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I. Gardin

► **To cite this version:**

I. Gardin. Methods to delineate tumour for radiotherapy by fluorodeoxyglucose positron emission tomography. *Cancer/Radiothérapie*, 2020, 24 (5), pp.418-422. 10.1016/j.canrad.2020.04.008 . hal-02922485

**HAL Id: hal-02922485**

**<https://hal.science/hal-02922485>**

Submitted on 18 Jul 2022

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## **Methods to delineate tumour for radiotherapy by fluorodeoxyglucose positron emission tomography**

### *Méthodes de délinéation tumorale en radiothérapie par tomographie par émission de positons au fluorodésoxyglucose*

Isabelle GARDIN <sup>a\*,b</sup>

<sup>a</sup>Service de médecine nucléaire, centre Henri-Becquerel, 1, rue d'Amiens, 76000 Rouen, France

<sup>b</sup>Litis (EA 4108), université de Rouen Normandie, 685 avenue de l'Université, 76800 Saint-Étienne-du-Rouvray

Correspondance :

Tel.: 33 2 32 08 22 54

Fax: 33 2 32 08 25 50

E-mail: [isabelle.gardin@chb.unicancer.fr](mailto:isabelle.gardin@chb.unicancer.fr)

#### **Abstract**

Numerous articles have been published showing the interest to delineate tumours using fluorodeoxyglucose positron emission tomography/computed tomography images in radiotherapy planning. This imaging is used to identify tumour tissues with increased glucose metabolism compared to healthy surrounding tissues. This volume corresponds to the metabolic tumour volume. Despite extensive research on metabolic tumour volume segmentation methods, there is currently no consensus on the optimal segmentation method to use. In this review, the main methods proposed in the literature are presented, as well as their advantages and disadvantages in the context of radiotherapy.

#### **Keywords**

Delineation, FDG PET, Metabolic tumour volume

#### **Résumé**

De nombreuses publications font état de l'intérêt d'utiliser l'imagerie par tomographie par émission de positons–scanographie au fluorodésoxyglucose pour la délinéation du volume cible tumoral dans la

planification des traitements par radiothérapie. Elle est utilisée pour identifier les tissus tumoraux ayant un métabolisme glucidique accru par rapport aux tissus sains avoisinants. Ce volume correspond au volume tumoral métabolique. Malgré des recherches approfondies sur les méthodes de segmentation du volume tumoral métabolique, il n'existe pas actuellement de consensus sur la méthode optimale de segmentation à utiliser. Dans cette revue, les principales méthodes proposées dans la littérature sont présentées, ainsi que leurs avantages et inconvénients dans le contexte de la radiothérapie.

## **Mots clés**

Délimitation, TEP FDG, Volume tumoral métabolique

### **1. 1. Introduction**

Segmentation is a process of partitioning an image into a set of volumes of interest (functional, anatomical or anatomical-pathological) or extracting one, in particular. Computed tomography (CT) is the most commonly used imaging modality to define the gross tumour volume in radiotherapy. However, studies from the literature have shown the adding value of combining positron emission tomography (PET) imaging with (<sup>18</sup>F)-fluorodeoxyglucose (FDG) with CT [1]. FDG-PET is used to identify tumour tissues with increased glucose metabolism, considered as positive tissues, compared to surrounding healthy tissues. This volume corresponds to the metabolic tumour volume. For example, Ashamalla et al. reported that metabolic tumour volume defined using PET and CT images had better interobserver reproducibility in lung cancer than gross tumour volume delineated on CT alone [2]. Thus, metabolic tumour volume delineation resulted in a clinically significant change in gross tumour volume in 52% of patients.

Although many studies have shown the contribution of metabolic tumour volume measurement in predicting treatment response and tumour delineation for radiotherapy treatment planning, there is no consensus on the optimal method to delineate metabolic tumour volume in FDG-PET imaging [1,3]. This is due to the fact that there is a significant partial volume effect in PET imaging responsible for a blurry edge at the tumour. This is illustrated in Figure 1 representing a theoretical slice of a phantom with spheres of different volumes filled with the same concentration of FDG. The corresponding PET image shows that the two smallest spheres appear to contain a lower FDG concentration than the others (Figure 1b). In addition, on the plot of the standard uptake value profile passing through a sphere, it can be seen (see Figure 1.d) that the edge of the sphere is not clearly defined and that it is difficult to know exactly where it is located. This is characterized by an area of a few voxels of thickness for which it is not known whether they belong to the tumour or to healthy tissues. In addition, glucose metabolism in the vicinity of the tumour is highly dependent on its environment. In particular, it may be of the same order of magnitude than the lesion for some healthy tissues. In radiotherapy, it is not uncommon to have hypoxic or necrotic parts within the tumour characterized by

significant variations in FDG uptake complicating the segmentation task, as shown in Figure 2. All these factors, as well as the physiological movements responsible for additional blurring in the images, make the task complex.

The different metabolic tumour volume segmentation methods proposed in the literature are presented, as well as their advantages and disadvantages. Given the difficulty of solving the problem, many delineation algorithms have been proposed in the literature [1,3]. They are generally classified into three main approaches:

- the contour-based approach looking for sharp variations in intensity in the image, characterizing the presence of boundaries between regions;
- the region-based approach to locate homogeneous areas in the image, showing the presence of a region;
- the classifier-based approach, corresponding to classification of voxels aiming to define for each voxel to which region it belongs.

Since glucose metabolism differs from organ to organ, metabolic tumour volume segmentation methods first define a volume of interest, also called a volume of work. Usually this volume corresponds to a cube, defined manually, encompassing the tumour. Then the segmentation method is applied in this volume. As a result, some methods are not reproducible because they are sensitive to this volume of work.

## **2. Contour-based approaches**

### ***2.1. Threshold-based methods***

In thresholding methods, the volume of work is divided into two categories of voxels. Those with a standard uptake value above the threshold are attributed to the tumour, and those below are considered to belong to healthy tissues. The main advantage of these methods is their simplicity of use and their speed of execution. In addition, they immediately lead to the definition of a single closed contour. Several methods have been proposed in the literature to define the optimal threshold value.

#### ***2.1.1. Fixed absolute threshold***

Fixed absolute thresholds of standard uptake value have been proposed in the literature to delineate metabolic tumour volume. The commonly used value is 2.5 [4]. This value was chosen because it would correspond to a differential diagnosis between malignant and benign pulmonary nodules [5], but it does not find its justification in image processing and generally leads to a delineation very far from the truth [4].

### 2.1.2. Fixed relative threshold

Fixed relative thresholds, defined as a percentage of the maximum value of standard uptake in the tumour ( $SUV_{max}$ ), are also commonly used to delineate the metabolic tumour volume. In one of the first studies conducted on the delineation of high uptake in FDG-PET imaging, Erdi et al found, on phantom, that relative thresholds of 36 to 44% allowed the accurate measurement of the sphere volume of different sizes for different contrasts [6]. As a result, the 42% value proposed by Erdi et al. is generally used in the literature. For the sake of simplicity, some authors have rounded it down to 40%.

Other studies have shown that the use of a fixed relative threshold of 42% is appropriate when the structure is sufficiently homogeneous (in the case of a phantom), static, large and well contrasted. On the other side, it quickly reaches its limits for heterogeneous or small lesions, of low contrast or in movement [4,7]. A value of 20% was recommended for metabolic tumour volume delineation for lung tumours in the absence of respiratory gating [8]. The spreading and therefore the decrease in signal intensity caused by respiratory movements does not allow the 42% value recommended for static tumour to be used. In fact, a single threshold seems impossible given a movement of different breathing amplitude between patients, also depending on the location of the lung tumour.

### 2.1.3. Adaptive threshold

Figure 3 shows an example of curves showing the optimal threshold value to be applied depending on the sphere size and the contrast between the sphere and the background of a phantom. It can be seen that this threshold depends on these two characteristics. As a result, thresholding methods more complex than a fixed relative threshold value have been proposed in the literature to adapt the threshold to be applied on a case-by-case basis according to certain characteristics of the lesion such as its volume, global or local contrast, mean standard uptake value, etc. [6,9,10].

The principle of defining the optimal threshold to be applied, is generally divided into two distinct steps: the calibration phase of the method, then the clinical use. The calibration phase consists in defining mathematical expressions to calculate the optimal threshold from preliminary phantom studies. These expressions are then used clinically for the delineation of the lesion on patient's data. We have also shown that the calibration phase can be performed from clinical data [11].

Initial calibration of the method, followed by regular quality control, are common approaches in radiotherapy, but are not appreciated in diagnostic imaging. This partly explains the low use of these methods. In addition, the application of a threshold may exclude cold regions within heterogeneous tumour uptake, or may inadvertently include healthy tissues with a significant glucose metabolism. As a result, more advanced algorithms have been developed.

## ***2.2. Gradient-based methods***

These methods look for sharp variations in intensity in the image, characterized by strong gradients or slopes between standard uptake values of neighbouring voxels [12,13]. These methods have several major disadvantages. They are sensitive to PET image reconstruction parameters, noise and uptake heterogeneities. It is generally difficult to obtain closed contours. Therefore, they must be associated with extensive image processing that greatly determines the performances of the algorithm and the contour obtained.

## ***2.3. Active contour methods***

In order to overcome the difficulty of obtaining closed contours with gradient-based methods, approaches based on deformable models have been proposed in image processing [14]. These methods are also called active contours or "snakes". They aim at providing closed contours from the very beginning. The basic principle is to choose an initial closed contour, using for example a thresholding method, and to deform it from its initial position to an end position. Like a snake, the contour is deformed to better fit the edges of the tumour. The deformation is controlled by a function that takes into account different image characteristics.

The main disadvantage of these methods is that they remain sensitive to their initialization. Their convergence towards the final form can be slow. Active contours have been used in many image processing applications, particularly in CT imaging, by being adaptable to complex structures such as anatomical ones through the addition of deformation constraints. They seem less adapted to PET images. However, we can quote the method proposed by Abdoli et al. [15].

## **3. Region-based approaches**

### ***3.1. Seeded region growing methods***

The seeded region growing algorithms start from an initial voxel called seed, chosen within the region to be segmented and seek to make it growing by gradually aggregating voxels according to a criterion. The neighbouring voxels of the seed are successively examined and if they verify the aggregation criterion then they are included in the region and become new seeds. Otherwise, they are rejected. This iterative process is repeated until there are no more voxels that meet the aggregation criterion.

The proposed algorithms differ according to the method of definition of the initial seed (number and size of the seed, manual or automatic initialization) and the aggregation criterion (directions travelled, discriminant values). The latter are often based on a local criterion based on the homogeneity of the voxel intensity. It is generally expressed as an intensity range in which the intensity of the voxel studied must lie.

As with thresholding methods, these algorithms are fast. However, they do not take into account the hypoxic and necrotic areas within the tumour. The use of these methods for the segmentation of FDG positive tissues in PET imaging has been poorly reported in the literature. However, we can quote [16].

### **3.2. Random walk algorithms**

In this method, the user or algorithm defines several seeds in each of the regions of interest (here the lesion and surrounding healthy tissues). For each of the other voxels in the volume of work, the algorithm answers the following question: what is the probability that a random walker leaving this voxel will first reach one of the seeds of each region? The walker is also constrained, making it even more difficult for him to move in a direction corresponding to a significant gap between grey levels. Then the voxel is assigned to the most likely region [17].

We have shown that this algorithm is robust to metabolic tumour volume segmentation in lesions with very heterogeneous FDG uptake [18].

## **4. Classifier-based approaches**

Given the partial results of the previous methods, many authors have focused on approaches with a very different paradigm, based on the classification of voxels, also called pattern recognition methods. Given the very large number of methods proposed and the complexity of the algorithms, the exhaustive list of methods and their detailed description is beyond the scope of this literature review. It is possible to refer to the following articles [1,3].

The segmentation methods presented above analyse the data from a strictly image point of view since the elements are contours (cf. § 2. Contour-based approaches) or regions (cf. § 3. Region-based approaches). Here, we are interested in each voxel individually and try to determine to which region it belongs. More formally, it is a problem of classifying individuals (voxels) among a set of classes (volumes of interest). Each volume of interest is defined by characteristics. The goal is then for each voxel from the volume of work to study its own characteristics and compare them with the characteristics of volumes of interest to determine to which region it most likely belongs based on its degree of similarity. At the end of this pattern recognition process, each voxel is assigned a label corresponding to its volume of interest of belonging.

The process can be separated into four complementary axes, making the originality of the method:

- the definition of characteristic parameters of the voxel. In general, we are only interested in its intensity (here standard uptake value);

- the number of volumes of interest. In general, it is assumed that there are two volumes of interest [19,20,21], but it may be useful to define others, such as a volume of interest with voxels that are difficult to classify [22];
- the definition of the characteristic parameters of volumes of interest. In most cases, this is the mean value and variance of standard uptake values from volumes of interest;
- the construction of decision rules making it possible to define for each voxel its membership of a volume of interest according to three mechanisms: assignment, rejection and non-decision. This is the voxel labelling phase. This step is most often based on a theoretical foundation, including probability theory, fuzzy theory and belief function theory [19-22].

The principle of the methods described above does not take into account essential information when segmenting the image. Indeed, the voxels of a volume of interest are not randomly distributed in the image. On the contrary, they are connected. Several methods can be used to take this contextual information into account [20,21,22].

The advantage of these methods is that they are more robust than thresholding methods to the presence of noise and heterogeneity in the image. However, they can be slower and their diffusion in clinics remains very marginal.

## **5. Discussion and conclusion**

Many methods for segmentation of FDG PET positive tissues have been proposed in the literature. Unfortunately, there is no consensus on the most accurate and robust method.

Threshold methods are widely used because of their speed of execution, ease of use and availability on PET image processing stations and treatment planning systems. A fixed relative threshold value of 42% or 40% is often proposed. While it is interesting to use, it should be applied with great caution for small tumours, low contrasts (standard uptake value below 3), or in the presence of uptake heterogeneity within the lesion, as well as for lung locations in case of significant respiratory movement of the tumour. As a result, methods using a mathematical adjustment of the optimal threshold value have been proposed in the literature. Those based on iterative approaches to determining the optimal threshold value are preferred, as they take into account the characteristics of the patient's data. Their main disadvantage is the requirement for a calibration phase specific to each PET device and PET data reconstruction parameters.

In order to overcome these limitations, much more sophisticated methods have been proposed, mainly based on voxel classification algorithms including contextual information on the neighbourhood of voxels in the same region. Unfortunately, these methods are not widely available on PET image processing stations or on treatment planning systems.

## Conflict of interests

The author declares that she has no conflict of interests.

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**Figure legends**

**Figure 1.** Tumour delineation for radiotherapy by fluorodeoxyglucose positron emission tomography.

a) Schematic slice of a cylindrical phantom containing spheres of different diameters filled with the same concentration of fluorodeoxyglucose. b) Corresponding positron emission tomography image. c) Theoretical profile corresponding to the line in a). d) The same profile corresponding to the positron emission tomography image b).

**Figure 2.** Tumour delineation for radiotherapy by fluorodeoxyglucose positron emission tomography:

transverse thoracic PET/TDM slice showing a lesion with a very high heterogeneity of fluorodeoxyglucose uptake.

**Figure 3.** Tumour delineation for radiotherapy by fluorodeoxyglucose positron emission tomography:

example of optimal relative threshold values to be applied, as well as the corresponding calibration curves to optimize the delineation of different spheres of different volumes and five contrasts between the background and the spheres.











