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Does the algorithms process of post processing in imaging PET replace liver biopsy to determine the stage of differentiation of cells in hepatocellular carcinoma (HCC)?

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Abstract

The positron emission tomography (PET) is a tool reference in routine clinical oncology. His applications has concerned the management and therapeutic monitoring, identification and definition of targets for radiotherapy, and quantification. The most frequently radiotracer's used are fluo-deoxyglucose(FDG) and Fluo-choline (18F-choline).
In addition to the functional information, PET with algorithms of post treatment could give information on the stage of cell differentiation in HCC.
The objective is to determine the stage of cell differentiation in HCC on imaging PET. We have apply the process of imaging post treatment on the image of PET Choline and PET FDG of patient whose stage of cell differentiation is known at histology.
The same result as histology were found. The volume of HCC lesions detected using 18F-FDG was slightly better than that using 18F-choline. The capacity of these two radiotracers to detect rate of fixation of HCC depend of the type of lesion.
This combination could be a new tool which can substitute the liver biopsy if there are not indicated.

Keywords: PET, Quantification, HCC, Choline, FDG

1. Introduction

The positron emission tomography (PET) is now a tool reference in routine clinical oncology [18].
Recent applications of this functional imaging concern the management and therapeutic monitoring , identification and definition of targets for radiotherapy , and quantification of Region of interest (ROI) [20,2,18,10] .
This imaging technique uses radiotracers emitting positron and the most frequently used are fluodeoxyglucose (FDG) and Fluo choline (18F-choline).
The lack of specificity of these radiotracers, makes it necessary to have a precise location of the organ and of the study area. For this , the methods of post treatment segmentation allowing better quantification regions become increasingly attractive due to progress in the development of algorithms .
Segmentation is a process to decompose the image into a plurality ROI or to extract one region in particular.
At the current state several segmentation methods of lesion uptake in PET imaging have been proposed in the literature.
The objective is to determine the stage of cell differentiation in HCC on imaging PET. We have apply the process of imaging post treatment on the image of PET Choline and PET FDG of patient whose stage of cell differentiation is known at histology.

1.1. Interest and Principle of the PET

In imaging PET the delineation of pathological uptake gives main applications:

- correction of partial volume effect [20,18];
- quantifying the activity as Standard Uptake Value (SUV) or any other quantitative parameter present on average in the lesion [2];

Clinically, segmentation routine method is operator-dependent, non-reproducible and flawed [19, 17].
The principle of fixation is based on the detection of gamma rays emitted by annihilation following the emission of a positron fixed by the radiotracer.

1.2. FDG binding mechanism

FDG enters cells in a similar way as his analog, glucose, via the glucose transporters [GLUT]. Once inside cells, both glucose and FDG are phosphorylated by hexokinase. Glucose-6-phosphate then enters the glycolytic pathway. Further metabolism of FDG-6-phosphate is blocked, however, so it is retained in the cells. Hence, cellular uptake reflects glucose metabolism. It is important to remember that glucose and FDG are competing for the same GLUT transporters, so elevated blood levels of glucose will decrease cellular uptake of FDG. In some diseases such as cancer, the hyper metabolism and the need of glucose are important, with secondary uptake of FDG.

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In a normal patient, there is high uptake in brain, variable uptake in heart, and moderate uptake in liver, trace in marrow. F-18 FDG filtered by the kidneys is not reabsorbed by the distal tubules so it remains in the urine, demonstrating activity in the renal collecting system, ureters, and bladder [12].

1.3. Choline binding mechanism

Choline (CH) is a component of base phosphatidylcholines and acetylcholine. The availability of choline has a profound impact on liver function.
After absorption from the small intestine, choline is transported to the liver and then distributed into the tissues. In the HCC there is a cell hyperactivity resulting in an increased need for choline which then binds longer and in larger amounts than usual. And its distribution can then be quantified through the positron emitter associated with it [16]

1.4. Different segmentation methods

There are thousands methods of image segmentation.
The method used depends greatly on the type of images and the intended application.

1.4.1. Automatic Segmentation via FLAB

The Fuzzy Locally Adaptive Bayesian (FLAB) is based on using a statistical measure taking into account simultaneously the two main characteristics of PET images, namely the statistical noise and blur related to the spatial resolution. It allows to achieve both segmentations: binary to 2 classes (a class to the tumor and for background) and non-binary to three classes in the case of heterogeneous attachment within the tumor (a class to the bottom and two classes for heterogeneous tumor). [9-11]

1.4.2. Thresholding variation approach

The principle is based on the minimization of energy functional on using active contour. The derivation of the criterion can be obtained either by the Eulerian derivative or by variation calculation methods. The minimization process guide the segmentation to the local minima of the energy which define the contours of the search object. [1]

1.4.3. Adaptive threshold:

An adaptive thresholding algorithm that separates the foreground from the background with non-uniform illumination.

1.4.4. Growing regions

The region is iteratively grown by comparing all neighboring pixels to the region. The difference between a pixel's intensity value and the region's mean, is used as a measure of similarity .The pixel with the smallest difference measured this way is allocated to the respective region.
This process stops when the intensity difference between region mean and new pixel become larger than a certain threshold. [15]

1.4.5. Watershed

It is based on the analogy of a topological surface filling with water. [20]

2. Materiel and Method:

We did the different PET exams with choline and FDG; and images were exported in nifti format. For opening and extraction image, ITK-Snap was used. The choice of image section was based on the slice that the fixation of the radioactive cells is the largest (fig1). The software MATLAB R2013 was used to do the histograms, the thresholding, and the segmentation by active edge and show the quantification.
All the process was done on each image and the results compared.

3. RESULTS

3.1. Process on image PET_CH

The selection of an image section were done in the slice where the fixation of the radioactive cells is the largest.

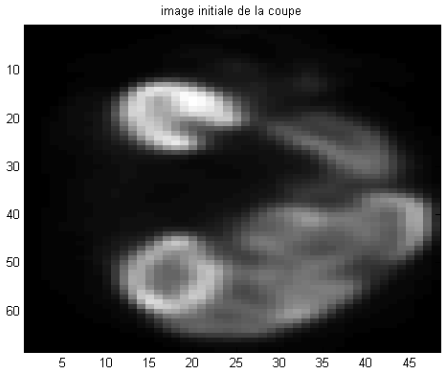

Fig 1: slice where the fixation of the Choline cells is the largest.

To see clearly these cells we use the equalization. Then we notice that in addition of the tumors we see kidneys (fig2).

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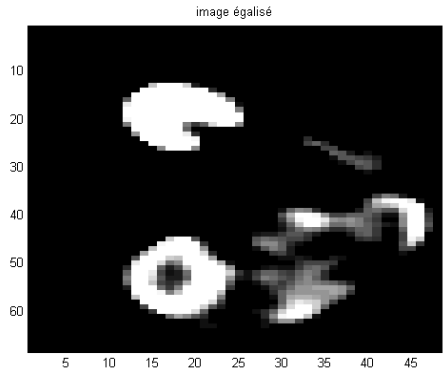

Fig 2: equalized Choline's image

To get finally only tumor region we applied thresholding, and create a mask to eliminate the kidneys from image (fig3) and use this method for all image sections to detect all the tumor volume

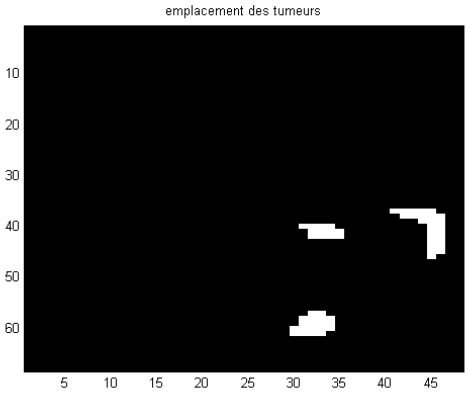

Fig 3: Tumor binding choline

3.2. PET_FDG

The same methods used on choline's image are applied for quantification of the tumor volume.

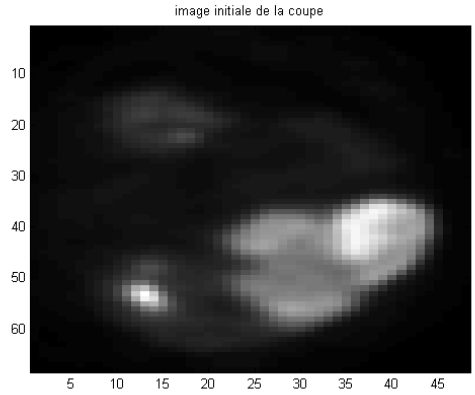

Fig 4: slice where the fixation of the FDG cells is the largest.

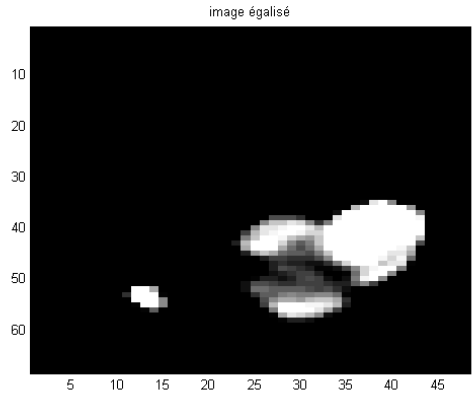

Fig 5: equalized FDG's image

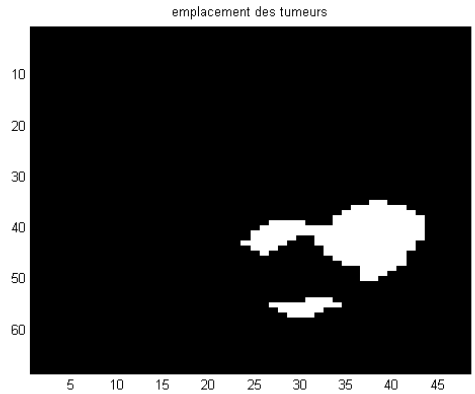

Fig 6: Tumor binding FDG

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3.3 Plot of volume quantification on 3D

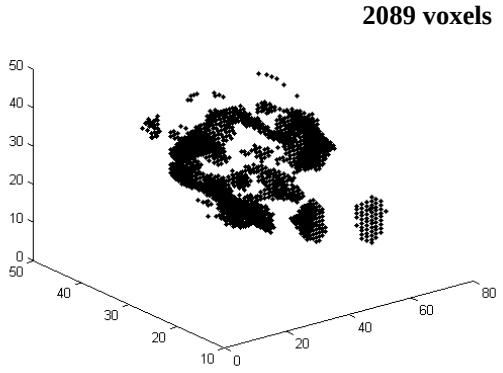

Fig 7 **Plot 3D of tumor in PET Choline:**

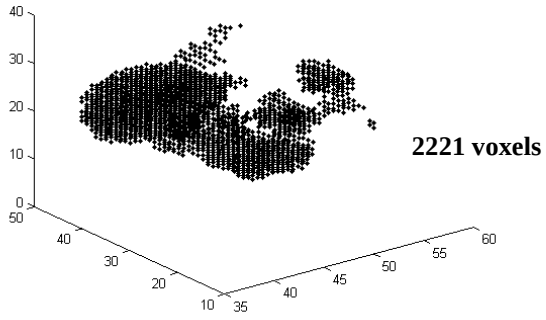

Fig 8 **Plot 3D of tumor in PET FDG:**

4. DISCUSSION

Comparing the quantity of voxels belonging to the tumor in the PET_CH and PET_FDG, for the same patient we found the tumor volume detected in CH (2089 voxels) is less than the volume in FDG (2221voxels).

Our result show that the HCC of our patient is a lesion poorly differentiated which is the same conclusion as the histological exam

In the literature, The PET-FCH is more sensitive than PET-FDG in the detection of HCC in patients with a small number of nodules, due to the differentiated nature of tumors. Conversely, the PET / FDG is more sensitive in patients with a more aggressive tumor disease. [7]

Fartoux L. al. [6] noted a better sensitivity for the detection of HCC nodules with 18F-fluorocholine (FCH) than FDG.

Lin C. et al [14] show that sensitivity and specificity of FDG PET in the detection of recurrent HCC were respectively 81.7%, and 88.9%.

In a study of Yamamoto Y [21], choline PET showed a slightly higher overall detection rate than did FDG PET for detection of HCC lesions (63% vs. 50 %,) respectively), although this difference was not statistically significant.

For Delbeke et al. [4], in particular, for detection of moderately differentiated

HCC lesions, the detection rates with choline and FDG were 75% versus 42%, respectively. FDG is a useful diagnostic method for metastatic liver tumors [4]

The detection rate appears to be dependent on tumor differentiation. The detection rate is higher for moderately differentiated HCC lesions with 18F-choline PET. It is higher for poorly differentiated HCC lesions with 18F-FDG PET. These 2 tracers may complement each other in the detection of HCC lesions. [14].The detection rate in FDG depend to the phosphorylate of glucose and it changes if the feature of cells change. Using choline or FDG for quantify the volume of tumor will depend of the histological results which can give information about the type of differentiation. But if the objective is to determine the histological type, they were used booth and using finally the appropriate segmentation.

Contour detection by analysis of the gradient of image to define an inner region and an outer region was inconclusive because the contours are blurred and difficult to identify gradients.

Conversely several studies have investigated to define metabolically active volume in PET, as for example, the watershed method.

Another approach is based on the detection of the gradient peaks to identify the contours of objects of interest [8, 9]. It has also been proposed to improve the result of adaptive thresholding by using an active contour [13].

The methodologies based on clustering voxels as Fuzzy C-Means ([FCM) were used by several studies [11, 5, 3]. Note that the original algorithm is relatively simplistic and does not take into account the spatial correlations between voxels, for example, and leads to disappointing results [11, 3] .The study proposed the most successful method based on FCM used a modified version incorporating information additional as the automatic detection of the number of classes (or clusters), the spatial correlation and analysis of voxels the heterogeneity of the tracer [3]. Our process of segmentation and quantification can be considered to robust. It will be a good alternative if the result of cell differentiation is emergency, because histological results were not available every time. It will be too a big solution in case of liver biopsy is forbidden.

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5. CONCLUSION

The difference of volume of HCC lesions detected by using 18F-FDG PET or 18F-choline PET depends of the type of cell differentiation. These 2 tracers are not concurrence but complementary. Choline is tracer of lipid metabolism or FDG is tracer of glucose metabolism. This method permitting to compare the volume of fixation of these radio tracers for determine the stage of cell differentiation will be a new solution which can substitute the liver biopsy if it is not indicated.

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