Automatic Lesion Detection for Measuring Response using Dynamic FDG-PET

Xiujuan Zheng, Guangjian Tian, Shaoli Song, Gang Huang, David Dagan Feng

Abstract: The fluorodeoxyglucose positron emission tomography (FDG-PET) has demonstrated advantages in the assessment of tumor response to therapy. The high-quality quantitative assessment usually relied on the accurate lesion detection. Hence, we aim to develop an objective method to automatically detect lesions for measuring tumor response to therapy using dynamic FDG-PET images. In our proposed method, the time-activity curves of dynamic PET images were modeled by linear subspaces with additive Gaussian noise. The matched subspace detectors coupled with unsupervised one class support vector cluster were introduced to detect the malignant lesions both in baseline and follow-up images. The physiological parameter was then estimated for each identified lesion in order to measure the tumor response to therapy. From the results, the automatic lesion detection method showed its great potential in clinical practice for facilitating tumor diagnosis and therapy assessments.

Keywords: support vector cluster, matched subspace detector, lesion detection, dynamic FDG-PET, treatment assessment.

1. INTRODUCTION

By quantitatively imaging tumor glucose metabolism and therapy-related changes, the fluorodeoxyglucose positron emission tomography (FDG-PET) has demonstrated advantages over anatomical imaging in the assessment of tumor response to therapy (Allen-Auerbach and Weber, 2009). Although conventional static PET imaging had been widely used in clinical practice, several limitations for further applications still exist. For example, standard uptake value (SUV) got from static PET images can be influenced by the acquisition time after the tracer injection, because of the character that tumors can continue uptake FDG even from a rather low blood level. Thus, acquisition time is critical for the assessment of tumor response to therapy. Different acquisition time for pre/post therapy imaging may cause varied results and lead to different treatment plans. The kinetic parameters, such as influx rate $K_i$ derived from dynamic PET images are not dependent on the acquisition time. Moreover, they can provide more valuable physiological information for guiding the oncologist to tailor the individual cancer therapy (Song et al., 2010). As a result, there is growing interest in dynamic PET imaging with quantitative assessment as a routine tool for measuring tumor response to therapy. For the quantification, a region-of-interest (ROI) is usually placed on the malignant lesion conducting by the visual inspection and diagnosis. However, such manual approach is subjective and time-consuming. Furthermore, the limited spatial resolution and low signal-to-noise ratio of PET images can influence the accuracy and reliability of the manual lesion ROI delineation, especially for small-size lesions. Based on kinetic analysis methods, the high-quality quantitative evaluation usually relied on the accurate lesion detection. Since the kinetics of tracer uptake in malignant lesions are quite different from these in normal/benign tissues (Zhuang et al., 2001), the temporal information in dynamic PET images provides additional features for improving the accuracy of lesion detection. In this condition, the motivation of our research is to develop an automatic lesion detection method for facilitating the assessment of tumor response to therapy using dynamic PET imaging.

To make full use of temporal information in dynamic PET images, the kinetic modeling method is usually adopted to characterize the FDG kinetics in FDG-PET studies. If the individual model parameters ($k_1$, $k_2$, $k_3$ and $k_4$) as well as the influx rate $K_i=k_3/(k_3+k_4)$ is estimated for the time-activity curve (TAC) at each voxel, the voxel-based parametric image can be reconstructed for guiding lesion detection and disorder diagnosis (Feng et al., 2008). Nevertheless, the voxel-based parametric image often has the poor quality for classifying the small lesions due to the high noise level in single voxel kinetic. Meanwhile, the plasma input function is required in model parameter estimations. The heavy computational burden is also a challenge for generating the parametric image voxel by voxel.

To address these issues, the matched subspace detection has been proposed to achieve lesion detection in dynamic PET images (Li et al., 2009). In this method, predefined ROIs of one primary lesion and one background region are required for subspace training. The predefined ROIs are varied for different operators and could potentially introduce the measurement errors. The incorrect predefined ROIs can directly impact the results of lesions detection and limit the matched subspace method implementing in automatic lesion detection.
detection for therapy evaluations with a sequence of dynamic PET images. Hence, we developed an improved method based on the matched subspace detector with one class support vector cluster (OCSVC) to guide automatic lesion detections in the baseline and follow-up PET images. This method was then implemented as the first step for the later quantitative assessments of tumor response to therapy.

2. METHODS

2.1 Clinical Data Acquisition

Seven lung cancer patients (4 males, 3 females) were underwent FDG-PET/CT scans before the initiation and after one day of chemotherapy with paclitaxel to acquire the baseline and follow-up FDG-PET images for the assessment of tumor response to therapy. All the patients were fasted at least 6 hours and then had blood glucose levels of <140mg/dl during the imaging. The dosage of FDG injection was 5.55 MBq per kg body weight. After CT scanning, a dynamic 30-min FDG-PET imaging was performed with the protocol: 6×5s, 6×10s, 3×20s, 5×30s, 5×60s, 6×150s, 1×300s. The spatial resolution (full width at half maximum of the line spread function) was 4.25 mm. The PET images were reconstructed with CT-based attenuation correction by ordered-subsets expectation maximization (OSEM) algorithm.

2.2 Automatic Lesion Detection

An automatic approach that adopted statistical hypothesis test to the TACs at each voxel was developed to distinguish tumors from background in baseline and follow-up PET images. We assumed that the primary lesion can be easily defined in the baseline images. The kinetic information of the primary lesion was then used to train the matched subspace detector for achieving metastatic lesions in baseline images and all the lesions in follow-up images. To avoid the measurement errors, the TACs of the voxels in the predefined primary lesion were classified to the target and noise groups by OCSVC algorithm (Ben-Hur et al., 2002, Lee, 2005). The TACs of target group were the main component, while the TACs of noise group were treated as outliers in OCSVC. The main component of OCSVC was then used as the input for estimating matched subspace detector.

In the matched subspace detector model, TACs were expressed by a combination of linear subspaces with additive Gaussian noise. The measured TAC at voxel i from a p-frame dynamic PET image is represented as a p × 1 vector \( x_i \). Lesion detection is based on a hypothesis test, in which two competing hypotheses \( H_0 \) and \( H_1 \) are tested for an input spectrum, as expressed by (1). The null hypothesis \( H_0 \) is that \( x_i \) consists of a normal TAC (background) and noise. The lesion present hypothesis \( H_1 \) is that \( x_i \) consists of a malignant tumor TAC and noise.

\[
\begin{align*}
H_0: x_i &= A\theta_i + e_{0i} \\
H_1: x_i &= B\phi_i + e_{1i}
\end{align*}
\]  

(1)

where \( p \)-vector \( x_i \) denotes the measured TAC at voxel \( i \) from dynamic PET images; \( A \) is the unknown \( p \times m \) matrix representing a basis for an \( m \)-dimensional normal subspace; \( \theta_i \) is an unknown \( m \times 1 \) vector representing the coordinates of the TAC at voxel \( i \) to \( A \); \( B \) is the unknown \( p \times q \) matrix representing a basis for an \( q \)-dimensional tumor subspace. \( \phi_i \) is an unknown \( q \times 1 \) vector representing the coordinates of the TAC at voxel \( i \) to \( B \); \( e_{0i} \sim N(0, \sigma_0^2 I) \) and \( e_{1i} \sim N(0, \sigma_1^2 I) \) represent two Gaussian noises.

Generalized likelihood ratio (GLR) test for the hypotheses in (1) can be defined by (2).

\[
l(x_i) = \frac{\max_{\theta} p_i(x_i|H_1)}{\max_{\theta} p_i(x_i|H_0)}
\]  

(2)

where \( p_i(x_i|H_0) \) and \( p_i(x_i|H_1) \) represent the class conditional probability densities of \( x_i \) given the hypotheses \( H_0 \) and \( H_1 \), respectively. They can be expressed as Gaussian probability densities \( N(\theta_i, \sigma_0^2 I) \) and \( N(B\phi_i, \sigma_1^2 I) \).

The maximum likelihood estimates of \( \theta_i \), \( \phi_i \), \( \sigma_0^2 \), and \( \sigma_1^2 \) can be described as (3).

\[
\begin{align*}
\hat{\theta}_i &= (A^TA)^{-1}A^Tx_i, \quad \hat{\sigma}_0^2 = \frac{1}{p} \|x_i - A\hat{\theta}_i\|^2 \\
\hat{\phi}_i &= (B^TB)^{-1}B^Tx_i, \quad \hat{\sigma}_1^2 = \frac{1}{p} \|x_i - B\hat{\phi}_i\|^2
\end{align*}
\]  

(3)

Substituting (3) into (2), the GLR at voxel \( i \) can be calculated by (4).

\[
l(x_i) = \frac{\max_{\theta} p_i(x_i|H_1)}{\max_{\theta} p_i(x_i|H_0)} = \left( \frac{\hat{\sigma}_0^2}{\hat{\sigma}_1^2} \right)^{\frac{p}{2}}
\]  

(4)

If the \( l(x_i) \) is larger than a given threshold \( \eta \), the hypothesis \( H_1 \) is accepted. Otherwise, the hypothesis \( H_0 \) is accepted. The linear subspace \( A \) and \( B \) can be constructed by applying principle components analysis (PCA) to the training data sets obtained by unsupervised OCSVC for predefined primary tumor region and background region. With the identified subspace \( A \) and \( B \), the GLR can be determined for every voxel in dynamic PET images. Thus, the GLR statistic maps can be generated voxel by voxel for dynamic PET images. The resulting statistic map is then thresholded to locate the primary and metastatic lesions in the baseline and follow-up PET images. The ROIs of the detected lesions were defined for the further quantitative assessment.

2.3 Assessment of Response to Therapy

The tumor TACs were acquired from the ROIs of detected lesions in baseline and follow-up PET images for each patient. Blood TAC was derived as the mean TAC of an elliptical region excluding blood pool in the left ventricle. The derived plasma input function was used to extract the image-derived plasma input function (Wahl et al., 1999). The kinetic FDG behaviour in tumor was characterized by the three-compartment four-parameter model with vascular volume, whose corresponding differential equations are given by (5).
\[
\begin{align*}
\frac{dC_e(t)}{dt} &= k_1C_p(t) - (k_2 + k_3)C_e(t) + k_4C_m(t) \\
\frac{dC_m(t)}{dt} &= k_3C_e(t) - k_4C_m(t) \\
C_i(t) &= C_e(t) + C_m(t) + V_pC_p(t)
\end{align*}
\]

where \(C_e(t)\) and \(C_m(t)\) are the TACs of FDG and FDG-6-PO₄ in the tissue, respectively; \(C_i(t)\) is the total tissue TAC; \(C_e(t)\) denotes the FDG input function in kinetic modeling; \(k_1, k_2, k_3,\) and \(k_4\) are the rate constants of the model; \(V_p\) denotes vascular volume; The influx rate \(K_i\) is calculated as \(k_1k_3/(k_2 + k_3),\) which is an important physiological parameter proportional to metabolic rate of glucose (MRGlc).

The five kinetic model parameters \((k_i, k_2, k_3, k_4, V_p)\) were estimated by non-linear least squares method for calculating \(K_i\). For each detected lesion, the individual model parameters and \(K_i\) were all calculated for the baseline and follow-up PET images, noted by ‘pre’ and ‘post’ in subscript.

3. RESULTS

3.1 Detected Lesions in Dynamic PET images

At the beginning of lesion detection, the primary tumor ROI and background ROI were roughly defined in baseline images by oncologists with the guide of CT image. The dynamic data within these predefined ROIs were processed by OCSVC and then used to train the matched subspace detectors. Fig. 1 gives an example of the predefined ROIs in baseline PET image with aligned CT image.

![Fig. 1. The definitions of primary tumor and background ROIs in baseline PET image.](image1)

After applying the automatic lesion detection approach, there were eleven malignant lesions detected from seven patients both in the baseline and follow-up images, including those lesions with activity uptake reduced significantly after chemotherapy. The identified lesions were evaluated by experienced oncologists. One example result of lesion detection is demonstrated in Fig. 2. The sub-pictures (A) and (B) shows the estimated GLR statistic maps for the slices included the primary lung tumors in the baseline and follow-up PET images. The corresponding lesions detected based on these statistic maps are given in the sub-pictures (C) and (D). In addition, the GLR statistics maps of the specific slices with metastasis liver lesions in baseline and follow-up images are illuminated in the sub-pictures (E) and (F), while the resulting ROIs of these detected lesions are depicted in the sub-pictures (G) and (H).

![Fig. 2. The demonstration of lesion detection for one patient’s FDG-PET studies pre/post chemotherapy. (A), (B), (E), (F) show the estimated GRL statistics maps. (C) and (D) show the primary lung tumor detected from the baseline and follow-up images. (G) and (H) show the metastasis lesions in liver. The contours of the detected lesion ROIs are sketched by red solid line upon the last frame of PET images for display.](image2)

3.2 Changes in Kinetic Parameters

For these eleven detected malignant lesions, the TACs were derived as the mean TACs of the automatically delineated ROIs in the baseline and follow-up PET images. Fig. 3 shows the TACs of one malignant lesion respectively derived from the baseline and follow-up PET images. For all these lesions, the kinetic parameters were estimated based on the compartment model (as expressed by (5)). The results are listed in Table 1. In the assessment of the tumor response to therapy, the kinetic parameters \((k_i, k_j)\) and influx rate were inspected by their changes.

![Fig. 3. The TACs of the detected malignant lesion in baseline and follow-up PET images.](image3)
Table 1. The estimates of parameters for each detected lesions.

<table>
<thead>
<tr>
<th>ID</th>
<th>Pre Chemotherapy</th>
<th>Post Chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( k_{1,pre} )</td>
<td>( k_{1,post} )</td>
</tr>
<tr>
<td>P1</td>
<td>0.14</td>
<td>0.28</td>
</tr>
<tr>
<td>P2</td>
<td>0.09</td>
<td>0.26</td>
</tr>
<tr>
<td>P3</td>
<td>0.31</td>
<td>0.29</td>
</tr>
<tr>
<td>P4</td>
<td>0.29</td>
<td>0.30</td>
</tr>
<tr>
<td>P5</td>
<td>0.12</td>
<td>0.16</td>
</tr>
<tr>
<td>P6</td>
<td>0.84</td>
<td>0.65</td>
</tr>
<tr>
<td>P7</td>
<td>1.24</td>
<td>1.07</td>
</tr>
<tr>
<td></td>
<td>0.34</td>
<td>0.25</td>
</tr>
<tr>
<td></td>
<td>0.12</td>
<td>0.22</td>
</tr>
<tr>
<td></td>
<td>0.02</td>
<td>0.10</td>
</tr>
<tr>
<td></td>
<td>0.13</td>
<td>0.18</td>
</tr>
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</table>

According to the results, the decreases of \( k_i \) (>8%) were observed in six lesions from four patients after chemotherapy, while the values of \( k_i \) were reduced more than 20% in seven lesions from five patients. The significant decreases (>25%) of influx rate \( K_i \) were obtained in two primary tumor lesions from two patients. Six more lesions from five patients had the decreased \( K_i \). The changes of \( K_i \) with chemotherapy for these detected lesions are depicted in Fig. 4.

![Fig. 4. The changes of influx rate \( K_i \) before and after chemotherapy. The solid circle denotes the \( K_i \) obtained from baseline images. The open circle is for the \( K_i \) derived from follow-up images after chemotherapy.](image)

### 4. DISCUSSION

In this study, we combined the features from functional imaging and kinetic modeling together for better understanding the tumor response to chemotherapy. The validation of the detected lesions in the baseline and follow-up PET images were performed based on the experiences of oncologists with the visual guidance from aligned CT images. The more objective approaches are required for fairly evaluating the proposed method. In future, the Monte Carlo simulation of a digital phantom can provide the objective ground truth for validating the lesions automatically detected by the proposed method. After applying the matched subspace detector with OCSVC to dynamic PET images, a GLR statistic map was obtained. Then, it required a threshold method to localize the lesions. The inaccurate threshold of the statistic maps could induce the false decisions in lesion detection. In this case, the simple histogram threshold approach used in this study would be improved in the future work by adopting more accurate method, such as the PCA method or random field theory.

### 6. CONCLUSIONS

We have developed an automatic lesion detection method for molecular imaging, which can be potentially used in clinical practice for measuring tumor response to therapy with minimum supervision from the initial diagnosis.

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### REFERENCES


SONG, S.-L., DENG, C., WEN, L.-F., LIU, J.-J., WANG, H., FENG, D., WONG, C.-Y. O. & HUANG, G. 2010. 18F-FDG PET/CT-related metabolic parameters and their value in early prediction of chemotherapy response in a...
VX2 tumor model. *Nuclear Medicine and Biology*, 37, 327-333.
