University of Szeged

Albert Szent-Györgyi Medical School

Doctoral School of Clinical Medicine

Modern Imaging Methods in Radiation Therapy Planning

Ph.D. Thesis

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Szeged

2025

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2. List of Publications

Viktor R. Paczona, Marta E. Capala, Borbála Deák-Karancsi, Emőke Borzási, Zsófia Együd, Zoltán Végváry, Gyöngyi Kelemen, Renáta Kószó, László Ruskó, Lehel Ferenczi, Gerda M. Verduijn, Steven F. Petit, Judit Olah, Adrien Cserhati, Florian Wiesinger, Katalin Hideghety: Magnetic Resonance Imaging−Based Delineation of Organs at Risk in the Head and Neck Region. *Advances in Radiation Oncology*, 2022, DOI: https://doi.org/10.1016/j.adro.2022.101042

IF: 2.3

SJR indicator: Q2

Vanda Czipczer, Bernadett Kolozsvári, Borbála Deák-Karancsi, Marta E. Capala, Rachel A. Pearson, Emőke Borzási, Zsófia Együd, Szilvia Gaál, Gyöngyi Kelemen, Renáta Kószó, **Viktor Paczona**, Zoltán Végváry, Zsófia Karancsi, Ádám Kékesi, Edina Czunyi, Blanka H. Irma, Nóra G. Keresnyei, Petra Nagypál, Renáta Czabány, Bence Gyalai, Bulcsú P. Tass, Balázs Cziria, Cristina Cozzini, Lloyd Estkowsky, Lehel Ferenczi, András Frontó, Ross Maxwell, István Megyeri, Michael Mian, Tao Tan, Jonathan Wyatt, Florian Wiesinger, Katalin Hideghéty, Hazel McCallum, Steven F. Petit, László Ruskó: Comprehensive deep learning-based framework for automatic organs-at-risk segmentation in head-and-neck and pelvis for MR-guided radiation therapy planning. *Frontiers in Physics*, 2023, DOI: https://doi.org/10.3389/fphy.2023.1236792

IF: 3.1

SJR indicator: Q2

Viktor R. Paczona, Zoltán Végváry, Gyöngyi Kelemen, Ágnes Dobi, Emőke Borzási, Linda Varga, Adrienne Cserháti, Angéla Csomor, Bence Radics, Sándor Dósa, Márton Balázsfi, Emese Fodor, Ferenc Borzák, Árpád Puskás, Zoltán Varga, Judit Oláh, Katalin Hideghéty: Magnetic resonance imaging in glioblastoma radiotherapy − beyond treatment adaptation. *Physics and Imaging in Radiation Oncology*, 2025, DOI: https://doi.org/10.1016/j.phro.2025.100754

IF: 3.4

SJR indicator: Q1

Linda Varga, Zsuzsanna Besenyi, Viktor R. Paczona, István Farkas, Szabolcs Urbán, Gábor Sipka, László Pávics, Zoltan Varga, Emese Fodor, Katalin Hideghéty, Judit Olah, Zoltán Bajory, Anikó Maráz: Prostate-specific membrane antigen-based imaging for stereotactic

irradiation of low-volume progressive prostate cancer: a single-center experience. *Frontiers in Oncology*, 2023,
DOI: https://doi.org/10.3389/fonc.2023.1166665
IF: 4.7
SJR indicator: Q2

3. List of Abbreviation

3D: three-dimensional

AI: artificial intelligence

ART: adaptive radiation therapy

BBB: blood-brain barrier

BTV: biological target volume

CBCT: cone-beam computed tomography

CR: complete response

CT: computed tomography

CTV: clinical target volume

CNN: convolutional neural network

CNS: central nervous system

DL: deep learning

DSC: Dice similarity coefficient

FSU: functional swallowing unit

GTV: gross target volume

H&N: head-and-neck

IMRT: intensity-modulated radiation therapy

MDT: metastasis-directed treatment

MRI: magnetic resonance imaging

OAR: organ-at-risk

PC: prostate cancer

PCM: pharyngeal constrictor muscle

PD: progressive disease

PET: positron emission tomography

PET/CT: positron emission tomography/computed tomography

PR: partial response

PSA: prostate-specific antigen

PSMA: prostate-specific membrane antigen

PSMA-PET/CT: prostate-specific membrane antigen positron emission tomography/computed tomography

PSMA-SPECT/CT: prostate-specific membrane antigen single-photon emission computed tomography/computed tomography

PTV: planning target volume

RP: radical prostatectomy

RTP: radiation therapy planning

SBRT: stereotactic body radiotherapy

SD: stable disease

SRT: stereotactic radiotherapy

SPECT: single-photon emission computed tomography

SPECT/CT: single-photon emission computed tomography/computed tomography

SRS: stereotactic radiosurgery

TV: target volume

VOI: volume of interest

4. Introduction

The idea of treating malignant tumors with the help of ionizing radiation can be traced back to the discovery of X-rays. Roentgen's innovation marks the birth of two independent, but due to the common origins closely related branches of medicine, radiology and radiation oncology.

Following the early decades characterized by two-dimensional X-ray based treatment planning, the invention of computed tomography (CT) was the first determining step towards the three-dimensional (3D), personalized radiation therapy that is today considered as the standard practice. Accordingly, planning CT performed in treatment position counts as the backbone of 3D radiation therapy planning worldwide. Technical development enabled the most spectacular progress of the past twenty years; the implementation of intensity-modulated radiation delivery resulting in highly selective treatment approaches (intensity-modulated radiation therapy; IMRT, stereotactic radiosurgery; SRS, stereotactic body radiotherapy; SBRT). These revolutionary irradiation methods require precise structure definition, which would not have become feasible without the simultaneous evolution of medical imaging, above all magnetic resonance imaging (MRI) and positron emission tomography (PET).

Certain areas of the human body, primarily the central nervous system (CNS), can only be visualized on MRI in enough detail to carry out sophisticated treatments such as adapted radiation therapy (ART), stereotactic radiosurgery or the repeated irradiation of a previously treated area of the brain. In other cases, the presence of residual malignancy or loci of early disease progression amenable for stereotactic ablative body radiotherapy can only be detected by radionuclide scanning.

One of the primary fields of application of modern imaging methods in radiotherapy (RT) is precise and reliable target volume (TV) definition. This enables safe escalation of daily doses into magnitudes that seemed to be unimaginable even in the near past. However, it has to be kept in mind that radiation therapy always requires a compromise between tumoricidal radiation and the tolerance of the neighbouring healthy tissues. Organ-at-risk (OAR) definition, the other pivotal aspect of radiation oncology can also be facilitated and standardized by high quality diagnostic images with or without co-registration to the planning CT scan.

5. Aims

The purpose of the research is to examine four domains of radiation oncology closely related to modern imaging methods, namely multiparametric MRI, prostate-specific membrane antigen-based imaging (PSMA-PET and PSMA-SPECT) and artificial intelligence (AI) assisted contouring. 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 software 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?

6. Methodology and Findings

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

In the era of individualized, precision radiation therapy, accurate organ at risk definition became more important than ever before. Though the high doses used for stereotactic radiotherapy (SRT) result in improved tumor control, they pose a bigger threat to the surrounding healthy tissues than conventional dosage. At the same time, regardless of the fractionation scheme, the reduction of radiation-induced side effects via enhanced OAR protection is one the principal objectives of modern radiation oncology.
The prerequisite of optimal healthy tissue sparing is reliable, accurate organ-at-risk delineation. Several strategies are utilized for this purpose, including better visualization of organs involving multimodal imaging, standardization of contouring through guidelines and the use of artificial intelligence. In the following section, we will examine each of the enumerated possibilities.

6.1.1. Better visualization of organs

Both traditionally and at the present time, the generally used imaging method for organ-at-risk contouring is computed tomography (CT). This modality provides sufficient soft tissue resolution and adequate organ demarcation in most localizations without the need for auxiliary image fusion. In certain cases, visibility is restrained by the anatomical properties of the given body region, such as the cranial cavity or the spine. Therefore, OAR delineation in the central nervous system has been predominantly carried out on MR images for decades. The significance of MRI has also increased in the delineation of the OARs of the head-and-neck (H&N) region, since the dose constraints of more and more delicate, small structures are taken into consideration during the treatment planning process.

The hegemony of CT is challenged by magnetic resonance imaging as the basic imaging method for radiation therapy planning as well. MRI-only radiotherapy has several clinical advantages, such as the avoidance of multiple imaging processes and exposure to ionizing radiation during imaging. Nevertheless, due to the more complex physical background, selecting and interpreting adequate sequences require more experience. Moreover, getting to know the specific MRI characteristics of the given OARs may take a longer time and more practice. In the future, owing to automated OAR delineation, this learning process will become needless, and errors due to human mistakes will be less likely to occur. With the

availability of such modalities, the need for a large number of accurate OAR contours in the H&N region, including subunits of larger organs and organelles, can be satisfied.

The Department of Oncotherapy, University of Szeged had the opportunity to participate in the multicentric project „Deep-Learning MR-only Radiation Therapy" brought to life by EIT Health. The consortium aimed to develop a software that can provide automatic OAR contours on high resolution T2 weighted magnetic resonance images. in the head and neck region.

The first step of the development required numerous precise, manually contoured expert cases. During this work phase, the review of multiple MRI sequences was carried out and compared based on the visibility of OARs, the sharpness of their margins and their demarcation from the surrounding tissues. Our findings were objectivized in a scoring table attached below **(Table 1.)**.

Organ	**T1w**	**T2w**	**CT**	**Remarks**
Parotid glands	2	3	2	Any diagnostic T2w MRI sequence is eligible for delineation purposes because the saliva content of the glands creates a well-visible contrast with the surrounding tissues
Submandibilar glands	2	3	2	Similar MRI morphology to the parotid glands
Mandible	2	2	3	Contouring the mandible on CT is easier owing to the sharp contrast between the hyperdense bone and the surrounding soft tissues. On T2w MRI, the cortical bone appears as a low signal intensity layer enveloping the inhomogeneous spongious bone
Supraglottic larynx	2	2	2	
Glottic larynx/glottic area	2	2	2	Non ossified cartilages appear with intermediate signal intensity on T2w images. Ossified cartilages are similar to bone (i.e., high signal central marrow

				and low signal cortical rim) [1]
Oral cavity	2	2	1	The visibility of the muscles of the floor of the mouth and palate is poor on CT; therefore, the cranial and caudal borders of the region is hard to define. The usage of coronal and sagittal MRI slices beside the axial plane is crucial to correctly define the craniocaudal and laterolateral extent of the oral cavity [2]
Pharyngeal constrictor muscles	2	3	1	The constrictor muscles are virtually not distinguishable on CT
Inner ear	1	2	2	The fluid content of both the cochlea and semicircular canals is discernible on T2w MRI images; it is surrounded by a narrow, hypointense zone, corresponding to the compact substance of the bony labyrinth
Eye (eyeball)	2	3	2	Greater contrast on T2 between the tunics of the eyeball (i.e., outer border of organ; hypointense), fluid (hyperintense), and tissues of the orbit
Lens	3	3	3	Well visible on T1 and T2
Optic nerve	3	3	2	
Optic chiasm	3	3	1	
Lacrimal glands	1	2	1	Similar MRI morphology to the parotid and submandibular glands
Brainstem	3	3	1	The demarcation of the organ from the liquor is clearly visible on T2w MRI. On these scans, the nigral substance appears as a longitudinal stripe of higher signal intensity compared with the

				neighboring red nucleus and pes pedunculi [3]
Spinal cord	2	3	1	Only the spinal cord proper is included in the contour, not the entire spinal canal. Contouring the spinal canal was performed mainly owing to the poor image quality and low contrast on native topometric CT scans [4]
Brain	3	3	2	
Pituitary gland	2	2	2	Thin MRI slices (thickness: 1 mm) with CT correlation is recommended for delineation purposes [5]
Thyroid gland	2	2	2	Similar MRI morphology to the parotid and submandibular glands
Brachial plexus	2	2	1	
Esophagus	2	2	2	Hyperintense to muscle on T2w images [5]
Sum	43	50	35	

Table 1.: The visibility of the OARs was evaluated on T1- and T2-weighted MRI sequences, as well as on CT. A scale ranging from 1 to 3 was used, where 3 stood for excellent, 2 for average, and 1 for poor visibility.

Based on the results of this evaluation, we found that T2-weighted MRI sequences are more suitable for OAR delineation than T1 sequences. Their richness in detail and the crisp margins of the neighboring anatomical structures even without the administration of intravenous contrast agent makes them more adequate for contouring purposes than T1-weighted sequences. More precisely, 2- and 3-dimensional, T2-weighted, fast-spin echo (FSE) sequences with sufficient geometric coverage to include all relevant OARs (ie, top of head to middle of neck) were selected to be the gold standard in our project. The T2 FSE sequences included 2-dimensional fast-recovery FSE, 2-dimensional PROPELLER (GE Healthcare, Waukesha, WI), and 3-dimensional CUBE (GE Healthcare, Waukesha, WI). Detailed

sequence parameters are outlined in **Table 2.** Additionally, a contouring atlas was compiled to visually illustrate our findings and to be used in daily practice.

	2-Dimensional T2 fast-recover, fast-spin echo	**2-Dimensional T2 PROPELLER**	**3-Dimensional T2 CUBE**
Magnetic resonance scanner model	GE DISCOVERY MR750w	GE SIGNA Artist	GE SIGNA Artist
Radiofrequency receive coil array	AIR RT Head&Neck	GEM Head&Neck	GEM Head&Neck
Main magnetic field strength, T	3.0	1.5	1.5
Bandwidth, kHz*	62.5	83.3	125
Repetition time, ms	11866	7624	2002
Echo time, ms	99.3	87.3	76.6
Echo train length	22	26	100
Scan time, s	332.6	229.1	259.0
Scan orientation	Axial	axial	sagittal
Field of view, mm2	300 × 300	300 × 300	340 × 340
Acquired	1.04 × 1.04	1.04 × 1.04	1.18 × 1.18

resolution, mm2†	

Table 2.: Scan parameters for T2-weighted sequences used for organ-at-risk delineation

From the point of view of tissue contrast, no significant differences were found between the tested sequences. However, 2-dimensional sequences are more sensitive to patient motion (swallowing, eye movements); thus, imaging artifacts are more likely to occur. This is the main reason why the volunteer scan included in the contouring atlas is a 3-dimensional Sagittal T2 CUBE sequence, although our atlas is applicable to any diagnostic T2-weighted MRI sequence. The reconstruction diameter was 350 mm, the pixel size 0.664 mm, and the spacing between slices 0.5 mm. The selection criteria for the atlas case included high resolution, good contrast, and lack of imaging artifacts.

6.1.2. Standardization of contouring

Interobserver variability is a naturally occurring phenomenon caused by the different expertise, training and approach of professionals addressing the clinical problem. Its reduction is highly desirable in order to achieve uniform, reproducible, high-quality OAR and target volume contours. One of the best ways to achieve this goal is the use of well-built, straightforward contouring guidelines.

The last comprehensive CT-based consensus guideline on OAR delineation in the 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 that aim, the technical details of MRI acquisition for treatment planning, reasonably required MRI sequences, and an up-to-date set of OARs accompanied by contouring recommendations were compiled, relying on the latest existing publications [6; 7; 8; 9; 10; 11; 12; 13]. Our method consisted of the systematic review of the latest literature and discussions for a consensus on divergent points by representatives of the participating institutions.

To create a gold-standard model for our concept, MRI data collection was performed from the H&N region of 7 healthy volunteers in diagnostic setting (supine position, dedicated H&N coil; **Table 2.**). The OARs were delineated using the ECLIPSE treatment planning system (Varian Medical Systems, version 13.6) in the axial, coronal, and sagittal planes on T2-weighted sequences. Every contour defined was revised by 4 radiation oncologists and

subsequently by 2 independent senior experts (H&N radiation oncologist and radiologist). After this 2-step revision, the final structures were presented to the consortium partners in Rotterdam, The Netherlands. A definitive consensus was reached after a multi-institutional review. As mentioned earlier, our findings and suggestions were also presented in the form of an atlas containing an expert case as well as the detailed morphological description and recommended organ boundaries for each OAR. Our suggestions are summarized in the following section:

Parotid glands

Contouring suggestions

The delineation of the external carotid artery and retromandibular vein was carried out in a few cases to precisely define the medial border of the organ and distinguish between vessels and the styloid process, as well as the muscles arising from the latter. An accessory parotid gland is sometimes present alongside the parotid duct, on the outer surface of the masseteric muscle that has to be included in the contour. Fatty infiltration/replacement of the secretory tissue may be present in patients of older age, which may make the outline of the organ more difficult to define [14]. This may also arise as a therapeutic side effect of previous irradiation. **Table 3.** shows the recommended anatomic boundaries for the salivary glands.

Organ boundaries	**Parotid glands**	**Submandibular glands**
Anterior	Masseteric muscle, mandibular ramus, pterygoid muscles	Posterior margin of mylohyoid muscle, with the deep process spreading above the mylohyoid muscle
Posterior	Sternocleidomastoid muscle and the posterior belly of the digastric muscle	Parapharyngeal space, great vessels of the neck
Medial	Styloid process, styloglossus, stylohyoid, and stylopharyngeal muscles	Superior: lateral surface of hyoglossus and partly mylohyoid muscles Middle: lateral surface of styloglossus and stylohyoid muscles, digastric

		muscle Inferior: lateral surface of the body of hyoid bone, pharyngeal constrictor muscles
Lateral	Platysma, subcutaneous tissue	Superior: medial surface of medial pterygoid muscle Middle: medial surface of the body of the mandibular bone Inferior: platysma, investing layer of deep cervical fascia, fat tissue
Cranial	Superior wall of the external auditory canal, mastoid process	Medial pterygoid muscle
Caudal	No distinct border, the organ gradually disappears in the fat tissue of the neck	No distinct border, the organ gradually disappears in the fat tissue of the neck

Table 3.: Anatomic borders of salivary glands

Submandibular glands

Contouring suggestions

Table 3. shows the recommended anatomic boundaries for the salivary glands.

Mandible

Contouring suggestions

The alveoli or teeth sockets of the mandibular corpus are still included in the contour, but not the teeth. We omitted the coronoid process from the contour, because its cranial border is hard to define univocally on axial MRI slices, and radiation necrosis affects primarily the body [15].

Supraglottic and glottic larynx

The upper part of the larynx is composed of the epiglottis, aryepiglottic folds, false vocal or vestibular cords, arytenoid cartilages, and mucosa coating them. Brouwer et al. [6] defined the inferior border of the supraglottis as the cranial edge of arytenoid cartilages. However, this

contradicts the fact that the vestibular cords form an integral part of the supraglottic larynx, because their origin and insertion is situated below the apex of the arytenoids. The pyriform sinus belongs to the hypopharynx and is excluded from the contour.

The glottic larynx is an anatomic subsite of the larynx, below the supraglottis and above the subglottis. According to the seventh edition of the American Joint Committee on Cancer staging manual [1; 16], the glottis contains the true vocal cords, including its anterior and posterior commissures. The overall thickness of the structure is approximately 10 mm in the horizontal plane.

Contouring suggestions

Table 4. shows the recommended anatomic boundaries of the laryngeal structures and the oral cavity.

Organ boundaries	Supraglottic larynx	Glottic larynx	Oral cavity
Anterior	Hyoid bone, pre-epiglottic space, thyroid cartilage [6]	Thyroid angle	Inner surface of superior and inferior dental arches
Posterior	Posterior pharyngeal wall	Inner surface of cricoid and arytenoid cartilages	Posterior border of soft palate and uvula, root of the tongue [6]
Medial	NA (lumen of larynx)		NA
Lateral	Inner surface of thyroid cartilage		Inner surface of dental arches, maxilla, and mandible
Cranial	Tip of epiglottis [6]	Caudal boundary of supraglottic larynx (i.e., arytenoids)	Mucosa of hard and soft palates

Caudal	1-2 slices below the appearance of arytenoid cartilages, individually. Thus, the false vocal cords fall within the borders of the structure	Clinically, it varies from 0-1 cm below the free level of the true vocal cord, extending inferiorly from the lateral margin of the ventricle [16; 17]; from a practical point of view, the disappearance of the thyroid angle is a good landmark	Anterior: mylohyoid muscle + anterior belly of the digastric muscle Posterior: root of the tongue and hyoid bone [6]

Table 4.: Anatomic borders of laryngeal structures and oral cavity

Oral cavity

Our contour includes the hard and soft palates, as well as the lingual tonsils, because their mucosa must be spared from an excessive dose of ionizing radiation. This consideration led us to an OAR contour that is somewhat larger than the oral cavity proper (i.e., cavity behind dental arches, excluding oral vestibule between lips and teeth) [2].

Contouring suggestions

Table 4. shows the recommended anatomic boundaries of the laryngeal structures and the oral cavity.

Pharyngeal constrictor muscles

The muscles of the pharynx can be divided into an outer circular and inner longitudinal layer. The former includes the superior, middle, and inferior pharyngeal constrictor muscles (PCM), responsible for propelling the bolus into the esophagus.

Contouring suggestions

Apart from the pharyngeal constrictor muscles, various other structures play an indispensable role in the process of swallowing. These structures are the muscles of the floor of the mouth, thyrohyoid muscle, posterior digastric/stylohyoid muscle complex, longitudinal pair of the pharyngeal constrictors, hyoglossus/styloglossus complex, genioglossus muscle, and muscles responsible for tongue motion (intrinsic tongue muscles, referred to collectively as functional swallowing units [FSUs]) [8; 18].

The 3 major physiological roles of these structures are tongue motion, tongue base retraction, and hyolaryngeal elevation. The usefulness of FSU delineation in daily routine is a source of debate due to the extreme workload demand and eventual overlaps with other sensitive areas, such as the oral cavity and certain laryngeal structures. The contouring process might be facilitated in some cases by the usage of automatic OAR segmentation, as stated in the article by the MD Anderson Head and Neck Cancer Symptom Working Group [19]. To the best of our knowledge, neither dose constraints nor exact fields of implication have been defined for these structures. **Table 5.** shows the recommended anatomical boundaries of the pharyngeal constrictor muscles.

Organ boundaries	**Superior pharyngeal constrictor muscle**	**Middle pharyngeal constrictor muscle**	**Inferior pharyngeal constrictor muscle**
Anterior	Caudal tip of the pterygoid plates [12]	Hyoid bone, root of the tongue [12]	Soft tissue of the larynx [12]
Posterior	Longus capitis and colli muscles (ie, prevertebral muscles [12; 20])		
Medial	Not applicable (pharyngeal lumen) [12]		
Lateral	Medial pterygoid muscle [12], parapharyngeal space	Greater horn of hyoid bone [12]	Superior horn of thyroid cartilage [6; 12]
Cranial	Caudal tip of pterygoid plates [12; 21]	Cranial edge of C3 vertebra [12]	First slice caudal to the caudal edge of hyoid bone [12]
Caudal	Caudal edge of C2 vertebra [12]	Caudal edge of hyoid bone [12; 21]	Caudal edge of arytenoid cartilages [12]

Table 5.: Anatomical borders of pharyngeal constrictor muscles.

Inner ear

Contouring suggestions

The cochlea and vestibular system have been delineated separately in some cases. However, due to the proximity of the 2 structures, we defined the inner ear as 1 single OAR, per the practice of Sun et al. [22].

Eye (eyeball)

Contouring suggestions

A meticulous delineation of the fluid filling the anterior chamber and vitreous body can be carried out. The extension of this contour by 1 mm (corresponding to outer layers of the eye) in all dimensions may also lead to an adequate OAR contour.

Lens

Its overall diameter typically ranges between 9 and 10 mm, with a thickness of approximately 4.5 mm, although this varies with age.

Optic nerve

The orbital portion of the nerve is usually between 20 and 30 mm in length and 2 to 5 mm in thickness, while the intracranial segment is approximately 10 mm long.

Contouring suggestions

The optic nerve can be confused with the rectus superior and inferior muscles. The muscles have a flat, shorter appearance, and the nerve is slimmer and longer. The meningeal layers unsheathing the nerve have also been included in the contour.

Optic chiasm

The overall size of the structure is usually 14×8×5 mm [9].

Contouring suggestions

The x-shape is not always visible on 1 single section, especially when operating with small slice thickness (≤1 mm). In such cases, the fibers of the optic nerve entering the chiasma and the axons forming the optic tract can be delineated on consecutive MRI slices. The pituitary stalk and internal carotid arteries may be delineated additionally to help distinguish between the chiasm and the surrounding structures.

Lacrimal gland

Contouring suggestions

The easiest way to find the lacrimal gland is to look for an approximate 15×20×5 mm area with low signal intensity above the lateral rectus muscle and laterally to the superior rectus muscle [23]. The volume of the lacrimal gland is usually around 0.6 cm^3 with slight right-sided dominance [24; 25].

Brain stem

The rostral continuation of the spinal cord can be divided into 3 levels in rostrocaudal order. The lowermost one-third, the medulla oblongata, has no well-determined inferior border, because transition from the spinal cord to the brain stem is continuous. To overcome this uncertainty, we commenced the contouring of the medulla at the level where the tip of the odontoid process first appears in concordance with CT-based guidelines [6]. The rostral limit of the mesencephalon, or midbrain (uppermost third of brain stem) is similarly ill-defined. A recent study on OAR contouring in the central nervous system using MRI technique suggested the delineation of the midbrain until the nigral substance disappeared [9]. The previously mentioned CT-based consensus guideline defines the cranial beginning of the midbrain as the bottom section of the lateral ventricles. We do not entirely agree with this approach, because the temporal horns of the lateral ventricles appear already at the level of the pontomesencephalic junction and therefore, more caudally than the expected organ margin. We found that the central part of the lateral ventricle is a more reliable landmark for the upper border of the mesencephalon. Another study by Beddok et al. [26] suggested placing the brain stem between the upper- and lowermost endpoints of the Sylvian aqueduct, a cerebrospinal fluid–filled narrow cavity that is well visible in the sagittal plane.

Contouring suggestions

The average volume of the brain stem is expected to fall between 27 and 43 cm^3 [27].

Spinal cord

The spinal cord is the caudal continuation of the brain stem, extending from the lowermost section of the medulla to the intervertebral disc between the first and second lumbar vertebrae [28].

Brain

The brain contour includes the brain stem, diencephalon, cerebellum, hemispheres of the telencephalon, smaller cerebral vessels, and cerebrospinal fluid. Our approach treats the brain

stem as a subunit of the OAR brain; therefore, the lowermost section of these 2 is located in an identical plane.

Contouring suggestions

The contouring of this organ mainly involves following the outline of the cerebrospinal fluid in the subarachnoid space.

Pituitary gland

Contouring suggestions

The hypophysis rests in a small, saddle-shaped, bony nest of the sphenoid bone, the sella turcica. The organ itself is usually well visible on any diagnostic T2-weighted MRI sequences, although the sella itself is difficult to find. On CT scans with an appropriate bone window, the clinoid processes, dorsum and tuberculum sellae, important anatomic landmarks bordering the hypophyseal fossa, and thus, hypophysis, can be localized.

Thyroid gland

The size may vary on a wide range, but the average anteroposterior diameter of the organ usually falls between 13 and 28 mms, with a length of 40 to 60 mm. The volume of the OAR is 12 to 18 mL in the male and 10 to 15 mL in the female population [29; 30].

Brachial plexus

Contouring suggestions

The recommended anatomic boundaries for the brachial plexus are included in **Table 6.**

Roots	Trunks	Divisions, cords
First, the intervertebral foramina between C_4-C_5 and T_1-T_2 should be identified [31; 32]. Of note, cervical spinal nerves emerge above their corresponding vertebrae, which is why the fifth cervical spinal nerve is	The next step is delineating the trunks of the brachial plexus in the scalene hiatus [31; 32]. The anterior and middle scalene muscles may also be contoured to better understand anatomic	The last 2 portions of the brachial plexus are defined as the posterior part of the subclavian and axillary neurovascular bundle, below the insertion of the middle scalene muscle and the sternal extremity of the clavicle [31; 33]. A 5-mm paint tool thickness is recommended for the delineation of the organ at risk

found above the fourth cervical vertebra. relations.	[32; 33]. Furthermore, Van der Velde et al suggested adding a margin of 4.7 mm around this brachial plexus contour to achieve full coverage of organ-at-risk and anatomic variants [34].

Table 6. Anatomic borders of brachial plexus. The course of the plexus can be divided into 4 distinct portions, each related to characteristic anatomic landmarks.

Oesophagus

Starting at the level of the sixth cervical vertebra, the thumb-thick food pipe interconnects the pharynx with the cardia of the stomach, and rests on the vertebral bodies, just behind the larynx and trachea [5].

Contouring suggestions

Between the ventral trachea and dorsal esophagus runs the shallow tracheoesophageal groove, which contains the recurrent laryngeal nerve. The sparing of this nerve may be desirable to prevent late-onset radiation-induced neuropathy [35; 36].

6.1.3. Use of Artificial Intelligence (AI)

As presented in the previous sections, magnetic resonance imaging is increasingly used for cancer diagnosis and treatment due to its superior soft-tissue contrast compared to CT, even without intravenous contrast agent. Despite the improved image quality, manual segmentation of organs-at-risk is still a time-consuming task and often suffers from large intra-and inter-observer variability. This is particularly the case in the head and neck region, where the number of organs-at-risk can be as high as 20-25, requiring 2-3 hours of manual contouring. Therefore, it is highly desired to develop accurate and reliable methods to automatically segment organs on MR images – a novelty, since most of the AI-based OAR segmentation tools are available for CT only.

During the past decade, convolutional neuronal networks (CNNs) have demonstrated spectacular results for image segmentation and accordingly, have now become the method of choice for deep-learning (DL) based automatic OARs and tumor segmentation with the prospect of shortening labor-intensive manual delineation and reducing intra- and interobserver variability [37–45].

Within the framework of “Deep-Learning MR-only Radiation Therapy”, our medical team was responsible for the compilation of the contouring guideline that served as gold standard throughout the project. Additionally, our physicians took part in the evaluation of the interim results and the final contours produced by the algorithm.

The project highlighted particular points of cooperation between physicians, data scientists and other information technology experts working for the same goal but approaching the issues from different perspectives.

After reaching consensus on the organs-at-risk to be included in the project and their delineation, organ model development could begin. For this work phase, a combination of public and private datasets was used; a total of 86 T2-weighted MR images originated from the RTMAC (Radiation Therapy—MRI Auto-Contouring) challenge and the IXI dataset, while 45 sets were provided by consortium partners. Out of these scans, 24 were acquired for protocol tests on healthy volunteers, and 21 scans were from cancer patients, prospectively collected for this project. Using T2 images as input 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.

The proposed method uses 2D U-Nets for localization and 3D U-Net for segmentation of the various structures. As mentioned before, the models were trained using public and private datasets, but evaluation was exclusively carried out on the latter.

The accuracy of the organ segmentation models was evaluated on the private test cases in quantitative and qualitative ways. One possible way to evaluate an MR-based organ auto-contour is to compare it with CT-based manual- or auto- contour after registration. However, in such cases the registration can introduce small contour mismatch that is measured as segmentation error. Furthermore, some of the organs are better visible on MR which allows a more precise definition of the ground-truth. In an MR-only workflow, where synthetic CT is generated from MR scan, there is no CT available. In this work the evaluation was based on the T2-weighted MR image without incorporating other (MR or CT) scans.

Qualitative evaluation

Radiation oncologists from two independent institutions reviewed the contours and evaluated them using Likert scores.

The Likert score was defined to reflect the clinical usability of the auto-contour as presented later. This scoring provides more information compared to the binary (acceptable/unacceptable) classification, where small differences can get lost in the reviewing process. The Likert scores were defined as follows:
Score 1: clinically unacceptable contour requiring complete recontouring (e.g., due to wrong organ localization or severe under-or over-segmentation)—considered as failed segmentation.
Score 2: clinically unacceptable contour requiring significant correction and/or recontouring (e.g., on several slices, which would take a long time)—considered as failed segmentation.
Score 3: clinically unacceptable contour that can be used for radiation treatment after some correction, which requires significantly less time than recontouring—considered as successful segmentation as it has clinical value.
Score 4: clinically acceptable contour with minor, optional corrections. This option was introduced to handle inter-operator variability and individual preferences.
Score 5: clinically acceptable contours, no modifications required.
Additionally, a contour was rated N/A when the organ was not considered relevant from radiation therapy's point of view. This rating covers scenarios when the contour accuracy cannot be assessed (due to insufficient image quality, incomplete organ coverage) or the contour was not considered as an OAR (tumor infiltration, artificial eye lens).

Quantitative evaluation

The auto-segmentation results were also evaluated using common quantitative metrics that are widely used in the medical image segmentation domain: DSC, precision, recall, and Surface DSC scores. Since this part of the evaluation process did not involve any input from the clinical partners, we do not go into further details.

According to qualitative revision performed by two independent institutions, 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.

It can be concluded that the software performed outstandingly well in case of sharply demarcated and/or large-sized OARs. The organs that received lower scores were the ones that pose a challenge for living observers as well, thus truly mimicking human intelligence.

The reason behind the difficulty are indistinct margins (PCMs), small size (lacrimal gland), spatial variability (optic chiasm) or the combination of all of these factors (laryngeal structures).

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

6.2.1. Introduction

Adaptive radiotherapy (ART), the method of adapting the radiation plan to the anatomical changes occurring over the course of treatment [46], is gaining ground steadily in personalized radiation oncology. This approach may allow improved local control, reduced toxicities [46] and eventually dose escalation in certain tumor localizations. Its usefulness has been confirmed in the treatment of head-and-neck, lung and prostate cancer [47]. Interestingly, in the past, less emphasis had been placed on its implication in the radiotherapy of intracranial tumors. Recently, the utility of pre-radiotherapy MRI and monitoring changes in target volume have further been validated [48], [49].

The standard treatment for glioblastoma is post-surgery chemoradiotherapy with Temozolomide, a radiation-enhancing cytostatic agent. However, different approaches are employed for target volume delineation and dose-delivery. The “single-phase” approach recommended by the European Organization for Research and Treatment of Cancer (EORTC) and endorsed by the latest ESTRO-EANO guideline [50] consists of a 30x2 Gy external beam radiotherapy treatment course. According to this approach, the initially defined target volumes remain unaltered (gross tumor volume − GTV, clinical target volume − CTV, i.e. GTV plus a security margin of 5–15 mm, planning target volume − PTV; CTV plus a margin of 0–5 mm) throughout the treatment. This method recommends the selective use of T2/FLAIR abnormalities as some are more specific for tumor infiltration (eg. cortex and grey matter infiltration, mass effect or ventricular compression) than others (eg. oedema following white matter tracts and respecting the cortex) [50]. In contrast, the two-step treatment proposed by the Radiotherapy and Oncology Group (RTOG) begins with the irradiation of a larger brain area (GTV1, CTV1, PTV1) up to 46 Gy, followed by the delivery of the remaining 14 Gy to smaller volumes (GTV2, CTV2, PTV2) [51]. Lately, numerous US-based institutions as well as the Adult Brain Tumor Consortium (ABTC) also advocate for a limited-field approach. Recent trials have shown that omitting T2 hyperintensity and reducing margin expansions does not result in inferior outcomes or alter patterns of failure. [52; 53]. The target volume delineation and fractionation scheme of the MD Anderson Cancer Center (MDACC)

reflects this limited-margin approach. At the initial phase, a dose of 40 Gy is delivered, followed by a sequential boost of 20 Gy with volume reduction [53]. The motivation to reduce treatment volumes stems from the goal of minimizing late effects, such as cognitive decline and radiation-induced lymphopenia [54], [55]. Given the trend of decreasing target volumes over the decades, it is imperative to enhance definition accuracy and adapt radiation delivery to the changes that occur during the treatment.

Our institutional protocol is closely aligned with the RTOG scheme but includes two significant differences. First, though the course of treatment is also split into two phases, the transition occurs at 40 Gy rather than 46 Gy. Second, after the first 40 Gy, a repeated MRI scan is performed to assess the anatomical changes that have occurred during the initial phase of the treatment, allowing for adjustments to the target volumes. The modified target volumes then receive the remaining 20 Gy.

During treatment delivery, ionizing radiation induces an inflammatory response in the endothelium of small blood vessels [56], resulting in temporarily increased vascular permeability and contrast media extravasation [57]. Since blood–brain barrier (BBB) is not present in the blood vessels of the tumor [58], areas containing cancer cells in low volume and tumorous neovasculature may become discernible following radiation exposure, as these vessels tend to let through more contrast agent in comparison to the healthy brain tissue with functional BBB.

In a previous pilot study [59] conducted at our Department, we demonstrated that good tumor response during chemoradiotherapy (CRT) had a significant impact on the disease outcome. Importantly, repeated imaging-based replanning with target volume reduction resulted in improved overall survival ($p = 0.026$). These findings prompted further investigation. Consequently, a larger cohort of patients was enrolled, and Gadolinium-enhanced interval imaging was applied.

6.2.2. Materials and methods

108 consecutive patients with histologically verified glioblastoma 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. All the patients had a preoperative brain MRI and underwent an immediate postoperative MRI (<48 h) following surgery. Informed consent was obtained

from all the participants. The study was approved by the National Ethic Committee/TUKEB, ethical approval ID: BM/17723–3/2024.

Target volume delineation and treatment planning: All enrolled patients were immobilized in supine position using 3-point individual thermoplastic masks. Planning CT was performed on a GE DiscoveryTM 590 RT scanner with slice thickness of 2.5 mm. Pre-and postoperative MRI scans were coregistered to the planning CT, and in 12 cases amino-acid based PET/CT was also utilized. All MRI scans were acquired on 1.5 T/3 T devices (GE SignaTM Artist 1.5 T, GE DiscoveryTM MR750w GEM), as per routine, according to institutional glioblastoma protocol (for details, see the supplementary material). Operative bed and eventual macroscopic tumor were defined using gadolinium-enhanced T1-weighted scans, while for the nonenhancing portion T2-and/or FLAIR sequences were taken into consideration. Gross tumor volume included visible macroscopic tumor on pre-and post-surgery MRI as well as the surgical cavity. To obtain the clinical target volume, GTV was extended by 15 mm in all dimensions, constrained at anatomical barriers (bone, falx, ventricles, visual pathways/optic chiasm, cerebellar tentorium and brainstem). CTV was manually adjusted to overlap with the T2/FLAIR high signal intensity areas supposedly containing viable tumor cells. The planning target volume was a further 3 mm expansion of the CTV, accounting for eventual positioning uncertainties. All patients underwent repeated brain MRI at ⅔ of the chemoradiotherapy.

Adjusted target volumes, specifically GTV1 and PTV1 (with PTV1 being a 10 mm extension of GTV1, necessarily adjusted to anatomical boundaries and pathology), were defined. The 10 mm adaptive GTV-PTV margin was inspired by the two-step guideline of the American Brain Tumor Consortium (ABTC) [60]. This workgroup recommends the utilization of a 5 mm GTV-CTV extension for tumor boost, and a further 3–5 mm set-up margin to obtain the planning target volume. However, for the sake of simplicity and easier comparison, adapted CTV and PTV were merged into one volume called PTV1 (i.e. 5 mm for CTV1 + 5 mm for PTV1). When performing the target volume adaptation, all the MRI sequences that were primarily used were re-evaluated and taken into consideration. Based on this interim study, the new contours were created on the initial planning CT, following CT-repeated MRI image fusion.

Prior to each treatment session, cone-beam CT image verification was performed. IMRT planning (VMAT) was exclusively used throughout the study.

After chemoradiation patients received systemic therapy according to the Stupp regimen [61]. The follow up consisted of a monthly onco-neurological examination and brain MRI every 3 months.

Statistical analysis: The primary endpoint of our study was overall survival (OS), defined as the period between the histopathological confirmation of the malignancy and the date of the patient's death. In addition, progression free survival (PFS) was also investigated in certain cases, i.e. the time between the histopathological confirmation of the tumor and the detection of recurrence.

The Kaplan-Meier method was utilized in the analysis of categorical variables. If statistical significance was found, Cox proportional hazard regression models were also employed for the given variables, as well as for all the continuous values.

Statistical analysis was conducted using the SPSS statistical analysis software package (version 20; IBM, Armonk, NY, USA). Statistical significance was set at a threshold of $p < 0.05$. The software used for the graphical representation of our findings was SRplot (https://www.bioinformatics.com.cn/srplot).

6.2.3. Results

Patient characteristics are summarized in **Table 7 and 8.**

Characteristic	
Gender	
- Male	66
- Female	42
Age (years)	55.6 [23–78][a]
Histology	
- Glioblastoma (IDH1 Wild-Type)	89
- Astrocytoma Grade 4 (IDH1 Mutant)	19
Type of surgery	
- Biopsy	9

- Partial resection	57
- Gross tumor resection	42
Time interval between surgeryand start of CRT (days)	29.5 [7–61]
Karnofsky performance status prior to CRT	
- > 60 %	101
- ≤ 60 %	7
MGMT promoter methylation status (available in 83 cases)	52

[a]Average, minimum and maximum in square brackets

Table 7.: The numbers indicate the number of patients, if not specified otherwise.

Therapeutic lines	
Therapy	
- Chemoradiotherapy	108
First line of treatment	
- Temozolomide monotherapy	
Number of recipients	87
Average number of cycles	11.7 [1–72][a]
Second line of treatment	
- Bevacizumab therapy	
Number of recipients	41
Average number of cycles 16.9	16.9 [2-66]
Third line of treatment	

- Lomustine therapy Number of recipients Average number of cycles	 9 8.2 [1-16]
Reoperation	
- Repeated surgery following chemoradiotherapy	3
- Repeated surgery following progression on Temozolomide	19
- Repeated surgery following progression on Bevacizumab	6
Reirradiation	
- Repeated irradiation following progression on Temozolomide	12
- Repeated irradiation following progression on Bevacizumab	8

[a]Average, minimum and maximum in square brackets

Table 8.: The numbers indicate the number of patients, if not specified otherwise.

This study population represents real-world data, with no patient selection throughout the inclusion period. The overall survival (OS) for the entire cohort was 20.7 months, and the disease-free survival (DFS) was 10.7 months. In case of IDH1 Wild-Type tumors, the OS was 18.9 months and the PFS 9.2 months. Patients with IDH1 mutation had better prognosis, i.e. the OS was found to be 28.9 months and the PFS 18.1 months.

Median follow-up time was defined as the period between the last day of CRT and the date of the patient's death, or his/her last visit. According to this train of thought, the median follow-up time was 19.7 months.

Volumetric changes of the gross tumor volume and planning target volume are summarized in **Table 9.**

Target volume	Initial volume (cm^3)	Adapted volume (cm^3)	Absolute volume change (cm^3)	Relative volume change (%)
GTV	61.4 [3.8-170.9][1]	45.3 [0-206.8]	-16.2 [-115.3-115.5][2]	-24.5 [-100-258.9]
PTV	347.1 [109.1-811.3]	260 [39.2-582]	-79.2 [-490.5-182.9]	-22.9 [-72.9-90.6]

[1]Average, minimum and maximum in square brackets

[2]Minus (-) sign signifies volume shrinkage

Table 9.: Volumetric changes of the gross tumor volume and planning target volume

Both absolute and relative tumor volume changes had a significant influence on disease outcome. Absolute 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). However, when assessing PFS, absolute tumor volume change did not reach statistical significance ($p = 0.257$). In contrast, relative volume reduction demonstrated significant correlation with PFS ($p = 0.049$), underscoring its potential prognostic value.

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

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

6.3.1. Introduction

Beyond treatment adaptation, a further potential benefit of MRI verification of the intracranial status during chemoradiotherapy is that information can be obtained on 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 (i. e. new lesion outside the radiation field) is detected, precious time can be saved by modifying the radiotherapy (i.e. additional stereotactic irradiation of the new lesion) or directing the patient towards second line systemic treatment or repeated surgery. It needs to be noted that any of the listed salvage modalities are potentially eligible. However, since all are lacking high-level scientific evidence, treatment choice must be made on an individual basis. Apart from evident radiological signs suggesting disease progression, we hope 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.

6.3.2. Materials and methods

Patient pool, target volume definition, treatment course and statistical analysis were in every aspect identical to the scheme outlined in points 4.1.2. and 4.1.3. Beside target volume adaptation, the repeated MRI scans were also compared to postoperative, pre-radiotherapy images to assess the changes that occurred within the cranial cavity during the first phase of chemoradiation. For this purpose, a six-point evaluation system was established, which can be seen in **Table 10.** and **Table 11.**

Radiological feature	**Not present[1]**	**Present, no change[2]**	**Increase[2]**	**Decrease[2]**
Midline shift	47	20	3	38
Perifocal edema	15	20	14	59
Contrast enhancement	2	25	40	41
Ventricular compression	62	22	2	22

[1]On	the	pre-RT	MRI
[2]On	the	interim	MRI

Table 10.: The numbers indicate the number of patients

Radiological feature	
Initial ventricular status	
- Normal	51
- Enlarged	30
- Compressed	27
New lesion outside PTV	
- Yes	7
- No	101

Table 11.: The numbers indicate the number of patients

6.3.3. Results

The presence of contrast enhancement, midline shift and perifocal edema on the pre-RT MRI scans had no effect on the overall survival at all. 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. A similar tendency was observed if change in ventricular compression was compared to overall survival. No change throughout the radiotherapy corresponded to a hazard ratio of 2.53. An even more dramatic result was obtained if ventricular compression increased during the treatment, as this phenomenon 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 found to pair 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. Similar tendency was observable when contrast enhancement was plotted against progression free survival (PFS). In this case, no significant difference was shown between the control (decreased contrast enhancement on the repeated MRI) and

stationary groups, but contrast agent uptake increase was associated with higher hazard (HR: 1.73).

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

6.4. How can prostate-specific membrane antigen-based imaging be used for stereotactic irradiation of low volume progressive prostate cancer?

6.4.1. Introduction

Prostate cancer (PC) is the second most common malignancy among men worldwide [62]. Its treatment has vastly improved due to adjuvant androgen deprivation treatment and the increased efficacy of radiotherapy [63]. Recently, as a consequence of the new isotopic modalities, the accuracy of diagnosis and treatment has continued to ameliorate.

An increasing number of studies prove that prostate-specific membrane antigen (PSMA)-based positron emission tomography/computer tomography (PET/CT) provides excellent accuracy and can be a suitable replacement for conventional imaging methods (CT and bone scintigraphy) in primary staging, as well as in restaging of patients with biochemical recurrence. PSMA-based molecular imaging is emerging as the most promising tool in this field [64]. The early detection of oligometastatic lesions over all other imaging modalities open the possibility of their elimination with effective stereotactic radiation.

There is growing interest in using PSMA-based imaging in gross target volume delineation for radiation therapy planning since molecular imaging enables the delineation of the biologically active tumor based on increased PSMA expression on specific information essential for effective treatment. It also allows the potential identification of small lymph nodes and small bone or hidden soft tissue metastases, missed by conventional CT and magnetic resonance imaging. Initial studies comparing multiparametric MRI and PSMA-PET/CT in defining gross tumor volume have shown that GTV measured by PET is significantly larger than that determined by MRI. However, MRI was later observed to underestimate the actual tumor volume. (Simon K.B. Spohn, Anca-L. Grosu: Impact of PSMA PET on Radiation Oncology Planning, Seminars in Nuclear Medicine, 2025)

Although PSMA-PET tracers have extensively been investigated and an increasing number of studies prove the efficacy of PSMA-PET, fewer data exist on investigations with PSMA–single-photon emission computed tomography (SPECT) radiopharmaceuticals. Several studies have demonstrated that 99mTc-PSMA-SPECT/CT could be a reasonable and cost-

effective alternative to PSMA-PET/CT [65; 66; 67; 68]. To the best of our knowledge, this is the first study to investigate the role of 99mTc-PSMA SPECT/CT for radiotherapy planning.

In an earlier pilot study, we analyzed data from 19 patients. In 52.6% (10 cases), the PSMA-SPECT/CT revealed a more advanced disease than conventional imaging modalities, and in 15.8% (three cases), osseal and/or lymphatic metastases suggested on CT examination could be excluded. The target volume was unaffected by the PSMA-SPECT/CT findings in only 31.6% (six cases). Definitive radiotherapy was carried out in 15 cases (78.9%). In four cases (21.1%), we had to opt for systemic treatment due to disseminated disease. If only conventional imaging techniques were used to define the target volume, the volume would be on average 2.2 times larger (1.3–4.6) than the one based on PSMA-SPECT/CT [68].

Our aim 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 body 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).

6.4.2. Materials and methods

363 PSMA-based examinations were carried out between 14 November 2017 and 4 October 2022, from which patients who received definitive radiotherapy at the Department of Oncotherapy, University of Szeged, were selected for our present study. PSMA-positive lesions were irradiated using a stereotaxic technique, the delivered dose was prescribed according to international guidelines, and the dose per fraction was always higher than 5 Gy [69].

Inclusion criteria were histologically verified prostatic adenocarcinoma and clinical data (prostate-specific antigen (PSA) level and conventional imaging) suggesting local recurrence after radical prostatectomy (RP) or distant metastasis. If the clinical data, such as PSA level and conventional imaging findings (chest–abdomen–pelvis CT scan, bone scintigraphy) suggested that residual, recurrent, or metastatic tumor tissue might be present, PSMA-based nuclear imaging was carried out. The findings were later used in the target volume definition.

Patients with multiple metastases and cases of palliative radiotherapy were excluded from this study. Those who were not suitable for stereotaxic radiotherapy (performance status) or did not accept the treatment were also left out.

Imaging: The PET/CT scans were performed on a GE Discovery IQ Gen 2 PET/CT System (GE Healthcare, Chicago, IL, USA), 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). The PET scan was performed in three-dimensional (3D) modes for 2.5 min per bed position, the field of view was 20 cm with 30% overlap, and the data collection was completed by plain low-dose CT (120 kV and 70 mA·s) mapping). The routine whole-body mapping was performed extending from the skull base to the upper third of the thighs. In 2017, we started our work with SPECT-CT, and in 2022, we switched to PET/CT.

For PSMA SPECT/CT data acquisition, mean activity of 668 ±95 MBq 99mTc-mas3-y-nal-k (Sub-KuE) (Institute of Isotopes Co. Ltd., Budapest, Hungary) was administered intravenously. Prior to imaging, patients were given oral contrast material (1,000 ml of polyethylene glycol solution) to drink continuously, starting 60 min before the examination. Scans were performed on an integrated whole-body SPECT/CT system (Mediso AnyscanTRIO, Mediso Medical Imaging Systems Ltd., Budapest, Hungary) 6 h after the administration of the radiopharmaceutical (360°; 96 projections, 10 s/frame, matrix 128 × 128, reconstructed pixel size 4.22 mm), and data collection was completed by low-dose CT (120 kV and 70 mA·s).

Treatment planning CT: During patient preparation, the target region was positioned and immobilized with All-in-One (AIO) Solution (ORFIT, Wijnegem, Belgium), with individual immobilization system and six-point thermoplastic mask fixation (Pelvicast system, ORFIT, Wijnegem, Belgium) depending on the target area. Planning CT was carried out according to institution protocols on a Somatom Emotion 6 CT simulator (Siemens, Erlangen, Germany) with CT slice thickness of 3 mm. Target volumes and organs-at-risk were delineated after image fusion in ARIA Oncology Information System (Varian Oncology Systems, Palo Alto, CA, USA) with the review of an experienced radiologist, based on the recommendations of the RTOG GU Radiation Oncology Specialists Reach Consensus [70]. For treatment planning, the Eclipse system was used (Varian Oncology Systems), and intensity-modulated radiation therapy (IMRT) technique was applied with inverse planning. Prior to each treatment session, online and offline monitoring and data recording were performed by cone-beam computed tomography (CBCT).

Whole-body 99mTc-PSMA SPECT/CT (N = 51) or 18F-JK-PSMA-7 PET/CT (N = 14) was completed in some cases by a multiparametric MRI of the small pelvis for validation purposes. The evaluation of the scans and metabolic tumor volume contouring was performed at the Department of Nuclear Medicine, University of Szeged, whereas target volume delineation on the planning CT scan was carried out at the Department of Oncotherapy, taking into account the PSMA-based imaging. The comparison of the two volumes was done by image fusion. The PSMA-based examination and the planning CT were performed in different body positions, the former being carried out on a concave, the latter on a flat surface. Thus, during image fusion, differences in size and geometry may have occurred.

Visual analysis of PSMA imaging: The reconstructed SPECT/CT and PET/CT images were interpreted based on the reporting guidelines [71] by consensus reading of two experienced nuclear medicine and radiology specialists.

Quantitative analysis: Gross tumor volume definition was manually performed on the planning CT (GTVCT) by an experienced radiation oncologist, taking into account earlier contrast CT or MRI scans as well. PSMA-based biological target volume (BTVPSMA) delineation was also performed manually on the axial slices of 18F-PSMA PET or 99mTc PSMA SPECT images by a skilled nuclear medicine and radiology specialist, and the contours were finalized with the help of co-registered CT part of SPECT or PET. GTVCT and BTVPSMA were defined independently. Tumor volumes were determined in units of cm^3. In each case, the BTVPSMA was compared to the gross tumor volume provided by the planning CT, and their difference was described both in cm^3 and in percentage.

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 segmentations. In the case of full overlap, the DSC is 1, whereas in full diversity, the DSC is 0 [72].

The total patient population was divided into subgroups based on applied imaging modality of PSMA-PET/CT or PSMA-SPECT/CT. The aforementioned volumetric and geometrical comparisons were analyzed in both subgroups.

Follow-up: PSA control, conventional imaging (CT, MR, bone scintigraphy), and, in some cases, PSMA isotope-based examination were performed to determine the effectiveness of the treatment (complete remission (CR), partial remission (PR), stable disease (SD), and

progressive disease (PD)). The most important indications for PSMA-based imaging were increasing PSA-levels and suspected osseal metastases on bone scan.

6.4.3. Results

Patient characteristics: 84 lesions of 64 patients were treated with stereotaxic radiation using PSMA isotope-based examinations. The mean age of the patients was 66.6 (range = 55.6–79.7 years, ±SD = 6.5) years. Most of the patients being overweight the mean BMI (body mass index) was 26.96 (range=19.37-41.62 kg/m^2) kg/m^2. The average Gleason score was 7.9 (range = 6–10, ±SD = 1.2). All patients received androgen deprivation therapy. Furthermore, androgen receptor and biosynthesis inhibitor therapy (abiraterone and enzalutamide) and, in case of massive progression, docetaxel chemotherapy have been utilized. However, a detailed review of the systemic drug therapies and oncological outcomes was not in the scope of our paper.

Intermodality comparison of delineated target volumes: Of the 64 irradiated patients, 14 patients were excluded from the rigorous comparative analysis because of registration bias (patient movement, different patient position, different bladder and intestinal status). Therefore, 70 lesions of 50 patients were selected for intermodality comparison.

Tumor volumes defined by the different imaging modalities were non-identical in 100% of cases. Decrease in size was observed in 76% (53 lesions), while increase in only 24% (17 lesions) of the cases upon comparison of the BTVPSMA to the GTVCT. In three out of 70 lesions, the difference in the percentage of volumes was lower than 10%, while higher than 10% in the remaining 67 lesions (96% of all lesions detected).

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 remain hidden on the conventional diagnostic images.

The target volume defined by the PSMA density was significantly smaller (paired t-test, $p < 0.0001$) than the tumor size defined by the planning CT scan: GTVCT, 27.58 ±46.07 cm^3 (0.44–258.2 cm^3); BTVPSMA, 16.14 ±29.87 cm^3 (0.38–190.85 cm^3).

Intermodality difference (independent of which modality was higher or lower) was 15.04 ± 23.20 cm^3 (0.03–126.14 cm^3), which describes a difference of 65.37% ±72.70% (1.36–545.31%). During geometrical analyses, DSC was 0.56 ±0.20 (0.07–0.85).

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

The prescribed doses were defined in an individualized manner, taking into consideration the localization of the tumor and eventual prior irradiation.

Follow-up: In order to evaluate the effectiveness of the treatment, 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.

7. Discussion

Modern imaging methods have two paramount roles in radiation therapy planning. Firstly, they can be utilized to enhance organ-at-risk protection and secondly, to improve the precision of target volume delineation. In this thesis, both major fields of implication were studied, and the findings are discussed in this section.

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.

The visibility of the OARs is one of the key factors that can be improved, especially in the complicated, delicately built region of the head and neck. MRI-based delineation can dramatically improve the quality of organ-at-risk contours in the mentioned anatomical site. T2w sequences are particularly useful for this purpose, as they are largely accessible and provide excellent OAR visibility in comparison to T1w sequences or CT. Magnetic resonance imaging as the primary tool of OAR delineation is already present in the treatment of

numerous malignancies, such as the tumors of the central nervous system, cervix, prostate and lately the head and neck. The list is constantly expanding, and it is possible that in the future MRI will entirely replace computed tomography in radiation treatment planning. It needs to be noted that MRI-only RT planning requires synthetic CT to enable dose calculation. However, the technical feasibility of MRI-based synthetic CT was demonstrated previously by several studies [73; 74]. Without standardized contours regulated by well-defined guidelines, interobserver variability may spoil such acquired advantages. Furthermore, with the growing number of clinical trials requiring MRI-based RT planning, the need for well-built, straightforward contouring guidelines is on the rise [75; 76]. Therefore, regular updates of the directives by experts are advisable, preferably in the form of multi-institutional meetings. At this point, we also need to add that all medical developments should be governed by clinical rationality. OAR delineation must take into account disease stage, tumor volume, and involvement/infiltration of different anatomic structures, functional units, as well as the curative or palliative intent of the radiation therapy itself. Finally, the rapid evolution of artificial intelligence in the process of organ-at-risk-delineation may take a huge burden off the shoulders of radiographers and radiation oncologists, and result in the expansion of the proposed organ set. Radiation oncologist specialists play a pivotal role in the development process of software dedicated for such purposes, as their expertise is valuable during the phase of conceptualization, training and evaluation processes. With the use of convolutional neuronal networks, results comparable to human contouring can be achieved even in the anatomically complex head and neck region. In addition, inter-observer variability can thus be eliminated, improving the reproducibility and comparability of the results [77; 78].

One of the key hypotheses of our work was that MRI-based adaptive radiotherapy in glioblastoma has a beneficial effect on patient survival. Furthermore, we theorized that certain morphological MR features may correlate with disease outcome and can therefore be identified as prognostic factors.

The use of adaptive radiotherapy in the treatment of glioblastoma is sparsely documented, and articles usually report on a small patient population. To our best knowledge, our present study has enrolled the highest number of patients in the topic.

Though the latest guidelines [50] recommend a fresh MRI within 2 weeks prior to the RT start date, it has traditionally been acceptable to use the post-surgery MR exam for RT planning purposes [79], [80]. The average waiting time from the 48 h post-surgery MRI to the planning

CT was 20 days, as we were committed to start the adjuvant radiotherapy as soon as clinically possible. This means that we should have performed an extra MRI just one week after the surgery. However, in case of subtotal tumor resection, surgery-related complications on the postoperative MRI or extended convalescence, a new MRI was always performed before the RT planning.

In a recent research [81], MRI-Linac was utilized for weekly re-planning of glioblastoma patients. The daily T2–weighted images proved to be sufficient to track the shrinkage of the surgical cavity that occurred in 50 % of the cases. On this basis, it has been concluded that the adaptive approach may prevent radiation-induced neurocognitive deterioration by allowing improved hippocampal and brain sparing. The same finding was made by a Japanese workgroup [82] using single-step replanning. In their study contrast-enhanced T1-weighted MR images were taken at an irradiation dose of 34–38 Gy and the final 20 Gy boost was delivered after the adaptation of the target volume. A Turkish workgroup [83] followed the RTOG scheme in their adaptive trial and performed a repeated MRI after the first 46 Gy. They have pointed out that adaptive boost treatment planning may be beneficial for two primary reasons. Firstly, target volume expansion and consequent underdosage is more likely to occur if the patient only underwent subtotal tumor resection or biopsy. Secondly, adaptive boost planning is also worth considering for patients with gross tumor resection, since this group is inclined to have target volume decrease, mainly due to surgical cavity shrinkage. With the adaptive approach, we may potentially offer more optimized dose coverage.

In other tumor localizations, the most important benefit of adaptive radiotherapy is allowing the delivery of higher doses to the tumor to achieve improved local disease control. Since glioblastoma recurs in about 80 % of cases in the close vicinity of the original tumor site [84], dose escalation beyond 60 Gy would be desirable. However, these attempts are restricted by the dose constraints of the central nervous system. When it comes to the remaining 20 %, it is possible that peritumoral tractography might be a helpful tool in the prediction of the potential recurrence site, based on probabilistic models [85].

Pre-and post-treatment FLAIR volumes corresponding to micrometastasis-containing edema have been identified as a radiologically verifiable prognostic factor for glioblastoma by a study conducted by Matthew D. Garrett and al. [86].

A new strategy that may play a pivotal role in the identification of individual tumoral patterns as well as prognostic and/or predictive factors for glioblastoma patients is the use of MRI-derived radiomics. This method can extract a broad range of microscale textural patterns from

MR images, mostly invisible for the human eye. The scanning of the resection cavity and its surroundings [87] is expected to uncover valuable information on the efficacy of the applied antitumoral therapy and to help differentiate treatment-related changes from tumor recurrence.

A recent comparison demonstrated that postoperative chemoradiation according to RTOG/NRG principles did not differ significantly in terms of treatment-related toxicities and efficacy from treatment according to EORTC recommendations. It needs to be mentioned that this study included grade 3 gliomas beside glioblastoma and grade 4 tumors [88].

Our study confirmed that valuable imaging information can be collected during RT. Based on this data, we could conclude that both relative and absolute GTV shrinkage serve as prognostic factors for the disease, as they demonstrate positive correlation with survival.

Neither absolute, nor relative PTV changes significantly correlated with survival in proportional hazards regression model, reinforcing the safety of our limited margin approach. More crucially, by reducing PTV based on the interim MRI, we achieved substantial sparing of critical normal tissues, particularly the brain, without compromising survival outcomes. This demonstrates that our adaptive margin reduction strategy is not only no inferior to conventional methods, but also more advantageous. With survival rates matching or exceeding those reported in the literature [89; 90], our approach not only preserves survival but also minimizes dose to surrounding healthy brain tissue, making it a highly effective treatment strategy for glioblastoma.

However, it should be noted that the study has limitations due to its single-institution, retrospective nature. The sample size was not prospectively determined and may be insufficient to reveal small differences. Additionally, the lack of control group limits the possibility of drawing definitive conclusions on the accuracy and efficacy of the proposed delineation strategies. The benefit of any intervention, including the ART performed in this study, needs to be tested in prospective trials.

Nevertheless, we have established important evaluation categories that facilitate the systematic review of interim MRI findings. Furthermore, our data supports the use of a limited PTV approach, particularly the PTV1 strategy.

In the final section of our work, we examined the impact of prostate-specific membrane antigen-based imaging on the management of low-volume progressive prostate cancer. According to our hypothesis, PSMA-based SPECT and PET/CT have a significant impact on

target volume definition for stereotactic body radiotherapy compared to conventional anatomical imaging. Furthermore, these modalities also possess the capability to detect disease recurrence and/or metastases allowing for SBRT in clinical scenarios where increasing PSA level is the only sign of disease activity.

Metastasis-directed treatment (MDT) using SBRT is a new approach in the therapeutic armamentarium of oligometastatic prostate cancer, hormone-sensitive and castrate-resistant alike [91; 92; 93]. The most common metastases treated with SBRT are osseal and nodal lesions, but visceral manifestations may also be eligible [93].

In recent years, molecular imaging techniques exerted a strong influence on the management of prostate cancer [94]. These methods play a crucial role in the early diagnosis of local recurrence as well as of distant spread and can also be used in radiation therapy planning.

Multiple radioactive tracers have been tested in prostate cancer, starting with FDG, the backbone of PET/CT imaging. Despite being the most widespread mean of tumor tracking, FDG has seen limited indications in this type of cancer, namely the initial assessment of highly malignant tumors (Gleason score 7 or above) as well as the treatment response evaluation of patients with castrate-resistant metastatic disease [95].

The fine differences between SPECT and PET scans are well charted. While the spatial resolution of PET scans is somewhat higher, the functional sensibility of both methods remains high. However, for target volume definition and SBRT planning, the morphological information provided by the CT component of both SPECT/CT and PET/CT is taken into account. Therefore, the differences between the two modalities do not influence our results significantly.

In our present work, 363 PSMA isotope-based tests were performed on prostate cancer patients, of which approximately 20% were used for stereotaxic radiation treatment for postoperative local recurrence and oligometastasis.

In case of biochemical relapse after radical prostatectomy, which occurs in up to 50%, salvage RT of the prostate bed is performed to achieve long-term disease control depending on the stage and adverse factors [96]. However, with a PSMA isotope-based scans, isotope accumulation can be detected in a negative (with conventional imaging) tumor bed [97]. In our present work, local recurrence was treated with SBRT in eight cases.

In a retrospective multicentric study, Kirste et al. examined the role of 68Ga-PSMA-PET/CT-based elective radiotherapy, evaluating the data of 394 patients with oligo-recurrent 68Ga-

PSMA-PET/CT-positive prostate cancer. The combination of the two methods improves the outcome of oligo-recurrent prostate cancer, but there is great heterogeneity in terms of doses, treatment areas, and radiation techniques [98].

More than 50% of the metastases treated with the stereotactic radiation technique were located in the bone and approximately 40% in the lymph node, which corresponds to the international distribution in the literature [96].

Although much literature data is available on SBRT for prostate cancer bone metastases [99], up until very recently, there were fewer clinical data on stereotactic radiosurgery for local recurrences and rare metastases. However, numerous recent studies proved that even the re-irradiation of local recurrences after curative/salvage radiotherapy using SBRT is a safe and effective method (Christina Schröder, Hongjian Tang et al.: Re-irradiation to the prostate using stereotactic body radiotherapy (SBRT) after initial definitive radiotherapy – A systematic review and meta-analysis of recent trials. Clinical and Translational Radiation Oncology, 2024). The treatment of adrenal metastases with stereotactic body RT provides good local control with tolerable toxicity in the case of several cancer types, including PC [100]. Though not very common, the stereotactic irradiation of prostate cancer lung metastases shows comparable results to the treatment of osseal and nodal oligometatases (Maximilien Rogé, Patrick Bowden et al.: Stereotactic body radiotherapy for lung oligometastatic prostate cancer: An international retrospective multicenter study. Clinical and Translational Radiation Oncology, 2025), and similar results were obtained with intracranial metastases as well (Stylianos Pikis, Adomas Bunevicius et al.: Stereotactic radiosurgery for prostate cancer cerebral metastases: an international multicenter study. Journal of Neurosurgery, 2021)

In a randomized two-arm clinical trial [101], 165 patients were selected for salvage radiotherapy after radical prostatectomy. In one treatment arm, only conventional imaging methods were utilized for target volume delineation, while in the other arm, additional information provided by 18F-fluciclovine-PET/CT was also taken into account. In 3-year event-free survival, a significant difference was observed between the two arms in favor of the latter (63% vs. 75.5%).

A retrospective study [102] demonstrated that radiotherapy plans had to be modified by an average of 60.5% due to PSMA-PET/CT findings. However, these data are to be treated with caution since the total number of patients enrolled in the trial was low (43), and the indications for irradiations were heterogeneous (curative, salvage, and metastasis treatment).

Nowadays, PSMA PET/CT is an accepted tool in prostate cancer patient management and has become a substantial part of the imaging of PC. In some guidelines, it is the preferred method for lesion detection in biochemical relapse after primary treatment and is mandatory prior to PSMA-directed radionuclide therapy. The role of PSMA SPECT/CT is under evaluation, but SPECT/CT scan with 99mTc-PSMA is also gaining acceptance to detect prostate cancer metastases. Some comparative analyses between 68Ga-PSMA and 99mTc-PSMA have been reported. Albalooshi et al. aimed to directly compare these two techniques in patients with prostate cancer. In the 28 patients investigated, they found that in M staging, 99mTc-PSMA SPECT/CT is as accurate as 68Ga-PSMA PET/CT, and the detection rate was not significantly different between the two techniques in patients with PSA levels >2.1 ng/ml. However, PSMA PET/CT detected more lesions [103]. Fallahi et al. in patient-based evaluation showed absolute correlation between 99mTc-PSMA SPECT/CT and 68Ga-PSMA PET/CT in 22 patients involved with metastatic lesions or highly suspicious places for the presence of metastasis [104]. It is reasonable to consider using a 99mTc-PSMA tracer instead of PET-based PSMA ligands. 99mTc-PSMA can effectively detect metastatic lesions in prostate cancer patients with a lower financial burden and radiation exposure [105; 106].

In our work, we found that GTVCT contoured on the basis of conventional imaging (CT, MRI, and bone scintigraphy) appears to be larger than BTVPSMA determined by PSMA - imaging, independently of whether PSMA-SPECT/CT-or PET/CT was used and what the size of the lesion was. In 15 patients, the volume of GTVCT was significantly larger than the volume of BTVPSMA. In these cases, lymph node chains (three patients) or multiple vertebral metastases (12 patients) were treated. Target volume in radiotherapy is based on conventional imaging, where enlarged lymph nodes with abnormal structure and pathological bone structure deviations need to be treated regardless of the degree of isotope accumulation.

No correlation was detected in terms of the pre-RT PSA value and the pre-RT PSA duplication time and GTVCT or BTVPSMA. Apart from increased precision, thanks to the high sensitivity of the method, recurrent disease can be detected even at very low PSA values [107], granting valuable time for treatment planning and/or interdisciplinary consultations, which is supported by our current findings.

In our analysis three times more PSMA SPECT/CT than PET/CT were included. Therefore, relevant data could be evaluated on the integration of PSMA SPECT/CT in the definition of SBRT target volume of low-volume progressing prostate cancer. To the best of our knowledge, our research was the first to investigate the role of 99mTc-PSMA SPECT/CT as a

tool for radiotherapy planning. Both modalities were found to be effective in metastatic lesion detection and target delineation.
Currently, the use of PSMA isotope-based tests is not a routine procedure in determining the radiation treatment volume and the information provided by the planning CT is indispensable anyway. By using conventional imaging methods, planning CT (GTVCT), and PSMA-based imaging (BTVPSMA), more accurate target volume delineation is possible for SBRT. In relation to the overlapping, we can assume that there is a difference in volume and geometry, and it would be advisable to use the same immobilization system.

PSMA theranostics represent a new approach in the armamentarium of nuclear medicine that combines diagnosis and therapy by targeting the PSMA protein found on cancer cells. It uses a radioactive molecule for both imaging (via PET scans) and delivering radiation directly to cancer cells. A recent international phase III trial tested 177Lu-PSMA-617 in patients with advanced PSMA-positive metastatic prostate cancer and demonstrated improved PFS and OS compared to standard care, without having significant impact on life quality. Thus, became 177Lu-PSMA-617, sold now under the brand name Pluvicto an available therapy for metastatic castrate-resistant prostate cancer and more will follow in the near future.

8. Conclusions

Our work explored the dual role of modern imaging techniques in radiation therapy; enhanced organ-at-risk protection and improved target volume definition.
OAR sparing in the head-and-neck region can significantly be improved by using T2-weighted MRI sequences for contouring, as they provide better visibility and orientation in this complex anatomical site. Standardized contouring guidelines are essential to reduce interobserver variability and should be updated regularly through expert, multi-institutional collaboration. Artificial intelligence, particularly convolutional neural networks, shows promise in automating and standardizing OAR delineation, reducing time and variability while maintaining accuracy.
We have confirmed that magnetic resonance imaging-based target volume adaptation using reduced security margins is a safe strategy in the treatment of glioblastoma patients. Monitoring the resection cavity and residual tumor during chemoradiotherapy and adapting the PTV to these changes enhances dose coverage of the tumor while sparing normal brain tissue. This may contribute to improved therapeutic ratio and eventually better clinical outcomes.

The following morphological features on the interim MRI were identified as risk factors for unfavorable disease outcome: compressed ventricles, increase in contrast enhancement, and smaller absolute as well as relative tumor volume shrinkage. These phenomena shall be regarded as warning signs necessitating stricter follow-up and possibly more frequent imaging. This increased vigilance is expected to shorten reaction time when tumor progression becomes evident, and patients may benefit earlier from potentially effective second line therapy.

With the help of PSMA-binding radioactive tracers, metastases or local recurrence of prostate cancer become detectable at an early stage, when increasing PSA-level is the only sign of disease activity, without clinical signs and demonstrable lesions by conventional anatomical imaging. This early detection allows us for accurate target volume definition and the stereotactic ablation of the progressing lesions.
As a conclusion, modern imaging techniques, including MRI and isotope diagnostic methods, offer significant advantages in radiation therapy planning. They enhance treatment precision, improve OAR protection, and provide new prognostic insights—though further prospective, multicenter studies are needed to validate these findings.

9. Novel scientific results

9.1. 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 complex 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 clinical accuracy.

9.2. Safety and Efficacy of MRI-Guided Adaptive Radiotherapy for Glioblastoma

The research confirmed that magnetic resonance imaging-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.

9.3. Identification of Prognostic MRI Biomarkers During Glioblastoma Radiochemotherapy

The interim MRI performed mid-treatment revealed 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.

9.4. 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. These findings enable precise target volume definition and support the use of stereotactic radiotherapy to ablate limited metastatic lesions at an early stage of disease progression.

9.5. 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 localization. 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.

10. References

1. Castelijns JA, Doornbos J et al.: MR imaging of the normal larynx. J Comput Assist Tomogr. 1985; 9: 919–925. doi: 10.1097/00004728-198509000-00015.
2. Dean JA, Welsh LC et al.: A novel method for delineation of oral mucosa for radiotherapy dose–response studies. Radiother Oncol. 2015; 115: 63–66. doi: 10.1016/j.radonc.2015.02.020.
3. Adachi M, Hosoya T et al.: Evaluation of the substantia nigra in patients with Parkinsonian syndrome accomplished using multishot diffusion-weighted MR imaging. AJNR Am J Neuroradiol. 1999; 20: 1500–1506.
4. Wada M, Premoselli L et al.: Determination of accuracy in the delineation of spinal cord and canal/thecal sac on CT and MRI in head and neck planning. Int J Radiat Oncol Biol Phys. 2006; 66: S450. doi: 10.1016/j.ijrobp.2006.07.843.
5. Combs SE, Baumert BG et al.: ESTRO ACROP guideline for target volume delineation of skull base tumors. Radiother Oncol. 2021; 156: 80–94. doi: 10.1016/j.radonc.2020.11.014.
6. Brouwer CL, Steenbakkers RJHM et al.: CT-based delineation of organs at risk in the head and neck region: DAHANCA, EORTC, GORTEC, HKNPCSG, NCIC CTG, NCRI, NRG Oncology and TROG consensus guidelines. Radiother Oncol. 2015; 117: 83–90. doi: 10.1016/j.radonc.2015.07.041.
7. Hoebers F, Yu E et al.: A pragmatic contouring guideline for salivary gland structures in head and neck radiation oncology: The MOIST target. Am J Clin Oncol. 2013; 36: 70–76. doi: 10.1097/COC.0b013e31823a538e.
8. Gawryszuk A, Bijl HP et al.: Functional swallowing units (FSUs) as organs-at-risk for radiotherapy. PART 2: Advanced delineation guidelines for FSUs. Radiother Oncol. 2019; 130: 68–74. doi: 10.1016/j.radonc.2018.09.022.
9. Eekers DBP, in ’t Ven L et al.: The EPTN consensus-based atlas for CT- and MR-based contouring in neuro-oncology. Radiother Oncol. 2018; 128: 37–43. doi: 10.1016/j.radonc.2017.12.013.
10. Beddok A, Faivre JC et al.: Practical contouring guidelines with an MR-based atlas of brainstem structures involved in radiation-induced nausea and vomiting. Radiother Oncol. 2019; 130: 113–120. doi: 10.1016/j.radonc.2018.08.003.

11. Wu AJ, Bosch WR et al.: Expert consensus contouring guidelines for IMRT in esophageal and gastroesophageal junction cancer. Int J Radiat Oncol Biol Phys. 2015; 92: 911–920. doi: 10.1016/j.ijrobp.2015.03.030.

12. Christianen MEMC, Langendijk JA et al.: Delineation of organs at risk involved in swallowing for radiotherapy treatment planning. Radiother Oncol. 2011; 101: 394–402. doi: 10.1016/j.radonc.2011.05.015.

13. Truong MT, Nadgir RN et al.: Brachial plexus contouring with CT and MR imaging in radiation therapy planning for head and neck cancer. Radiographics. 2010; 30: 1095–1103. doi: 10.1148/rg.304095105.

14. Sousa Garcia D, Bussoloti Filho I.: Fat deposition of parotid glands. Braz J Otorhinolaryngol. 2013; 79: 173–176. doi: 10.5935/1808-8694.20130031.

15. Rathy R, Sunil S et al.: Osteoradionecrosis of mandible: Case report with review of literature. Contemp Clin Dent. 2013; 4: 251–253. doi: 10.4103/0976-237X.114882.

16. Edge SB, Byrd DR et al.: Springer; New York, NY: 2010. AJCC Cancer Staging Manual Seventh Edition. Trotti A III, eds.

17. Ferlito A, Rinaldo A.: The pathology and management of subglottic cancer. Eur Arch Otorhinolaryngol. 2000; 257: 168–173. doi: 10.1007/s004050050217.

18. Gawryszuk A, Bijl HP et al.: Functional swallowing units (FSUs) as organs-at-risk for radiotherapy. PART 1: Physiology and anatomy. Radiother Oncol. 2019; 130: 62–67. doi: 10.1016/j.radonc.2018.10.028.

19. MD Anderson Head and Neck Cancer Symptom Working Group Beyond mean pharyngeal constrictor dose for beam path toxicity in non-target swallowing muscles: Dose-volume correlates of chronic radiation-associated dysphagia (RAD) after oropharyngeal intensity modulated radiotherapy. Radiother Oncol. 2016; 118: 304–314. doi: 10.1016/j.radonc.2016.01.019.

20. Dirix P, Abbeel S et al.: Dysphagia after chemoradiotherapy for head-and-neck squamous cell carcinoma: Dose–effect relationships for the swallowing structures. Int J Radiat Oncol Biol Phys. 2009; 75: 385–392. doi: 10.1016/j.ijrobp.2008.11.041.

21. Popovtzer A, Cao Y et al.: Anatomical changes in the pharyngeal constrictors after chemoirradiation of head and neck cancer and their dose-effect relationships:

MRI-based study. Radiother Oncol. 2009; 93: 510–515. doi: 10.1016/j.radonc.2009.05.013.

22. Sun Y, Yu XL et al.: Recommendation for a contouring method and atlas of organs at risk in nasopharyngeal carcinoma patients receiving intensity-modulated radiotherapy. Radiother Oncol. 2014; 110: 390–397. doi: 10.1016/j.radonc.2013.10.035.

23. Scoccianti S, Detti B et al.: Organs at risk in the brain and their dose-constraints in adults and in children: A radiation oncologist's guide for delineation in everyday practice. Radiother Oncol. 2015; 114: 230–238. doi: 10.1016/j.radonc.2015.01.016.

24. Bulbul E, Yazici A et al.: Evaluation of lacrimal gland dimensions and volume in Turkish population with computed tomography. J Clin Diagn Res. 2016; 10: TC06–TC08. doi: 10.7860/JCDR/2016/16331.7207.

25. Totuk OMG, Kalkay AB et al.: Evaluation of lacrimal gland dimensions with MR imaging in a Turkish population sample. Int J Morphol. 2018; 36: 1431–1438.

26. Beddok A, Faivre JC et al.: Practical contouring guidelines with an MR-based atlas of brainstem structures involved in radiation-induced nausea and vomiting. Radiother Oncol. 2019; 130: 113–120. doi: 10.1016/j.radonc.2018.08.003.

27. Mayo C, Yorke E et al.: Radiation associated brainstem injury. Int J Radiat Oncol Biol Phys. 2010;76:S36–S41. doi: 10.1016/j.ijrobp.2009.08.078.

28. Wada M, Premoselli L et al.: Determination of accuracy in the delineation of spinal cord and canal/thecal sac on CT and MRI in head and neck planning. Int J Radiat Oncol Biol Phys. 2006; 66: S450.

29. Chaudhary V, Bano S.: Thyroid ultrasound. Indian J Endocrinol Metab. 2013; 17: 219–227. doi: 10.4103/2230-8210.109667.

30. Kang T, Kim DW et al.: Magnetic resonance imaging features of normal thyroid parenchyma and incidental diffuse thyroid disease: A single-center study. Front Endocrinol (Lausanne) 2018; 9: 746. doi: 10.3389/fendo.2018.00746.

31. Truong MT, Nadgir RN et al.: Brachial plexus contouring with CT and MR imaging in radiation therapy planning for head and neck cancer. Radiographics. 2010; 30: 1095–1103. doi: 10.1148/rg.304095105.

32. Hall WH, Guiou M et al.: Development and validation of a standardized method for contouring the brachial plexus: Preliminary dosimetric analysis among patients treated with IMRT for head-and-neck cancer. Int J Radiat Oncol Biol Phys. 2008; 72: 1362–1367. doi: 10.1016/j.ijrobp.2008.03.004.

33. Yi SK, Hall WH et al.: Validating the RTOG-endorsed brachial plexus contouring atlas: An evaluation of re-producibility among patients treated by intensity modulated radiotherapy for head-and-neck cancer. Int J Radiat Oncol Biol Phys. 2012; 82: 1060–1064. doi: 10.1016/j.ijrobp.2010.10.035.

34. Van de Velde J, Audenaert E et al.: An anatomically validated brachial plexus contouring method for intensity modulated radiation therapy planning. Int J Radiat Oncol Biol Phys. 2013; 87: 802–808. doi: 10.1016/j.ijrobp.2013.08.004.

35. Shultz DB, Trakul N et al.: Vagal and recurrent laryngeal neuropathy following stereotactic radiation therapy in the chest. Pract Radiat Oncol. 2014; 4: 272–278. doi: 10.1016/j.prro.2013.08.005.

36. Jaruchinda P, Jindavijak S et al.: Radiation-related vocal fold palsy in patients with head and neck carcinoma. J Med Assoc Thai. 2012; 95: S23–S28.

37. Dai X, Lei Y et al.: Multi-organ auto-delineation in head-and-neck MRI for radiation therapy using regional convolutional neural network. Phys Med Biol. 2022; 67(2): 025006. doi:10.1088/1361-6560/ac3b34

38. Strijbis VIJ, de Bloeme CM et al.: Multi-view convolutional neural networks for automated ocular structure and tumor segmentation in retinoblastoma. Sci Rep. 2021; 11(1): 14590. doi:10.1038/s41598-021-93905-2

39. Korte JC, Hardcastle N et al.: Cascaded deep learning-based auto-segmentation for head and neck cancer patients: Organs at risk on T2-weighted magnetic resonance imaging. Med Phys. 2021; 48(12): 7757–72. doi:10.1002/mp.15290

40. Elguindi S, Zelefsky MJ et al.: Deep learning-based auto-segmentation of targets and organs-at-risk for magnetic resonance imaging only planning of prostate radiotherapy. Phys Imaging Radiat Oncol. 2019; 12: 80–6. doi:10.1016/j.phro.2019.11.006

41. Nie D, Wang L et al.: STRAINet: Spatially varying sTochastic residual AdversarIal networks for MRI pelvic organ segmentation. IEEE Trans Neural Netw Learn Syst. 2019; 30(5): 1552–64. doi:10.1109/tnnls.2018.2870182

42. Chen X, Ma X et al.: Personalized auto-segmentation for magnetic resonance imaging–guided adaptive radiotherapy of prostate cancer. Med Phys. 2022; 15793. doi:10.1002/mp.15793

43. Savenije MHF, Maspero M et al.: Clinical implementation of MRI-based organs-at-risk auto-segmentation with convolutional networks for prostate radiotherapy. Radiat Oncol. 2020; 15(1): 104. doi:10.1186/s13014-020-01528-0

44. Jia H, Cai W et al.: Learning multi-scale synergic discriminative features for prostate image segmentation. Pattern Recognit. 2022; 126: 108556. doi:10.1016/j.patcog.2022.108556

45. Hammouda K, Khalifa F et al.: A deep learning-based approach for accurate segmentation of bladder wall using MR images. In: Proceedings of the 2019 IEEE international conference on imaging systems and techniques (IST). Abu Dhabi, United Arab Emirates: IEEE; August 2019.

46. K. Kristy Brock: Adaptive radiotherapy: moving into the future. Semin Radiat Oncol. 2019; 29(3): pp. 181-184. doi: 10.1016/j.semradonc.2019.02.011

47. C.K. Glide-Hurst, P. Lee et al.: Adaptive radiation therapy (ART) strategies and technical considerations: A state of the ART review from NRG Oncology. Int J Radiat Oncol Biol Phys. 2020; 109(4): pp. 1054-1075. doi: 10.1016/j.ijrobp.2020.10.021

48. U. Bernchou, T.S.T. Arnold, et al.: Evolution of the gross tumour volume extent during radiotherapy for glioblastomas. Radiother Oncol. 2021; 160: pp. 40-46. doi: 10.1016/j.radonc.2021.04.001

49. C. Hassanzadeh, S. Rudra, et al.: Evolution of interim MRI changes during limited-field radiation therapy for glioblastoma and implications for treatment planning. Radiother Oncol. 2021; 158: pp. 237-243. doi: 10.1016/j.radonc.2021.01.040

50. M. Niyazi, N. Andratschke, et al.: ESTRO-EANO guideline on target delineation and radiotherapy details for glioblastoma. Radiother Oncol. 2023; 184: Article 109663, doi: 10.1016/j.radonc.2023.109663

51. T.J. Kruser, W.R. Bosch, et al.: NRG brain tumor specialists consensus guidelines for glioblastoma contouring. J Neurooncol. 2019; 143(1): pp. 157-166. doi: 10.1007/s11060-019-03152-9

52. G. Minniti, P. Tini, et al.: Feasibility of clinical target volume reduction for glioblastoma treated with standard chemoradiation based on patterns of failure analysis. Radiother Oncol. 2022; 181: Article 109435, doi: 10.1016/j.radonc.2022.11.024

53. N. Kumar, R. Kumar, et al.: Impact of volume of irradiation on survival and quality of life in glioblastoma: a prospective, phase 2, randomized comparison of RTOG and MDACC protocols. Neurooncol Pract. 2020; 7(1): pp. 86-93. doi: 10.1093/nop/npz024

54. Benjamin W. Corn, Meihua Wang et al.: Health related quality of life and cognitive status in patients with glioblastoma multiforme receiving escalating doses of conformal three dimensional radiation on RTOG 98-03 J Neurooncol. 2009; 95: 247–257. doi: 10.1007/s11060-009-9923-3

55. S.A. Grossman, S. Ellsworth, et al.: Survival in patients with severe lymphopenia following treatment with radiation and chemotherapy for newly diagnosed solid tumors. J Natl Compr Canc Netw. 2015; 13(10): pp. 1225-1231. doi: 10.6004/jnccn.2015.0151

56. Roxane M. Bouten, Erik F. Young et al.: Chapter Two - Effects of radiation on endothelial barrier and vascular integrity. In Tissue Barriers in Disease, Injury and Regeneration 2021; pp. 43-94. doi: 10.1016/B978-0-12-818561-2.00007-2

57. O. Guipaud, C. Jaillet, et al.: The importance of the vascular endothelial barrier in the immune-inflammatory response induced by radiotherapy. Br J Radiol. 2018; 91(1089): Article 20170762, doi: 10.1259/bjr.20170762

58. S. Rosińska, J. Gavard: Tumor vessels fuel the fire in glioblastoma. Int J Mol Sci. 2021 22(12): p. 6514. doi: 10.3390/ijms22126514

59. Z. Végváry, B. Darázs, et al.: Adaptive radiotherapy for glioblastoma multiforme - the impact on disease outcome. Anticancer Res. 2020; 40(8): pp. 4237-4244. doi: 10.21873/anticanres

60. A.R. Cabrera, J.P. Kirkpatrick, et al.: Radiation therapy for glioblastoma: an ASTRO evidence-based clinical practice guideline. Pract Radiat Oncol. 2016; 6(4): pp. 217-225. doi: 10.1016/j.prro.2016.03.007

61. M.D. Roger Stupp, W.P. Mason, et al.: Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med. 2005; 352(10): pp. 987-996. doi: 10.1056/NEJMoa043330

62. Sung H, Ferlay J et al.: Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021; 71: 209–249. doi: 10.3322/caac.21660

63. Juloori A, Shah C et al.: Evolving paradigm of radiotherapy for high-risk prostate cancer: current consensus and continuing controversies. Prostate Cancer. 2016; 2016: 2420786. doi: 10.1155/2016/2420786

64. Tsechelidis I, Vrachimis A.: PSMA PET in imaging prostate cancer. Front Oncol. 2022; 12: 831429. doi: 10.3389/fonc.2022.831429

65. Werner P, Neumann C et al.: [99cmTc]Tc-PSMA-I&S-SPECT/CT: experience in prostate cancer imaging in an outpatient center. EJNMMI Res. 2020; 10: 45. doi: 10.1186/s13550-020-00635-z

66. Schmidkonz C, Cordes M et al.: SPECT/CT with the PSMA ligand 99mTc-MIP-1404 for whole-body primary staging of patients with prostate cancer. Clin Nucl Med. 2018; 43: 225–31. doi: 10.1097/RLU.0000000000001991

67. Su H-C, Zhu Y et al.: Evaluation of 99mTc-labeled PSMA-SPECT/CT imaging in prostate cancer patients who have undergone biochemical relapse. Asian J Androl. 2017; 19: 267–71. doi: 10.4103/1008-682X.192638

68. Farkas I, Besenyi Z et al.: Kezdeti tapasztalatok a 99mTc-PSMA-SPECT/CT-vel prosztatarákos betegekben [Initial experiences with 99mTc-PSMA-SPECT/CT in patients with prostate cancer]. Orv Hetil. 2018; 159(35): 1433–40. doi: 10.1556/650.2018.31128

69. Tipton KN, Sullivan N et al.: Stereotactic Body Radiation Therapy. Rockville (MD: Agency for Healthcare Research and Quality (2011). Available at: https://www.ncbi.nlm.nih.gov/books/NBK55717/.

70. Poortmans P, Bossi A et al.: Guidelines for target volume definition in post-operative radiotherapy for prostate cancer, on behalf of the EORTC Radiation Oncology Group. Radiother Oncol. 2007; 84(2): 121–7. doi: 10.1016/j.radonc.2007.07.017

71. Fendler WP, Eiber M et al.: 68Ga-PSMA PET/CT: Joint EANM and SNMMI procedure guideline for prostate cancer imaging: version 1. 0 Eur J Nucl Med Mol Imaging. 2017; 44(6): 1014–24. doi: 10.1007/s00259-017-3670-

72. Müller D, Soto-Rey I et al.: Towards a guideline for evaluation metrics in medical image segmentation. BMC Res Notes. 2022; 15(1): 210. doi: 10.1186/s13104-022-06096-y

73. Wiesinger F, Bylund M et al.: Zero TE-based pseudo-CT image conversion in the head and its application in PET/MR attenuation correction and MR-guided radiation therapy planning. Magn Reson Med. 2018; 80: 1440–1451. doi: 10.1002/mrm.27134.

74. Blanc-Durand P, Khalife M et al.: Attenuation correction using 3D deep convolutional neural network for brain 18F-FDG PET/MR: Comparison with Atlas, ZTE and CT based attenuation correction. PLoS One. 2019; 14. doi: 10.1371/journal.pone.0223141.

75. Grégoire V, Evans M et al.: Delineation of the primary tumour clinical target volumes (CTV-P) in laryngeal, hypopharyngeal, oropharyngeal and oral cavity squamous cell carcinoma: AIRO, CACA, DAHANCA, EORTC, GEORCC, GORTEC, HKNPCSG, HNCIG, IAG-KHT, LPRHHT, NCIC CTG, NCRI, NRG Oncology, PHNS, SBRT, SOMERA, SRO, SSHNO, TROG consensus guidelines. Radiother Oncol. 2018; 126: 3–24. doi: 10.1016/j.radonc.2017.10.016.

76. Lin D, Lapen K et al.: A systematic review of contouring guidelines in radiation oncology: Analysis of frequency, methodology, and delivery of consensus recommendations. Int J Radiat Oncol Biol Phys. 2020; 107: 827–835. doi: 10.1016/j.ijrobp.2020.04.011.

77. Ayyalusamy A, Vellaiyan S et al.: Auto-segmentation of head and neck organs at risk in radiotherapy and its dependence on anatomic similarity. Radiat Oncol J. 2019; 37: 134–142. doi: 10.3857/roj.2019.00038.

78. Tong N, Gou S et al.: Fully automatic multi-organ segmentation for head and neck cancer radiotherapy using shape representation model constrained fully convolutional neural networks. Med Phys. 2018; 45: 4558–4567. doi: 10.1002/mp.13147.

79. R.D. Kraus, C.R. Weil et al.: Incidence and extent of disease progression on MRI between surgery and initiation of radiotherapy in glioblastoma patients. Neurooncol Pract. 2022; 9(5): pp. 380-389. doi: 10.1093/nop/npac044

80. R.R. Kotecha, M.P. Mehta: Optimizing the radiotherapy treatment planning process for glioblastoma. Neurooncol Pract. 2022; 9(5): pp. 351-353. doi: 10.1093/nop/npac051

81. B. Guevara, K. Cullison et al.: Simulated adaptive radiotherapy for shrinking glioblastoma resection cavities on a hybrid MRI–linear accelerator. Cancers. 2023; 15(5): p. 1555. doi: 10.3390/cancers15051555

82. T. Matsuyama, Y. Fukugawa et al.: A prospective comparison of adaptive and fixed boost plans in radiotherapy for glioblastoma. Radiat Oncol. 2022; 17(1): p. 40. doi: 10.1186/s13014-022-02007-4

83. Ö. Şenkesen, E. Tezcanlı et al.: Limited field adaptive radiotherapy for glioblastoma: changes in target volume and organ at risk doses. Radiat Oncol J. 2022; 40(1): pp. 9-19. doi: 10.3857/roj.2021.00542

84. R.J. Piper, K.K. Senthil et al.: Neuroimaging classification of progression patterns in glioblastoma: a systematic review. J Neurooncol. 2018; 139(1): pp. 77-88. doi: 10.1007/s11060-018-2843-3

85. D. Kis, L. Szivos et al.: Predicting the true extent of glioblastoma based on probabilistic tractography. Front Neurosci. 2022; 16: Article 886465, doi: 10.3389/fnins.2022.886465

86. M.D. Garrett, T.K. Yanagihara et al.: Monitoring radiation treatment effects in glioblastoma: FLAIR volume as significant predictor of survival. Tomography. 2017; 3(3): pp. 131-137. doi: 10.18383/j.tom.2017.00009

87. S. Chiesa, R. Russo et al.:MRI-derived radiomics to guide post-operative management of glioblastoma: Implication for personalized radiation treatment volume delineation. Front Med. 2023; 10: Article 1059712, doi: 10.3389/fmed.2023.1059712

88. Y. Qiu, Y. Li et al.: Toxicity and efficacy of different target volume delineations of radiation therapy based on the updated radiation therapy oncology group/national research group and european organization for research and treatment of cancer guidelines in patients with grade 3-4 glioma: a randomized controlled clinical trial. Int J Radiat Oncol Biol Phys. 2025; 121(5): p1168-1181. doi: 10.1016/j.ijrobp.2024.11.094

89. N.F. Brown, D. Ottaviani et al.: Survival outcomes and prognostic factors in glioblastoma. Cancers. 2022; 14: p. 3161. doi: 10.3390/cancers14133161

90. M.T.C. Poon, C.L.M. Sudlow et al.: Longer-term (≥2 years) survival in patients with glioblastoma in population-based studies pre- and post-2005: a systematic review and meta-analysis. Sci Rep. 2020; 10(1): Article 11622, doi: 10.1038/s41598-020-68011-

91. Phillips RM, Deek MP et al.: Metastasis-directed therapy in prostate cancer. Why, when, and how? Oncology. 2019; 33(10): p394-399. doi: 686509.

92. Triggiani L, Mazzola R et al.: Metastasis-directed stereotactic radiotherapy for oligoprogressive castration-resistant prostate cancer: a multicenter study. World J Urol. 2019; 37(12): p2631–7. doi: 10.1007/s00345-019-02717-7

93. Connor MJ, Smith A et al.: Targeting oligometastasis with stereotactic ablative radiation therapy or surgery in metastatic hormone-sensitive prostate cancer: A systematic review of prospective clinical trials. Eur Urol Oncol. 2020; 3(5): 582–93. doi: 10.1016/j.euo.2020.07.004

94. Choyke PL, Bouchelouche K.: Prostate specific membrane antigen (PSMA) imaging: the past is prologue. Trans Androl Urol. 2017; 8(4): p283–5. doi: 10.21037/tau.2019.07.20

95. Jadvar H.: Is there utility for FDG PET in prosate cancer? Semin Nucl Med. 2016; 46(6): p502–6. doi: 10.1053/j.semnuclmed.2016.07.004

96. Mottet N, Cornford P et al.: EAU - EANM - ESTRO - ESUR - ISUP – SIOG Guidelines on Prostate Cancer - European Association of Urology (2022) Available at:

https://d56bochluxqnz.cloudfront.net/documents/full-guideline/EAU-EANM-ESTRO-ESUR-ISUP_SIOG-Guidelines-on-Prostate-Cancer-2022_2022-04-25-063938_yfos.pdf.

97. Gillessen S, Bossi A et al.: Management of patients with advanced prostate cancer. Part I: intermediate-/high-risk and locally advanced disease, biochemical relapse, and side effects of hormonal treatment: report of the advanced prostate cancer consensus conference 2022. Eur Urol. 2023; 83(3): p267–93. doi: 10.1016/j.eururo.2022.11.002

98. Kirste S, Kroeze SGC et al.: Combining 68Ga-PSMA-PET/CT-directed and elective radiation therapy improves outcome in oligorecurrent prostate cancer: A retrospective multicenter study. Front Oncol. 2021; 11: 640467. doi: 10.3389/fonc.2021.640467

99. Sage EK, Vogel MME et al.: Stereotactic Body Radiotherapy (SBRT) für die Behandlung von Knochenmetastasen beim oligometastasierten Prostatakarzinom [Stereotactic body radiotherapy (SBRT) for the treatment of bone metastases in oligometastasised prostate cancer]. Aktuelle Urol. 2020; 51(3): p265–70. doi: 10.1055/a-1140-5646

100. Yin C, Ho B, Chan L et al.: Asymptomatic prostate cancer brain metastases on 68Ga-PSMA PET/CT. *Clin Nucl Med*. 2019; 44(6): e382–4. doi: 10.1097/RLU.0000000000002548

101. Jani AB, Schreibmann E, Goyal S, Halkar R, Hershatter B, Rossi RJ, et al. 18F-fluciclovine-PET/CT imaging versus conventional imaging alone to guide postprostatectomy salvage radiotherapy for prostate cancer (EMPIRE-1): a single centre, open-label, phase 2/3 randomised controlled trial. Lancet. 2021; 397(10288): 1895–904. doi: 10.1016/S0140-6736(21)00581-X

102. Karagiannis V, Wichmann V, Saarinen J, Eigeliene N, Andersen H, Jekunen A. Radiotherapy treatment modification for prostate cancer patients based on PSMA-PET/CT. Radiat Oncol. 2022; 17(1): 19. doi: 10.1186/s13014-022-01989-5

103. Albalooshi B, Al Sharhan M et al.: Direct comparison of 99mTc-PSMA SPECT/CT and 68Ga-PSMA PET/CT in patients with prostate cancer. Asia Ocean J Nucl Med Biol. 2020; 8: 1–7. doi: 10.22038/aojnmb.2019.43943.1293

104. Fallahi B, Khademi N et al.: 99mTc-PSMA SPECT/CT versus 68Ga-PSMA PET/CT in the evaluation of metastatic prostate cancer. Clin Nucl Med. 2021; 46(2): e68–74. doi: 10.1097/RLU.0000000000003410

105. Moghadam SZ, Askari E et al.: K. 99mTc-PSMA left behind: a call for collaboration. Nucl Med Mol Imaging, 2022; 56: 218–9. doi: 10.1007/s13139-022-00753-7

106. Urbán S, Meyer C et al.: Radiation dosimetry of 99mTc-PSMA I&S: A single-center prospective study. J Nucl Med. 2021; 62(8): p1075–81. doi: 10.2967/jnumed.120.253476

107. Mena E, Lindenberg L et al.: The impact of PSMA PET/CT imaging in prostate cancer radiation treatment. Semin Nucl Med. 2022; 52(2): p255–62. doi: 10.1053/j.semnuclmed.2021.12.008