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Original Article

Dosimetric feasibility of hypofractionation for SBRT treatment of lymph node oligometastases on the 1.5T MR-linac

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ABSTRACT

Purpose: At our department, MR-guided stereotactic body radiation therapy (SBRT) using the 1.5T MR-linac system (Unity, Elekta AB, Stockholm, Sweden) has been initiated for patients with lymph node oligometastases. Superior soft tissue contrast and the possibility for online plan adaptation on the Unity may allow for hypofractionated treatment. The purpose of this study was to investigate the dosimetric feasibility and compare the plan quality of different hypofractionated schemes.

Methods and materials: Data was used from 12 patients with single lymph node oligometastases (10 pelvic, 2 para-aortic), which were all treated on the Unity with a prescribed dose of 5x7 Gy to 95% of the PTV. Hypofractionation was investigated for 3x10 Gy and 1x20 Gy schemes (all 60 Gy BED α/β = 10). The pre-treatment plans were evaluated based on dose criteria and plan quality. If all criteria were met, the number of online adapted plans which also met all dose criteria was investigated. For pre-treatment plans meeting the criteria for all three fractionation schemes, the plan quality after online adaptation was compared using the four parameters described in the NRG-BR001 phase 1 trial.

Results: Pre-treatment plans met all clinical criteria for the three different fractionation schemes in 10, 9 and 6 cases. 50/50, 45/45 17/30 of the corresponding online adapted plans met all criteria, respectively. Violations were primarily caused by surrounding organs at risk overlapping or adjacent to the PTV. The 1x20 Gy treatment plans were, in general, of lesser quality than the 5x7 Gy and 3x10 Gy plans.

Conclusion: Hypofractionated radiotherapy for lymph node oligometastases on the 1.5T MR-linac is feasible based on dose criteria and plan quality metrics. The location of the target relative to critical structures should be considered in choosing the most suitable fractionation scheme. Especially for single fraction treatment, meeting all dose criteria in the pre-treatment situation does not guarantee that this also applies during online treatment.

Stereotactic body radiation therapy (SBRT) is a non-invasive treatment option which is often considered for focal ablation of oligometastatic disease or primary tumours which are not suitable for surgical resection [1–3]. In SBRT a relatively high irradiation dose is delivered in a limited number of fractions to the target in a highly conformal manner with steep dose gradients to achieve good sparing of the organs at risk (OARs) [4,5]. Many different fractionation schemes are currently being used in clinical practice. Most commonly dose is delivered in 3 fractions of 8–12 Gy or 5 fractions of 5–10 Gy using the Cyberknife or a regular cone-beam computed tomography (CBCT)-linac [6]. In particular cases the whole dose is delivered in one fraction of 12–24 Gy [7–10].

These hypofractionated treatments are given to increase patient comfort by reducing the number of fractions and deliver a higher biological equivalent dose (BED), which is often associated with improved and durable local tumour control [11,12]. Ramlov et al. reported that there seems to be no indication of a general benefit of delivering a total lymph node dose beyond 60 Gy $EQD2_{\alpha/\beta=10}$ [13]. However, several other studies have linked SBRT fractionation schedules with higher BED with better outcomes. Ost et al. showed a prolonged progression-free interval for oligometastatic prostate cancer recurrence after SBRT treatment with a $BED_{\alpha/\beta=3}$ > 100 Gy [14]. Park et al. showed that SBRT with a dose of $BED_{\alpha/\beta=10}$ > 90 Gy for recurrent or oligometastatic cervical cancer resulted in excellent local control, especially with a long disease-free interval [5]. The amount of dose that can be given to the target is however often limited by dose constraints for OARs, especially with OARs in the vicinity of the planning target volume (PTV). De

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Bleser et al. reported that elective nodal radiotherapy, as an alternative to SBRT, can be associated with fewer nodal recurrences, but with higher toxicity [15].

Single fraction SBRT yields further potential advantages compared to fractionated SBRT. The main advantages may be found in greater convenience for the patient by reducing the treatment to a single fraction and logistics as the slots on the treatment machines and costs could be reduced [16]. Additionally with single fraction treatment, delivered dose can be evaluated more accurately and advanced intra-fraction adaptation strategies can be more easily implemented [17]. Evidence also indicates that SBRT with doses >10 Gy per fraction cause tumor vessel damage causing secondary and additional tumor cell death and may produce enhanced antitumor immunity [18,19].

Most treatments are currently performed with CBCT-based position verification. Relatively poor soft tissue contrast on CBCT-linacs can make it difficult to accurately identify the tumor and surrounding OARs. This makes it more challenging to incorporate daily patient anatomy and to correct for inter-fraction variations using adaptive treatment planning approaches. While most studies report no incorporation of daily anatomy, recent studies showed a dosimetric benefit when doing so [20–22].

Several magnetic resonance imaging (MRI) guided radiotherapy treatment systems are in clinical use [23–25]. The 1.5T MR-Linac (Unity, Elekta AB, Stockholm, Sweden) [26] provides diagnostic quality imaging which gives better soft tissue contrast compared to CBCT imaging used on conventional linacs and allows for the use of MR-guided online adaptive workflows [27–29]. The increased soft tissue contrast can provide improved visualization of the target and surrounding OARs [30]. Better visibility of lymph nodes may allow for reduction of the planning target volume (PTV) margins around the tumor [31]. Reducing the PTV can result in better sparing of the surrounding tissues and reduce potential toxicity.

Hypofractionated MR-guided SBRT treatment of lymph node oligometastases allows for single fraction treatment. It is however uncertain to which extent these fractionation schemes can actually be given, without being limited by OAR constraints. The aim of this R-IDEAL [32] stage 0 study is to investigate the feasibility of hypofractionated schemes for treatment on the 1.5T MR-linac.

Methods and materials

Patient data characteristics

For this planning study, patient data was used from 12 patients with single lymph node oligometastases (10 pelvic, 2 para-aortic) with a median volume of 3.4 cm^3 [range, 1.1–15.2 cm^3], which were all treated on the 1.5T MR-linac (Unity, Elekta AB, Stockholm, Sweden) with a prescribed dose of 5x7 Gy to 95% of the PTV (3 mm GTV-PTV margin). The exact lymph node locations are representative for lymph node oligometastases as treated in our clinic (Supplementary material: Fig. S1). All patients gave written informed consent for the use of their data as part of an IRB-approved observational cohort study. Each dataset contained a pre-treatment CT and contours, as well as a daily MRI and a daily contour set for each of the five fractions.

Plan generation

Hypofractionation was investigated in an isotoxic manner based on the pre-treatment data; pre-treatment plans were initially made for a 5x7 Gy fractionation scheme, as used in the online MR-guided clinical treatment for these patients. If all planning constraints (Table 1) were met, a 3x10 Gy pre-treatment plan was created. If this plan also met all constraints, a 1x20 Gy pre-treatment plan was created (all 60 Gy $BED_{\alpha/\beta=10}$). All pre-treatment plans were made using IMRT technique with 7 or 9 beams for lateral and medial targets, respectively. The pre-treatment plans were generated using Monaco version 5.4 by Elekta AB (Stockholm, Sweden) with the 7MV FFF MR-Linac beam model and a 1.5T magnetic field in superior-inferior patient direction. As long as OAR constraints were not violated, PTV coverage was kept at $V_{100\%}$ > 95% and OAR dose was lowered as much as possible. The statistical uncertainty for the Monte Carlo dose calculations was 3% per control point. The maximum amount of segments per plan was 45 with a minimum area of 1.5 cm^2 and width of 0.5 cm. For the patients in which the pre-treatment plans met all clinical dose criteria, the plan was adapted to the daily patient anatomy and contours. Since clinical data from a 5x7 Gy treatment is used, also the single fraction 1x20 Gy plans were evaluated on 5 data sets to evaluate the dosimetric feasibility on different daily anatomies.

Dosimetric and plan quality evaluation

All pre-treatment plans were evaluated based on clinical dose criteria for the target and OARs to determine whether the plans

Table 2
Plan quality metrics as described in the NRG-BR001 phase 1 trial [34].

Parameter	Definition	Criteria
PD*	Actual prescription dose: $D_{95\%}$ of PTV	
HI	PD* as a percentage of D_{max}	≥60% and ≤ 90%
$R_{100\%}$	V_{PD^*}/V_{PTV}	<1.2, acceptable till 1.5
$R_{50\%}$	$V_{0.5xPD^*}/V_{PTV}$	<5.5–7.5 depending on PTV volume
D_{2cm}	max dose at 2 cm from PTV as % of PD*	<57%–94% depending on PTV volume

Table 1
Clinical dose criteria for SBRT lymph node oligometastases plans as used in the evaluation of the treatment plans based on the UK SABR consortium guidelines 2016[a], Grimm et al.[b] [43], in-house constraints[c] and Maenhout et al.[d] [44].

Structure	5x7 Gy	3x10 Gy	1x20 Gy
PTV	V_{35Gy} > 95% $D_{0.1cm^3}$ < 47.25 Gy	V_{30Gy} > 95% $D_{0.1cm^3}$ < 40.5 Gy	V_{20Gy} > 95% $D_{0.1cm^3}$ < 27.0 Gy
Aorta	V_{53Gy} < 0.5cm^3 [a]	V_{45Gy} < 0.5cm^3 [a]	V_{25Gy} < 0.5cm^3 [c]
Bladder	V_{42Gy} < 0.5cm^3 [c]	V_{33Gy} < 0.5cm^3 [c]	V_{22Gy} < 0.5cm^3 [c]
Bowel bag + Colon	V_{32Gy} < 0.5cm^3 [c]	$V_{25.2Gy}$ < 0.5cm^3 [a]	V_{16Gy} < 0.1cm^3 [b]
Duodenum	V_{35Gy} < 0.5cm^3 [a]	$V_{22.2Gy}$ < 0.5cm^3 [a]	V_{14Gy} < 0.1cm^3 [c]
Esophagus	V_{34Gy} < 0.5cm^3 [a]	$V_{25.2Gy}$ < 0.5cm^3 [a]	V_{14Gy} < 0.1cm^3 [b]
Nerve root + Sacral plexus	V_{32Gy} < 0.1cm^3 [a,c]	V_{24Gy} < 0.1cm^3 [a,c]	V_{16Gy} < 0.1cm^3 [a,c]
Rectum	V_{40Gy} < 0.5cm^3 [c]	$V_{28.2Gy}$ < 0.5cm^3 [a]	V_{16Gy} < 0.1cm^3 [c]
Sigmoid	V_{32Gy} < 0.5cm^3 [c]	$V_{25.2Gy}$ < 0.5cm^3 [a]	V_{16Gy} < 0.1cm^3 [b]
Spinal cord	V_{28Gy} < 0.1cm^3 [b]	V_{22Gy} < 0.1cm^3 [b]	V_{12Gy} < 0.1cm^3 [b]
Stomach	V_{35Gy} < 0.5cm^3 [a]	$V_{22.2Gy}$ < 0.5cm^3 [a]	V_{16Gy} < 0.1cm^3 [c]
Ureter	V_{42Gy} < 0.5cm^3 [c]	V_{40Gy} < 0.5cm^3 [a]	$V_{17.7Gy}$ < 0.1cm^3 [c,d]

Table 3
Guidelines for the ratio of the 50% prescription isodose volume ($R_{50\%}$) and the maximum dose at 2 cm from the PTV (D_{2cm}) as a percentage of the actual prescription dose (PD* = $D_{95\%}$ of PTV) from the NRG-BR001 phase 1trial [34]. The 50% isodose volume may be elongated to avoid OARs. Linear interpolation between table entries is required for volumes not specified. This table only reports the values for PTV volumes observed in this study.

PTV [cm^3]	$R_{50\%}$ [−]	D_{2cm} [%]
1.8	<7.5	<57
3.8	<6.5	<57
7.4	<6.0	<58
13.2	<5.8	<58

met all requirements (Table 1). Additionally, the pre-treatment plan quality was quantified using the plan quality metrics described in the NRG-BR001 phase 1 trial [33,34] (Table 2). The $R_{50\%}$ and the D_{2cm} (D_{max} at 2 cm from the PTV as % of PD*) were compared with benchmarks depending on the size of the PTV (Table 3).

Then, for all cases in which a pre-treatment plan could be made that met all criteria, we evaluated the dosimetric feasibility of the online adapted plans by determining how many met all clinical dose criteria. Also, we compared the plan quality of these online adapted plans according to the described quality metrics, for the cases in which the criteria were met for all fractionation schemes. Significance was determined using the Wilcoxon matched-pairs signed rank test. A $p < 0.05$ was considered significant.

Results

Fig. 1 shows how many patients pass or fail the dose criteria for the different fractionation schemes in the pre-treatment situation. For 10 of the 12 (83%) plans with a prescribed dose of 5x7 Gy all dose criteria were met. Both pre-treatment plans that did not meet the criteria did not have sufficient target coverage with a V_{35Gy} of 90.5% and 93.9% because of limiting OAR constraints of a nerve root and the sacral plexus, respectively. For the 10 patients that were eligible for 5x7 Gy, 9/10 plans (90%) met all dose criteria for the prescribed dose of 3x10 Gy. One plan failed with a violation of the duodenum $V_{22.2Gy}$ dose constraint with 1.5 cm^3. Finally, for the 9 patients that were eligible for both 5x7 Gy and 3x10 Gy, 6/9 plans (66%) met all dose criteria for a single fraction of 20 Gy. Two pre-treatment plans that did not meet the criteria did not have sufficient target coverage with a V_{20Gy} of 80.3% and

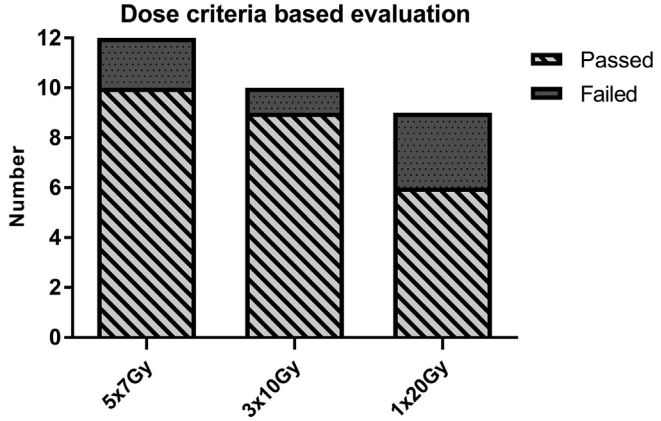

Fig. 1. Number of pre-treatment plans that passed or failed all dose criteria with a prescribed dose of $V_{100\%} > 95\%$ to the PTV for 12 patients evaluated in this study which were treated with SBRT of lymph node oligometastases using IMRT on the 1.5T MR-linac.

88.4%, respectively. One plan violated the ureter $V_{17.7Gy}$ dose constraint with 0.2 cm^3. In almost all cases with violations, the PTV overlapped with, or was adjacent to, an OAR.

Based on the pre-treatment plans, six patients were eligible for treatment with a single fraction of 20 Gy, based on the clinical dose criteria. However, when assessing the dosimetric feasibility of daily adaption by looking at the online adapted fractions (for these 6 patients, based on 5 fractions from 5x7), 13/30 (43%) would result in violations of the dose criteria. These violations occurred in the simulated adapted online fractions for three patients. For two of these three patients we were able to create a single online adapted plan that met all dose criteria, however the dose criteria were barely met.

From the remaining six patients, not eligible for single-fraction treatment, three (50%) would be eligible for a 3x10 Gy fractionated treatment, based on the pre-treatment plan. Out of the remaining three patients, in our dataset, for one patient it would be possible to create a 5x7 Gy pre-treatment plan that met all clinical dose constraints. For all cases in which a 3x10 Gy and a 5x7 Gy pre-treatment plan could be made that met all dose criteria, all (45/45 and 50/50, respectively) adapted online fractions would also meet all criteria. For the remaining two patients (67%) individual isotoxic dose de-escalation would have to be applied.

Retrospective analysis of the plan quality was performed for the 6 patients for whom pre-treatment plans could be made that met all criteria for all three fractionation schemes. Of these 30 adapted online plans, the NRG-BR001 SBRT plan quality criteria were investigated. For the 5x7 Gy plans, the HI benchmark was met for all cases with a median HI of 81% [range, 79–87%]. The $R_{100\%}$ benchmark was also met for all cases with a median value of 1.0 [range, 1.0–1.2]. The $R_{50\%}$ benchmark was only met in 15/30 online fractions (50%) with a median value of 7.1 [range, 5.4–9.3]. The benchmark for the D_{2cm} was met in 30 (100%) of the online plans with a median value of 50% [range, 44–56%].

For the 3x10 Gy plans, the HI criteria were also met for all cases with a median value of 81% [range, 78–84%]. The $R_{100\%}$ benchmark was met for all cases with a median value of 1.0 [range, 1.0–1.2]. The $R_{50\%}$ benchmark was met for 23/30 online plans (77%) with a median value of 6.7 [range, 5.6–7.7]. The D_{2cm} was met in 26/30 (87%) of all plans with a median value of 48% [range, 42–58%].

The 1x20 Gy plans, all online adapted plans also met the HI benchmark with a median value of 79% [63–87%]. The benchmark for the $R_{100\%}$ was met for 26/30 cases (87%) with a median value of 1.0 [1.0–2.1]. The $R_{50\%}$ benchmark was only met for 3/30 online plans (10%) with a median value of 7.7 [6.4–21.4]. The D_{2cm} benchmark was met in 15/30 (50%) of all plans a median value of 58% [43–88%]. The resulting 5x7 Gy and 3x10 Gy treatment plans were not significantly different (Wilcoxon matched-pairs signed rank test, $p > 0.05$). The 1x20 Gy treatment plans resulted into a significantly (Wilcoxon matched-pairs signed rank test, $p < 0.05$) lower HI, but higher $R_{100\%}$, $R_{50\%}$ and D_{2cm}. An overview of the previously described benchmark values are shown in Fig. 2. All pre-treatment plans which met the clinical dose criteria, also met the plan quality criteria.

Discussion

In this study we showed that it is possible to deliver hypofractionated SBRT for lymph node oligometastases on the 1.5T MR-linac, meeting the clinical dose criteria for online adaptive treatment in the majority of cases. For cases in which the clinical dose criteria were not met, the limiting factor was often the presence of OARs in the vicinity of the target. With an OAR nearby it is difficult to reach sufficient PTV coverage, especially for single fraction SBRT treatment, without violating OAR constraints. The vicinity of OARs

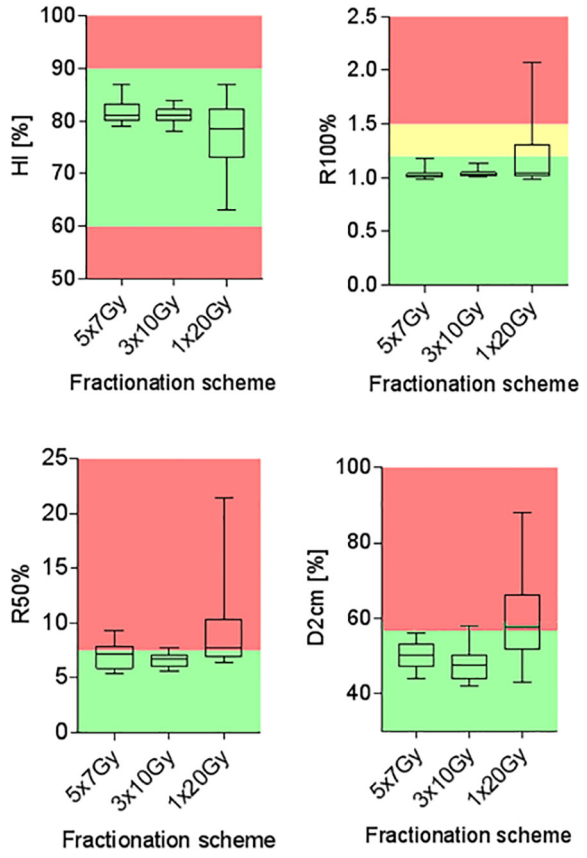

Fig. 2. Boxplot of 1.5T MR-linac IMRT SBRT plan quality metrics for online adapted plans from the different fractionation schemes for the 6 patients (30 fractions, based on online MRI of 5x7 Gy single lymph node treated on the 1.5T MR-linac) for whom it was possible to create a pre-treatment plan that met all clinical dose constraints. The quality of the different plans was evaluated using four parameters: heterogeneity index HI (=PD* the actual prescription dose defined as $D_{95\%}$ of the PTV as a % of D_{max}), conformity index $R_{100\%}$ (=V_{PD*}/V_{PTV}), $R_{50\%}$ (=$V_{0.5xPD*}/V_{PTV}$) and D_{2cm} (=D_{max} at 2 cm from PTV as % of PD*). The bars show the upper and lower quartiles. The whiskers show the minimum and maximum values. Green indicates preferred values, yellow indicates acceptable values and red indicates values outside of these ranges. The 1x20 Gy treatment plans resulted into a significantly (Wilcoxon matched-pairs signed rank test, $p < 0.05$) lower HI, but higher $R_{100\%}$, $R_{50\%}$ and D_{2cm}.

relative to the target can become more critical when simply applying the treatment plan for each fraction, not accounting for inter-fraction anatomical variation such as changes in size and shape of the target and OARs [35]. To mitigate the risk of unplanned violations of the dose constraints and insufficient target coverage, it is helpful to incorporate daily replanning [20–22,36].

In our results we also showed that delivering single fraction treatment is challenging in some cases, for in this limited exploration, already 50% of the patients did not meet the planning aims in pre-treatment planning. Reduction of the PTV margin could perhaps make it possible to deliver sufficient target coverage, without violating constraints of the OARs for a single fraction of 20 Gy or higher more often. Some studies already reported the use of reduced PTV margins of 1 or 2 mm on the CyberKnife system, but this would often require the use of implanted fiducial markers [7,37,38], which is invasive for the patient and not always feasible. MR-guided online adaptive radiotherapy allows to correct for inter-fraction motion of the PTV without implanted fiducial markers. Further methods should be investigated to reduce or compensate for intra-fraction motion, to deal with longer delivery times in hypofractionated schedules, such as the use of patient immobilization techniques [39,40]. Further technical developments of the MR-linac could allow for intra-fraction plan adaptation [17] and adequate tissue tracking which could aid in compensating for intra-fraction motion, especially given the longer treatment session times on an MR-linac. Real-time dose accumulation and reconstruction can also be used as an input for further inter and-intra fraction plan adaptation [17,41].

The plan quality metric benchmark values [33,34], which were analyzed for this study, were not always met. For a large amount of cases it was particularly difficult to meet the criteria for the $R_{50\%}$ or the D_{2cm} when moving towards further hypo-fractionation. The guidelines however state that for very small tumors the $R_{100\%}$ benchmark is difficult to meet. A more conformal dose distribution with steeper dose gradients could potentially be achieved by introducing more beam angles or when volumetric modulated arc therapy (VMAT) becomes available on the MR-linac. Although improved plan conformity is expected, also with using VMAT a large differences in plan conformity and dose falloff can be observed [42]. Additionally, plan quality could be improved by incorporating such quality metrics as a standard in the treatment planning and evaluation process.

For the 1x20 Gy fractionation scheme, the online adapted plans violated the dose criteria in 13/30 (43%) cases. These violations occurred in three patients. In the first patient, the target was located close to the sigmoid. In the second patient, the target was located very close to the ureter (Fig. 3) and in the third patient, the target was located close to both the sigmoid and ureter. This caused violations for the 1x20 Gy fractionation scheme, as the OAR constraints for single-fraction treatment are more limiting compared to more fractionated treatment schemes. For these three patients, treatment planning towards a pre-treatment plan that met all dose criteria, was also difficult and dose objectives were barely met. For the three patients in which the online adapted plans did meet all dose criteria, no OARs were present in the near vicinity of the target. This indicates that the pre-treatment plan alone is not an optimal indicator for the success of meeting all dose criteria in online plan adaptation. The location of the target relative to critical structures and expected inter-fraction geometric deformations should be considered in choosing the most suitable fractionation scheme.

Online adaptive SBRT of lymph node oligometastases is a further step to safely reducing treatment fractions, which will increase comfort and efficiency for the patient. CBCT-guided online adaptive techniques are becoming more available. Our results can potentially be translated to a CBCT-based approach following the described data-processing infrastructure and, if applicable, correcting for missing tissue. However, the increased noise level and low soft-tissue contrast may be limiting for cases in which the lymph nodes are not visible on CBCT. With MR-guided treatment however, the increased soft tissue contrast and lymph node visibility allow for all daily variations to be taken into account more accurately and could result in more fractions where the treatment plan would meet all clinical dose criteria.

Based on this study, further investigation is being performed for the safe clinical introduction of ultra-hypofractionated treatment with the MR-linac. New techniques such as intra-fraction plan adaptation are coming up, paving the way for further hypo-fractionation towards single fraction treatment.

In conclusion, hypofractionated radiotherapy for lymph node oligometastases on the 1.5T MR-linac is feasible based on dose criteria and plan quality metrics. The location of the target relative to critical structures should be considered in choosing the most suitable fractionation scheme. Especially for single fraction treatment, meeting all dose criteria in the pre-treatment situation does not guarantee this also applies during online treatment.

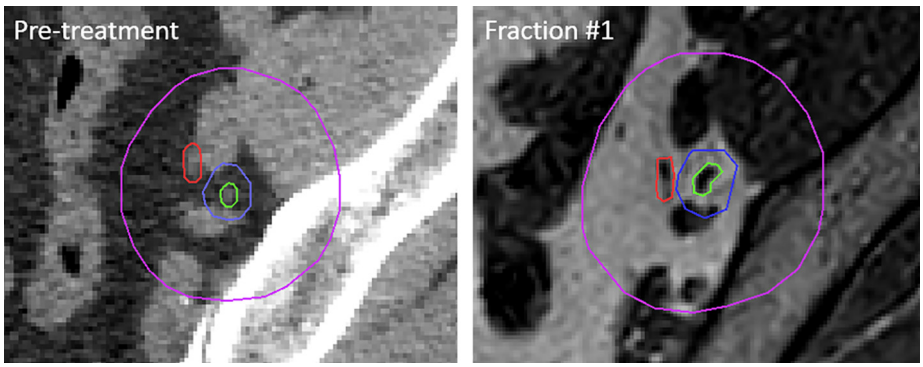

Fig. 3. Example case in which the target, lymph node metastases, was located very close to the ureter. For this particular case it was possible, however difficult, to generate a pre-treatment plan that met all requirements. Simulated online plan adaptation of 1x20 Gy treatment would result in plans violating the OAR constraint for the ureter or insufficient target dose coverage. Visible are the ureter (red), GTV (green), PTV (blue) and the PTV + 2 cm (purple) in which contours are manually adapted by the radiation oncologist during online treatment, if necessary [28].

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: The University Medical Center Utrecht MR-linac scientific project, including employment of multiple authors, has been partly funded by Elekta AB (Stockholm, Sweden).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2020.09.020.

References

[1] Yeung R, Hamm J, Liu M, Schellenberg D. Institutional analysis of stereotactic body radiotherapy (SBRT) for oligometastatic lymph node metastases. Radiat Oncol 2017;12:105. https://doi.org/10.1186/s13014-017-0820-1.
[2] Baumann R, Koncz M, Luetzen U, Krause F, Dunst J. Oligometastases in prostate cancer : Metabolic response in follow-up PSMA-PET-CTs after hypofractionated IGRT. Strahlenther Onkol 2018;194:318–24. https://doi.org/10.1007/s00066-017-1239-1.
[3] Loi M, Frelinghuysen M, Klass ND, Oomen-De Hoop E, Granton PV, Aerts J, et al. Locoregional control and survival after lymph node SBRT in oligometastatic disease. Clin Exp Metastasis 2018. https://doi.org/10.1007/s10585-018-9922-x.
[4] Benedict SH, Yenice KM, Followill D, Galvin JM, Hinson W, Kavanagh B, et al. Stereotactic body radiation therapy: the report of AAPM Task Group 101. Med Phys 2010;37:4078–101. https://doi.org/10.1118/1.3438081.
[5] Park HJ, Chang AR, Seo Y, Cho CK, Jang WI, Kim MS, et al. Stereotactic body radiotherapy for recurrent or oligometastatic uterine cervix cancer: A cooperative study of the Korean radiation oncology group (KROG 14–11). Anticancer Res 2015;35:5103–10.
[6] Ponti E, Lancia A, Ost P, Trippa F, Triggiani L, Detti B, et al. Exploring all avenues for radiotherapy in oligorecurrent prostate cancer disease limited to lymph nodes: A systematic review of the role of stereotactic body radiotherapy. Eur Urol Focus 2017;3:538–44. https://doi.org/10.1016/j.euf.2017.07.006.
[7] Detti B, Bonomo P, Masi L, Doro R, Cipressi S, Iermano C, et al. Stereotactic radiotherapy for isolated nodal recurrence of prostate cancer. World J Urol 2015;33:1197–203. https://doi.org/10.1007/s00345-014-1427-x.
[8] Muldermans JL, Romak LB, Kwon ED, Park SS, Olivier KR. Stereotactic body radiation therapy for oligometastatic prostate cancer. Int J Radiat Oncol Biol Phys 2016;95:696–702. https://doi.org/10.1016/j.ijrobp.2016.01.032.
[9] Pasqualetti F, Panichi M, Sainato A, Matteucci F, Galli L, Cocuzza P, et al. [(18)F] Choline PET/CT and stereotactic body radiotherapy on treatment decision making of oligometastatic prostate cancer patients: preliminary results. Radiat Oncol 2016;11:9. https://doi.org/10.1186/s13014-016-0586-x.
[10] Ingrosso G, Trippa F, Maranzano E, Carosi A, Ponti E, Arcidiacono F, et al. Stereotactic body radiotherapy in oligometastatic prostate cancer patients with isolated lymph nodes involvement: a two-institution experience. World J Urol 2017;35:45–9. https://doi.org/10.1007/s00345-016-1860-0.
[11] Greco C, Zelefsky MJ, Lovelock M, Fuks Z, Hunt M, Rosenzweig K, et al. Predictors of local control after single-dose stereotactic image-guided intensity-modulated radiotherapy for extracranial metastases. Int J Radiat Oncol Biol Phys 2011;79:1151–7. https://doi.org/10.1016/j.ijrobp.2009.12.038.
[12] Triggiani L, Alongi F, Buglione M, Detti B, Santoni R, Bruni A, et al. Efficacy of stereotactic body radiotherapy in oligorecurrent and in oligoprogressive prostate cancer: new evidence from a multicentric study. Br J Cancer 2017;116:1520–5. https://doi.org/10.1038/bjc.2017.103.
[13] Ramlov A, Kroon PS, Jürgenliemk-Schulz IM, De Leeuw AA, Gormsen LC, Fokdal LU, et al. Impact of radiation dose and standardized uptake value of (18)FDG PET on nodal control in locally advanced cervical cancer. Acta Oncol 2015;54:1567–73. https://doi.org/10.3109/0284186x.2015.1061693.
[14] Ost P, Jereczek-Fossa BA, As NV, Zilli T, Muacevic A, Olivier K, et al. Progression-free survival following stereotactic body radiotherapy for oligometastatic prostate cancer treatment-naive recurrence: a multi-institutional analysis. Eur Urol 2016;69:9–12. https://doi.org/10.1016/j.eururo.2015.07.004.
[15] De Bleser E, Jereczek-Fossa BA, Pasquier D, Zilli T, Van As N, Siva S, et al. Metastasis-directed therapy in treating nodal oligorecurrent prostate cancer: a multi-institutional analysis comparing the outcome and toxicity of stereotactic body radiotherapy and elective nodal radiotherapy. Eur Urol 2019;76:732–9. https://doi.org/10.1016/j.eururo.2019.07.009.
[16] Konski A, James J, Hartsell W, Leibenhaut MH, Janjan N, Curran W, et al. Economic analysis of radiation therapy oncology group 97–14: multiple versus single fraction radiation treatment of patients with bone metastases. Am J Clin Oncol 2009;32:423–8. https://doi.org/10.1097/COC.0b013e31818da9f7.
[17] Kontaxis C, Bol GH, Stemkens B, Glitzner M, Prins FM, Kerkmeijer LGW, et al. Towards fast online intrafraction replanning for free-breathing stereotactic body radiation therapy with the MR-linac. Phys Med Biol 2017;62:7233–48. https://doi.org/10.1088/1361-6560/aa82ae.
[18] Kim M-S, Kim W, Park IH, Kim HJ, Lee E, Jung J-H, et al. Radiobiological mechanisms of stereotactic body radiation therapy and stereotactic radiation surgery. Radiat Oncol J 2015;33:265–75. https://doi.org/10.3857/roj.2015.33.4.265.
[19] Brown JM, Carlson DJ, Brenner DJ. The tumor radiobiology of SRS and SBRT: are more than the 5 Rs involved?. Int J Radiat Oncol Biol Phys 2014;88:254–62. https://doi.org/10.1016/j.ijrobp.2013.07.022.
[20] Henke L, Kashani R, Yang D, Zhao T, Green O, Olsen L, et al. Simulated online adaptive magnetic resonance-guided stereotactic body radiation therapy for the treatment of oligometastatic disease of the abdomen and central thorax: characterization of potential advantages. Int J Radiat Oncol Biol Phys 2016;96:1078–86. https://doi.org/10.1016/j.ijrobp.2016.08.036.
[21] Winkel D, Kroon PS, Werensteijn-Honingh AM, Bol GH, Raaymakers BW, Jürgenliemk-Schulz IM. Simulated dosimetric impact of online replanning for stereotactic body radiation therapy of lymph node oligometastases on the 1.5T MR-linac. Acta Oncol 2018;1–8. https://doi.org/10.1080/0284186X.2018.1512152.
[22] Henke L, Kashani R, Robinson C, Curcuru A, DeWees T, Bradley J, et al. Phase I trial of stereotactic MR-guided online adaptive radiation therapy (SMART) for the treatment of oligometastatic or unresectable primary malignancies of the abdomen. Radiother Oncol 2018;126:519–26. https://doi.org/10.1016/j.radonc.2017.11.032.
[23] Mutic S, Dempsey JF. The ViewRay system: magnetic resonance-guided and controlled radiotherapy. Semin Radiat Oncol 2014;24:196–9. https://doi.org/10.1016/j.semradonc.2014.02.008.
[24] Acharya S, Fischer-Valuck BW, Kashani R, Parikh P, Yang D, Zhao T, et al. Online magnetic resonance image guided adaptive radiation therapy: first clinical applications. Int J Radiat Oncol Biol Phys 2016;94:394–403. https://doi.org/10.1016/j.ijrobp.2015.10.015.
[25] Bohoudi O, Bruynzeel AME, Senan S, Cuijpers JP, Slotman BJ, Lagerwaard FJ, et al. Fast and robust online adaptive planning in stereotactic MR-guided adaptive radiation therapy (SMART) for pancreatic cancer. Radiother Oncol 2017;125:439–44. https://doi.org/10.1016/j.radonc.2017.07.028.
[26] Lagendijk JJW, Raaymakers BW, Raaijmakers AJE, Overweg J, Brown KJ, Kerkhof EM, et al. MRI/linac integration. Radiother Oncol 2008;86:25–9. https://doi.org/10.1016/j.radonc.2007.10.034.

[27] Raaymakers BW, Jurgenliemk-Schulz IM, Bol GH, Glitzner M, Kotte A, van Asselen B, et al. First patients treated with a 1.5 T MRI-Linac: clinical proof of concept of a high-precision, high-field MRI guided radiotherapy treatment. Phys Med Biol 2017;62:L41–50. https://doi.org/10.1088/1361-6560/aa9517.

[28] Werensteijn-Honingh AM, Kroon PS, Winkel D, Aalbers EM, van Asselen B, Bol GH, et al. Feasibility of stereotactic radiotherapy using a 1.5 T MR-linac: Multi-fraction treatment of pelvic lymph node oligometastases. Radiother Oncol 2019;134:50–4. https://doi.org/10.1016/j.radonc.2019.01.024.

[29] Winkel D, Bol GH, Kroon PS, van Asselen B, Hackett SS, Werensteijn-Honingh AM, et al. Adaptive radiotherapy: The Elekta Unity MR-linac concept. Clin Transl Radiat Oncol 2019. https://doi.org/10.1016/j.ctro.2019.04.001.

[30] Noel CE, Parikh PJ, Spencer CR, Green OL, Hu Y, Mutic S, et al. Comparison of onboard low-field magnetic resonance imaging versus onboard computed tomography for anatomy visualization in radiotherapy. Acta Oncol 2015;54:1474–82. https://doi.org/10.3109/0284186X.2015.1062541.

[31] Winkel D, Werensteijn-Honingh AM, Kroon PS, Eppinga WSC, Bol GH, Intven MPW, et al. Individual lymph nodes: ‘‘See it and Zap it”. Clin Transl Radiat Oncol 2019. https://doi.org/10.1016/j.ctro.2019.03.004.

[32] Verkooijen HM, Kerkmeijer LGW, Fuller CD, Huddart R, Faivre-Finn C, Verheij M, et al. R-IDEAL: A framework for systematic clinical evaluation of technical innovations in radiation oncology. Front Oncol 2017;7:59. https://doi.org/10.3389/fonc.2017.00059.

[33] Al-Hallaq HA, Chmura S, Salama JK, Winter KA, Robinson CG, Pisansky TM, et al. Rationale of technical requirements for NRG-BR001: The first NCI-sponsored trial of SBRT for the treatment of multiple metastases. Pract Radiat Oncol 2016;6:e291–8. https://doi.org/10.1016/j.prro.2016.05.004.

[34] Chmura S, Salama JK, Robinson C, Pisansky TM, Borges V, Al-Hallaq HA, et al. A Phase 1 Study of Stereotactic Body Radiotherapy (SBRT) for the Treatment of Multiple Metastases. ClinicalTrials.gov NCT022063342015.

[35] Schippers MG, Bol GH, de Leeuw AA, van der Heide UA, Raaymakers BW, Verkooijen HM, et al. Position shifts and volume changes of pelvic and para-aortic nodes during IMRT for patients with cervical cancer. Radiother Oncol 2014;111:442–5. https://doi.org/10.1016/j.radonc.2014.05.013.

[36] Winkel D, Bol GH, Werensteijn-Honingh AM, Intven MPW, Eppinga WSC, Hes J, et al. Target coverage and dose criteria based evaluation of the first clinical 1.5T MR-linac SBRT treatments of lymph node oligometastases compared with conventional CBCT-linac treatment. Radiother Oncol 2020;146:118–25. https://doi.org/10.1016/j.radonc.2020.02.011.

[37] Jereczek-Fossa BA, Beltramo G, Fariselli L, Fodor C, Santoro L, Vavassori A, et al. Robotic image-guided stereotactic radiotherapy, for isolated recurrent primary, lymph node or metastatic prostate cancer. Int J Radiat Oncol Biol Phys 2012;82:889–97. https://doi.org/10.1016/j.ijrobp.2010.11.031.

[38] Kurup G. CyberKnife: A new paradigm in radiotherapy. J Med Phys 2010;35:63–4. https://doi.org/10.4103/0971-6203.62194.

[39] Wiersema L, Borst G, Nakhaee S, Peulen H, Wiersma T, Kwint M, et al. EP-1838: First IGRT results for SBRT bone and lymph node oligometastases within the pelvic region. Radiother Oncol 2017;123:S1006. https://doi.org/10.1016/S0167-8140(17)32273-9.

[40] Heerkens HD, Reerink O, Intven MPW, Hiensch RR, van den Berg CAT, Crijns SPM, et al. Pancreatic tumor motion reduction by use of a custom abdominal corset. Phys Imag Radiat Oncol 2017;2:7–10. https://doi.org/10.1016/j.phro.2017.02.003.

[41] Stemkens B, Glitzner M, Kontaxis C, de Senneville BD, Prins FM, Crijns SPM, et al. Effect of intra-fraction motion on the accumulated dose for free-breathing MR-guided stereotactic body radiation therapy of renal-cell carcinoma. Phys Med Biol 2017;62:7407–24. https://doi.org/10.1088/1361-6560/aa83f7.

[42] Al-Hallaq HA, Chmura SJ, Salama JK, Lowenstein JR, McNulty S, Galvin JM, et al. Benchmark credentialing results for NRG-BR001: The first national cancer institute-sponsored trial of stereotactic body radiation therapy for multiple metastases. Int J Radiat Oncol Biol Phys 2017;97:155–63. https://doi.org/10.1016/j.ijrobp.2016.09.030.

[43] Grimm J, LaCouture T, Croce R, Yeo I, Zhu Y, Xue J. Dose tolerance limits and dose volume histogram evaluation for stereotactic body radiotherapy. J Appl Clin Med Phys 2011;12:3368. https://doi.org/10.1120/jacmp.v12i2.3368.

[44] Maenhout M, Peters M, van Vulpen M, Moerland MA, Meijer RP, van den Bosch MAAJ, et al. Focal MRI-guided salvage high-dose-rate brachytherapy in patients with radiorecurrent prostate cancer. Technol Cancer Res Treat 2017;16:1194–201. https://doi.org/10.1177/1533034617741797.