A (60% vs. 8%; p=0.016). There was no difference according to age (p=0.92) or by sex (p=0.303), tumor size (p=0.082), or AFP serum level (p=0.4). The main results are summarized in TABLE 3.

TABLE 3. Tumor response of 30 patients according to mRECIST

Variables	Tumor Response n(%)			p
	Partial response	Stable disease	Progresive disease	
Sex				
• Male	2 (7.4)	20 (74.1)	5 (18.5)	0.303
• Female	1 (33.3)	2 (66.7)	0	
Age				0.920
Main tumor location				
• Right lobe	3 (12)	20 (80)	2 (8)	0.016
• Left lobe	0	2 (40)	3 (60)	
Number of tumor				
• Solitary	2 (100)	0	0	0.001
• Multiple	1 (3.6)	22 (78.6)	5 (17.8)	
Maximum tumor size				0.082
Child-Pugh score				
• Class A	3 (12)	20 (80)	2 (8)	0.016
• Class B	0	2 (40)	3 (60)	
AFP levels				
• < 400 IU/mL	2 (18.2)	8 (72.7)	1 (9.1)	0.414
• > 400 IU/mL	1 (5.2)	14 (73.7)	4 (21.1)	

DISCUSSION

Most HCC patients in this study sample were men with the age group 40-49 years. The American Cancer Society reported that the incidence of hepatoma in men is three times higher than in women in most regions of the world with the highest frequency at the age of 45-65 years.[1] Age and sex were not significantly correlated with tumor response to TACE. Men and women, both showed the same patterns of tumor response. There was no tendency for an increase in tumor response to age. Nishikawa *et al.*[11] also reported that the therapeutic response in hepatoma patients undergoing TACE is not affected by age or sex. Bryant *et al.*[12] also reported that there is no significant differences in age or gender between the favorable response and inadequate response of patients to TACE.

Tumor location was strong correlated with tumor response to TACE therapy in this study. Tumors located in the right lobe of the liver generally had a stable tumor response.In contrast, tumor located in the left lobe of the liver, had a tumor response that tends to be progressive. Previous studies reported

that tumor location is an important predictive factor for disease progression and tumor response to therapy. Miki *et al.*[7] reported that the efficacy of TACE increases in HCCs located in the peripheral zone of the right lobe and medial segment. Furthermore, the HCC located in first and fourth liver segment may weakens the complete response.[9] To explain why this location is a pejorative factor, the substantial variations of the liver vascularization (especially for the caudate segment) and the common intrahepatic collaterals and anastomosis in the center of the liver, running between right and left hepatic arteries should kept in mind.[13]

The number of tumors were correlated with tumor response to TACE therapy in this study. All patients with a single tumor showed a partial tumor response, whereas patients with multiple tumors showed a varied but generally stable tumor response. This result is proper, considering more tumors as much vascularity. In a single HCC, the interventionist can close the main arterial flow that supplies the tumor. Conversely in multinodular HCC, the interventionist generally has to choose which arterial flow will be shut and is usually selected in the most significant tumor especially if the nodules spread in both lobes.

In this study, the HCC patients generally had tumor sizes that tended to be large, with the smallest size of 6.6 cm and the largest of 19.4 cm. However, the tumor size did not correlate with tumor response to TACE therapy in this study. Previous studies reported that tumor size is a significant predictive factor in tumor response to TACE. Vessele *et al.*[9] reported that tumor size <5cm is a predictive factor for CR. Moreover, Bryant *et al.*[12] demonstrated the better response rate in the <3 cm tumor group than in the 3 to 5 cm or>5cm tumors after TACE.[12] This might explain there were none of the samples reached CR and tumor size did not show a correlation with tumor response in this study. When the tumor size is>5cm, then CR is challenging to achieve, as well as the tumor response to therapy becomes difficult to predict. Some experts agree that a large size of HCC (> 10 cm) have a worse therapeutic intervention with the possibility of more significant vascular invasion and extrahepatic spread.[14]

Child-Pugh scores were correlated with tumor response to TACE therapy in this study. HCC patients with a Child-Pugh A score showed a better tumor response compared to patients with a Child-Pugh B score. It seems that the efficacy of TACE tends to decrease with decreasing liver function. Miki *et al.*[7] also reported that the efficiency of TACE increases in patients with Child-Pugh A score.

In 2001, European Association for the Study of the Liver-European Organization for Research and Treatment of Cancer (EASL-EORTC) concluded that serum AFP levels are one of the criteria used as a reference in determining the diagnosis of HCC. In 2005, in collaboration with the American Association for the Study of Liver Diseases (AASLD), the non-invasive criteria were revised, and the evaluation of AFP serum levels removed from the diagnostic algorithm.[6] However, some experts still consider that AFP levels> 400 IU/mL are reliable marker of HCC, and as important predictive factor for prognostic therapy. In this study, AFP levels were not correlated with tumor response to TACE. Patients with AFP levels below or above 400 IU/mL did not show significant differences in tumor response. Previous study reported that the sensitivity of AFP in diagnosing hepatoma is only 54% and the prognostic value is low.[15]

Some limitations of this study were reported including starting from a small sample size and then response was observed after the first cure, while several tumors need more than one cure to reach complete response,

unusually large tumors. Finally, the lack of histological proof can lead to overestimated responses.

CONCLUSION

Tumor response to TACE varies among the HCC patients. It increases in HCC patients with solitary tumors, while the response decreases in tumors located in the left lobe and patients with Child-Pugh B scores. Clinicians should consider these results before determining the most definitive therapy for HCC patients.

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