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Original Research Article

Effect of 0.35 T and 1.5 T magnetic fields on superficial dose in MR-guided radiotherapy of laryngeal cancer

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ABSTRACT

Background: Treatment of head and neck cancer on linear accelerators with on-board magnetic resonance imaging (MR-linac) might be beneficial to reduce side effects and increase accuracy. For many head and neck cancer patients, dose coverage of the often superficially located planning target volumes (PTVs) is required. This study examines the impact of the electron return effect (ERE) on the surface dose in MR-guided radiotherapy (MRgRT) compared to conventional radiotherapy.

Materials and methods: For this bicentric dosimetric study, 14 cases of laryngeal carcinomas with PTVs reaching up to the skin surface were included. For each patient, five different plans were compared, two VMAT plans (with and without a 5 mm bolus) and three IMRT MRgRT plans (0.35 T, 1.5 T and 0 T, each without bolus). Dose distributions were also validated with film measurements.

Results: A similar coverage on the most superficial 3–5 mm of the PTV was achieved in the VMAT plans with bolus and the MRgRT plans for both 0.35 T and 1.5 T. However, coverage on this region was usually not achieved for VMAT without bolus and the 0 T plans. The film measurements on phantoms confirmed the results with the relative error never exceeding the calculated differences between the plans.

Conclusion: The present study could demonstrate that the ERE for both commercially available MR-linac variants provides sufficient coverage of the superficial tissue layers in MRgRT-plans for laryngeal carcinoma.

1. Introduction

Planning target volumes (PTV) in the head and neck region may be situated in contact or within a few millimetres of the patient's skin, thus requiring superficial coverage [1]. However, superficial coverage can be limited by the build-up effect [2]. One of the most prominent examples of targets requiring superficial dose coverage in the head and neck region are laryngeal carcinomas involving the anterior commissure and/or more advanced ones with indication for irradiating nodal level VI [3].

A commonly used solution to reach superficial coverage is to use a bolus, in which the build-up can happen, thus increasing superficial dose to the patient [4]. Bolus can, though, be associated with an increased skin toxicity, positioning variability, dose uncertainties and inhomogeneity and are labour-intensive [5–7]. Nevertheless, in lack of better solutions most published series on larynx radiotherapy, even larger prospective trials [8], implemented a bolus to tackle underdosage of the superficial target.

Recently, the advent of hybrid platforms, combining a linear accelerator with on-board MR-imaging (MR-linacs) provided additional possibilities and technical advances. These MR-linacs are increasingly used also for treating head and neck cancer [9], and moving targets such as the larynx can be a reasonable indication due to the possibility of target-gating. Moreover, the physical property of the electrically charged electrons to bend their track inside a magnetic field (electron return effect, ERE) could lead theoretically to an increased surface dose [10]. Currently, there is no evidence of increased skin toxicity with or without the use of bolus during MR-linac treatments, or that there are specific concerns in such situations, as the vast majority of MR-linac series published address stereotactic treatments with PTVs in the depth of the body [11]. This makes this topic worth exploring before routine implementation in the clinical routine.

In this bicentric planning study, we investigated whether the ERE

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existing in MR-guided radiotherapy (MRgRT) can provide sufficient superficial coverage to the PTV without bolus.

2. Material and methods

2.1. Patient cohort

A total of 14 consecutive patients with cT1-cT3 glottic carcinoma were retrospectively analysed in this dosimetric study. The patient characteristics are reported in Table 1. The clinical target volume (CTV) included only the involved cord(s) (both cords in case of T1b/ bilateral involvement). Furthermore, the CTV included the elective lymphatic volumes for T2/T3 disease. PTV is defined as CTV with an added margin of 3 mm. For all 14 cases the PTV had to be contoured at least up to the skin-surface due to involvement of the anterior commissure or need for elective irradiation of level VI.

All the treatments were performed at the Department of Radiation Oncology of the University Hospital Zurich in the period November 2018 – April 2022. Two patients were treated at the MR-Linac within the MARTHA clinical trial (NCT03972072) while the remainder received standard of care treatment at a C-Arm Linac. Anonymized data transfer between the University Hospital Zurich and Radboud University Medical Centre was regulated by a data transfer agreement following the institutional guidelines. All patients gave their consent for retrospective anonymized data analysis.

2.2. Treatment plans

For each patient in the cohort, five different plans were compared, two VMAT plans and three IMRT MRgRT plans (Fig. 1). To simplify the analysis and the comparison, each plan was rescaled to a prescription of 33 fractions of 2 Gy.

Supplementary Table 1 summarises the optimization constraints. Whenever possible, the organ at risk (OAR) objectives were fulfilled. If not possible, the acceptable variation values were considered. Targets have a priority of 2 and OARs either 1 or 3. Priorities were defined such as, when objectives of two volumes were contradictory, the objectives of the volume with the smaller priority were met in priority, and the variations were used for the volume with the higher priority, if necessary. OARs that were always prioritised were the oral cavity, submandibular glands, parotids, spinal cord, brain and brainstem.

Table 1
Patient characteristics.

Patient	Smallest distance PTV-skin [cm]	Stage	Nodal PTV originally included (Y/N)
1	0.1	cT1a cN0 cMx	N
2	0.15	pTis cNx cMx	N
3	0	cT2 cN0 cM0	Y
4	0.15	pT2 pN1 cM0	Y
5	0	cTis cN0 cM0	N
6	0	cT3 cN0 cM0	Y
7	0	cT1 cN0 cM0	N
8	0.15	cT2 cN0 cM0	Y
9	0	cT2 cN0 cM0	Y
10	0	cT3 cN0 cM0	Y
11	0	cT1b cN0 cMx	N
12	0	cT2 cN0 cM0	Y
13	0	cT3 cN0 cM0	Y
14	0	cT3 cN0 cM0	Y

Two VMAT plans were generated per patient on the Eclipse TPS for delivery at a TrueBeam C-Arm linear accelerator (Varian Medical Systems Inc., Palo Alto, USA) with Millenium 120 Leaf MLC. Two arcs were used with a full gantry rotation. The dose grid was 1.5 mm and the algorithm was Accuros 16.1 with heterogeneity corrections activated. All plans were optimised firstly without a bolus (plan VMAT) and then re-optimised with a 5 mm bolus having manually assigned HU = 0 (plan VMAT + Bolus). The beam quality was 6 MV.

Two IMRT MRgRT plans per patient were generated using the ViewRay TPS for delivery at a MRIdian MR-Linac (ViewRay Technologies Inc., Oakwood Village, USA). All plans used 19 beams equally spaced, except for the ones leading to exactly opposing beams which were tilted by up to 10°. Angles 29–34° were avoided because of the cryostat. The number of segments was limited to a maximum of 120 and the dose grid was 1.5 mm. The algorithm used was ViewRay Monte Carlo with uncertainty of 0.5% per calculation. The plans were first optimised with the magnetic field correction on (plan 0.35 T) and then recalculated with the magnetic field correction off (plan 0 T). The beam quality was 6 MV FFF.

One IMRT MRgRT plan per patient was generated using the Monaco TPS for delivery at a Unity MR-Linac (Elekta, Stockholm, Sweden). The planning approach was analogous to the MRIdian, except for the following: angles 8-18° avoided, segment limit 200, uncertainty 1%, corrections activated for the 1.5 T field and beam quality 7 MV FFF.

The plans were compared by evaluating the dose statistics of different structures. First, the PTV coverage was evaluated. The achieved coverage by the different plans was evaluated with D95%, excluding the air voxels (HU < -750) within the PTV from the computation. However, the focus of the study was on the superficial parts of the PTV. In this regard, two structures were specifically defined as the intersection between the PTV and the skin minus 3 mm (PTV_3mm) and 5 mm (PTV_5mm), as shown in Fig. 2A.

For each patient and each plan described above, the dose of the three structures of interest was recorded. This allowed comparing the differences in global coverage as well as superficial dose across the different types of plans. To evaluate the statistical differences between the different types of plans, paired Wilcoxon signed-rank tests [12] were performed for PTV D95%, PTV_3mm Dmean and PTV_5mm Dmean. If the result of the statistical test yielded a value $p < 0.05$, the two plans were considered significantly different.

2.3. Film measurements and evaluation

TPS results were validated by 2D dose measurements in the coronal and transverse planes. EBT3 GafChromic films (Ashland, Bridgewater, USA) were used. In both cases, the films were irradiated with plans optimised as described above. To obtain such plans for both phantoms, the structures of one patient were copied onto the phantoms. In particular, the PTV was placed as close as possible to the surface of the phantom. The plans could then be reoptimized on the phantoms (see Supplementary Fig. 1B and D).

Surface doses in the coronal plane were measured with 2x2cm^2 films taped on the surface of a Delta4 phantom (ScandiDos AB, Uppsala, Sweden). The surface of this phantom is curved in a way that reproduces approximately the curvature of the neck while allowing the film to be taped without any air between the film and the phantom itself (Supplementary Fig. 1A).

For the coronal plane film measurements, a VMAT and a VMAT + Bolus plan were reoptimized. To evaluate the effect of a bolus in the presence of the 0.35 T magnetic field, two different plans were reoptimized: one with a bolus and one without. Films were irradiated with one treatment plan fraction of 2 Gy. At both linear accelerators (Varian

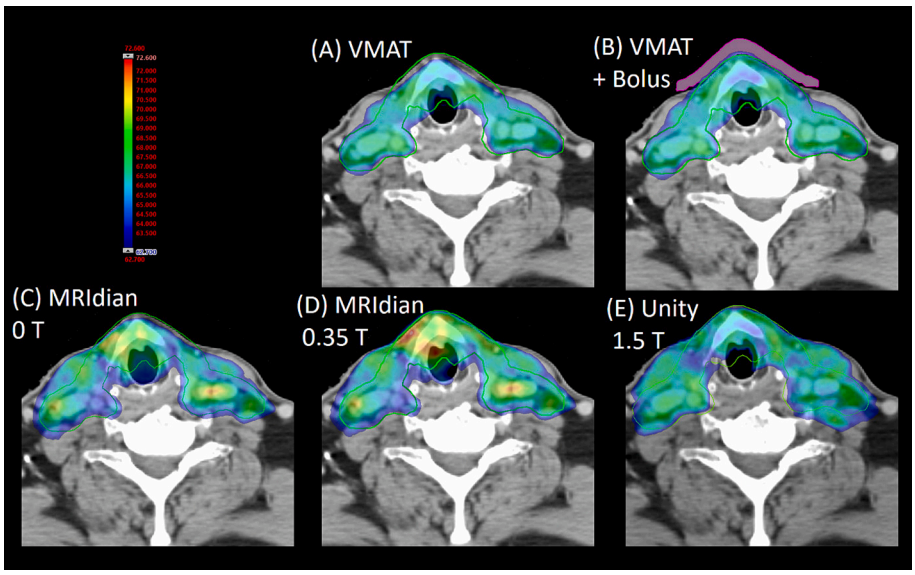

Fig. 1. Example of the dose distributions obtained for the different types of plans for patient 3. The isodose 95% is shown (62.7 Gy) and the colourwash scale is reported. A: plan VMAT. B: plan VMAT + Bolus, the bolus is indicated in pink. C: plan 0 T. D: plan 0.35 T. E: plan 1.5 T. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

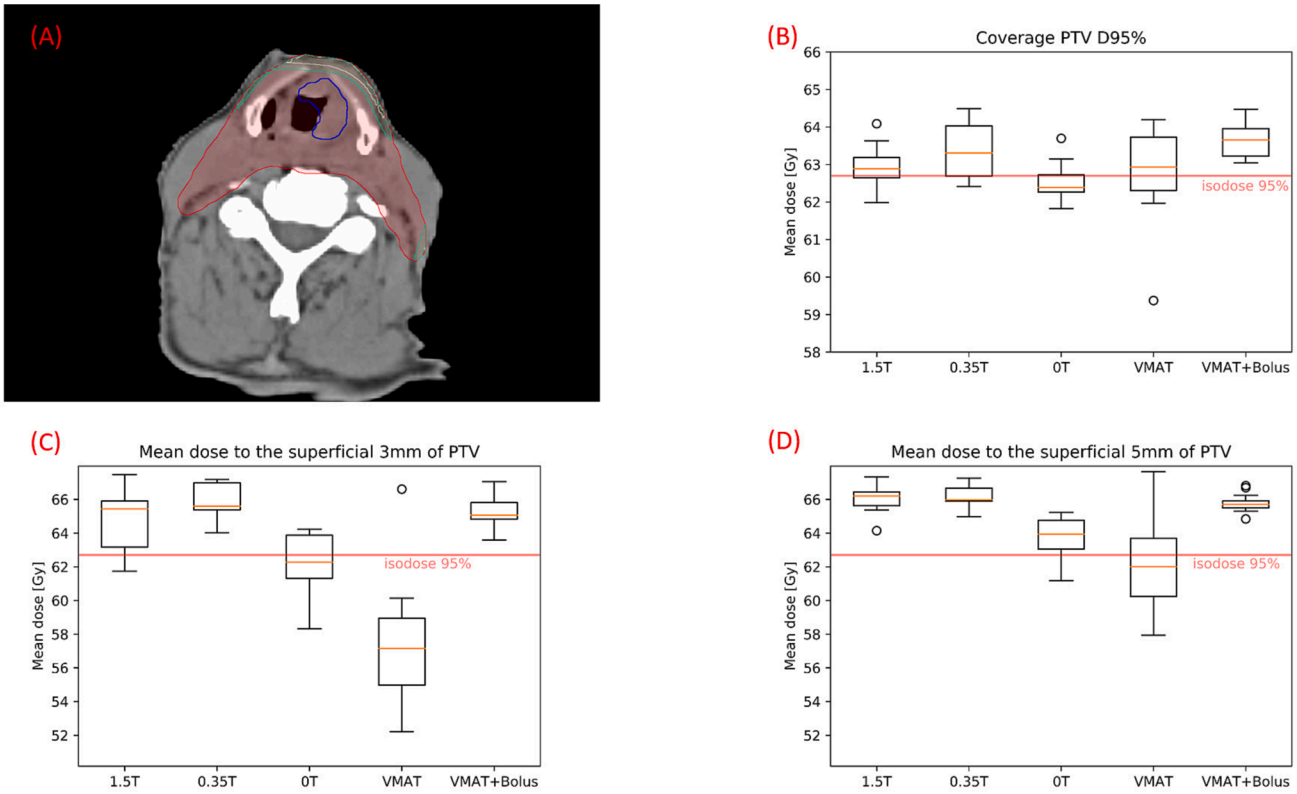

Fig. 2. Evaluation of the different types of plans. A: The structure used to evaluate the plans were the whole PTV (red) and the intersection between the PTV and the skin minus respectively 3 mm (PTV_3mm in yellow) and 5 mm (PTV_5mm in green). The GTV (blue) is also shown. B: PTV D95% for the different plans and the whole cohort of patients. C: Mean dose to PTV_3mm for the different plans and the whole cohort of patients. D: Mean dose to PTV_5mm for the different plans and the whole cohort of patients. The red line indicates the 95% isodose. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

TrueBeam and ViewRay MRIdian), films were also irradiated with 100 MU with open field from gantry at 0°.

For the Varian TrueBeam and ViewRay MRIdian the depth doses in the transverse plane were also measured by placing films in between the neck pieces of an anthropomorphic Alderson male phantom (Alderson-Rando, RSD Radiology Support Devices, Long Beach, CA, USA) (Supplementary Fig. 1C). Films were cut to follow the shape of the neck and to extend far enough in the sagittal direction. For the depth doses in the Alderson phantom, a complete set of plans was reoptimized. Films were irradiated with one fraction of the plans.

The films were analysed with FilmQA Pro 4.0 (Ashland, Bridgewater, USA). Surface doses were extracted from the mean dose of a 1x1cm^2 square in the centre of the 2x2cm^2 films. To obtain depth dose curves from the films in the Alderson phantom, five adjacent depth profiles were extracted and the depth dose was averaged over those five profiles. This averaged depth dose was then compared with the dose profile extracted directly from the TPS plan (Supplementary Fig. 1D).

3. Results

3.1. Dosimetric analysis

Fig. 1 presents an example of each of the plans described in the Methods section for one of the patients of the cohort (Patient 3). For each plan, the 95% isodose is shown. As expected, coverage is not achieved on the most superficial millimetres of the PTV for plan VMAT (Fig. 1A). Coverage on this superficial part is however achieved with the help of a bolus, as shown with plan VMAT + Bolus (Fig. 1B). For plans 0.35 T and 1.5 T, it can be seen that the ERE also allows the coverage of the superficial part of the PTV (Fig. 1D-E). When the magnetic field is turned off, this effect disappears and superficial coverage is lost (Fig. 1C).

The results for all patients for the three structures of interest defined in the Methods section are shown in Fig. 2. In regards to overall coverage as well as superficial dose, the VMAT plan without bolus is the worst, for which only 8/14 patients achieved the 95% isodose coverage for 95% of the volume, compared to 10/14 for 0.35 T and 9/14 for 1.5 T. For the VMAT and 0 T plans, the mean dose to PTV_5mm was higher than for PTV_3mm. This effect is not seen for plans VMAT + Bolus, 0.35 T and 1.5 T, where the prescribed dose is already achieved close to the surface. Moreover, those three plans offer similar good results in both overall coverage and superficial dose.

Table 2 summarises the results of the Wilcoxon signed-rank tests. The results show consistent differences between Dmean to the superficial 3 and 5 mm among the five plans. In detail, the presence of bolus or magnetic field leads to equivalent superficial doses. The absence of one of the two leads to a significant decrease in superficial dose. This is valid also when comparing PTV D95% for 1.5 T–0.35 T, 0.35 T – VMAT+ bolus and VMAT – VMAT+ bolus. In other cases, PTV D95% presents differences that may be attributed to the several TPS adopted in this study.

3.2. Comparison TPS to measurements

Fig. 3 shows the surface dose measurements on the Delta4 phantom in presence or absence of the 0.35 T field and the bolus. The expected 2 Gy for one fraction of the re-optimized plans are indeed delivered at the surface for plans VMAT+ Bolus and 0.35 T, but not for VMAT (Fig. 3A), in accordance to what was shown on Figs. 1 and 2. Moreover, the effect of adding a bolus to plan 0.35 T is negligible. On the contrary, when the gantry is set to 0°, only the presence of the bolus will influence the dose to the surface, and not the presence of the magnetic field (Fig. 3B).

Depth doses measured in the transverse plane in the Alderson phantom are shown on Fig. 4. For both VMAT and VMAT+ Bolus plans, the relative error between measurement and TPS calculation decreases with the depth, with an average difference of 4.3% on the first 3 mm, 3.7% on the first 5 mm and 2% for a depth bigger than 5 mm (Fig. 4A and B). Similar results are obtained for plan 0.35 T, as shown on Fig. 4C, where an average difference of 2.7% is observed for the first 3 mm, 2.4% for the first 5 mm and 1.8% for depths larger than 5 mm.

Table 2
Wilcoxon signed-rank tests result. Each line represents one test performed on the pair of sets of plan indicated in Plan1 and Plan2. For both set of plans, the mean dose over all the patients were evaluated for the three structures of interest indicated. The p-value resulting of the test is reported in the correspond column for the structures of interest analysed. Significant differences ($p < 0.05$) are highlighted in bold.

Plan 1	Plan 2	p-value for the analysed parameter:		
		PTV D95%	PTV_3mm Dmean	PTV_5mm Dmean
1.5 T	VMAT + bolus	**0.005**	0.657	0.245
1.5 T	VMAT	0.638	**0.005**	**0.002**
1.5 T	0.35 T	0.074	0.091	0.975
1.5 T	0 T	0.158	**0.013**	**0.002**
0.35 T	VMAT + bolus	0.177	0.286	0.074
0.35 T	VMAT	0.124	**0.004**	**0.002**
0.35 T	0 T	**0.001**	**0.003**	**0.001**
VMAT	VMAT + Bolus	**0.002**	**0.004**	**0.002**

4. Discussion

Irradiating laryngeal cancer, as a mobile target, with clinical benefits using hypofractionated regimens, and especially with dosimetric issues due to the air-tissue borders both on the body surface and on the epithelia of the airways, could be a very attractive indication for MR-linac implementation. Laryngeal carcinoma with involvement of the anterior commissure, especially in the cases of advanced tumour infiltrating the thyroid cartilage and/or in need of irradiation of nodal level VI, is a prime example of implementation of bolus to increase target coverage. These two clinical scenarios (anterior commissure in GTV and/or irradiation of level VI) are very common, otherwise the PTV can be cropped to the skin surface. As there is a lack of upstream tissue layers at the beam entrance points, there is also no build-up effect to produce enough secondary electrons. Moreover, the multiple-angles and modulated beams used in IMRT further decrease the entrance dose, thus leading to underdosage of superficial structures [13]. Yet, there are many disadvantages of the bolus-technique, such as “hot” and “cold” spots and positioning uncertainties, and even the improvements demonstrated by individualised 3D-printed boluses can be tedious and costly.

In this study we investigated the impact of the ERE on slightly increasing and homogenising the surface dose in real-life patients with laryngeal carcinoma and compared IMRT plans generated for the two commercially available MR-linacs. Both the different magnetic field strengths of the two devices (0.35 T and 1.5 T), as well as VMAT plans on a conventional linac with and without bolus were evaluated separately. The calculated results were successfully validated via film dosimetry on phantoms, confirming the observed significant differences. The dose differences should be attributed to the ERE, given that the depth dose curves acquired at gantry 0° in water phantoms present limited differences in the value at the surface (Supplementary Fig. 2). Taken together, the dose coverage of the superficial 3 mm and 5 mm in the presence of a magnetic field is significantly improved compared to the coverage without magnetic field or to VMAT plans without bolus and very similar to the VMAT plans with bolus. Interestingly, the differences in the effect between magnetic fields of 0.35 T and 1.5 T do not appear to be significant (Fig. 3 and Table 2).

In recent years, hybrid platforms allowing for irradiation in a magnetic field are more often used also in the treatment of head and neck cancer, allowing with increasing user-experience for good-quality IMRT-plans [14] and possible dosimetric and clinical advantages, such as improved sparing of moving organs. This has been demonstrated amongst others in the example of the interfractional movement of the salivary glands [15], but could be exercised also in the much more complicated intrafractional movement of the larynx during laryngeal cancer radiotherapy [16]. Moreover, the online image-guidance without additional dose exposure allows for higher precision, an important prerequisite for safe application of hypofractionated regimens. Several large retrospective and prospective studies could already demonstrate the improved local control after hypofractionated radiotherapy of laryngeal cancer on the conventional linacs [8,17]. Even phase I-II trials

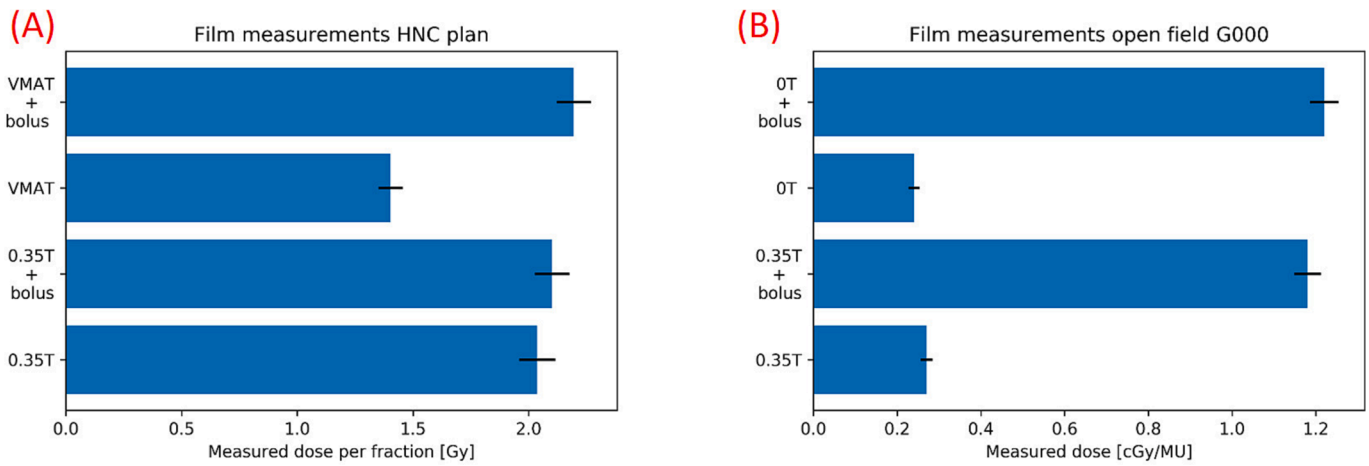

Fig. 3. Surface dose film measurements. A: Results of the irradiation of the films with one fraction of the different reoptimized plans. B: Results of the irradiation of the films with 100MU with gantry at 0° and open field at the conventional linear accelerator in absence of magnetic field, i.e. 0 T (Varian TrueBeam) and MR-Linac in presence of the 0.35 T magnetic field (ViewRay MRIdian).

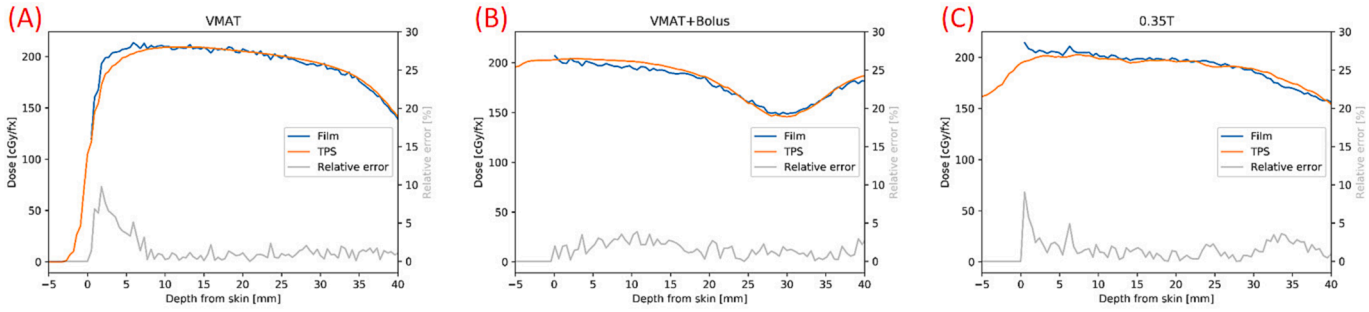

Fig. 4. Comparison between depth dose profiles extracted from the films placed in the Alderson phantom (blue) and calculated by the TPS (orange) for plans VMAT (A), VMAT + Bolus (B) and 0.35 T (C). The grey line indicates the relative error between measurement and TPS calculation. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

applying stereotactic radiotherapy in up to only 5 fractions have been published, demonstrating promising short-term results, but also enhanced toxicity using conventional IGRT-methods [18,19]. MR-linacs might be used for this indication in the future. The reduced number of fractions could compensate for the longer "on-couch" times for the patients, making this indication a very good candidate for MRgRT.

As described before, irradiating a superficial target inside a magnetic field has some very interesting theoretical physical "side-effects" like the ERE. This bending of the electron tracks back to the irradiated surface in an MR-linac has been already objectified and measured by several groups, both for 1.5 T and 0.35 T devices [20–23]. It is particularly prominent when irradiating curved surfaces and/or with oblique fields, but negligible in case of perpendicular beams on flat surfaces, as shown by the films measurements with the gantry set at 0° (Fig. 3B) and in accordance with previous studies by Raaijmakers and colleagues [24,25]. The application to real-life patients has shown a significant increase in skin dose in presence of a 1.5 T field for head and neck treatments [26], the comparison with lower fields MR-linacs or conventional linacs was however not investigated and it is reported for the first time in the current study. Van Heijst et al. recently described this effect clinically in breast cancer, concluding that for accelerated partial breast irradiation -which is more comparable to hypofractionated larynx-regimens, both in terms of dose and field-size- there were no unexpected negative effects observed on the skin of the patients [27]. Similar results were presented by Nachbar et al. after irradiating a patient with breast cancer on an 1.5 T MR-linac, where the ERE was not associated with an increased acute skin toxicity [28]. In a further study by the same group, and when taking the ERE into account, there was also no additional projected risk of secondary radiation-induced cancer [29], which can be easily explained since the additional dose of daily ionising radiation exposure is replaced by MR-imaging. The findings from these studies, as well as from the present analysis, could lead also to other applications in the future, where a sufficient superficial dose coverage remains important [30] without the issues originating from bolus-use like the underlying air–gap [31].

These results could raise some concerns regarding skin toxicity after the routine use of MRgRT for head and neck cancer or other indications with PTVs close to the skin like breast cancer or sarcomas. Yet, previous studies demonstrated excellent plan quality for head and neck treatment both in presence of 0.35 T and 1.5 T [14,32]. No concerns were reported regarding challenges in reducing superficial dose outside the PTV. Therefore, it has to be assumed that MRgRT is capable of reducing surface dose in those cases to clinically acceptable levels, always depending on the number of beams and the depth of the PTV. Nevertheless, the first prospective trials evaluating toxicity after MRgRT for head and neck cancer are still ongoing. However, caution is warranted in cases where there is no indication for increased superficial dose in laryngeal cancer, i.e. where there is no need for irradiation of the anterior commissure or level VI. In these cases, the PTV can be cropped to the skin (or even 1–3 mm from the skin) or multiple beams from different angles could be implemented.

There are limitations of this study. First of all, as the investigations were conducted only in two centres with the respective available software and hardware and in a small cohort of cases, the generalisation of the results has to be demonstrated in larger cohorts, more centres and maybe also other platforms available in the future. Second, multiple

dose algorithms were employed depending on the linac for which the plan was prepared, but a benchmark with a common dose calculation engine for all case was not possible because not available at the time this study was performed. The film measurements aimed to overcome this limitation. Future studies with a common dose engine may also investigate the benefit of internal ERE in the air gaps, which was not investigated in the current study due to the uncertainty between the algorithms and limited the PTV coverage analysis to the volume excluding the air voxels. Third and most important, as this is a strict planning study, any possible dosimetric benefits have to be examined in prospective clinical series, where also clinical endpoints like toxicity can be carefully evaluated. To the best of our knowledge, this is the first study evaluating any dosimetric benefits of MR-linacs for irradiating laryngeal carcinomas and also taking both 0.35 T and 1.5 T machines into consideration.

5. Conclusion

The present study could demonstrate for the first time that sufficient coverage of the superficial tissue layers can be achieved even without bolus with the help of the ERE for both commercially available magnetic-field variants. Moreover, this is, to the best of our knowledge, the first study comparing the ERE in a clinical application in low- and high-magnetic fields.

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 data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctro.2023.100624.

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