Role of 18-F FDG-PET/CT in the Assessment of Extra Hepatic Metastatic Disease in Patients with Hepatocellular Carcinoma (HCC) Post Hepatic Intervention

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Abstract

Background: Hepatocellular Carcinoma (HCC) is the cause of 250,000 deaths worldwide each year. Early HCC is typically clinically silent, and the disease is often well advanced at the first manifestation.

Complete surgical resection and hepatic transplantation offer the best chance of a cure for HCC. However, surgery is often precluded by extensive disease or poor hepatic functional reserve.

Positron Emission Tomography (PET) performed with 2-[Fluorine-18] Fluoro-2-Deoxy-D-Glucose (FDG) has proved valuable in providing important tumor-related qualitative and quantitative metabolic information that is critical to diagnosis and follow-up. PET-Computed Tomography (CT) is a unique combination of the cross-sectional anatomic information provided by CT and the metabolic information provided by PET, which are acquired during a single examination and fused.

Several minimally invasive percutaneous techniques are now available to help manage localized HCC. The most used loco-regional therapy consists of imaging-guided percutaneous ethanol or thermal ablation, such as Radiofrequency Ablation (RFA) and microwave ablation, TACE, and trans-arterial radioembolization.

Many studies have indicated a greater accuracy of metastatic staging and detecting recurrent HCC by FDG-PET than by CT and other standard diagnostic modalities.

Metastatic extra hepatic lesions show focal increased FDG uptake at regional and distant lymph nodes, pulmonary nodules and bones.

Objective: The purpose of this study is to emphasis the role of combined PET/CT examination in detection of metastatic extra hepatic lesions in Hepatocellular Carcinoma (HCC) post hepatic intervention.

Patients and Methods: This is a retrospective study carried out in Alfa Scan Radiology Center from March 2013 to March 2015 for in patients pathologically proven to have HCC on top of liver cirrhosis after session or more of local therapy. A total number of 40 patients: 33 (82.50%) males and 7 (17.50%) females with a median age 57.55±6.93 (range, 42-75). The reference standard to determine the accuracy of the imaging findings is follow-up of the patient by PET/CT and other modalities and clinical data.

Results: CECT had sensitivity and specificity of 76.7%, 100% respectively with Positive Predictive Value (PPV) of 100%, Negative Predictive Value (NPV) of 58.8% and accuracy of 82.5%. PET had sensitivity and specificity of 96.7%, 100% respectively with Positive Predictive Value (PPV) of 100%, Negative Predictive Value (NPV) of 90.9% and accuracy of 97.5%.

Conclusion: FDG-PET/CT proved to be highly sensitive and specific in the assessment of hepatic bed after local therapy of HCC regardless the degree of tumor vascularity that could limit detecting residual disease based on contrast CT/MRI imaging.

Key Words: Extra hepatic metastasis – Hepatocellular Carcinoma (HCC) – PET/CT.

Introduction

HEPATOCELLULAR carcinoma is the most common primary malignant tumor of the liver. It is the fifth most common cancer in men and the eighth in women. The risk factors for HCC are well established and include viral hepatitis, alcoholic liver cirrhosis, and exposure to hepatotoxins [1].

Loco-regional therapy is an important part of the management of HCC because tumors are resectable or meet transplant criteria at the time of diagnosis in only 5-10% of patients. In addition, loco-regional therapy has the advantages of preservation of hepatic parenchyma and overall less morbidity and mortality compared with resection [2].
The most used techniques are imaging-guided percutaneous ethanol or thermal ablation, such as Radiofrequency Ablation (RFA) and microwave ablation, TACE, and trans-arterial radioembolization [3].

CT has long been a mainstay of liver and HCC imaging for both initial tumor characterization and post treatment follow-up for local tumor recurrence and extra hepatic metastatic lesions response assessment [4].

While FDG-PET provides low sensitivity for detecting primary HCC lesions, it has clinical value for identifying distant metastases. The visibility of the distant metastases may be due to relatively low background areas as compared to the normal liver. In addition, most metastatic lesions are of poorly differentiated HCC, which have higher FDG uptake, similarly FDG-PET is useful for early detection of recurrence [5,6].

Therefore, as several investigators have previously reported 18F-FDG PET might be useful for monitoring response and for being a guide in following treatment by TACE [7].

In contrast to morphological image diagnosis, FDG-PET, which evaluates viability based on glucose metabolism [8].

FDG PET/CT can be an important diagnostic method for the early detection of recurrent/metastatic disease. Metastatic disease manifests as focal, nodular, and extra zonal FDG uptake [9].

18F-FDG PET/CT has higher sensitivity as compared to CT for the detection of extra hepatic metastatic lesions of HCC after TACE seen as focal areas of increased FDG uptake [10].

Aim of the work: The purpose of this study is to emphasis the role of combined PET/CT examination in detection of metastatic extra hepatic lesions in Hepatocellular Carcinoma (HCC) post hepatic intervention.

Patients and Methods

This is a retrospective study carried out in Alfa Scan Radiology Center from March 2013 to March 2015 for in patients pathologically proven to have HCC on top of liver cirrhosis after session or more of local therapy.

A total number of 40 patients: 33 (82.50%) males and 7 (17.50%) females with a median age 57.55±6.93 (range, 42-75).

The patients were subjected to the following:

- Detailed careful history taking before doing the study especially that of previous allergy or reactions to contrast material.
- Laboratory analysis including serum creatinine and tumor marker (AFP).

Reference standard:

The reference standard to determine the accuracy of the imaging findings is follow-up of the patient by PET/CT and other modalities, clinical data, laboratory findings and previous imaging.

Patient preparation:

All patients were asked to fast for six hours prior to scan. All metallic items were removed from the patient, including, pants with zipper, etc. An I.V. cannula was inserted in the patient's arm for administration of 18F-FDG. The patients were instructed to avoid any kind of strenuous activity prior to the examination and following injection of the radioisotope to avoid physiologic muscle uptake of FDG and the patient was asked to void prior to scanning.

Protocol of PET/MDCT technique:

All exams performed using a Philips Gemini TF (Time-of-Flight) PET/CT machine equipped with LYSO crystals (Philips, Holland) and 64 slices CT, Philips Gemini GXL 16 PET/CT and Siemens Biograph mCT20 Excel PET/CT.

Examinations were performed using two MDCT scanners: 4-detectors GE Light Speed scanner (General Electric, Milwaukee, USA and 320-detector row scanner (Aquilion ONE; Toshiba Medical Systems, Otawara, Japan).

We administered one liter of negative oral contrast agent (5% mannitol) approximately one hour before and of 10-20mCi (370MBq; approximate dose to patient, 3-5MBq/Kg) 18F-FDG 45-90 minutes before examination. This period is referred to as the uptake phase and is the necessary amount of time for the FDG to be adequately bio-distributed and transported into the patient's cells. Patients were asked to rest in a quiet room, devoid of distractions, and they were also asked to keep their movements, including talking, at an absolute minimum. This minimizes physiologic uptake of FDG into skeletal muscle, which can confound interpretation of the scan. Patients should be comfortable and relaxed.

We performed low dose non enhanced CT scan first, then a whole body PET study followed by
The contrast enhanced helical CT was performed following injection of 1-2ml/Kg of a low-osmolarity iodinated contrast medium at a rate of 4mU/sec by using a power injector. After injection of intravenous contrast material, liver was scanned in arterial (scanning delay, 20-40 seconds), portal (scanning delay, 60-90 seconds), and equilibrium (scanning delay, 2-5 minutes) phases.

For a typical whole body PET-CT study (neck, chest, abdomen, and pelvis), scanning began at the level of the skull base and extended caudally to the level of the upper thighs. The total length of CT coverage was an integral number of bed positions scanned during acquisition of PET data. The study was performed with the patient breathing quietly. Typical scanning parameters would be a collimator width of 5.0mm, pitch of 1.5, gantry rotation time of 0.8 second, and field of view of 50cm. The helical data are retrospectively reconstructed at 1mm intervals.

PET was performed following the CT study without moving the patient. Approximately six to seven bed positions are planned in the three-dimensional acquisition mode for scanning the entire patient with 3-5 minute acquisition at each bed position.

Delayed PET scan was done 3h after administration of the tracer and this will be conducted whenever the result of 1st PET acquisition is inconclusive. If the 1st acquisition revealed overt pathologic uptake, then this step will omitted. The maximum standardized uptake value (SUVmax) was calculated for PET imaging of both time points, and the change in SUVmax (Retention Index, RI) was defined as the ratio of the increase in SUVmax between early and delayed scans to the SUVmax in the early stage. The whole acquisition time for an integrated PET/CT scan was approximately 25min. PET image data sets were reconstructed using CT data for attenuation correction and coregistered images were displayed using special software.

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For evaluation of liver lesions in PET, PET-positive malignant lesions are defined as lesions with visually increased 18F-FDG-accumulation in comparison to the surrounding normal liver tissue. The standardized uptake value (SUVmax) was determined measuring a spherical Volume of Interest (VOI). Benign lesions are defined in PET as lesions with no FDG accumulation either similar to the normal liver activity or less than the liver activity (photopenic).

Quantitative analysis was applied to the attenuation-corrected images by calculating the SUV of areas of abnormal FDG uptake, corrected for the injected dose of FDG and adjusted for the patient’s weight. Tumor mass was identified by areas of pathologically increased FDG uptake avoiding physiologic uptake. SUV was independently measured by using Region of Interest (ROI) drawn on the area of maximal metabolic activity.

Results

According to clinical data, laboratory findings, previous imaging and follow-up, 19 patients were categorized to have extra hepatic metastatic lesions at the intervention bed and 21 patients were categorized to be negative for extra hepatic metastasis.

A- Metastatic lymphadenopathy:

Among the 40 patients in our study all cases show regional lymphadenopathy by CT images that could be either metastatic or reactive. Based on follow-up 14 cases (35%) proved to have metastatic lymph nodes. CECT detected metastatic lymphadenopathy in 6 cases however PET detected metastatic lymphadenopathy in 14 cases.

CECT showed true positive results in 6 cases, true negative in 26 cases, false negative in 8 cases with no false positive results however PET shows true positive results in 14 cases, true negative in 26 cases with no false positive or false positive results.

On patient based analysis:

CECT had sensitivity and specificity of 42.86% and 100% respectively with Positive Predictive Value (PPV) of 100%, Negative Predictive Value (NPV) of 76.47% and accuracy of 80%.

PET had sensitivity and specificity of 100% and 100% respectively with Positive Predictive Value (PPV) of 100%, Negative Predictive Value (NPV) of 100% and accuracy of 100%.

B- Pulmonary nodules:

Among the 40 patients in our study 16 cases (40%) showed pulmonary nodules; 5 cases of them showed pathological FDG uptake and matches with metastases and 11 cases of them showed no FDG uptake. On follow-up we found that one case of
the 11 cases that previously showed no metabolic activity develops activity with increased size and number of the nodules that considered metastatic as well. Further follow-up is needed.

C- Bone deposits:
Among the 40 patients in our study, 7 (17.5%) cases showed bone deposits. CECT detected bone deposits in 5 cases however PET detected abnormal FDG within the marrow of 9 cases.

CECT showed true positive results in 5 cases, true negative in 33 cases and false negative in 2 cases with no false positive results. PET shows true positive results in 7 cases, true negative results in 31 cases, no false negative results and false positive results in 2 cases.

On patient based analysis:
CECT had sensitivity and specificity of 71.43% and 100% respectively with Positive Predictive Value (PPV) of 100%, Negative Predictive Value (NPV) of 94.29% and accuracy of 95%.

PET had sensitivity and specificity of 100% and 93.94% respectively with Positive Predictive Value (PPV) of 77.78%, Negative Predictive Value (NPV) of 100% and accuracy of 95%.

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![Fig. (1): Male patient 56 years old with left hepatic lobe (segment II) focal lesion proved to be HCC underwent TACE & RF ablation. (A, B, C): Axial PET image, axial CT image (arterial phase), axial fused PET/CT image of the liver. (D, E, F): Axial PET image, axial CT images (arterial phase), axial fused PET/CT image at lower level. Segment II shows rounded hypodense area representing the ablation zone; it shows no pathological enhancement in CT images and appears photopenic in PET images. "white arrow". Small droplet of lipidol residue seen within segment VII with no pathological enhancement or pathological FDG uptake. "yellow arrow" small segment VII sub-capsular nodule of pathological enhancement (early arterial enhancement with rapid washout) with increased FDG uptake matching with HCC. "arrow head" Enlarged hyper metabolic porto-caval and coeliac axis lymph nodes with SUVmax 3.8.](image1)

![Fig. (2): Male patient 52 years old with segment III HCC underwent TACE. (A, B, C): Axial PET image, axial CT image (arterial phase), axial fused PET/CT image of the liver. Droplets of lipidol residue are seen at segment III with adjacent ill defined focal increased FDG uptake showing SUVmax 9.4 with no detectable enhancement in CT images in keeping with local residual viable tumor tissue. "arrow" (A, B): Axial PET image of the lung, axial CT image lung window. A small pulmonary nodule is seen at the left upper lung lobe showing SUVmax 2 and measuring 7mm. "arrow head".](image2)
Fig. (3): Male patient 61 years old with right hepatic lobe (segment VII) focal lesion proved to be HCC underwent RF ablation. (A, B, C): Axial PET image, axial CT image (arterial phase), axial fused PET/CT image of the liver the anterior aspect of the ablation zone shows no FDG uptake in PET images or pathological enhancement in CT images, however the posterior aspect of the ablation zone shows irregular increased FDG uptake with SUVmax 3.7 with no definite enhancement in CT at this site. (A, B, C): Axial PET image, axial CT images, axial fused PET/CT image at the level of upper humerus. Focal increased FDG uptake by the proximal portion of right humerus showing SUVmax 3.9 with no underlying CT changes. (D, E, F): Axial PET image, axial CT images, axial fused PET/CT image at the level of the pelvis. Destructive right iliac bone lesion associated with large extra osseous soft tissue component extending to the iliacus, gluteus medius and minimus muscles with SUVmax 3.7 and heterogenous enhancement in CT images.

Chart (1): Diagnostic indices (sensitivity, specificity, PPV, NPV and accuracy) of CECT and PET in detection of metastatic lymphadenopathy.

Chart (2): Diagnostic indices (sensitivity, specificity, PPV, NPV and accuracy) of CECT & PET in detection of bone deposits.
Table (1): Demographic features of the studied group.

<table>
<thead>
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<th>Patients group (n=40)</th>
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<tr>
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<td>Mean ± SD</td>
<td>57.55±6.93</td>
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</tr>
<tr>
<td>Female</td>
<td>7 (17.50%)</td>
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<tr>
<td>Male</td>
<td>33 (82.50%)</td>
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<td>Mean ± SD</td>
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Discussion

Early detection and treatment of recurrent/metastatic HCC are keys to patient survival after hepatic surgery and interventional treatment. US, CT and MRI are generally used to assess the size or the internal structure. However, in some liver tumors, the diameter does not change \[^7\]. Cross sectional dynamic imaging including triphasic CT scan and dynamic MRI are the most widely used tools to assess patients underwent loco-regional interventional procedures for extra hepatic metastasis \[^11\].

PET/CT is unique combination of the cross-sectional anatomic information provided by CT and the metabolic information provided by PET. It has the advantage of both qualitative and quantitative assessment of the tumor and also has the advantage of examining the whole body assessing the intra and extra hepatic disease in single examination which is crucial for patient planned for hepatic transplantation \[^12\].

PET/CT currently used for follow-up after loco-regional therapies when they showed rising tumor markers with inconclusive other imaging modalities, patient with portal vein thrombosis to exclude malignant thrombus, patient planned for hepatic transplantation to exclude vascular invasion and extra hepatic metastatic disease \[^13\].

Our study demonstrated high sensitivity of PET in detection of metastatic lymphadenopathy. Sensitivity and specificity of CECT were 42.86% and 100% respectively. Positive Predictive Value (PPV), Negative Predictive Value (NPV) and accuracy of CECT were 100%, 76.47% and 80%. Sensitivity and specificity of PET were 100% and 100%. Positive Predictive Value (PPV), Negative Predictive Value (NPV) and accuracy of PET were 100%, 100% and 100%.

CECT detected metastatic lymphadenopathy based on morphological criteria in 6 cases however PET detected metastatic lymphadenopathy in 14 cases based on FDG uptake. Superiority of PET is related to its ability to detect small subcentimetric lymph nodes based on their metabolic activity.

Our study demonstrated higher sensitivity but slight lower specificity of PET than CT in detection of bone deposits. Sensitivity and specificity of CECT were: 71.43% and 100% respectively. Positive Predictive Value (PPV), Negative Predictive Value (NPV) and accuracy of CECT were: 100%, 94.29% and 95% respectively. Sensitivity and specificity of PET were: 100% and 93.94% respectively. Positive Predictive Value (PPV), Negative Predictive Value (NPV) and accuracy of PET were: 77.78%, 100% and 95% respectively.

The slight lower sensitivity of PET corresponds to false positive results in 2 cases showed areas of higher uptake seen within the anterior aspect of ribs in two cases with no underlying CT correlates likely of post traumatic etiology.

CECT detected pulmonary nodules in 16 cases, 5 cases of them showed pathological FDG uptake and matches with metastases and 11 cases of them showed no FDG uptake. On follow-up we found that one case of the 11 cases that previously showed no metabolic activity develops activity with increased size and number of the nodules that considered metastatic as well. Further follow-up is needed. Some consideration were to be taken with pulmonary nodules; suspicious nodule should considered positive even if PET is negative, if nodule less than 1cm and demonstrate any activity should be considered potentially malignant, respiratory mis-registration can decrease uptake in lung nodule near the diaphragm.

Our results are comparable to the results of (Sharma et al, \[^14\]) who studied role of 18F-FDG PET/CT in detection of extra hepatic metastases in patient with HCC in 48 patients. PET had sensitivity, specificity, PPV and NPV are 89.4%, 96.5%, 94.4% and 93.3% however those of CECT are 27.7%, 93.3%, 71.4% and 68.2%. They found that 18F-FDG PET-CT detected more lymph nodal and lung metastasis compared to conventional imaging. Although 18F-FDG PET-CT detected more lesions, the difference was not significant for bone metastasis.

Conclusion:

In conclusion, FDG-PET/CT proved to have high sensitivity and specificity in spotting extra
hepatic metastatic disease. Regarding the examination; it is crucial in disease staging particularly in candidates for liver transplantation.

We had only limitation with patients with low grade (well differentiated) tumors due to the low biological activity of such neoplasms.

However reviewing our results and in view of the literature, our study had some limitations regarding the lack of histopathological proof of many patients with disease residue/recurrence that we mainly relied on follow-up. This was also limited by the relatively short term of such retrospective study and limited number of cases in such a prevalent disease problem.

Further comparative studies with the more sensitive and specific dynamic MRI with diffusion imaging may provide added value in this context.

References
الملخص العربي

يعتبر التصوير بالبروتورنين المتبع أحد تقنيات التصوير الجزيئي الجزيئي، حيث تستخدم النظائر المشعة لتعقب وظيفة بيوثولوجية داخل الجسم ووفقا لزوج جزيئيات التتبع المستخدمة، تمكّن هذه التقنية من معرفة معلومات قيمة عن أمراض مختلفة وكثير من العمليات الفسيولوجية داخل الجسم. وبالتالي يتم الاستعانة بتقنية التصوير بالبروتورنين المتبع في تصور الأرامل مع استخدام مادة (18 F-FDG) للكشف عن الخلايا السرطانية التي تتسم بزيادة معدل أيض الجلوكر.

الجهاز الرئيسي لتصوير الأرامل عن طريق التصوير الطبي البوزيتيوني هو الغشاء الكاشف للعظام التشريحي والذين يحقق التحديث لحجم ونوعية على ذلك فإن الجلوكوز لا ينتشر فقط بالخلايا السرطانية ولكن أيضاً بمواقع الأنتهاء التشريحي.

وقد تم تحسين تقنية التصوير بالميكسيون المتبع بتقنية الأشعة المقطعية في جهاز واحد. مما ممكّن اكتشاف أمراض وأداء متغير. تتمكّن هذه تقنية الحديثة من تصور كائن للجسم مع توفير معلومات وظيفية قيمة عن المرض بالإضافة إلى التقضيات التشريحيه اللازمة. فهي تجمع بين القياسات الفسيولوجية في الكشف عن الأرامل وبين تحديد مكانها وأبعاد انتشارها بدقه بالغة. جدير بالذكر أن هذا ممكن في صور ذات تماثل وتيرة عبارة بعد قيام بعض الأشعة المقطعية بتصحيح توقع البروتورنين داخل الجسم.

سرطان الكبد يتمثل السبب الخامس للوفاة بسبب السرطان في العالم وعلى الرغم من أن التدخل الجراحي باستعمال التورم يعد أفضل طرق العلاج لكن الحالة الجراحية ليس مناسبة للكثير من الحالات وذلك بسبب سوء الوظائف الحيوية للمريض وخاصة وظائف الكبد. وأهم طرق العلاج الفجراحي هي التدخل عن طريق القسطرة وكذلك الترد الدواري.

كما أن الاكتشاف المبكر يعد ركيزة أساسية لعلاج فشل تلك المتابعة الجيدة للمرض بعد التدخل الجراحي وغير الجراحي تحصين من نسب علاج المريض وتشابه في سرعة اكتشاف نظام الورم بعد التدخل أو ارتباطه.

الفرق بين التغيرات السمية بعد التدخل الجراحي وغير الجراحي ويصاغ الورم أو ارتباطه تتم ركيزة أساسية في علاج سرطان الكبد. الأشعة السينيغنتوائية والأشعة المقطعية وكذلك الرين المغناطيسي هي أساليب التصوير تمكّنها على التغيرات الشكلية للمنطقة المصابة بينما تقنية التصوير الطبي البوزيتيوني تتمكنها بعد فحص التصوير الإلكتروني للورم وعند مراقبة الخلايا داخل الجسم وعن طريق الدم مع الأشعة المقطعية يتصفح على معلومات تشريحيووظيفية للورم.

التصوير الطبي البوزيتيوني المتبع المميز مع الأشعة المقطعية أيضاً يعتبر من أكثر فحوصات الأشعة على تحديد وجود تأسيسات للورم خارج الكبد وكذلك فهو يمنحنا تصويرا للجسم كله في فحص واحد.

تضمّنت هذه الدراسة 40 مريضاً يعانون من أورام أورام في الكبد وبسوس إبعادهم عن طريق الأشعة التشريحيه.