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Modern Imaging Methods in Radiation Therapy Planning

Ph.D. Thesis

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1. Introduction

The discovery of X-rays marks the birth of two now independent, but closely related fields of medicine, radiology and radiation oncology. The introduction of computed tomography (CT) led to the shift from two-dimensional to three-dimensional (3D) personalized radiation therapy, which is now the gold standard worldwide. Over the past decades, advancements such as intensity-modulated radiation therapy (IMRT), stereotactic radiosurgery (SRS), and stereotactic body radiotherapy (SBRT) have allowed for highly precise dose delivery. These techniques rely heavily on advanced medical imaging, above all magnetic resonance imaging (MRI) and positron emission tomography (PET). Modern imaging plays a crucial role in ensuring optimal target volume coverage as well as minimizing damage to surrounding healthy tissue. Both goals are achieved by improving the visibility of the macroscopic tumor and the adjacent uninvolved organs-at-risk (OARs).

2. Aims

The purpose of the research is to examine four domains of radiation oncology closely related to modern imaging methods. Throughout the dissertation, we seek the answer to the following scientific questions:

- How can organ-at-risk definition be optimized and accurate delineation supported by neural network softwares for high-precision radiation therapy?
- What is the clinical impact of structure adaptation and replanning during postoperative radiochemotherapy of glioblastoma patients?
- What conclusions can be drawn beyond target volume adaptation from the interim MR examination performed during the radiochemotherapy of glioblastoma patients?
- How can prostate-specific membrane antigen-based imaging be used for stereotactic irradiation of low volume progressive prostate cancer?

3. Methodology and findings

3.1 How can organ-at-risk definition be optimized and accurate delineation supported by neural network softwares for high-precision radiation therapy?

Beside improved tumor control, the high daily doses used in contemporary radiotherapy pose a larger burden on the neighboring healthy tissues. In these high-precision treatments, accurate OAR delineation is particularly important to reduce radiation-induced side effects.

For this purpose, several strategies have been examined, such as improved imaging, standardization through guidelines, and the use of artificial intelligence.

3.1.1 Better visualization of organs

Up to the present date, the generally used imaging method for organ-at-risk delineation is computed tomography (CT) worldwide. However, MRI is gaining importance due to its formidable soft tissue resolution and lack of ionizing radiation during image acquisition. Furthermore, it possesses the capability to visualize in great detail the central nervous system and the head-and-neck (H&N) region, anatomical sites where CT has limited use. However, MRI requires more expertise due to its complex physics and longer learning curve for interpreting organ characteristics.

The Department of Oncotherapy, University of Szeged had the opportunity to participate in the multicentric project „Deep-Learning MR-only Radiation Therapy", a collaboration aiming to develop a software that can provide automatic OAR contours on high resolution MR images.

The first step of the development required numerous precise, manually contoured expert cases. During this work phase, various MRI sequences have been tested for OAR visibility and objectively compared with the use of a scoring table. This evaluation scale ranged from 1 to 3, where 3 stood for excellent, 2 for average, and 1 for poor visibility.

Based on the results of our evaluation, T2-weighted MRI sequences were found to be more suitable for OAR delineation than T1-weighted ones, even without contrast agent administration. Correspondingly, two-and three-dimensional T2 fast-spin echo (FSE) sequences were selected to act as the gold standard throughout the project. To visually illustrate our findings, a contouring atlas was also compiled, practical for everyday use, ensuring more accurate and efficient OAR delineation.

3.1.2 Standardization of contouring

Interobserver variability is a phenomenon caused by the different expertise, training and approach of professionals addressing a certain clinical problem. Reducing this variability is important for achieving consistent, high-quality delineation of organs-at-risk and target volumes alike. A valuable method to reduce variability is through using well-built and effective contouring guidelines.

The last comprehensive CT-based guideline for OAR delineation in the head-and-neck (H&N) region was published in 2015. Due to the differing imaging modality, the need quickly emerged within the „Deep-Learning MR-only Radiation Therapy" project for a new, exclusively MRI-based contouring guideline. To address this need, technical details of MRI acquisition for treatment planning, required MRI sequences, and an up-to-date set of OARs accompanied by contouring recommendations were compiled. The work of our team consisted of the systematic review of the latest literature and discussions for a consensus on divergent points by representatives of the participating institutions.

The team collected MRI data from 7 healthy volunteers in a diagnostic setting and used the ECLIPSE treatment planning system (Varian Medical Systems, version 13.6) for delineating OARs on T2-weighted sequences. Contours were reviewed by 4 radiation oncologists and two senior experts before final approval. Definitive consensus was reached after multi-institutional review.

The results were consolidated into an atlas, including an expert case as well as the detailed morphological description and recommended organ boundaries for each OAR. Unfortunately, the point by point presentation of all the organs exceeds the frame of this thesis.

3.1.3 Use Artificial Intelligence (AI)

As presented in the earlier points, magnetic resonance imaging is becoming increasingly important in radiation therapy. Better visibility has, however, only minimal impact on the manual segmentation of organs-at-risk, a task that remains time-consuming and error-prone. This is particularly valid for the head-and-neck-region, containing 20-25 OARs requiring several hours to contour. Therefore, there is a growing need for automated segmentation methods for MRI, as most AI-based tools have traditionally been developed for CT.

Convolutional neural networks (CNNs) have shown great promise in improving image segmentation, and today can be regarded as the backbone of deep-learning (DL) based OAR and tumor segmentation algorithms.

Within the frame of "Deep-Learning MR-only Radiation Therapy", our medical team was responsible for the compilation of the above presented contouring guideline and took part in the evaluation of the interim results as well as the final contours produced by the algorithm. After reaching consensus on the organs-at-risk to be included in the project and their delineation, organ model development began. For this purpose, 86 T2-weighted MR images were selected from the RTMAC (Radiation Therapy—MRI Auto-Contouring) challenge and

the IXI dataset, while 45 sets - 24 healthy volunteers and 21 cancer patients - were provided by consortium partners. Using T2-weighted images was motivated by the image contrast that allows confident contouring of all types of organs, and being part of a standard clinical imaging protocol, the scanning process required no additional sequences and the result was adequate for tumor delineation as well.

A combination of 2D U-Nets for localization and 3D U-Nets for segmentation was used to create the models. The accuracy of the segmentation was assessed on the volunteer scans using both qualitative and quantitative methods.

Qualitative evaluation was performed by radiation oncologists from two independent institutions who reviewed the segmented contours and scored their clinical acceptability using a Likert scale. The scores ranged from 1 to 5; where 1 meant clinically unacceptable organ contours requiring major corrections and 5 stood for acceptable contours not necessitating any modifications.

The quantitative evaluation involved traditional metrics commonly used in the medical image segmentation domain: DSC, precision, recall, and Surface DSC scores.

According to the qualitative revision the lens, spinal cord, body, whole brain, eye, brainstem, and inner ear showed the best accuracy (>4). Moderate average score (3.7-4) was assigned to parotid gland, optic nerve, mandible, pituitary, and middle PCM, while the lowest scores (3-3.6) were assigned to chiasma, supraglottic larynx, lacrimal gland, oral cavity, glottic larynx, and inferior PCM, and superior PCM. The average Likert scores were in good agreement with average DSC scores for most of the organs.

These findings suggest that the software performs well for easily identifiable OARs, but faces challenges with organs that have unclear boundaries or complex shapes. Overall, the approach shows promise in reducing the time and variability involved in OAR segmentation.

3.2 What is the clinical impact of structure adaptation and replanning during postoperative radiochemotherapy of glioblastoma patients?

Adaptive radiotherapy (ART); the method of adapting the radiation plan to the anatomical changes occurring over the course of treatment may potentially improve local control, reduce toxicy, and enable dose escalation. While ART has been proven effective in treating head-and-neck or lung cancer, its application in intracranial tumors has received less attention. Recently, the utility of pre-radiotherapy MRI and monitoring changes in target volume have further been validated.

The treatment of glioblastoma involving post-surgery chemoradiotherapy with Temozolomide is well standardized, but various approaches exist for target volume delineation and dose delivery. The European Organization for Research and Treatment of Cancer (EORTC) recommends a "single-phase" approach consisting of 30x2 Gy to fixed target volumes. This school uses T2/FLAIR abnormalities selectively, only taking into account the ones that are more specific for tumor infiltration such as cortex and grey matter infiltration, mass effect or ventricular compression. On the contrary, the Radiotherapy and Oncology Group (RTOG) advocates for a two-step approach, with an initial larger brain area receiving 46 Gy, followed by the delivery of the remaining 14 Gy to a smaller field. The target volume delineation scheme of the MD Anderson Cancer Center (MDACC) also reflects a limited-margin approach, though the fractionation is slightly different. Furthermore, the concept is endorsed by the Adult Brain Tumor Consortium (ABTC) along with other US-based institutions, as recent trials have demonstrated that omitting T2-hyperintensity and reducing security margins does not result in inferior outcomes, but might mitigate late onset cognitive decline.

According to our institutional protocol, an MRI scan is performed after 40 Gy to assess the anatomical changes that have occurred during the first phase of the treatment, allowing for adjustments to the target volumes. The modified target volumes then receive the remaining 20 Gy.

In a previous pilot study, we demonstrated that good tumor response during chemoradiotherapy (CRT) had a significant impact on the disease outcome and repeated imaging-based replanning with target volume reduction resulted in improved overall survival ($p = 0.026$). Based on these findings, we expanded our investigation to a larger cohort and validated a simple 6-point evaluation system to assess key prognostic factors and facilitate decision-making based on interim MRI results, further enhancing the potential benefits of adaptive radiotherapy.

108 glioblastoma patients were selected in our retrospective study. The study population received adjuvant radiation therapy with or without concomitant chemotherapy at the Department of Oncotherapy, University of Szeged between July 2018 and March 2024. Informed consent was obtained from the participants and the study was approved by the National Ethic Committee/TUKEB, ethical approval ID: BM/17723–3/2024.

Patients were immobilized in supine position using 3-point individual thermoplastic masks. Planning CT was performed with slice thickness of 2.5 mm and coregistered with pre-and postoperative MRI scans. In 12 cases, amino-acid based PET/CT was also utilized. All the

patients had a preoperative brain MRI and underwent an immediate postoperative MRI (<48 h) following surgery. MRI scans were acquired on 1.5 T/3 T devices as per routine, according to institutional glioblastoma protocol. Gross tumor volume (GTV) was defined using gadolinium-enhanced T1-weighted scans and included visible macroscopic tumor on pre-and post-surgery MRI as well as the surgical cavity. The clinical target volume (CTV) was a 15 mm isotropic extension of the GTV, constrained at anatomical barriers and manually adjusted to overlap with the T2/FLAIR high signal intensity areas. The planning target volume (PTV) was a further 3 mm expansion of the CTV. All patients underwent repeated brain MRI at ⅔ of the chemoradiotherapy, and adjusted target volumes, namely GTV1 and PTV1 were defined. For the sake of simplicity and easier comparison, adapted CTV and PTV were merged into one volume called PTV1, this being a 10 mm extension of GTV1, necessarily adjusted to anatomical boundaries and pathology. All the MRI sequences that were primarily used were re-evaluated and taken into consideration during target volume adaptation. Cone-beam CT verification was conducted before each treatment session, and intensity-modulated radiation therapy (IMRT) was used throughout the study.

After chemoradiation, patients received systemic therapy according to the Stupp protocol, with follow-up including monthly onco-neurological exams and MRI every 3 months. The primary endpoint of the study was overall survival (OS), while progression-free survival (PFS) was also evaluated. Kaplan-Meier and Cox regression models were used for statistical analysis, with statistical significance set at $p < 0.05$.

The study analyzed real-world survival data with no patient selection biases. The overall survival (OS) for the entire cohort was 20.7 months, with disease-free survival (DFS) at 10.7 months. Patients with IDH1 wild-type tumors had a poorer prognosis, with an OS of 18.9 months and progression-free survival (PFS) of 9.2 months. On the other hand, those with IDH1 mutations had better outcomes, with an OS of 28.9 months and PFS of 18.1 months. Median follow-up time was 19.7 months.

Volumetric changes of the gross tumor volume and planning target volume were evaluated. Absolute tumor volume shrinkage, measured in cubic centimeters, showed a slightly stronger impact on survival compared to relative tumor size reduction, expressed as a percentage (HR: 1.009 vs. 1.007). When assessing PFS, absolute tumor volume change did not reach statistical significance ($p = 0.257$), while relative volume reduction demonstrated significant correlation with it($p = 0.049$).

In multivariate analysis, tumor volume change was the factor that played an independent role in the overall survival.

3.3 What conclusions can be drawn beyond target volume adaptation from the interim MR examination performed during the radiochemotherapy of glioblastoma patients?

MRI verification of the intracranial status during chemoradiotherapy may also provide insight into the biological behavior of the tumor. Within the frame of the research described in point 4.2; a distinct section was dedicated to the identification of radiomorphological features that may correlate with the latter. By interpreting the interim MRI with caution and necessary experience, useful conclusions can be drawn. If unfavorable tumor response is assumable on the images, or unambiguous progression is detected, precious time can be saved by modifying the radiotherapy or directing the patient towards second line systemic treatment or repeated surgery. Any of the listed salvage modalities are potentially eligible, since all are lacking high-level scientific evidence. Therefore, treatment choice must be made on an individual basis. Apart from evident radiological signs suggesting disease progression, we hoped to identify morphological features that may indicate resistance to chemoradiotherapy and might exert an effect on the overall outcome.

In addition to highlighting the clinical benefit of repeated MR imaging during CRT, we validated a simple 6-point evaluation system to assess key prognostic factors and facilitate adaptation to target volume changes. This structured algorithm aims to enhance the clinical decision-taking process based on interim MRI findings.

The patient pool, target volume definition, treatment course and statistical analysis were in every aspect identical to the scheme outlined in point 4.2. The interim MR scans were compared to the pre-radiotherapy images to assess the changes that occurred during the first phase of chemoradiation The evaluation algorithm analyzed the six following radiological features: midline shift, perifocal edema, contrast enhancement, ventricular compression, initial ventricular status and the presence or absence of new lesion(s) outside the planning target volume. In the first four cases, the dynamics of the parameters throughout the treatment were monitored, while initial ventricular status was only assessed on the pre-RT images, as the name suggests.

The presence of contrast enhancement, midline shift and perifocal edema on the pre-RT MR scans had no effect on overall survival and change in the two latter did not influence the outcome of the disease either. The initial ventricular status, however, demonstrated significant

correlation with the OS, as enlarged (HR: 1.56) and compressed (HR: 3.07) ventricles were associated with unfavorable prognosis. Beyond that, no change in ventricular compression over the course of radiotherapy corresponded to a hazard ratio of 2.53, while increasing compression was associated with a HR of 13.58. The control group was defined as the patient population with no ventricular compression on the pre-radiotherapy MRI.

Though predictable, the decrease in tumor enhancement also proved to correlate significantly with improved life expectancy. Increased enhancement on the repeated MRI was paired with a HR of 2.11, while no change in contrast uptake corresponded to a hazard ratio of 1.18, compared to the control group. When contrast enhancement was plotted against progression free survival (PFS), no significant difference was found between the control (decreased contrast enhancement on the repeated MRI) and stationary groups, but contrast uptake increase was associated with higher hazard (HR: 1.73).

In multivariate analysis, change in contrast enhancement and ventricular status played an independent role in the overall survival.

3.4 What impact does prostate-specific membrane antigen-based imaging have on the management of low-volume progressive prostate cancer?

Being the second most common malignancy among men worldwide, prostate cancer (PC) has been in the focus of research interest for several decades. One of the most important recent innovations is the widening palette of isotopic modalities, allowing for better results in prostate cancer diagnosis and treatment.

Prostate-specific membrane antigen (PSMA)-based positron emission tomography/computer tomography (PSMA-PET/CT) has been shown to be a highly accurate diagnostic method to replace traditional imaging modalities in primary staging as well as in restaging of patients with biochemical recurrence. Furthermore, it can also be utilized for target volume delineation, permitting the identification of biologically active lesions and metastases potentially overlooked by conventional imaging. The early detection of these oligometastatic lesions open the possibility of their elimination with effective stereotactic radiotherapy.

Fewer data exist on investigations with PSMA–single-photon emission computed tomography (PSMA-SPECT) radiopharmaceuticals, though it could be a reasonable and cost-effective alternative to PSMA-PET/CT. To the best of our knowledge, ours was the first study to investigate the role of 99mTc-PSMA SPECT/CT for radiotherapy planning.

The primary aim of our study was the integration of PSMA-based imaging in the personalized radiation therapy of prostate cancer patients and the evaluation of its impact on target volume definition for stereotactic radiotherapy in case of local recurrences and oligometastatic tumors. The study was approved by the Regional Committee for Human Medical Research Council (229/2017-SZTE).

Between November 2017 and October 2022, 363 PSMA-based examinations were carried out at the University of Szeged. Based on these examinations, 84 lesions of 64 patients were treated with stereotactic radiotherapy. Patient selection criteria were histologically verified prostate adenocarcinoma and clinical data suggesting local recurrence after radical prostatectomy (RP) or distant metastasis. Cases with multiple metastases and palliation were excluded, as well as frail patients unsuitable for curative SBRT or unwilling to cooperate.

For PSMA SPECT/CT data acquisition, mean activity of 668 ±95 MBq 99mTc-mas3-y-nal-k (Sub-KuE) was administered intravenously. Prior to imaging, patients were also given oral contrast material. Scans were performed on an integrated Mediso AnyscanTRIO whole-body SPECT/CT system 6 h after the administration of the radiopharmaceutical and data collection was completed by low-dose CT.

The PET/CT scans were performed on a GE Discovery IQ Gen 2 PET/CT System, and the acquisitions were carried out 90 min post-injection of 3.7 MBq/kg of intravenous [18F]fluoro-JK-PSMA((2S)-2-({{(1S)-1-carboxy-5-[(6-[18F]fluoro-2-methoxypyridin-3-yl)formamido]pentyl}carbamoil}amino)pentanedioicacid). Data collection was completed by a plain low-dose CT scan. In 2017, we started our work with SPECT-CT, and in 2022, we switched to PET/CT.

During patient preparation, the target region was positioned and immobilized with All-in-One (AIO) Solution, with an individual immobilization system and six-point thermoplastic mask fixation depending on the target area. Planning CT was carried out according to institution protocols on a Somatom Emotion 6 CT simulator with a slice thickness of 3 mm. Target volumes and organs-at-risk were delineated after image fusion in ARIA Oncology Information System with an additional review from a radiologist.

Radiation treatment plans were established using the Eclipse system (Varian Oncology Systems), and intensity-modulated radiation therapy was utilized. Prior to each treatment session, online and offline monitoring and data recording were performed by cone-beam CT.

Gross tumor volume definition was performed on the planning CT (GTVCT) by an experienced radiation oncologist at the Department of Oncotherapy, University of Szeged, taking into account earlier diagnostic CT or MRI scans as well. PSMA-based biological target volume (BTVPSMA) delineation was done independently on the axial slices of 18F-PSMA PET or 99mTc PSMA SPECT images at the Department of Nuclear Medicine by a skilled nuclear medicine and radiology specialist. BTVPSMA was then compared to GTVCT, and their difference was described both in cm3 and as a percentage. Comparison was enabled by the fusion of the two contours. Since the PSMA-based examination and the planning CT were performed in different body positions, differences in size and geometry may have occurred during image fusion.

For the topometric comparison of each tumor volume of interest (VOI), the Dice similarity coefficient (DSC) was calculated to measure the spatial overlap between the two contours. In the case of full overlap, the DSC is 1, whereas in full diversity, the DSC is 0.

PSA levels and conventional imaging (CT, MRI, and bone scintigraphy) were used for monitoring treatment effectiveness. In case of increasing PSA-levels and suspected osseal metastases on bone scan, additional PSMA-based imaging was performed.

The average age of patients was 66.6 years, with a BMI of 26.96 kg/m². The average Gleason score was 7.9, and all patients received androgen deprivation therapy. Additionally, androgen receptor and biosynthesis inhibitors (abiraterone, enzalutamide), as well as chemotherapy (docetaxel) were also utilized. Of the 64 irradiated patients, 14 cases were excluded from the comparative analysis due to registration bias. Therefore, only 70 of the total 84 target volumes were selected for intermodality comparison. The tumor volumes defined by PSMA imaging and conventional, anatomical modalities differed in 100% of cases. In the vast majority of cases (76%), PSMA-based imaging led to smaller target volumes compared to CT. The exact volumes were the following: GTVCT: 27.58 ±46.07 cm3 (0.44–258.2 cm3) and BTVPSMA: 16.14 ±29.87 cm3 (0.38–190.85 cm3). Intermodality difference (independent of which modality was higher or lower) was 15.04 ±23.20 cm3 (0.03–126.14 cm3), giving us a difference of 65.37% ±72.70% (1.36–545.31%). During geometrical analyses, DSC was 0.56 ±0.20 (0.07–0.85). The difference in the percentage of volumes was higher than 10% in 67 lesions, corresponding to 96% of all detected cancer manifestations.

In 47,15% (33 cases), both conventional imaging and PSMA-based methods demonstrated consecutively the same lesions. In 12,85% (9 cases), the radionuclide scan was able to rule

out the possibility of an eventual metastatic lesion suggested by anatomical imaging. And most importantly, in 40% (28 cases), the additional metabolic information provided by the PSMA-based imaging techniques enabled us to discover and successfully target metastases that remained hidden on the conventional diagnostic images.

Stereotactic treatment was performed for 84 lesions. In eight cases, local recurrence was treated, the half of which could only be detected by PSMA-based imaging. For 76 lesions, metastasis-directed radiotherapy was carried out: 46 osseal, 28 lymph nodes, one adrenal gland, and one cerebral metastasis were treated, the latter in postoperative setting.

PSA level test was performed in every case; the mean pre-RT PSA value being 23,09 ng/ml and the post-RT PSA level at 3 months after SBRT 11.19 ng/ml. Accordingly, the average magnitude of PSA-decrease was 11,9 ng/ml, roughly corresponding to a drop by 50%.

Three-month post-therapy PSMA-based imaging was performed in 14 cases (21.9% of the total) after radiation treatment, in which we observed a decrease or cessation of isotope uptake. Conventional imaging control was performed in 42 cases (65.6%) showing the following distribution: 22 (52.4%) - complete response, 14 (33.3%) - partial response, 4 (9.5%) - stable disease, and 2 (4.8%) - progressive disease.

4. Discussion

Modern imaging modalities play a pivotal role in contemporary radiation therapy planning, serving two key purposes: enhancing the protection of organs at risk and improving the accuracy of target volume delineation. The thesis investigates both domains in depth, with a particular focus on MRI-based strategies for OAR sparing and adaptive RT, as well as PSMA-based molecular imaging in prostate cancer management.

In the first section of the thesis, we proposed a set of strategies that offer optimized organ-at-risk definition for high-precision radiation therapy.

Precise delineation of OARs is a cornerstone of safe and effective radiation treatment, especially in anatomically intricate regions such as the head-and-neck. The findings emphasize that T2-weighted MRI sequences markedly improve OAR visibility compared to CT or T1-weighted MRI, thereby increasing the accuracy of contouring and reducing planning uncertainties. MRI-based planning has become a standard tool in several malignancies - including central nervous system, cervical, prostate, and head-and-neck cancers - and may eventually replace CT-based planning altogether. However, MRI-only

workflows require synthetic CT generation for accurate dose calculation, a method that has been validated in several studies.

To fully exploit these advantages, standardized contouring guidelines and consensus-driven protocols are essential. Without such frameworks, interobserver variability may undermine the advantages of MRI-based delineation. Given the growing number of clinical trials incorporating MRI-based RT planning, regular updates to contouring guidelines through multi-institutional collaborations are strongly recommended. Importantly, delineation strategies should always reflect clinical context, including disease stage, tumor volume, anatomical involvement, and therapeutic intent.

The integration of artificial intelligence into OAR delineation represents a transformative step forward. Convolutional neural networks have demonstrated performance comparable to human experts, even in challenging anatomical areas like the head-and-neck. AI has the potential to dramatically reduce contouring workload, minimize interobserver variability, and standardize delineation, thus improving reproducibility and efficiency in RT planning.

A key hypothesis tested in this thesis was that MRI-based adaptive RT has a beneficial impact on survival in glioblastoma and certain MRI features can serve as prognostic markers. This study represents one of the largest patient cohorts analyzed to date in this domain.

Adaptive RT in GBM leverages serial MRI scans to monitor dynamic anatomical changes, such as resection cavity shrinkage or tumor progression, allowing real-time modifications of the planning target volume. This approach enables a reduction of safety margins without compromising tumor coverage, thereby achieving substantial sparing of critical brain structures. Survival outcomes achieved with this margin reduction strategy are comparable to or better than those reported in the literature, underscoring its clinical safety and efficacy.

Morphological changes observed on interim MRI scans - including increased contrast enhancement, ventricular compression, and diminished absolute or relative tumor shrinkage - were identified as markers of poor prognosis. Recognition of these high-risk features may warrant closer imaging surveillance and earlier therapeutic intervention, potentially improving patient outcomes.

The study acknowledges certain limitations, including its single-institution, retrospective design, lack of a control cohort, and a sample size that may not capture subtle effects. Nonetheless, the findings provide compelling evidence supporting MRI-guided ART as a

viable, resource-efficient strategy for GBM. Prospective multicenter studies are warranted to validate these observations and establish standardized imaging-driven adaptation protocols.

The final section of the thesis examined the role of PSMA-targeted molecular imaging using SPECT/CT and PET/CT in defining stereotactic body radiotherapy target volumes for oligometastatic or recurrent prostate cancer. The results confirm that PSMA-based imaging enables lesion detection at very low PSA levels, often before abnormalities become apparent on conventional anatomical imaging. This early detection supports precise treatment planning and individualized metastasis-directed therapy.

In this study, 363 PSMA-based imaging procedures were analyzed, with approximately 20% contributing to SBRT planning. Volumetric comparisons revealed that gross tumor volumes defined by conventional imaging were often larger than biological target volumes determined by PSMA imaging. This discrepancy highlights a tendency of conventional modalities to overestimate target size and underscores the importance of multimodality imaging integration for accurate dose delivery.

PSMA PET/CT has already become a preferred modality for detecting biochemical recurrence and guiding PSMA-targeted radioligand therapy, while SPECT/CT can act as a cost-effective alternative. Comparative studies show that ^99mTc-PSMA SPECT/CT achieves diagnostic accuracy comparable to ^68Ga-PSMA PET/CT in selected patients, supporting broader accessibility of molecular imaging in prostate cancer management.

Moreover, PSMA theranostics, exemplified by ^177Lu-PSMA-617, represents a paradigm shift in prostate cancer treatment by combining diagnostic imaging and targeted radionuclide therapy. Recent phase III trials demonstrated that PSMA-directed therapy improves progression-free and overall survival without compromising quality of life in patients with advanced metastatic castration-resistant prostate cancer.

5. Conclusions

The results of this work demonstrate that modern imaging modalities significantly enhance the precision and personalization of radiation therapy. MRI-based contouring improves OAR delineation in complex anatomical regions, and adaptive MRI-guided planning in GBM patients allows dynamic treatment adjustments that spare healthy tissue without reducing tumor control. Identification of prognostic imaging biomarkers on interim MRI scans further refines risk stratification and follow-up strategies.

PSMA-targeted imaging enables earlier detection of metastatic or recurrent prostate cancer, leading to SBRT targeting and individualized MDT approaches. Both PET-and SPECT-based PSMA imaging were found to be effective for treatment planning, with SPECT/CT offering a practical, widely accessible alternative. Furthermore, PSMA theranostics exemplifies the integration of molecular imaging and targeted therapy, signaling a shift toward precision oncology in prostate cancer management.

Overall, this thesis highlights the transformative potential of advanced imaging technologies in radiation oncology. While retrospective analyses provide compelling evidence for their clinical utility, large-scale prospective and multicenter studies remain essential for validating these approaches and integrating them into standardized treatment protocols. With the rapid development of imaging technologies and AI-based automation, radiation therapy is poised to become increasingly precise, adaptive, and patient-centered.

6. Novel scientific results

Integration of MRI and AI for Improved OAR Delineation in Head-and-Neck Radiotherapy

The study demonstrated that the use of T2-weighted MRI sequences significantly enhances anatomical visibility in the head-and-neck region. Meticulous definition and standardization of structural boundaries facilitate more precise delineation of organs-at-risk. Moreover, the application of convolutional neural networks enables standardized and automated OAR definition, reducing interobserver variability and contouring time while maintaining accuracy.

Safety and Efficacy of MRI-Guided Adaptive Radiotherapy for Glioblastoma

The research confirmed that MRI-based target volume adaptation using reduced security margins during the chemoradiotherapy of glioblastoma is a safe and clinically feasible strategy. This approach leads to improved dose conformity to the dynamic tumor volume while sparing healthy brain tissue, thereby enhancing therapeutic ratio.

Identification of Prognostic MRI Biomarkers During Glioblastoma Radiochemotherapy

The interim MRI performed mid-treatment identified specific morphological features - compressed ventricles, increased contrast enhancement and limited tumor shrinkage - as predictive of poorer clinical outcomes. These radiological risk indicators may support early treatment intensification or closer follow-up strategies.

Clinical Utility of PSMA-Based Molecular Imaging for SBRT of Local Recurrence and Oligometastatic Prostate Cancer

The work demonstrated that PSMA-PET/CT and PSMA-SPECT imaging detect early biochemical recurrence and oligometastatic progression in prostate cancer with significantly higher sensitivity than conventional imaging. This enables precise target volume definition and supports the use of stereotactic radiotherapy to ablate limited metastatic lesions at an early stage of disease progression.

Establishment of Standardized Imaging and Contouring Protocols for Modern Radiation Oncology

The thesis contributed to the development and validation of imaging-based standardized protocols for OAR and target volume delineation as well as dynamic follow-up during the course of radiotherapy in different localizations. These protocols, supported by expert consensus and multi-institutional data, form a foundation for harmonized radiotherapy planning practices, enhanced accuracy and improved comparability in multicenter studies.