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Couwenberg, A.; Heide, U. van der; Janssen, T.; Triest, B. van; Remeijer, P.; Marijnen, C.; ... ; Nowee, M.

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Short Communication

Master protocol trial design for technical feasibility of MR-guided radiotherapy

Alice Couwenberg *, Uulke van der Heide, Tomas Janssen, Baukelien van Triest, Peter Remeijer, Corrie Marijnen, Jan-Jakob Sonke, Marlies Nowee

Department of Radiation Oncology, The Netherlands Cancer Institute, Amsterdam, The Netherlands

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ABSTRACT

The master protocol trial design aims to increase efficiency in terms of trial infrastructure and protocol administration which may accelerate development of (technical) innovations in radiation oncology. A master protocol to study feasibility of techniques/software for MR-guided adaptive radiotherapy with the MR-Linac is described and discussed.

In radiation oncology, numerous evolving innovations aim to improve the outcomes of cancer patients. Adaptive radiotherapy with the use of a magnetic resonance imaging (MR)-guided linear accelerator is such a promising innovation [1]. MR-guided radiotherapy enables reduction of uncertainties in the shape and position of both tumour and organs at risk before and during treatment due to superior soft tissue contrast compared with computed tomography (CT). In addition, the use of daily online plan adaptation may allow smaller margins and higher doses to the tumour which may result in higher efficacy and/or lower toxicity compared with conventional radiotherapy.

The MR-Linac (Elekta Unity, Elekta AB, Stockholm, Sweden) is an MR-guided linear accelerator which integrates a state-of-the-art linear accelerator, a 1.5 Tesla diagnostic quality MRI scanner and an online adaptive workflow. Currently, numerous technical innovations are under development to improve adaptive radiotherapy on the MR-Linac. These innovative technologies will enable the investigation of clinical research questions in large multicentre trials. Hence, feasibility studies on these techniques are essential and often require evaluation in various tumour sites. As supported by the R-IDEAL (Radiotherapy - Idea, Development, Exploration, Assessment, and Long-term evaluation) framework [2], feasibility of radiotherapy innovations is preferably evaluated and reported systematically to improve transparency, to share knowledge, and to ensure safety. However, to perform a feasibility study for each single innovation and for each single tumour site is time consuming when using a standard trial protocol. Instead, a master protocol trial design can be considered which comprises one general protocol that includes multiple subgroups and/or multiple interventions [3].

In this paper, we describe the use of a master protocol trial design to study feasibility of in-house developed techniques/software for MR-guided adaptive radiation therapy on the MR-Linac. In addition, we will describe the advancement of the protocol after the initial approval.

Methods

UMBRELLA-II is an ongoing trial (ClinicalTrials.gov: NCT04351204) at the department of Radiation Oncology of the Netherlands Cancer Institute (NKI-AVL, Amsterdam, the Netherlands). It is designed as a master protocol containing prospective, non-randomised trials with the aim to evaluate feasibility of various in-house developed techniques/software on the MR-Linac in various tumour sites. Secondary, acute toxicity of patients treated at the MR-Linac is collected in the context of these technical innovations.

* Corresponding author at: Plesmanlaan 121, postbus 90203, 1006 BE Amsterdam, The Netherlands.
E-mail address: a.couwenberg@nki.nl (A. Couwenberg).

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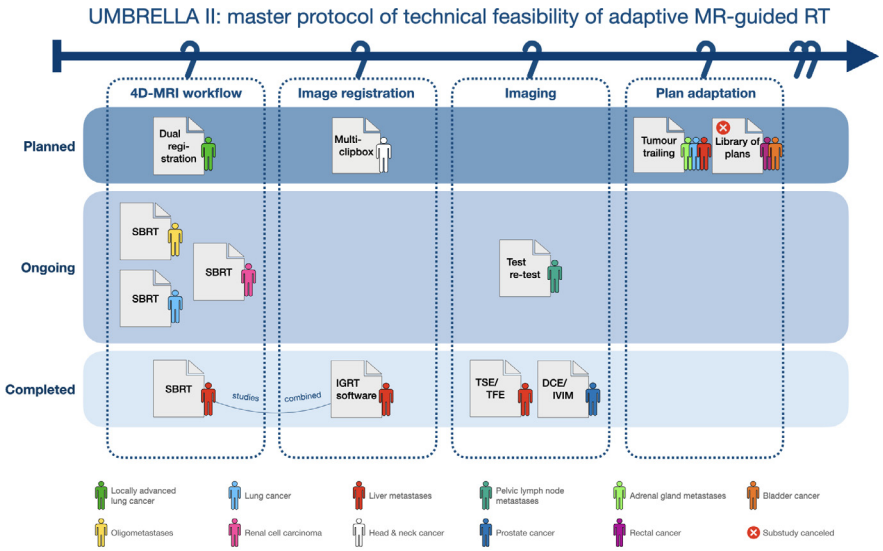

Fig. 1. Schematic overview of UMBRELLA II. Substudies comprise techniques/software for 4D-MRI workflow, image registration, imaging, or plan adaptation and are planned, ongoing or yet completed. Each substudy includes one or multiple tumour sites. New substudies in either of the clusters or a new cluster can be initiated at any time by amendment. *DCE: dynamic contrast enhanced; IGRT: image-guided radiotherapy; IVIM: incoherent voxel independent motion; MRI: magnetic resonance imaging; SBRT: stereotactic body radiotherapy; RT: radiotherapy; TSE/TFE: turbo spin echo/turbo field echo.*

UMBRELLA-II comprises a general protocol, trial design, and outcome definition to uniformly evaluate multiple techniques/-software in multiple substudies (Fig. 1). Patients can be enrolled in substudies that run parallel or sequentially, each defined by tumour type(s) and a technical manual. Substudies can be added based on new insights and available techniques and are unlimited in number. UMBRELLA-II was approved by the medical research ethical committee (METC) of the NKI-AVL in August 2018. The METC did not require major amendments of the protocol. After the initial approval of the master protocol, substudies are reviewed as amendment by the local METC and requires approval before start. UMBRELLA-II was preceded by UMBRELLA-I, a master protocol to optimise the MR-Linac workflow and MR-sequence protocols for various tumour sites.

Cancer patients ≥18 years with WHO performance 0–2 are eligible for enrolment. Exclusion criteria are contra-indications for MRI, pregnancy, claustrophobia, patient weight of >140 kg and/or a body width >60 cm, patients with any other clinically significant medical condition which, by discretion of the treating physician, makes it undesirable to participate. Additional inclusion and exclusion criteria may apply to a specific substudy. Patients sign informed consent to be enrolled in a substudy, with a matching tumour type and a specific technique for guidance/adaptation, with collection of technical and clinical data related to the MR-Linac treatment used for research purposes. Furthermore, most patients treated on the MR-Linac give consent to participate in a prospective cohort study of the MR-Linac consortium (MOMENTUM study, clinicaltrials.gov NCT04075305). In this study, participants consent to share data to MR-Linac partners, Elekta and Philips Healthcare.

In each substudy a technique for treatment guidance/adaptation on the MR-Linac is studied conform the specific technical manual (see Supplement 1 for an example technical manual). The manual of each technique describes background, specific inclusion and exclusion criteria, description of the technique, description of the intervention per patient, safety, and contingency of the procedure. The use of 'adapt to shape' or 'adapt to position' on the MR-Linac is described by the clinical protocol of each tumour type / radiotherapy schedule and not specifically by the substudy (unless it is part of the technique under evaluation).

All substudies adhere to the same primary outcome criteria. Feasibility of the technique under study is demonstrated if the technique is successfully applied in 9 out of 10 consecutive patients (success rate of 90%), with a maximum of 20 patients to be included per cohort. If a technique is unsuccessfully applied in three consecutive patients or the technique is not successfully applied in nine consecutive patients after the inclusion of 20 patients, it is considered unfeasible. For all substudies, success is defined by four general criteria (each of the four criteria should be met to reach feasibility):

1. All fractions per patient which are intended to be delivered on the MR-Linac are completed as planned i.e., the technical procedure that was tested functioned as expected and the treatment did not deviate from the intended protocol as described in the technical manual.
2. The total duration for a patient on the treatment couch (including imaging and treatment) was completed within 1 hour in ≥90% of fractions or, in case of stereotactic treatments, in all minus one fraction.
3. Absence of geographical miss in ≥85% of fractions or, in case of stereotactic treatments, in all minus one fraction, unless clinical guidelines on a cone beam CT (CBCT)-guided linear accelerator accept more geographical miss or a dose accumulation strategy shows a sufficient dose coverage over all fractions (as determined by current clinical practice). Geographical miss is defined as the clinical treatment volume outside the treated volume on post-treatment imaging.
4. No unexpected grade >3 acute toxicity has occurred. Extra toxicity related to the addition of the techniques/software evaluated in this protocol is not expected.

The feasibility criteria were defined by the MR-Linac steering committee of the NKI-AVL including radiation-oncologists and (medical) physicists. If a fraction fails, the specific technical manual will describe the consequences and the procedure to follow i.e., the contingency of the substudy. Treatment associated grade ≥3 acute toxicity is scored according to the Common Terminology Criteria of Adverse Events (CTCAE version 4.03) from start of treatment until 90 days after the completion of radiotherapy which marks the end of the follow-up within this study.

Sample size

Per sub-study, a maximum of 20 patients can be enrolled. No formal sample size calculation was performed because this is not a hypothesis-driven research. Rather, it is based on the needs of demonstrating feasibility of techniques/software.

Results

Between August 2018 and April 2021, 12 substudies were proposed (of which six are at protocol initiation stage) and all were ethically approved (Table 1). Substudies submitted as amendment, which included a technical manual and patient information folder, took approximately one-month submission lead-time (range 9 days to 7 weeks).

Up to now, substudies comprise techniques/software for 4D-MRI workflow, imaging, plan adaptation and image registration and aim to include patients with the following tumour sites: liver, prostate, lung, oligo-metastases (lymph node metastases and adrenal gland metastases), kidney, rectum, head and neck, and bladder. Sixty-nine of the 211 (33%) patients treated on the MR-Linac at the NKI-AVL so far, have been included in one of the substudies of this master protocol.

Five substudies involve feasibility of a self-sorting 4D-MRI workflow in different treatment sites, a technique which is developed to compensate for motion on the MR-Linac [4]. In stereotactic body radiotherapy (SBRT) for liver metastases, this 4D-MRI technique successfully met the feasibility criteria (N = 20 patients, study completed in 9.5 months) after which substudies were initiated for SBRT for oligometastases, lung and kidney tumours and for fractionated radiotherapy for locally advanced lung cancer.

Three substudies involve feasibility of various imaging sequences on the MR-Linac. The substudy on perfusion MRI sequences (DCE and IVIM) in prostate cancer patients for monitoring of perfusion changes successfully met the feasibility criteria (N = 20 patients, study completed in 25 months). Feasibility was also successful in the substudy on improvement of visibility of liver metastases prior and during radiation using two anatomical MRI sequences (TSE and TFE) within the 4D-MRI workflow (N = 20 patients, study completed in 10.5 months).

Two substudies involve feasibility of techniques involving plan adaptation. The substudy on library of plan (LOP) selection in bladder and rectal cancer patients was cancelled because of (unforeseen) availability of commercial software for a LOP approach. Preparations of the substudy on intra-fractional tumour trailing are ongoing.

Two substudies involve feasibility on software involving image registration. Feasibility of the implementation of in-house developed registration software used for CBCT-guided linear accelerators was combined with the 4D-MRI workflow substudy in liver metastases. Preparations for feasibility of region of interest (multiclipbox) image registration in head and neck tumours are ongoing.

Discussion

The principle of a master protocol trial design has been developed for biomarker-driven studies in medical oncology [3,5,6]. Mainly, three variants of master protocols are practiced: basket trial (i.e., a single targeted intervention for multiple diseases), umbrella trial (i.e., multiple targeted interventions for a single disease), and platform trial (i.e., multiple targeted interventions for a single disease with addition and removal of interventions based on planned interim analyses) [7]. UMBRELLA II includes multiple interventions and multiple tumour sites and can therefore be considered as a combination of a basket and umbrella trial. Despite the increasing use of a master protocol trial design in medical oncology, its use is still uncommon in radiation oncology research. The tumour-agnostic radiotherapy workflow makes this design however very interesting, especially for the evaluation of treatment devices such as the MR-Linac [8].

Few radiotherapy master protocol trials have been reported [8,9]. Welsh et al. published a basket phase II trial of ipilimumab with concurrent or sequential SBRT to liver or lung metastases on toxicity and out-of-field response [9]. Bitterman et al. presented a master protocol initiative to evaluate feasibility, safety, and efficacy of MR-guided adaptive SBRT in lung, pancreatic, and kidney tumours [8]. Feasibility was defined as enrolling patients and delivering MR-guided adaptive SBRT; assessing tumours using MR-guidance before, during, and after treatment; and generating adaptive plans. In contrast to UMBRELLA-II, this master protocol also describes phase II trials, randomization and statistical considerations and aims to pool endpoints for feasibility and cancer type-agnostic outcomes. Currently, several radiotherapy master protocol trials are initiated/ongoing, for example, the PLATO platform trial for anal cancer (ISRCTN88455282), the CONCORDE platform trial for lung cancer (NCT04550104) [10], the EXTEND basket trial for oligometastatic disease (NCT03599765), the AGADIR basket trial for combination of immunotherapy and radiotherapy (NCT03915678), and several MRI-guided radiotherapy trials (NCT04545957, NCT04115254 and NCT04368702).

The greatest advantage of a master protocol trial design is the increased efficiency in trial administration and infrastructure. This

Table 1
Overview of approved substudies within the UMBRELLA-II master protocol.

Cluster	Technique/software	Tumour site(s)	Status	Feasibility
4D-MRI workflow	SBRT	Liver	Completed	Successful
	SBRT	Lung	Ongoing	–
	SBRT	Oligometastases	Ongoing	–
	SBRT	Kidney	Ongoing	–
	Fractionated RT with dual registration[‡]	Lung (locally advanced tumours)	Planned	–
Imaging	DCE and IVIM perfusion MRI	Prostate	Completed	Successful
	TSE and TFE MRI for 4D-MRI	Liver	Completed	Successful
	Test-retest quantitative MRI	Pelvic lymph nodes	Ongoing	–
Plan adaptation	Library of plan selection	Bladder, rectum	Cancelled*	N.A.
	Tumour trailing	Lung, liver, adrenal gland	Planned	–
Image registration	In-house IGRT software	Prostate, rectum, oligometastases	Combined[#]	N.A.
	Multiclipbox	Head and neck	Planned	–

DCE: dynamic contrast enhanced; IGRT: image-guided radiotherapy; IVIM: incoherent voxel independent motion; NA: not applicable; RT: radiotherapy; SBRT: stereotactic body radiotherapy; TFE: turbo field echo; TSE: turbo spin echo.

*Cancelled because of unforeseen availability of commercial software for library of plan selection.

‡ Dual registration of the primary tumour and the (mediastinal) lymph nodes during fractionated radiotherapy.

Integrated in the substudy on 4D-MRI workflow in liver SBRT.

may lower trial duration, costs and harms because of early abandonment/modification of unfeasible innovations, and may accelerate selection of promising interventions for phase II/III [8,11]. Furthermore, it facilitates the complex systematic evaluation of innovations in radiation oncology which is of great importance to patients, users, vendors, and society [2,8].

A challenge of a master protocol trial is the complexity of the protocol. In UMBRELLA-II, feasibility criteria had to be adequate for various types of (future) techniques/software where it may be difficult to predefine potential substudies at time of protocol initiation as technical development is ongoing. Some predefined substudies in UMBRELLA-II appeared redundant and were cancelled/combined. Also, it may be debatable which interventions are eligible to evaluate in a master protocol. In UMBRELLA-II, current substudies evaluate feasibility of techniques/software in the scope of standard treatment to minimise the risk of toxicity. Furthermore, funding a master protocol trial may be difficult as they are often open-ended without a maximum sample size. In UMBRELLA-II, costs are limited by the short-term outcomes of feasibility and acute toxicity.

Conclusions

We have presented a master protocol trial, UMBRELLA-II, to study feasibility of multiple in-house developed techniques/software for MR-guided adaptive radiotherapy on the MR-Linac in various tumour sites using a general infrastructure and criteria for technical feasibility. Twelve substudies have been initiated in 2.5 years of which three are completed and confirmed feasible implying that these techniques are ready for further evaluation. Despite challenges related to the complexity of the design, we encourage the use of a master protocol trial for feasibility purposes aiming to accelerate technical development of MR-guided adaptive radiotherapy.

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None.

Conflicts of interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2021.11.009.

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