Journal of Medical Radiation Sciences

Open Access

PRACTICE GUIDELINE

Deforming to Best Practice: Key considerations for deformable image registration in radiotherapy

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Received: 8 January 2020; Revised: 15 May 2020; Accepted: 12 June 2020

J Med Radiat Sci **67** (2020) 318–332

doi: 10.1002/jmrs.417

Abstract

Image registration is a process that underlies many new techniques in radiation oncology – from multimodal imaging and contour propagation in treatment planning to dose accumulation throughout treatment. Deformable image registration (DIR) is a subset of image registration subject to high levels of complexity in process and validation. A need for local guidance to assist in high-quality utilisation and best practice was identified within the Australian community, leading to collaborative activity and workshops. This report communicates the current limitations and best practice advice from early adopters to help guide those implementing DIR in the clinic at this early stage. They are based on the state of image registration applications in radiotherapy in Australia and New Zealand (ANZ), and consensus discussions made at the 'Deforming to Best Practice' workshops in 2018. The current status of clinical application use cases is presented, including multimodal imaging, automatic segmentation, adaptive radiotherapy, retreatment, dose accumulation and response assessment, along with uptake, accuracy and limitations. Key areas of concern and preliminary suggestions for commissioning, quality assurance, education and training, and the use of automation are also reported. Many questions remain, and the radiotherapy community will benefit from continued research in this area. However, DIR is available to clinics and this report is intended to aid departments using or about to use DIR tools now.

Introduction

Image registration, whether rigid image registration (RIR) or deformable image registration (DIR), is a core process used in the radiotherapy treatment chain. Given two images, I_A and I_B, image registration is the process by which the spatial transformation from I_A is performed, such that its similarity with I_B is maximised. This transformation can then be used to transform any data residing in the frame of reference of I_A to the frame of reference of I_B. Image registration can be computed within a general framework presented in Figure 1. RIR is the registration of images using only rigid translations and rotations between frames of reference, while DIR can provide a non-linear registration of each point in

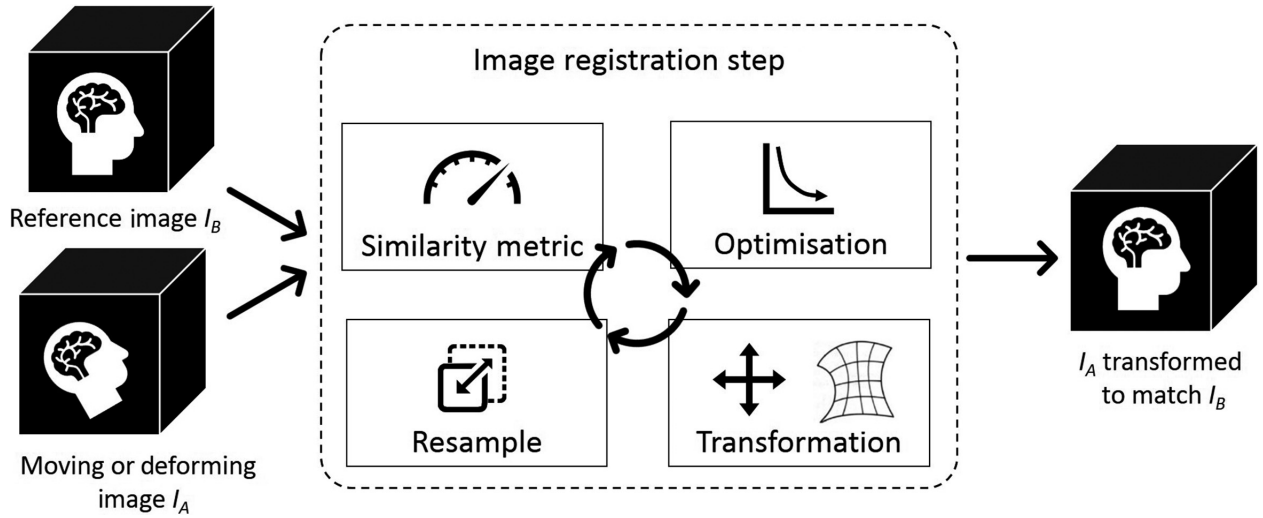

Figure 1. The typical image registration process, where a moving or deforming image is transformed to match a reference image. The same process is used for rigid and deformable registration; however, different similarity metrics, optimisation and transformation algorithms are used.

the images. The theory of similarity metrics, optimisation, regularisation and transformation has been well reported[1,2] and is outside the scope of this report. Image registration, as illustrated in Figure 2, is used for multimodality treatment planning, image segmentation, image-guided treatments, treatment response assessment, replanning and plan adaptation. DIR is becoming widely used, with commercially available modules within radiotherapy treatment planning systems and specific medical image toolkits. DIR has the potential to provide improved ability to more accurately map data between multiple image sets, providing efficiency gains, enhanced use of multimodality imaging and improved quantification of radiotherapy treatments. DIR, however, must be implemented and used with caution, as it is an ill-defined process, the accuracy of which is highly subject to variation in algorithm and user input. Most DIR algorithms do not explicitly model biomechanical properties, and it is entirely possible for results to be physically implausible. For a comprehensive summary of the state of DIR in radiotherapy, see Rigaud et al.[3]

A recent report from the American Association of Physicists in Medicine (AAPM) Task Group 132, 'Use of image registration and fusion algorithms and techniques in radiotherapy',[1] reviews the status of RIR and DIR in radiotherapy and makes recommendations for treatment planning and delivery. The report covers commissioning and quality assurance (QA) of image registration systems, clinical issues and sources of uncertainty. However, the report does not provide recommendations on the advanced applications of DIR such as image or dose deformation, and some recommendations are specific to the US workforce and practice.

A need for local guidance to assist in high-quality utilisation and best practice was identified within the Australian community, leading to the collaborative activity and workshops outlined below. This report aims to communicate the key areas of concern based on the state and limitations of RIR and DIR applications in radiotherapy for Australia and New Zealand (ANZ) and provide advice for use based on consensus from discussions made at the 'Deforming to Best Practice' workshops and with local experts.

Methods

A collaborative group of radiation oncology medical physicists (ROMPs), radiation therapists (RTs) and radiation oncologists formed the 'Society for Medical Image Registration and Fusion (or SMIRF)' to look at safe, high-quality implementation of DIR. SMIRF facilitated two workshops with local expert presenters. The aims were to provide education on RIR and DIR and their application in radiotherapy; provide a forum to discuss implementation and use of current clinical tools; and collect consensus opinion on the current state of the art.

Deforming to Best Practice workshops were convened on 15-16 June 2018 in Sydney and 13 July 2018 in Melbourne. The workshops were attended by 125 and 55 registrants in Sydney and Melbourne, respectively, comprising medical physicists (43%), radiation therapists (47%), radiation oncologists (ROs, 2%), computer scientists and other professionals (8%). Prior to the workshops, registrants were asked to complete a survey on their clinic's use of RIR and DIR, which was used to

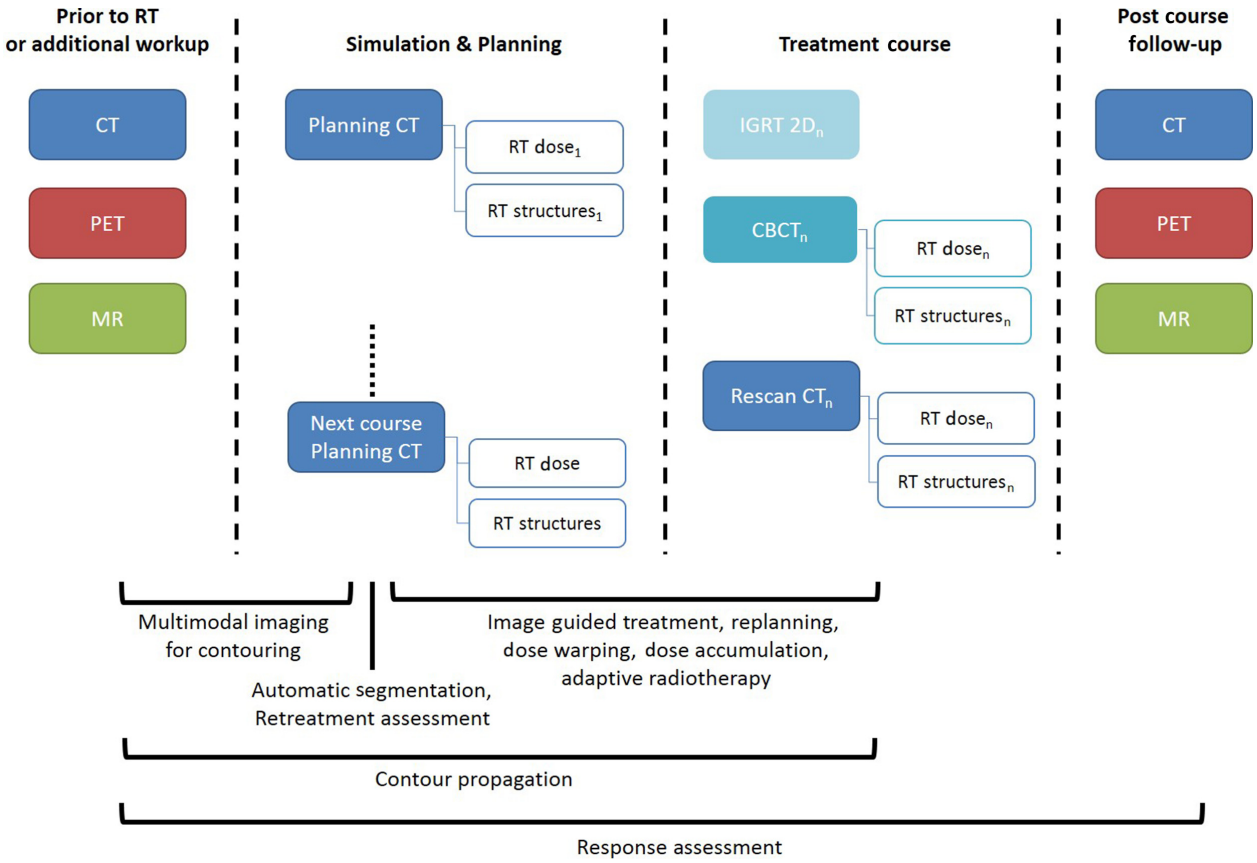

Figure 2. An example patient process map, indicating the imaging data that can be acquired at each phase of treatment, and below, the image registration-related tasks (both deformable and rigid) are indicated across the time period and types of images they may occur.

structure the workshop content and guide discussion. Throughout the workshops, an online polling tool (Mentimeter, Stockholm, Sweden) was used to collect responses from the audience in real time, for display and subsequent discussion. Informal raise-of-hand polling was also used for questions arising from discussion. Key considerations for DIR are drawn from the content experts presented and discussion which was transcribed during the workshop. Where no consensus was decided, further literature review by SMIRF content experts was undertaken to provide advice. Figure 3 describes the process to form the presented advice. The AGREE[4] and RIGHT[5] checklists for clinical guideline development were used where relevant in the drafting of these findings.

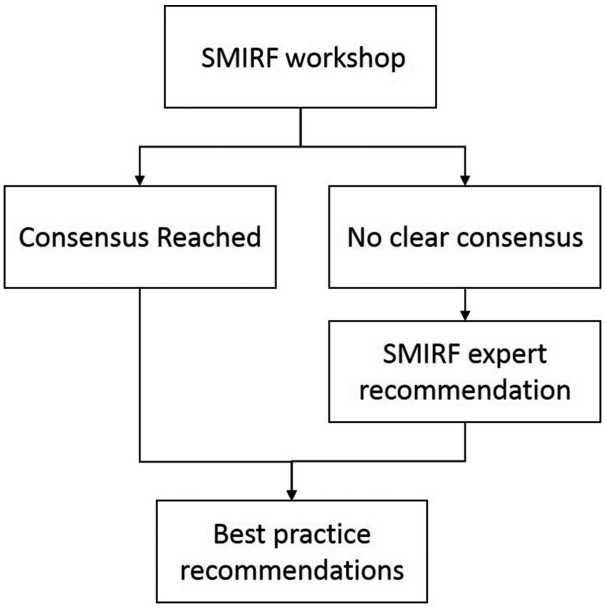

Figure 3. Development process of the advice in this report.

Results

Definitions of terms used in this report are listed in Table 1. Results are presented as general good image registration practice, the current status of image

registration use and applications from workshop participants in Australasia, and then, consensus advice for specific clinical applications of DIR is suggested.

Key considerations for DIR

General best practice considerations for performing DIR are outlined in Table 2 (technical) and Table 3 (process-based), but these are not intended to be a simple recipe for good registrations as it is impossible to provide standardised instructions that can apply to every algorithm and application. The initial manual RIR is a critical step for effective automated RIR and DIR. The best RIR may not be the best starting point for DIR, so it is important to understand how specific image registration software packages work. For instance, two packages may have the same algorithm, but one package may work on the actual image voxel values of the image while another package works based on the displayed window levels. Image registration can only work with the information the user provides, and so, it is critical to use appropriate bounding boxes and thresholds and work directly on the images of interest to obtain acceptable results. By setting bounding box subregions, a registration can focus directly on areas of interest without affecting or accounting for the whole image. A common key point to all registration tasks is to reduce 'upstream' issues/differences where possible and to minimise impact on 'downstream' tasks.

General principles of good image registration practice, RIR or DIR, should be applied when registering and fusing images in the treatment planning process: define the purpose of registration and accuracy required, document which images are being registered, focus on the areas of importance and communicate/document uncertainty and compromises in the registration for the benefit of all downstream processes. Image registration request and report forms such as those given in TG-132 Appendix B are recommended as a model for communicating the quality of all image registrations used for treatment planning.

Table 1. Definitions and acronyms used in this report, following the AAPM TG-132 report.[1]

Term	Definition
Image registration (IR)	The process to generate a transform to convert one image to another image. Registration involves minimising the difference between moving and fixed images, using a similarity metric, to find a satisfactory solution. May also refer to the transform itself.
Rigid image registration (RIR)	A registration using a single 3D or 6D vector applied to the whole image. This may be manually performed by a user or an automatic process using an iterative optimisation process.
Deformable image registration (DIR)	A registration where the transform can vary across the image (i.e. a non-rigid mapping of voxels). Transforms may be free form (spline-based), flow-based (e.g. demons), piecewise or finite-element models.
Deformation vector field (DVF)	A transform describing the vector needed for each voxel to generate a warped image. Can be visualised as an overlaid grid, arrow vector field or colour map.
Warped image	The result of applying a DIR to the moving image. It is now a derived image and should be considered synthetic or a secondary source.
Fusion	The viewing of two images overlaid with a registration applied.
pCT	Radiotherapy simulation or planning CT.
rCT	A rescan CT or additional planning CT acquired during treatment.

Current status and considerations for clinical applications

A summary of advice for each clinical application is given in Table 4 (DIR between particular imaging modalities) and Table 5 (applications of DIR for deriving contours and dose). The following describes the current status of applying DIR to clinical applications by image modality.

CT-pCT registration

While RIR of a planning CT (pCT) with other (diagnostic) CT images is routine practice in treatment planning, the use of DIR between CT images is still in the early stages of adoption.[6,7] Due to the similar nature of the information in each image, it may be the best performing of DIR applications. DIR between CT sets may be useful, for instance, when registering images acquired with the patient in different positions such as arms-up or arms-down positions, or flat and round couch tops.

CBCT-pCT registration

Online and offline CBCT image-guided treatments are routinely performed by all clinics. There is variation in how advanced tools and matches are performed. Most departments now have at least one linear accelerator (linac) couch able to correct 6 degrees of freedom, with use limited to select cases. Matching low-contrast soft tissue information in CBCT is considered an important skill for RIR and IGRT,[7] and necessary for assessing DIR.

When using CBCT for image registration applications, it is important to remember accuracy is impacted by

Table 2. General technical considerations when performing DIR.

Determining the bounding box or Region of Interest (ROI) for registration

- For the initial RIR, be careful not to include/clip high-contrast structures that move relative to the target soft tissue structures within a rectangular ROI as these will bias the registration, for example pubis when registering prostate.
- Individual ROIs should be defined appropriately for each registration application, based on the clinical goal of the registration.
- If bounding boxes are used for DIR, the box should include enough contrast and, if possible, should encompass entire organs that may deform, to avoid discontinuity at borders.
- If a good result cannot be obtained for the full registration ROI, try using sequentially smaller regions to progressively tune the result. Watch out for discontinuity between regions.

Initial RIR is critical for effective DIR

- Ensure the RIR is accounting for systematic variation between images (provides a global/coarse fit in the region of interest), so that the DIR can focus on deformation alone.
- In images with large variations, the RIR should be optimised to provide the strongest registration at areas of greatest clinical importance. Potentially, multiple registrations are needed to focus on separate areas across the image.

Contrast within the ROI

- Regions of low contrast provide little intensity variation 'features' for algorithms to compute the deformation and thus may give incorrect or non-physical results when using DIR. This is of importance when deforming PET or dose images according to the registration between two CT images.
- Use thresholds and window/level settings to improve contrast where possible.

Understand the limitations of RIR and DIR

- Image registration is a mathematical tool, with limited or no biological information involved in the process. There are limitations in compensating for large changes in pose, expansions and contractions, and differential movement of tissues with varying biomechanical properties and attachment.
- Recognise when RIR/DIR is appropriate, and consider viewing images side by side if neither RIR/DIR provide accuracy required.
- Communicate and document the accuracy or uncertainty level which represents a recommendation for end use; include residual errors or uncertainties for downstream processes.
- Limitations may be due to software, the images used, operator experience or the task itself.

Iterative deformation can improve accuracy

- Where available, tools that allow refinement of deformations can be used to iteratively improve DIR and correct poorly performing areas, for example focus structures and anchor points.

Table 3. General process and workflow considerations when performing DIR.

Review registrations

- The amount of QA should reflect the risk of the task. This may indicate that multiple QA tools are used to assess the registrations, preferably by multiple staff.
- Reviews of registration should contain both quantitative and qualitative assessments of the performance of the similarity term and the transform term (feasibility of deformation vectors).
- Consider using the RIR if the DIR does not improve the accuracy level significantly.
- Ultimate approval lies with the radiation oncologist, taking into account the clinical scenario.

Registration naming and storage conventions

- RIR and DIR should be saved and accessible with naming that conveys date and purpose of IR.
- Use comment fields to record information that may change downstream (dates, users, etc.).
- Keep records indicating how a structure has been derived, resampled and finalised from DIR.
- Clarity and consistency in naming increase the safety of using DIR.

Consider reproducibility of registrations

- Where user-dependent interactions are required, protocols should be employed to ensure consistency. For example: when utilising tools that are user-dependent (such as local registration lock points or contours), the process may not be repeatable, or the method may not be evident at a future date.[67] It is also possible to make deformations that may look 'correct' but are unrealistic. Caution is urged with user-dependent tools.

Acquire all images in similar position where possible

- Discussions with radiology and nuclear medicine staff can lead to standard procedures for better diagnostic scans that more closely match RT planning scans – optimised acquisition parameters, creating flat couch areas, etc.; 'low-tech' solutions like using MR-safe and small-bore compatible radiotherapy immobilisation equipment during MR or PET imaging to replicate treatment positions, and RT attendance for imaging, can result in more accurate imaging tasks downstream.

limited field of view, limited image length, decreased image quality of CBCT and artefacts inherent to CBCT.[8] The accuracy of CBCT HU is complex and changes with image dose, size and geometry of the subject and beam spectrum. The achievable accuracy of dose calculation on CBCT can be within 2% in some simple geometries or up to 20% in a region straddling the shoulders and neck.[9] It is important to consider the above factors when evaluating dose calculated on CBCT and consider using tissue, air and bone override regions.[10]

MR-pCT registration

Few attendees had experience with attempting DIR with MR images (13%). The tools available in commercial packages varied, but typically apply a mutual information

Table 4. Summary of key considerations for DIR between various image modalities used in radiotherapy.

Image modalities	Key Considerations	Ref
CT-pCT registration	No specific considerations extending Table 2.	
CBCT-pCT registration	Limitations of CBCT (FOV, HU accuracy, length limits) should be evaluated when estimating dose calculated on CBCT. Consider using tissue, air and bone overrides.	8
MR-pCT registration	MR-pCT DIR should not be used routinely with the current tools available, unless multiple users have evaluated results on both technical and clinical grounds.	11
PET-pCT registration	Validate the consistent frame of reference between the PET and its attenuation correction CT before coupling other registrations. PET-pCT DIR should only be performed using the intermediate registration between the attenuation correction CT and pCT.	15

similarity metric. DIR of MR-pCT is often unsuccessful, and RIR is ultimately used in most cases.[11–15] DIR of MR-pCT to correct MR distortion in controlled situations such as cranial stereotactic radiotherapy scans acquired in the same position may be successful with careful review. For most scenarios, workshop attendees considered RIR as the best approach to register MR imaging for radiotherapy planning. Current DIR algorithms struggle with dissimilar image information.[16–18] With the advent of MR-linacs and MR-guided adaptive treatments, there is a range of workflows reported using both rigid and deformable registration processes.[19–22]

Direct planning on MR images may be considered where soft tissue definition is not sufficient from CT images (e.g. bilateral hip prostheses). In such a case, registration should be performed on the high-contrast features that are visible between CT and MR, avoiding CT artefacts. In all cases where MR is to be used for planning, it is imperative that routine QA of MR image spatial distortion is performed.[23–25]

It is considered that MR-pCT DIR is not used routinely with the current tools available, except in individual cases where results are evaluated as suitable by multiple users on both technical and clinical grounds.

PET-pCT registration

Some attendees had experience with DIR for PET/CT-pCT registration (26%). Within that group, there was agreement that in many cases, the uncertainties in DIR were equivalent or not significantly more than using RIR,

Table 5. Summary of key considerations for clinical application use cases of DIR

Clinical Application	Key considerations	Ref
Contour propagation between pCT and rCT	Any structure derived from another should not be propagated, but instead re-created from the corrected propagated anatomical structures (e.g. margin expansions and Boolean products).	1
	Propagation of rigid/deformed isodose contours (e.g. for retreatments) are to be assessed for accuracy level achieved, as they cannot be corrected with subsequent editing.	31
	All deformably propagated structures should be reviewed and any errors corrected/assessed prior to further use	
Atlas Segmentation	Dice similarity coefficient should be used in combination with other metrics such as volume, location and surface measures.	1,33
	The clinical impact of automatically generated contours should be evaluated through determination of the dosimetric differences when using automatic versus manual segmentation for each department.	36
	Use pre- and post-processing steps to save time (e.g. build atlases with smoothed and cleaned contours; atlas contours contain every third slice then interpolate as a final step).	37
Adaptive Radiotherapy	Offline adaptation is feasible with current tools but resource-intensive. Each department needs to assess their capacity to implement.	31
	Online adaptation tools may be available, but workflows and expertise are not necessarily developed yet. More development is needed.	66
Replanning	DIR can increase efficiency of replanning workflows for contouring. Automated workflows reduce manual steps and may reduce errors. The same careful review as manual replanning is required.	31,68
Retreatment	The best estimate of previous dose depends on the scenario and available tools. Uncertainties of warping previous dose should be weighed against gains from providing a spatially correlated indication of past treatment.	
Dose Accumulation	Current tools and workflows for dose accumulation are not ready for routine clinical application, and the	3,31,69,

(*Continued*)

Table 5. Continued.

Clinical Application	Key considerations	Ref
	value gained from dose accumulation is not yet proven. Use should be evaluated as suitable by multiple users on both technical and clinical grounds.	
Brachytherapy	Many challenges exist in brachytherapy DIR, and it should not be used in routine clinical application yet. Use should be evaluated as suitable by multiple users on both technical and clinical grounds.	52
Response Assessment	Large potential for quantitative response assessment and combination with functional or radiomic information. Scope for significant research.	57,58

given the innate uncertainties of using PET images.[26–28] This is disputed in some literature, which indicates it provides minimal value.[15,29,30]

Validation is needed for the consistent frame of reference between the PET and its attenuation correction CT before coupling other registrations, in case there is patient movement between scans or if the two bores of the PET/CT scanner are not well aligned. PET-pCT DIR should only be performed by making use of the intermediate registration between the attenuation correction CT and pCT.[15]

Contour propagation (same subject, e.g. pCT to rCT)

Deformable image registration is commonly used for contour propagation tools in replanning, atlas segmentation or adaptive planning for translating delineated structures defined on one image to another. The opinion on time and resource efficiency using DIR methods compared to recontouring from scratch depended on the clinical/anatomical site, accuracy required and individual patient anatomy.

Any structure derived from another (Boolean combinations or margin expansions) should not be automatically propagated, but instead re-created from the corrected propagated anatomical structures.[31] Use caution when deforming tumour structures during a treatment course, as the deformation algorithm may not change the shape of the structure the same way that the actual cells are behaving.[32]

Rigid or deformable propagated isodose contours (e.g. for retreatments) are not correctable with editing but require assessment as to the accuracy level achieved. All propagated structures should be reviewed and any errors considered prior to further use.

Automatic segmentation

A majority of attendees had developed or implemented atlas-based automatic segmentation (54%). A range of anatomical site atlases is in use, with head and neck and pelvis being the most common. Setting up atlases requires significant resources and agreement on nomenclature.[33] Machine learning methods for automatic segmentation, particularly deep learning, are showing promising developments.[34]

Some atlases were ultimately not routinely used clinically after development, often due to lack of stakeholder consultation, differences in delineation between clinicians or efficiency gains not eventuating in practice. Robust agreement on structures between all users of an atlas is a key starting point, or differences in practices must be accounted for in the atlas creation.

While Dice similarity coefficient (DSC) is commonly used to assess atlas performance, it should be used in combination with other metrics such as volume, location and surface measures such as mean distance to agreement (MDA) or Hausdorff distance.[35] Ideally, the clinical impact of automatically generated contours should be evaluated through determination of the dosimetric differences when using automatic versus manual segmentation.[36]. That is, the accuracy of the automatically generated contours should be evaluated based on the eventual use of those contours.

To reduce editing time and improve computational performance, use pre- and post-processing steps.[37] For example, build atlases with smoothed and cleaned contours. Reducing atlas contours to every third slice can be more efficient for correcting and then interpolating to all slices as a final step.

Sharing of atlases was viewed favourably by attendees. Infrastructure and governance factors can be solved (privacy requirements, data transfer, storage and effort required). Adopting an atlas across multiple departments would most likely require changing local practice to conform to the atlas contours. Large cooperative trials or professional groups may be well placed to test shared atlases.

Adaptive radiation therapy (ART)

Most attendees stated performing some form of ART (93%), typically utilising a replan CT triggered by image guidance during treatment or patient set-up variations, for example mask not fitting. Precisely, combining and

accounting for adaptations often require DIR. Other types of ART not commonly in routine use include adaptive dose monitoring, daily adaptation and online replanning. Replanning is specifically addressed below.

Consensus indicated that offline adaptation (scheduled replans, adaptive dose monitoring and regular replans between treatments) is feasible with current tools. However, it is resource-intensive and should be undertaken with care to ensure it is feasible within a specific working departmental environment. Online adaptation tools are often available, but workflows and expertise are not necessarily developed sufficiently in many cases. This is likely to improve in the near future as vendors provide more integrated solutions. This will bring challenges for the radiotherapy community to cope with the additional information and decisions in an optimal manner [38].

Replanning

Deformable image registration is often used as part of replanning processes, including for registration between pCT and rCT (rescan planning CT), propagating the original contours to the rCT (manually or as an atlas). Anecdotally, increased image guidance increases replan rates amongst attendees, and typical rates were 5-10% of head and neck plans and up to 30% of lung plans. Breast and prostate plans were also occasionally replanned during treatment. The turnaround of a replan was typically 3 days.

The introduction of DIR to replanning workflows can increase the efficiency and improve plan turnaround time, as well as reduce the number of manual tasks required. However, automated DIR processes still need careful review as would normally be performed for manual replans [39]. Investigations that ultimately do not result in replanning take considerable department resources, and DIR can be utilised to make these more efficient also.

Dose warping

Dose warping is rarely used clinically at present, but may be used for example to evaluate historical dose for retreatments. Another application is to compare total dose for nearby irradiated regions when the planning images were acquired in different positions (such as one arms-up and one arms-down). Some scenarios where it may be beneficial to use dose warping include between images in a 4DCT set,[40] treatment dose accumulation, retreatment (local and distant) and for assessing dose–response relationships to functional imaging. Other applications of dose warping were limited to research settings.

Dose warping (or dose deformation) is a purely mathematical tool and does not always directly relate to physical processes,[41] but it can be valuable in some scenarios, especially as dose–volume histograms cannot be summed between plans calculated on different underlying anatomy.

For retreatment scans in different patient positions, it may be better to use DIR instead of the traditional practice of rigidly registering two images and assessing overlap, and accept the uncertainties present.

Dose deformation should be rigorously reviewed by a RT and ROMP together to consider the accuracy of the resulting dose, and the radiation oncologist (RO) involved or informed of the processes taken to inform approval of the process.[1,42]

Retreatment

Patients receiving more than one course of radiotherapy are a significant part of radiotherapy department workloads – a multi-institutional study reported an average retreatment rate for 16% of patients and 25% of courses.[43] With improved treatment techniques and better data on normal tissue dose–volume relationships,[44,45] there is demand for improved accuracy of historical dose in subsequent courses of treatment (distant or local). DIR can be used to warp previous treatment dose to the new scan, to indicate overlap or response to treatment. In such cases, the DIR uncertainties may be deemed minor compared to other clinical uncertainties in decisions for retreatments.

There was general agreement that DIR for retreatment has a positive benefit/risk ratio, particularly when there is (1) significant time lapse between courses and already high uncertainties in tissue changes, forgotten dose, etc., or (2) simulation images acquired in different positions (high uncertainty in correspondence of dose due to anatomy deformation, difficult to indicate range of dose overlap).

Increased uncertainty in a retreatment may result in practical impacts such as larger target volumes, increased toxicity or changing from radical to palliative intent. The best estimate of previous dose possible should be used, with the tools available.

For retreatments with different fractionations, radiobiological equivalent dose scaling might be considered. In the case of summation of photon dose and proton or ion treatment dose, care should be taken to consider the differences in charged particle deliveries: the PTV concept does not translate well, and robust optimisation strategies may be applied to ensure coverage.[46] Doses may be reported in a DVH band, for a range of delivery scenarios. This uncertainty, as well as

radiobiological effectiveness (RBE), increases the difficulty of dose summation.

Treated dose accumulation

It is possible to calculate dose using a CBCT, but to do this in a meaningful way requires careful analysis.[32] It should not be considered validated as a general solution.[3] The result can be warped to the planning CT to build a cumulative treated dose distribution. Alternatively, the previous day's cumulative dose can be warped to the current day's image and calculated dose for summation. Refer to above section CBCT-pCT Registration for the issues and corrections. Some reports of calculating daily accumulated dose have required a full-time staff member to perform it;47 however, improvements to workflow and automation may make this viable.

Considerable experience and understanding of the local treatment systems are required to be able to make meaningful decisions based on dose accumulation results.[48] RT, ROMP and RO should assess as a team before clinical decisions are made. The value of dose accumulation is not yet proven, and it is unclear if treated dose correlates with response in the same manner as the current planned dose evidence base.[49,50] At present, any dose accumulation should be rigorously reviewed due to inherent uncertainties before being used for clinical decision-making.

Brachytherapy

Brachytherapy may rely on registration of multiple CT, MR and US images. These images may be acquired in different positions and in the presence of differing applicators, seeds and probes. These changing parameters make the task non-trivial; however, DIR in brachytherapy is typically only used in research applications. Despite these uncertainties, DIR may have an important role in accumulating dose between sequential brachytherapy insertions and in adding external beam to brachytherapy dose.[51–53] DIR in brachytherapy is not used routinely with the current tools available, except in individual cases where results are evaluated as suitable by multiple users on both technical and clinical grounds.

Response assessment

Deformable image registration can create a common reference for assessing images prior to, during and after treatment. There is potential for significant advances in quantitative response assessment, beyond the Response Evaluation Criteria In Solid Tumours (RECIST) rules.[54] Combining functional imaging with DIR methods is creating new opportunities such as mapping changes in lung function with perfusion and ventilation imaging.[55–57] Future advances in radiomics will also need to work with or alongside DIR.[58,59]

Implementation of DIR

Commissioning

Using DIR in the clinic brings enhanced functionality and responsibility to commission and QA appropriately. The TG-132 report provides a framework for commissioning DIR, which this report endorses. It consists of commissioning tests for data integrity, collection of baselines for periodic testing after upgrades and performing end-to-end tests for each new application in the clinic. Ideally, the performance of DIR should be evaluated for all possible clinical scenarios using local clinical data sets prior to clinical implementation. However, this may not be feasible in practice, and a pragmatic approach can be used that covers a range of example data sets representing desired clinical applications or use cases, and a risk-based approach assessing DIR as part of the overall radiotherapy treatment chain. Similarly, routine ongoing QA should follow from baselines acquired during commissioning and reflect clinical usage.

Patient-specific QA and documentation

There was strong consensus agreement for adoption of the TG-132 Request and Report forms to be used as a transparent and documented method for patient-specific QA of both RIR and DIR. The request allows the RO detail areas of importance, registration technique and what a registration will be used for. The report form details what was performed, quality assurance results and an estimate of accuracy to guide decision-making. Using the forms for communication is important for both clinical efficiency and effectiveness of the IR. While experience and understanding are being built, it is advisable to have multiple redundant checks of all uses of DIR.

Department-specific workflows should ensure trained staff are assigned clear tasks at each part of the process for image registration as well as upstream and downstream processes. Guidelines on what constitutes a satisfactory registration should be based on metrics determined from commissioning data sets. Despite many attempts in the literature, no robust quantitative measure for individual DIR accuracy has been developed, and the required evaluation and QA are dependent on application.[3] As such, a range of quantitative QA metrics

and qualitative QA (e.g. visual inspection) should be used in all clinical applications. Examples of QA for various clinical applications are given in Table 6. For example, contour propagation may require visual inspection only, with all contours to be reviewed and adjusted by the RO before further use. However, a retreatment dose summation may require qualitative review of the deformation vector field (DVF) for plausibility, quantitative measures such as mean distance to agreement (MDA) and Dice similarity coefficient (DSC) applied to structures of interest in the summation, an independent user check of the correct images and structures being propagated and resampled, as well as any isodoses from the resampled dose that might then be used for input to a new plan optimisation. Depending on the accuracy required, point-to-point landmark correspondence may need to be evaluated. There is a range of metrics and methods proposed in the literature that can also supplement these methods or be useful in specific situations [60,61].

Clinical implementation, workflows and automation

Consideration of the appropriate model for clinical roll-out is needed. Identify which aspects/techniques are to be prioritised (e.g. retreatments). It may be beneficial to choose a single anatomical site as a pilot to begin, driven by need. Develop communication channels and common language for discussing image registration. Roles, responsibilities and QA mechanisms should also be defined upfront between RO, RT and ROMP, including clear and consistent communication and interfacing between and across the different group tasks. Multidisciplinary review of DIR, at least during early stages of implementation, can be highly beneficial. Each profession brings a different expertise to the problem, and shared experience will improve understanding and skills across the board. Ultimately, as the tools and experience in each department will be different, local implementation strategies and protocols are needed that are specific to equipment, expertise and clinical needs.

Data management policies are useful for tracking data, performing tasks in the correct order and deciding where each task is performed if multiple systems are used (e.g. contouring may be performed in multiple workspaces, but consider use of one system where contours are finalised for consistency). Standard operating procedures and automated workflows in image registration toolkits can be created in parallel. Naming conventions, approval processes and version control all need to be considered.[62,63]

Deformable image registration can quickly become a complex process with many steps which are laborious and

Table 6. Suggested patient-specific QA tasks by clinical DIR application. This is an example list, and each case may have its own requirements. Replanning, retreatment and adaptive processes may include multiple of the below applications

Clinical Application	QA tasks
Multimodal image registration for contouring as input to a treatment plan	• IR Request from RO specifying series and regions of interest, purpose of registration • Visual inspection of registration by RT and/or ROMP • Visual inspection of DVF to comprehend deformation by RT and/or ROMP • Check registration appropriate for each series in image set if propagating across multiple series • New data sets resampled and named according to department rules • Report to RO the IR performed, limitations and accuracy for desired purpose per request
Anatomical contour propagation pCT/rCT	• Visual inspection of registration by RT and/or ROMP • Review and editing of contours by RO
Dose-derived contour propagation pCT/rCT (e.g. isodoses)	• IR Request and Report forms • Visual inspection of registration results by experienced ROMP • Report accuracy attained following a system based on commissioning results and TG-132 accuracy levels. An example method to quantify accuracy is the mean and maximum from a structure DVF cumulative histogram.
Atlas Segmentation	• Visual inspection of result, editing and post-processing by atlas user • Review and editing of contours by RO
Dose warping	• IR Request and Report forms • Visual inspection of DVF by ROMP • Quantitative metrics such as DVF histogram, Jacobian maps, inverse consistency and harmonic energy • New data sets resampled and named according to department rules

(*Continued*)

Table 6. Continued.

Clinical Application	QA tasks
	• Independent check of correct data sets and processes used
Dose Accumulation	• IR Request and Report forms • Visual inspection of DVF by ROMP • Quantitative metrics such as DVF histogram, Jacobian maps, inverse consistency and harmonic energy (59) • New data sets resampled and named according to department rules • Independent check of correct data sets and processes used, and correct weighting applied to each input dose

error-prone. Using automated workflows is encouraged to reduce the chance of simple errors, but enough checkpoints are needed to allow for manual review and validation of the automated results. Education and experience become critical as automation is introduced. When the automation fails at a task, manual processing will be required, and so, expertise and a fundamental understanding of the algorithms need to be maintained within a department for this situation.

The resources required to perform and quality assure DIR need to be considered. Adding delays in the patient's planning processes should be avoided. Inevitably, careful introduction of this new technology will put increased pressure on the time required to plan a patient's treatment; however, with increased adoption and user experience/confidence, this will ease. DIR has the potential to reduce time, for example atlas-based segmentation and contour propagation, and is integral to fast automated plan adaptation.

Education and training

Training for RIR and DIR is important, and consideration needs to be made for the appropriate model of training for a department. Example models include all staff trained to minimum level in both theory and software, or a small group of expert users to support the wider group. The minimum level of understanding for an application or software package will vary but should include a basic understanding of algorithms, comparable to IMRT optimisation for radiotherapy planning. Vendors should be able to provide material describing specific algorithms. Training amongst all staff groups involved is required. Differences in training needs between disciplines should be considered. Traditionally, roles in performing image registration have been segregated, with RTs performing the majority of image registration in ANZ. However, DIR requires a collaborative approach as uncertainties, technical limitations and clinical decisions associated with using DIR need to be understood by all groups. Site visits and discussions with experienced departments are encouraged. Training should cover 'how-to' training for new software, as well as background theory to develop critical analysis to identify and rectify suboptimal results.

There is limited formal training available in this area beyond vendor-specific application courses, and further opportunities for teaching in DIR theory and application should be considered in the future by the professional organisations. While the workshops gave general advice for DIR in various clinical applications, participants in the workshops expressed a desire for more detailed help to perform DIR tasks. Software differences make it difficult to provide universal solutions, but there is scope for future workshops, training and credentialing packages to address this for a particular software.

Utilising a risk-based framework

Risk-based approaches allow for assessment of relative risks of all processes that are unique to departments, enabling quality controls that target vulnerabilities. To enable effective, feasible, and practical quality control, quality measures in place can target the root causes, combined with appropriate data and models [64].

The overall image registration process can be evaluated for residual risk and uncertainty with departmental consensus on acceptable risk, uncertainty and trade-offs based on available solutions available (e.g. side-by-side images, rigid only, deformable only, re-image, do not use). For an example approach, see the paper by Yuen et al [65].

The workshop identified that there are varying risks in the use of DIR, depending on the application of the DIR results. For example, the risk of DIR for propagating deformed contours is far lower than the use of DIR for propagating deformed images and/or doses. Validation of deformed contours can be done with existing expertise and software by fixing contours and does not require DIR-specific evaluation such as DVF analysis. Validation of deformed images and/or doses requires more DIR-specific quality assurance with validation requirements depending on the intended use and accuracy level required. Departmental DIR commissioning and experience will guide understanding of risk factors

relating to DIR which can be used to modulate the quality assurance required.

DIR research packages

Open source and research tools are not recommended for routine clinical use. They require specialised expertise and, if used clinically, should be within a well-documented protocol, for example clinical trials.

They can, however, supplement existing practices as tools for training, benchmarking or extending clinical systems. All data going in and out of an oncology information systems and treatment planning systems should be parsed through, for example, an Australian Therapeutic Goods Administration (TGA)-approved software first to ensure integrity. These packages generate virtual phantoms, perform cross-validation with different DIR algorithms and test advanced concepts like masking, multi-algorithm registrations and prototype pipelines for workflows. If used in the context of clinical trials, research tools should be validated/commissioned carefully to ensure the outcome of the trial is not invalidated.

Conclusions

The applications of DIR are still maturing without a set of definite practice standards. The workshops provided an avenue for knowledge sharing and constructive discussion on both theory and practice in image registration. Conclusions reached by the majority of active participants in the discussions resulted in a set of agreed best practices for clinics integrating DIR.

It is impossible to provide standardised instructions for all DIR cases. An understanding of the processes involved is important to assess and revise the results obtained. When viewed in a risk framework, DIR has many applications with a positive benefit/risk ratio if implemented with care. However, this is not so for all applications. There is no single quantitative measure that can fully evaluate DIR for different applications and use cases, and so, professional judgement and multidisciplinary input are normally required for evaluation. Different DIR algorithms will behave differently; therefore, users need to be aware of specifics of their software before clinical use. The TG-132 Request and Report forms are an example tool for combining relevant information for all parties to improve the benefit/risk ratio.

Education and training are vital for high-quality utilisation of image registration and effective implementation of DIR. There is a scarcity of resources and training events at present. RIR may be a mature and routine task in many departments; however, it is a fundamental requirement to performing DIR tasks optimally. It should not be ignored when training for DIR. Automation should be utilised where possible, but a general understanding of the processes and what can realistically be achieved needs to be conveyed to all users.

The SMIRF group responsible for the workshop and this report has transformed into the Medical Image Registration Special Interest Group (MIRSIG) of the Australasian College of Physical Sciences and Engineering in Medicine (ACPSEM). Future developments, research and guidance from this group will follow in this rapidly developing area.

Acknowledgements

The authors would like to thank all the workshop participants who provided robust and thoughtful discussion that has been aggregated into this report, as well as all members of SMIRF who have provided discussion and ideas.

Conflict of Interest

The authors declare no conflict of interest.

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