Identifying the dominant prostate cancer focal lesion using image analysis and planning of a simultaneous integrated stereotactic boost

Citation for published version:

Digital Object Identifier (DOI):
10.3109/0284186X.2015.1063782

Link:
Link to publication record in Edinburgh Research Explorer

Document Version:
Peer reviewed version

Published In:
Acta oncologica

General rights
Copyright for the publications made accessible via the Edinburgh Research Explorer is retained by the author(s) and / or other copyright owners and it is a condition of accessing these publications that users recognise and abide by the legal requirements associated with these rights.

Take down policy
The University of Edinburgh has made every reasonable effort to ensure that Edinburgh Research Explorer content complies with UK legislation. If you believe that the public display of this file breaches copyright please contact openaccess@ed.ac.uk providing details, and we will remove access to the work immediately and investigate your claim.
INVITED REVIEW - IMAGE REGISTRATION IN VETERINARY RADIATION

ONCOLOGY: INDICATIONS, IMPLICATIONS AND FUTURE ADVANCES

Yang Feng¹,²,³, Jessica Lawrence², Kun Cheng¹, Dean Montgomery¹, Lisa Forrest⁴, Duncan B. McLaren¹, Stephen McLaughlin⁵, David J. Argyle², William H. Nailon¹

¹The University of Edinburgh, Department of Oncology Physics, Edinburgh Cancer Centre, Western General Hospital, Edinburgh, UK. ²The University of Edinburgh, Royal (Dick) School of Veterinary Studies and Roslin Institute, UK. ³Healthcare, Philips Research China, Shanghai, 200233, P.R.C. ⁴The University of Wisconsin-Madison, Department of Surgical Sciences, 2015 Linden Drive, Madison WI, USA. ⁵Heriot-Watt University, School of Engineering and Physical Sciences, Edinburgh, EH14 4AS, UK.

Keywords: Oncology, Image Registration, Computed tomography, Radiation therapy, Magnetic resonance imaging

Running Head: Image Registration in Radiation Oncology

Funding Sources: This work was generously supported by NHS Lothian, Edinburgh and Lothians Health Foundation (charity number SC007342), the James Clerk Maxwell Foundation, the Jamie King Uro-Oncology Endowment Fund, a University of Edinburgh Darwin Award and a University of Edinburgh Individual Stipend.
Previous Abstracts: Material has not previously been presented.

Abstract

The field of veterinary radiation therapy (RT) has gained substantial momentum in recent decades with significant advances in conformal treatment planning, image-guided radiation therapy (IGRT) and intensity-modulated (IMRT) techniques. At the root of these advancements lie improvements in tumor imaging, image alignment (registration), target volume delineation, and identification of critical structures. Image registration has been widely used to combine information from multi-modality images such as computerized tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography (PET) to improve the accuracy of radiation delivery and reliably identify tumor-bearing areas. Many different techniques have been applied in image registration. This review provides an overview of medical image registration in RT and its applications in veterinary oncology. A summary of the most commonly used approaches in human and veterinary medicine is presented along with their current use in IGRT and adaptive radiation therapy (ART). It is important to realize that registration does not guarantee that target volumes, such as the gross tumor volume (GTV), are correctly identified on the image being registered, as limitations unique to registration algorithms exist. Research involving novel registration-frameworks for automatic segmentation of tumor volumes is ongoing and comparative oncology programs offer a unique opportunity to test the efficacy of proposed algorithms.
Introduction

Imaging data from multiple anatomical and functional imaging studies is becoming a routine component of veterinary patient management for a variety of medical and surgical conditions. Spanning from initial diagnosis to determining therapeutic options to assessing response or recrudescence of disease, these data help direct decisions regarding disease management, efficacy of treatment and patient outcome. While computed tomography (CT) and magnetic resonance (MR) imaging are readily available in veterinary medicine, novel imaging techniques such as molecular imaging offer complementary information to aid in disease recognition, extent and treatment planning. In order to optimally use information gathered from these various techniques, the data must be easily compared despite differences in image acquisition and presentation. Image registration is defined as the process of aligning two or more images from the same or different imaging modalities to allow for data mapping (data fusion) and interpretation. While registration carries importance across imaging disciplines, the purpose of this review is to provide a broad overview of image registration and data fusion techniques used in radiation therapy (RT), given the high frequency with which it is utilized and radiation oncologists’ reliance on registered images. While RT is the focus of the review, the principles outlined for registration techniques can be broadly applied to non-oncologic applications.

It is estimated that greater than 60% of human patients with cancer will receive RT and although there is no similar strong data in dogs and cats, RT has become a common therapeutic modality in veterinary oncology.¹ There is a large body of evidence supporting the use of RT for
optimal local tumor control, therefore identification of the tumor volume is of utmost importance when determining a treatment plan or evaluating changes in tumor volume. In practice, medical images acquired from different imaging modalities are used to guide the entire RT process from the initial treatment plan to fractionated radiation delivery through to dose verification. While radiation oncologists have always been guided by images in some form, the advent of image-guided radiation therapy (IGRT) has revolutionized how integral images are to modern radiation oncology. In a broad sense, IGRT may reflect any aspect of RT that utilizes imaging to improve treatment, such as weekly or twice weekly portal imaging. In a stricter sense, IGRT refers to contemporaneous functional and structural imaging to improve target delineation, adjust for target motion and/or uncertainties in patient positioning, and potentially adapt treatment to the response of the tumor during adaptive radiation therapy (ART). While radiation oncologists are highly dependent on image registration to ensure that IGRT is successful at targeting tumor and limiting dose to adjacent normal tissue, the underlying process is complex and often not fully explained. A typical IGRT process, using veterinary images as an example, where image registration is vital in order to merge information from multi-modality images and therefore provide an accurate guide for radiation delivery is illustrated in Fig. 1.

Image registration provides a geometric transform that makes it possible to map information between the images, often with sub-pixel resolution. As the use of multimodality image data in RT increases, medical image registration is essential to combine the information from each modality. As a result, it has become a very active area of research. Images utilized in
RT can be registered to obtain comprehensive information regardless of patient positioning, time point with respect to therapy, or type of imaging acquisition. Registration may also be used to combine multiple images from the same imaging modality,\textsuperscript{4} or to combine information from multiple modalities such as CT, MR imaging, positron emission tomography (PET) and single-photon emission computed tomography (SPECT).\textsuperscript{5} For the purpose of this review, a reference image is defined as the source image containing the reference information, while a target image is defined as the movable image spatially matched to the reference. After registration, information from the reference image, such as contoured structures, can be used on the target image.

Image registration methods have been widely used both in human medicine\textsuperscript{6-11} and in preclinical studies\textsuperscript{12-18} to improve matching between images acquired on different modalities such as PET and MR,\textsuperscript{19} SPECT and CT,\textsuperscript{20} and PET and CT.\textsuperscript{21} Registration approaches applied to humans are also suitable for companion animals\textsuperscript{22-31} and may prove useful in comparative oncology, which refers to the study of cancer etiology, biology and treatment in companion animals that develop spontaneously-occurring cancer.\textsuperscript{1,32-34} Comparative oncology presents a unique opportunity to improve RT for both human and veterinary patient groups given the number of similarities in tumor biology, imaging techniques and therapeutic modalities. Image registration methodologies, regardless of the species imaged, will help facilitate this by finding the optimal geometric transformation between corresponding image data.\textsuperscript{35}
In general, an image registration algorithm can be divided into four parts: image conditioning, geometric transformation, similarity function and optimization (Fig. 2). Any step that alters the original data to make it more suitable for applying image registration is known as image conditioning. Due to the diversity of the methods used for this, a comprehensive review of image conditioning falls outside the scope of this manuscript but may be found elsewhere.\textsuperscript{5, 36-37}

**Image Registration**

Table 1 provides a comprehensive list of the most commonly used terminology in image registration.\textsuperscript{5} Key technical details of the transformation function, similarity function and optimization process (Fig. 2) are introduced in this section.

**Transformation**

As it is common for patient orientation and immobilization to vary between imaging studies, the first essential component of registration is transformation. This describes the geometrical shift that is required for the target image to match it to the reference image. Rigid transformation methods are most commonly used and are usually applied on images that have no distortion, such as CT to CT. Generally, a rigid geometric transformation can be achieved by translation and rotation and is commonly used to match between bones on medical images, such as the skull.\textsuperscript{38-39}

An affine transformation, which is an extension of the rigid transformation, allows for rotations,
translations, scaling and shearing.\textsuperscript{40} Rigid transformations can also be applied before a non-rigid registration as an image conditioning step.\textsuperscript{41-42}

The assumption that rigid movement of anatomy occurs globally is incorrect in any number of situations, therefore limiting widespread use of rigid registrations for sites other than the head.\textsuperscript{40} Most non-rigid registration methods are based on deformable models. These range in complexity and may vary from simple with relatively few parameters to complicated where each point or voxel moves independently.\textsuperscript{40} There are two directions in deformable registration: free form deformable registration (often abbreviated FFD) and guided deformable registration, which are controlled by models based on prior knowledge of the registered objects or organs. The fundamental difference between them is that the free form deformable registration allows any deformations by moving the positions of its control grid. The most commonly used guided deformable registration methods are elastic-based and flow-based. Elastic-based methods treat organs as elastic solids and define two forces: internal forces that oppose the deformation and external forces that try to deform the images. The best transform can be obtained by finding equilibrium between both internal and external forces. Flow-based methods such as fluid flow and optical flow treat registration as a motion problem and therefore achieves the best match by meeting a pre-set constraint in a physical model. The application of the popular B-spline based FFD method registering pre- and post-treatment CT images of a dog with a sinonasal tumor is demonstrated in Fig 3.\textsuperscript{43} A similar method called thin-plate spline (often abbreviated TPS) can
also generate FFD registration. However, compared to the B-spine method this approach is limited by the fact that the deformation is applied globally.  

**Similarity Function**

The transformation, or alignment, of the image datasets is assessed by measuring the similarity between them. There are two predominant similarity measurements: intensity-based and feature-based measurements. The most popular intensity-based similarity function is based on intensity difference or intensity correlation. Feature-based similarity functions depend on the feature structure extracted, such as anatomic structures (bones) or artificial landmarks (fiducials).

Most feature-based algorithms use points, lines, or surfaces for matching. A minimum of three or four pairs of points are required in order to compute the rotations and translations for a rigid or affine transformation. Unlike point matching, line and surface matching do not require a one-to-one match between images but rather attempt to maximize the overlap between equivalent lines and surfaces such as the skull surface, ribs or pelvis. The transformation process and the corresponding similarity calculation used in the registration of images from a dog with a nasal tumor is illustrated in Fig 4.

**Optimization**

Optimization is the process used to search for a numerical value produced by the similarity function, which is indicative of when the best match between the images has been found. The
goal of the optimization algorithm is to find a maximum or minimum value of the similarity measure accepted; it is common for optimal registration to be accomplished when the similarity measures are defined by their minimal value. It is an important step in a registration method because the similarity function can often produce several local minima, which produces sub-optimal results.

Assessment

The obvious motivation for registering images from different studies is to map clinically useful information from one study onto another, for example in treatment planning prior to radiation delivery. If data can be successfully fused, radiation oncologists can then map tumor volumes such as the GTV, clinical target volume (CTV) and planning target volume (PTV) or organs at risk (OAR) directly onto the CT needed for dose calculations (structure mapping). Therefore, relying on the ability of a bespoke software system to adequately register images is of utmost importance in order to adhere to current radiation guidelines – namely to appropriately outline tumor volumes and limit normal tissue toxicity. In this vain, it is important to realize the difficulties in accurately validating the performance of a complex registration method. In some cases, a registration algorithm can be assessed using phantom data, but this is not commonly done as performance on phantoms cannot ensure comparable performance on clinical cases. A common approach is to use synthetic images on which manual definition of corresponding points such as fiducial markers provides a straightforward assessment of a registration method.
Dice coefficient, which measures the overlap between clinical and registered contours, places a numerical value on the registration accuracy.\textsuperscript{50-51} Within the range 0\% to 100\%, a Dice value of 100\% indicates excellent geometric agreement while a Dice value of 0\% represents poor geometric agreement (Fig. 5). The Jaccard index and Tanimoto coefficient (both vary from 0\% to 100\%), which can be calculated directly from the Dice coefficient, are also used to measure the similarity between regions. However, they need prior knowledge (contours of the same region) on both reference and target images.

Once the registration process has been completed, there are a number of techniques that can be used to visualize fused data, including the use of overlays, pseudo-coloring, grey scale coloring, and side-by-side display of anatomic planes.\textsuperscript{40} This allows the radiation oncologist to evaluate the fused images and to map volumes of interest or calculated 3D dose distributions from the CT treatment plan to the coordinate system of another imaging study, such as MR. Not only is this helpful to define the tumor and normal tissue dose for tissues that are not optimally imaged with CT (such as canine or feline intracranial tumors), but the fusion of 3D dose distributions or volumes of interest (such as GTV and CTV) to post-treatment imaging scans improve detection and understanding of radiation changes over time (Fig. 5). As veterinary radiation oncology advances into the realm of IGRT and ART with the use of volumetric imaging systems (on-board kilovoltage CT or megavoltage CT units), the concept of accurate registration becomes increasingly critical.
Current State of Image Registration in Veterinary Radiation Oncology

Image registration and data fusion are useful in veterinary radiation oncology with most modern treatment planning systems now facilitating the use of a secondary datasets for target and OAR delineation. It is also possible to map dose information to the secondary dataset following an appropriate registration.

Dose distributions generated for conformal radiation therapy (CRT) have been accurately predicted with CT-based treatment planning systems and are already widely used in veterinary oncology. CT data includes the Hounsfield units as a linear transformation of radiation beam attenuation that varies with electron densities of materials as the beam progresses through tissue.

Most RT planning software obtains the relative electron density from the relationship between the linear attenuation coefficients and Hounsfield unit values in order to determine heterogeneity in the dog or cat’s body. Non-contrast CT images are typically utilized for treatment planning, given that contrast agents are high-Z radio-opaque materials, which would attenuate a radiation beam more than normal, resulting in higher than normal electron density. Post-contrast CT data used for a treatment plan would theoretically give rise to higher monitor unit (MU) values, and therefore radiation dose, compared to MU values taken from calculating a plan using pre-contrast CT data. As veterinary radiation oncologists often use commercially available human treatment planning software, automatic registration methods may be built-in to the software, although other “in house” registration algorithms may be adapted for use. One of the most common automatic registrations used in routine treatment planning is the merging of pre-contrast and
post-contrast CT data in order to delineate the GTV, CTV, PTV and OAR. Because regions of interest are often best identified on post contrast CT images, many commercial software programs (such as Eclipse™, Varian Medical Systems, Palo Alto, used at the authors’ institutions) automatically permit DICOM-coordinated registration and facilitate contouring on fused multimodality images. However, there are often limited registration capabilities between multimodal image acquisitions; our current planning system is capable of a fully automatic, mutual-information-based rigid registration but results are often unsatisfactory between modalities (i.e. CTs obtained with different DICOM origins or MRI and CT data acquired with vastly different animal positioning). Automatic registration partially eliminates a potential source of error as radiation oncologists historically may have estimated tumor volume on the pre-contrast CT data based on visual examination of alternative imaging studies. Upon evaluation of the veterinary literature to date, it is often difficult to firmly understand how tumor volumes were identified prior to treatment; for example in one study evaluating RT for canine intracranial tumors, the GTV was defined on planning CT scans by the contrast-enhancing area on CT or MR data.\textsuperscript{54} It is presumed that contours for the GTV were drawn on pre-contrast CT images after evaluation of diagnostic scans, however this presumption may be incorrect. In most other veterinary studies, it is unclear how the GTV was derived, as irradiated volumes have been inconsistently defined.\textsuperscript{52} The delineation of target volumes is paramount to effective RT, as geographic miss could occur if the GTV, CTV and PTV are ineffectually contoured and/or unexpected toxicity could result from a poorly defined OAR. Proper radiation reporting is also
critical to permit reproducibility of clinical studies across institutions.\textsuperscript{52} It is also important to note that dose distributions generated by treatment planning are estimated dose distributions, thereby introducing an additional uncertainty to planning. The variation in registration methods introduces bias that could lead to erroneous conclusions about the extent and location of various volumes compounded by variations in dose distribution algorithms. As veterinary reporting of RT planning improves, information regarding registration should be included.

In addition to RT planning, image registration has made its way into the routine assessment of daily patient positioning, enabling better tumor targeting.\textsuperscript{25-29, 55-57} One of the key concepts of IMRT, stereotactic radiation therapy (SRT) or radiosurgery (SRS) and IGRT planning is that tight dose constraints are placed around the PTV provided the clinician is confident that the animal’s positioning will be reproducible during treatment. One of the most common practices immediately prior to treatment delivery is to generate a pair of orthogonal digitally reconstructed radiographs (DRRs) from the planning CT and to register simulated radiographs with MV radiographs acquired by a flat-panel imager (electronic portal imaging devices or EPIDs) attached to the linear accelerator (Fig. 6).\textsuperscript{55,56} More advanced on-board imaging equipment involves cone-beam CT systems or helical CT systems built into the treatment unit.\textsuperscript{25-29, 57} Automated image registration at the treatment unit can determine the rotations and translations required to align the datasets, thus decreasing some of the variability with daily patient setup and intra-patient shifts.\textsuperscript{25-29, 40} Challenges still exist with registration of different modalities with different positioning and therefore fiducials and other landmarks may
be needed to improve alignment (Fig. 7). Dose delivered to patients throughout a treatment protocol also rely on accurate patient positioning and registration (i.e. daily cone beam CT registered with treatment-planning CT) in order to sum dose delivered over time; monitoring of dose deviations from the expected distribution allows for intra-treatment adjustments in order to better target tumor yet limit normal tissue dose. Little veterinary literature has evaluated the utility or validity of various registration algorithms other than an early study demonstrating an in-house computer program that was developed for brain imaging.\textsuperscript{22} This study highlighted the widespread potential of image registration by evaluating corresponding images from CT and MR, CT images before and after surgical treatment, and CT and post-mortem cryosection images in dogs or cats.\textsuperscript{22} Currently at our institution, for follow-up imaging, standardized response criteria are applied when assessing tumor response following treatment.\textsuperscript{58} Responses for tumors of the head and neck (intracranial, sino-nasal, cervical) are often assessed by the radiology and radiation oncology team on serial CT scans, without consideration for image registration over time, which may not accurately reflect the response of the tumor or the assessment of treatment-induced toxicity.\textsuperscript{27} Toxicities are often inferred by tissue changes, however easier implementation of image registration in the clinic may provide more objective information regarding tumor and normal tissue changes following radiation, particularly as varying fractionated protocols are used across veterinary radiation oncologists.\textsuperscript{52,53,59,60}

With the incorporation of functional imaging into veterinary oncology, determination of structural and, indirectly, pathological changes may be better assessed. Changes such as fibrosis
and tumor recurrence can be difficult to distinguish on CT and MR; functional imaging with PET may help clarify differences and alter future therapy. Currently in veterinary medicine, 2-deoxy-2-[^18F]-fluoro-deoxyglucose (FDG), 3'-deoxy-3'-[^18F]-fluorothymidine (FLT), and copper(II)-diacetyl-bis (N4-methylthiosemicarbazone) (Cu-ATSM) have been used to assess various neoplastic conditions in dogs and cats. In particular, several studies have evaluated functional imaging over time in an attempt to correlate pre-treatment scans to post-treatment scans; ideal comparisons would require registration of image datasets to avoid interpretation errors. One study that assessed pre-radiation therapy FDG, FLT and Cu-ATSM PET/CT scans to post-treatment FDG PET/CT scans demonstrated the complexity and utility of registration methods in dogs with sinonasal tumors. Dogs in this study underwent a radiation-planning CT scan that served as the reference dataset; bony anatomy from pre-radiation PET/CT scans was registered to the bony anatomy of the radiation-planning CT; rigid registration using cross-correlation resulted in affine transformations that were applied to the corresponding PET images. The translated and rotated PET matrices were subsequently resampled using a spline filter defined by the reference PET image that was obtained at the same time as the treatment-planning CT. While complex, the registration process ensured that each voxel index of the pre-treatment PET/CT scans corresponded as closely as possible to the same region in the post-treatment FDG PET image for each patient, enabling assessment of changes in tracer uptake. Imaging and registration advances will undoubtedly lead to more work being performed in a similar fashion and may alter current criteria for response assessment and/or response prediction.
Proposed Advances in Veterinary Image Registration

In general, RT is delivered to patients over the course of several weeks in both human and veterinary oncology. While the GTV, CTV and PTV are currently considered standard targets in radiation oncology, the PTV is created to make sure that dose plans are robust to uncertainties. The GTV and CTV are oncological-anatomical concepts, which are heavily dependent on the experience and judgment of the radiation oncologist and radiologist. The PTV, on the other hand, is a geometrical scheme used for treatment planning in order to ensure that the prescribed dose targets the CTV. Alternatively, one might view the PTV as decreasing the risk that patient positioning, setup uncertainties, and OAR or target position uncertainties will lead to a severe under-dosage of the CTV. As the impact of setup uncertainties decreases with IGRT, the CTV to PTV margins may be reduced, thus decreasing normal tissue toxicity. Taking this a step further, if diagnostic imaging, interpretation, and registration with the initial treatment plan are performed frequently while a patient is on therapy, the treatment plan can be “adapted” to optimize tumor control and minimize normal tissue damage.

ART is defined as changing a radiation plan during RT to account for anatomy or biology changes of the patients. Studies have shown clear advantages and gains in clinical application of adaptive radiation therapy. However, clinical implementation is limited as ART is time-consuming and places an additional workload on clinicians to quickly contour follow-up images manually. Adaptive planning could be used at different fractions (off-line) and at different time...
points within one fraction (on-line).\textsuperscript{73} Identifying changes in the GTV between images acquired for the purpose of RT planning and images acquired for the purpose of assessing response to RT is challenging. This is mainly because of: 1. Uncertainties in soft tissues and internal organ motion;\textsuperscript{74} 2. The response of the GTV to radiation or other treatments is difficult to predict, which may cause anatomical changes;\textsuperscript{75} 3. Distortions or contrast variability between different modalities, which makes it difficult to register the information between multi-modality images.\textsuperscript{76}

To overcome these difficulties, image guided adaptive radiation therapy (IGART) is the most reliable method for a comprehensive ART approach.\textsuperscript{77} Research into known, documented uncertainties in soft tissue and organ motions in prostate,\textsuperscript{78} head and neck\textsuperscript{79} and lung\textsuperscript{80} is well developed and directly impact ART approaches. Furthermore, registration methods that combine information and realize deformable mapping between structural and functional images are essential to make individualized IGART rapid and feasible.\textsuperscript{81}

**Conclusion**

In its simplest context, image registration simply refers to the comparison of one dataset to another. The complexity behind making quantitative use of this imaging data has been reviewed here, illustrating that it is necessary to determine the transformations needed to relate coordinates of one dataset to another. The impact of image registration on RT from treatment planning to image-guided delivery to post-treatment follow-up is enormous and has already impacted veterinary patients. Novel registration frameworks may be ideally tested on companion
animals undergoing RT given similarities between human and veterinary radiation oncology.

Ultimately optimized image registration and data fusion techniques should aid in targeting tumor volumes and organs-at-risk, improve response assessment and increase the availability and utility of an efficient ART approach.

Acknowledgements:

We are grateful for the generous support from NHS Lothian, Edinburgh and Lothians Health Foundation (charity number SC007342), the James Clerk Maxwell Foundation, the Jamie King Uro-Oncology Endowment Fund, a University of Edinburgh Darwin Award and a University of Edinburgh Individual Stipend.
References


doi:10.1371/journal.pone.0090028


42. Hellier P, Barillot C. A hierarchical parametric algorithm for deformable multimodal
473
474 43. Rueckert D, Sonoda LI, Hayes C, Hill DLG, Leach MO, Hawkes DJ. Non-rigid registration
477
479 accuracy and clinical versatility of mutual information for automatic multimodality
480 image fusion using affine and thin-plate spline warped geometric deformations. Med
482
483 45. Kessler ML, Pitluck S, Petti PL, Castro JR. Integration of multimodality imaging data for
485
486 46. Pelizzari CA, Chen GT, Spelbring DR, Weichselbaum RR. Accurate three-dimensional
487 registration of CT, PET, and/or MR images of the brain. J Comput Assist Tomogr.
489
490 47. Studholme C, Constable RT, Duncan JS. Accurate alignment of functional EPI data to
493
495 Validation of nonrigid image registration using finite element methods: application to
491 49. Maes F, Collignon A, Vandermeulen D, Marchal G, Suetens P. Multimodality medical
492 image registration by maximization of mutual information. IEEE Trans Med Imaging.
495 MR prostate images with biomechanical modeling and nonlinear parameter estimation.
497 51. Vercauteren T, Pennec X, Perchant A, Ayache N. Nonparametric diffeomorphic image
498 registration with the demons algorithm. In: Ayache N, Ourselin S, Maeder A, editors. Proceeding of the 10th International Conference on Medical Image Computing and
499 Computer-Assisted Intervention; 2007; Brisbane, Australia.
500 52. Keyerleber MA, McEntee MC, Farrelly J, Podgorsak M. Completeness of reporting of
501 radiation therapy planning, dose, and delivery in veterinary radiation oncology
507 55. Kent MS, Gordon IK, Benavides I, Primas P, Young J. Assessment of the accuracy and
508 precision of a patient immobilization device for radiation therapy in canine head and


63. Leblanc AK, Jakoby BW, Townsend DW, Daniel GB. 18FDG-PET imaging in canine


77. Court LE, Tishler RB, Petit J, Cormack R, Chin L. Automatic online adaptive radiation therapy techniques for targets with significant shape change: a feasibility study. Phys


Table 1: The Classification Of Registration Method By Maintz And Viergever In 1998.5

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Dimensionality</td>
<td>A. Spatial dimensions only: 2D-2D; 2D-3D; 3D-3D</td>
</tr>
<tr>
<td></td>
<td>B. Time series (more than two images), with spatial dimensions:</td>
</tr>
<tr>
<td></td>
<td>2D-2D; 2D-3D; 3D-3D</td>
</tr>
<tr>
<td>II. Nature of Registration Basis</td>
<td>A. Extrinsic: 1. Invasive (stereotactic frame, fiducials); 2. Non-invasive (mould-frame, dental adaptor)</td>
</tr>
<tr>
<td></td>
<td>C. Non-image based</td>
</tr>
<tr>
<td>III. Nature of Transformation</td>
<td>A. Rigid; B. Affine; C. Projective; D. Curved</td>
</tr>
<tr>
<td>IV. Domain of Transformation</td>
<td>A. Local; B. Global</td>
</tr>
<tr>
<td>V. Interaction</td>
<td>A. Interactive; B. Semi-automatic; C. Automatic</td>
</tr>
<tr>
<td>VI. Optimization Procedure</td>
<td>A. Parameters computed; B. Parameters searched for</td>
</tr>
<tr>
<td>VII. Modalities Involved</td>
<td>A. Mono-modal; B. Multimodal; C. Modality to model; D. Patient to modality</td>
</tr>
<tr>
<td>VIII. Subject</td>
<td>A. Intrasubject; B. Intersubject; C. Atlas</td>
</tr>
<tr>
<td>IX. Object</td>
<td>A. Head; B. Thorax; C. Abdomen; D. Pelvis and peritoneum; E. Limbs; F. Spine and vertebrae</td>
</tr>
</tbody>
</table>
Figure Captions

**Fig. 1.** A typical flow chart of image-guided radiation therapy (IGRT), highlighting the need for registration, using a canine nasal tumor as an example. Diagnostic images are obtained and registered to the reference image for treatment-planning. Each fraction of radiation is administered with the aid of an electronic portal imaging device (EPID) or cone-beam computed tomography (CBCT) images that are registered to the treatment-planning reference image.

**Fig. 2.** A typical flow chart of image registration demonstrating the steps – transformation function, similarity function, and optimization – that are required to obtain a registration result.

**Fig. 3.** An example of a B-spline control grid on the reference and target image of a dog with a nasal carcinoma. This demonstrates a 20x20 control grid on pre-treatment and post-treatment computed tomography (CT) (512x512) images (manually warped).

**Fig. 4.** The variability in the similarity function (SSD) is shown and demonstrated from canine nasal tumor images when the transformation function (rotation) is applied on the target image and makes it rotate around the reference image from -90° to +90°. The rotation degree was defined as the angle between the directions of the reference (black) and the target (white) images.
As a result, the image in A illustrates an approximately -70° rotation while B illustrates an approximately 30° rotation.

**Fig. 5.** Illustration of a multi-step automatic registration-segmentation framework in a dog with a nasal tumor in which images show registration of a pre-treatment computed tomography (CT) study with the post-treatment CT 6 weeks after definitive intensity-modulated radiation therapy. The series demonstrates the target CT image with the pre-treatment (reference) gross tumor volume (GTV) contour (blue), target GTV contour (yellow) and an automatically generated contour using a multistep process (red). A represents registration between the original reference GTV and the target GTV (Dice coefficient = 42%); B represents the rigidly registered reference GTV and target GTV (Dice coefficient = 86%); C represents an additional step in which non-rigid registration is performed between the reference GTV and target GTV (Dice coefficient = 91%); and D represents a segmentation step in which an automatically generated GTV is created on the target image (Dice coefficient = 97%, indicating excellent agreement between the automatically generated target GTV and the manually contoured target GTV). Automatically generated tumor volumes that are accurate aim to improve efficiency of ART by defining topology changes and reducing planning time.

**Fig. 6.** Portal images obtained from a dog with a sinonasal tumor undergoing definitive intent radiation therapy prior to 6 MV photon therapy with a linear accelerator (Varian 2100 CD;
Varian Medical Systems, Palo Alto, USA); orthogonal images were obtained and analyzed immediately prior to treatment delivery. An on-board flat panel imager permits acquisition of the dog’s position prior to treatment (image in the lower right), which can be compared with the digitally reconstructed radiograph (DRR) obtained from the planning computed tomography (CT) (image in the upper right). Images were evaluated using commercially available treatment planning software (Eclipse v.11.0, Varian Medical Systems). The larger image on the left demonstrates registration of the electronic portal image and the DRR. (A) Images were obtained with the linear accelerator gantry at 0 degrees; the larger image on the left demonstrates evaluation of the registered images using a “moving window” technique that allows the window to move the DRR over the dog’s daily portal image. The orange graticule grid represents the dog’s position at acquisition of the portal image while the green graticule grid represents shifts needed in the dog’s position to match the ideal planning position. (B) Images were obtained with the linear accelerator gantry at 90 degrees; the larger image on the left demonstrates evaluation of the images using a “split window” technique, in which the central axis can be moved to reveal more of the DRR image or the electronic portal imaging device (EPID) image as needed. Manual alignment may be performed as was done here in which the daily image is moved to match the DRR; alternatively semi-automated or point matching registration can be performed.
Fig 7. A series of rigidly registered images acquired on a human patient treated for prostate cancer highlighting the difficulty in interpreting critical structures in different imaging modalities. T1- (A) and T2- (B) weighted MR images acquired on a Siemens Symphony 1.5T scanner (Siemens, Munich, Germany) were registered to a radiotherapy planning CT (C) acquired on a Philips Brilliance Big Bore CT scanner fitted with a flat couch. The hyper-intense gold markers implanted within the prostate gland and used for positional verification are clearly visible. The corresponding pre-treatment CBCT image (D) acquired on a Varian Clinac and used for positional verification. Alignment is complete and treatment begins when the hyper-intense markers are aligned on CT and CBCT. Soft tissue matching is difficult because of the atrophy induced in the prostate by the neo-adjuvant hormones administered between MR and CT acquisition.
Figure 2
Figure 3
Figure 5
Figure 6
Figure 7