

## THE VALUE OF PET/CT COMBINED WITH COMPLEMENTARY MRI IN THE FOLLOW-UP OF HEPATOCELLULAR CARCINOMA AFTER TRANSARTERIAL CHEMOEMBOLIZATION

Ahmed Fathy Abdou Elhadad<sup>1</sup>, Gamal Eldin Mohamed Niazi<sup>2</sup>  
and Heba El Naggar<sup>2</sup>

### ABSTRACT:

**Background:** Hepatocellular carcinoma (HCC) is the most common primary liver malignancy and the third leading cause of cancer-related death worldwide.

**Aim of the work:** To assess the potential value of combining PET/CT and complementary MRI in the follow-up of HCC treated by trans-arterial chemoembolization (TACE).

**Patients and Methods:** This prospective study was done including forty patients having HCC treated by TACE. These patients were examined by 18F-FDG PET/CT combined with complementary MRI. PET/CT and MRI findings were analyzed. As a result, the included patients were divided into four groups: true positive, true negative, false negative and false positive. Serial alpha-fetoprotein (AFP) levels were also reviewed using serial AFP measurement as the diagnostic standard of reference.

**Results:** By combining PET/CT and MRI findings, results were true positive in 14 patients, true negative in 14 patients, false negative in 9 patients and false positive in 3 patients. Consequently, true results represented 70%; whereas false results represented 30%.

**Conclusion:** The combination of PET/CT and complementary MRI did not have any added value in the follow-up of HCC after TACE.

**Keywords:** 18F-Fluorodeoxyglucose positron emission tomography/computed tomography (18F-FDG PET/CT), Magnetic resonance imaging (MRI), Hepatocellular carcinoma (HCC), trans-arterial chemoembolization (TACE), Alpha-fetoprotein (AFP)

<sup>1</sup>Ismailia general Hospital -  
Ismailia -Ministry of health and  
<sup>2</sup>Department of Radiodiagnosis,  
Faculty of Medicine - Ain Shams  
University.

### Corresponding author:

Ahmed Fathy Abdou Elhadad  
Mobile: +2 01554902442

### E-mail:

[radiologyahmed@gmail.com](mailto:radiologyahmed@gmail.com)

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### INTRODUCTION:

Hepatocellular carcinoma (HCC) is the most common primary liver cancer. It is the sixth most common cancer worldwide, however, in Egypt, it represents the fourth most common cancer. It is considered the most common cause of mortality and morbidity-related cancer in Egypt. Its high mortality rate and short survival time make it a serious health burden<sup>(1)</sup>. Hepatic resection and liver transplantation are Surgical interventions considered the most effective treatment for HCC, however, some of HCC

patients (less than 20%) can't be treated surgically<sup>(2)</sup>.

Trans arterial chemoembolization is an interventional procedure applied to patients inoperable for HCC due to its therapeutic efficacy that has been proved by the combined action of ischemia and chemoembolization of tumor's feeding artery<sup>(2)</sup>. Despite the good results of TACE, recurrence is common. Recurrent HCCs may be controllable in the early stages. Successful

treatment is based on the early detection of any tumor re-activation so follow-up is important in order to early detect either intrahepatic re-activity (recurrence) or extrahepatic activity (metastasis)<sup>(3)</sup>.

The excellent diagnostic value of 18f-fluorodeoxyglucose positron emission tomography/computed tomography (18F-FDG PET/CT) based on its ability to detect abnormalities either metabolic or morphological makes it an important and effective tool in the assessment treatment response patient prognosis<sup>(3)</sup>. The decreased glucose metabolism of the moderate and well-differentiated HCCs presenting them as photopenic areas is an important PET/CT pitfall caused by the high activity of FDG-6-phosphatase reducing FDG accumulation in the lesion, while, high glucose metabolism of the poorly differentiated HCCs leads to increased uptake of 18F-FDG by the lesion presenting them as hot spots in PET scan<sup>(4)</sup>.

Magnetic resonance imaging (MRI) has the ability to assess specific lesion features like hyperintensity on diffusion-weighted images (DWI) and hypo intensity on T1-weighted images (T1W) allowing better diagnosis of moderate and well-differentiated HCC lesions<sup>(5)</sup>. Also, magnetic resonance imaging is preferred over computed tomography (CT) in the patients' surveillance after trans arterial chemoembolization because of the beaming artifact of lipiodol that hinders the assessment of residual tumor activity. Other advantages of MRI include its intelligible resolution differentiating post-therapy changes from residual active tumor tissue, as well as minimizing the radiation exposure and contrast agents' hazards<sup>(6)</sup>. Thus, this combination of PET/CT together with MRI can play a role in the early detection of intrahepatic tumor recurrence even with small or minimal residual viable tissues facilitating successful retreatment at an early stage which improves the outcome, prognosis and survival rate of patients. Late diagnosis makes retreatment very difficult<sup>(7)</sup>.

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### **AIM OF THE WORK:**

The current study aimed to evaluate the potential value of combining PET/CT and complementary MRI in the assessment of treatment response of HCC after trans-arterial chemoembolization.

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### **PATIENTS AND METHODS:**

From January 2022 to June 2023, forty patients were referred to the Diagnostic Radiology department, Ain Shams Hospital. Adult patients having hepatocellular carcinoma treated by TACE were included in our study. Patients with any past history of allergy to contrast agents, those with impaired renal functions (high serum creatinine >2mg/dl), uncontrolled diabetic patients who had a blood glucose level of more than 200 mg/dl at the time of the examination and patients who had any contraindication to perform MRI (having a heart pacemaker, metallic foreign body in their eye or aneurysm clip in the brain) were excluded from our study.

All included patients were examined by 18F-FDG PET/CT and complementary non-contrast enhanced MRI. These patients were subjected to full history taking and clinical examination. In addition, serial alpha-fetoprotein levels were also reviewed which was used as the diagnostic standard of reference.

### **PET/CT:**

Before performing PET/CT examination, the included patients were asked to avoid exercise or eating carbohydrates and to control their serum blood sugar. They were also asked to fast for a minimum of 6 hours before the examination. Upon arrival at the Radiology department, patient's body weight and serum blood sugar were assessed to ensure having serum blood sugar below 200 mg/dL. Then, an intravenous cannula was fixed and 1 mCi of 18F-FDG/10kg was given

to each patient 60 minutes before the examination (7–10 mCi of <sup>18</sup>F-FDG according to the patient's body weight). For these 60 minutes, the patients stayed in the waiting room and were asked to avoid cold exposure, avoid talking, and they were asked to empty bladder before the examination. The examination was acquired using an integrated PET/CT scanner (**GE Discovery IQ 5 ring PET/CT scanner, India**). Patients were imaged supine with arms placed above the head. Whole body PET/CT scan began at the level of the skull and extended downwards to the mid-thighs level. The total length of the triphasic CT coverage equals to integral number of bed positions during acquisition of the PET data.

Triphasic CT was performed with a field of view 50cm after giving patients IV contrast (Ultravist) with a dose of 1.5ml/kg (the overall dose range is 105-150ml according to patient weight). The liver was scanned in the arterial phase, portal phase, and delayed washout phase. The lesion enhancement was evaluated in each phase, and the lesions were classified according to the enhancement pattern into; hyper, hypo, iso and mixed enhanced regarding liver parenchyma.

PET was performed following the attenuation correction Triphasic CT scan without moving the patient in the same session. Approximately 6-7 bed positions were determined in the 3-D acquisition mode for scanning the entire patient in two minutes for image acquisition at each bed position. Fusion images were formed by combining the two types of data using special software producing anatomical and functional images simultaneously.

Assessment of the <sup>18</sup>F-FDG PET/CT was based on drawing region of interest (ROI) on the background liver and measuring its SUV average, then measuring the SUV max of the lesion. The lesion was considered avid ( $\pm$ ve uptake) if its SUV max was more than the SUV average of the liver background, however, it was considered not-

avid (-ve uptake) if the SUV max of the lesion was less than the liver SUV average.

#### **MRI:**

All patients were placed in supine position with arms placed above the head. The MR examination was done using two MRI scanners (Philips 1.5T MRI unit, Netherlands) and (GE 1.5T MR unit, USA) using torso-phased array coils and breath-hold technique. The following sequences were acquired; T1-weighted (T1-WI), in-phase and out-phase: (field of view: 320–400 mm; matrix: 192 × 160; slice thickness: 7.3 mm; TR: 10 msec; TE: TE = 4.6 msec for T1WI and in-phase and 2.3 msec for out-phase, receiver band-width: 64 kHz; and flip angle: 10°), **T2-weighted (T2WI) and heavy T2WI** (field of view: 320–400 mm; matrix: 192 × 160; slice thickness: 7.3 mm; TR: 1200 msec; TE: TE = 80 msec for T2WI and 130 msec for heavy-T2WI, receiver band-width: 64 kHz; and flip angle: 10°), **DWI** (matrix: 128 × 128; slice thickness: 7.3 mm; interslice gap: 2 mm; b-value = 50 and 800 s/mm<sup>2</sup>; TR: 1700-2000 msec; TE: 66-70 msec; and receiver bandwidth: 64 kHz) and **ADC map** is the graphical representation of the ratio of DW signal intensities and its measurements may discriminate between benign and malignant lesions.

The concerned morphological features including size, border and signal characteristics on T1, T2, Heavy T2, In-phase and out-phase were recorded. Moreover, the DWI images and ADC maps were interpreted and classified into two groups of lesions, either diffusion-free presented with hypo-intense signals in the DWI and hyper-intense signal in ADC or diffusion-restricted with hyper-intense signal in DWI and hypo-intense signal in ADC maps.

#### **Ethical consideration:**

The study was done after approval of ethical board of Ain Shams University (FWA 000017585). All patients were consented by informed written form.

**RESULTS:**

Forty patients were included in this study, 30 males and 10 females, their ages ranged from 45 to 81 years with a mean age 49.45±8.97.

The signal intensities of different MRI sequences included in the study were

reviewed. By accurate interpretation, we finally concluded that the functional images (DWI and ADC map) were the most significant MRI sequences for predicting viable HCC. All the other sequences revealed variable signal intensities of the different HCC lesions making them less significant for distinguishing between active and non-active tumor tissue Tables (1 & 2).

**Table 1:** Variability of the signal intensities of the different MRI sequences in both active and non-active tumor tissue.

		Tumoral activity			
		Non-active		Active	
		No.	%	No.	%
T1	Isointense signal	3	18.8%	5	20.8%
	Low signal	6	37.5%	13	54.2%
	High signal	7	43.8%	6	25.0%
T2	Isointense signal	3	18.8%	4	16.7%
	Low signal	6	37.5%	4	16.7%
	High signal	7	43.8%	16	66.7%
Heavy T2	Isointense signal	6	37.5%	12	50.0%
	Low signal	5	31.3%	0	0.0%
	High signal	5	31.3%	12	50.0%
In phase	Isointense signal	4	25.0%	6	25.0%
	Low signal	6	37.5%	13	54.2%
	High signal	6	37.5%	5	20.8%
Out phase	Isointense signal	7	43.8%	13	54.2%
	Low signal	5	31.3%	8	33.3%
	High signal	4	25.0%	3	12.5%

**Table 2:** Percentage of restricted diffusion and non-restricted diffusion in both DWI and ADC map of active and non-active tumor tissue.

		Tumoral activity			
		Non-active		Active	
		No.	%	No.	%
DWI	Non-restricted	16	100.0%	1	4.16%
	Restricted	0	0.0%	23	95.84%
ADC	Non-restricted	16	100.0%	1	4.16%
	Restricted	0	0.0%	23	95.84%

In the current study, the accuracy, sensitivity and specificity of the MRI were calculated being 97.5%, 95.8% and 100% respectively with positive predictive and negative predictive values of 100% and 94.1% respectively.

Similar values were calculated for

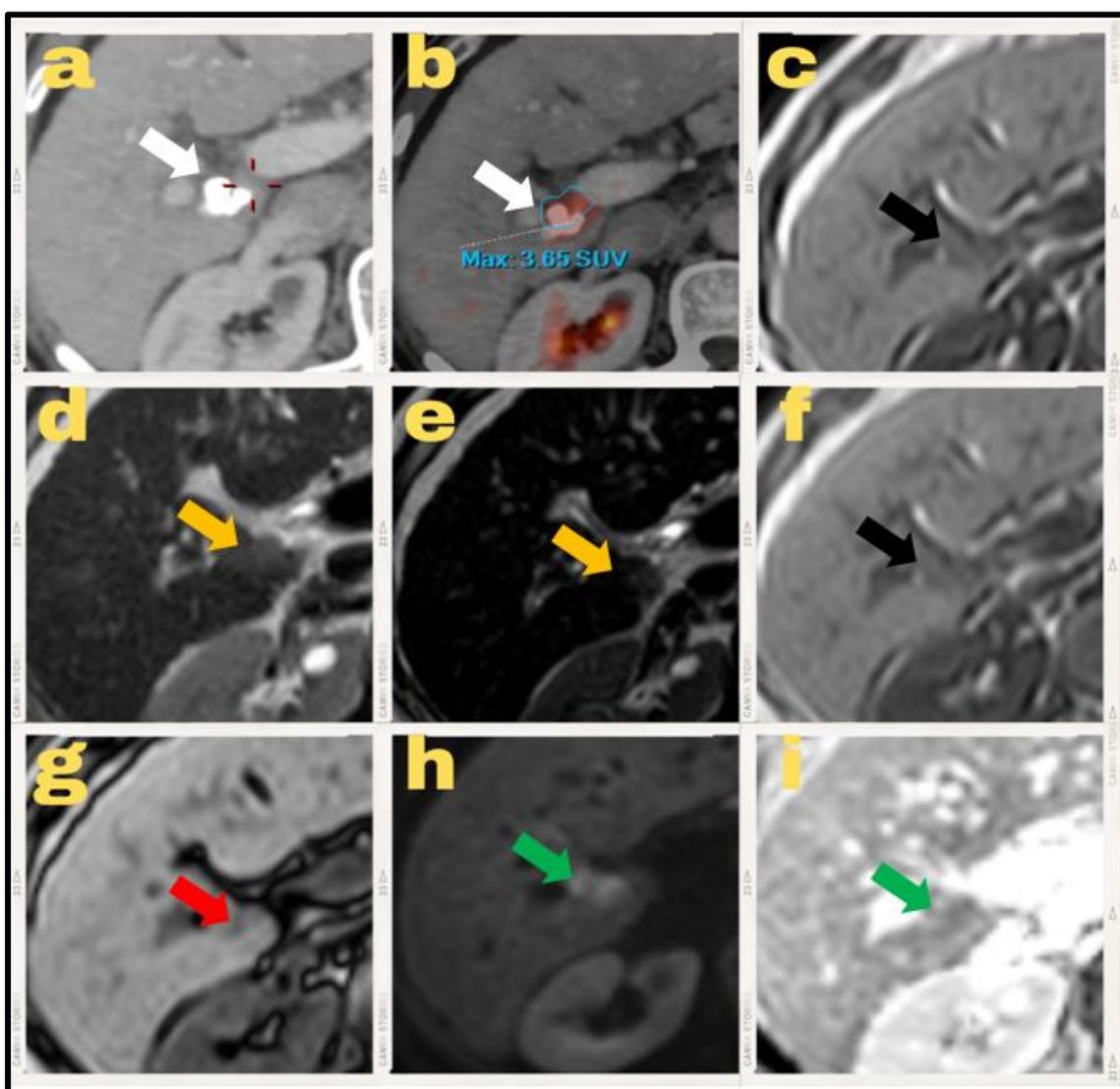
PET/CT revealing accuracy, sensitivity and specificity of 72.5%, 62.5% and 87.5% respectively with positive predictive and negative predictive values of 88.2% and 60.9% respectively.

According to the imaging results of the combination (PET/CT and complementary

*Valubility of combining PET/CT and MRI in follow up of post TACE treated HCC*

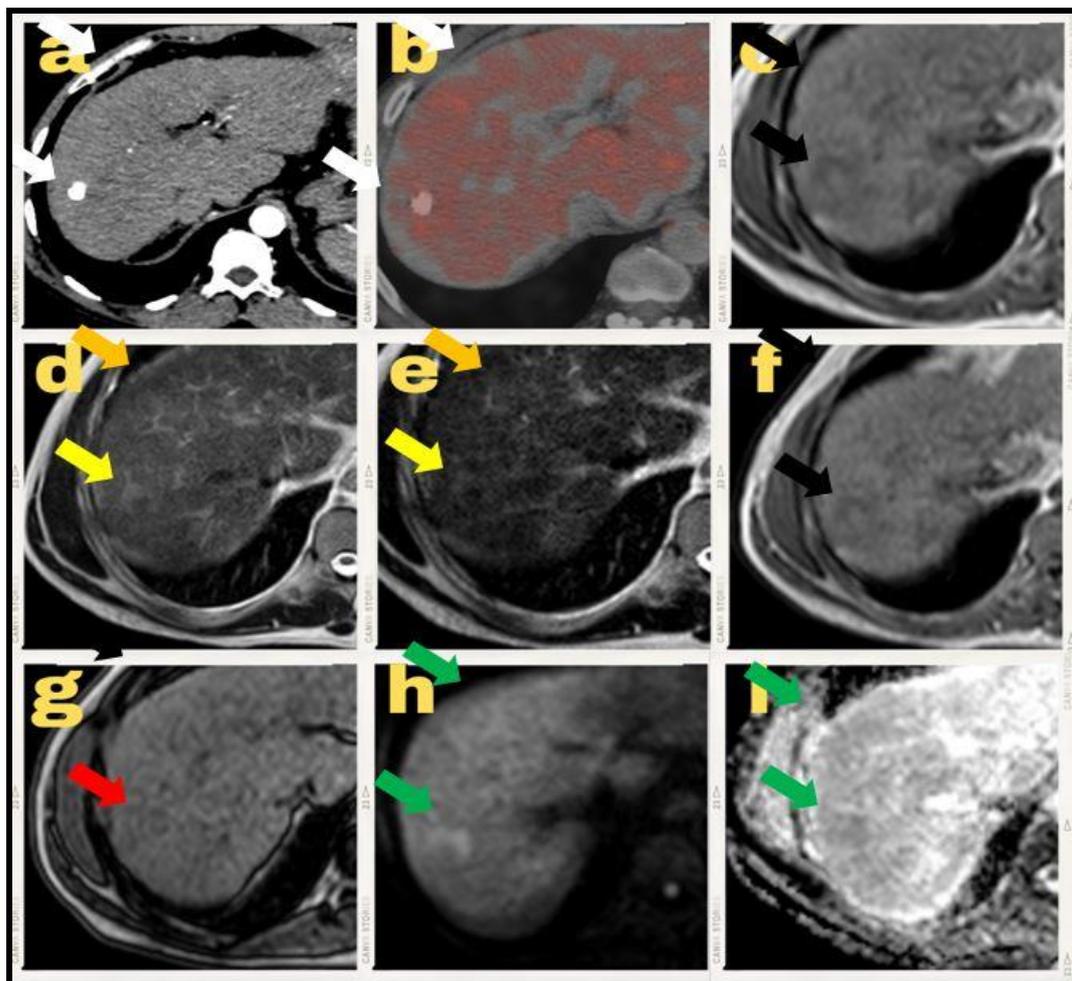
MRI) using serial AFP measurement as the diagnostic standard of reference, the patients were divided into four main groups as follows:

- **True positive** (true tumoral uptake): (+ve PET/CT and +ve MRI) 14 patients (35%).
- **True negative** (true tumoral ablation): (-ve PET/CT and -ve MRI) 14 patients (35%).
- **False negative** (false photopenic appearance of tumors with low glucose metabolism): (-ve PET/CT and +ve MRI) 9 patients (22.5%).
- **False positive** (false physiological uptake): (+ve PET/CT and -ve MRI) 3 patients (7.5%).



**Figure 1:** Sixty-three years old male patient presented with history of liver cirrhosis and hepatic focal lesion (HCC) in which TACE was done, AFP is elevated. (a) CECT shows previously chemo-embolized subsegment VI focal lesion presenting dense lipiodol particle (white arrow), (b) Axial fused PET/CT shows associated regional mild increased metabolic activity achieving up to 3.65 SUVmax (white arrows) that reflects partial residual/recurrent tumoral activity.

The other images are non-contrast enhanced MRI sequences: (c) T1WI reveals abnormal hypointense signal alteration of the previously chemo-embolized lesion (black arrow), (d) T2WI reveals abnormal hyperintense signal alteration of the chemo-embolized lesion (yellow arrow), (e) heavy T2WI also reveals hyperintense signal alteration of the lesion (yellow arrow), (f) in-phase reveals hypointense signal alteration of the lesion (black arrow), (g) out-phase reveals isointense signal of the lesion (red arrow), (h) DWI reveals increased signal intensity of the ablated and (i) ADC map reveals low signal intensity representing restricted diffusion (green arrows) denoting residual tumor activity. Thus, he was considered a true positive case.



**Figure 2:** Fifty-two years old male patient presented with a history of liver cirrhosis and hepatic focal lesion (HCC) in which TACE was done, AFP is elevated.

(a) CECT shows previously chemo-embolized subsegment VII focal lesion demonstrates lipiodol concentration with no related enhancement (white arrow), (b) axial fused PET/CT, the lesion shows no appreciable FDG uptake (white arrow) suggesting well-embolized lesion.

The other images are non-contrast enhanced MRI sequences: (c) T1WI reveals marginal crescent-shaped abnormal low signal alteration related to the periphery of the previously chemo-embolized lesion (black arrow), (d) T2WI reveals marginal crescent-shaped abnormal high signal alteration related to the periphery of the chemo-embolized lesion (yellow arrow), (e) heavy T2WI reveals also marginal high signal alteration (yellow arrow), (f) in-phase reveals marginal crescent-shaped abnormal high signal alteration related to the lesion's periphery (black arrow), (g) out-phase reveals isointense signal of the lesion (red arrow), (h) DWI reveals crescent shaped hyperintense signal and (i) ADC map reveals hypointense signal representing corresponding diffusion restriction (green arrows) denoting residual tumor activity. Thus, he was considered a false negative case.

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## DISCUSSION:

Hepatocellular carcinoma is the most common type of liver cancer and the third deadliest cancer worldwide<sup>(3)</sup>. Early detection and treatment of residual or recurrent hepatocellular carcinoma (HCC) is crucial for patient survival after locoregional interventions such as trans arterial chemoembolization (TACE). Therefore, assessing the tumor response after TACE is essential to determine whether the tumor has been completely eradicated or requires further treatment<sup>(8)</sup>.

While CT was originally the most common imaging modality for monitoring HCC patients after TACE. However, its accuracy can be limited by the following pitfalls: beam-hardening artifacts from high-attenuation lipiodol masking intra-lesional viable tumor and the significantly thinner feeding arteries of the residual tumor reducing contrast enhancement of the tumor<sup>(7)</sup>. FDG PET/CT and MRI are better than CT for detecting hepatic focal lesions<sup>(7)</sup>.

Considering PET/CT, a completely photopenic lesion suggests successful ablation after TACE, focal or nodular intense FDG uptake indicates residual tumor tissue, while a uniform low-grade FDG uptake at the lesion's periphery suggests reactive tissue changes<sup>(9&10)</sup>. It is well known that poorly differentiated HCCs show avid FDG uptake on PET due to low glucose-6-phosphatase, while well and moderately differentiated HCCs may show low FDG uptake, appearing normal on PET which considered as PET/CT pitfall<sup>(4,11,12)</sup>. Alternatively, MRI is a perfect tool overcoming this pitfall because it is sensitive to all types of HCC regardless of their differentiation. Additionally, MRI signals are not degraded by lipiodol droplets. Finally, the high resolution of MRI, especially with subtracted images can be used to distinguish post-therapy changes from residual or recurrent tumors, as well as to detect newly developed lesions<sup>(6)</sup>.

The aim of our study was to assess the value of combining PET CT and MRI in the routine follow-up of HCC patients after TACE and not a comparative study between the two modalities. We utilized serial AFP measurement as the diagnostic standard of reference to monitor the treatment response of HCC as is well-established and is recommended by several expert groups for the assessment of the treatment efficacy<sup>(13)</sup>. In the current study, the accuracy, sensitivity and specificity of the MRI were calculated being 97.5%, 95.8% and 100% respectively with positive predictive and negative predictive values of 100% and 94.1% respectively. Similarly, *Nashi et al.*,<sup>(14)</sup> found that MRI assessment of HCC patients after therapeutic interventions had a sensitivity of 90.48%, specificity of 100.0%, PPV of 100.0%, and NPV of 83.3%. Also, Lu and Pan<sup>(15)</sup> found a high pooled sensitivity (84%) and specificity (94%) for non-contrast MRI in HCC detection; while Jalli et al.<sup>(16)</sup> established that MRI had a sensitivity of 83.33%, specificity of 100.0%, accuracy 94.79%, PPV of 100.0%, and NPV of 92.96% for detection of HCC.

Similar values were calculated for PET/CT revealing accuracy, sensitivity and specificity of 72.5%, 62.5% and 87.5% respectively with positive predictive and negative predictive values of 88.2% and 60.9% respectively. Correspondingly, the study performed by *Nashi et al.*,<sup>(14)</sup> showed that PET/CT had a sensitivity of 74.60%, specificity of 57.54%, PPV of 87.5%, NPV of 90.0% as well as accuracy of 88.2% respectively in the assessment of HCC patients after therapeutic interventions. On the other hand, *Abdelrahman et al.*,<sup>(7)</sup> established that the sensitivity, specificity, and accuracy of FDG PET/CT for the detection of residual viable tumoral tissue after TACE were 81.5%, 75%, and 80% respectively, whereas *Kim et al.*,<sup>(13)</sup> reported sensitivity of 87.5%, specificity of 71.4% and accuracy of 80% respectively.

In the current study, we analyzed the

obtained MRI sequences based on AFP levels as the diagnostic standard of reference and classified the included patients into 24 patients with active tumor tissue and 16 patients with non-active tumor tissue. In addition, we concluded that functional imaging techniques such as diffusion-weighted imaging (DWI) and apparent diffusion coefficient (ADC) were the most significant MRI sequences for predicting viable HCC. The optimal ADC value obtained in our study was  $1.35 \times 10^{-3}$  mm<sup>2</sup>/s having accuracy, sensitivity and specificity of the DWI and ADC 97.5%, 95.8% and 100% respectively with positive predictive and negative predictive values of 100% and 94.1% respectively. *Nashi et al.*,<sup>(14)</sup> obtained an ADC value of  $1.25 \times 10^{-3}$  mm<sup>2</sup>/s having a sensitivity of 90.48%, specificity of 100.0%, PPV of 100.0% and NPV of 83.3%. However, *Jalli et al.*,<sup>(16)</sup> found that DWI had sensitivity of 83.33%, specificity of 100.0%, accuracy of 94.79%, PPV of 100.0%, and NPV of 92.96%. Moreover, *Min et al.*,<sup>(17)</sup> reported that the diagnostic performance of MRI with DWI was fairly high (sensitivity 94.7% and accuracy 97.5%). Similarly, *Chung et al.*,<sup>(18)</sup> showed sensitivity and specificity of 94.3% and 84.3% respectively.

Eventually, we divided the included forty patients by combining imaging results of the main PET/CT and the complementary MRI into four main groups using the serial AFP measurement as the diagnostic standard of reference. The true positive (true tumoral uptake) and negative groups (true tumoral ablation) of 70% of the included patients (14 patients for each group) showed the same results in both PET/CT and MRI. On the other hand, the false positive group included the patients who had positive PET/CT and negative MRI findings which may be due to false or abnormal physiological uptake (infection or hyperemia) was found in 3 patients. Whereas the false negative group included patients with negative PET/CT (false photopenic appearance of tumors with low glucose metabolism) and positive MRI

findings which may be explained by the previously mentioned PET/CT pitfall in which the well and moderately differentiated HCCs didn't retain much glucose and so appeared in PET/CT as the normal hepatocytes was found in 9 patients. Consequently, we accomplished that the combination of PET/CT and complementary MRI did not have any added value in the follow-up of HCC after TACE.

#### **Conclusion:**

The combination between PET/CT and complementary MRI was not of great help in the routine follow-up of HCC after TACE.

#### **Conflict of interest:**

The study didn't encounter conflict of interest.

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## الاهمية التشخيصية للتصوير الطبقي بالبوزيترون المنبعث المدمج مع الاشعة المقطعية والتصوير بالرنين المغناطيسي التكميلي في متابعة سرطان الخلايا الكبدية بعد العلاج بالحقن الشرياني

أحمد فتحي عبده الحداد<sup>1</sup> و جمال الدين محمد نيازي<sup>2</sup> و هبة النجار<sup>2</sup>

مستشفى الاسماعيلية العام – الاسماعيلية – وزارة الصحة<sup>1</sup>

قسم التشخيص الشعاعي كلية الطب - جامعة عين شمس<sup>2</sup>

سرطان الخلايا الكبدية هو أكثر أورام الكبد الأولية الخبيثة شيوعاً. يعتبر الحقن الكيميائي للورم بواسطة القسطرة الشريانية الكبدية (TACE) علاجاً راسخاً منجزاً ويستخدم على نطاق واسع في علاج سرطان الخلايا الكبدية.

على الرغم من النتائج الجيدة للحقن الشرياني فان تكرار الورم شائع لذا فان المتابعة للكشف المبكر عن هذا التكرار مهم للغاية في استراتيجية العلاج.

هدفت دراستنا الى تقييم الجمع بين التصوير الطبقي بالانبعاث البوزيتروني المدمج بالتصوير المقطعي المحوسب (PET/CT) والتصوير بالرنين المغناطيسي التكميلي (MRI) في المتابعة الروتينية للاستجابة العلاجية للأورام الكبدية بعد الحقن الشرياني وليس دراسة مقارنة بين الطريقتين. لقد استخدمنا قياس الفا فيتوبروتين التسلسلي كمعيار تشخيص مرجعي لمراقبة استجابة العلاج لسرطان الخلايا الكبدية كما هو مثبت جيداً ويوصى به من قبل العديد من المجموعات الخبيرة لتقييم فعالية العلاج.

اشتملت هذه الدراسة على 40 مريضاً (30 ذكور و 10 اناث) جميعهم لديهم تاريخ بالمعالجة الموضعية للأورام الكبدية بواسطة القسطرة الشريانية الكبدية.

في النهاية، قمنا بتقسيم الأربعين مريضاً المتضمنين إلى أربع مجموعات رئيسية، وذلك من خلال الجمع بين نتائج التصوير الطبقي بالانبعاث البوزيتروني المدمج بالتصوير المقطعي المحوسب الرئيسي والتصوير بالرنين المغناطيسي التكميلي. أظهرت النتائج ان المجموعة الإيجابية الحقيقية والمجموعات السلبية الحقيقية تمثلان 70٪ من المرضى المتضمنين (14 مريضاً لكل مجموعة) حيث أظهرت كلا المجموعتين نتائج متماثلة في كلا الفحصين.

من ناحية أخرى، شملت المجموعة الإيجابية الكاذبة المرضى الذين كانت لديهم نتائج PET/CT إيجابية ونتائج MRI سلبية، والتي قد تكون ناتجة عن امتصاص فيزيولوجي خاطئ أو غير طبيعي (عدوى أو احمرار) تم العثور عليه في 3 مرضى. بينما شملت المجموعة السلبية الكاذبة المرضى الذين كانت لديهم نتائج PET/CT سلبية (مظهر زائف للفقر الضوئي للأورام ذات التمثيل الغذائي المنخفض للسكر) ونتائج MRI إيجابية، حيث لا تحتفظ HCCs المتباعدة جيداً والمتباعدة بشكل معتدل بالكثير من الجلوكوز وبالتالي ظهرت في PET/CT على أنها الخلايا الكبدية الطبيعية تم العثور عليها في 9 مرضى.

في الختام: يمكن القول بان الدراسة انتهت الى ان الجمع بين التصوير المقطعي بالانبعاث البوزيتروني المدمج بالتصوير المقطعي المحوسب والتصوير بالرنين المغناطيسي التكميلي لم يكن مفيداً بشكل كبير في المتابعة الروتينية لسرطان الخلايا الكبدية بعد استئصال الكبد عن طريق الشريان.