Review Article

Lipiodol Retention Pattern After cTACE as predictor For Disease Response in HCC Lesions with Complete Response According to mRECIST in Egyptian Patients

Samar Ramzy Raghib, Mostafa Metwally Elewa and Amr Mahmoud Abd El-Samad

Department of Radiology, Faculty of Medicine, Ain Shams University, Egypt

ABSTRACT

Background: Hepatocellular carcinoma (HCC) in Egypt represents the fourth common cancer. It is the leading cause of death and morbidity-related cancer. Loco regional treatments that employ image guidance has a big role in the management of patients with HCC, cTACE (conventional trans arterial chemo embolization) is the reference treatment in HCC intermediate stage according to the BCLC (Barcelona Clinic Liver Cancer) guidelines, in which patients who are not suitable for curative treatment like ablation, surgery, or liver transplant. This enlarged the possibility of interventional radiologists in the treatment of HCC.

Objective: Investigating the differential disease response of HCCs with a CR (complete response) in the horizon of mRECIST (modified response evaluation criteria in solid tumors) after the cTACE session based on complete and incomplete lipiodol retention pattern.

Materials and Methods: In our research work, we had two groups each with 10 patients (i.e. total number of patients are 20), each group depict the two patterns of lipiodol retention (complete Vs in incomplete retention post cTACE considering mRECIST criteria with (CR) complete response) and its relation to the disease progression on following up those patients

Results: There's a relation between the lipiodol retention and the disease response regarding its course of progression or not, in cases with incomplete lipiodol retention after cTACE even if their response according to mRECIST was complete, then there was increased chance by 80 % of disease progression, another session of cTACE is recommended. compared to the other group of with complete lipiodol retention the chance of locally disease progression is 30 %

Conclusion: After the first session of cTACE, Local progression appears to be especially relevant in cases of incomplete lipiodol retention, and patients seem to require retreatment. On the other hand, patients who had complete lipiodol retention, who has subsequently a significantly lower probability of local progression, may benefit from MR imaging to detect viable tumor remains if clinically suspected.

Key Words: cTACE; egyptians; HCC; lipiodol; mRECIST criteria.

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Corresponding Author: Mostafa Metwally Elewa, Department of Radiology, Faculty of Medicine, Ain Shams University, **Tel.:** +2 010 1494 8052, **E-mail:** dr.mostafa.metwally@hotmail.com

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INTRODUCTION

Hepatocellular carcinoma (HCC) in Egypt represents the fourth common cancer.It is the leading cause of morbidity and mortality related cancer[1]. Conventional transarterial chemo embolization (cTACE) is among one of the loco regional therapies that uses image guidance techniques which has a significant role in the management of patients with HCC. The concept of cTACE in the treatment of HCC is tumor devascularization by the (lipiodol-doxorubicin) emulsion both act on the hemodynamics of the tumor preventing it from the blood supply which brings oxygen and nutrients, and this leads to tumor necrosis.

cTACE with its palliative potential is a reference treatment for patients who are intermediate stage HCC patients according to BCLC[2] and unfit for curative treatment modalities like ablation, surgical resection and liver transplantation, this highlights the role of interventional radiologists in managing HCC.

One of the imaging technique for monitoring the efficacy of cTACE is multi detector triphasic CT, through studying the enhancement (vascularity) pattern, and evaluating the presence of viable tumor, hence it is essential to determine the necessity of a subsequent treatment and to prevent superfluous treatment, the need for the follow up imaging

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post cTACE therapy for accurate response assessment is therefore important by knowing the post procedure changes and subtle signs of residual or recurrent disease.

The findings from this study is focusing on an imaging and therapeutic parameter (Lipiodol) by demonstrating that not only the presence of the lipiodol but also its pattern of deposition within the tumor on follow-up CT, which act as a prognostic indicator for the disease progression or regression (disease response) in the lesion that showed CR on mRECIST scope.

AIM OF THE WORK

Depending on the pattern of complete or incomplete lipiodol retention under study the disease response of HCCs with a CR according to mRECIST after a cTACE session may differ in this study.

MATERIAL AND METHODS

Patient selection

Egyptians, Male and females, Presence of a Hepatic focal lesion which has the radiological features of HCC and Patients with good renal functions. Past clinical history: viral hepatitis (C & B), Child Pugh classification: (A or B), BCLC recommendations regarding proper treatment (cTACE) according to BCLC staging.

The Inclusion criteria for the HCC lesions were

The presence of at least one HCC, Contrast-enhanced computed tomography (CT) is employed prior to the procedure of cTACE, throughout follow-up, and in the circumstance that up to three HCCs are present to detect the local progression of individual tumors more accurately. The following points were defined as the exclusion criteria; the presence of more than 3 HCCs lesions, a prior systemic treatment before cTACE and Infiltrative tumors and/or hypo enhancement on arterial phase are examples of hypovascular lesions that were unable to be evaluated using mRECIST criteria.

Conventional TACE procedure

The treatment of choice was always discussed with patient's tumor board for each patients including the appropriate palliative care, at which cTACE is one of them.

One senior radiologist with over five years of experience in liver interventional oncology performed each cTACE procedure under local anesthesia. The Seldinger technique was employed to achieve a right femoral approach, utilizing a 5F introducer sheath. 5F Cobra or Simmons angiographic catheters were employed to gain access to the celiac or superior mesenteric artery. Each target lesion and its vascular tributaries were visualized using digital subtraction angiography.

The chemotherapy (up to 60 mg of doxorubicin) and emulsified poppy seed oil (Lipiodol, Gerbet) were administered selectively using 2.4-2.7-F micro catheters in the procedure. Gelatin material was injected to achieve embolization. cTACE showed selectivity when administered directly into tumor feeders but lacked selectivity when not injected in this manner. The European Association for the Study of the Liver (EASL) and the European Society of Medical Oncology (ESMO) have recommended that TACE to be employed in Hepatocellular Carcinoma (HCC) that is "selectively targetable" and "accessible to supraselective catheterization. "[3].

Dynamic CT scanning protocol

Contrast-enhanced abdominal CT examinations were conducted using a 64-detector multidetector CT both before and after cTACE. A two-step acquisition was conducted in the following manner: following a scan of the abdomen without enhancement, the nonionic iodinated contrast agent was administered intravenously, with a concentration of 340 mg/mL, using a 16–18-gauge cannula. An average of 2mL/kg of contrast agent was administered through a vein in the arm at a rate of 4mL/s.No oral contrast agent was utilized. Images were captured at 35, 80, and 180 seconds after contrast injection during the arterial, portal, and late venous phases, respectively.

Each acquisition yielded 2. 5mm maximum thickness per slice.

Image interpretation and disease reaction

Regarding Baseline tumour features

XX and YY, two senior radiologists with XX and YY years of experience in liver imaging, conducted the evaluation on pre- and post-cTACE contrast-enhanced CT images. Baseline characteristics of a tumor were assessed. The images were evaluated collaboratively on a picture archiving and communication system (PACS). The listed factors were assessed and documented for every tumour that received treatment: Biggest measurement (in

millimetres); The existence of a capsule described as a smooth, consistent, the lesion's location is determined by Couinaud's liver segment categorization. It is identifiable as an enhancing border in portal or delayed phase images and is distinguished by a distinct margin that is significantly denser or more prominent than the fibrotic tissue surrounding the nodules; it is a thrombotic complication of the portal vein.

Regarding Lipiodol retention pattern on the first Follow up CT

Using pre-contrast images from post-cTACE CT, which were taken 6 weeks following treatment, the retention pattern of lipiodol was estimated. To thoroughly examine the entire tumour volume, the hepatic arterial phase CT scans that were conducted prior to cTACE were compared to the images. Complete lipiodol retention was described as the whole nodule volume appearing hyper attenuated in pre-contrast images compared to the surrounding liver tissue, with retention being either patchy or uniform if present throughout the tumour volume. If the nodule volume on post-TACE pre-contrast pictures only displayed moderate hyper attenuation, lipiodol retention was incomplete retention.

Regarding tumour response and disease progression

A tumour-by-tumour study was used to assess the tumour response. HCC lesion with a CR, or those without hyper enhanced areas on arterial phase imaging following cTACE, were the subject of the current study. The local progression of each tumour was monitored by follow-up CT after three months, which was defined as the emergence of a hyper-enhanced nodular region with washout on portal or delayed phase imaging within two cm of the treated lesion, also taking in consideration the AFP protein level. Hepatic MR imaging was carried out if there was any uncertainty about local progression especially if rising AFP is noticed. If the most recent available follow-up CT scan for a malignancy did not demonstrate any local progression, it was determined that the nodule was a persistent CR.

Regarding Statistical analysis

The collected data was then coded and entered the Statistical Package for the Social Sciences (SPSS) by IBM, version 27. The range, standard deviation, and mean were given when the quantitative data was found to be parametric. Median with inter-quartile range (IQR) was used when the data was determined to not be parametric. To further illustrate qualitative traits, percentages and numbers were also employed. For qualitative data, when the predicted count in any cell was less than 5, the Chi-square test and/or Fisher exact test were used for comparison across groups. The independent t-test was used for comparing two groups with quantitative data and parametric distribution, whereas the Mann-Whitney U test was used for groups with non-parametric distribution. Two quantitative parameters within the same group were evaluated for their association using Spearman correlation coefficients. The confidence interval was set at 95%, and the allowed margin of error was 5%. Consequently, the following was the reasoning behind the *p-value's* significance: The results are considered non-significant (NS) if the *p-value* is more than 0.05, significant (S) if the *p-value* is less than 0.05, and highly significant (HS) if the *p-value* is less than 0.01.

ETHICAL CONSIDERATION

The research had been reviewed by Research Ethics Committee (REC) at the Faculty of Medicine Ain Shams University and approved it. (Code: FMASU MS 786/2022)

RESULTS

The study was carried out over two groups, each group consists of 10 patients (total number 20) each group depict the two patterns of lipiodol retention (complete Vs incomplete retention post cTACE) and its relation to the disease progression on following up those patients.

The following Table is showing the studied patients mean age and their genders.

Table 1: Characteristics of the studied patients, most cases were males, and this reflecting the fact that prevalence of HCC in males in comparison to females.

		Total No. = 20
Age	Mean ± SD Range	56.20 ± 7.42 44 – 70
Gender	Mean ± SD Range	7 (35.0%) 13 (65.0%)

Table 2: The average size of studied HCC lesions in (mm).

		Total No. = 20
HCC (mm)	Mean ± SD Range	33.95 ± 9.06 20 – 52

Table 3: Comparison between group (I) complete lipiodol retention (C-Lip) and group (II) incomplete lipiodol retention (Ic-Lip) regarding characteristic of the studied patients.

		Group I (C-Lip)	Group II (Ic-Lip)	Test value	*P-value*	Sig.
		No. = 10	No. = 10			
Age	Mean ± SD Range	57.6 ± 8.63 48 – 70	54.8 ± 6.12 44 – 62	0.837•	0.414	NS
Gender	Female Male	2 (20.0%) 8 (80.0%)	5 (50.0%) 5 (50.0%)	1.978*	0.160	NS

P-value > 0.05: Non-significant; *P-value* < 0.05: Significant; *P-value* < 0.01: Highly significant *: Chi-square test.

The previous table showed that there was no statistically significant difference between group I (C-Lip) and group II (Ic-Lip) regarding age and gender of the studied patients with p-value = 0.414 and 0.160 respectively.

Table 4: Comparison between the lipiodol retention pattern in the two groups; group I (C -Lip) and group II (Ic-Lip) and Alpha feto protein (AFP) ng/ml levels of the studied patients before & After treatment ,regarding AFP level (ng/ml), post cTACE, AFP could be lower in cases showing complete lipiodol retention (better response).

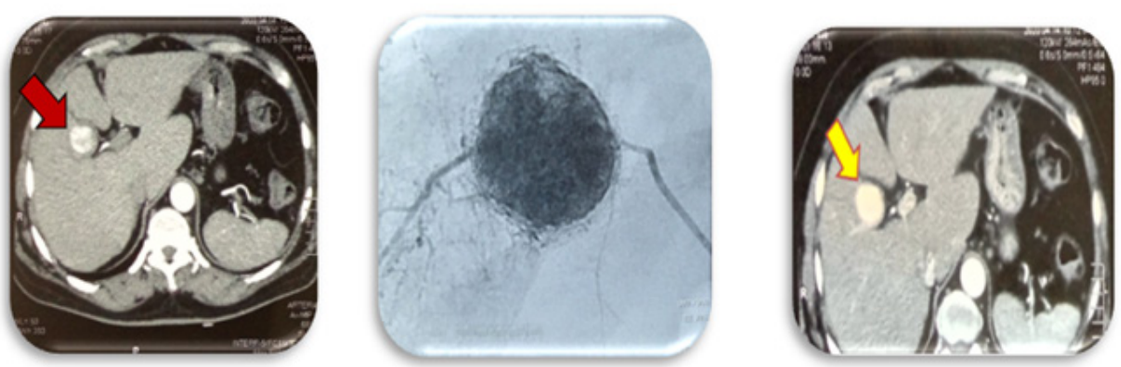
AFP Level (ng /ml)		Group I (C-Lip)	Group II (Ic-Lip)	Test value	*P-value*	Sig.
		No. = 10	No. = 10			
Before	Median (IQR) Range	42.5(17 − 200) 12 – 500	21(13 − 50) 10 – 500	-1.098≠	0.272	NS
After	Median (IQR) Range	11 (10 – 50) 6 – 80	55 (30 – 80) 15 – 400	-2.472≠	0.013	S

P-value > 0.05: Non-significant; *P-value* < 0.05: Significant; *P-value* < 0.01: Highly significant ≠: Mann-Whitney test.

Table 5: Comparison between group I (C-Lip) and group II (Ic-Lip) regarding local progression of the studied patients

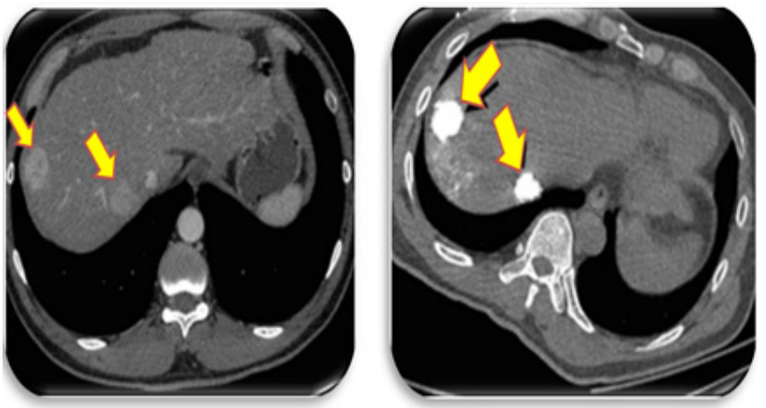
Local progression	Group I (C-Lip)	Group II (Ic-Lip)	Test value	*P-value*	Sig.
	No. = 10	No. = 10			
No	7 (70.0%)	2 (20.0%)	5.051*	0.025	S
Yes	3 (30.0%)	8 (80.0%)			

P-value > 0.05: Non-significant; *P-value* < 0.05: Significant; *P-value* < 0.01: Highly significant *: Chi-square test;



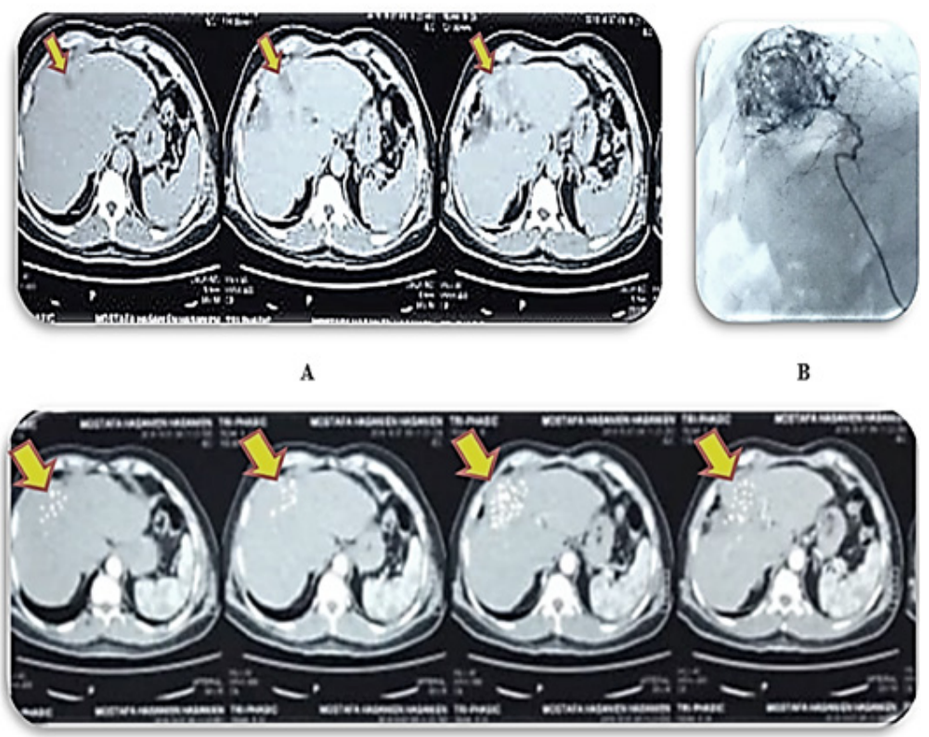
A B C

Fig. 1: A 70 years old female patient with history of HCV, BCLC classification: intermediate stage, AFP level:12 ng/ml.: A: Arterial phase enhancement of hepatic lesion focal nodule segment IV with early enhancement on the arterial phase with rapid washout of contrast characteristic of HCC (red arrow). B: Selective chemoembolization .C: Follow up triphasic CT 6 weeks after the cTACE session showed complete lipiodol retention, after another 6 weeks another Triphasic CT was done and still noted the complete lipiodol retention with no reactivation occurred within/nearby the lesion, (complete response) , after three months later another Tri phasic CT scan of the live was performed and no evidence of tumoral activation , nearby the lesion (2 cm around) .



A B

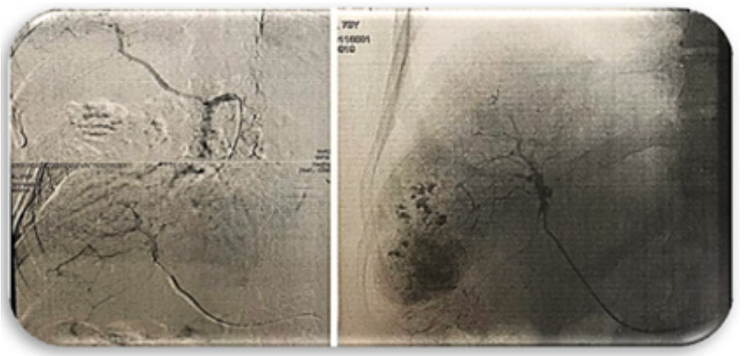
Fig. 2: A 48 years old male patient, with history of HBV, with BCLC classification intermediate stage, AFP level: 300 ng/ml, A: Triphasic CT scan of the liver characteristic feature for two HCC segments VII & VIII. B: pre contrast CT scan following cTACE showing complete lipiodol retention at both lesions, after another 6 weeks another Triphasic CT was done and still noted the complete lipiodol retention with no reactivation occurred within / nearby the lesions, (complete response), also AFP levels dropped to 100 ng/ml post cTACE compared to 300 ng/ml pre cTACE.



A B

C

Fig. 3: A 67 years old male patient, with history of HCV, BCLC classification intermediate stage, AFP level: 500 ng/ml. A: Triphasic CT scan of the liver showed arterial phase enhancement of two HCC at segments IV. B: Selective arterial chemoembolization of the right hepatic artery. C: CT triphasic of the Abdomen showed incomplete lipiodol retention within the lesion.



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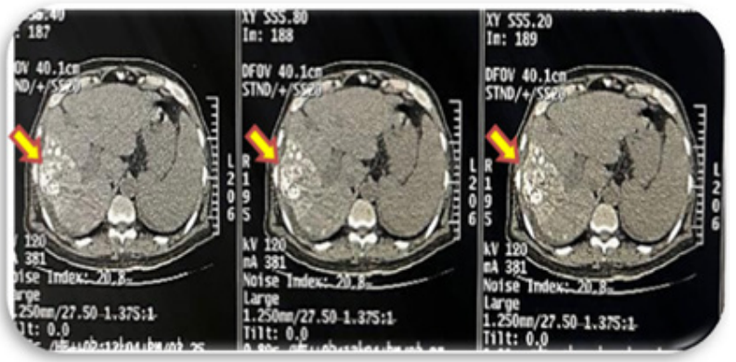

B

Fig. 4: A 66 years old, male patient, BCLC classification: intermediate stage, AFP level: 20 ng/ml. A: Selective trans arterial chemoembolization of HCC lesion segment V&VIII B: Follow up 6 weeks, triphasic CT scan of liver, showed incomplete lipiodol retention within the entire tumor volume, no tumor reactivation occurs. After another 6 weeks another= Triphasic CT was done and still noted the incomplete lipiodol retention with no tumour reactivation occurred, i.e. complete response with partial lipiodol retention. Three months later, CT triphasic was done and emergence of a hyper enhanced areas are noted within the lesion, i.e. disease progression within the lesion showing incomplete lipiodol retention, another cTACE session was planned for that patient.

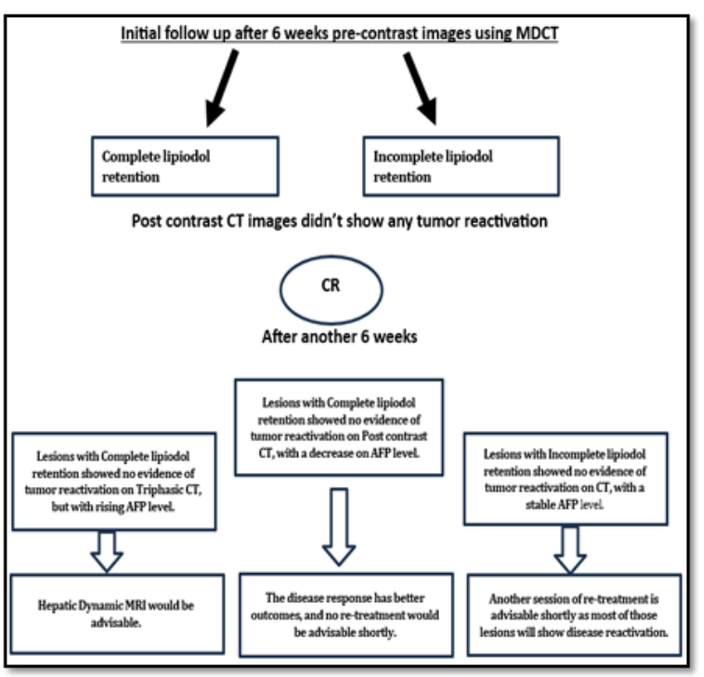

Fig. 5: Algorithm for HCC management following cTACE in case of complete response (CR) according to mRECIST.

DISCUSSION

In our study we demonstrated the follow up of HCC lesions treated by cTACE using tri-phasic CT that nearly all HCC lesions presenting with complete response (CR) according to mRECIST criteria following cTACE treatment, 80% of the cases with lesions showing inadequate retention of lipiodol exhibited disease progression (tumoral residual reactivation) on follow-up, in contrary 70 % of cases with lesions having adequate (complete) lipiodol retention, showed up no evidence of disease progression (lipiodol retention patterns have a prognostic significance following cTACE has been a subject of sveral author's studies[4-6].

Takayasu et al.[4] study showed that the retention of lipiodol was believed to be indicative of necrosis, as evidenced by the strong association between tumor necrosis on pathology and CT imaging[4]. Additionally, a study found a correlation between the heterogeneous lipiodol pattern and a higher chance of recurrence[5] Furthermore, a different study discovered that patients undergoing trans arterial chemotherapy for unresectable HCC had a better prognosis when compact lipiodol retention was present in at least 75% of the lesions., ***Kim et al.***[7] reported improved survival[7]. These findings are suggesting that not only lipiodol to be visualized in the chemo embolized lesion but also the pattern of its condensation within the lesion.

Dioguardi Burgio et al.[8] demonstrated that pathology results showed considerably greater rates of tumor necrosis in tumors that obtained a complete response according to mRECIST criteria and were able to preserve full lipiodol.

Assessment of questionable areas of enhancement on CT, MR is advantageous. The high attenuation density of the lipiodol on CT scans after chemoembolization may obscure a small, enhancing, viable tumor portion within or adjacent to the lesion due to the beam-hardening artifact[9] as the lipiodol deposition in the tumor does not affect the MR signal intensity, Gadolinium-enhanced dynamic MRI can determine areas of tumor enhancement. It is important to note that, in terms of cancer treatment, only tumors that have shown a complete response pose a challenge, Re-treatment is necessary for patients with viable sections, comparable to those with partial responses or stable illness, independent of the lipiodol retention pattern.

Incomplete lipiodol retention should be considered as an indicator of a residual active tumoral tissue, even in residual arterial hyper enhancement absence, and in that horizon, several writers suggesting that MR imaging should be utilized following TACE to evaluate tumor response rather than CT[9].

The diagnostic accuracy in a cohort of transplant patients, MR was more effective than CT (55% vs. 43%) in determining the survivability of the tumor following TACE. In fact, because lipiodol retention does not skew MR's interpretation, it is thought to be a more reliable method than CT for detecting tumor remains[10].

Nevertheless, MR imaging is more expensive, less accessible than CT, and patients may not be able to have it because of pacemakers or claustrophobia, among other contraindications.

When it comes to patient follow-up after TACE treatment, many teams still use CT, either alone or in combination with MR imaging[11,12].

CONCLUSION

Two groups with distinct prospective local outcomes should be established following the initial cTACE session for HCCs that demonstrate a complete response based on mRECIST criteria on CT scans. If lipiodol retention is incomplete, patients are at a high risk of disease progression and will likely require retreatment. Conversely, patients who have complete lipiodol retention have a substantially reduced risk of local progression and may obtain MR imaging to identify viable tumor remains if clinically indicated.

RECOMMENDATIONS

Our results imply that in the initial close follow up (6 weeks) of the patients post cTACE that showed incomplete lipiodol retention and no tumor residual tumoral enhancement could be depicted and according to modified response evaluation criteria in solid tumors (mRECIST) criteria those patients showed a complete response to the treatment, but our study demonstrated that the local progression and disease reactivation were higher in lesions with incomplete lipiodol retention even they showed initial non tumoral reactivation in the early triphasic CT follow up, and so anther cTACE would be advised for that patient to increase the lipiodol retention and so more tumoral necrosis could be resulted. On The other hands in some patients who showed complete lipiodol retention and there was a doubt about the presence of viable tumor

tissue that couldn't not be elicited on triphasic CT due to lipiodol artifact or in case of rising AFP, hence we suggest that limiting MR imaging to individuals whose tumors demonstrate both a complete lipiodol retention on post contrast CT and showing a complete response according to mRECIST.

CONFLICT OF INTERESTS

There are no conflicts of interest.

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نمط الإحتفاظ بمادة الليبيودول بعد الحقن الانغلاقى الشريانى لأورام الكبد هو مؤشر تنبؤى للإستجابة المرضية فى أورام الكبد الاولية ذات الإستجابة الكاملة طبقاً للمعايير المعدلة لتقييم اللإستجابة فى الأورام الصلبة فى المرضى المصريين

سمر رمزى راغب، مصطفى متولى عبد الستار و عمرو محمود عبد الصمد

قسم الأشعة التشخيصية و التداخلية، كلية الطب، جامعة عين شمس، القاهرة

الخلفية: يمثل سرطان الخلايا الكبدية في مصر رابع أكثر أنواع السرطان شيوعًا. وهو السبب الرئيسي للوفاة والسرطان المرتبط بالمرض. تلعب العلاجات الإقليمية المحلية التي تستخدم التوجيه بالصور دورًا كبيرًا في إدارة مرضى سرطان الخلايا الكبدية، حيث يعد cTACE (الانسداد الكيميائي التقليدي عبر الشرايين) هو العلاج المرجعي في المرحلة المتوسطة من سرطان الخلايا الكبدية وفقًا لإرشادات BCLC (عيادة برشلونة لسرطان الكبد)، حيث يتم علاج المرضى غير المناسبين للعلاج العلاجي مثل الاستئصال أو الجراحة أو زراعة الكبد. وقد أدى هذا إلى توسيع إمكانية أخصائي الأشعة التداخلية في علاج سرطان الخلايا الكبدية.

الهدف: التحقيق في الاستجابة المرضية التفاضلية لسرطان الخلايا الكبدية مع CR (استجابة كاملة) في أفق mRECIST (معايير تقييم الاستجابة المعدلة في الأورام الصلبة) بعد جلسة cTACE بناءً على نمط الاحتفاظ الكامل وغير الكامل بالليبيودول.

الطريقة: في عملنا البحثي، كان لدينا مجموعتان كل منهما تضم 10 مرضى (أي أن العدد الإجمالي للمرضى 20)، تصور كل مجموعة نمطين لاحتباس الليبيودول (الاحتفاظ الكامل مقابل الاحتفاظ غير الكامل بعد cTACE مع مراعاة المعايير mRECIST مع الاستجابة الكاملة (CR) وعلاقتها بتقدم المرض عند متابعة هؤلاء المرضى.

النتائج: هناك علاقة بين احتباس الليبيودول واستجابة المرض فيما يتعلق بمسار تقدمه أم لا، في الحالات التي تعاني من احتباس الليبيودول غير الكامل بعد cTACE حتى لو كانت استجابتهم وفقًا لـ mRECIST كاملة، كانت هناك فرصة متزايدة بنسبة ٪80 لتقدم المرض، يوصى بجلسة أخرى من cTACE. بالمقارنة مع المجموعة الأخرى التي تعاني من احتباس الليبيودول الكامل فإن فرصة تقدم المرض محليًا هي ٪30.

الاستنتاج: بعد الجلسة الأولى من cTACE، يبدو أن التقدم المحلي له أهمية خاصة في حالات احتباس الليبيودول غير الكامل، ويبدو أن المرضى يحتاجون إلى إعادة العلاج. من ناحية أخرى، قد يستفيد المرضى الذين لديهم احتباس ليبيودول كامل، والذين لديهم بعد ذلك احتمال أقل بكثير للتقدم المحلي، من التصوير بالرنين المغناطيسي للكشف عن بقايا الورم القابلة للحياة إذا كان هناك اشتباه سريري.