

# MRI for Target Delineation in Radiotherapy – an Overview of Treatment Indications

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## Abstract

Imaging used for target delineation and treatment planning plays a critical role for treatment success in radiotherapy. Due to its superior soft tissue contrast, MRI is essential for many radiotherapy treatment cases. In the present article, we summarize and discuss the role of MRI for the most relevant radiotherapy treatment indications.

## Introduction

Radiotherapy has different demands on MR imaging than diagnostic radiology. In routine radiologic imaging, depending on the site and patient history, imaging primarily needs to be able to detect previously unknown pathologies and provide information on differential diagnosis while the accurate depiction of the true three-dimensional extension of tumors is of less importance. In contrast, MRI for radiotherapy planning primarily needs to accurately and clearly depict the tumor perimeter in three-dimensional space for precise gross tumor volume (GTV) delineation.

Different radiotherapy treatment indications and sites also may have specific demands on MR sequences and tissue contrasts. Frequently target delineation for treatment planning is based on contrast-enhanced T1 sequences. However, usually multiple tissue contrasts and sequences are integrated when creating target volumes for radiotherapy.

Magnetic resonance imaging is routinely required for treatment planning in many indications in radio-oncology [1]. In the present article we summarize the role of MRI for the most relevant radiotherapy treatment indications and discuss the varying specific requirements each treatment site puts on MR imaging.

## Intracranial radiotherapy

One of the most important areas for MR imaging in radiotherapy are intracranial treatment indications. Intracranial targets, especially when small in size or low-enhancing, usually are not visualized on CT at all, rendering MR imaging critical for treatment planning. At the same time intracranial diseases are one of the most important indications for radiotherapy. Irradiation can be delivered very accurately to intracranial targets, as the skull can be positioned with submillimeter accuracy using thermoplastic mask immobilization and X-ray-based imaging during treatment delivery [2]. The high overall accuracy of intracranial radiotherapy enables precise target volumes and high radiotherapy doses with minimal impairment of normal tissues. This leads to high treatment efficacy and low or minimal side effects in a variety of malignant intracranial tumors like brain metastases, benign tumors like vestibular schwannoma and functional disorders like trigeminal neuralgia. In these diseases the requirements for geometric accuracy in MR imaging are particularly demanding, as commonly used margins of  $\leq 1$  mm do not account for additional MR imaging-related uncertainties [2, 3].

Another group of frequent intracranial treatment indications are gliomas, which are more difficult to treat as they are usually larger in size and show diffuse infiltration in the surrounding brain tissue, thus rendering precise delivery of high irradiation doses to all tumor cells is impossible without impairing normal brain tissue. In these tumors improved MR imaging could help with precise tumor delineation or potentially identifying candidate regions for dose-escalation and -sparing.

## Brain metastases

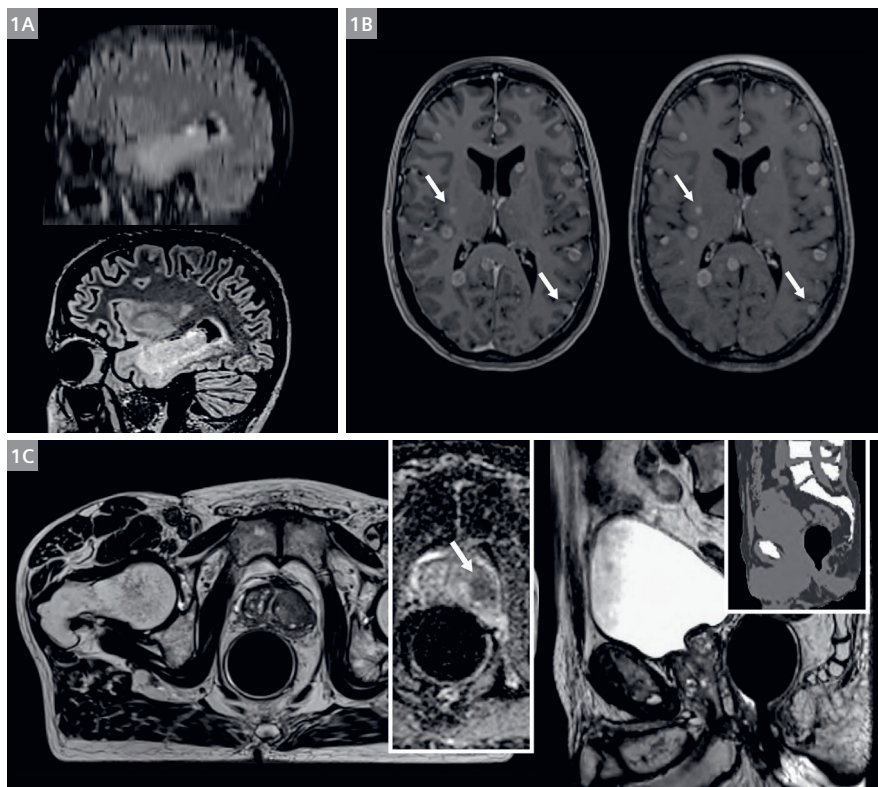
When being referred to treatment today, brain metastases are usually small (mostly < 1 cm diameter) solitary or multiple spherical lesions, which are best visualized in post-contrast T1 sequences. They show no or minimal infiltration into the surrounding brain tissue [4] and thus are usually irradiated with an isotropic uncertainty margin of less than 2 mm [2]. Due to the small size high-resolution isotropic 3D sequences are usually best-suited as they enable accurate multiplanar reconstruction and minimize partial volume effects [5, 6].

Inversion-recovery gradient echo sequences (IR-GRE) like the T1-MPRAGE [7], have been the most commonly used 3D MR imaging technique for brain tumors and have been included in the standardized Brain Tumor Imaging Protocol (BTIP) [8, 9]. However, multiple sources suggest that a 3D-turbo-spin-echo (TSE) T1-SPACE could be superior to the frequently used T1-MPRAGE gradient-echo sequence for intracranial radiotherapy target volume delineation [8, 10-12]. While T1-SPACE provides less contrast between grey and white matter [8], this is negligible in most cases for radiotherapy treatment planning and may in fact even help with the delineation of intracranial metastases, as does the suppression of vessels in the T1-SPACE [12]. Conversely, T1-MPRAGE suffers from a known reduced enhancement if low contrast agent uptake is present, which could lead to underestimation of lesion boundaries [8, 13] (Fig. 1).

Additional important requirements for radiotherapy in brain metastases are the minimization of distortions from gradient-non-linearities and susceptibility effect-induced distortions [14, 15].

Due to the malignant nature of brain metastases, they have a high growth rate [16, 17] and are usually surrounded by perifocal edema [18], which may change in configuration spontaneously or when corticosteroid dosage is modified (Fig. 2) [19]. Salkeld et al. found profound changes with imaging intervals  $\leq 7$  days before radiosurgery. Change in management was required for 41% of patients with interval  $\leq 7$  days and even for 78% if the delay exceeded 7 days. The most frequent reason for replanning was an increase in tumor or resection cavity size [17, 20]. Therefore, the interval between imaging and treatment delivery should be as short as possible. While same-day imaging would be optimal, in our university medical center in Erlangen we currently have established the requirement that the interval between imaging and treatment delivery must not exceed 5 days.

In addition to pretreatment changes, brain metastases may also undergo profound changes during radiotherapy due to transient swelling, changes in perifocal edema and treatment response (Fig. 2). Hessen et al. in a recent study evaluated the significance of a repeated MRI scan in the fractionated stereotactic radiotherapy of 18 brain metastases and 20 resection cavities. For cases with in-situ brain metastases, reductions in coverage of up



### 1 Examples of sequences used for target delineation.

(1A) T2 SPACE FLAIR (1 mm slice thickness – bottom) vs. conventional T2 FLAIR (5 mm slice thickness – top) in a patient with glioma.

(1B) T1 SPACE 3D TSE sequence (right) vs. T1 MPRAGE IR GE sequence (left). Some metastases are only very faintly visible in the T1 MPRAGE (arrows). Note also: Suppression of vessels and less contrast between gray and white matter in the T1-SPACE.

(1C) Isotropic T2 SPACE sequence in prostate cancer (left) with high-resolution sagittal reconstruction (right). Left inset: ADC map from diffusion-weighted imaging with reduced volume excitation (ZOOMit) showing focal diffusion restriction in the top lobe of the prostate (arrow). Right inset: Synthetic CT of the pelvis showing proper detection of air inside rectal balloon.

to 34.8% were found due to changes during fractionated radiotherapy [21].

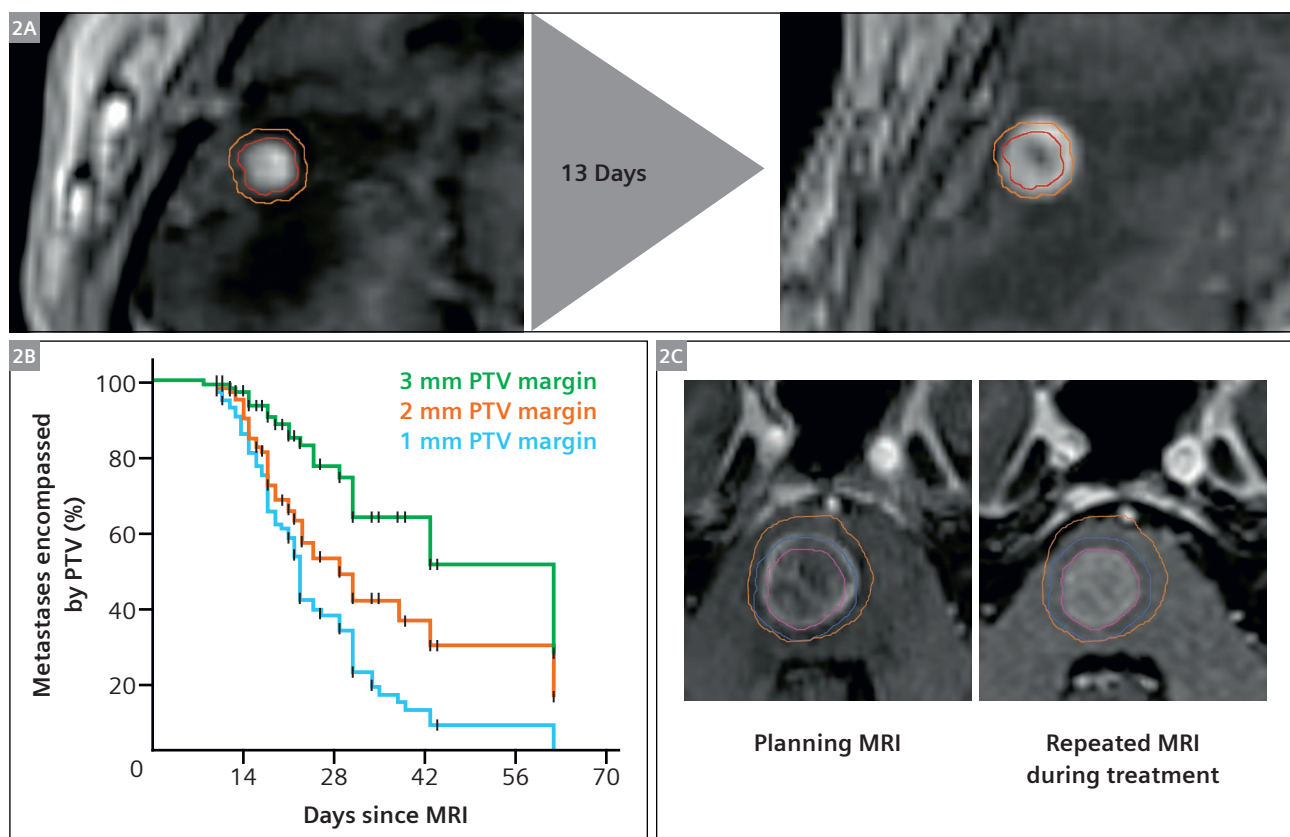
This accumulating evidence for rapid tumor growth and accompanying anatomic changes in brain metastases might mean that optimal MR imaging for treatment planning needs to be performed daily. Considering the trend that more and more brain metastases are treated with stereotactic radiotherapy alone and life expectancies increase due to advances in immunotherapy and targeted agents [22], alternatives to contrast-enhanced T1 sequences might become necessary to reduce exposure to gadolinium-based contrast agents. Promising results recently have been achieved with deep learning-based prediction of synthetic contrast-enhanced T1 sequences from non-enhanced MR sequences, which could reduce cumulative gadolinium doses patients need to receive for radiotherapy [23].

There is a real potential for improving clinical outcomes with optimized MR imaging in brain metastases: In prospective clinical trials, local control rates of around 70% at 1 year post-radiotherapy have been consistently shown

for stereotactic radiotherapy alone, while control rates for stereotactic radiotherapy with adjuvant whole brain radiotherapy measured at around 90% [24]. As increasing radiotherapy dose due to additional whole-brain radiotherapy is a less likely explanation, marginal miss in stereotactic radiotherapy because of suboptimal imaging could account for a substantial part of the observed difference in local efficacy.

## Gliomas

While MRI was introduced many decades ago for target volume delineation in gliomas [25–28], these tumors are more difficult to treat and improvement in outcomes for the most part has stalled in recent years. Target delineation is more challenging in gliomas than in brain metastases. High-grade gliomas usually show strong contrast-enhancement, which is the main target for radiotherapy. However, while the surrounding T2 hyperintensity in brain metastases merely represents vasogenic edema and microscopic infiltration is minimal in brain metastases [4],



**2 Importance of the time interval between MR imaging and treatment delivery in brain metastases. (2A)** Brain metastasis increasing to 281% in volume in an interval of only 13 days. Orange: planning target volume (PTV) definition based on initial MRI would have missed 31.5% of GTV volume. **(2B)** Kaplan-Meier plot showing the diminishing fraction of metastases encompassed by the initial PTV volume over time for margin definitions of 1–3 mm (preliminary analysis of 85 metastases). **(2C)** Repeated planning MRI during fractionated stereotactic radiotherapy in a patient with brainstem metastasis. Note: Substantial reduction in tumor volume and in accompanying edema results in profound shifting of the brainstem. The radiotherapy plan was adapted based on the repeated planning MRI.

T2 abnormalities may constitute an important or the only visible tumor portion in low-grade gliomas or IDH-mutant glioblastomas [29–31].

Additionally, aside from imaging changes, extensive microscopic tumor cell infiltration into the adjacent brain is present in gliomas with microscopic infiltration even expected to extent into the contralateral brain hemisphere [32].

To make matters worse, contrast-enhancing tumor needs to be differentiated from treatment effects due to prior surgery and radiation as well as pseudo-progression.

For visualization of contrast-enhancing tumor, 3D contrast-enhanced T1-sequences like the T1-MPRAGE and T1-SPACE are usually used. In stark contrast to the millimeter margins employed in stereotactic radiotherapy for brain metastases, current guidelines recommend giving an isotropic margin of 2 cm around any contrast-enhancing tumor [29, 33]. Geometric accuracy therefore usually is less critical in radiotherapy for gliomas than in other intracranial treatment indications. The non-contrast enhancing tumor usually is delineated in 2D T2-FLAIR sequences with 3–5 mm slice thickness [34]. While current guidelines also recommend a margin of around 2 cm for T2-FLAIR hyperintensities in lower-grade gliomas, recommendations are conflicting in primary, IDH-wildtype, glioblastoma with the ESTRO recommending not considering the T2-FLAIR hyperintensity at all [29, 33].

As discussed above, thick slice 2D FLAIR sequences could lead to unnecessarily high treatment volumes in cases of small tumor volumes. Coarse depiction of non-enhancing tumor parts in conventional T2-FLAIR sequences should be of particular relevance in cases of stereotactic reirradiation, where much smaller margins are used.

We currently evaluate high-resolution 3D T2-SPACE FLAIR sequences in patients with malignant low-grade gliomas in comparison to conventional T2-FLAIR imaging. In our preliminary experience a 3D T2-SPACE FLAIR sequence allows for more precise delineation of non-enhancing tumor volumes with high-resolution multiplanar reconstruction being particularly beneficial to target delineation in radiotherapy (Fig. 1).

Moreover, RT-optimized perfusion and diffusion sequences could help with differentiating true tumor from other reasons for contrast-enhancement and T2-FLAIR hyperintensity. We are currently evaluating an EPI with reduced volume excitation (ZOOMit) to help with target volume delineation in gliomas.

## Benign tumors and functional disorders

Vestibular schwannomas are an important benign tumor, frequently treated with stereotactic radiotherapy. In these cerebellopontine neoplasms excellent long-term

control and functional outcome is achieved with local radiotherapy [35]. As vestibular schwannomas show strong contrast enhancement, 3D T1-sequences like the T1-MPRAGE are frequently used for delineation in radiotherapy treatment planning. In addition, high-resolution 3D-CISS sequences depict tumors and surrounding cerebrospinal fluid with high contrast and are important for delineation of adjacent cranial nerves. They also allow high-resolution segmentation of inner ear structures which may reduce cochlea doses and help with preservation of hearing. Post-radiotherapy these tumors frequently show transient enlargement before regressing in size, which sometimes is challenging to differentiate from treatment failure [35, 36].

Another benign brain tumor frequently treated with radiotherapy is meningioma, in which contouring mainly relies on contrast-enhanced T1 3D sequences like the T1-MPRAGE. In delineation of meningiomas for stereotactic radiotherapy the accurate estimation of the amount of dural extent (“Dural tail”) is frequently challenging to determine and contouring of meningioma cases is frequently very time-consuming because of complex geometric tumor configurations and imaging changes due to previous surgery.

Trigeminal neuralgia is a functional disorder that may be treated with stereotactic radiosurgery in patients refractory to analgesics and surgical decompression. A very large radiosurgery dose (70–90 Gy) is given to the trigeminal root entry zone or cisternal portion of the nerve making accurate high-resolution MRI for treatment planning crucial. We usually employ a high-resolution 3D CISS, which enables clear distinction of the trigeminal and surrounding cranial nerves [37].

## Head and neck cancer

Radiotherapy of the head and neck region is a highly effective curative treatment for wide variety of tumors ranging from malignant entities like squamous cell cancers of the oral cavity and throat, malignant paranasal sinus tumors and lymphomas to benign indications like paraganglioma.

Substantial improvements in treatment side effects have been achieved with intensity-modulated radiotherapy (IMRT) by sparing of salivary glands, mucosal surfaces and skin [38]. By improving precision in tumor and lymph node level delineation, MR imaging for radiotherapy treatment planning has the potential to further reduce uncertainty margins and treatment side effects.

Important structures for radiotherapy planning in head and neck cancer show superior depiction in MRI compared to CT. These include salivary glands and cervical lymph nodes [39], but also malignant tissues. Rasch et al. observed that tumor volumes in advanced head and neck



cancer delineated in MRI are smaller and show less interobserver variability than using CT alone [40] and in nasopharyngeal cancer, Chung et al. showed in a study of 258 patients that MRI was far superior than CT for the detection of intracranial and pterygopalatine fossa invasion [41].

MRI for radiotherapy treatment planning in the head and neck region benefits greatly from image acquisition in treatment position as anatomic changes may become extensive, if the configuration of the cervical spine, mandible or scapula is different [1]. The anatomic changes usually are too large to be solved by non-rigid registration techniques with clinically desired accuracy [42]. Multiple groups therefore have developed solutions to acquire the MRI in treatment position with mask immobilization. A common challenge for acquiring MR studies in treatment position is that thermoplastic mask systems do not fit into routine head and neck coils. The most common solution therefore is to use flexible surface coils instead [1, 43, 44], with high-channel coils enabling decently good image quality.

Fat-saturated 3D post-contrast T1w-sequences are generally considered to be the backbone for radiotherapy target delineation [1, 43]. With 3D T2-FLAIR sequences and diffusion-weighted sequences providing additional information for delineation [43, 45].

## Liver and abdominal tumors

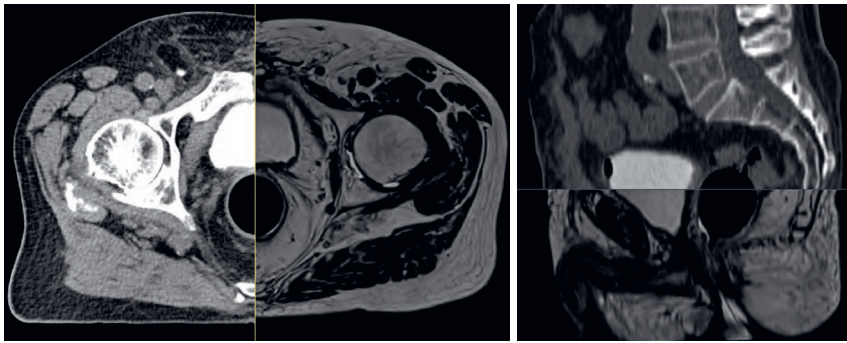
Patients suffering from hepatic tumors can undergo a broad range of treatment options including surgery, radiofrequency ablation (RFA) and stereotactic body radiotherapy (SBRT). Large lesion size or close proximity to bigger vessels generally favor SBRT in comparison to RFA. A 2016 study published by Wahl et al. in the *Journal of Clinical Oncology* showed significantly improved tumor control for hepatocellular carcinoma treated with SBRT compared to RFA, if tumor diameter was  $\geq 2$  cm [46].

MR imaging is crucial for radiotherapy planning of hepatic tumors as the boundary of most lesions cannot be adequately discerned on CT and many tumors are not visible on CT at all.

Hepatic tumors usually show complex motion patterns during respiration as the liver not only undergoes movement but also deformation during the respiratory cycle and is additionally influenced by abdominal peristalsis [47, 48]. At the same time, uncertainty margins need to be minimized to spare surrounding liver and bowel while escalating radiotherapy dose to the target. Tumor motion and integration with the remaining SBRT workflow therefore are the main challenges in liver MRI for radiotherapy treatment planning.

Strategies for respiratory motion management in liver SBRT include internal target volume (ITV) concepts, expiration breath-hold, gating and tracking of tumor motion. As X-ray-based image guidance available at conventional linear accelerators does not visualize hepatic lesions, additional fiducials need to be invasively placed to allow for real-time image guidance. If radiotherapy is delivered exclusively in one respiratory phase, e.g. expiration, breath-hold or navigator-triggered MR sequences can be acquired to best reflect the respiratory position during treatment. As usual, MR imaging in radiotherapy treatment position using a flat table-top and similar immobilization equipment minimizes anatomic differences due to positioning. We currently use a navigator-triggered fat-saturated T2 TSE and EPI diffusion sequence as well as multiple breath-hold T1 VIBE Dixon sequences in different contrast phases for treatment planning.

4D MRI techniques are very promising for radiotherapy target volume delineation as they provide multiple 3D datasets during the respiratory cycle. 4D respiratory-correlated MRI acquires respiratory motion across multiple breathing cycles, which are subsequently sorted according to respiratory phase [49]. In contrast to 4D CT, 4D respiratory-correlated MRI thus provides data on an average breathing cycle that might be more representative of the actual respiration during treatment. 4D MRI datasets can be used to create an internal target volume, that encompasses all possible tumor positions and is treated in free-breathing, but it can also be exploited for expiration breath-hold, gating and tracking strategies that limit dose to surrounding structures. One limitation for tumor tracking on conventional linear accelerators is that only the position of the fiducial itself is tracked and changes in tumor shape and position in relation to the fiducials are not captured. An interesting method was published in 2018 by Harris et al. to use a pre-treatment 4D MRI together with LINAC on-board kV projections to generate a synthetic on-board 4D MRI on conventional linear accelerators [50]. Real-time image guidance of abdominal tumors is of course also a prime use case for new MR-LINAC systems and a technique for generating synthetic volumetric cine-MRI using the MR-LINAC on-board 2D-cine imaging as well as a pretreatment 4D MRI was developed by the same group before [51]. We currently acquire a transversal 4D T1 StarVIBE-based respiratory self-gating series with and without contrast in MRI simulation for liver SBRT reconstructing 5 to 7 respiratory bins. In our preliminary experience subtraction of pre- and postcontrast acquired 4D series further improves contrast ratio of target lesions.



### 3 Advantages of acquiring the planning MRI in treatment position.

Planning MRI in prostate cancer showing good correspondence of bladder and rectum with endorectal balloon in the planning CT and dedicated planning MRI.

## Prostate cancer

Prostate radiotherapy shows large benefits from MR imaging. Accurate delineation of the prostate is impossible in CT alone and it has been shown that prostate segmentations in CT are significantly larger than MRI, which leads to unnecessary high doses to penile and surrounding nerve and vascular structures and increases the risk for long-term urologic side effects [52, 53]. Precise radiotherapy delivery also reduces acute and late rectal side effects like proctitis. We therefore currently employ a rectal balloon and bladder filling protocol to enable a reliable anatomic configuration at each treatment session [53]. To assure accurate registration, we perform a dedicated MRI for radiotherapy treatment planning using the same positioning with rectal balloon and bladder filling as at daily treatment session. (Fig. 3) While a range of different non-rigid registration solutions are available, these algorithms may be associated with problematic uncertainties. For example, Brock et al. have observed errors of up to 8.7 mm for the prostate itself in intramodality non-rigid registration of repeated prostate MRIs [54]. As errors with non-rigid registration largely depend on the amount of deformation [7], performing MR measurements in treatment position also increases the accuracy of any subsequent registration steps.

We currently employ an isotropic, axial T2 SPACE with compressed sensing acceleration as the main sequence for delineation of the prostate, seminal vesicles and pelvic lymph nodes in patients with prostate cancer (Fig. 1). In our experience, this sequence provides high tissue contrasts, large field of view and allows for high-resolution sagittal reconstruction for differentiation of the caudal prostate margin and structures of the pelvic floor. As detailed sagittal imaging of the prostate and pelvic floor structures is of high importance in our experience, we currently still employ an additional sagittal T2 BLADE, which suppresses motion artifacts and provides high signal-to-noise in the prostate region. We use an EPI diffusion sequence with reduced volume excitation (ZOOMit) of the prostate region to get additional information on the location of malignant tumor inside the prostate (Fig. 1).

## Summary

Optimal MR imaging for radiotherapy target delineation has distinct requirements that may be different from routine diagnostic indications. Demands on MR imaging in radiotherapy frequently are indication and site-specific, which needs to be addressed with specialized protocols. MRI for radiotherapy planning primarily needs to accurately and clearly depict the tumor perimeter in three-dimensional space for precise gross tumor volume delineation. In addition, 4D MRI techniques are capable of integrating tumor motion and have large potential to improve precision in radiotherapy of moving targets.

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