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Review Article

Challenges and opportunities in the development and clinical implementation of artificial intelligence based synthetic computed tomography for magnetic resonance only radiotherapy

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ABSTRACT

Synthetic computed tomography (sCT) generated from magnetic resonance imaging (MRI) can serve as a substitute for planning CT in radiation therapy (RT), thereby removing registration uncertainties associated with multi-modality imaging pairing, reducing costs and patient radiation exposure. CE/FDA-approved sCT solutions are nowadays available for pelvis, brain, and head and neck, while more complex deep learning (DL) algorithms are under investigation for other anatomic sites. The main challenge in achieving a widespread clinical implementation of sCT lies in the absence of consensus on sCT commissioning and quality assurance (QA), resulting in variation of sCT approaches across different hospitals. To address this issue, a group of experts gathered at the ESTRO Physics Workshop 2022 to discuss the integration of sCT solutions into clinics and report the process and

Abbreviations: AI, Artificial Intelligence; B0, Main Magnetic Field Strength; CBCT, Cone-Beam Computed Tomography; CPU, Central Processing Unit; CT, Computed Tomography; DICOM, Digital Imaging and Communications in Medicine; DRR, Digitally Reconstructed Radiography; DL, Deep Learning; DDR, Dose Distribution Reconstruction; DSC, Dice Similarity Coefficient; DVH, Dose Volume Histogram; ESTRO, European Society for Radiotherapy and Oncology; FOV, Field Of View; GAN, Generative Adversarial Network; GPU, Graphics Processing Unit; HFMEA, Healthcare Failure Mode and Effect Analysis; HU, Hounsfield Unit; IGRT, Image-Guided Radiation Therapy; IGRT-Linac, A linear accelerator combined with kV-kV or CBCT imaging capability; MAE, Mean Absolute Error; ME, Mean Error; MRI, Magnetic Resonance Imaging; MR-Linac, Magnetic Resonance Linear Accelerator; MR, Magnetic Resonance; MU, Monitor Unit; OAR, Organ-at-Risk; PACS, Picture Archiving and Communication System; pCT, planning CT; PSQA, Patient Specific Quality Assurance; PSNR, Peak Signal-to-Noise Ratio; QA, Quality Assurance; RF, Radiofrequency; RT, Radiation Therapy; SBRT, Stereotactic Body Radiation Therapy; SNR, Signal to Noise Ratio; sCT, Synthetic CT; SSIM, Structural Similarity Index Measure; TPS, Treatment Planning System.

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its outcomes. This position paper focuses on aspects of sCT development and commissioning, outlining key elements crucial for the safe implementation of an MRI-only RT workflow.

Introduction

Synthetic computed tomography (sCT) images generated from magnetic resonance imaging (MRI) provide the means to deliver radiation therapy (RT) without the geometric uncertainty stemming from multi-modality image registration [1–3]. Substituting the planning CT (pCT) by the sCT in an MR-only RT workflow has also the potential to reduce costs and patient radiation exposure [4], as well as the patient burden from multiple imaging sessions. The adoption of sCT algorithms in magnetic resonance guided radiotherapy (MRgRT) is of particular interest, as the ability to generate a sCT directly from the image-of-the-day would accelerate the introduction of ultra-hypofractionated treatments, significantly improving spatial dose accuracy [5,6].

Several methods for sCT generation, ranging from the simplest bulk-density override to more complex deep learning (DL) algorithms, have been proposed and evaluated so far, but only a handful are currently used clinically.

Implementation of an MR-only RT workflow is a multi-step process that, apart from demonstrating equal or improved patient outcomes when compared to routine RT workflows, must also ensure safe use and sustainability of the sCT solution [7,8]. With no consensus on image quality and dosimetric performance evaluation metrics provided by the international community, each hospital has resorted to developing its own implementation procedure with ad-hoc quality assurance (QA) protocols. Moreover, the lack of consensus also hampers the standardisation of products marketed by industrial partners.

As a first step to overcome these issues, a group of expert developers (research and commercial) and clinical users with expertise in managing sCT solutions gathered in the ESTRO Physics Workshop 2022 with the topic "Next generation MR-guided radiotherapy: AI applications for planning and image guidance" to discuss about the experiences of developing or integrating artificial intelligence (AI)-based sCT solutions into the clinic. The objective of this position paper is to present the participants' perspective on the topic by identifying key elements to be considered during the development and clinical commissioning processes: these identified elements aim to be eligible for standardisation.

This paper is divided into three sections. The first, oriented towards technical developers, is dedicated to the aspects to be considered for the development and validation of sCT solutions prior to clinical implementation. The second, oriented towards clinical users, gives an overview of the aspects to be included in the QA process for a safe implementation and application of an MRI-only RT workflow. In this part, the main differences between a cone-beam CT- and MR-Linac workflow have been highlighted. The focus is set on photon-based RT, without discussing the so-far limited applications to electron, proton and ion beam RT. Finally, suggestions to the vendors are provided in the third section.

Technical development of sCT

Data curation

The performance of any DL-based sCT model is influenced by the training data utilised in its development. The initial trade-off is choosing between the goal of creating an accurate site- and machine-specific sCT model or compromising accuracy to achieve generalizability. The preferable approach is the site-specific one, as the ultimate objective is to generate a sCT with high accuracy in both dose and patient positioning metrics. Therefore, the development of a sCT model requires training data that accurately represents the clinical cohort for which the model is intended to be used (e.g. male pelvis without hip implants). This can include – but is certainly not limited to – the appropriate range of the patients' age, height, gender, body mass index, etc. The model should then not be applied for patients outside of such ranges. In general, sufficient data heterogeneity is required to ensure model robustness, but the interpretation of the term heterogeneity will depend on the model's clinical intent. While restricting to a site-specific approach, it will be still necessary to ensure that a sufficient amount of data from different MR scanners is retrieved. It is advisable to include in the training set as much variation of patients' anatomy as possible for the given site, especially when diverse clinical situations are considered, such as prior surgical procedure, potential presence or absence of stents [9,10], or tumour properties in terms of location, size, and impact on deformation of surrounding healthy tissue.

Compared to models with strict exclusion criteria, a larger heterogeneity of the training data and therefore wider applicability of the model require a larger training set, leading to a more complex neural network. Exclusion criteria could involve the presence of imaging artefacts or abnormal anatomies in the MR image, which could be detected by visual inspection [11], or an insufficient field-of-view for the patient size. However, artefacts or abnormalities that have a quantifiable and negligible impact on dose calculation, such as post-operative swelling or artefacts at the edge of the MRI field of view contralateral to the treated volume, may still be included in the training set. If paired data is required, a time consideration between CT and MR acquisition is important. The latter is site-specific and ranges from times as short as half an hour for physiological movements in the abdominal region [12] up to a day or two for slowly-changing anatomies in the head and neck area [13] or beyond for the brain [14]. If the time difference extends beyond the time scale of the anatomical changes in the investigated site, one may consider excluding this data or reducing its weight during a paired training process.

The amount of data required for optimal training can be addressed by the analysis of training and validation learning curves through the different epochs. Boulanger et al. [15] summarised in their comprehensive review the performance of different sCT solutions published between 2010 and 2021, as a function of tumour location and the number of patients included in the studies. The authors concluded on the need to increase the variety of data collected to favour the model robustness, and mentioned data augmentation as a mandatory step in case of a low number of samples collected. This was recently confirmed by Farjam et al. [16], who showed an improvement of CT to sCT image similarity using data augmentation starting from a training cohort of 20 prostate patients. Analogous approaches including data augmentation are also reported in literature [17–19].

Boulanger et al. [15] concluded that at least 10 patients should be included in the training set, which seems to be a rather low number in view of the capacity to collect large cohorts today, highlighting the moderate complexity of the task. However, the amount of data remains the main factor that influences the quality of a network; therefore valuable training sets, while being site-dependent, should include a minimum of 20 to 40 patients [15]. If the number of patients is limited, different approaches have been proposed to extend training sets: artificial expansion with data augmentation techniques [13,20], expansion without patient data transfer from hospitals through federated learning [21] and expansions based on previously trained models using transfer learning [22]. While the last two methods are promising, they still have a limited use in the sCT research community. On the other hand, data augmentation strategies have already been applied and can be divided into two categories: methods transforming the original data by applying several image manipulation techniques and methods aiming to create new artificial data using generative models [23]. In the first case, the

manipulations range from simple affine transformations (e.g. translation, rotation, flipping, scaling, cropping and shearing, or any combination of these operations) to more complex transformations that alter intensity pixel values to change image characteristics such as brightness, contrast, saturation and noise, allowing the network to be more robust to changes in the scanner device or imaging protocols. Other categories of manipulation methods include erasing transformation and elastic transformations. The generation of synthetic MRIs used for the training phase is another possible approach, which is not widely used in the literature yet.

In conclusion, to facilitate a secure clinical implementation and application, it is highly recommended to provide a detailed report on the characteristics of the training cohort, encompassing any data augmentation. Current efforts are proceeding towards the definition of a model fact sheet [24]. This practice is essential for a comprehensive understanding of the model's limits of applicability.

Data pre-processing and training process

Image pre-processing can be employed on MR images within the training data to enhance the generalisability of the developed models across varying levels of image quality. This process also serves to compensate for the presence of artefacts that could significantly impact the images.

Image pre-processing methods can include bias field correction, spatial resampling, geometric fidelity corrections, image registration if paired data are required and histogram equalisation or MR intensity normalisation. Intensity clipping can also be applied to remove outlier values, mostly corresponding to noise. It is recommended to include such steps since they have demonstrated the possibility of implementing robust sCT models, capable of handling and processing heterogeneous datasets coming from different institutions [25,26].

Another essential step is related to data partitioning, essential to ensure an unbiased evaluation of the network generalisability. Conventionally, images are separated into 3 datasets: training, validation, and test sets.

The training set represents the main source of data on which the network is trained. The training is commonly performed with a loss function based on image similarity metrics, discussed in a later section. The validation set is used to evaluate the intermediate performance of the neural network and optimise the network hyperparameters, while the test set represents an independent image set to provide an unbiased evaluation of the network performance. Ideally, an independent external test set should be considered in the process of evaluating the performance of the final model, to assess its generalisability to data that is often (slightly) different in terms of image quality. The division of data into training/validation/testing in the ratios 70 %/15 %/15 %, 80 %/10 %/10 % and 60 %/20 %/20 % is most frequently observed in connection with sCT generation [18,26].

To ensure robustness, especially with limited datasets, advanced learning strategies are recommended. This includes the K-fold cross-validation scheme, which divides the training and validation samples into K groups of equal size and then uses K-1 folds to train the network and the remaining samples to assess the network performance. The average of the performance metrics and its associated standard deviation are thus reported as the performance scores of the model trained with the full data set. The choice of the different folds becomes crucial when the training set is heterogeneous, containing images acquired on different imaging devices or using various image parameters. While more advanced methods like nested cross-validation exist, they remain unexplored in the field of sCT generation [27,28]. Recently, ensemble methods that combine the predictions from multiple learning algorithms to achieve better performance than using a single neural network, have been implemented [29–31].

Hardware requirements

The development of DL-based models requires the availability of computational resources capable of very high throughput parallel computing. Graphics Processing Units (GPUs) are therefore preferred over Central Processing Units (CPU) in this context, mainly because they have higher Arithmetic and Logic Units (ALU), which allows for more operations to be calculated [32]. They also offer the opportunity to handle large data sets, due to their design incorporating wider buses and higher memory clock rates as compared to CPUs, which makes them the preferred choice specially to train 3D networks. Three major characteristics must therefore be taken into account when choosing GPUs: (1) the floating-point operations per second, accounting for the computational speed of the system under consideration, (2) the memory bandwidth in GB/s, characterising the amount of data that can be read or stored in the memory per unit of time, and (3) the Random Access Memory (RAM) expressed in GB, representing the quantity of data that can be temporarily stored. In general, the higher the value, the better the performance of the GPU. However, the recommended amount of RAM for machine learning depends on the size and complexity of the datasets and models of interest. Several authors have reported computing times on different computing architectures. As an example, on an Nvidia Quadro RTX6000 (24 GB GDDR6) GPU card, the training computation times for 39 patients of a U-Net, GAN, and Pix2Pix were respectively 17, 57 and 39 h. The sCT generation computation time (per MRI scan) were respectively 9, 9, and 5 s [33].

Network selection

Data requirements and learning strategies differ with network selection. Methods classified as generator-only models aim to translate one image domain (MR) to another one (CT), predominantly by minimising an intensity-based voxel-wise loss function, requiring accurately spatially registered CT/MRI data pairs for training. Generator-only networks have been demonstrated in the cranial region and they were the first architectures generating high quality sCT images [34]. Regardless of the network, it should be noted that the common training approach of minimising an intensity-based voxel-wise loss function leads to optimising the image metrics, while more clinically relevant endpoints should be taken into account, such as the dose metrics and the patient positioning performances. Image-metric optimization is however the current widely accepted approach, due to the high degree of automation in the computation and the reduced computational burden.

In 2014, Generative Adversarial Network (GAN) architectures were first proposed aiming to expand the applicability of sCT to extra-cranial locations [35]. In a GAN, two models are trained at the same time: a generative model G maps the domain end-to-end, and a discriminative model D estimates the probability of a sample coming from the training data versus G's output. D's objective is to distinguish fake images generated by G from real user-provided images in the learning stage. GANs, like generative-only networks, require paired CT-MR for training and validation, although they have been shown to be robust to misregistration errors and mitigate CT-MR misalignments if implemented with dedicated loss function such as Mutual Information [15,36]. The most flexible architecture in terms of input data preparation is the CycleGAN architecture. Using a bi-directional cost function, it seeks to define the bijective transformation from one domain to another one, thus allowing the use of unmatched data.

Each of these architectures has disadvantages and advantages in terms of image quality with some experiences in literature that reported ad-hoc comparisons [37,38].

Finally, recent studies from 2023 proposed novel emerging techniques for sCT generation based on residual vision transformers [13] and diffusion probabilistic models [39–41]. The latter have the goal of creating sCT images starting from pure noise images, with the main drawback lying in the time generation.

Quality evaluation of a sCT image generator

Image metrics

The generated sCT can be compared to the pCT to assess the similarity between the voxel values in the two images. These similarity metrics can be computed with a high degree of automation, among other applications, during the loss function minimization and immediately after the network training is completed, thus allowing a direct comparison between studies performed at different institutions. An extensive set of quantitative metrics can be found in literature [15,42].

The Mean Absolute Error (MAE) has been widely reported in the literature for sCT evaluation [43]. Despite its voxel-wise difference highly penalises spatial inaccuracies resulting from sCT to CT registration and may average out large differences in small volumes (e.g bone) with small differences in large volumes (e.g. soft tissue), reporting this metric is crucial for future studies to enable a first and fast sCT quality evaluation.

A second metric is the Mean Error (ME), which presents the advantage to be more clinically relevant than the MAE, since it correlates more with beam attenuation, providing information on eventual systematic errors in Hounsfield units (HU) prediction [43]. However, it is less representative of the quality of the sCT due to the potential compensation from positive and negative differences.

An overview of recent results for MAE and ME is provided in Supplementary materials (Table 1S [100–161]). Inclusion criteria for the data included in the table were: "synthetic CT" or "pseudo CT" or "sCT" or "pCT" in the title, date range 2021–2023, including DL methods, including at least "MAE" or "ME" as quantitative metrics. Reviews were excluded. Reported MAE for Head and Neck has the highest values (median of 83 from available values in Table 1S) whereas Pelvis has the lowest (median of 34 from available values in Table 1S). For the two most common anatomical sites where sCT has been clinically implemented, ME ranges from −6 to +1 and from −15 to 7 for Brain and Pelvis, respectively.

The Dice Similarity Coefficient (DSC) has been used to quantify the overlap between CT and sCT given volumes. Despite its wide application, DSC presents the limitation of penalising small objects and disregarding the shape of the evaluated volume [44]. The use of various thresholds to obtain the evaluation volumes increases the metric uncertainty, which should be thus computed with caution and not for direct sCT quality evaluation. Such a metric, initially proposed to evaluate the performance of automatic segmentation algorithms, is not the most appropriate in this context.

Other quantitative metrics include: Peak Signal-to-Noise Ratio (PSNR) [42] and Structural Similarity Index Measure (SSIM) [42,45].

In general, studies aiming for quantitative evaluation and allowing comparison to previous and upcoming research should include as many from the previously reported metrics as possible and at least one among MAE and ME.

Dose metrics

The dose calculated on the electron density map derived from the sCT can be compared to the pCT to assess differences in the target coverage and OAR sparing. These metrics generally require some degree of manual input and the comparison among different studies is complicated by the large variety of technical parameters such as irradiation techniques, dose prescriptions, target volumes and locations, dose calculation algorithms and HU to electron density calibrations. Nonetheless, dose endpoints have a greater interpretability and provide quantitative parameters to define clinically relevant thresholds and limits. Therefore, whenever available, dose metrics should always be reported along with image metrics [43].

Gamma indices, quantifying the similarity between dose maps, are generally the most used and reported metrics. 3D global gamma indices with 10 % and 90 % dose thresholds, to respectively analyse the low and high dose regions, are commonly found in literature [12,26]. Tight criteria (e.g., 1 %/1mm) allow to highlight minimal dose differences and they can be crucial in the identification of local inaccuracies.

The results of the gamma analysis can be heavily influenced by the technical parameters such as the comparison modality (global or local), the dose threshold and the dimensionality evaluation (2D or 3D). Dose Volume Histogram (DVH) point differences have been used as complementary dosimetry quality markers, although several factors, such as segmentation inaccuracies can result in DVH differences [42]. To overcome the dependence on potential contour geometrical differences when calculating DVH parameters (e.g. D2%) on the CT (contours CT-based) or the sCT (contours MR-based) [42], the volumes encompassed by clinically relevant isodoses (e.g. 90 % isodose) of the CT and sCT can be derived and compared through DSC to achieve a more robust comparison. A good balance between clinical impact and dose precision should be identified and contextualised for each study.

Patient positioning performances

Lastly, the sCT-based patient setup accuracy must be evaluated, especially when the treatment is administered on an Image Guided Radiotherapy (IGRT) linear accelerator with CBCT or kV-kV patient positioning. The uncertainties in image matching can be evaluated with approaches used in other contexts of assessing IGRT positioning accuracy [46–48]. For brain treatments several authors reported differences in translation within +/-2 mm [49–51] and maximum rotation of 0.7° when the positioning was based on CBCT [50,51]. If Digitally Reconstructed Radiograph (DRR) and kV imaging were used, the authors reported lower differences [50,52]. For the pelvis, a maximum mean deviation of 0.28 mm in the three directions was achieved based on a rigid fusion of CT or sCT and CBCT [53]. For head-and-neck, maximum deviations of +/-3mm when rigidly matching CT or sCT derived DRR to the daily planar kV images were reported [54,55]. In general, it could be observed that the most recent sCT developments achieve matching quality to CBCT or kV-kV within the commonly adopted target volume margins [56].

Technical challenges

The actions outlined in the previous subsections share technical challenges that may impact the overall output quality and interpretability of the generated sCT. These challenges result in limitations of the sCT generator that should be carefully evaluated and integrated into the QA program discussed in the following section. While the limitations should be taken into account for the QA process, the research field is advancing and recent developments are expected to overcome the current technical limitations. The challenges can include, but are certainly not limited to, the following points:

- Limitations of MR imaging for bone-air interfaces, particularly challenging in regions such as the sinus cavities. Novel Ultrashort Echo Time (UTE) MR sequences may allow dedicated capability in bone imaging [57–59].
- Difference in terms of MR scanners and acquisition protocols between the training data and input data used in clinical routine. The risks should be mitigated by the manufacturer providing the applicability limitations of the software. Future advancements may involve expanding training datasets without patient data transfer through federated learning [21] or tuning datasets to specific scanners and sequences using transfer learning [22].
- Registration uncertainties between the MR and CT in the training data and absence of a real ground truth for paired MR-CT datasets. Novel approaches to mitigate the misalignment have been proposed [60] and networks not requiring paired data such as CycleGAN have been demonstrated [12,25,61,62].
- Potential network hallucinations, producing an output sCT that cannot be verified in absence of a planning CT, e.g. in presence of unexpected metal implants without MR contrast. The generation of

sCT with multiple independent networks has been proposed to identify hallucinations, which may differ across networks leading to a potential error recognition [10];

- The absence of standardised datasets makes it challenging to quantitatively determine the superiority of a specific model. Initiatives like Gold Atlas [63] and SynthRAD [64] are promoted to address this issue and encourage further benchmarking efforts.

QA program

Several studies have investigated the challenges and potential pitfalls of an MRI-only workflow [8,65–67], leading to the identification of significant issues summarised in Table 1. A QA program must tackle these issues through identifying potential failure modes and establishing additional safeguards where needed. The main components of a QA program for the safe clinical implementation of a sCT are described in this section.

Risk analysis

A prospective risk analysis should be performed to highlight potential failure modes. Apart from technical failures, the questions '*How to recognize if a patient QA fails?*' and '*What to do if a patient QA fails?*' are of particular interest. These issues should be discussed within the department following the Health Failure Mode and Effects Analysis (FMEA) methodology or equivalent. Table 2S, in the Supplementary materials,

Table 1
Possible issues encountered at different steps of an RT workflow, key questions highlighting potential risks, and associated suggestions when implementing sCT into clinical RT workflow.

RT workflow step	Issue description	Key Questions	General suggestions for implementation
Patient scheduling	Administrative personnel in charge of booking CT and MR imaging sessions need to be in communication with other staff to rebook sessions when necessary.	● Are the personnel aware to schedule MR instead of CT? ● If sCT is not generated or does not meet the QA criteria, are the personnel aware to schedule a planning CT?	Personnel need clarity on the group of patients eligible for MR-only workflows as well as use of clear communication channels between departments to allow quick scheduling of CT if needed.
MR acquisition	Geometric distortion can arise from the tissue-dependent chemical shift and susceptibility differences, from gradient field nonlinearity and from the static field inhomogeneity. Together with the presence of metal implants and MR-related artefacts these can lead to: ● inaccurate target delineation, ● improper restoration of the external contour, and ● erroneous electron density map.	● Are RT specific MR protocols available? ● Does the sCT image generation software require specific sequences? ● Are doctors or only technicians required during MR acquisition? ● Are technicians allowed to edit sequence parameters? If yes, which? ● To which department belongs the simulation MRI? Who is responsible for performing quality controls? (RT or Radiology department)	Internal guidelines on allowed image sequences and their acquisition parameters should be in place. If the developed sCT model has only been trained on fixed parameters, then those should be restricted. Scanner gradient non-linearity correction should be turned on, contrary to the MRI from the Radiology department.Routine MR QA must be performed, particularly a daily geometric distortion check using a large diameter phantom (>30 cm) [162,163] is advised. Clear responsibilities for each personnel group must be stated.
Patient immobilisation	The patients must be scanned in treatment position, using routine immobilisation devices when possible. Additionally, it must be considered that these devices may not be visible in MR and, hence, in the sCT reconstruction.	● How is patient positioning done for RT simulation? ● Are MR safe patient positioning devices available and are these increasing the coils to patient distance? ● Are lasers for positioning required and available at MR and does the staff at the MR know how to operate them? ● Is MR safe tattoo equipment required and available? ● Is RT staff required during MR acquisition?	The immobilisation devices must be MR safe and of proper size to avoid collision with coils or the machine. The use of a flat couch is advised.MR safe markers can be placed on the mask and support devices to correctly localise the immobilisation system in the TPS. Use of coil bridges to avoid distorting the body contours is advised.
sCT generation	This step provides the highest measure of risk. The use of sCT introduces additional issues based on the interpretation of images, the impact of segmentation and density assignments on dose calculation, and bone segmentation affecting DRR accuracy [8].	● When in the process is the sCT generated? ● Who is responsible for the quality of the sCT? Is the staff trained to judge the quality of the scan? ● What procedure to follow if quality is insufficient? ● Is there a procedure to include the RT fixation devices in the sCT?	Automatic sanity checks of sCT quality should be done either provided by the vendors or tailored if the sCT was developed in-house.Use of a complementary methodology for generating synthetic scans [10] would aid image quality control and/or HU assignment check.
Delineation & treatment planning	Transferability of the sCT from MR console (or the cloud if web-based solution is used) to the TPS is necessary for registration between image modalities. Identification of artefacts caused by air bubbles, stents, dental implants, post-op swelling, etc. that may affect the contouring procedure because of the proximity to the target volume.	● Is the DICOM connectivity ensured for transfer to TPS? ● Can the sCT be registered to secondary images like PET or functional MRI? ● If using multiple sequences, is the intrinsic registration between sCT and additional MRI good or did the patient move in between sequences? ● Does the staff need to be aware they are working on a sCT? ● Are all relevant anatomical structures and target volumes visible for delineation?	A DICOM header check to verify the required DICOM parameters could ease transferability between systems and registration procedures.Gathered information on artefact types, sizes and their influence in contouring and dose computation during commissioning can be used to establish local guidelines for sCT visual inspection and training of staff.Registration issues due to movement between image sessions can be mitigated by good patient preparation. Likewise, staff training on assessment of registration quality between sCT and MRI used for contouring is advised.Finally, a need for dose planning guidelines tailored to sCT (e.g. density override) should be assessed.
Treatment & image-guidance	Relevant for IGRT-Linac RT workflows. The quality of the images used for online registration is crucial for correct patient positioning. Bone and gold markers can be affected or not visible in the DRRs.	● Is the DICOM connectivity ensured for transfer between TPS and Linac console? ● Does the staff need to be aware they are working on a sCT? ● Are anatomical or artificial markers for image guidance properly visible?	Performing comparison analysis between sCT/sDRR and CT/DRR to assess matching ability to the IGRT CBCT or kV-kV images [71,83] will help identify special routines for correct identification of markers. Proper staff training to mitigate miss-identification of markers.

gives an example of a risk analysis tool focused on potential detriment to the patient. To capture as many risks as possible throughout the entire MR-only RT chain, it is important that all involved disciplines are represented, i.e., MR and CT personnel, medical physicists, radiation oncologists, RTTs, radiologists, radiographers, data managers, and administrative personnel in charge of booking imaging sessions.

Required machine QA

Performing MR QA for the use of MR in RT according to any published guideline [68–71] is a minimum requirement for the MR acquisitions to be suitable for sCT generation. Focus on geometric accuracy and image consistency of the whole scan e.g., large field of view, is necessary. These may be performed with vendor-provided QA software although complementary in-house checks can always be added if deemed necessary. A practical aspect is to define whether the radiology department or the RT department is responsible for machine QA. Both scenarios can be feasible, but good communication is crucial, and the minimum requirements of both departments should be satisfied.

As for QA on MR-Linac systems, only recently the first consensus expert opinion was published [72], however, some vendor specific experiences on the QA and clinical implementation are also available in the literature [73,74]. QA frequency and tolerance levels for on-board MR scanners may be more demanding compared to MR simulators due to the machine design i.e., interaction of MR with the integrated Linac (and vice versa), and the higher imaging burden that adaptive RT may require. B0-field homogeneity and gradient non-linearity tests are mandatory requirements. Uniformity and SNR of the body and surface coils should be performed monthly, whereas MR distortion as a function of different gantry angle positions should be performed on a yearly basis [70,75]. Faraday cage shields should also be tested regularly as small hardware damages may affect image quality.

MR imaging of RT specific devices

Some aspects to consider during the clinical commissioning of an MR scanner for sCT generation include ensuring the accurate restoration of the patient body contour for dose calculation, visibility of patient fixation devices or surrogates, and identification of external or internal IGRT markers. Strategies to correctly identify the couchtop position [76] or internal markers [77] have been reported in literature and should be implemented in the RT workflow if such systems are used. Designing a retrospective study analysing paired sCT-CT images can contribute to refine and ensure the accuracy of the RT workflow involving these systems.

Comprehensive workflow testing

The implementation of an end-to-end phantom-based testing as classically performed for RT workflows [78] is not applicable to MR-only RT due to the patient-specific generation of Relative Electron Density (RED) maps with DL algorithms. The closest approach could be performing a comprehensive workflow testing, which not only verifies the connectivity of all steps in the treatment chain but also ensures communication between personnel in case a deviation from routine is detected. The steps to check can differ between institutions as they should be based on the outcome of the risk analysis. General key points to test are:

- Transfer of sCT DICOM data into the TPS; ensure correct sCT DICOM header to avoid misinterpretation when transferred from the MR console or PACS into the TPS [49,65].
- Visual inspection of sCT for anatomic anomalies; ensure that coil positioning does not alter the patient body contour; ensure that tissue distortion due to metal implants, and body contour mishaps due to patient movement during MR acquisition, are within tolerance to not affect dose calculation [51].
- Fixation markers or other immobilisation devices; ensure their visibility or a surrogate for these on at least one MR sequence of the MR protocol if they are not discernible on the sCT [79].
- Auto-contouring tools compatibility; ensure that the generated contours on the sCT are within the tolerance levels established for CT auto-contouring [13].
- Dose calculation and optimisation algorithms; perform dose comparison study between sCT and CT following the dose metrics discussed above, and ensure use of appropriate dose matrix voxel size in relation to sCT and CT voxel size [80]. The internal test cohort must summarise as far as possible all the configurations that will be encountered in the clinic, in terms of image quality, patient population and clinical situations.
- Image quality of the generated DRR; ensure that the rendering of skeletal tissue is accurate enough for kV/kV matching, and ensure correct location of internal markers if routinely used [65,81].
- Independent dose calculation tools and plan verification (e.g. EPID measurements); ensure that sCT gamma pass rates are within the tolerance levels established for pCT.
- Third party sub-systems (e.g. optical surface guidance); ensure that the body contour from the sCT is of enough quality to be used for surface guidance.
- CBCT or kV/kV match at the treatment room; performing off-line sCT-CBCT and sCT DRR-kV/kV matching following the patient-position metrics discussed above [82].

A dummy run consisting of images from an anonymized patient is a simple and effective approach to evaluate some of these steps. A complementary comparative retrospective study involving a few patients can be designed to evaluate those steps that require establishing QA acceptance criteria.

Verification of accurate assignment of the RED, respectively HU, on the sCT should ideally be included in the comprehensive workflow testing. This is currently difficult due to the unavailability of commercial phantoms from which a sCT can be generated. Published studies have resorted to develop in-house anthropomorphic phantoms or phantoms with inserts of different materials visible on MRI [83,84] for multi-modality evaluation covering only certain aspects of the comprehensive workflow testing. Other reported solutions rely on modifications of commercially available phantoms, such as the Lucy 3D QA phantom with MRI visible silicon insert [85] or the adapted RUBY phantom with multi-modality QA insert [86]. Worth of note is that a sCT was not generated in any of these studies. Instead, they employed a CT or bulk overrides where the dosimetric evaluation was performed using either radiochromic films or ionization chambers. The studies focused on the geometrical accuracy of the MR-only workflow.

Patient specific QA

The lack of commercial tools for performing MR-only patient specific QA (PSQA) is another reason that has hindered the widespread implementation of sCT in the clinic. In general, the PSQA process could range from a first visual assessment to the comparison of the sCT HU values based on population-based distributions, to dose recalculations on independent RED maps or to more complex approaches depending whether the treatment is performed on an MR-Linac or an IGRT-Linac.

For MR-only with IGRT-Linac workflows, the first-day-of-treatment CBCT can be used to verify the dosimetric calculation [87,88] provided that the combined uncertainty from factors like HU deviations, limited field-of-view, and streaking artefacts is kept within the recommended 5 % global uncertainty for RT workflows [89] or the CBCT could be converted into an independent sCT [43,90]. Suggested methods for implementation of PSQA protocols that require in-house scripting and therefore may be time consuming, are application of population-based

calibration curves [87,88,91] preferably for each CBCT scanner, and bulk density method where patient specific HU-to-density curves are applied [92]. CBCT image quality enhancement with DL may become the best tool for performing PSQA as suggested by published research [10], thus enabling double sCT comparison. The metrics for dose evaluation discussed in Section "Quality evaluation of a sCT image generator" can be used to establish site-specific acceptance criteria through comparison studies between pCT, sCT and CBCT images [91,93]. It is at the discretion of every centre to apply PSQA on the first treatment fraction of all patients or only on those where the visual inspection of the sCT yielded suspicious artefacts. In the near future, commercial tools will open the possibility for faster PSQA enabling adaptive RT as it may be performed on every treatment session.

For MR-linac workflows, the PSQA currently relies on the possibility to use the pCT. In the consensus paper by Tanadini-Lang et al. [72], the necessity to perform visual checks of newly generated RED maps during the plan adaptation process for each individual patient is suggested. Alternatively, the dose calculation can be verified on an independent RED map generated through bulk overrides [94] or with an independent sCT generator [10]. In parallel, an automated comparison of plan parameters between plan of the day and pre-treatment plan calculated on the pCT is advisable. As more robust sCT are adopted by MR-linac systems and the pCT is no longer needed, the challenge will be to design a fast on-line PSQA performed on the sCT of the day in parallel to other tasks. Tools like APART, an in-house MATLAB based tool developed by Rippke et al [95] may be taken as a basis for on-line PSQA. Likewise, Tang et al [7] have introduced a step in the workflow where the plan-of-the-day is compared to a sCT generated from the planning imaging session in a maximum of 400 s.

An overview of the potential PSQA approaches for dose calculation is reported in Table 2.

QA role in software sustainability

Long-term requirements for QA management of sCT generators will become essential to maintain the accuracy of dose calculations over time. Because uncertainty in the sCT images can arise from a variety of sources such as hardware or software upgrades and variations in image acquisition protocols, it is important to perform periodic re-validations of the sCT generator to ensure that the uncertainty remains within acceptable limits over time [89]. Unfortunately, the few publications from centres that have implemented an MR-only workflow do not discuss QA for sustainability. Performing checks of the sCT against actual CT scans after each hardware and software update should be a minimum requirement, achievable by performing phantom measurements (if available) or a restricted number of actual patient studies to ascertain that RED/HU values and geometric accuracy remain within tolerance levels. Image metrics and dose computation on the sCT generated before and after the upgrade can be performed to evaluate whether the MR sequence required for sCT generation remains unaffected.

Suggestions to vendors

At the time of writing, four CE/FDA-approved sCT software are available in the market: syngo RT Image Suite (Siemens Healthineers, Erlangen, Germany), MR-Box (Therapanacea, Paris, France), MRI Planner (Spectronic Medical, Helsingborg, Sweden) and MRCAT (Philips, Amsterdam, Netherlands). A direct comparison between the former three solutions concluded that despite strengths and weaknesses of each of the approaches, all sCT generators are suitable for clinical use [96]. Clinical applicability was also reported for the latter [97]. While the dose calculation and IGRT positioning outcomes show negligible differences among the four commercial sCT software, the user should be aware of significant workflow differences if the MR sequence required for sCT generation is the diagnostic sequence adopted for contouring or if a separate dedicated sequence is required. Furthermore, there may be slight workflow differences based on whether the sCT software is integrated into the MR scanner console (with the MR scanner and sCT software from the same vendor) or if it necessitates an external server (involving different vendors).

To achieve wider adoption of MR-only RT workflows, the vendor community is encouraged to provide the following:

Table 2
Patient specific quality assurance methods for dose calculation on sCT.

Method	Input data required	Valuable aspects	Shortcomings
Dose recalculation on CBCT before delivery of the first fraction	1. sCT 2. CBCT 3. RT plan	● A real and not sCT modality (CBCT) of the patient is used for dose calculation. ● PSQA exploits data that is routinely acquired within the RT workflow. ● The quality of the CBCT can be enhanced with DL to obtain an independent CBCT-based sCT.	● PSQA can be performed only once the patient is on the couch for the first fraction. ● May have restricted applicability due to the limited field of view and CBCT artefacts. ● Inaccuracy of dose calculation on CBCT due to HU calibration. ● Not applicable to MR-Linac or IGRT based on kV-kV imaging.
Dose recalculation on bulk densities	1. sCT 2. CBCT or MR 3. RT plan 4. Contours of the structures for bulk density assignment	● PSQA can be performed during the planning stage if using MR as input. ● Applicable to MR-Linac or IGRT based on kV-kV imaging. ● The procedure can be automatized with auto-contouring of the bulk structures.	● Dose calculation accuracy depends on the choice of the assigned bulk densities. ● No availability of auto-contouring algorithms on MR or CBCT for the structures that require bulk density assignment (fat, air, bone, soft tissue, lung).
Dose recalculation on independent sCT	1. Primary sCT 2. Independent sCT 3. RT plan	● MR data falling outside the range of the training data leads to different network hallucinations in the two sCTs, thus identifying potential outliers. ● Applicable to MR-Linac or IGRT based on kV-kV/CBCT imaging. ● The procedure can be automated.	● Distortions or artefacts in the MR data propagate to both the primary and independent sCT. ● Requirement of two independent software for sCT generation.
Dose recalculation on patient-specific phantom	1. sCT 2. Patient specific phantom 3. RT plan 4. Film or chamber measurements	● Closest approach to classical end-to-end testing. ● Direct dose measurement.	● Dedicated hardware must be developed for PSQA with considerable time requirement. ● Not a standardised approach. ● Not applicable for daily PSQA.
Dose recalculation on a planning CT	1. sCT 2. CT 3. RT plan	● Gold standard for dose calculation. ● Applicable to cases for which the sCT has insufficient quality or other PSQA methods fail.	● Fall-back approach to the classical workflow, the patient will not be treated with MR-only workflow. ● A CT must have been previously acquired.

- Detailed description of the sCT algorithm (user manual, white papers, published studies).
- If the sCT is AI-based, a description of the training database would help setting tolerance values for the clinical quality controls such as range of patient weights, heights, age, clinical situations (e.g. presence of operated patients in the case of cranial tumours), input MRI sequences, magnetic field, CT protocols, ranges of MR/CT parameters, use of RED or HU maps for training, etc.
- Methods to reduce artefacts (craniotomy screws, dental implants, and prostheses).
- Flexibility to choose the size of FOV and automatic exclusion of FOV areas with low MR signal.
- Dedicated MR protocols for SBRT that guarantee an increased geometrical accuracy.
- DICOM tags that allow tracing back the algorithm version used, and source MR images employed to generate the sCT.

Anthropomorphic phantoms for QA and end-to-end testing are lacking which poses a challenge for many clinics, as they need to fulfil various requirements, including ensuring dosimetric equivalence conditions. Materials with both CT and MR contrast that remain stable over time are crucial as well as easy incorporation of 1D, 2D or 3D dosimeters in internal structures of interest should be considered. Compatibility with MR-linacs simulating internal organ kinematics at certain treatment sites would also be appreciated.

Finally, automated software is needed for dose performance QA, e.g. ability to use CBCT for dose comparison or availability of a second independent sCT generator. Likewise, for patient positioning in IGRT-Linac, the ability to register online MRI to CBCT would be helpful.

Looking into the future, the use of additional MR sequences for sCT training would be highly beneficial as the contouring could be performed on the same MR image used to generate sCT, avoiding the introduction of uncertainties due to patient motion during the MR imaging session in between sequences.

Discussion

The expected benefits of incorporating MR-only RT into IGRT-Linac and MR-Linac workflows have been extensively discussed in the literature [15,43], serving as primary motivation for the fast development of DL-based sCT solutions seen in recent years.

However, only a limited number of prospective studies on sCT clinical implementation can be found in the literature [96,97]. The lack of consensus on sCT clinical commissioning and QA was highlighted as the main hindrance for wide-spread usage of sCT during the discussions held at the ESTRO Physics Workshop 2022. This work revised the full process ranging from research and development to routine clinical use, involving several consecutive phases: (i) development and training of a sCT generator algorithm, (ii) validation on an independent retrospective cohort, (iii) clinical validation in a prospective study, (iv) rollout of a software product, (v) implementation in the clinical workflows with dedicated commissioning and (vi) periodic quality assurance.

Technical developers working on phases (i-ii), are encouraged to use Table 1S for benchmarking of new sCT solutions and as template to standardise the reporting of such metrics in any future work. This will facilitate reaching consensus values and establishing acceptance criteria per anatomy site. The requirements detailed in Section "Technical development of sCT" of this work do not distinguish between whether the solution is in-house or commercially developed. However, additional requirements on network architecture may be necessary for in-house algorithms to align with the recently introduced Medical Device Regulation [98]. Further studies will be required to assess the overall impact of MDR on academic research and sCT development [99].

Clinical staff involved in phases (iii, v–vi) may find in Tables 1, 2S and 2 a template to tackle sCT implementation and QA development. The issues discussed in Table 1 concern staff awareness which should be considered key for a seamless MR-only RT workflow. Table 2S, on the other hand, exposes elements that if covered by routine QA will ensure safe and sustainable use of the sCT. Section "QA program" not only serves as a starting point for clinical implementation but also raises awareness of the limitations (e.g., complete end-to-end testing and PSQA) that the clinical community faces. The methods described in Table 2 are examples on how some clinics have overcome some of the PSQA limitations. However, it is clear from the list of shortcomings that there are still challenges that need resolving. Therefore, it is important to encourage vendors to develop tools for QA that can facilitate development of robust protocols.

Information on MR-only workflow implementation provided by the clinical community in the form of prospective studies is still too sparse to be able to conduct analyses on the overall benefits of exchanging the pCT for the sCT. This work is reserved for the future, when harmonisation of evaluation metrics and implementation processes are adopted by the developer and clinical communities. For MRI-only workflows to be effectively implemented in clinical practice, it is essential to develop QA software capable of analysing a sCT image and providing prompt and tangible feedback on its reliability. This should involve a set of tests designed to examine the sCT without the corresponding pCT. Having companies working in this direction is crucial to make these systems increasingly integrable with clinical practice.

Conclusion

This paper summarises the challenges and opportunities faced by development and clinical implementation of AI-based sCT solutions as discussed during the ESTRO Physics Workshop 2022. The data presented and discussed in the current paper gives an insight to the current position of the research and clinical fields, highlighting elements that would lead to the harmonisation of these processes. We encourage focusing future efforts on developing international guidelines for clinical implementation of sCT and the associated quality assurance, which was beyond the scope of the current work; however, it represents a logical extension thereof.

CRediT authorship contribution statement

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Declaration of competing interest

The authors declare that they have no known competing financial

interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

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