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Original Research Article

Magnetic Resonance-based Response Assessment and Dose Adaptation in Human Papilloma Virus Positive Tumors of the Oropharynx treated with Radiotherapy (MR-ADAPTOR): An R-IDEAL stage 2a-2b/Bayesian phase II trial

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ABSTRACT

Background: Current standard radiotherapy for oropharynx cancer (OPC) is associated with high rates of severe toxicities, shown to adversely impact patients' quality of life. Given excellent outcomes of human papilloma virus (HPV)-associated OPC and long-term survival of these typically young patients, treatment de-intensification aimed at improving survivorship while maintaining excellent disease control is now a central concern. The recent implementation of magnetic resonance image – guided radiotherapy (MRgRT) systems allows for individual tumor response assessment during treatment and offers possibility of personalized dose-reduction. In this 2-stage Bayesian phase II study, we propose to examine weekly radiotherapy dose-adaptation based on magnetic resonance imaging (MRI) evaluated tumor response. Individual patient's plan will be designed to optimize dose reduction to organs at risk and minimize locoregional failure probability based on serial MRI during RT. Our primary aim is to assess the non-inferiority of MRgRT dose adaptation for patients with low risk HPV-associated OPC compared to historical control, as measured by Bayesian posterior probability of locoregional control (LRC).
Methods: Patients with T1-2 N0-2b (as per AJCC 7th Edition) HPV-positive OPC, with lymph node <3 cm and <10 pack-year smoking history planned for curative radiotherapy alone to a dose of 70 Gy in 33

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fractions will be eligible. All patients will undergo pre-treatment MRI and at least weekly intra-treatment MRI. Patients undergoing MRgRT will have weekly adaptation of high dose planning target volume based on gross tumor volume response. The stage 1 of this study will enroll 15 patients to MRgRT dose adaptation. If LRC at 6 months with MRgRT dose adaptation is found sufficiently safe as per the Bayesian model, stage 2 of the protocol will expand enrollment to an additional 60 patients, randomized to either MRgRT or standard IMRT.

Discussion: Multiple methods for safe treatment de-escalation in patients with HPV-positive OPC are currently being studied. By leveraging the ability of advanced MRI techniques to visualize tumor and soft tissues through the course of treatment, this protocol proposes a workflow for safe personalized radiation dose-reduction in good responders with radiosensitive tumors, while ensuring tumoricidal dose to more radioresistant tumors. MRgRT dose adaptation could translate in reduced long term radiation toxicities and improved survivorship while maintaining excellent LRC outcomes in favorable OPC.

Trial registration: ClinicalTrials.gov ID: NCT03224000; Registration date: 07/21/2017.

1. Background

1.1. Low risk HPV-Associated OPC

In the last decades, a change in the demographics of head and neck cancers has been observed, with an increasing incidence of human papillomavirus (HPV) – associated oropharyngeal cancers (OPC) reaching 60% of all OPC in the United States [1]. HPV-associated OPC is associated with markedly improved prognosis compared to non-HPV-associated OPC [2,3]. The favorable prognosis, along with the long-term survival and markedly younger age patients with HPV-positive disease, have supported that low-risk HPV-associated OPC may be suitable for treatment de-intensification [4]. Many treatment de-intensification strategies are currently being assessed in the context of clinical trials; these notably include use of minimally invasive surgery such as trans-oral robotic surgery [5], targeted therapies [6], and various radiation dose reduction strategies in the context of upfront radiotherapy [7] or after induction chemotherapy [8,9].

1.2. MRgRT dose adaptation

The principle of adaptive radiotherapy planning relies on adjusting the treatment plan based on observed changes over the course of therapy. While tumor responsiveness to radiotherapy in OPC has been shown to be associated with permanent tumor control outcomes [10], intra-treatment tumor shrinkage is observed as early as by fraction 11 [11] and complete response at mid-treatment is observed in as high as 50% of patients with HPV-associated OPC [12]. In a recent study, Lee et al. [7] reported excellent disease control outcomes of 10 Gy dose de-escalation to involved lymph nodes that presented early intra-treatment resolution of hypoxia on 18F-fluoromisonidazole - positron emission tomography (PET).

The increasing use of magnetic resonance imaging (MRI) for head and neck radiotherapy planning has the advantage of improved soft-tissue visualization [13], allowing for more confident assessment of anatomical tumor changes during treatment, at no ionizing radiation cost. The recent introduction of the MR-Linac technology, consisting in the combination of a linear accelerator and a 1.5 Tesla MRI, holds the promise to facilitate such adaptive MR-guided radiotherapy (MRgRT) workflows by mean of daily on-line MRI during radiation treatment [14,15]. In this study, we propose weekly RT dose-adaptation based on MRI-based tumor response. This adaptive radiation protocol will target a highly selected population of favorable risk HPV-associated OPC with a small (<5–7%) probability of locoregional failure with photon monotherapy. Our primary aim will be to assess the non-inferiority of MRgRT dose adaptation for patients with low risk HPV-associated OPC compared to historical control, as measured by Bayesian posterior probability of locoregional control (LRC). By virtue of its assessment of clinical effectiveness and safety of the use of weekly MRI for dose adaptation, this study is a stage 2a/2b study as per the R-IDEAL framework for systematic technology assessment in radiotherapy [16] (Annex 1 – Supplementary material).

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.ctro.2018.08.003.

2. Methods and design

2.1. Study design

This study uses a novel Phase II Bayesian two-stage adaptive design. The stage 1 of this study will enroll 15 patients to the experimental arm exclusively (MRgRT dose adaptation) to preliminarily assess the efficacy and safety of MRgRT. Bayesian decision rules will be used to make the go/no-go decision to move forward to stage 2, in which 60 patients will be randomized (1:1 ratio) into the MRgRT arm or the standard intensity modulated radiotherapy (IMRT) arm for comparison of LRC. Fig. 1 presents the study scheme. This study is approved by the MD Anderson Institutional Review Board and is registered on clinicaltrials.gov (NCT03224000).

2.2. Primary objective

To assess non-inferiority of MRgRT dose adaptation and elective volume de-escalation in low risk HPV-associated OPC treated with radiotherapy alone.

- Primary endpoint:
  - o LRC at 6 months. LRC will be defined from time of treatment completion to disease progression at primary site or regional lymph nodes.

2.3. Secondary objectives

1. To compare rates of acute and late toxicities of MRgRT vs. standard IMRT.
2. To assess health – related quality of life outcomes in both treatment groups.
3. To assess disease-related outcomes (2-year progression-free survival, distant metastasis-free survival, and overall survival) in both treatment groups.
4. To validate functional imaging kinetics as a correlate of early treatment response.

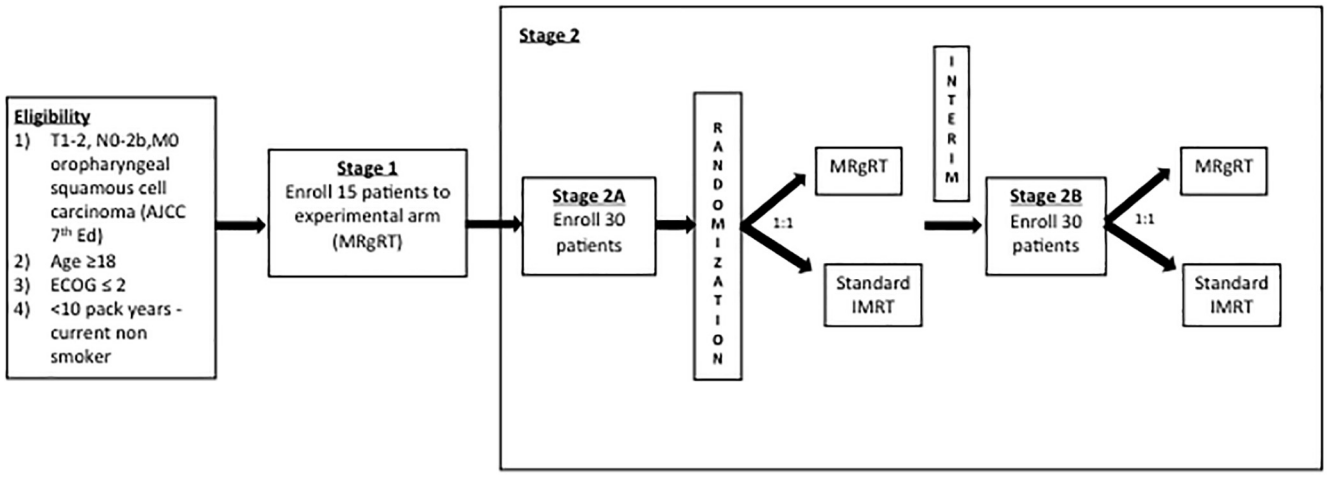

Fig. 1. Scheme of the 2-stage trial design. ECOG = Eastern Cooperative Oncology Group; MRgRT = Magnetic-Resonance guided radiotherapy; IMRT = Intensity Modulated Radiotherapy.

2.4. Conditions for patient eligibility

- Biopsy proven diagnosis of squamous cell carcinoma of the oropharynx (includes tonsil, soft palate, base of tongue, pharyngeal walls of oropharynx)
- Age ≥18 years
- Clinical stage T1-2, N0-1 (<3 cm), or small volume N2b (1–3 cm) M0, per AJCC 7th edition
- Positive for HPV by p16 immunohistochemistry or HPV in-situ hybridization
- Lifetime pack-year history of <10 years, and currently non-smoking
- No retropharyngeal nor level IV lymphadenopathy
- No head and neck surgery of the primary tumor or lymph nodes except for incisional or excisional biopsies
- Eastern Cooperative Oncology Group performance status 0–2
- Planned for single modality photon radiotherapy
- For females of child-bearing age, a negative pregnancy test

2.5. Conditions for patient ineligibility

- Previous radiation treatment for head and neck mucosal primary cancers within the past 5 years
- Pregnant or breast-feeding females
- Contraindications to MRI

2.6. Radiation therapy

Detailed description of target volumes and organs at risk (OAR) dose constraints are presented in Annex 2 (Supplementary material).

2.6.1. Dose specification

- MRgRT arm

Patients will receive an individualized prescription of *up to* 69.96 Gy in 33 fractions with radiotherapy administered once daily, 5 days a week. Initial prescription will cover a high-risk clinical region (CTV_6996) with 2.12 Gy/day. High-risk clinical region will include the gross tumor volume (GTV) plus an additional 5 mm margin. All uninvolved upper-neck elective nodal volumes outside of the CTV_6996 will be encompassed in an elective irradiation volume deemed CTV_5016, and prescribed 1.52 Gy/day for a total prescription of 50.16 Gy in 33 fractions.

- Standard IMRT arm

Patients will receive 69.96 Gy in 33 fractions to the high-risk CTV_6996, with radiotherapy administered once daily, 5 days a week. High-risk clinical region will include the GTV determined on MRI plus an additional 5 mm margin. All uninvolved upper-neck elective nodal volumes outside of the high-risk CTV will be encompassed in a volume deemed CTV_5412, and prescribed 1.64 Gy/day for a total prescription of 54.12 Gy in 33 fractions.

2.6.2. MRgRT arm: weekly adaptive workflow

Patients in the MRgRT arm will have pre-treatment and weekly CT simulation and MR-simulation at an interval of 5 ± 2 fractions serially on treatment. MRI imaging data will be acquired for all patients in **stage 1** of the trial using a non-hybrid MRI device (MAGNETOM Aera 1.5 T MR scanner; Siemens Healthcare, Erlangen, Germany). In **stage 2**, MRI imaging data will be acquired using the integrated MR-Linac, which combines Philips 1.5 T MRI (Marlin, Finland) with 7 MV photon beam Elekta Linear accelerator. Anatomic T1-weighted and T2-weighted MRI sequences will be acquired in the axial plane with diffusion weighting gradients in three orthogonal directions using multiple b-values in the range of 0–1500 s/mm^2. The radiation plan adaptation will be done once weekly and could be done online or offline. The diffusion weighted images will be obtained and analyzed retrospectively to correlate apparent diffusion coefficient (ADC) changes during treatment with final treatment response.

With the aim to integrate weekly replanning as the default workflow, weekly adaptation of the GTV (primary or nodal) will be performed when a minimally measurable shrinkage of ≥2 mm is observed. A new high-risk CTV_6996 will be generated to cover the weekly MRI-based GTV plus a margin of 5 mm. Any region previously involved by the tumor will remain in the CTV_5016 to receive the minimum daily dose of 1.52 Gy/day and ensure a minimum "floor" dose of 50.16 Gy.

On the standard IMRT arm, adaptation may be performed exceptionally in cases where volumetric verification imaging is concerning for inadequate coverage of the target volumes or dose deviation to OAR.

2.7. Radiation planning and IGRT

Patients will have planning CT and MRI positioned in a stable supine position, using immobilization devices as previously described [17]. All patients will be planned with IMRT or

volumetric arc therapy. All treatment plans are to be normalized to provide at least 95% volume coverage of the PTV with the prescribed dose. No voxel within the PTV should receive more than 110% of the prescribed dose. Patients will have daily image guidance using in-room volumetric imaging prior to daily treatment.

2.8. Patients' evaluations

Pre-treatment, patients will be evaluated independently by a head and neck surgeon, a medical oncologist and a radiation oncologist. Annex 3 (Supplementary material) summarizes evaluations at different time points of the study.

2.9. Statistical considerations

A novel Bayesian two-stage adaptive design will be used for this phase II trial (see Fig. 1). Stage 1 involve only the experimental arm (MRgRT), and 15 patients will be enrolled to preliminarily assess the efficacy and safety of the experimental MRgRT. If MRgRT demonstrates promising, non-inferior LRC with a margin of 5%, compared to the historical LRC rate of 96%, as well as a rate of grade $\geq$ 3 toxicity at 6-months < 30%, we will move forward to stage 2, in which 60 patients will be randomized (ratio 1:1) into the MRgRT arm or the standard IMRT arm. In stage 2, an interim analysis will be conducted to monitor the LRC and toxicity after 30 patients are randomized. Bayesian decision rules will be used to make the go/no-go decision for each stage (Annex 4, Supplementary material). The endpoint of LRC at 6 months was selected to allow for rapid Bayesian decision, and is based on evidence that the risk of locoregional recurrence after complete response within 12 weeks of treatment in HPV-associated OPC is associated with < 5% locoregional recurrence rate at 5 years [18].

3. Discussion

In the context of the rampant incidence of HPV-associated OPC, there is crucial need to improve toxicity profiles in this population of often young, long-term survivors. The overall goal of treatment de-intensification strategies is to maintain the current very good disease control outcomes while reducing treatment-induced morbidity. To this end, it is essential that any dose adaptation strategy be associated with appropriate selection of good radiotherapy responders without compromising the chances of cure of poor responders. By leveraging the ability of advanced MRI techniques to visualize tumor and soft tissue characteristics through the course of treatment, it is possible to identify these subgroups of good responders and offer personalized dose-reduction. The introduction of the MR-Linac technology offers a unique opportunity to facilitate such adaptive MRgRT workflows by mean of daily on-line MRI during treatment [14]. The use of a common hybrid MRI device in the stage 2 of this study will allow the development of a high volume adaptive radiotherapy workflow using standardized imaging across multiple institutions, facilitated by the use of an integrated tool set. However, the results of our study could ultimately be scaled to any MRI device in radiotherapy.

While the use of adaptive MRI-based radiotherapy has the advantage of inherently selecting good responders, there remain concerns regarding the minimal radiobiological dose required at the edge of the shrinking GTV. In a recent study by Hamming-Vrieze et al. [20] the behaviour of tissue surrounding the GTV edge of locally advanced oropharyngeal tumors was assessed by placing fiducal markers at the tumor surface. The authors reported a larger GTV displacement on MRI compared to that assessed using fiducial markers, suggesting that part of the GTV was likely dissolving instead of shrinking and, raising concern of possible underdosage of microscopic disease with adaptive field reduction following GTV shrinkage assessed on MRI. In our study, this concern is addressed on one part by maintaining a 5 mm margin around the shrinking GTV for the high dose CTV, and on the other part by preserving an unchanged elective volume throughout the treatment, regardless of tumor response, to ensure a tumoricidal floor dose in all areas previously involved by tumor.

Recent report from an *in silico* study by our group [19] evaluating the dosimetric advantage of the proposed MRgRT dose adaptation approach showed a mean dose reduction to target volume of 11 Gy, and a significant dose reduction to swallowing musculature and thyroid gland which translated into a reduction of normal tissue complication probability of dysphagia $\geq$grade 2, feeding tube persistence at 6-month, and hypothyroidism at 1-year post-treatment [19]. As a second step, our proposed clinical study will provide essential information on the clinical feasibility, safety and clinical toxicity reduction of MRgRT dose adaptation in well-selected patients. We propose a conservative approach to this MRgRT dose de-escalation model, whereby only patients with highly favorable, low stage and low volume burden HPV-associated OPC will be eligible to enroll in this study. Should the study demonstrate positive results, transposition of this adaptive model to more advanced HPV-associated OPC would be subject of additional investigation.

4. Co-author specific contributions

- HB, ASRM, SP- Manuscript drafting, editing and review of comments, clinical trial activation.
- YY- Statistical analysis.
- AA, CN, JH, JR, MA, IK, KN, KH, SB, AJM, PB, ASG, JP, JPPB, PD, LK, SB, SJF, CHJT: Clinical protocol development.
- KKB, PAB, MM, GC, MA, KKS, JG: Image segmentation, adaptive workflow development, cumulative dose calculation.
- JW, YD, JJS, UAH, XAL, UO, MEPP, CATB, CPJR: MRI sequence development, optimization and standardization.
- SL, KH, GBG, DIR: Toxicity assessment planning and functional outcome evaluation management.
- CDF: corresponding author; primary investigator; conceived, coordinated, and directed all study activities, responsible for data collection, project integrity, manuscript content and editorial oversight and correspondence; direct oversight of trainee personnel (HB, ASRM, SP, MA, YD).

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