A Framework using Multimodal Imaging for Longitudinal Monitoring of Patients in Neuro-oncology. Application to a SPECT/MRI study.

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Abstract— **This paper proposes a framework to assess the potential value of 99mTc Sestamibi SPECT in addition to Gadolinium-enhanced MRI for the monitoring of patients with high grade gliomas under antiangiogenic treatment. It includes: 1) multimodal and monomodal high precision registration steps achieved thanks to a registration strategy which selects the best method among several ones for each dataset, 2) tumor segmentation steps dedicated to each modality and 3) a tumor comparison step which consists in the computation of some global (volume, intensity) and local (matching and mismatching) quantitative indices to analyze the tumor using different imaging modalities and at different times during the treatment. Each step is checked via 2D and 3D visualization. This framework was applied to a database of fifteen patients. For all patients, except one, the tumor volumes decrease globally and locally. Furthermore, a high correlation (r=0.77) was observed between MRI and Sestamibi tumor volumes. Finally, local indices show some possible mismatches between MRI Gadolinium uptake and Sestamibi uptake, which need to be further investigated.**

I. Introduction

Gliomas are the most frequent primary central nervous system tumors in adults. The therapy proposed to patients depends on many factors such as the tumor location and the grade of malignancy. The possible treatments include surgery, radiotherapy, and possibly chemotherapy in case of tumor recurrences. Moreover, antiangiogenic treatments, which are supposed to reduce the neovascularization involved in the tumor growth, constitute a new promising therapy currently under investigation. As the prognosis of patients with high-grade gliomas remains poor and as new therapies may induce strong side effects, early evaluation of the tumor response to treatment is essential to select the most suitable therapy for each patient. Currently, the response assessment in neuro-oncology (RANO) criteria [1] are used. They are based on clinical indices and magnetic resonance imaging (MRI), including Gadolinium-enhanced studies and FLAIR studies. Moreover, Technetium-99m labeled Sesta-methoxyisobutyl-isonitrile (Sestamibi) is a radiopharmaceutical that accumulates in malignant gliomas. Sestamibi Single-Photon Emission Computed Tomography (SPECT) was suggested in addition to MRI [2] to monitor patients with high grade gliomas under chemotherapy, allowing the distinction between tumor recurrences and radionecrosis. In this study, a protocol was defined to evaluate the potential value of Sestamibi imaging in addition to Gadolinium (Gd) enhanced images in patients under antiangiogenic treatment.

In order to assess the tumor response to a treatment, global indices including the size of the tumor or the mean image intensity inside the tumor are generally computed. However, to go deeper into details, some methodologies which compute local indices were proposed such as differential MRI analysis [3] or the functional diffusion map in diffusion-weighted MR modality [4]. However these studies do not compare tumor information issued from different imaging modalities. That is why we propose a framework including high precision registration and tumor segmentation steps that allow us to compute global and local indices. The tumor information issued from different image modalities or/and at different times during the treatment can thus be compared.

II. Methods

Considering that multimodality imaging provides for instance anatomical and functional information, the proposed framework includes three main steps (Figure 1). First, functional and anatomical imaging modalities are aligned, and then each anatomical dataset acquired during the time course of the therapy is aligned with the first anatomical exam acquired before starting the therapy, to allow a voxel-by-voxel comparison. Then the tumor volumes are segmented for each modality on each aligned dataset. Finally, global and local indices are computed, including global volumes, mean image intensity in the volume, as well as indices related to the mismatch between the different tumor volumes. Two- and three-dimensional display modules were also defined to thoroughly check each processing step.

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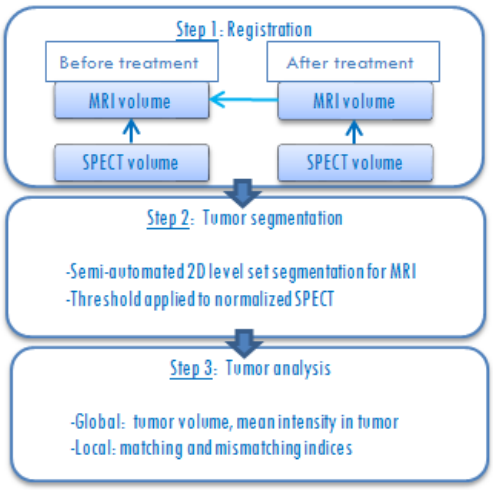

Figure 1. Flowchart of the framework. For Step 1, arrows indicate registration of datasets

A. Database

The protocol includes fifteen patients with recurrent high grade gliomas under antiangiogenic treatment. Each patient underwent one T1-weighted MRI (SignaHdxt 3T, GE) obtained after the injection of Gadolinium-DTPA and one SPECT volume (Irix, Philips) acquired 15 minutes after the injection of 99mTc Sestamibi before starting treatment. The same protocol was repeated one month later, for an early assessment of the antiangiogenic drug. The SPECT volumes were composed of 66 axial slices of isotropic voxels (2.3 mm according to each direction). The MRI volumes contained 248 axial slices with a thickness of 0.69 mm and a pixel size of 0.48x0.48 mm².

B. Registration strategy

In order to compare datasets locally, it is necessary to co-register all SPECT and MRI volumes onto the same reference volume. The "anatomical" MRI volume acquired before treatment was chosen as the reference volume. The SPECT volume before treatment and the MRI after treatment were directly registered on the MR volume before treatment. The SPECT volume after treatment was first aligned on the MRI after treatment and then the "MRI after to before treatment" transformation was applied to both volumes.

For all MRI/MRI and SPECT/MRI datasets, we use the individualized registration strategy previously described for the multimodal SPECT/MRI registration problem [5]. This strategy consists in applying several registration methods to each dataset and selecting the best one thanks to an evaluation criterion. This best result is then visually checked by an expert. For a better coherence, the evaluation criteria are not the same for the multimodal SPECT/MRI and for the monomodal registration MRI/MRI problems.

a) Registration methods

Since the registration concerned intra-patient data and the examined region was the brain, a rigid transformation (3 translations and 3 rotation angles) was chosen after adjusting volumes to identical voxel size. For the multimodal problem eighteen methods were applied. Eight were implemented in the SPM environment and were based on the maximization of Mutual information (MI), Normalized Mutual Information (NMI), Entropy Correlation Coefficient (ECC), and Normalized Cross Correlation (NCC).Ten were available in the Brainvisa environment and included MI, Correlation Ratio (CR) and Chamfer Distance (CD). For the monomodal registration problem (MRI/MRI), which appeared to be less complex, only ten methods were applied, including eight iconic algorithms and two CD algorithms. These methods differ from each other not only by the similarity criteria, but also by the transformation direction (from the first volume to the second volume or from the second volume to the first volume), and the preprocessing steps.

b) Evaluation criteria and ranking

For the SPECT/MRI registration problem, the "Uptake Criterion" (UC) previously defined [5] was retained. This criterion is based on the physiological uptake (excluding the pathological uptake) of Sestamibi. Thus, the definition of UC is based on the high uptake in the pituitary gland and the extraocular muscles, and the low uptake in the eyeballs.

To estimate this criterion, the defined structures were segmented on MRI. The eyeballs were segmented using a spherical Hough Transform (after the manual definition of a rectangular region of interest); the pituitary gland was coarsely segmented considering it as a cylinder. The extraocular muscles were segmented in 3D using an iterative forest watershed algorithm with a manual initialization of the seeds. These segmentations were then reported on the SPECT volume and UC was defined as follows:

$$UC(d,M) = \frac{\sum_{p\in V_{hu}} I(d,M,p)}{|V_{hu}|} - \frac{\sum_{p\in V_{lu}} I(d,M,p)}{|V_{lu}|} \quad (1)$$

with $UC(d,M)$ being the value of the uptake criteria for the registration of the dataset d with the method M, V_{hu} being the volume of high uptake of dataset d, V_{lu} being the volume of low uptake of dataset d and $I(d,M,p)$ being the SPECT intensity at voxel p of dataset d registered by method M. For a volume structure V, |V| denoted the number of voxels inside V.

The higher the UC value, the better the registration; thus, for each dataset d, the method which obtains the highest UC value was considered as the best one.

For the evaluation of brain MRI/MRI registration, distances between skull edges or brain edges are classically used. However, as this distance was optimized with CD approaches, we have considered that it could bias the evaluation. To get around this difficulty, we chose to define a mean Dice index, MD, computed for each of the previously segmented structures (eyeballs, pituitary gland, four extraocular muscles of the left eye and four extraoculor muscles of the right eye):

$$MD(d,M) = \frac{1}{N}\sum_{i=1}^{N} 2\,\frac{|V_{1,i}(d,M)| \cap |V_{2,i}(d,M)|}{|V_{1,i}(d,M)| + |V_{2,i}(d,M)|} \quad (2)$$

with N being the number of anatomical structures (N= 4), $V_{1,i}(d)$ being the volume of the i^{th} structure of the first MRI

of dataset d and $V_{2,i}(d, M)$, being the volume of the i^{th} structure of the second MRI of dataset d registered by method M. The higher the MD value, the better the registration. Thus the best registration was the one providing the highest MD value.

c) Visual validation by experts

For each dataset, the quality of the best registration was visually checked by an expert who attributed a quality score: excellent, correct or poor.

C. Tumor segmentation and analysis

a) Segmentation of Gd enhancement

The Gd enhancement area corresponding to the tumor was segmented on each MRI (except for one patient for which the MR after treatment was not available). An expert used a semi-automatic 2D level-set method implemented in the MIPAV software. This segmentation was then subsampled to the SPECT resolution.

b) Segmentation of Sestamibi uptake

SPECT images were first normalized by a value corresponding to the uptake in the frontal brain. This coefficient was set equal to the mean intensity within a spherical region of interest localized in the frontal lobe and avoiding physiological or tumor uptake. The tumor was segmented on SPECT exams by selecting all voxels within a region of interest including the tumor with relative intensity greater or equal to 40% of the maximal value in this region.

c) Tumor volume analysis

To compare the datasets before and after treatment (longitudinal study) or the SPECT and MRI exams at a same time (multimodal study), global indices such as volume size, mean volume intensity and relative variations in volume ($r\Delta V$) and intensity ($r\Delta I$), expressed by equations 3 and 4, are conventionally used:

$$r\Delta V(m) = \frac{|T_{t2}(m)| - |T_{t1}(m)|}{|T_{t1}(m)|} \times 100 \quad (3)$$

$$r\Delta I(m) = \frac{I_{t2}(m) - I_{t1}(m)}{I_{t1}(m)} \times 100 \quad (4)$$

with $|T_{t1}(m)|$ the tumor volume and $I_{t1}(m)$ the mean image intensity inside the tumor volume before treatment (t1) for the modality m (SPECT or MRI), and $|T_{t2}(m)|$ and $I_{t2}(m)$ the tumor volume and the mean image intensity inside the tumor volume after treatment (t2).

However such global indices do not give any information about the relative localization of volumes. Although Dice coefficient allows quantifying the matching between two volumes, it does not indicate at which distance are the mismatched areas. Thus we proposed a five level indicator, K=(k_1, k_2, k_3, k_4, k_5) which consists in classifying the voxels belonging to the union of the two tumor volumes (T_{t1} and T_{t2}) into 5 classes:

- C_1: voxels belonging to T_{t1} and distant from T_{t2} by two or more voxels;
- C_2: voxels belonging only to T_{t1} and distant from T_{t2} by more than one and less than two voxels;
- C_3: voxels belonging to T_{t1} and T_{t2};
- C_4: voxels belonging only to T_{t2} and distant from T_{t1} by more than one and less than two voxels;
- C_5: voxels belonging only to T_{t2} and distant from T_{t1} by two or more voxels.

This classification was based on the computation of the chamfer distance maps from T_{t1} and T_{t2} volumes. The number of voxels in each class was then computed and normalized by the total number of voxels of T_{t1}, leading to $k_i = \frac{|C_i|}{|T_{t1}|} \times 100$. Furthermore, the mean intensities of voxels in the different classes were also computed.

III. Results and Discussion

A. Registration

For each patient, the multimodal SPECT/MRI registration and the monomodal MRI/MRI registration were first applied using the strategy described in Section II. The effectiveness of the registration strategy in the multimodal problem was previously demonstrated [5]. Due to the higher number of registration methods, results were largely improved. For this particular database of 30 datasets, 25 registrations were judged excellent and 5 correct. For the monomodal registration, all results were excellent (13 cases) or correct (1 case). For this MRI/MRI problem, using the target registration evaluation (TRE) criterion, the iconic methods provided a TRE value lower than the MRI voxel resolution and thus were nearly equivalent. The CD based methods provided less satisfying results.

B. Tumor analysis

a) Evolution of tumor using SPECT modality

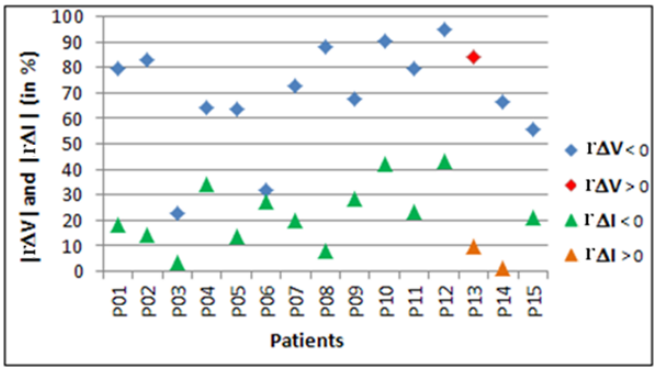

Figure 2. Relative variation of tumor volumes and intensities inside the tumors detected on SPECT datasets before and after treatment

Figure 2 shows the relative variations of volumes $r\Delta V(SPECT)$ and of intensities $r\Delta I(SPECT)$ for the whole database. The tumor volumes estimated with SPECT globally decreased ($r\Delta V < 0$ in blue color) after treatment for all patients, except for patient P013, showing a large increase ($r\Delta V > 0$ in red color). The same observations can be reported for mean intensities inside the tumor. However, these indicators are global indices and do not give spatial

information about the tumor volume modifications during the follow-up.

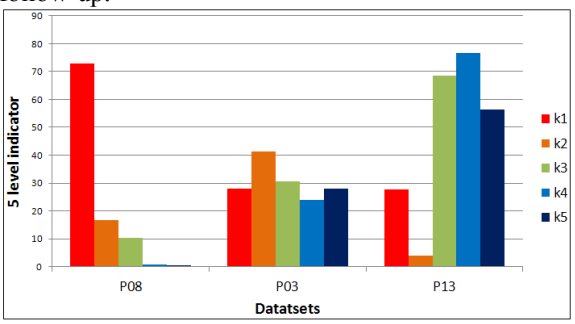

Figure 3. Relative local variation of tumor volumes estimated on SPECT before and after treatment for three typical examples

Figure 3 illustrates for three patients the five-level indicator K which compares SPECT before and after treatment. For dataset P08 and most of other cases (not represented in Figure 3), the number of voxels in the tumor before treatment and no more in the tumor after treatment (red and orange colors) is generally higher than the number of voxels present in the tumor after treatment and not present before treatment (in light and dark blue colors). This shows that the tumor volumes decreased without growing in another location. For dataset P03, Figure 3 suggests a local tumor growth (k_4+k_5 is about 50%) despite the decrease of the global tumor volume. Finally, for patient P13, there was a partial decrease of the tumor extent (k_1>25%) but a global increase of the tumor volume (k_4+k_5>120%). This result is confirmed in Figure 4.

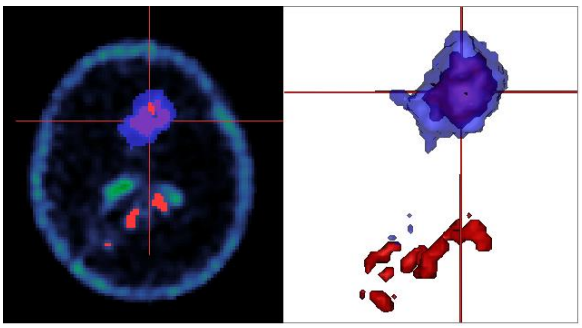

Figure 4. Example of patient P13. Left: Axial view of the SPECT before treatment with the tumor segmentations before treatment in red color and after treatment in blue color. Common areas appear in purple color. Right: 3D tumor visualization (after zoom) using the same color code.

b) Comparison between SPECT and MRI tumor volumes

The tumor volumes detected on SPECT and on MRI volumes are strongly correlated with a correlation coefficient r=0.77 and the equation y=0.72x+1.836, x being the volume (in cm^3) of the Gd enhancement in MRI and y the volume corresponding to Sestamibi uptake in SPECT. The five-level indicator shows that, in some cases, the Gd enhancement volume and the Sestamibi uptake volume do not match well (Figure 5). Indeed, in this example, the quality of the SPECT/MRI registration was visually judged as excellent, the tumor volumes have a similar size, but 31% of the voxels of the MRI tumor volume were at a distance of more than 2 voxels from the SPECT tumor volume and 47% of the SPECT tumor voxels were at a distance of more than 2 voxels from the MRI tumor volume. This is illustrated by the 3D view of the tumor volumes. Thus Sestamibi uptake and Gd enhancement may provide slightly different local information.

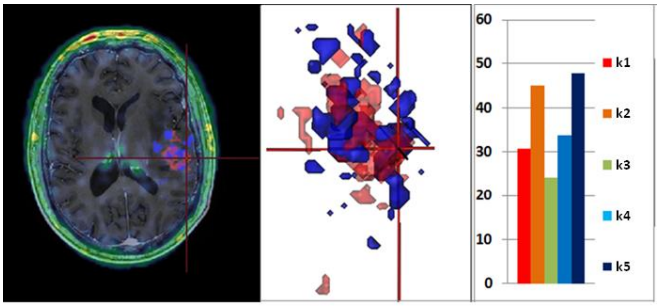

Figure 5. Example of patient P01 after treatment. Left: Axial view of the fusion of aligned MRI/SPECT images with the segmentation of the MR tumor in red color and the sestamibi tumor in blue color. Middle: 3D SPECT and MRI tumor visualization using the same color code. Right: five classes indicator with T_{t1} corresponding to tumor delineated on MRI and T_{t2} to the tumor delineated on SPECT.

IV. Conclusion

A new framework was proposed to quantitatively assess the potential value of 99mTc Sestamibi SPECT in addition to Gd enhanced MRI for the monitoring of patients with high grade gliomas under antiangiogenic treatment. This framework includes high precision registration and segmentation steps which allow us to compute global indices (tumor volumes, image intensity inside tumors) and local indices. We apply this approach to a clinical database, including fifteen patients who underwent MRI and SPECT exams before and one month after treatment. Results showed that tumor volumes decrease for all patients, except one. In addition, local indices show in most cases that the residual SPECT tumor volumes were inside the initial SPECT tumor volumes. Furthermore, global indices showed a good correlation between SPECT and MRI tumor volumes while local indices suggested a possible mismatch between Sestamibi uptake and Gd enhancement. This framework is thus a contributive tool to assess the potential value of radiotracers in nuclear medicine in addition to MRI for the monitoring of patients with tumors.

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