



HAL
open science

Multimodal imaging in radiotherapy: Focus on adaptive therapy and quality control

A. Talbot, L. Devos, F. Dubus, M. Vermandel

► To cite this version:

A. Talbot, L. Devos, F. Dubus, M. Vermandel. Multimodal imaging in radiotherapy: Focus on adaptive therapy and quality control. *Cancer/Radiothérapie*, 2020, 24, pp.411 - 417. 10.1016/j.canrad.2020.04.007 . hal-03492253

HAL Id: hal-03492253

<https://hal.science/hal-03492253>

Submitted on 18 Jul 2022

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial 4.0 International License

Multimodal imaging in radiotherapy: focus on adaptive therapy and quality control

Imagerie multimodale en radiothérapie : focus sur la thérapie adaptative et le contrôle qualité

Antoine TALBOT ^{a,b}, Laura DEVOS ^{b,c}, François DUBUS ^{a,b}, Maximilien VERMANDEL ^{a*,b,c,d,e,f}

^a Medical Physics Department, CHU de Lille, 59037 Lille, France

^b Neurosurgery Department, hôpital Roger-Salengro, CHU de Lille, 59037 Lille, France

^c Nuclear Medicine Department, hôpital Roger-Salengro, CHU de Lille, 59037 Lille, France

^d Université de Lille, 59000 Lille, France

^e Inserm, U1189, 59000 Lille, France

^f ONCO-THAI – Image-Assisted Laser Therapy for Oncology, CHU Lille, 59000 Lille, France

*Corresponding author: Maximilien Vermandel; e-mail: physique-medicale@chru-lille.fr

Abstract

Improved computer resources in radiation oncology department have greatly facilitated the integration of multimodal imaging into the workflow of radiation therapy. Nowadays, physicians have highly informative imaging modalities of the anatomical region to be treated. These images contribute to the targeting accuracy with the current treatment device, impacting both segmentation or patient's positioning. Additionally, in a constant effort to deliver personalized care, many teams seek to confirm the benefits of adaptive radiotherapy. The published works highlight the importance of registration algorithms, particularly those of elastic or deformable registration necessary to take into account the anatomical evolutions of the patients during the course of their therapy. These algorithms, often considered as "black boxes", tends to be better controlled and understood by physicists and physicians thanks to the generalization of evaluation and validation methods. Given the still significant development of medical imaging techniques, it is foreseeable that multimodal registration needs require more efficient algorithms well integrated within the flow of data.

Keywords

image registration, treatment planning, adaptive radiotherapy, patient positioning, multimodality imaging

Résumé

L'amélioration des ressources informatiques des établissements de cancérologie ont grandement facilité l'intégration de l'imagerie multimodale dans le flux de données des prises en charge. Aujourd'hui, les radiothérapeutes disposent de modalités d'imagerie plus informatives de la région anatomique à traiter. Ces images, souvent de bonne résolution, contribuent à augmenter la qualité de la thérapie grâce à une définition plus précise des cibles et un meilleur contrôle de la position de traitement. Dans un souci constant de personnaliser les prises en charge, de nombreuses équipes cherchent à confirmer les bénéfices de la radiothérapie adaptative. Les travaux publiés mettent en évidence l'importance des algorithmes de recalage, indispensables pour tenir compte des évolutions anatomiques au cours du parcours médical mais également pour le suivi post-thérapeutique. La maîtrise de ces algorithmes, souvent considérés comme des « boîtes noires », tend à s'améliorer grâce à la généralisation des méthodes d'évaluation et de validation. Compte tenu du développement encore important des techniques d'imagerie médicale, il est prévisible que les besoins en recalage multimodale requièrent des algorithmes plus performants et mieux intégrés au flux des données.

Mots clés

recalage, planification de traitement, radiothérapie adaptative, positionnement, imagerie multimodalité

1. Introduction

Modern radiotherapy is part of the field of image-assisted therapies and therefore benefits from the latest developments in multimodal imaging. In this article, we propose a review of the applications of multimodal imaging in radiotherapy. We do not discuss here the methodological aspects of image registration or fusion, but the interested reader may refer to the latest reviews of the literature in this still very active field of research (1-3). From an acquisition point of view, developments in imaging are accompanied by a better spatial and temporal resolution involving an ever-increasing number of images to be captured. Thus, the complexity of using multimodal images in radiotherapy lies, in particular, in the ever-increasing volume of data to be manipulated. Today, the democratization of parallel programming on graphic processor units (GPUs) and the use of faster microprocessors allow the implementation of more sophisticated algorithms while reducing computing time. This phenomenon is particularly observed in the calculation of dose on treatment planning system in which

Monte-Carlo simulations gradually replace convolution-based algorithms. Similarly, multimodal image registration benefits from this evolution and can now be easily integrated into an image processing workflow for dosimetric planning.

The planning or positioning of the patient at each session has been extensively documented in the literature (1, 9-15). In this article, we present in particular the needs and solutions that multimodal imaging provides for adaptive treatment or post-treatment follow-up. In addition, in an increasingly rigorous quality assurance context, we are also addressing the issue of the implementation of registration algorithms and associated quality controls. In particular, we present the recent recommendations of the American Association of Physicists in Medicine (AAPM) which aim to standardize evaluation methods and criteria.

2. Adaptive radiotherapy

Yan et al. were the first to describe the concept of adaptive radiotherapy in 1997 (16). As Badey et al. point out in their recent inventory of fixtures, adaptive radiotherapy consists in adapting the initial plan during treatment to take into account anatomical changes that have appeared and have dosimetric consequences on the target and/or high-risk organs (17). The vast majority of recently published techniques use deformable registration algorithms to match planning imagery and associated contours with imagery acquired during processing.

In clinical practice, adaptive radiotherapy can be implemented with several levels of complexity. The basic level that is not yet adaptive is first to assess whether the doses delivered during fractions from day imaging are in accordance with the initial plan. This assessment consists of verifying that the margins of the planned target volume cover changes (displacement/deformation) in the clinical target volume and that the doses to organs at risk do not exceed the planning constraints. Then, the most common practice of adaptive radiotherapy is called "offline" or delayed, i.e. the anatomical changes observed will require a modification of the treatment plan between two fractions. The new adapted plan(s) is/are based either on a new computed tomography scan (CT) or on images of the day (e. g. kilovolt cone beam computed tomography [kV-CBCT], megavolt CT [MV-CT], magnetic resonance imaging [MRI]). Another practice described in the literature and called "hybrid" is the use of a library of plans. In this case, the anticipated anatomical changes (example of the effect of bladder filling on pelvic irradiation) are at the origin of the preparation of several treatment plans that will be chosen during the treatment sessions to correspond as closely as possible to the anatomy of the day. The most advanced adaptive technique is called "online" or live. As with patient repositioning, the plan is modified while the patient is in the treatment position. The plan is adapted on the day's imagery and then delivered on the current fraction. One of the limitations of this technique is that the modified plan cannot be verified by measurements before it is issued.

Regardless of the methods used, the authors of the studies presented highlight the significant human and material resources needs required to implement adaptive radiotherapy strategies without always observing significant dosimetric and clinical results.

2.1. Monitoring of the delivered dose

Without necessarily adapting the treatment plan, teams proposed methods to assess whether anatomical changes observed by imaging during treatment significantly altered the daily dose planned by the treatment planning system. These methods are based on images registration between the images of the day and the images of the planning.

For example, Ziegler et al. presented the results of a study on patients treated for pancreatic cancer (18). The objective was to evaluate the impact of inter-fraction anatomical changes (intestinal and gastric filling) on the dose delivered to each fraction and thus on the total doses to the target and organs at risk to compare them with the planned doses. To calculate the dose delivered to each fraction, the authors evaluated and compared the best parameters to be used in their deformable registration algorithm (B-Spline) and applied it to the planning CT images to adapt to the patient's anatomy obtained by the kV-CBCT images acquired at each treatment session. To avoid intra-fraction modifications, kV-CBCTs were acquired in blocked breathing like the planning CT. In addition, to compensate for the low pancreatic contrast in the kV-CBCT images, a metallic fiducial marker was implanted in the tumour prior to the acquisition of the planning CT. Prior to the deformable registration on the CT, rigid image transformations were applied. The application of the deformable registration algorithm produced displacement fields necessary for the construction of deformed CT images at each fraction. The study evaluated and compared different metrics and regularization levels of the deformable registration algorithm based on two criteria: visual chessboard evaluation of images from both modalities by a single operator (score from 0 to 4 depending on the quality of the correspondence of anatomical landmarks) and measurement of the distance between the fiducial marker positions in the kV-CBCT images and in the images of the corresponding deformed CT.

The best deformable registration was used to calculate the dose distributions in the deformed CT images of each session. The cumulative dose distribution was then calculated (excluding fractions for which the distance between the trustee's positions exceeded 5 mm, a quantitative criterion considered to accept or not the deformable shift) and compared to the planned dose using dose–volume histograms, structure by structure (VWG, clinical target volume, stomach, duodenum).

2.2. Offline adaptive radiotherapy

The study by Veiga et al. concerned head and neck cancers and the evaluation of the doses delivered each day of radiotherapy taking into account anatomical changes in the target and the according organs at risk (spinal cord, brain stem and parotid glands) (19). This study retrospectively took data from four

patients for whom treatment replanning had been decided and performed using a new planning CT and to compensate for the displacement of the bone marrow or brain stem observed in daily CBCT images. The authors registered the initial planning CT on the daily CBCTs using two approaches: a rigid registration and a deformable registration (B-Spline) available in the NiftyReg open source software solution. The objective was to compare their effect on the calculation of the daily dose. The comparison was initially geometric and applied to deformed contours (C1, C4, C7 vertebrae, sternocleidomastoid muscles, external contours), initially delineated by an expert on the planning CT, and on contours delineated manually by the same expert on each CBCT at each fraction. The metrics were the Dice coefficient, distance transform and centroid position error.

Then, the authors compared the images registrations in terms of dosimetric effects. For dose evaluation purpose, the gold standard was the dose calculated on the new planning CT acquired when treatment replanned was scheduled. The authors compared the dose recalculated from the rigid registration of the planning CT to daily CBCT, from the deformable registration of the planning CT to CBCT and from CBCT calibrated in electronic densities. The dose distributions were compared in terms of dose difference, gamma analysis and similarity of the regions covered by 95% isodose. The results of the study showed a clear superiority of the deformable registration in terms of both the geometric comparisons and the dose evaluation.

A study by Ciarmatori et al. dedicated to the management of patients treated for head and neck cancers with Tomotherapy® (20). This study was particularly focused on the risk of overdosage of the parotid glands when tumour shrinking and therefore evaluates the interest of adaptive radiotherapy in delayed mode. The purpose of the study was to evaluate the doses actually delivered over the sessions without adaptation of the plan and to compare them with two adaptation strategies using a simple intervention approach (a single dosimetric replanning).

After establishing the Hounsfield unit/electronic density conversion curve, the daily doses received by the patient were calculated by applying the dose distribution from the initial plan to the MVCT images acquired daily in Tomotherapy®. The initial structures of the planning CT were propagated on each MVCT using a deformable image registration (Anaconda algorithm under the treatment planning system Raystation). Deformation vector fields were used to deform daily dose distribution on the planning CT, and thus, enabled to compute the actual cumulative dose received by the patient.

The two adaptive strategies were based on dosimetric replanning at the 18th fraction (out of 30). The first strategy, more conservative, was applied to the deformed organs at risk but without changing the initial planned target volume. Indeed, the low quality of MVCT images does not allow for reliable delineation of the clinical target volume. The second strategy, more realistic, was applied to a deformed planned target volume and deformed organs at risk. The daily dose sums for these two strategies were calculated over the entire treatment and compared to the sum without adaptation.

The results of this study first confirmed the significant decrease in parotid volumes during treatment. The lack of adaptation resulted in an increase in parotid dose compared to the initial plan. The two types of plan adaptation proposed by the authors allowed significant dose reductions.

The study by Marin Anaya et al. presented their experience with adaptive radiotherapy using the Smartadapt® (Varian) deformable image registration tool applied to prostate cancer treatments (21).

At each fraction, the planning CT and associated structures were transferred to the kV-CBCT of the day using Smartadapt®. A first rigid registration to place structures in the same coordinate system and then deformable and automatic (demon-based algorithm) were applied to both CT and structures. At the same time, to evaluate the performance of the deformable registration, the structures were manually contoured on the kV-CBCTs and then propagated on the deformed images of the CT.

The evaluation of the Smartadapt® tool was divided into two parts. First a geometric evaluation of the structures (CTV and rectum) was carried out: the deformed structures generated by the Smartadapt® tool were compared to the structures contoured by the physician on the kV-CBCT (considered as the reference), this comparison was also made with the structures obtained after a rigid registration only. The metrics available in Smartadapt® (volume, weight centre shift, Dice coefficient, average compliance distance) were used for comparisons. Then, a dosimetric evaluation was carried out: a reference plan was established by recalculating the doses on the CBCTs with the structures contoured by the physician. The initial plan and the plan calculated on the images and structures deformed by Smartadapt® were compared to the reference plan using dose volume histograms and conformity indices.

From either a geometric or dosimetric point of view, the authors did not find a significant superiority of deformable registration over rigid registration. After this study, they decided not to implement Smartadapt® routinely but recognize that the tool can be very useful to assist the physician in contour delineation and dosimetric evaluation of planes.

2.3. Hybrid (plan library)

Buschmann et al. presented their experience of the clinical implementation of the "plan of the day" technique, which consisted in having a library of treatment plans before the start of treatment in order to select at each session the most suitable plan for the anatomy of the day (22).

This study involved patients treated for cervical cancer for whom significant anatomical changes are observed in the pelvic region. In the planning phase, two CT scans were performed: one with a full bladder and the other with an empty bladder. In addition, each patient receives an MRI on the same day but without instructions on bladder filling. The three series of images are rigorously registered by bone markers with the iPlan software. The gross tumour volume is outlined on the. In addition to these

data, a set of structures corresponding to the position of the cervix with a half full bladder has been artificially created. To do this, the authors either used an imaging available in this bladder state or used a structural interpolation tool based on a home implemented deformation method (under Matlab and implemented in the free software 3DSlicer). From all the contoured structures, they established three planning volumes (PTV-full, PTV-empty and PTV-robust) to calculate three treatment plans likely to respond to all uterine position and bladder filling situations. These plans constituted the library.

In the treatment phase, patients followed the same bladder filling protocol as the planning CT every day. The CBCT of the day is adjusted to the planning CT in a rigid (bone) and automatic manner with manual adjustment if necessary. The 95% isodoses of each shot are displayed on the CBCT images. Operators had to choose between the full bladder plane and the empty bladder plane. If they did not cover enough, the "robust" plan was selected.

The plan selection procedure subject to intra-/interobserver variations was evaluated by a group of experts beyond the treatment sessions in order to compare the choice of the plan by the sole operator constrained by time and that of the unconstrained group. In addition, in order to evaluate the dosimetric benefit of the adaptive approach, a simulation of the non-adaptive approach was performed by selecting for each fraction the "robust" design. The total doses of the two approaches were compared. The authors did not observe any significant difference in clinical target volume coverage between the two approaches, while the adaptive approach slightly reduces the dose to SROs (bladder and rectum).

2.4. Live (online)

Winkel et al. presented the possibilities of adaptive radiotherapy on the MRI-linear accelerator Unity recently marketed by Elekta and developed in collaboration with Philips (23). The adaptation of the treatment plan was carried out on this device according to two methods: the "adapt-to-position" mode and the "adapt-to-shape" mode. These two methods allow to adapt the initial treatment plan online but differ in the management of the anatomical changes that the MRI of the day highlights compared to the pre-treatment MRI.

The "adapt-to-position" mode is based on a rigid registration of the planning CT to the daily MRI. The CT isocenter is therefore updated to the patient's new position. The plan is reoptimized and recalculated on the CT and initial contours.

The "adapt-to-shape" mode is based first on a rigid registration of the planning CT and MRI of the day and then the initial contours are propagated by a deformable shift algorithm on the MRI of the day. The average electron densities of the structures are taken from the CT and applied to the daily MRI. Reoptimization and dose calculation are therefore performed on the day's MRI and deformed structures.

In addition, both methods offer several options of increasing complexity for beam calculation and optimization. The simplest option is a calculation that keeps the segments of the initial plane (position of the blades of the multiblade collimator); the most complex eliminates the initial segments, reoptimizes the fluence and then the shape and weighting of the segments.

The authors emphasize the importance of balancing the accuracy of the calculation of the new plan with the time it requires since the longer this time is, the greater the risk that the patient on the treatment table will move and find himself in a different position from the MRI.

3. Post-therapeutic follow-up

The main objective of post-therapeutic follow-up is to evaluate the effectiveness of the treatment performed and to detect a possible recurrence as early as possible in order to adapt the treatment. The following articles clarify the value of multimodal imaging in this follow-up.

As part of post-therapeutic cancer follow-up and for different locations (head and neck, rectum or cervix), MRI and PET (positron emission tomography)/CT are generally performed about 12 weeks after irradiation to limit the risk of false positive, or pseudo progression, due to possible residual metabolic hyperactivity in the treated area (24, 25).

In this context of the use of metabolic imaging, the AAPM Working Group 174 detailed in particular the conditions of use of PET/CT with [¹⁸F]-fluorodeoxyglucose in radiotherapy (26). In particular, it describes the comparison of metrics such as mean or maximum standard uptake values or metabolic volume between pre- and pertherapeutic PET images (after the first radiotherapy sessions) to differentiate between cells that will respond to treatment and non-responders in order to find an appropriate therapeutic alternative. The comparison of pre- and post-therapeutic PET/CT necessarily relies on registration strategies to better observe the effectiveness of the treatment.

Graff et al. specified that PET can be used in follow-up in addition to CT or MRI if they are not contributing because there is no argument of superiority for PET use alone for post-therapeutic evaluation of tumour response (24). This was also confirmed by Gage et al. who added that PET/CT has a sensitivity of 92% and a specificity of 95% for the detection of recurrences of head and neck cancers (25).

Kabarriti et al. recently presented a study on locoregional recurrences for laryngeal cancer after intensity-modulated radiotherapy (27). Based on the PET/CT monitoring, the authors defined two methods to locate the origin of recurrence (one geometric approach and another based on maximum standard uptake value). To do this, they used a deformable algorithm (MIM Maestro®) to shift the PET/CT images to the planning CT, ensuring that the neck was correctly matched. The consistency of

the registration obtained was verified using specific metrics and finally showed that most of the recurrences came from the high-dose regions of the treatment plans.

4. Quality assurance

The most recent international recommendations were published by the AAPM Radiation Therapy Committee Task Group No. 132 in July 2017 (3). The main recommendations of the AAPM are as follows.

4.1. Commissioning and validation of image registration software

The validation must concern separately the image management (transfer, integrity) and the application dedicated to registration. If the registration software is included in a treatment planning system, validation of image management is part of the general implementation of the system.

The following three methods should be part of the program:

- end-to-end tests on physical phantoms;
- digital phantom tests (data available online at https://www.aapm.org/pubs/reports/RPT_132ElectronicResources.zip);
- tests on clinical data.

The commissioning tests listed in Table 1 must be repeated annually and after any update of any of the process elements.

4.2. Validation of the accuracy of an image registration (patient-specific quality control)

The main parameters recommended for evaluating and validating a registration are listed in Table 2.

Other intensity-based parameters also called "similarity measures" can be used if they are not used by the registration algorithm itself. The main parameters are:

- the sum of the square of differences if the image series have identical intensities (single mode)
- cross correlation if there is a linear relationship between the intensity of voxels in the 2 image series (single mode or limited region in multimodality);
- for a multimodal registration where the interesting anatomy has different intensities (e.g. CT/MRI) the mutual information measurement (MI) is the most appropriate parameter. This parameter assumes that there is a statistical relationship of voxel intensity between the two image series (single mode or multimodality).

In the absence of a quantitative validation available in clinical routine, the AAPM TG132 gives some recommendations to qualitatively validate the image registration performed by a software. Most often, validation is done on the merging of the two series of images following the registration.

Before proceeding with the registration, it is first essential to adapt the grey-scale windowing to facilitate the visualization of the anatomical structures (bone, air, soft tissue) that will be used to verify the registration. If necessary, the validation must therefore be carried out in different windows. Appendix A of the report recommends anatomical benchmarks for different sites to be relocated. The four recommended qualitative comparison methods to validate a shift are as follows:

- The most common tool is the display of the two images in a floating window, split screens, chessboard, etc. This tool is particularly effective for comparing high contrast areas.
- It is possible to compare images by superimposing them with, for example, one grayscale mode and the other in colour levels. Often, the user can change the proportion of viewing intensity of the two images.
- In case of comparison of images from the same modality (e.g. CT/CT, MRI/MRI), it may be useful to compare them by subtracting the intensity of the aligned voxels. Thus, if the image displays the absolute value of the subtraction, the perfectly aligned voxels have a zero value and appear in black. The voxels displayed in grey/white are the least matching. This method is limited because it depends a lot on the initial intensity values in the two aligned series.
- The contouring of anatomical structures on one modality before being superimposed on the other modality is interesting to validate a shift. This method is however limited because it depends on the visualization of the anatomy on both modalities.

4.3. Examples of validation and commissioning of image registration software

Jamema et al. presented their study on the commissioning and validation of the SmartAdapt® deformable image registration software used for contour adaptation in adaptive radiotherapy (28). The validation was applied to the accuracy of contour propagation and to the tracking of anatomical landmarks.

For the accuracy of contour propagation, the method first relied on the use of physical phantoms composed of objects of varying shapes, volumes, and densities. These phantoms have undergone known deformations of varying complexity. They were scanned before and after the deformations. The objects were manually delineated. The images and contours after deformations were transferred with SmartAdapt® to the images and contours before deformations. The assessment of deformable registration was performed by comparing the contours propagated by SmartAdapt® with those propagated manually by quantitative parameters such as Dice similarity coefficient, mass center shift and Hausdorff distances. Similarly, the accuracy of contour propagation was also assessed on clinical cases (skull, head and neck, prostate and cervix locations). The authors used images of patients previously treated with radiotherapy who had a new CT scan after two to three weeks of treatment. With CT scans before and after deformation, the manually delineated structures ("gold standard") were compared to those propagated by SmartAdapt® For the tracking of anatomical landmarks, freely

downloadable virtual phantoms (<https://sites.google.com/site/dirphantoms/virtual-phantom-download>) were used. The authors of the study therefore evaluated their SmartAdapt®-based method and were able to compare it with the results of other commercial algorithms.

In conclusion, the results allowed the authors to validate SmartAdapt® for anatomical regions such as the brain, head and neck, prostate and cervix. However, they point out that the accuracy of the algorithm is limited in the event of significant changes (e.g. bladder volume). A visual validation of the propagated contours is necessary in all cases.

Velec et al. presented their validation study of the Morfeus biomechanical deformable registration algorithm initially developed within an academic framework and then integrated into the Raystation® commercial TPS (Morfeus v0.9, RayStation v4.5-4.6, RaySearch Laboratories, Stockholm, Sweden) (29). Morfeus is an algorithm based on the finite element method. The objective of this validation was to evaluate the accuracy of deformable registration in clinical use in multimodal images (CT, 4D CT and MRI) of the abdomen, chest and pelvis. A cohort of 74 patients whose reference and target images contained manually delineated structures and anatomical points of interest was used. The results of the registration in Raystation® were compared to the results obtained in the previous "in-house" version of Morfeus and to the other registration algorithm (Anaconda v2.0) based on the similarity of the intensity present in the treatment planning system.

The parameters considered for the assessment of accuracy are the Dice similarity coefficient, the distance to agreement measurement and the target registration error. Similarity parameters of the aligned images (cross correlation, mutual information) were also calculated.

The authors validated the algorithm for its multimodal use since the mean calculated accuracy of the registration remained below the voxel size.

5. Conclusion

The benefit of multimodal imaging in radiotherapy is well established. Current imaging technologies whose development seems to be accelerating in recent years (spectral CT, MRI-linear accelerator, artificial intelligence, etc.) provide more and more information to physicians and contribute to the preparation and delivery of more precise and personalized treatments (30).

The great diversity of methods available to align multimodality imaging data encourages scientific and professional organizations to define standards such as those recommended by the AAPM. Developers are now expected to include these standards into their solution updates.

Given the growing importance of molecular imaging, it is certain that the need for registration methods, particularly deformable methods, will increase in the future. It is therefore critical that

registration techniques become more robust so that molecular imaging information becomes fully integrated within the therapy planning.

Author contributions

AT, LD, FD, MV: manuscript writing- reviewing and editing.

References

1. Song G, Han J, Zhao Y, Wang Z, Du H. A review on medical image registration as an optimization problem. *Curr Med Imaging Rev.* 2017;13(3):274-83.
2. Paganelli C, Meschini G, Molinelli S, Riboldi M, Baroni G. Patient-specific validation of deformable image registration in radiation therapy: Overview and caveats. *Med Phys.* 2018;45(10):e908-e22.
3. Brock KK, Mutic S, McNutt TR, Li H, Kessler ML. Use of image registration and fusion algorithms and techniques in radiotherapy: Report of the AAPM Radiation Therapy Committee Task Group No. 132. *Med Phys.* 2017;44(7):e43-e76.
4. Czajkowski P, Piotrowski T. Registration methods in radiotherapy. *Rep Pract Oncol Radiother.* 2019;24(1):28-34.
5. Devic S. MRI simulation for radiotherapy treatment planning. *Med Phys.* 2012;39(11):6701-11.
6. Klein S, Staring M, Murphy K, Viergever MA, Pluim JP. Elastix: A toolbox for intensity-based medical image registration. *IEEE Trans Med Imaging.* 2010;29(1):196-205.
7. Knopf A, Nill S, Yohannes I, Graeff C, Dowdell S, Kurz C, et al. Challenges of radiotherapy: Report on the 4D treatment planning workshop 2013. *Phys Med.* 2014;30(7):809-15.
8. Fortin D, Basran PS, Berrang T, Peterson D, Wai ES. Deformable versus rigid registration of pet/ct images for radiation treatment planning of head and neck and lung cancer patients: A retrospective dosimetric comparison. *Radiat Oncol.* 2014;9:50.
9. Reynaert N. PET and MRI based RT treatment planning: Handling uncertainties. *Cancer Radiother.* 2019;23(6-7):753-60.
10. Akino Y, Tohyama N, Akita K, Ishikawa M, Kawamorita R, Kurooka M, et al. Modalities and techniques used for stereotactic radiotherapy, intensity-modulated radiotherapy, and image-guided radiotherapy: A 2018 survey by the Japan Society of Medical Physics. *Phys Med.* 2019;64:182-7.
11. Yan D, Lockman D. Organ/patient geometric variation in external beam radiotherapy and its effects. *Med Phys.* 2001, 28(4):593-602.

12. Sarrut D. Deformable registration for image-guided radiation therapy. *Z Med Phys.* 2006;16(4):285-97.
13. Chen M, Huang Y, Chen W, Chen X, Zhang H. [High-quality reconstruction of four-dimensional cone beam CT from motion registration prior image]. *Nan Fang Yi Ke Da Xue Xue Bao.* 2019;39(2):201-6.
14. Miyakawa S, Tachibana H, Moriya S, Kurosawa T, Nishio T. Evaluation of deformation parameters for deformable image registration-based ventilation imaging using an air-ventilating non-rigid phantom. *Phys Med.* 2018;50:20-5.
15. Moriya S, Tachibana H, Kitamura N, Sawant A, Sato M. Dose warping performance in deformable image registration in lung. *Phys Med.* 2017;37:16-23.
16. Yan D, Vicini F, Wong J, Martinez A. Adaptive radiation therapy. *Phys Med Biol.* 1997;42(1):123-32.
17. Badey A, Barateau A, Delaby N, Fau P, Garcia R, De Crevoisier R, et al. [Overview of adaptive radiotherapy in 2019: From implementation to clinical use]. *Cancer Radiother.* 2019;23(6-7):581-91.
18. Ziegler M, Nakamura M, Hirashima H, Ashida R, Yoshimura M, Bert C, et al. Accumulation of the delivered treatment dose in volumetric modulated arc therapy with breath-hold for pancreatic cancer patients based on daily cone beam computed tomography images with limited field-of-view. *Med Phys.* 2019;46(7):2969-77.
19. Veiga C, McClelland J, Moinuddin S, Lourenco A, Ricketts K, Annkah J, et al. Toward adaptive radiotherapy for head and neck patients: Feasibility study on using CT-to-CBCT deformable registration for "dose of the day" calculations. *Med Phys.* 2014;41(3):031703.
20. Ciarmatori A, Maffei N, Mistretta GM, Ceroni P, Bernabei A, Meduri B, et al. Evaluation of the effectiveness of novel single-intervention adaptive radiotherapy strategies based on daily dose accumulation. *Med Dosim.* 2019;44(4):379-84.
21. Marin Anaya V, Fairfoul J. Assessing the feasibility of adaptive planning for prostate radiotherapy using Smartadapt deformable image registration. *Med Eng Phys.* 2019;64:65-73.
22. Buschmann M, Majercakova K, Sturdza A, Smet S, Najjari D, Daniel M, et al. Image-guided adaptive external beam radiation therapy for cervix cancer: Evaluation of a clinically implemented plan-of-the-day technique. *Z Med Phys.* 2018;28(3):184-95.
23. Winkel D, Bol GH, Kroon PS, van Asselen B, Hackett SS, Werensteijn-Honingh AM, et al. Adaptive radiotherapy: The Elekta Unity MR-linac concept. *Clin Transl Radiat Oncol.* 2019;18:54-9.

24. Graff P, Blanchard P, Thariat J, Racadot S, Lapeyre M. [Post-treatment follow-up of head and neck cancer patients]. *Cancer Radiother.* 2019;23(6-7):576-80.
25. Gage KL, Thomas K, Jeong D, Stallworth DG, Arrington JA. Multimodal imaging of head and neck squamous cell carcinoma. *Cancer Control.* 2017;24(2):172-9.
26. Das SK, McGurk R, Miften M, Mutic S, Bowsher J, Bayouth J, et al. Task group 174 report: Utilization of [¹⁸F]-fluorodeoxyglucose positron emission tomography ([¹⁸F]-FDG-PET) in radiation therapy. *Med Phys.* 2019;46(10):e706-e25.
27. Kabarriti R, Brodin NP, Ahmed S, Vogelius I, Guha C, Kalnicki S, et al. Origin of locoregional recurrences after definitive intensity-modulated radiation therapy (IMRT) for laryngeal cancer determined based on follow-up PET/CT imaging. *Cureus* 2019;11(1):e3856.
28. Jamema SV, Phurailatpam R, Paul SN, Joshi K, Deshpande DD. Commissioning and validation of commercial deformable image registration software for adaptive contouring. *Phys Med.* 2018;47:1-8.
29. Velec M, Moseley JL, Svensson S, Hardemark B, Jaffray DA, Brock KK. Validation of biomechanical deformable image registration in the abdomen, thorax, and pelvis in a commercial radiotherapy treatment planning system. *Med Phys.* 2017;44(7):3407-17.
30. Maier A, Syben C, Lasser T, Riess C. A gentle introduction to deep learning in medical image processing. *Z Med Phys.* 2019;29(2):86-101.

Table 1. Multimodal imaging in radiotherapy: quality measurements and tolerances recommended by the American Association of Physicists in Medicine Radiation Therapy Committee Task Group No. 132 for the commissioning and quality control of image registration software.

Quality assesement	Method	Tolerance
Data transfer (orientation and image size, data integrity)	With physical phantom as part of an end-to-end test	Exact
Rigid registration accuracy	With digital phantom	Local references to be defined
Deformable registration accuracy	With digital phantom	
Anatomic location assessment	Standard clinical cases	

Table 2. Multimodal imaging in radiotherapy: Parameters for quantitative validation of the accuracy of an image shift.

Measuring technology	Metric	Tolerance	Definition and limits
Target registration error (TRE)	Average residual error between the identified points that are closer after image registration	Below the size of the voxel	This parameter quantifies the alignment of anatomical points defined in two series of images to be registered. The higher the number of points, the more valid the registration will be. The closer the ERR is to 0, the more reliable the registration is for the points concerned. However, in the event of distortions between image series, the shift may not be valid at a distance from the points
Mean distance to agreement (MDA)	Average distance of the surfaces of two contours on aligned images	Lower than the uncertainty of the contours of the structure or than the size of the voxel	The limitation of these parameters is that they are very sensitive to the modalities and structures to be delineated. Indeed, it is known that large intra- and interoperator variabilities are observed in the delineation task. In any case, the American Association of Physicists in Medicine Radiation Therapy Committee Task Group No. 132 recommends that these two parameters be available in commercial image registration software.
Dice similarity coefficient (DSC)	Volumetric overlap of two contours on aligned images	Lower than the uncertainty of the structure contour (DSC > ~0.80-0.90)	

Jacobian determinant	Expansion or reduction of a volume resulting from a deformable image registration	No negative value possible. Equal to 1 means no change. Between 0 and 1: volume reduction Above 1: volume expansion	Mathematical modelling adapted to the evaluation of a deformable registration
Consistency	Independence of the algorithm with respect to the direction of registration (image A to image B or image B to image A)	Below the size of the voxel	Allows to check the stability of the algorithm