Nonrigid image registration, PET, Radiotherapy treatment planning, Head and neck cancer.

INTRODUCTION

Head and neck cancer treatment planning with PET

Improved availability of functional imaging such as positron emission tomography (PET) and the limitations of morphological computed tomography (CT) and magnetic resonance imaging (MRI) have generated increased interest in the role of PET in the management of head and neck cancer. In particular, the additional metabolic information about the primary tumor and lymph nodes may be useful when planning radiotherapy treatment (1–3).

Ideally patients would have virtual simulation performed on a dedicated PET/CT scanner for treatment planning. The main advantage is that both PET and CT images are acquired sequentially during a single imaging session, which minimizes patient movement and provides inherently registered images, unless there is obvious patient movement. Although a small number of centers may have this facility (4, 5), in practice it is

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likely that separate PET/CT and treatment planning CT will remain more common for the majority of patients for whom PET imaging is an option (2, 6). Even when a PET/CT system is used to acquire the treatment-planning CT, image registration may still be required (1).

A number of methods have been applied to the problem of head and neck PET to planning CT image registration, including the use of fiducial markers (1, 6) and registration via the transmission PET (7, 8). Most applications have involved either manual–interactive registration (2, 9) or automatic rigid registration (8), whereas Schwartz et al. applied a nonrigid algorithm (10, 11). However, when a PET/CT system is used, the availability of the CT acquired during the same imaging session as the PET provides the opportunity to improve the registration accuracy of PET to radiotherapy planning CT. In this article, automatic methods, including intensity-based nonrigid algorithms, are used to first register the attenuation correction CT to treatment planning CT. Then, because PET is assumed to be “hardware” registered to the attenuation correction CT, the derived CT to CT image transformation is applied directly to the PET to provide the necessary PET to planning CT registration.

For the functional data to be used in head and neck treatment planning, it is necessary to estimate the accuracy of the PET/CT to treatment planning CT image registration and to assess the impact of nonrigid deformations (8, 9). Therefore, the first original contribution of our study was to quantify the accuracy of both rigid and nonrigid image registration of CT acquired during a PET imaging session to CT acquired for radiotherapy treatment planning.

Patient setup

When PET is used for radiotherapy target volume delineation, Goerres et al. (12) proposed that patients should be positioned in the exact treatment position. However, this requires custom-made immobilization to be available early enough for the PET/CT to be acquired before the start of patient treatment. Because of the significant costs and logistical problems involved, it is unlikely that many patients would undergo both a staging and dedicated treatment planning PET/CT as part of their routine patient management. Furthermore, significant differences can occur between a staging and treatment planning PET (13). Therefore, a decision must be made as to the most useful timing of PET/CT imaging in the patient pathway (Table 1). When PET/CT is used early in the diagnostic and staging phase of patient management, nodal involvement can be established early, but treatment planning with PET/CT is complicated by the lack of custom immobilization. In contrast, if PET is used after a decision has been made to proceed with radiotherapy, the potential for assessing nodal involvement remains, but the data are available much later in the patient management with the further disadvantage that a flatbed and custom immobilization may be required.

In practice, it would be useful to obtain the PET/CT earlier as part of the diagnostic and staging workup for the patients but also to be able to use the information for radiotherapy planning. This would require an accurate and reliable method of image registration that can accommodate the nonrigid deformations that can occur in the head and neck region. Therefore, the second original contribution of this study was to investigate the feasibility of using a standard method of immobilization in conjunction with nonrigid registration to achieve the desired PET/CT to planning CT image fusion.

### METHODS AND MATERIALS

#### Patients

Five patients with head and neck cancer underwent PET/CT in addition to conventional X-ray CT for radical radiotherapy treatment planning. All patients gave written informed consent to participate, and the study was approved by the Local Research Ethics Committee.

#### Image acquisition

Positron emission tomography 18-F fluorodeoxyglucose (FDG) imaging was conducted on a Millenium VG Hawkeye dual headed gamma camera capable of coincidence detection (GE Healthcare, Chalfont St. Giles, Bucks, UK), with a 40 cm field of view (FOV) extending from the top of the skull to the upper thorax. Following PET acquisition and with the patient in the same position, CT for attenuation correction and image registration was acquired using an integrated, low-dose Hawkeye CT system. The Hawkeye CT was acquired over 10 minutes and consisted of 256 x 256 pixels, with pixel size 2 mm and slice thickness 10 mm.

To address the question of whether PET/CT acquired in diagnostic position can subsequently be registered to treatment planning CT, patients underwent repeated PET/CT in two setup positions. First, patients were imaged with their custom-made immobilization shell attached to a modified base plate that was placed on a flat bed. The upper half of the shell was adapted for improved patient comfort around the mouth and eyes while maintaining suitable immobilization of the neck during the 40-min imaging procedure. Second, after an interval of a few minutes, each patient underwent a repeated PET/CT with a Repovac vacuum cushion (Sinmed Radiotherapy Products, Reeuwijk, The Netherlands) and standard-sized headrest on a conventional diagnostic curved bed.

### Table 1. Comparison of diagnostic/staging PET and treatment planning PET

<table>
<thead>
<tr>
<th></th>
<th>Diagnostic/staging PET</th>
<th>Treatment planning PET</th>
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</thead>
<tbody>
<tr>
<td>Identification of nodes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Timing during patient management</td>
<td>Early</td>
<td>Late</td>
</tr>
<tr>
<td>Time to assess treatment options</td>
<td>Yes</td>
<td>Limited</td>
</tr>
<tr>
<td>Custom immobilization</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Flat bed</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Abbreviation: PET = positron emission tomography.
Radiotherapy planning CT was performed with patients on a flat bed wearing a full custom-made immobilization shell. Images were acquired at 512 × 512 pixels with pixel size determined by the field of view (FOV). The first two subjects were imaged on a PQS CT (Philips Medical Systems, Eindhoven, The Netherlands) (slice thickness 3 mm, FOV 48 cm), and the other 3 patients were scanned on a GE LightSpeed RT CT (slice thickness 2.5 mm, two patients at FOV 65 cm, one patient at FOV 36 cm).

Hawkeye CT was registered to treatment planning CT using both rigid and nonrigid three-dimensional algorithms. The nonrigid method (14) provides a robust pseudoelastic deformation and incorporates a constraint to ensure that the transformation between the two images is smooth and continuous.

The nonrigid deformation is defined on a cubic grid of points. The distance between points is a user-chosen parameter. The value of the deformation between points is found by minimizing a cost function. If the vector of parameters is \( \mathbf{a} \), the fixed or reference image is \( f \) and the moved image, after a deformation with parameters \( \mathbf{a} \) has been applied to the image, is \( M(\mathbf{m}; \mathbf{a}) \) then the cost function is given by

\[
J(\mathbf{a}) = \frac{1}{2} \left( M(\mathbf{m}; \mathbf{a}) - f \right) \left( M(\mathbf{m}; \mathbf{a}) - f \right)^\top + \frac{1}{2} \lambda \mathbf{a}^\top L \mathbf{a}.
\]

The first term is a sum of squares of intensity difference between the two images, and the second term is a term that constrains the deformation (defined by the parameter vector \( \mathbf{a} \)) to be smooth. \( L \) is a discrete second derivative (Laplacian) operator. The weighting parameter \( \lambda \) is chosen by the user. It is well known that the sum of squares of intensity differences can be sensitive to large differences in intensity between the registered images. However, Barber and Hose (14) have shown how a position-dependent intensity correction can be incorporated into the deformation that compensates for such differences and removes the sensitivity of the registration algorithm to them. The minimization of \( J \) can be formulated in terms of the iterative solution of a set of linear simultaneous equations. Although the equation set is large, the construction is sparse and an efficient solution can be constructed.

In practice, images were first segmented to remove the immobilization mask when applicable. The planning CT was interpolated to 256 × 256 pixels then cropped for efficient nonrigid registration. The Hawkeye CT was then interpolated and cropped to match the voxel dimensions of the planning CT. All interpolation was performed using cubic interpolation and image volumes were typically cropped to 140 × 100 × 55 voxels.

Registration was performed in three stages (Fig. 1). First, images were manually translated to a starting position (Fig. 1b). The exact precision of this stage did not impact on the subsequent automatic registration methods. Second, images were rotated and translated using a voxel-based rigid algorithm, the result of which was used as the starting point for nonrigid registration (Fig. 1c). Third, the nonrigid registration (14) was implemented with a multiresolution algorithm, which initially matches the coarse details in the images and then resolves the finer features as the mesh density increases (Fig. 1d). The rigid and nonrigid automated procedure took an average of 44 s in total (range, 29–67 s) using a 2.13 GHz Windows PC with 1 GB RAM.

Quantification of image registration accuracy

Custom Matlab (www.mathworks.com; Natick, MA) software that displays CT volumes in three orthogonal projections was used by four observers to set five anatomic landmarks of their choice on both fixed and registered CT. The distance between the marked points on the two image volumes was calculated as the root mean squared (RMS) error (15).
**Observer error**

One consultant radiologist, one radiographer, and two physicists, all experienced at viewing CT images, identified anatomic landmarks on the study data. Each observer was provided with equal training with the Matlab software. Landmarks clearly visible on both volumes were selected, which included the anterior–inferior corner of the vertebral body of C2, the tip of the odontoid peg, and the top of the hyoid bone. Observer error and reproducibility was quantified by twice marking landmarks on two head and neck CT volumes with a registered data set at a known, rigid registration error.

**Impact of CT resolution**

The Hawkeye CT is acquired at a different resolution to the planning CT. Therefore, the effect of in-plane CT resolution on observer error was assessed by using four CT volumes with simulated registered data with a known registration error. Initially, observers marked anatomic landmarks with registered volumes at the same “sharp” resolution as the fixed CT volume. Second, the process was repeated for the same registered volumes that had been smoothed to simulate the effective in-plane resolution of Hawkeye CT. For all four observers, registration accuracy was compared for the sharp and smooth cases to assess the impact of resolution on observer accuracy.

**Rigid and nonrigid registration**

To compare the accuracy of the rigid and nonrigid registration methods, both methods were applied to register Hawkeye CT studies to a corresponding treatment planning CT.

**Statistical analysis**

All data are presented as mean ± standard deviation, and statistical analysis was conducted with the paired samples *t* test.

**RESULTS**

Five patients provided written informed consent and successfully completed the study. All patients had histologically proven head and neck cancer. All patients tolerated the PET/CT imaging without difficulty despite the length of the procedure. No significant movement artifacts were observed on images acquired with either the custom-made or standard immobilization techniques.

**Image registration**

For the four sharp test data sets, observer error calculated from user-specified anatomic landmarks was 0.29 ± 0.34 mm. Repeating the identification of landmarks with the registered data smoothed to simulate the effect of the Hawkeye CT resolution significantly increased the observer error to 1.06 ± 1.22 mm (*p* = 0.017). Observer reproducibility was 0.35 ± 0.37 mm for the sharp data and 0.91 ± 1.01 for the filtered data.

For patients set up in treatment position (Table 2), the RMS error for rigid registration was 4.96 ± 2.38 mm, compared with 2.77 ± 0.80 mm for nonrigid registration (*p* = 0.001). For patients set up in diagnostic position, the RMS error for rigid registration was 5.96 ± 1.05 mm while for nonrigid registration the error was 3.20 ± 1.22 mm (*p* < 0.001).

Applying the nonrigid registration to diagnostic position PET/CT produced a more accurate match to the planning CT than rigid registration of treatment position PET/CT (3.20 ± 1.22 mm and 4.96 ± 2.38 mm, respectively, *p* = 0.012).

**DISCUSSION**

**Image registration of head and neck PET and CT**

Several studies have considered rigid registration in combination with careful patient immobilization. For example, Wong et al. (16) reported a mean 3.77 mm RMS error of anatomic landmarks when assessing rigid registration accuracy of PET to CT acquired with patients immobilized. Lavely et al. (6) performed phantom validation of a mutual information rigid algorithm for head and neck cancer and applied the method to a single patient PET/CT with mean error of 3.9 mm. Daisne et al. (9) evaluated rigid registration of four patients who had been immobilized and found registration errors within 5.8 mm.

The impact of immobilization itself was investigated by Klabbers et al. (8), who compared five immobilized patients and two patients who were scanned without a mask to assess the impact of nonrigid deformations. Using rigid registration only, significantly larger translation errors (mean, 11 mm) were recorded without the mask compared with a mean of 4.8 mm with immobilization. To account for such errors, nonrigid registration has been used by Schwartz et al. (10, 11), who applied the algorithm to register head and neck PET to preoperative CT that had not been conducted with radiotherapy immobilization. However, the registration accuracy was not quantified in this case.

Hence, the first aim of our study was to quantify the accuracy of a nonrigid image registration algorithm for matching CT acquired during a PET imaging session to CT acquired for head and neck radiotherapy treatment planning. Having first established observer accuracy with a set of 4 simulated CT registrations, anatomic landmarks were used to assess the PET/CT to planning CT registration accuracy. The results shown in the previous section demonstrate that for the set of patients studied, the nonrigid algorithm significantly reduces the registration error compared with rigid registration for PET/CT acquired in treatment position.

**Patient setup**

In addition to quantifying the registration error, the second original aspect of our work is the analysis of head and neck PET/CT acquired in both diagnostic and treatment
position on the same day. Because the attenuation correction CT is acquired during the same imaging session as PET, intensity-based nonrigid registration can be used to register this CT to radiotherapy-planning CT. The calculated image transformation can then be applied to the PET to provide the PET to planning CT image registration. This procedure has enabled us to investigate whether nonrigid registration can compensate for the lack of customized radiotherapy immobilization. The results in the previous section show that even for PET/CT acquired in diagnostic position, the nonrigid registration provides good registration accuracy within the 5 mm tolerance proposed by Paulino et al. (2) and is significantly better than rigid registration of treatment position PET/CT to planning CT.

Although this study demonstrates that custom-made immobilization is not necessarily required for accurate PET/CT to planning CT image registration, care must be taken to acquire the diagnostic images with an appropriate, generic form of immobilization that ensures the neck is at an angle similar to treatment position. In our study, diagnostic position images were acquired with a standard-sized headrest and a vacuum cushion head restraint. The advantage of using this form of immobilization in conjunction with nonrigid image registration is that PET/CT can be used in treatment planning even though custom-made immobilization has not been used during the acquisition of the functional images.

It should also be noted that the application of the image transformation derived from the CT to CT registration depends on the PET/CT being “inherently hardware” registered. However, because the PET is acquired over many minutes, additional checks must be made to ensure the validity of this assumption, and, ideally, an estimate of PET to attenuation correction CT misregistration should be taken into account (17). For the system used in this study, the PET to CT registration tolerance is estimated to be within 4 mm in the transaxial plane.

Other registration issues

Quantification of registration accuracy is a difficult problem (18). As in a related article on the role of nonrigid registration in treatment planning (19), in this study anatomic landmarks are used to provide a measure of registration accuracy. One of the limitations of using anatomic landmarks over a fully three-dimensional voxel-based error measure is that the landmarks only provide the error at specific points and makes no assessment of voxels in between. We believe, however, that provided the assessment is made in conjunction with a visual confirmation of image registration validity, the landmark method provides a useful, practical method of quantifying registration accuracy.

Regarding CT resolution, the Hawkeye CT system used in this study is an integrated, low-dose system that provides images with lower resolution than newer commercial PET/CT systems. The impact of CT resolution is apparent on observer error and reproducibility; however, image registration accuracy is also affected if the planning CT and PET/CT image resolution is different. This is because the registration algorithm is an intensity-based method that works best when the two sets of images have been acquired at the same resolution. Therefore, it is likely that using PET/CT acquired at the same resolution as planning CT would further improve both registration accuracy and observer accuracy of registration error.

Contrast

In this study, contrast-enhanced CT has not been used for the treatment planning CT as contrast is not routinely used at our institution for this purpose (20). The use of contrast–enhanced planning CT could have an impact on the accuracy of the image registration as contrast would not normally be used for the attenuation correction CT acquired for PET. It may be possible to alleviate this problem by changing the density on the contrast-enhanced CT (21).

CONCLUSIONS

For patients with head and neck cancer, this study provides quantitative evidence that a nonrigid algorithm can provide a more accurate registration of PET/CT to radiotherapy planning CT than a rigid transformation. In addition, nonrigid registration of PET/CT acquired with the patient in a standardized, diagnostic position can provide images registered to planning CT with greater accuracy than a rigid registration of PET/CT images acquired in treatment position. For suitable patients, this may enable a staging PET/CT, rather than a treatment position PET/CT, to be used in radiotherapy treatment planning. Further improvements to the image registration of PET/CT to treatment planning CT can be expected with improved PET/CT image resolution and by further development of the nonrigid registration algorithm.

REFERENCES

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