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Original Research Article

Detectability and intra-fraction motion of individual elective lymph nodes in head and neck cancer patients on the Magnetic Resonance Image guided linear accelerator

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ABSTRACT

Background and purpose: Individual elective lymph node irradiation instead of elective neck irradiation is a new concept for head-and-neck cancer (HNC) patients developed for the Magnetic Resonance Image guided linear accelerator (MR-linac). To prepare this, the detectability, volume changes and intra-fraction motion of elective lymph nodes on the MR-linac was assessed.

Materials and methods: A total of 15 HNC patients underwent diagnostic pre-treatment MRI. Additionally, two MR-linac scans were obtained with a 10-minute time difference in the first week of radiation treatment. Elective lymph node contours inside lymph node levels (Ib-V) were segmented on the pre-treatment MRI and the MR-linac scans and compared on number and maximal transversal diameter. Intra-fraction motion of elective lymph nodes on the MR-linac was estimated using Center of Mass (COM) distances and incremental isotropic expansion of lymph node segmentations.

Results: Of all 679 detected lymph nodes on the pre-treatment MRI, eight lymph nodes were not detectable on the first MR-linac scan and 16 new lymph nodes were detected. Lymph node diameters between the pre-treatment MRI scan and the MR-linac scan varied from −0.19 to + 0.13 mm. COM distances varied from 1.2 to 1.7 mm and lymph node contours had to be expanded with 3 mm.

Conclusions: Nearly all elective lymph nodes were detectable on the 1.5T MR-linac scan with no major changes in target volumes compared to the pre-treatment MRI. Simulated intra-fraction motion during the MR-linac scans was smaller than the 5-mm margin that will be used in the first elective lymph node radiation treatment.

1. Introduction

Radiotherapy is one of the main treatment modalities for Head-and-Neck Cancer (HNC) patients. Unfortunately, radiotherapy is still associated with relatively high rates of long-term toxicity such as xerostomia, dysphagia, carotid stenosis and hypothyroidism [1–4], reducing the quality of life of HNC patients [5,6]. In order to improve the quality of life of these patients, there is a great need to de-intensify radiotherapy treatment without compromising oncological effectiveness.

Radiotherapy for HNC is delivered in two dose levels. A high dose targeting the primary tumor and metastatic lymph nodes, and a low dose targeting the neck regions at risk for containing occult metastases. This treatment is referred to as Elective Neck Irradiation (ENI). ENI may currently be considered overly aggressive, since regional recurrences are rarely seen in HNC patients (1–5 %) [7,8].

Several groups have successfully decreased the dose of ENI to 35–40 Gy [9,10], while others are performing studies in which the elective targets are minimized based on lymph node drainage patterns [11] or Positron Emission Tomography (PET) uptake [12]. All studies use conventional lymph node levels for ENI based on Computed-Tomography

Abbreviations: HNC, Head-and-Neck Cancer; ENI, Elective Neck Irradiation; CT, Computed-Tomography; PET, Positron Emission Tomography; MRI, Magnetic Resonance Imaging; OARs, Organs At Risk; SNR, Signal-to-Noise Ratio; HNSCC, Head-and-Neck Squamous Cell Carcinoma; T2 mDixon TSE, multiple Dixon T2-weighted Turbo Spin Echo; COM, Center Of Mass; IQR, Inter-Quartile Range.

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(CT) according to international guidelines [13]. However, with modern imaging modalities such as Magnetic Resonance Imaging (MRI) smaller soft tissue structures, such as individual lymph nodes, can be better visualized compared to CT [14]. As occult metastases are expected to harbor inside lymph nodes, it would be logical to restrict ENI to only individual lymph nodes instead of the larger lymph node levels they are located in.

During the past years, the concept of elective individual lymph node irradiation has been developed in the UMC Utrecht. The term "elective lymph nodes" is used for lymph nodes inside the conventional lymph node levels not suspect for containing metastases based on radiology or histology, but occult metastases cannot be fully excluded and therefore treatment is indicated. With the MR-Linac it would be possible to visualize and treat individual lymph nodes. The MR-linac combines a MRI-scanner and a linear accelerator enabling MRI scans just before, and during radiotherapy treatment. In case of elective lymph node irradiation, the MR-linac will be used to precisely monitor if all lymph nodes receive sufficient dose. Also, radiotherapy treatment plans can be adapted on a daily or weekly basis if lymph nodes move outside the predefined target areas.

In a previous study we proved that large dose reductions (>5 Gy) could be achieved with elective lymph node irradiation for several Organs At Risk (OARs) such as the submandibular glands, carotid arteries and thyroid [14]. In another study, the MRI visibility and displacement of elective lymph nodes during radiotherapy in HNC patients was described [15], in order to estimate safe inter-fraction radiotherapy margins for this new treatment concept. The first patients receiving elective lymph node irradiation will be treated on the MR-linac according to the protocol that was developed in the UMC-Utrecht [16].

However, before treating the first patients with elective lymph node irradiation it needs to be confirmed that lymph nodes detected on the diagnostic MRI scanner (3.0T) can also be visualized on the MR-linac. The MRI of the MR-linac has a lower magnetic field strength (1.5T) which might result in images with a lower Signal-to-Noise Ratio (SNR). Additionally, the intra-fraction motion (i.e. the displacement during one fraction) of lymph nodes needed to be determined.

The aim of this study was to assess the detectability, changes in volume and intra-fraction motion of individual elective lymph nodes in head-and-neck cancer patients on the MR-linac. Therefore, we compared segmentations of individual elective lymph nodes on 3T MRI scans with 1.5T MR-linac scans in HNC patients.

2. Materials and methods

2.1. Study design and patient selection

In this observational imaging study, 15 patients with cT0-4 N0-3 M0 biopsy proven Head-and-Neck Squamous Cell Carcinoma (HNSCC) of the oropharynx, larynx or hypopharynx were included. Patient and tumor characteristics are included in Supplementary Table 1. All patients gave written consent for the participation in this study (trial number: NL59820.041.17, approved by 'NedMec': the UMC Utrecht ethical committee).

2.2. Imaging

2.2.1. Conventional pre-treatment imaging

According to the clinical scanning protocol, patients were fixated in a custom-made thermoplastic mask as part of the diagnostic workup. The clinical scanning protocol included CT and MRI regardless of patient and tumor characteristics. The CT was acquired with a minimal in-plane resolution of 1.00 × 1.00 mm^2 and a slice thickness of 2.00 mm. The diagnostic MRI scanner incorporates a 3.0T magnetic field strength with two flexible surface coils placed on both sides of the neck and an anterior coil and posterior coil inside the tabletop (Fig. 1). The pre-treatment MRI sequences included a multislice multiple Dixon T2-weighted Turbo Spin Echo (T2 mDixon TSE) [17] with a slice thickness of 3.00 mm and a reconstructed in-plane resolution of 0.94 × 0.94 mm^2

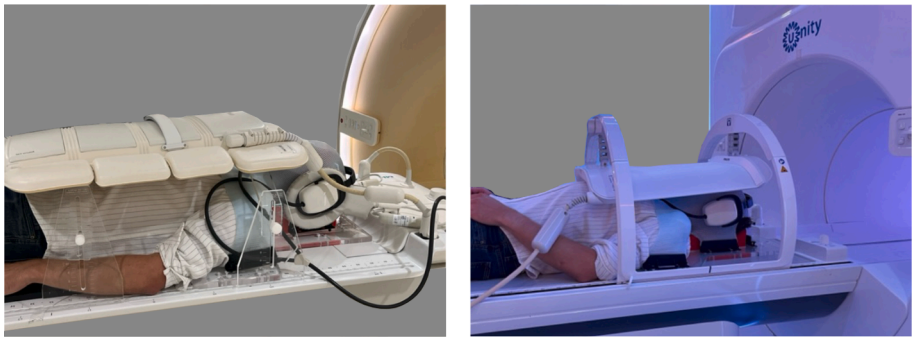

Fig. 1. Patient and coil setup during the MRI scans. Patients were fixated in a thermoplastic mask. The diagnostic MRI scanner incorporates two flexible coils placed on both sides of the neck and an anterior and posterior 16-channel coil (left). The MRI scanner of the MR-linac contains a 4-channel posterior coil in the tabletop and a 4-channel anterior coil (right).

Table 1
Scanning parameters of the MRI sequences of the diagnostic MRI and the MR-linac.

Scanning parameters MRI	Diagnostic MRI (T2 mDixon TSE)	MR-linac MRI (T2 mDixon TSE)
Acquired resolution (mm)	1.3 × 1.3	1.1 × 1.3
Acquire slice thickness (mm)	3.0	4.0
Reconstructed resolution (mm)	0.82 × 0.82 × 3.0 (Gap 0)	0.95 × 0.95 × 4.0 (Gap −1)
Field of view (mm)	270 × 277 × 249	457 × 297 × 199
Echo time (TE)	100 ms	60 ms
Repetition time (TR)	3000 ms	3486 ms
Flip angle (°)	90	90
Refocusing angle (°)	100	100
Sense/Compressed Sense	Sense (2.0)	Compressed Sense (2.0)
Scan time	6 min. 39 sec.	4 min. 32 sec.

(Table 1). Lymph nodes were identified on the water-only image of the T2 mDixon TSE. The CT and the in-phase image of the T2 mDixon TSE provided additional visual information to distinguish elective lymph nodes from other structures such as blood vessels.

2.2.2. Additional imaging on the MR-linac

After completing the conventional pre-treatment scanning protocol, patients were also scanned on the MR-linac in the same mask in the first week of radiotherapy treatment. The MR-linac scan was acquired within the first week of radiotherapy treatment since we were not interested in volume changes of lymph nodes due to the effect of radiotherapy [15]. The MR-linac incorporates a magnetic field strength of 1.5T with a 4–channel posterior coil in the tabletop and a 4-channel anterior coil (Fig. 1). A multislice T2 mDixon TSE was specifically designed and optimized for optimal visualization of head-and-neck anatomy on the MR-linac (Table 1). The MRI sequence was acquired twice with a time difference of approximately 10 min to stimulate the start and end of a radiotherapy fraction.

2.3. Contours of lymph nodes and lymph node levels

Individual elective lymph nodes were identified and delineated on both T2 mDixon TSE water-only scans of the diagnostic MRI and the MR-linac. Individual lymph nodes could be identified by its hyper-intense signal and kidney-bean shape. Only individual lymph nodes in at least two adjacent transverse MRI slices inside the conventional ENI target areas (lymph node level Ib-V) and a minimal in-plane diameter of 4 mm were included in this analysis. Pathological or suspect lymph nodes based on biopsy or imaging that were treated with 70 Gy were excluded.

Lymph node levels (Ib-V) were delineated according to international guidelines [13] on the T2 mDixon TSE water-only scans to be able to select only elective lymph nodes inside these conventional elective neck volumes. The lymph node level contours also allowed the analysis of the detectability and intra-fraction motion of individual lymph nodes per lymph node level. The in-phase image of the T2 mDixon TSE was used as additional information to distinguish lymph node levels from adjacent musculature.

All contours were made by one observer (medical PhD-student) and checked by one of the two radiation oncologists at our department with over 5 and 10 years' experience in the HNC radiotherapy treatment.

2.4. Registration techniques

Scans were registered using a rigid box registration around the tumor, conventional elective lymph node levels and the spine. The transformation matrix was then used to rigidly propagate contours of lymph nodes and lymph node levels from the pre-treatment scan to the MR-linac scans. The contours on both MR-linac scans were manually adjusted if necessary.

2.5. Analysis

2.5.1. Detectability of elective lymph nodes

To assess the detectability of lymph nodes on the MR-linac scans compared to the diagnostic MRI-scan, elective lymph nodes were divided in three categories based on their maximum transverse diameter (<5 mm, 5–10 mm, >10 mm). For each category the number of lymph nodes per lymph node level were assessed on the pre-treatment MRI scan and the visibility of the lymph nodes on the first MR-linac scan was checked.

2.5.2. Volume changes of elective lymph nodes

As lymph nodes are sensitive to radiation treatment it was checked if lymph node volumes changed between the pre-treatment scan and the MR-linac scan in the first week of treatment. Since the MRI scans have a relatively large slice thickness of 3 mm, differences in lymph node volume were examined by measuring the maximal in-plane diameter instead of the total volume.

2.5.3. Intra-fraction motion of elective lymph nodes

The intra-fraction motion of lymph nodes was estimated by the difference of the Center Of Mass (COM) of the lymph nodes between both MR-linac scans that were acquired with a time difference of 10 min. Center of mass differences were determined in x (left–right), y (anterior-posterior), z directions (feet-head), as well as the vector length. Furthermore, lymph node segmentations of the first MR-linac scan were incrementally expanded with steps of 1 mm until 95 % of the volume of 95 % of all elective lymph nodes were covered in the second MR-linac scan.

2.6. Statistical analysis

Ordinal variables were expressed in absolute values. Continuous variables were expressed in median with Inter-Quartile Range (IQR) or maximum values. Descriptive statistics were used for the lymph node count and intra-fraction motion. A paired *t*-test was used to compare lymph node diameters per lymph node level. The Bonferroni correction was used to correct for multiple testing for the different lymph node levels and therefore the alpha level was set at 0.01. Graphs and statistical analyses were produced by GraphPad prism (version 8.0.2.).

3. Results

3.1. Detectability of elective individual lymph nodes

On the pre-treatment MRI scans of 15 patients, a total of 679 lymph nodes and a median number of 44 lymph nodes per patient were delineated in level Ib-V. The median lymph node count per patient was 5 (IQR: 4 – 7) in level Ib, 18 (IQR: 15 – 23) in level II, 8 (IQR: 5 – 11) in level III, 2 (IQR: 1 – 5) in level IV and 6 (IQR: 3 – 12) in level V (Supplementary Table 2). Most lymph nodes had a transverse diameter of 5–10 mm and were situated in level II.

The median number of days between the pre-treatment MRI scan and the MR-linac scans was 16 days (IQR: 13 – 22). Per patient, a median number of zero lymph nodes (IQR: 0 – 0, maximum: 3) was not detectable on the first MR-linac scan compared to the pre-treatment MRI scan. The non-detectable lymph nodes (n = 8, 1.2 % of all segmented lymph nodes) were located in level II / III / V and all had a diameter < 5 mm, except 1 lymph node in level III that had a diameter of 8 mm. Per patient, a median number of zero lymph nodes (IQR: 0 – 1, maximum: 3) were identified on the first MR-linac scan that were not detected on the pre-treatment MRI. In total 16 new lymph nodes (2.4 % of all delineated lymph nodes) were seen in the first MR-linac scan across all lymph node levels (<5 mm: n = 5, 5–10 mm: n = 9, >10 mm: n = 2) (Fig. 2).

3.2. Volume changes of elective lymph nodes

No statistical significant differences were found between the maximum transverse diameter of lymph nodes between the pre-treatment MRI scans and the MR-linac scans in level Ib (+0.1 mm, IQR: −0.6 – +1.0, p = 0.12), level III (−0.04 mm, IQR: −0.7 – +0.7, p = 0.95), level IV (+0.04 mm, IQR: −0.9 – +1.0, p = 0.60) and level V (+0.06 mm, IQR: −0.7 – +0.7, p = 0.93). In level II however, a reduction of −0.2 mm was found between both scans (IQR: −0.9 – 0.5, p = 0.01). The largest differences (medians varied from + 1.3 to −2.0 mm) were observed for lymph nodes with a diameter > 10 mm with (Fig. 3/Supplementary Table 3).

3.3. Estimating intra-fraction motion of elective lymph nodes

3.3.1. COM differences

The displacement during an MR-linac treatment was assessed as

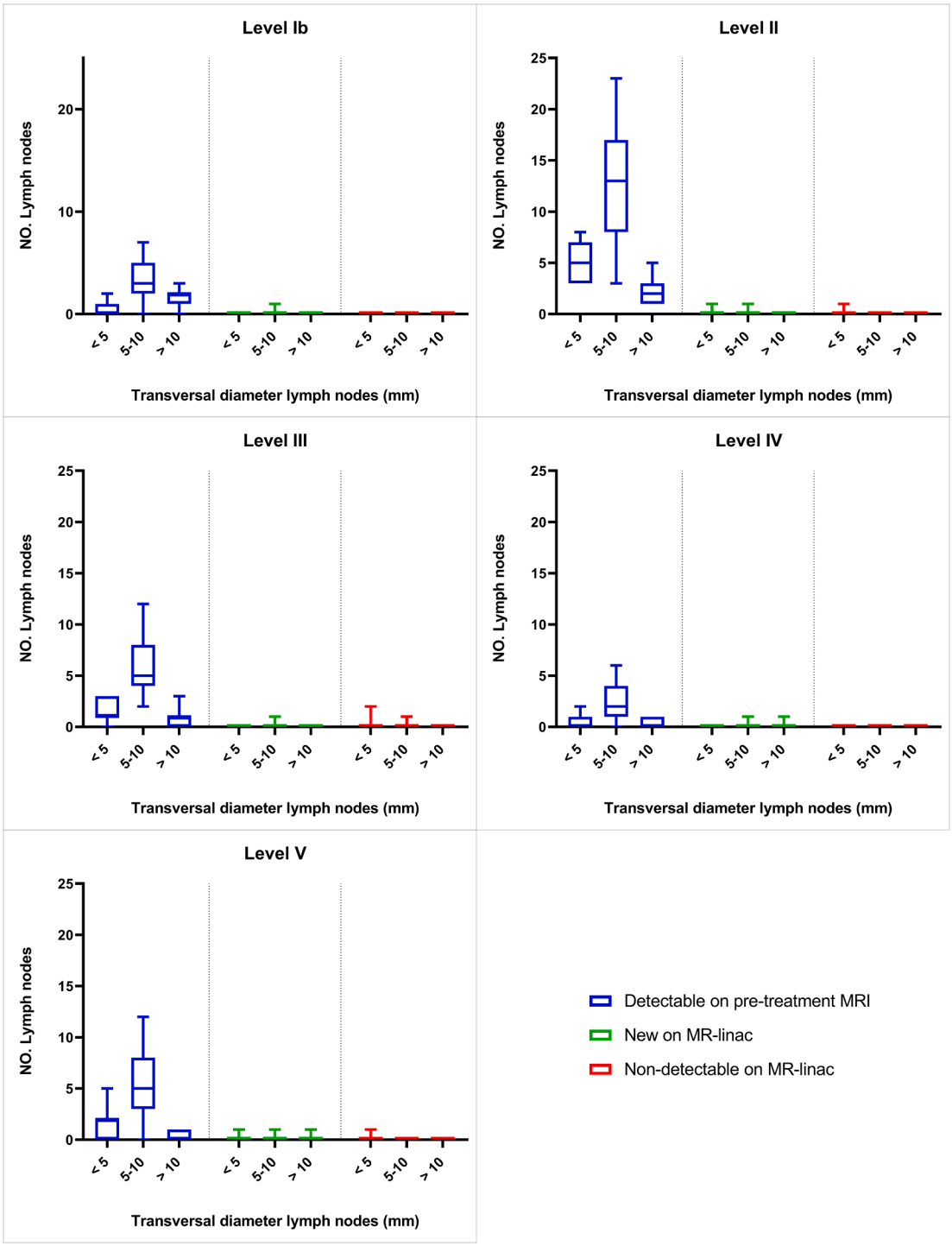

Fig. 2. The lymph node count per patient in the pre-treatment MRI scan (blue) per lymph node level and size category (<5, 5–10 and > 10 mm), compared to new (green) and non-detectable lymph nodes (red) identified on the first MR-linac scan. Boxes represent the first, second (median) and third quartile whereas the whiskers represent the 5/95 percentile of all values. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

median COM distances between lymph nodes of the first and second MR-linac scan which were 1.1 mm in level Ib (IQR: 0.7 – 1.9), 1.3 mm in level II (IQR: 0.8 – 2.0), 1.6 mm in level III (IQR: 1.1 – 2.4), 1.42 mm in level IV (IQR: 1.1 – 2.2) and 1.7 mm in level V (IQR: 1.1 – 2.7). There was a random distribution of x, y, and z COM coordinates with no clear motion pattern of lymph nodes in all lymph node levels (Fig. 4/Supplementary Table 4). One patient shifted during the MR-linac scans causing the largest distortions seen in all lymph nodes across all levels with a median COM distances of 8.5 mm (IQR: 7.7 – 9.5) and was excluded in Fig. 4.

3.3.2. *Lymph node coverage*

In order to obtain geographical coverage of lymph node contours on the first MR-Linac scan, the contours in the first scan were isotropically expanded with 3 mm in levels Ib–V to cover 95 % of the volume of 95 % of all lymph nodes in the second MR-Linac scan (Fig. 5/Supplementary Table 5). One patient moved in the mask during the two MR-linac scans and was omitted from this analysis. The lymph nodes of this patient

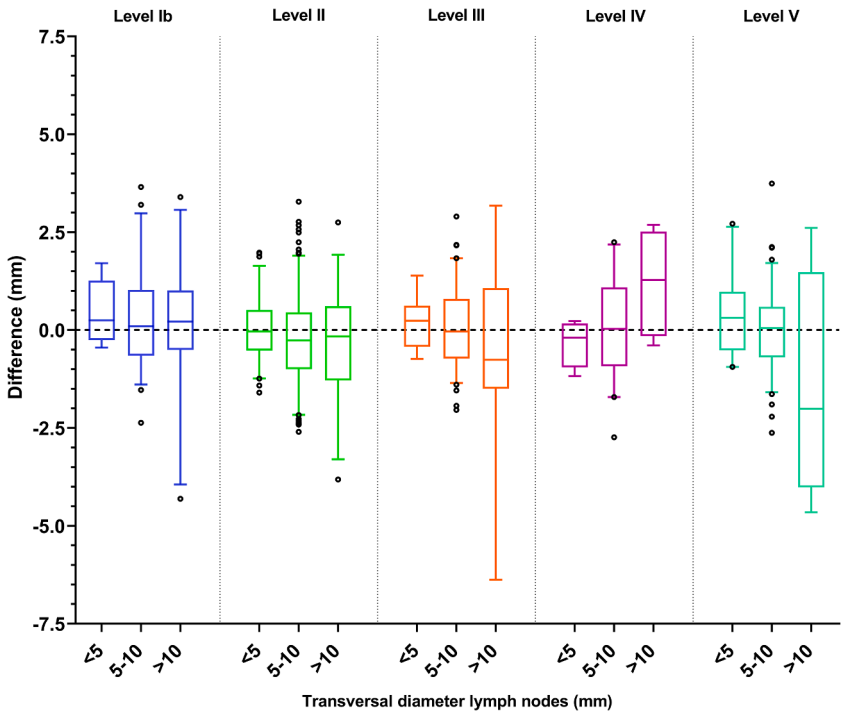

Fig. 3. The difference in maximum transverse diameter of lymph nodes between the pre-treatment scan and the first MR-linac scan per lymph node level (Ib–V) and maximal transverse diameter (<5mm, 5–10 mm and > 10 mm). Boxes represent the first, second (median) and third quartile whereas the whiskers represent the 5/95 percentile of all values.

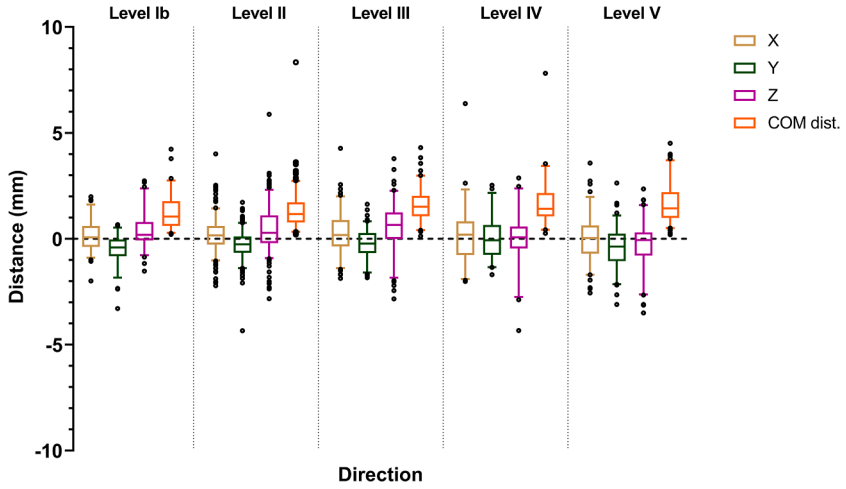

Fig. 4. Center Of Mass (COM) differences of lymph nodes between the first and second MR-linac scan per lymph node level (Ib–V). COM differences are given in x = left–right (light brown), y = anterior-posterior (green) and z = feed-head (pink) directions as well as the shortest distance between both center of masses (orange). Boxes represent the first, second and third quartile whereas the whiskers represent the 5/95 percentile of all values. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

needed margins of 9 mm in level Ib–III, 6 mm in level IV and 12 mm in level V.

4. Discussion

In this study the detectability, changes in volume and intra-fraction motion of individual elective lymph nodes in head-and-neck cancer patients on the MR-linac was assessed. Most elective lymph nodes inside the conventional lymph node levels (Ib/II/III/IV/V) remained detectable on the 1.5T MR-linac scan compared to the diagnostic pre-treatment 3T MRI scan. No major changes were seen in lymph node volumes between the pre-treatment MRI scan and the MR-linac scan in the first week of radiotherapy treatment. Also, the displacement during a treatment fraction is estimated to be small as the maximum median COM distance differed between 1.2 mm and 1.7 mm and the lymph node contours of the first MR-linac scan had to be isotropically expanded with 3 mm to cover 95 % of the volume of 95 % of all elective lymph nodes in the second MR-linac scan.

The number of detected elective lymph nodes in this study was similar to a previous study that examined the MRI visibility and displacement of lymph nodes during radiotherapy in HNC patients (level Ib: 5 vs. 5, level II: 18 vs. 21, level III: 8 vs. 11, level IV: 2 vs. 7 and level V: 6 vs. 8) [15]. Pathology studies that investigated neck dissections in HNSCC patients reported a lymph node yield varying from 34 to 46

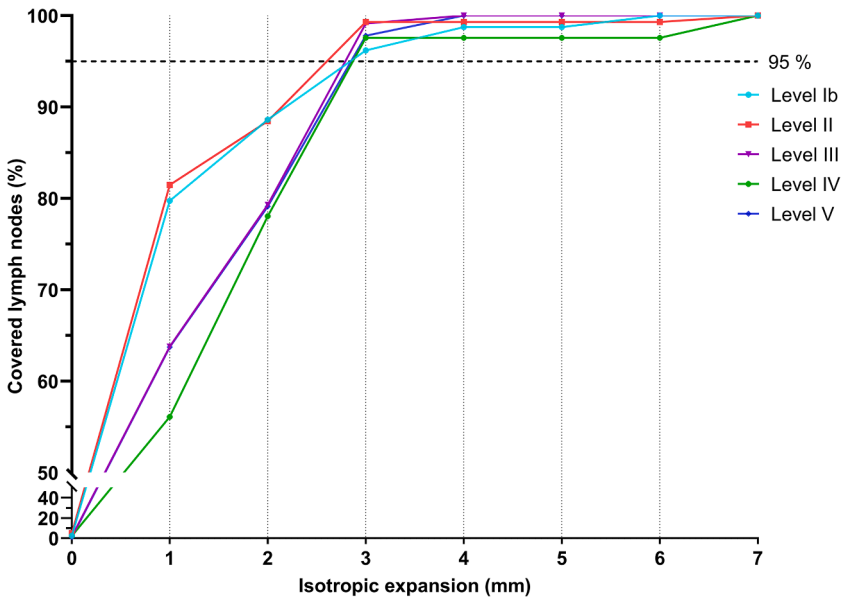

Fig. 5. Percentage of covered elective lymph nodes in the second MR-linac scan if the segmented volumes of the first MR-linac scan were isotropically expanded with incremental steps of 1 mm. 95 % of the lymph node volumes had to be within the expanded volume to be considered covered. Lymph nodes are divided per lymph node level Ib (light blue), II (red), III (purple), IV (green) and V (dark blue).

[18–21] on each side of the neck, which is higher than the number of lymph nodes seen in the present study. However, in the present study lymph nodes with a maximal transverse diameter < 4 mm, lymph nodes suspect for containing metastases, and lymph nodes only visible in one MRI slice were excluded. Moreover, lymph nodes could have been missed with MRI slices of 3 mm in the transverse direction. Still, we do not expect that small non-detected lymph nodes will provoke an increased risk of regional recurrence since these lymph nodes are expected to be close to larger lymph nodes and therefore will probably still receive an acceptable radiation dose.

Compared to the pre-treatment MRI, only 8 lymph nodes were not detectable on the first MR-linac scan. Moreover, 16 new lymph nodes were detected. As the inconsistency in lymph node detection between these scans is low, it is expected that elective lymph nodes can be well monitored during treatment on the MR-linac. Non-consistent detection of lymph nodes between scans was mainly caused by their small size, as these structures were hard to distinguish from other anatomical structures especially around blood vessels (see Supplementary Fig. 1 for examples). Another reason for inconsistent detection of lymph nodes was that some were only visible in only one slice on one of the two MRI scans and therefore were not counted (see Supplementary Fig. 1 for examples). A smaller slice thickness for both the pre-treatment MRI and the MR-linac scan, for example 2 instead of 3 mm, could decrease the inconsistency of detected lymph nodes between scans. Still, it should be questioned if decreasing the slice thickness is desirable as the MRI scanning time will increase with a possible negative impact on patient burden and increase of lymph node motion during scanning.

In this study it was confirmed that the maximum transverse diameter of elective lymph nodes remained constant between the 3T pre-treatment MRI scan and the 1.5T MR-Linac scan in the first week of treatment except for lymph nodes in level II. However, the differences in diameter of lymph nodes in level II were small and therefore not deemed clinical relevant. It is known that lymph nodes decrease in size during radiotherapy treatment [15] as lymphatic tissue is sensitive to radiation [22]. However, the results of this study indicate that this effect is not already visible in the first week of treatment. Therefore, target volumes of elective lymph nodes do not have to be adapted in the first week of radiotherapy treatment due to lymph nodes that decrease in size.

The intra-fraction motion of elective lymph nodes was estimated with median COM distances varying from 1.2 to 1.7 mm across all lymph node levels. Also, 3 mm isotropic expansion of all lymph nodes in the first MR-linac scan covered >95 % of all lymph nodes in the second MR-linac scan. One patient moved inside the fixation mask during the MR-linac scans and was excluded from this analysis as it had a disproportional impact on the outcomes. Yet this could also happen during a treatment, emphasizing the importance of monitoring lymph node movement during each radiation fraction. In the first HNC patients that will be treated with individual elective lymph node irradiation [16] a margin of 5 mm will be used for all elective lymph nodes. Before and after the administered treatment fraction on the MR-linac, MRIs will be obtained to ensure the 5-mm margin is sufficient to compensate for both interfraction and intrafraction motion of elective lymph nodes. If lymph nodes are detected or displaced outside the margin, a new plan with adjusted contours or PTV margin will be made for the next treatment day.

This study contains several limitations. First, the study population was small with only 15 patients. However, as many lymph nodes per patient were present a total of 679 lymph nodes were analyzed. Secondly, the MR-linac scans that were used to simulate intra-fraction motion only represented two time points. Lymph nodes could have moved between these time points which could have underestimated the simulated intra-fraction motion. Thirdly, it remains difficult to distinguish lymph nodes from other structures especially when lymph nodes are small since there is no histopathological validation possible. At last, lymph nodes of level VI and VII were not included as these are only irradiated under specific circumstances. Still it would be interesting to see if these lymph nodes show the same results.

In this retrospective imaging study, elective lymph nodes detected on the 3T pre-treatment MRI were compared to the elective lymph nodes detected on the 1.5T MR-linac scan obtained in the first week of radiotherapy treatment. Elective lymph nodes mainly remained detectable on the 1.5T MR-linac scan with no major changes in target volumes compared to the pre-treatment MRI. Moreover, estimated intra-fraction motion of elective lymph nodes during the MR-linac scans were generally small with average COM distances of 1.2 to 1.7 mm across all lymph node levels.

CRediT authorship contribution statement

Floris C.J. Reinders: Conceptualization, Methodology, Validation,

Formal analysis, Investigation, Data curation, Writing – original draft, Visualization, Project administration, Funding acquisition. **Mischa de Ridder:** Methodology, Validation, Writing – review & editing, Supervision. **Peter R.S. Stijnman:** Methodology, Validation, Formal analysis, Writing – review & editing. **Patricia A.H. Doornaert:** Writing – review & editing, Visualization, Supervision. **Cornelis P.J. Raaijmakers:** Methodology, Validation, Writing – review & editing, Supervision. **Marielle E.P. Philippens:** Conceptualization, Methodology, Validation, Formal analysis, Investigation, Resources, Writing – review & editing, Visualization, Supervision, Project administration, Funding acquisition.

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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Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.phro.2024.100532.

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