

ESTRO-ACROP recommendations on the clinical implementation of hybrid MR-linac systems in radiation oncology.

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Highlights:

- Online magnetic resonance-guided radiotherapy (oMRgRT) using hybrid MR-linac systems is a novel innovative application in radiation oncology
- This ESTRO-ACROP recommendation provides guidance for best practice in the implementation phase of these systems
- The recommendations discuss the specific challenges in oMRgRT, including preparations prior to go live, MRI safety and specific training, adequate patient selection, online adaptive treatment planning workflows and treatment delivery.

Abstract:

Online magnetic resonance-guided radiotherapy (oMRgRT) represents one of the most innovative applications of current image-guided radiation therapy (IGRT). The revolutionary concept of oMRgRT systems is the ability to acquire MR images for adaptive treatment planning and also online imaging during treatment delivery. The daily adaptive planning strategies allow to improve targeting accuracy while avoiding critical structures. This ESTRO-ACROP recommendation aims to provide an overview of available systems and guidance for best practice in the implementation phase of hybrid MR-linac systems. Unlike the implementation of other radiotherapy techniques, oMRgRT adds the MR environment to the daily practice of radiotherapy, which might be a new experience for many centers. New issues and challenges that need to be thoroughly explored before starting clinical treatments will be highlighted.

Keywords:

MR-guided radiotherapy, MR-Linac, radiotherapy, ESTRO, ACROP, implementation, adaptation, online adaptive, workflow

Introduction

Online magnetic resonance image (MRI)-guided radiotherapy (oMRgRT) represents one of the most innovative applications of current image-guided radiation therapy (IGRT) [1]. The revolutionary concept of oMRgRT is the ability to create new perspectives towards personalized treatment approaches, based on the use of high-quality image guidance. MR images acquired immediately before and during treatment enable daily online planning adaptation strategies to improve targeting accuracy while avoiding critical structures [2].

Online MRgRT is being increasingly used in routine clinical settings with a considerable ongoing pace of hybrid units installations. With these recommendations, we aim to provide an overview of available systems and guidance for best practice in the implementation phase of the different systems. We will here discuss the specific challenges in oMRgRT, including preparations prior to go live, MRI safety and specific training, online adaptive workflow and treatment delivery. Furthermore, we will highlight the potential benefits and limitations of oMRgRT, providing support for optimal patient selection and treatment delivery optimization.

Currently available systems

To date, two hybrid oMRgRT systems are available in clinical practice, each with its own specifications. The technology was first introduced in 2014, with the first patients treated with the ⁶⁰Cobalt version of the MRIdian system of Viewray (ViewRay Inc, USA) [3] and since 2017 using hybrid MR-linac systems with the Unity system of Elekta (Elekta AB, Sweden) [4] and the MRIdian MR-linac system of Viewray (see figure 1).

The Viewray MRIdian uses a 0.35 T MR scanner with a split magnet design, where the magnetic field force lines are oriented along the cranio-caudal patient axis. The ring-gantry is positioned between the two magnets. In a first release starting from 2014, patients were treated using three ⁶⁰Co sources positioned around the gantry, each of them equipped with double focused and double stacked multileaf collimators [3,5]. Since 2017, the system is equipped with a 6 MV flattening filter free linear accelerator (linac) instead of the ⁶⁰Co heads [6]. The linac and its components are hosted in dedicated shielding compartments (buckets) mounted inside the gantry and the beam is collimated with a double focused and stacked multileaf collimator. Due to the split-magnet design, the radiation does not pass through the magnets and is absorbed only by 5 mm thick connecting fiberglass placed between the two magnets.

The Elekta Unity system originated from the work that started in 1999 in UMC Utrecht [7]. The system consists of a 1.5 T MRI system with a gantry in the mid-transversal plane around the isocenter that houses a 7 MV flattening filter free linac. Active magnetic shielding is used to magnetically de-couple the MRI and the linac, so that they can be operated independently without mutual interference [8]. The magnetic field force lines are directed along the cranio-caudal axis of the patient. In both systems, the impact of the magnetic field on the secondary electrons is modelled inside the treatment planning system and it can be compensated by means of dedicated strategies of IMRT multi beams optimization [9].

The commissioning and acceptance of a hybrid oMRgRT system require modified procedures, but only concerning those aspects which are unique and new to oMRgRT, while otherwise they are similar to traditional RT systems [10,11]. Besides the innovative technological innovations, one of the essential components of these systems is the introduction of the online adaptive workflow into clinical practice.

To date, multiple options for online plan adaptation, ranging from the use of the original plan or its re-optimization, to full online replanning are available [12] and will be discussed later.

Preparations prior to “go live”

Online adaptive treatments with MR-linacs are fundamentally different from treatments on conventional delivery units and therefore require dedicated teams, typically consisting of radiation technologists/therapists (RTTs), radiation oncologists and medical physicists.

MR-linac workflows include three major components: 1) MRI safety aspects and image acquisition; 2) image registration and (re-)contouring of target and organs at risk (OAR); and 3) treatment planning and delivery.

The training required prior to the implementation of a hybrid MR-linac system will include:

- MR safety training for all professionals working in the MR environment with clear guidance, authorization and responsibilities (RTTs, radiation oncologists, medical physicists, cleaning staff).
- Vendor specific training – to learn the different aspects of the online workflow (including alternative workflows in case of system errors), to be able to make the required choices for safe online adaptive treatments. Vendors may offer special training consoles for planning and simulation of adaptive RT, which enable dry runs to assess potential challenges and pitfalls. Those training consoles also offer the possibility to obtain initial experience with the specific treatment planning system (TPS) before the first patient treatment.
- Training specific to each role, which initially will be based on traditional roles and responsibilities, includes the following aspects: RTTs are a stable component of the workflow and may need specialized training to upskill: for example, MRI training to ensure safe patient screening, understand MR sequences and troubleshoot imaging problems. Radiation oncologists or dedicated RTTs must be trained for using the online contouring tools and algorithms by keeping in mind that time for (re-)contouring is limited during online adaptive procedures, since the patient is in treatment position, and it should not prolong the entire treatment time unnecessarily. Guidelines for contouring should be provided to maintain consistency between team members, for example defining a specified region in the proximity around the target volume within which contours are to be amended during the online adaptive procedures. Medical physicists or dosimetrists specialized in treatment planning will be responsible for the online treatment planning process. Their training should include, besides knowing the online treatment planning possibilities, eventual pre-planning offline actions, creation of treatment planning templates and specific plan quality assurance (QA) procedures. Training can be provided in many different ways and can consist of online modules and onsite training sessions. It should include the different aspects of the respective online workflows (including alternative solutions in case of errors or system failures), software modules, i.e. treatment calendars, MRI console use, tools for data transfer, image registration, contouring and treatment planning, as well as data storage and actionability. Furthermore, peer-to-peer onsite visits at highly experienced centers might offer useful clinical and technical insights.

Despite the initial sub-specialization, all team members should principally know the importance of every step in the entire treatment in case of unforeseen events and need for rapid online decision making. As the workflow develops, roles and responsibilities may cross traditional boundaries, to

enable a more prompt and less resource intensive treatment delivery [13]. Furthermore, due to the potential adaptive nature of every single treatment fraction, it is essential that critical online decisions are made swiftly and consistently within the team. This will require close multidisciplinary team work to define and optimize treatment workflows and thresholds for decision making and action levels. The dedicated training has to cover aspects of the machine itself and all the above mentioned aspects of the workflow to enable new treatment plans to be created, based on the daily anatomy of target volumes and OAR. The clinical implementation of adaptive MRgRT also has considerable logistical consequences for radiation oncology departments because of the need for rapid availability of radiation oncologists and/or physicists for each treatment fraction. In contrast to traditional radiotherapy delivery, adaptive MRgRT requires approving of re-contoured target- and OAR contours and adapted plans for each separate fraction, either at the treatment console or remotely.

As the clinical implementation of online adaptive MRgRT incorporates new challenges for the entire team, a risk-analysis for a safe and efficient workflow may be found to be useful [14]. One potential structured framework, within which the multidisciplinary team can assess and mitigate risk to enhance the quality and safety, is a process failure mode and effect analysis (P-FMEA) [15–17]. In a first step, the clinical team develops a process map for MR-guided adaptive radiotherapy. In a second step, possible failure modes are identified, and risk probability numbers are assigned based on the probability of occurrence, the severity of risks and the detectability. Risk mitigation strategies support the generation of a standardized workflow, clearly defined protocols and the definition of checklists as well as standard operating procedures (SOPs) for the safe and effective implementation of MR-guided adaptive radiotherapy.

Before the clinical implementation, it is advised to test the adopted oMRgRT workflows on volunteers in dry run training sessions. On-line testing and adjustment of positioning, gaining experience with the MR-linac equipment, and training with the specific software for generating high-resolution scans for the different anatomical regions is essential [18].

MRI specific training and equipment

Before implementing oMRgRT, it is very important to prepare written SOPs for MRI safety, and the staff have to undergo dedicated training to get used to the MRI environment (e-learning, observer ship in radiology departments, etc). The following aspects should to be addressed:

- Access restriction (Fringe field, safety zones, MR unsafe/conditional/safe, screening of the patient (implants, foreign body metals, pacemaker or ICD implants), authorized and safety certified staff).
- Potential hazards and risks (magnetic field risk, radio frequency field risk, cryogen risk, biological effects due to magnetic field, projectile incident risk).
- Acoustic noise (patient compliance, hearing loss).
- Radio frequency and gradient fields (RF absorption, looped conductors, patient contact with bore or wires).
- Magnet quench (emergency procedure).
- Emergencies (guidelines for the staff to ensure a safe evacuation of the patient).

It is strongly recommended to have internally approved guidelines for the management of emergencies in the MRI environment. These guidelines must be readily available to all involved staff (e.g. the emergency response team, which includes physicians, nurses, etc.). These emergency guidelines should also be consistent with other institutional MRI regulations.

Before MR simulation and access to the MR-linac is granted, patients should be screened for MR-compatibility (metal screening, implant screening, pacemaker/ICD screening), informed about the procedure to familiarize with the equipment (i.e. hearing protection, squeeze bulb alarm) and instructed on how the staff will communicate with them during the treatment.

Before entering the treatment room, patients must remove any items from their person that might constitute a risk in the MR environment or alternatively patients might be asked to change into hospital gowns. Ferromagnetic detection systems (i.e. entry control systems, hand-held metal detectors) can be used for additional screening of patients, but only after all the conventional screening methods described above have been completed, not as a substitute for them. Furthermore, for each subsequent fraction, the staff should be informed about any procedures the patient may have had between the last and current fractions [19].

Regarding equipment, currently not all available patient setup tools have been tested or even designed for use in a MR environment. Therefore, it is critical to ensure safety of any material that is transferred near a MR-linac device. For this reason, it is recommended to differentiate between 1) ferromagnetic safety, 2) imaging artefact assessment, 3) proper coil handling and usage and 4) dose attenuation degree.

For ferromagnetic safety, vendors should provide a written confirmation of safe use within a MR environment. Nevertheless, as part of the risk and QA management strategy, all material should be tested on site and any ferromagnetic properties should be excluded. Phantom measurements should be performed to assess both susceptibility as well as distortion artifacts, and to quantify their impact on image quality and spatial accuracy and to evaluate possible dose attenuation. Finally, proper coil placement needs to be tested to ensure optimal distance and location to the area of interest and to avoid imaging deterioration due to insufficient signal generation and detection.

With regard to MR imaging, knowledge of the acquisition, processing and interpretation of MR images and the respective sequences is a prerequisite for oMRgRT [20–22]. As the national professional education for RTT, physicists and radiation oncologists varies greatly from country to country, it is difficult to define and provide an obligatory core set of minimum requirements. Nevertheless, some guidance can be derived from the initial experience that is currently being made with MR-linac implementation. During the clinical implementation phase, the core team for oMRgRT should consist of RTTs, physicists and radiation oncologists with specialized training in MR technology. This core team should have received MR-specific training either as part of their national professional board certification or visited specific courses that provide basic knowledge of MR imaging. A refresher course or internship in the in-house radiology department can also be helpful for all professions. In addition, radiotherapy tailored and MR-linac vendor specific training should be considered. This can be done by MR specific teaching courses provided e.g. by the ESTRO [23], University of Utrecht [24], The Institute of Cancer Research [25], or by site visits and peer-to-peer training at experienced MR-linac departments providing direct exchange and teaching opportunities.

Treatment delivery

The potential to alter the treatment plan on a daily basis in oMRgRT is a pivotal change to the usual radiotherapy paradigm. The anatomy changes from moment to moment, and oMRgRT brings us close to the pinnacle of adaptive radiotherapy, as it is able to take into account tumor and OAR motion and morphologic changes in real time. It also opens the door to real time biological targeting based on

biomarkers of differential response, resistance and hypoxia, and introduces the key elements of the radiomics concept into daily clinical practice of radiation therapy [26–28].

The components of an adaptive workflow are patient positioning, pre-delivery imaging, recontouring or adjustment of superimposed original contours, shifting/replanning, plan quality assurance, reimaging (3D MRI or cineMRI) and online image guidance with motion management approaches (i.e. gating), and, if indicated, adjustments as a result of observed intrafractional changes. Figure 2 describes a typical workflow for oMRgRT.

The goal of daily plan adaptation can be represented by improved target coverage, OAR sparing or both, depending on whether tumor coverage or OAR sparing is the primary consideration. Early clinical experience shows that the benefit of daily plan adaptation varies between different tumor sites treated, and may for instance be less important for lung tumors than for pancreatic lesions [29–32]. It is recommended to define individual institutional threshold values and action levels on when a plan adaptation is performed or considered necessary. This depends on the clinical relevance of the daily anatomical changes (target/organ relation), the type of dose distribution (homogeneous dose distribution or SBRT treatment) and total dose and fractionation. The higher the dose per fraction and the proximity to sensitive OARs, the smaller is the therapeutic window for different anatomical situations and indications. There are different strategies how this can be implemented in clinical practice. One approach is to predefine the type of plan adaptation for each treatment [31,33]. It seems to be helpful to implement clear dose constraints and target coverage parameters to define if a plan is acceptable for dose delivery (e.g. traffic light system) with different action levels for easy online decision making. Furthermore, it might be useful to define a time frame for online contouring and a maximum number of optimization rounds to avoid too long adaption times.

Future deformable dose accumulation in combination with daily adaptation can be expected to refine current knowledge on toxicity parameters, because dosimetry will be based on actual delivered, rather than planned radiation dose. Each oMRgRT TPS platform presents differences, but both commercially available systems allow assessment of the anatomy on MRI prior to replanning or shifting. This assessment can be with respect to reference plan dosimetry (MRIdian) or reference anatomy (Unity). Changes in OAR or target anatomy mandate replanning, especially when minimal CTV to PTV margins, steep dose-gradients and/or ultrahypofractionation are used.

The daily treatment plan is created selecting the required complexity of optimization, ranging from simple shifts in MLC positions to full, cold start reoptimization based on the patient's anatomy [12,34,35]. The contours used for replanning can be brought in rigidly from a reference plan, automatically deformed and adjusted to the anatomy of the day using proprietary software or can be contoured from scratch. With regard to interobserver variation in contouring, a particularly relevant issue in daily plan adaptation, each center should assess the accuracy of its recontouring process against a reference gold standard and have a quality assurance program for online contouring procedures. In order to make the adaptive process fast and feasible in daily clinical routine, several centers have adopted a workflow with partial recontouring of OAR only in the proximity of the PTV (i.e. surrounding 2-3 cm), since the recontouring is performed with the patient waiting in the treatment position [34,36]. In this case, OAR constraints have to be adapted to this concept (use of absolute volumes in cc) for a fast and reliable plan evaluation. As the replanning process can be time consuming (e.g. up to 15 minutes) a second positioning MRI can be repeated prior to actual dose delivery, and minor table or plan shifts made to ensure the new plan remains optimal [37].

During beam on, cine MRI prevents geographical miss. The MRIdian system can track to account for intrafractional motion as it enables direct gating of the tumor on up to 8 frames per second sagittal

cine-MRI images, while the Unity system provides images on three planes even if at present it can only pause the beam manually [30,38].

Each center should set an action threshold for intervention in the event of target movement outside of the high dose area, which is dependent on, amongst other factors, the used PTV margins. The MRIdian system enables respiratory-gated treatments using breath-hold techniques with automated real-time anatomy structure tracking for lesions in the abdomen and thorax [39]. Several initiatives for visual feedback to patients have been implemented in clinical practice, e.g. MR-compatible monitors in combination with an adjustable mirror in the gantry or prism-glasses. These real-time visual (and/or audio) feedback systems facilitate voluntary breath-hold delivery at the appropriate respiratory phase. Initial clinical experience has shown that this approach is well-tolerated, and that the active contribution to treatment delivery is appreciated by patients [40,41]. An analysis in patients with lung, adrenal and pancreatic tumors treated with such gated MRIGRT showed a mean duty cycle efficiency between 67% and 87% [38].

The Unity system on the other hand, offers different types of MRI sequences that can be acquired during beam on [42]. This enables the reconstruction of the delivered dose to be compared with the intended dose delivery for more precise treatment evaluation and/or dose response assessment (e.g. Menten et al. [43], Kontaxis et al. [44]). These data can be used for off-line adaptation, while in the next step this approach can be used for intra-fraction dose guided adaptation.

MR-specific patient selection and indications for MR-linac

Patient selection is a critical decision point in determining the indication for oMRgRT treatment and in addressing patients to such an advanced treatment technology. Two main criteria can be identified for this assessment: patient characteristics and characteristics of the target volume. This guideline focuses on the implementation of hybrid MR-linac systems, it is not intended to review the current evidence of oMRgRT. Since this technology is new and requires more resources than conventional treatments (e.g. with CT-based high-precision radiotherapy) we generally recommend that all treatments are evaluated prospectively. This evaluation should be conducted according to the principles of health technology assessment for cost-benefit analysis and the principles of evidence based medicine. While new treatment paradigms, for example such as adaptive focal boost, will be tested in clinical trials, the collection of prospective multicenter cohort data on the outcome after oMRgRT in established indications for radiotherapy such as hypofractionation and SBRT will provide important evidence and assure quality and patient safety.

All patients should be thoroughly screened for MRI compatibility, according to the adopted institutional guidelines [45]. Patients should be classified as: physically incompatible (i.e. non-MRI-conditional pacemaker carriers due to interaction with magnetic fields); clinically incompatible (i.e. severe psychiatric disorder, severe claustrophobia, inability to understand instructions); borderline compatible (i.e. mild claustrophobia) and fully compatible for oMRgRT. Patients who are assessed as incompatible or who refuse oMRgRT treatment, should be directly referred to standard RT delivery units, while appropriate interventions (e.g. psychological intervention, anesthesia, pharmacological or supportive techniques such as music or aromatherapy [46–48]) could be used for borderline compatible patients.

In addition to physical compatibility, the radiation oncologists should carefully evaluate the general clinical status of the patient, especially with regard to the required degree of compliance and in consideration of the clinical benefits expected from the use of oMRgRT. Treatment slots for online

adaptive treatments using full online replanning are significantly longer than on conventional linacs and can last up to 60 minutes [30,31,36,49]. Elderly age and frailty do not represent direct exclusion criteria, and specific scoring systems can be used as decisional support systems [50]. Patients with severe obesity or significant cachexia (body mass index > 40 or a weight of less than 40 Kg) should be evaluated on a case by case basis, especially considering the possibility to have imaging artefacts, patients heating and bore size issues (<70 cm) [6,51].

Conceptually, the second criterion for patient selection refers to target volume characteristics and the surrounding normal tissues in clinical situations where the soft-tissue contrast by the real-time MR-guidance provides new opportunities for safe high-precision radiotherapy with optimal sparing of healthy tissues. With the increasing use of oMRgRT and the growing database, we expect in the near future a fast growing of evidence-supported best-practice recommendations for clinical indications and patient selection[52]. As far as current evidence is concerned, the ideal target volume for oMRgRT is within anatomical sites where the CT density is homogeneous, which reduces the discriminative power of traditional CT-based imaging (i.e. head&neck, upper abdomen, pelvis) and makes the impact of MRI in identifying the therapy volumes more significant. An example is the case of localized prostate cancer: compared to CBCT, onboard MRI can potentially reduce the daily uncertainties in identifying the interface between the posterior part of the prostate gland and the anterior rectal wall or between the prostate apex and penile bulb, allowing a better definition of the daily critical structures for adaptive purposes in SBRT or ultrahypofractionated RT [53,54].

Moreover, moving targets are preferred for oMRgRT [55–57], especially if they are particularly close to sensitive organs at risk, thanks to the application of online adaptive approaches with motion management and, where available, also automated gating systems. These indications preferably include lung lesions, locally advanced pancreatic cancer, primary or secondary liver tumors, head-and-neck cancers, prostate cancer, breast cancer, pelvic lymph nodes or other oligometastases (as a primary approach or in previously irradiated areas), local recurrences within prostate previously irradiated as a primary treatment, kidney and adrenal gland metastases (see figure 4). In addition to the listed technical advantages (i.e. homogeneous CT density, location, mobility), oMRgRT should be performed in all other cases, where MRI adds valuable information (e.g. shrinkage of tumor or early toxicity onset; radiomics applications).

Backup solutions

The technical complexity and costs of this technology generally prevent RT centers having more than one active treatment unit, making backup solutions in the event of a machine failure particularly challenging. Moreover, some systems are stand-alone solutions and patients cannot easily be shifted between different centers. Various strategies can be pursued to prevent a therapy interruption and reduce its consequences. Support agreements with nearby centers equipped with the same technology represent the best solution as they ensure that therapy is continued with the same standards (i.e gating parameters) and are strongly recommended, whenever feasible. Other possible solutions are represented by conversion to a conventional linac plan, using the same patient positioning set up and the simulation CT used for the electron density transfer or acquiring a new dedicated simulation CT. In this setting, more sophisticated plan summations and dose accumulation calculations are needed and may represent a difficult obstacle to be overcome.

Discussion

Successful translation of innovative technologies into clinical practice remains challenging. The implementation of oMRgRT in daily clinical routine of radiation oncology could be affected by novel issues and challenges that need to be thoroughly investigated before starting clinical treatments in new centers.

This consensus recommendation provides a broad overview of the available technical solutions of oMRgRT and its challenges in the clinical implementation phase. It is obvious that several factors influence the choice of the optimal workflow and procedures for each individual institution, as there are different strategies available and the scarcity of published evidence does not allow us to define which approach performs at best. Unlike the implementation of other radiotherapy techniques, oMRgRT adds the MR environment to the daily practice of radiotherapy – which might be a new experience for many of the centers. Therefore, the implementation of oMRgRT includes the need of adequate staff training and patient screening regarding MR safety. Dedicated SOPs and emergency plans have to be elaborated prior to go live.

Furthermore, the workflow and interdisciplinary work in the team have to be adapted from conventional RT. The online treatment planning workflow requires specialized training for all team members (radiation oncologists, RTTs, physicists), as the plan adaptation and troubleshooting has to be performed in a timely manner, while the patient is on the treatment table. This new circumstance may require that traditional roles and responsibilities cross traditional boundaries as workflows develop and should be addressed in the implementation phase by defining individual protocols, SOPs, risk analysis and checklists. Moreover, it is recommendable to conduct peer-to-peer training of experienced users and dummy runs with volunteers to train the workflow and challenges for the entire MR-linac team.

As far as future perspectives of oMRgRT are concerned, the currently available oMRgRT technologies are at the beginning of their clinical use and continuous improvements are likely to be seen soon. A new scenario, in which new software can be used to extract large amounts of features from multiple MR images (including functional images) using data characterization algorithms (radiomics, deep learning), or to develop data-intensive computer-based solutions to support medical decisions (through artificial intelligence applications) for fast and reliable auto-contouring and auto-planning processes, is likely to change the perspectives, possibilities, management and adapted workflow in the field oMRgRT in the future.

The implementation of oMRgRT is a resource intensive investment as indicated by the recommendations in this work. However, the future potential in combination with the current clinical experience make this a worthwhile investment because it offers the possibility to meet patient expectations that the radiotherapy should be adapted to their anatomy every day to achieve maximum efficacy and minimal toxicity.

Figure legends

Figure 1: Hybrid systems combining magnetic resonance imaging with radiation therapy. A) MRIdian system with a 0.35 T MR-linac (ViewRay Inc., USA) B) Unity system with a 1.5 T MR-linac (Elekta AB, Sweden).

Figure 2: Exemplar oMRgRT workflow

Figure 3: Exemplar daily plan adaptation A): full re-optimization for a lung cancer patient on treatment fraction 12 to fulfill constraints of organs at risk. B) full re-optimization for a prostate patient on treatment fraction 3 to fulfill constraints of organs at risk.

Figure 4: Examples of MR-guided radiotherapy stereotactic treatments: A) prostate cancer, B) lung metastasis, C) spinal metastasis, D) liver metastasis, E) pelvic lymph node metastasis, F) renal metastasis, G) locally advanced pancreatic cancer, H) cardiac sarcoma, I) bone metastasis

Conflicts of interest

CB and SC have received research grants and speaker fees/travel support from Elekta, Viewray and Brainlab. FA is a consultant and has received speaker honoraria from Elekta, Varian and Boston scientific. NA has received funding from Brainlab and ViewRay and speaker fees/travel support from ViewRay. DA has received institutional research funding from ViewRay. OB has received speaker fees from ViewRay. LB has received research grants from Varian and ViewRay and speaker fees/travel support from ViewRay. AB has received speaker fees and travel support from ViewRay inc. Amsterdam UMC has research agreements with ViewRay inc. JHR has received speaker fees and travel reimbursement from ViewRay Inc, as well as travel reimbursement from IntraOP Medical and Elekta Instrument AB outside the submitted work. FL has received speaker fees and travel support from ViewRay inc. Amsterdam UMC has research agreements with ViewRay inc. HMcN is funded by a National Institute for Health Research and Health Education England (HEE/NIHR), Senior Clinical Lecturer award. BR has received research support and/or funding from Elekta, Philips, Modus QA, Sun Nuclear, IBA, PTW, Scandidos and speaker fees from Elekta. AT has received research funding from Elekta, Varian and Accuray, and speaker fees/travel grants from Elekta and Genesis Healthcare. VV has received departmental research grants from Varian Medical Systems, ViewRay Inc., Elekta, Merck-Serono, Roche. DZ receives within the framework of research agreements financial and technical support as well as sponsoring for travels and scientific symposia from Elekta, Philips, Siemens, PTW and Sennewald. Research in MRgRT is funded by the German Research Council (DFG, ZI 736/2-1; PAK997/1). The other authors declare that they have no competing interests.

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Figures:



Figure 1

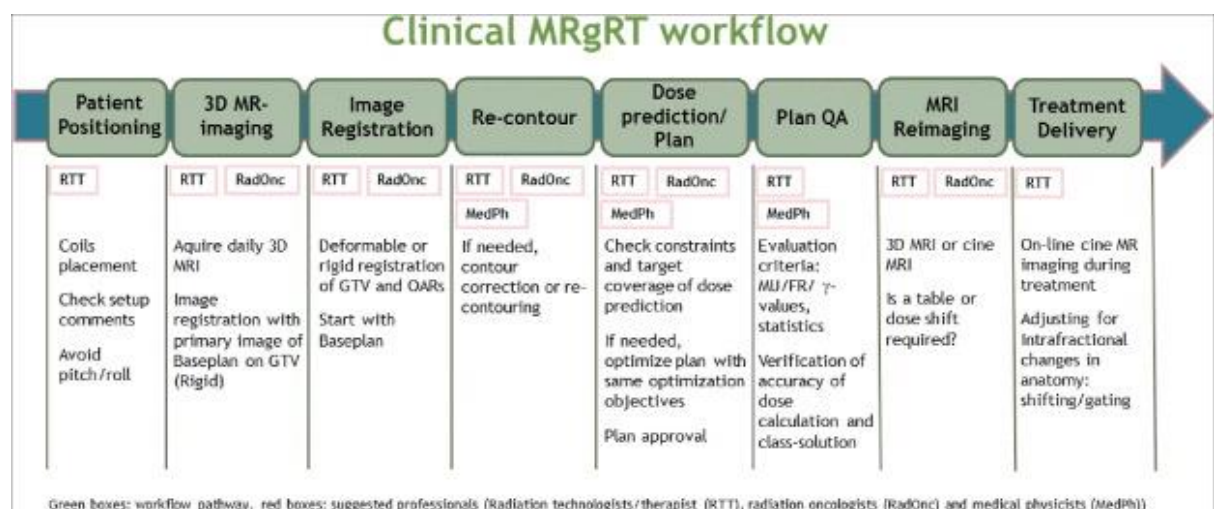


Figure 2

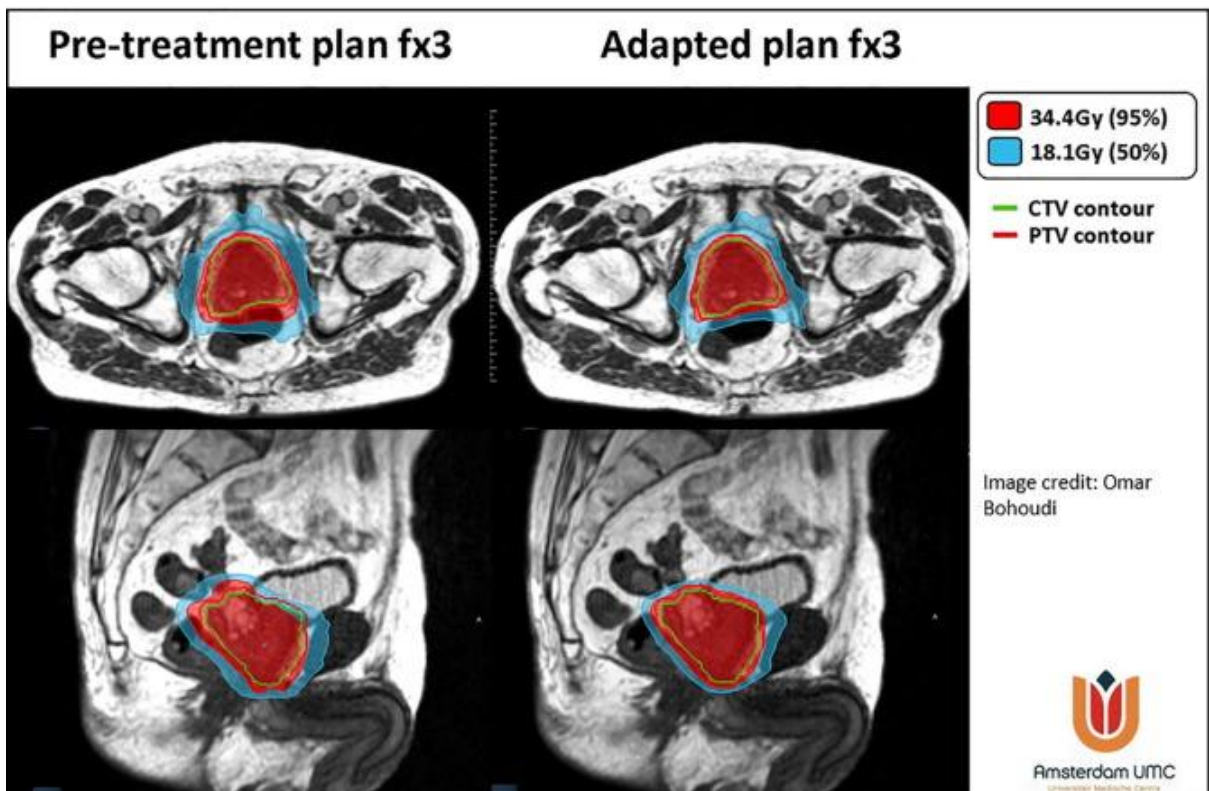
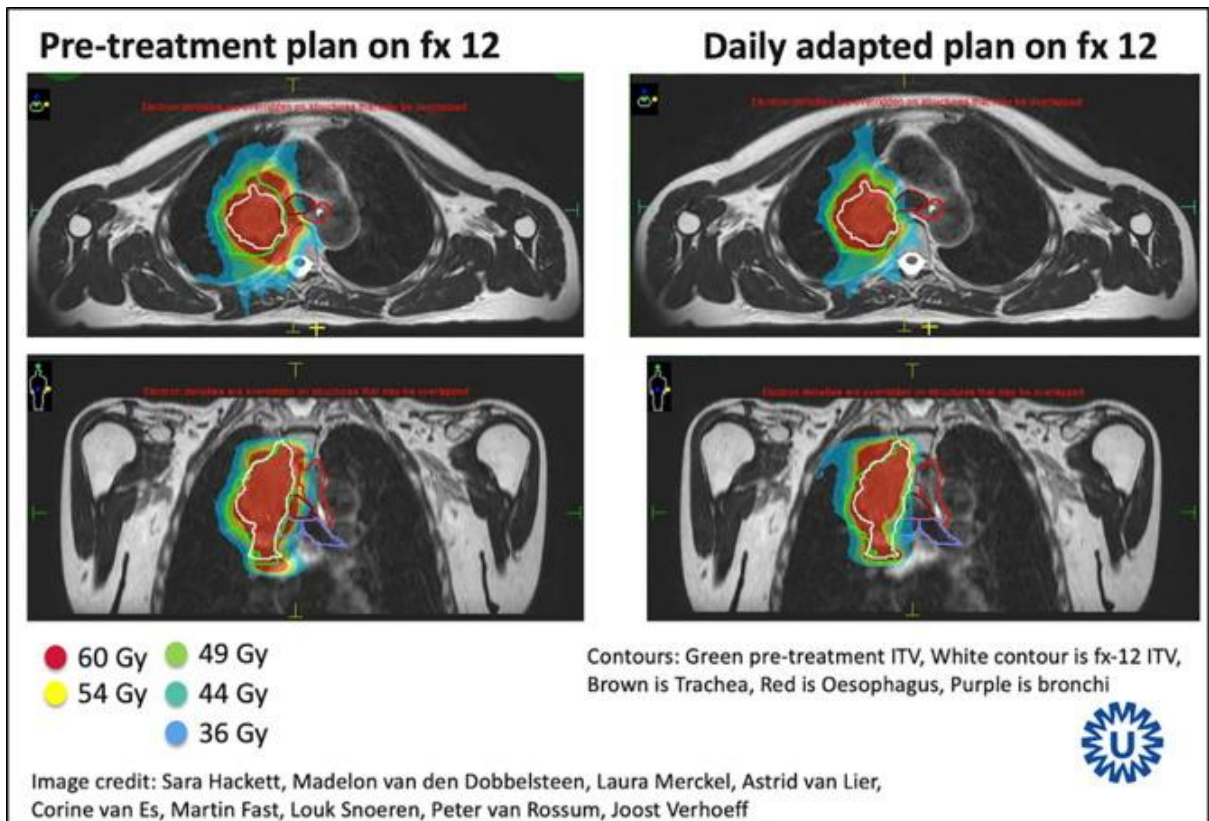


Figure 3

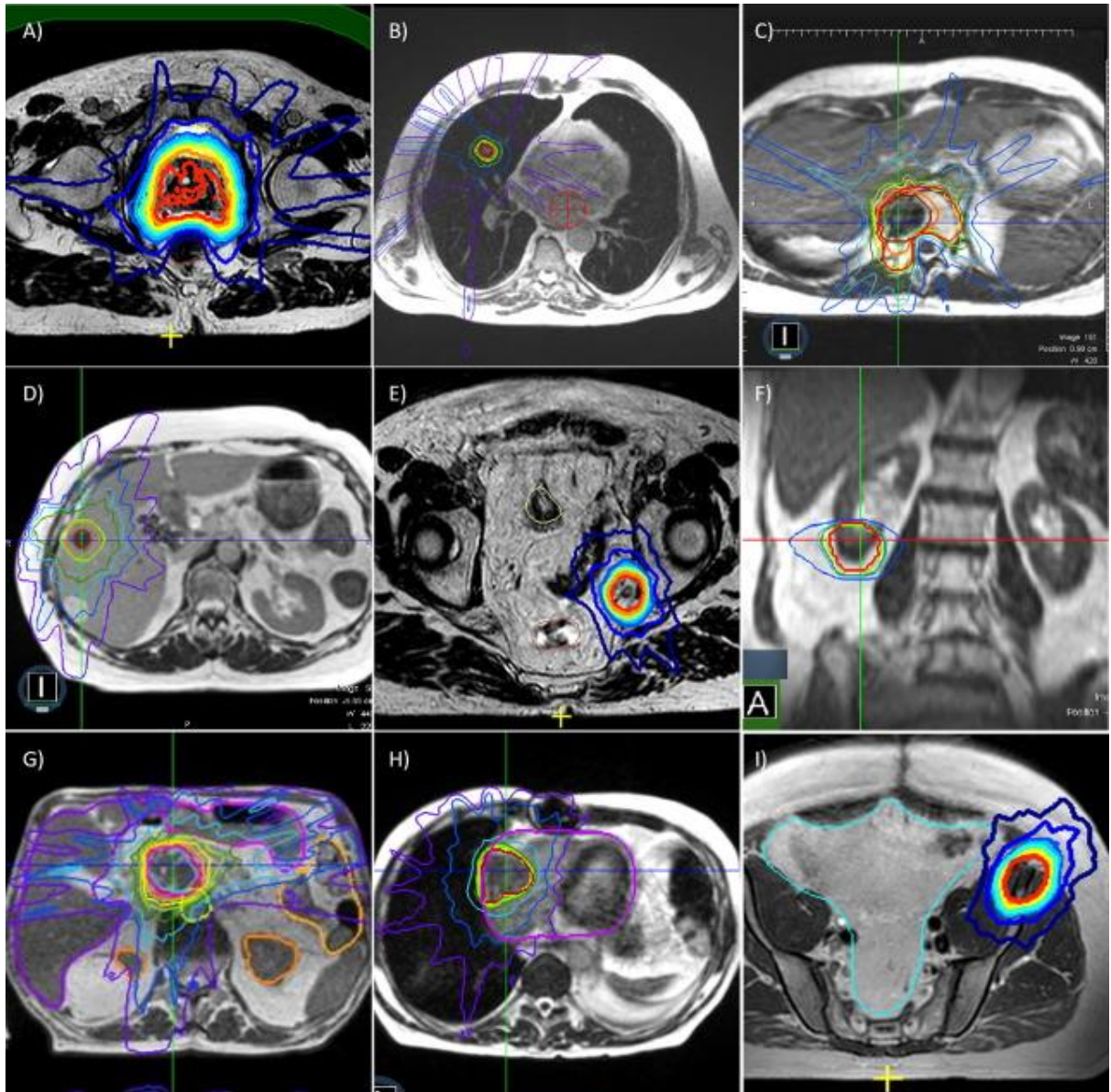


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Figure 4