Combining CT-Based Online Adaptive Radiotherapy with Offline MR Guidance: The Modular Adaptive Radiotherapy System (MARS)

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Introduction

Adaptive radiotherapy refers to a treatment adaptation in response to anatomic changes during the ongoing radiotherapy course. Treatment adaptation while the patient is still on the treatment couch is called online adaptive radiotherapy (oART) [1, 2]. Variations in anatomy include weight loss, but also short-term variations such as atelectasis of the lung or bladder and rectum filling. To account for these variations, large safety margins are applied or prophylactic areas are included in the treatment volume [3–5]. This in turn increases the irradiation dose applied to healthy tissue and hence leads to unnecessary toxicity. However, oART is highly resource intensive and requires a fast workflow, since it must fit a complete radiotherapy planning process into a reasonable time frame and has to be applicable "on table" [6, 7]. A hybrid system like the MR-Linac, which combines a linear accelerator with 0.35T or 1.5T magnetic resonance imaging (MRI), offers daily oART under direct, online MR guidance. Lately, a computed tomography (CT) guided oART (CToART) irradiation device was installed at the Clinical Cooperation Unit Radiation Oncology at the German Cancer Research Center (DKFZ). The Ethos radiotherapy system (Varian, a Siemens Healthineers Company, Palo Alto, CA, USA) offers artificial intelligence (AI)-aided radiotherapy in order to establish a streamlined and fast workflow. With a daily cone beam CT (CBCT) scan, a new treatment plan can be generated based on the on-table anatomy and compared with the original reference plan [8]. Session times between 20 and 35 minutes can be achieved with this workflow [9–13]. However, CT scans have a lower soft tissue contrast than MR images. In our previous work, we established a workflow which integrates MRI scans in the shuttle position into ongoing non-adaptive radiotherapy [14, 15].

We now describe a workflow at the DKFZ, for which a CToART system is connected to a high-field 3T MRI scanner (MAGNETOM Vida, Siemens Healthineers, Erlangen, Germany). The systems are connected through a Symphony shuttle (CQ Medical, USA). Patients can be shuttled in the treatment position from the MRI scanner to the Ethos system, which enables offline MR guidance. This allows re-contouring with the aid of newly obtained MR imaging. Furthermore, functional imaging makes early response assessment of the tumor tissue possible. In summary, we propose the concept of a modular adaptive radiotherapy system (MARS), where additional sophisticated imaging modalities (such as a 3T MRI) are integrated to enhance the possibilities of oART.

Materials and methods

Treatment planning and reference plan generation
Treatment planning begins with a conventional planning CT scan. Thereafter, the patient is directly shuttled from the planning CT scanner to the MRI scanner. A short protocol (20–30 minutes) including non-enhanced T1-weighted and T2-weighted imaging as well as functional imaging is performed. For treatment plan generation, the non-enhanced CT scan functions as the primary image.

The here presented option of combining MARS and MRI is not commercially available and was not tested by Siemens Healthineers in regards of compatibility. The information in this paper is based on research results that are not commercially available.

Secondary imaging comprises this planning imaging and imaging available from earlier scans (contrast-enhanced CT or MRI scans, as well as PET/CT scans). Image data is then uploaded into the Ethos treatment planning system (TPS) and is rigidly co-registered with the primary CT image. Treatment plan generation can be done in either the image-guided radiotherapy (IGRT) mode or the adaptive mode. The IGRT mode reflects the workflow at a conventional linac. The adaptive mode enables to use the daily CBCT scan not only for mere patient positioning, but also for re-contouring and for preparing an adapted treatment plan. At our institution, we always choose the adaptive workflow.

After delineating the organs at risks (OARs) and the target volume, the respective prescription doses and tolerance values for the OARs are set and then attributed priorities. Based on these priorities, planning goals are arranged in a hierarchy. These priority levels decide whether a structure is displayed and edited during daily oART or is invisible and can only be monitored in a dedicated area of the Ethos software called "monitoring". Afterwards, a quick dose preview is obtained. During this step, priorities can be modified. As a last step, definitive treatment plans can be generated as previously selected, including 9- or 12-field sliding window intensity modulated radiotherapy (IMRT) and volumetric modulated arc radiotherapy (VMAT). The treating radiation oncologist can then pick the most suitable plan. As well as medical approval, technical approval from the medical physicist is required. At our institution, we perform patient-specific quality assurance (QA) with an Octavius phantom (PTW, Freiburg, Germany) and Mobius dose calculation tools (Varian, a Siemens Healthineers Company, Palo Alto, CA, USA).

Daily oART workflow

Daily oART begins with patient positioning, followed by a CBCT scan. Based on the CBCT scan, the influencers are contoured. Influencers are pre-set anatomic structures that depending on the treatment area. In the case of the thorax, the influencers are the esophagus, the heart, and both lungs. Based on the re-contouring of these influencers, the Ethos software then suggests derived structures for the other OARs as well as the treatment volume. These structures can then again be re-contoured. At our institutions, these steps (except for target volume delineation) are performed by the radiotherapy technologists. Afterwards, an adapted plan is generated, which can then be compared with the scheduled plan. The scheduled plan is the original reference plan, which is shifted to match the present anatomy. The radiation oncologist can then choose between the adapted and the scheduled plan. If the adapted plan is chosen, the medical physicist performs additional QA, which at our center is done with the Mobius dose calculation tools.

1 Patient positioning after the MRI scan.

2 Shuttling the patient from the MRI scanner to the Ethos system.

3 Patient positioning on the Ethos system.

Offline MRI guidance and shuttle workflow
Once a week, a non-enhanced MRI scan is performed in the treatment position. The protocol is the same as during the shuttled MRI scan after the planning CT scan. Afterwards, the patient is shifted onto the shuttle (Fig. 1). By inflating the air mattress, staff can easily transfer patients in the treatment position. The Ethos system is located directly next door (Fig. 2).

The patient is then positioned on the Ethos treatment couch (Fig. 3). During the shuttling process, the MRI sequences are sent to the Ethos system. These newly obtained sequences are included in the current workflow as secondary imaging. Afterwards, the secondary imaging available during online re-contouring is expanded. The whole process of MRI scan, shuttling, and integrating the newly obtained images amounts to approximately 50 minutes.

Clinical case

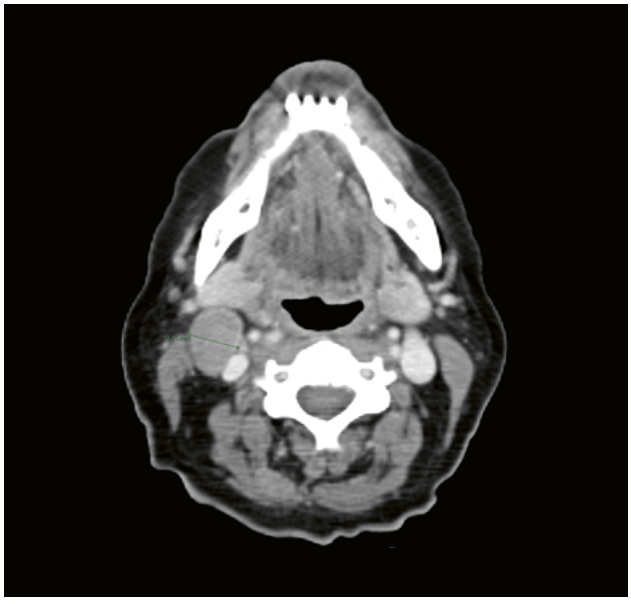
Current trials evaluating CToART mainly focus on the pelvis due to the variable status of bladder and rectum filling and the expected benefit of online adaptive radiotherapy. Nonetheless, enhancing CToART with offline MR guidance unlocks further use cases, including radiotherapy for patients with (daily altering) atelectasis, which is particularly difficult to distinguish from tumor tissue. We therefore present a clinical case in which repeated MRI scans during CToART treatment proved useful. The patient is a 68-year-old woman, who was presented at our institution with limited stage small cell lung cancer (LS-SCLC; 8th AJCC: cT4cN2cM0). She had already had intrathoracic progressive disease after the first cycle of cisplatin-based chemotherapy and was referred to our department for thoracic salvage radiotherapy. However, a large cervical lymph node metastasis was detected in our planning CT scan (Fig. 4). Moreover, the patient was beginning to experience problems with swallowing solid food, which was a clinical reflection of the progressing mediastinal lymph node metastases.

After thorough interdisciplinary discussions with the patient, definitive hypofractionated radiotherapy with 45 Gy in 15 fractions was planned.

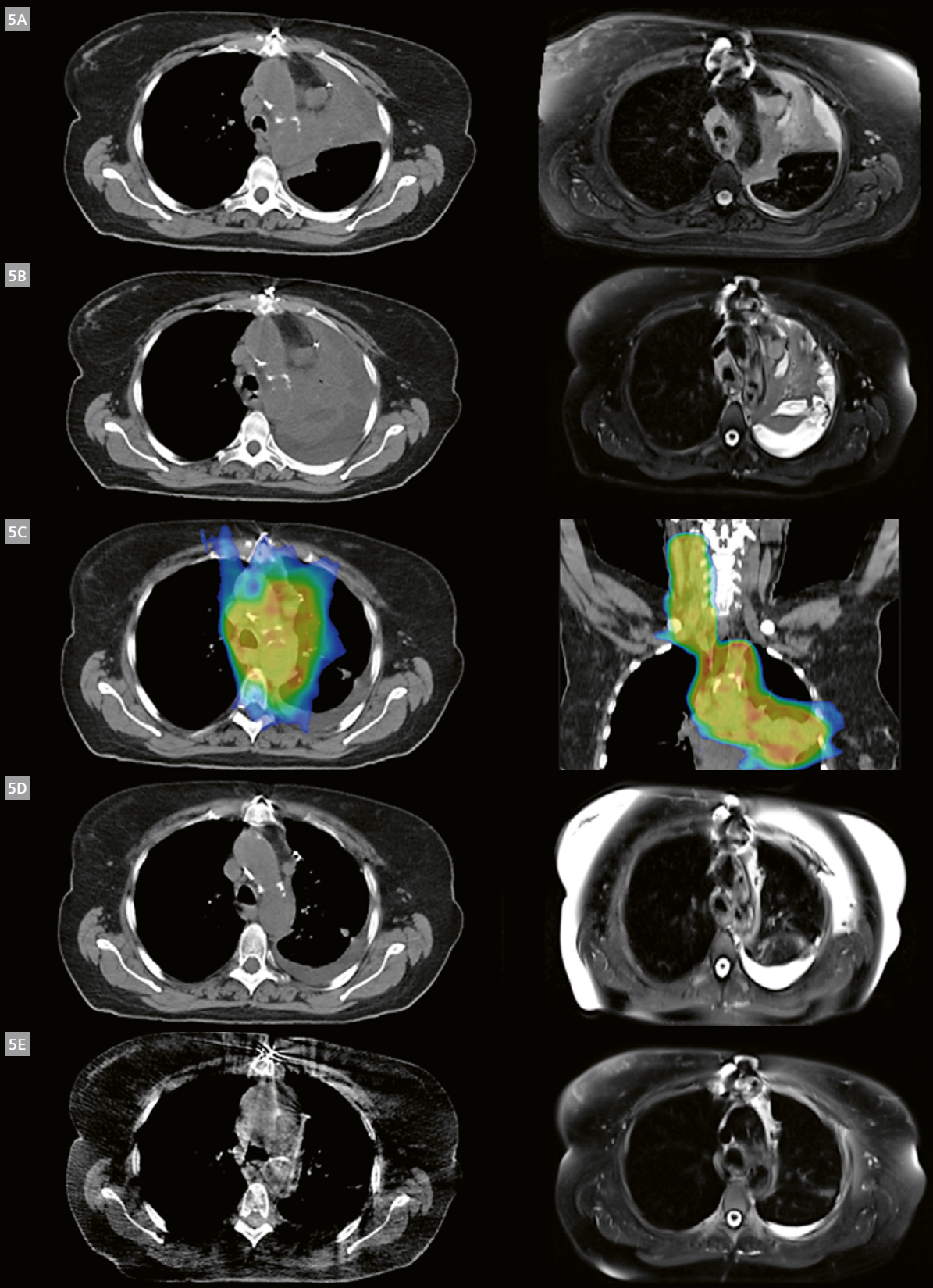
Given the extensive treatment area, which extended from the upper right cervical area down to the lower left lung lobe, the irradiation field focused on the gross tumor volume (GTV) with a clinical target volume (CTV) margin of 5 mm excluding anatomical borders. Due to a relatively low variability of the treatment area in the additionally performed 4D planning CT scan, a tight planning-target-volume (PTV) margin of 5 mm (isotropic) was chosen. From the outset, a "shrinking approach" was chosen, making it possible to reduce the target volume during the treatment course and thus spare healthy lung tissue. As per institutional standard, a PTV coverage of 95% with at least 95% of the prescription dose (i.e., 42.8 Gy) was aimed for, with a PTV maximum dose of 110% (i.e., D0.03 cc below 49.5 Gy). The resulting plan achieved the following dose metrics: Dmean (esophagus): 25.8 Gy; Dmean (both lungs): 13.7 Gy; V20 Gy (both lungs): 22.2%; Dmean (heart): 20.0 Gy. In order to gain maximum security and monitoring of patient immobilization, during the first fraction, a second CBCT scan was performed immediately before commencing the treatment beam and again after completed irradiation. All three CBCT scans suggested robust patient immobilization. From then on, a second CBCT scan was only performed if the close video monitoring of the patient during the respective session suggested significant patient movements.

Figure 5A shows the planning CT scan with the corresponding MRI (T2-weighted Half Fourier Single-shot Turbo spin-Echo; HASTE), which was performed in shuttled position right after the planning CT. However, during the first week of treatment, the tumor had already progressed and the consecutive atelectasis increased in size, which then affected nearly the entire left lobe. Another planning CT scan was performed (Fig. 5B).

The reason for performing the re-planning CT was as follows: At the time of this case presentation, the CBCT upgrade (HyperSight, Varian, a Siemens Healthineers Company, Palo Alto, CA, USA) and the Ethos 2.0 software were not implemented at our institution. As a consequence, daily re-planning did not rely on the CBCT alone. Instead, dose calculation was performed with synthetic



4 Planning CT scan revealing a cervical lymph node metastasis.



5 **(5A)** First planning CT scan and corresponding T2w HASTE; **(5B)** second planning CT scan and corresponding T2w HASTE; **(5C)** treatment plan; **(5D)** third planning CT scan and corresponding T2w HASTE; **(5E)** CBCT scan of fraction 13 and corresponding T2w HASTE.

CT, which is the original reference CT deformably registered to the respective CBCT. We therefore recommended performing a new planning CT if the patient anatomy changed in such a significant way that the difference between the CBCT and reference CT scans was deemed too high. This was judged on a case-by-case assessment by the medical physicist and the radiation oncologist.

After another week of treatment, due to significant tumor regression, the atelectasis had nearly resolved and a third reference plan based on a third planning CT scan was created (Figs. 5C, 5D). After 13 out of 15 fractions, no gross tumor could be detected in the CBCT scan or the respective MRI scan (Fig. 5E).

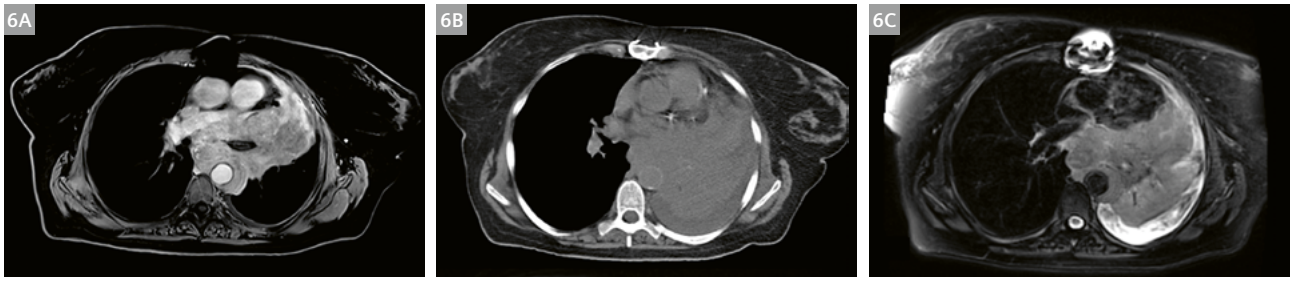
An initial contrast-enhanced MRI scan from before the treatment planning (T1w volumetric interpolated breath-hold examination, VIBE, Fig. 6A) helped, in combination with the repeated shuttled non-enhanced MRI scans, to distinguish residual tumor from atelectasis during the ongoing treatment course (Figs. 6A, 6C).

Furthermore, repeated MRI imaging supported the delineation of the esophagus as demonstrated in Figure 7A (CBCT from fraction 4) and the corresponding same-day shuttled non-enhanced MRI (Fig. 7B).

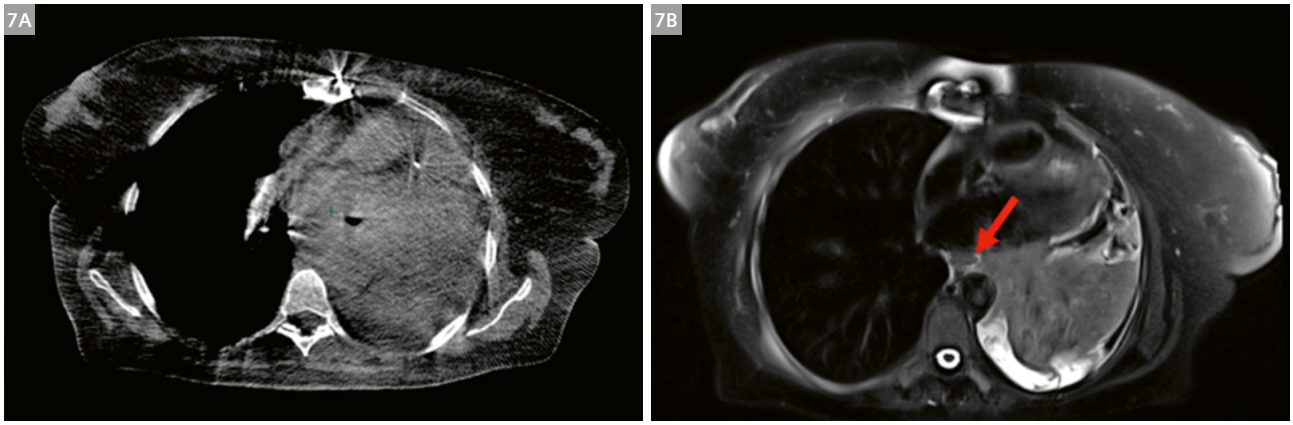
On the last treatment day, the patient only presented mild esophagitis (CTCAE v5.0: grade 1). However, the obstructive sensations while swallowing had already resolved completely, a sign of tumor regression in the mediastinal lymph nodes.

Further treatment course after online adaptive cervicothoracic irradiation

The first follow-up one month later showed complete regression of the cervical and thoracic tumor manifestation. Parts of the irradiated left lung showed asymptomatic radiation pneumonitis (CTCAE v5.0: grade 1). The esophagitis had resolved completely. However, the patient developed new retroperitoneal lymphatic node metastases medial of the left kidney and the contralateral paracardial area, as well as subcutaneous metastasis in the left thoracic wall, all of them far outside the previous treatment volume. Re-exposition with chemotherapy accompanied by immunotherapy with atezolizumab was planned. Due to persisting leukopenia since the last chemotherapy cycle, only immunotherapy could be administered repeatedly. After further progressive disease in the retroperitoneum two months later, immunotherapy was discontinued and second-line chemotherapy with topotecan was initiated.



6 **(6A)** Contrast-enhanced T1 VIBE sequence from before treatment planning; **(6B)** second planning CT scan; **(6C)** T2w HASTE



7 **(7A)** CBCT scan at fraction 4, esophagus difficult to identify; **(7B)** corresponding T2w HASTE; arrow: esophagus.

After repeat progressive disease in the retroperitoneal space two months later, the chemotherapy regime was switched to Adriamycin, Cyclophosphamide, and Vincristine (ACO). Two months later, re-staging showed progressive disease again in the retroperitoneum, with increasing consecutive pain. The patient was then again referred to our clinic for palliative radiotherapy. In total, 30 Gy was applied in 10 fractions. To date, the patient has not had further follow-up for her recent treatment. However, the patient had no more pain already after 3 fractions of palliative radiotherapy.

Discussion

Our current experience with oART and offline MR guidance is excellent. Every patient has tolerated the extended workflow with weekly MR imaging in the shuttle position. To the best of our knowledge, we are the first institution to report on integrating weekly shuttled MRI scans in the treatment position into ongoing online adaptive radiotherapy.

In general, oART is particularly promising in pelvic cancer sites, as it enables adaptation to daily changing anatomy of, for instance, the bladder and rectum. We are currently evaluating the potential of offline MR-guided oART, including in the prospective AIM-C1 trial [16]. The AIM-C1 trial evaluates offline MR guidance during concurrent chemoradiotherapy in patients with locally advanced cervical cancer. The primary endpoint of the trial is the overall early bowel and bladder toxicity of CTCAE v5.0 grade 2 or higher. The secondary endpoints include feasibility, patient-reported outcome, and imaging-based response assessment.

However, the potential benefit of our MARS concept might not be restricted to the pelvis. This was demonstrated in our clinical case, where we used the MRI scans in shuttled position for distinguishing the varying atelectasis from (regressing) tumor tissue.

The occurrence of a cervical lymph node metastasis marked the beginning of a metastasized tumor stage. It was highly likely that the patient would develop further distant metastases. Nonetheless, to prevent the patient from upper inflow congestion, and due to the beginning obstruction of the esophagus, we decided to perform radiotherapy. It is not uncommon for small cell lung cancer to respond quickly to radiotherapy. However, if offline MR-guided oART had not been available, this patient might not have been treated in the first place – or the treatment would not have encompassed all visible macroscopic tumor. Despite the large treatment area near or abutting the esophagus, the toxicity of offline MR-guided oART was mild. As per the definition of the Veterans Affairs Lung Study Group, an extensive disease stage is already present if the tumor cannot be "safely encompassed in a two-dimensional radiation field", even in the absence of distant metastases [17]. It can be speculated that the "limit of limited disease" could therefore be extended through (offline MR-guided) oART. Nonetheless, as in the presented case, distant metastases are a common phenomenon in small cell lung cancer. Currently, the ADRIATIC trial is evaluating immunotherapy after chemoradiotherapy of limited stage small cell lung cancer [18]. Unfortunately, in our presented clinical case, the tumor did not respond to any systemic therapy, neither before nor after radiotherapy.

Recent upgrades of the Ethos system, such as HyperSight, promise enhanced CBCT quality and short acquisition times of only 6 seconds [19]. It will be very interesting to see how these enhanced CBCT scans will perform compared to repeated shuttled MRI scans during therapy. Nonetheless, since it is difficult to distinguish an atelectasis from tumor tissue even on a diagnostic CT scan, MRI scans during ongoing radiotherapy still have the potential to be highly useful in treating patients with atelectasis.

Conclusion

Offline MR-guided oART is a promising treatment approach and is currently being evaluated in prospective trials. Our presented clinical case proposes the benefit of repeated shuttled MRI scans for the treatment of lung cancer patients, which might extend the "limit of limited disease".

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