

Review

Stereotactic Magnetic Resonance-Guided Adaptive and Non-Adaptive Radiotherapy on Combination MR-Linear Accelerators: Current Practice and Future Directions

John Michael Bryant , Joseph Weygand, Emily Keit, Ruben Cruz-Chamorro, Maria L. Sandoval, Ibrahim M. Oraiqat, Jacqueline Andreozzi, Gage Redler, Kujtim Latifi , Vladimir Feygelman and Stephen A. Rosenberg *

Department of Radiation Oncology, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL 33612, USA; john.bryant@moffitt.org (J.M.B.)

* Correspondence: stephen.rosenberg@moffitt.org

Simple Summary: Stereotactic body radiotherapy (SBRT) is an effective radiation therapy technique that heavily relies upon daily image guidance to achieve the necessary precision. Magnetic resonance imaging (MRI) offers significant advantages over computed tomography (CT), which has traditionally been used for daily image guidance for SBRT. Hybrid MRI and linear accelerators (MRLs) allow for the delivery of stereotactic MR-guided adaptive radiotherapy (SMART) and improve patient outcomes for many types of tumors. In this review, we summarized the evidence for SMART as it related to ablative treatments and explored how multi-parametric MRIs could continue to improve patient outcomes.



Citation: Bryant, J.M.; Weygand, J.; Keit, E.; Cruz-Chamorro, R.; Sandoval, M.L.; Oraiqat, I.M.; Andreozzi, J.; Redler, G.; Latifi, K.; Feygelman, V.; et al. Stereotactic Magnetic Resonance-Guided Adaptive and Non-Adaptive Radiotherapy on Combination MR-Linear Accelerators: Current Practice and Future Directions. *Cancers* **2023**, *15*, 2081. <https://doi.org/10.3390/cancers15072081>

Academic Editors: Sam Beddar and Michael D. Chuong

Received: 13 March 2023

Revised: 27 March 2023

Accepted: 29 March 2023

Published: 30 March 2023



Copyright: © 2023 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

Abstract: Stereotactic body radiotherapy (SBRT) is an effective radiation therapy technique that has allowed for shorter treatment courses, as compared to conventionally dosed radiation therapy. As its name implies, SBRT relies on daily image guidance to ensure that each fraction targets a tumor, instead of healthy tissue. Magnetic resonance imaging (MRI) offers improved soft-tissue visualization, allowing for better tumor and normal tissue delineation. MR-guided RT (MRgRT) has traditionally been defined by the use of offline MRI to aid in defining the RT volumes during the initial planning stages in order to ensure accurate tumor targeting while sparing critical normal tissues. However, the ViewRay MRIdian and Elekta Unity have improved upon and revolutionized the MRgRT by creating a combined MRI and linear accelerator (MRL), allowing MRgRT to incorporate online MRI in RT. MRL-based MR-guided SBRT (MRgSBRT) represents a novel solution to deliver higher doses to larger volumes of gross disease, regardless of the proximity of at-risk organs due to the (1) superior soft-tissue visualization for patient positioning, (2) real-time continuous intrafraction assessment of internal structures, and (3) daily online adaptive replanning. Stereotactic MR-guided adaptive radiation therapy (SMART) has enabled the safe delivery of ablative doses to tumors adjacent to radiosensitive tissues throughout the body. Although it is still a relatively new RT technique, SMART has demonstrated significant opportunities to improve disease control and reduce toxicity. In this review, we included the current clinical applications and the active prospective trials related to SMART. We highlighted the most impactful clinical studies at various tumor sites. In addition, we explored how MRL-based multiparametric MRI could potentially synergize with SMART to significantly change the current treatment paradigm and to improve personalized cancer care.

Keywords: radiation therapy; RT; ultra-hypofractionated radiation therapy; ablative radiation therapy; adaptive radiation therapy; image guided radiotherapy; magnetic resonance imaging; MRI; MR-guided radiation therapy; MRgRT; stereotactic body radiotherapy; SBRT; stereotactic ablative radiotherapy; SABR; stereotactic magnetic resonance-guided adaptive radiotherapy; SMART; plan optimization; tumor motion management; multiparametric MRI; mpMRI

1. Introduction

Cancer continues to be a major global health concern and a leading cause of death. There were an estimated 19.3 million new cancer diagnoses and 10.0 million cancer-related deaths worldwide in 2020 [1]. By 2040, it is estimated that there will be 29.5 million new cases and 16.3 million deaths annually worldwide [2]. Radiotherapy (RT) remains a fundamental component of an effective cancer treatment program [2]. An estimated 50% of all cancer patients receive RT as part of their care [3]. Therefore, advances within the field of radiation oncology are paramount to the improvement of cancer outcomes. Stereotactic body radiotherapy (SBRT) has emerged as a highly effective RT modality that allows for radiotherapeutic-dose escalation that can be delivered in fewer fractions, as compared to conventionally dosed RT [4]. However, this new modality requires more exact targeting to ensure that these high doses are delivered to the tumor, not the healthy, tissue. SBRT has traditionally relied on planar or volumetric (e.g., cone-beam computed tomography (CBCT)) X-ray imaging techniques to ensure proper treatment planning each day to improve accuracy [5]. However, X-ray imaging techniques are insensitive to morphological changes, relative to the tumor, in the surrounding soft tissue [6], which are often the most radiosensitive and at risk of significant treatment-related toxicity [7–9]. CBCT has lacked the ability to accurately delineate the interface between tumor and normal soft tissue, which has limited the dose that could be safely planned for delivery [10]. Additionally, intrafraction motion management with X-ray-based imaging has often relied on a surrogate, such as an external patient surface and internal fiducial markers [11]. A recent development within the field of radiation oncology is the magnetic resonance imaging-guided linear accelerators (MRLs) that can overcome some of the challenges associated with X-ray/CT-based systems.

Magnetic resonance imaging (MRI) offers improved soft-tissue delineation, allowing for the better visualization and discrimination of normal tissues and tumor targets, while being able to detect subtle physiological changes within the tissues, as well [12,13]. MR-guided RT (MRgRT) has traditionally used offline MRI to assist in defining volumes during the initial planning stages [14,15]. This contrasts with online MRgRT, which allows for daily on-table MRI and for the direct monitoring of targets and critical organs at risk (OARs) during treatment. Online MRI is the defining feature of MRL that provides all its unique capabilities and online adaptive workflow, as shown in Figure 1. MRL can acquire MR images for both treatment planning and daily set-up verification with the patient in the treatment position. Prior to treatment, each MRI acquired can be used for adjusting the plan to account for the exact positions of the targets and the normal tissue when fused with a treatment-planning CT [16,17]. When combined with dedicated software and efficient workflows, this daily MR-based adaptive planning allows for improved target coverage, opportunities for isotoxic dose delivery, and reduced normal tissue toxicity. This is called online adaptive radiotherapy and may increase the therapeutic window of RT. In addition, the MRL is capable of real-time (cine) MRI while the treatment is being delivered according to a rapid and balanced steady-state free-precession MRI acquisition technique [18], allowing for treatment-gating based on the patient anatomy directly (e.g., the tumor target) for motion control. These capabilities reduce the uncertainties in external beam radiation therapy delivery. Traditionally, larger planning target volume (PTV) margins have been used to account for these uncertainties and ensure that we treat the target appropriately. However, the unique capabilities of MRL allow for margin reduction. This, in turn, allows for higher tumor doses while conserving the normal tissue and, Therefore, widening the therapeutic window for the safe and effective delivery of MRI-guided SBRT (MRgSBRT).

This increased therapeutic window allows for safer isotoxic dose escalation. Online adaptive SBRT in an MRL is commonly referred to as stereotactic magnetic resonance-guided adaptive radiotherapy (SMART). SMART is an advanced SBRT modality that is currently being utilized for many tumor types in clinics around the globe to improve therapeutic efficacy and safety [17,19]. The global adoption of this novel MRL technology for SMART continues to accelerate. This has led to a multitude of innovative trials and registries [19,20] that explore and expand the impact of this new treatment modality. Table 1

lists all currently active trials exploring either nonadaptive MRL-based SBRT (MRL-SBRT) and SMART registered on [ClinicalTrials.gov](https://clinicaltrials.gov), accessed on 12 March 2023.

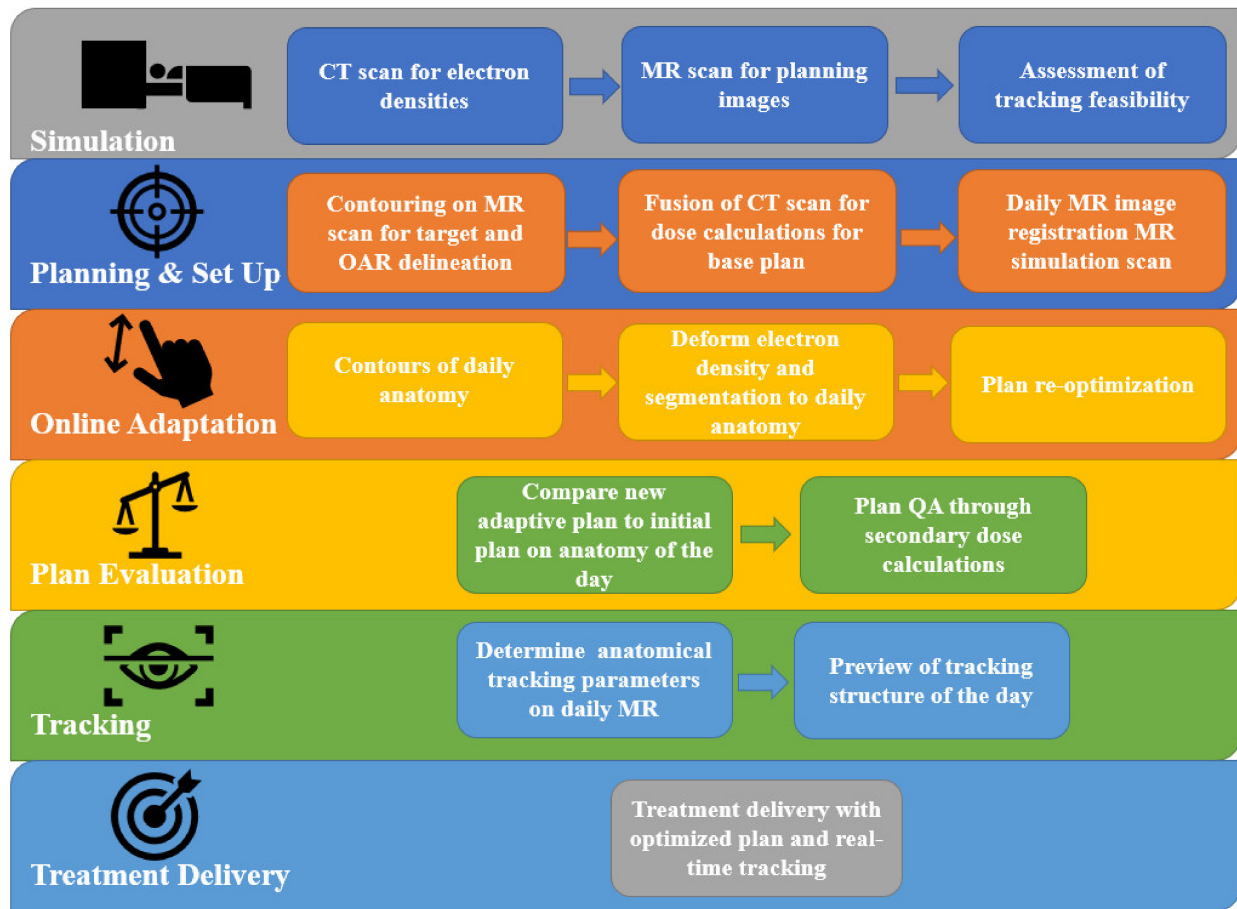


Figure 1. MRL workflow. CT: Computed tomography; MR: magnetic resonance; MRL: MR linear accelerator; OAR: organ at risk; QA: quality assurance.

Table 1. Active SMART and nonadaptive MRL-SBRT clinical trials registered on [ClinicTrials.gov](https://clinicaltrials.gov). Both actively recruiting and active but not-yet-recruiting trials were included.

Study Title	Sponsor	Site	Condition/Disease	Estimated Enrollment	ClinicalTrials.gov Identifier
A Master Protocol of Stereotactic Magnetic Resonance Guided Adaptive Radiation Therapy (SMART)	Dana–Farber Cancer Institute	All/Multiple sites	N/A	1000	NCT04115254
The MR-Linac Technical Feasibility Protocol (UMBRELLA-II)	The Netherlands Cancer Institute	All/Multiple sites	N/A	140	NCT04351204
The Multiple Outcome Evaluation of Radiation Therapy Using the MR-Linac Study (MOMENTUM)	UMC Utrecht	All/Multiple sites	N/A	6000	NCT04075305
Magnetic Resonance Guided Radiation Therapy (CONFIRM)	Dana–Farber Cancer Institute	All/Multiple sites	Gastric Cancer, Invasive Breast Cancer, in Situ Breast Cancer, Mantle Cell Lymphoma, Larynx Cancer, Bladder Cancer	70	NCT04368702

Table 1. *Cont.*

Study Title	Sponsor	Site	Condition/Disease	Estimated Enrollment	ClinicalTrials.gov Identifier
Immune Checkpoint Inhibitor and MR-guided SBRT for Limited Progressive Metastatic Carcinoma	Baptist Health South Florida	All/Multiple sites	Metastatic tumors	52	NCT04376502
Stereotactic MRI-guided Adaptive Radiation Therapy (SMART) in One Fraction (SMART-ONE)	Baptist Health South Florida	All/Multiple sites	Oligometastatic cancer, up to 10 sites of disease	30	NCT04939246
Real-Time MRI-Guided 3-Fraction Accelerated Partial Breast Irradiation in Early Breast Cancer (MAPBI)	University of Wisconsin, Madison	Breast	Breast Cancer, DCIS	30	NCT03936478
MR-Linac Guided Adaptive FSRT for Brain Metastases From Non-small Cell Lung Cancer	Sun Yat-Sen University	Central Nervous System	Brain Metastases from Non-Small Cell Lung Cancer	55	NCT04946019
Pilot Study of Same-session MR-only Simulation and Treatment With Stereotactic MRI-guided Adaptive Radiotherapy (SMART) for Oligometastases of the Spine	Washington University School of Medicine	Central Nervous System	Oligometastases of the Spine	10	NCT03878485
Locally Advanced Pancreatic Cancer Treated With ABLative Stereotactic MRI-guided Adaptive Radiation Therapy (LAP-ABLATE)	ViewRay Inc.	Gastrointestinal	Pancreatic Cancer	267	NCT05585554
Sequential Treatment With GEMBRAX and Then FOLFIRINOX Followed by Stereotactic MRI-guided Radiotherapy in Patients With Locally Advanced Pancreatic Cancer (GABRINOX-ART)	Institut du Cancer de Montpellier—Val d’Aurelle	Gastrointestinal	Pancreatic Cancer	103	NCT04570943
MR-Guided Adaptive SBRT of Primary Tumor for Pain Control in Metastatic PDAC (MASPAC)	Ludwig-Maximilians—University of Munich	Gastrointestinal	Pancreatic Cancer	92	NCT05114213
Stereotactic Radiotherapy vs. Best Supportive Care in Unfit Pancreatic Cancer Patients (PANCOSAR)	Amsterdam UMC	Gastrointestinal	Pancreatic Cancer	98	NCT05265663
Precision Radiotherapy Using MR-linac for Pancreatic Neuroendocrine Tumours in MEN1 Patients (PRIME)	J.M. de Laat	Gastrointestinal	Pancreatic Neuroendocrine Tumors	20	NCT05037461
MR-guided Pre-operative RT in Gastric Cancer	Washington University School of Medicine	Gastrointestinal	Gastric cancer	36	NCT04162665
Magnetic Resonance-guided Adaptive Stereotactic Body Radiotherapy for Hepatic Metastases (MAESTRO)	University Hospital Heidelberg	Gastrointestinal	Liver Metastases	90	NCT05027711
OAR-Based, Dose Escalated SBRT With Real-time Adaptive MRI Guidance for Liver Metastases	University of Wisconsin, Madison	Gastrointestinal	Liver Metastases	48	NCT04020276

Table 1. Cont.

Study Title	Sponsor	Site	Condition/Disease	Estimated Enrollment	ClinicalTrials.gov Identifier
Adaptative MR-Guided Stereotactic Body Radiotherapy of Liver Tumors (RASTAF)	Centre Georges Francois Leclerc	Gastrointestinal	Liver Metastases	46	NCT04242342
Radiotherapy With Iron Oxide Nanoparticles (SPION) on MR-Linac for Primary & Metastatic Hepatic Cancers	Allegheny Singer Research Institute	Gastrointestinal	Liver tumors	25	NCT04682847
Stereotactic MRI-guided Radiation Therapy for Localized Prostate Cancer (SMILE)	University Hospital Heidelberg	Genitourinary	Prostate Cancer	68	NCT04845503
Randomized Trial of Five or Two MRI-Guided Adaptive Radiotherapy Treatments for Prostate Cancer (FORT)	Weill Medical College of Cornell University	Genitourinary	Prostate Cancer	136	NCT04984343
MR-linac Guided Ultra-hypofractionated RT for Prostate Cancer	Chinese Academy of Medical Sciences	Genitourinary	Prostate Cancer	50	NCT05183074
Randomized Phase-II Trial of Salvage Radiotherapy for Prostate Cancer In 4 Weeks vs. 2 Weeks	Weill Medical College of Cornell University	Genitourinary	Prostate Cancer	134	NCT04422132
MR-Linac for Head and Neck SBRT	Sunnybrook Health Sciences Centre	Head and Neck	Head and Neck Cancer	30	NCT04809792
Nano-SMART: Nanoparticles with MR Guided SBRT in Centrally Located Lung Tumors and Pancreatic Cancer	Dana–Farber Cancer Institute	Thorax	Non-small Cell Lung Cancer, Pancreatic Cancer	100	NCT04789486
Magnetic Resonance Guided Adaptive Stereotactic Body Radiotherapy for Lung Tumors in Ultra-central Location (MAGELLAN)	University Hospital Heidelberg	Thorax	Non-small Cell Lung Cancer, Metastatic tumors	38	NCT04925583
Study of LUNG Stereotactic Adaptive Ablative Radiotherapy (LUNG STAAR)	Baptist Health South Florida	Thorax	Non-small Cell Lung Cancer	60	NCT04917224
A Multicenter Phase-II Study of Stereotactic Radiotherapy for Centrally Located Lung Tumors (STRICT-LUNG STUDY) and Ultra-centrally Located Lung Tumors (STAR-LUNG STUDY)	Rigshospitalet, Denmark	Thorax	Primary Lung Cancer, Metastatic tumors	138	NCT05354596

The two most common commercially available MRLs are the ViewRay MRIdian (ViewRay Technologies Inc., Oakwood Village, OH, USA) and Elekta Unity (Elekta AB, Stockholm, Sweden). The global adoption of MRL technology has been driven by these 2 systems, with 112 (56 of each) ViewRay MRIdian and Elekta Unity systems having been installed as of 31 December 2022 (Figure 2). Since 2019, these systems have combined to perform an estimated 37,500 treatments (Figure 3). The MRIdian system combines a 0.345 T-field strength split-bore magnet MRI with a 28 cm gap that contains the 6 MV flattening filter-free (FFF) linear accelerator components [21]. ViewRay originally produced a tri-⁶⁰Co unit; however, these have all been upgraded (except for one) to MRL [22]. The Elekta Unity combines a 1.5 T MRI (Philips, Amsterdam, The Netherlands) and a 7 MV FFF linear accelerator irradiating through a cryostat [16]. Although both ViewRay MRId-

ian and Elekta Unity are MRLs and can be utilized for the purposes of SMART, there are important distinctions between the two machines regarding their capabilities. The most obvious difference is the conventional (i.e., 1.5 T) static magnetic field (B_0) strength of Elekta Unity, as compared to the low-field (i.e., 0.345 T) MRIdian system. Higher B_0 improves the signal-to-noise ratio and generally improves overall image quality. However, the relationship between the field strength and contrast-to-noise ratio, which is important for target-tracking, is not straightforward [23]. The higher B_0 also makes multiparametric imaging easier to perform as well as provides the general capability to immediately utilize pulse sequences developed for diagnostic MRI purposes at the same field strength. However, since both system-specific and patient-induced (e.g., chemical shift and magnetic susceptibility effects) geometric distortion also scales with B_0 , it is easier to manage in the low-field machine [13,24]. Lastly, the MRIdian system has had real-time tumor-tracking with automatic beam-gating since its launch, whereas the Unity system achieved FDA approval for tracking on 28 February 2023.

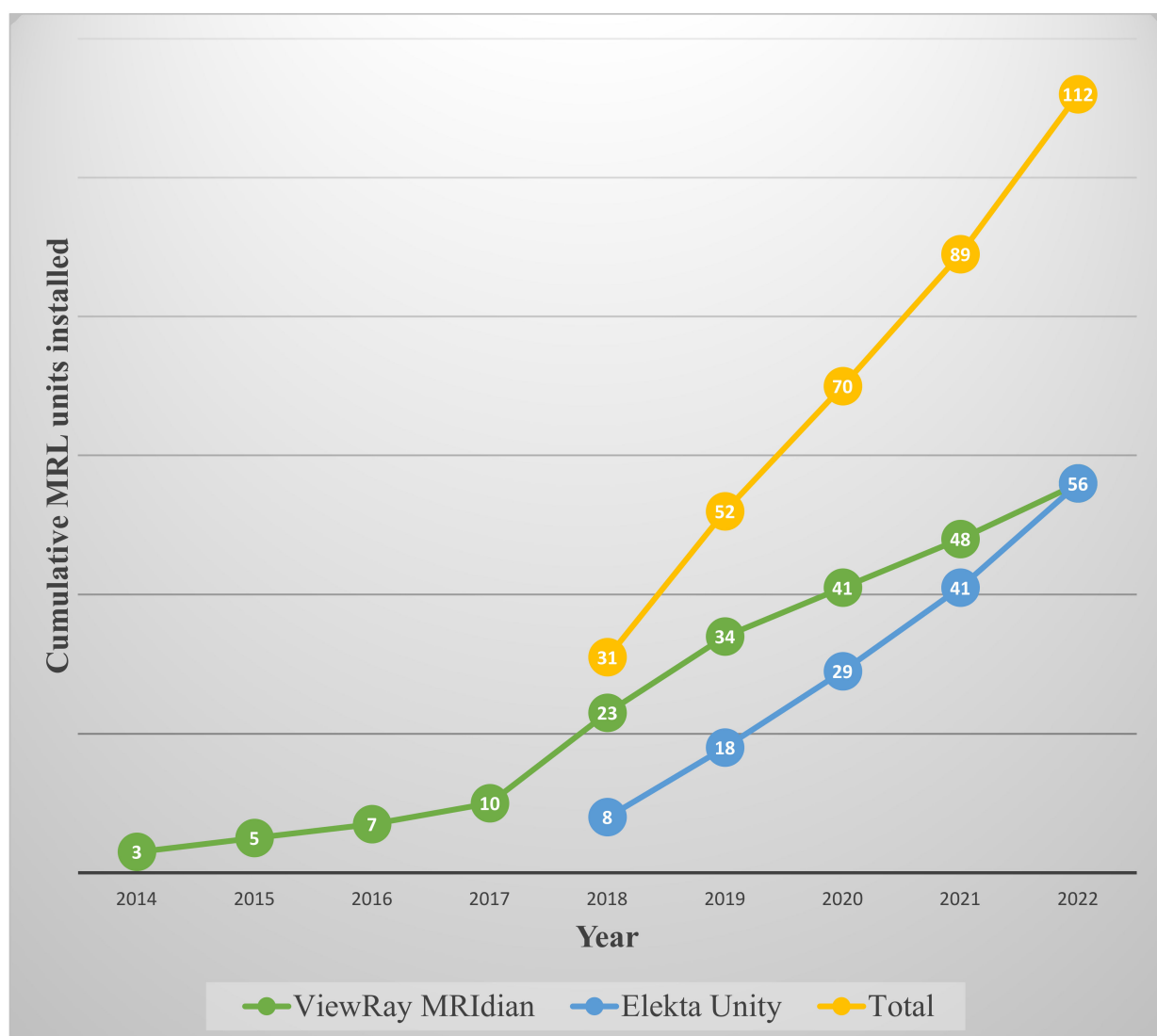


Figure 2. Cumulative installations of ViewRay MRIdian and Elekta Unity MRLs over time. ViewRay MRIdian was initially a tri- ^{60}Co system, with MRL installations beginning in 2017. All existing ViewRay MRIdian systems, except for one, have been upgraded to MRLs. Elekta Unity systems were initially pre-clinical until late 2019. All existing Elekta Unity systems have been upgraded to fully clinical systems. Data used for the creation of Figure 2 were directly provided by Elekta and ViewRay team members.

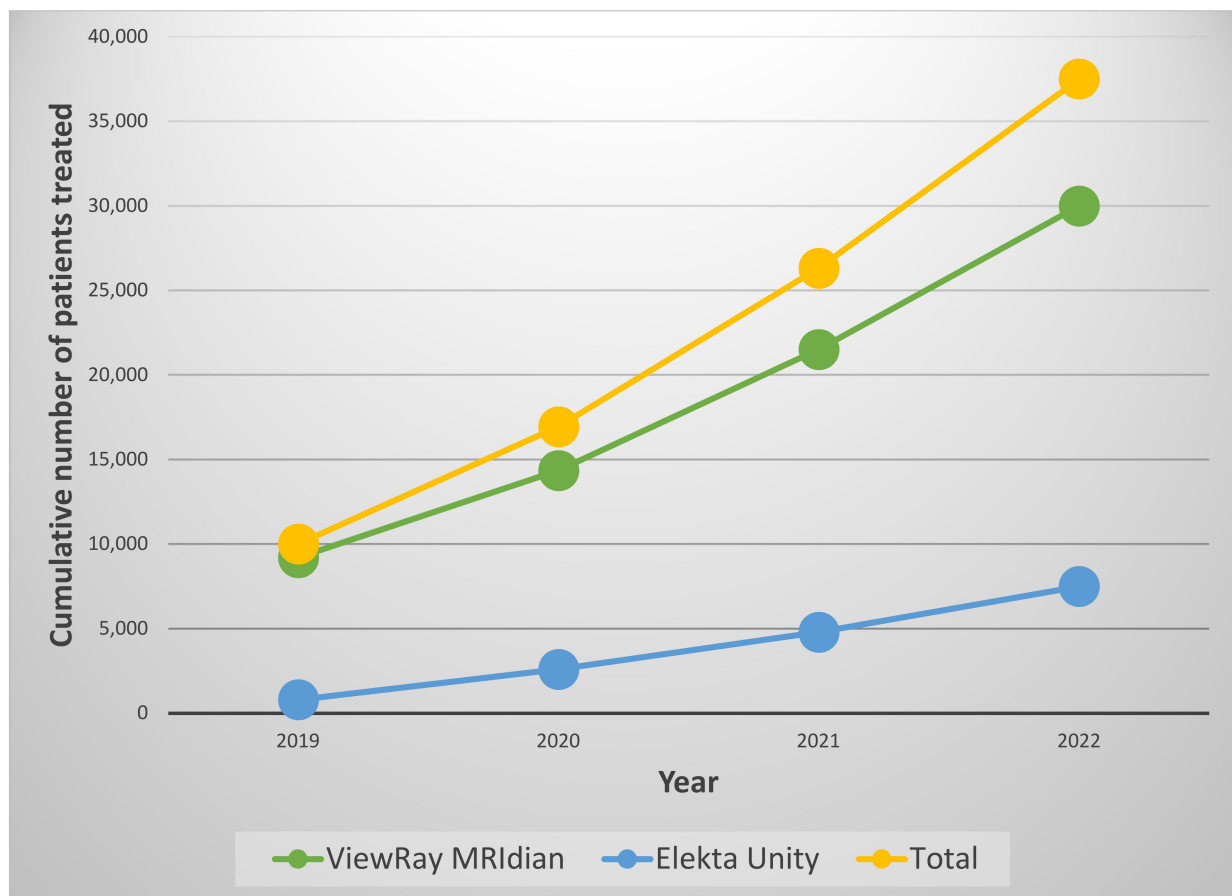


Figure 3. Cumulative treatments of ViewRay MRIdian and Elekta Unity MRLs per year since 2019. Data used for the creation of Figure 3 were directly provided by ViewRay and from data presented at the 9th annual MR in RT symposium [25].

Despite the improvements in personalized radiotherapy already achieved by MRLs, their full potential is not yet realized. MRLs could enable significant strides in personalized cancer therapy by analyzing the daily MR images for subtle intra- and peri-tumor anatomical and physiological/functional changes in response to ablative doses. The ability to identify and determine the clinical significance of the tumoral response during each fraction could be exploited for further individualized plan adaptation [26–28]; Therefore, these MRI radiomic features could allow for online biological and physiological, in addition to the current morphological, online plan adaptation in the future.

In this review, we summarized current and potential future directions for SMART clinical applications and trials, by cancer type. Although we only focused on sites that could benefit the most from SMART, this review was not comprehensive in scope. We focused on as many sites as possible where SMART has been actively improving care and has evidence of improvement over CT-based SBRT. In addition, in a separate section, we explored how existing technologies could potentially be integrated with current MRL systems to significantly improve personalized radiotherapy.

2. SMART Clinical Applications

2.1. Head and Neck Cancer

MRI plays an important role in the diagnosis and treatment of head and neck cancers (HNCs) due to the improved visualization of the muscle invasion, the perineural invasion, and the extracapsular extension [29,30]. Therefore, MRI could improve target delineation and expand the role of adaptive RT in these cancers [31]. Early data has suggested that an offline adaptation with MRL could be efficacious [32]. The limited evidence on the

treatment of HNC utilizing the tri-⁶⁰Co system demonstrated effective tumor control with low toxicity rates [33,34]. The early evidence on the treatment of HNC using an MRL demonstrated similar feasibility and safety [19,35,36]. An early report from the MOMENTUM study (NCT04075305) demonstrated the feasibility of MRgRT with a 1.5 T MRL in 13 patients with HNC [19]. These initial data have helped establish the feasibility of conventionally fractionated HNC radiotherapy using MRLs. SBRT has become an important tool for radiation oncologists in the treatment of many types of de novo and recurrent HNCs, although concerns remain regarding toxicity and appropriate tumor selection [37,38]. The advantages of SMART over conventional SBRT modalities could expand the therapeutic window of HNC SBRT. Currently, there is a prospective early-phase trial exploring SMART feasibility and safety for HNC utilizing the 1.5 T MRL (NCT04809792) that is expected to complete enrollment in late 2023.

2.2. Central and Ultra-Central Lung Tumors

SBRT is part of the standard of care for early-stage, non-operable non-small-cell lung cancer (NSCLC) [39] and has been commonly used to treat metastatic lesions in the lungs [40,41]. Lung SBRT has been demonstrated to have excellent local control and minimal toxicity rates [42–44]. However, concerns remain for using SBRT on more centrally located lung lesions due to high rates of toxicity [45]. These central lesions, defined as being within two cm of the proximal bronchial tree (PBT) by the Radiation Therapy Oncology Group (RTOG) [46], and ultra-central (UC) lesions, defined as being within one cm of the PBT, have had significantly higher rates of SBRT-related grade-3–5 toxicity, as compared to more peripherally located tumors [45–49]. Up to one-third of patients with UC lung tumors have experienced grade-3 or higher SBRT-related toxicity, and 15% died as a result of the treatment [49]. These high rates of toxicity were likely related to the uncertainty of the large internal target volume (ITV) and soft-tissue organs at risk (OARs) in the positional planning with CT-based SBRT, leading to unintentionally high doses delivered to the PBT.

SMART has overcome these limitations with the use of MR-guided online plan adaptation to push unacceptably high doses away from OARs and real-time tumor-tracking to control for respiratory motion during treatment [50–55]. SMART for central and UC lesions has been associated with local control rates approaching 96% for both primary and metastatic cancers [53]. In addition, the toxicity rates were comparable to those in peripheral lesions [53,54]. Importantly, recent evidence did not correlate the risk of late intrapulmonary hemorrhage with SMART [56], which was a primary cause of treatment-related death [49] with CT-based SBRT. These initial experiences led to the development of multiple prospective studies exploring SMART for central and ultra-central lesions. Trials such as LUNG Stereotactic Adaptive Ablative Radiotherapy (LUNG STAAR; NCT04917224) Stereotactic Radiotherapy for Centrally Located Lung Tumors (STRICT-LUNG STUDY; NCT04917224); and Ultra-Centrally Located Lung Tumors (STAR-LUNG STUDY; NCT05354596) are exploring the clinical outcomes of SMART for primary early-stage NSCLC and metastatic lesions.

2.3. Cardiac Metastases

The heart and pericardial tissues are rare sites of malignancy, with the most generous estimates of the incidence of primary and metastatic lesions being $\leq 0.03\%$ and $\leq 3\%$, respectively [57,58]. As survival continues to improve in the metastatic setting, particularly in melanoma, the incidence of cardiac metastases has increased [59,60]. The surgical resection of these lesions has traditionally been the only means of definitive therapy [61], with RT playing a purely palliative role [62]. Advances in the field of radiation oncology have indicated the feasible effective treatment of these lesions with SBRT [63]. SMART has the potential to improve the delivery of SBRT to these highly mobile lesions that have been difficult to identify with CT imaging. Currently, SMART data are very limited for these rare tumors. A single institutional experiment in five patients with cardiac lesions that were treated with SMART reported excellent tumor coverage and minimal toxicity [64]. Larger

series are required to optimize the dosage for various histologies and to better explore the role of MRgRT in cardiac tumors.

2.4. Pancreatic Cancer

The role of SBRT in borderline resectable (BRPC) and locally advanced pancreatic cancer (LAPC) has been controversial [65–70]. Although SBRT appeared to significantly improve local control, the concerns regarding the lack of improvement in overall survival and toxicity have persisted [65–72]. Data suggested that the dose escalation could have been associated with the improvements in both local control and overall survival [73–78]. Dose-escalated SBRT has historically been limited in practice due to the radiosensitive gastrointestinal organs that surround the pancreas. However, SBRT via SMART could overcome these toxicity-related challenges in pancreatic cancer due to the excellent soft-tissue visualization and online plan adaptation and gating [79–81].

Ablative SMART (A-SMART) demonstrated an excellent safety profile [82,83] and even appeared to be an effective option for elderly patients with unresectable pancreatic cancer who were at increased risk for treatment-related toxicities [84]. Initial studies exploring A-SMART for BRPC and LAPC demonstrated limited toxicity and improved clinical outcomes, with local control and overall survival rates approaching 90% and 70%, respectively [80,81,83,85–87]. In addition, pre-operative A-SMART for BRPC patients was associated with excellent negative resection rates and did not appear to increase the intra- or post-operative mortality [88]. The results of the multicenter phase-II trial, SMART for Locally Advanced Pancreatic Cancer (NCT03621644), were recently presented and demonstrated a median overall survival of 22.5 months and a 1-year overall survival of 94% [89]. The incidence of grade-3 or higher toxicity related to A-SMART was 2.2%. Due to these positive results, a phase-III trial has been announced, the Locally Advanced Pancreatic Cancer Treated with Ablative Stereotactic MRI-guided Adaptive Radiation Therapy (LAP-ABLATE) trial (NCT05585554), which will compare the standard chemotherapy to sequential chemotherapy, followed by A-SMART. Additional phase-II clinical trials exploring SMART for pancreatic pain control in metastatic disease (NCT05114213), SMART in frail and elderly patients (NCT05265663), a combination of intensified sequential chemotherapy with A-SMART (NCT04570943), and SMART for neuroendocrine pancreatic tumors (NCT05037461) are ongoing.

2.5. Liver Tumors

Surgical resection is the standard of care for primary hepatocellular carcinoma (HCC) [90] and hepatic oligometastases [91,92]; however, only one-fifth of patients are deemed eligible for surgery [93]. For unresectable hepatic tumors, SBRT could be a potential treatment option that has the advantage of not being an invasive procedure [94–96]. Over three years, SBRT achieved local control rates of over 90% for metastatic lesions, if treated with ablative doses [97]. Due to the parallel architecture of the liver, it can withstand high doses of radiation in small areas but is at high risk of radiation-induced liver disease (RILD) with larger targets [98]. In addition, the local radiosensitive gastrointestinal organs are at high risk of toxicity during liver irradiation. SBRT, in particular, has been associated with a risk of grade-3 or higher toxicity in up to one-third of patients [99], thus limiting patient selection and dose escalation. However, MR-guided SBRT can overcome many of the challenges faced by CT-based SBRT.

SMART has reduced irradiated liver volumes without an ITV (on some MRL systems that provide patient anatomy tracking/gating) and tighter PTV margins and ensured tolerances for nearby radiosensitive structures were safely and reliably respected while achieving the requisite ablative doses [50,87,100–102]. Patients have also forgone the need for invasive fiducial markers for gating and tracking with SMART. SMART for primary and metastatic liver lesions has been demonstrated to have local control rates between 75% and 100% at 21 months with a grade-3 toxicity rate of only 8% and no grade-4 toxicity or treatment-related deaths [101]. These initial reports of SMART in hepatic lesions

are promising but limited due to their retrospective nature and short follow-up periods. Multiple trials exploring liver-focused SMART have been initiated to better define its role. The phase-II Magnetic Resonance-Guided Adaptive Stereotactic Body Radiotherapy for Hepatic Metastases (MAESTRO) randomized trial is currently recruiting patients to compare ITV-based SBRT and SMART. The Adaptive MR-Guided Stereotactic Body Radiotherapy of Liver Tumors (RASTAF) phase-II trial (NCT04242342) is exploring dose escalation of up to 60 Gy in 5 fractions with SMART in all types of liver tumors. The OAR-Based, Dose-Escalated SBRT With Real-time Adaptive MRI Guidance for Liver Metastases trial (NCT04020276) is a 2-staged phase-I study that is exploring dose escalation of up to 80 Gy in a 4-plus-4 with a confirmatory expansion cohort design.

2.6. Adrenal Metastases

The adrenal gland is a common site of metastases from many malignancies [103] and the indications have been increasing for a definitive treatment in metastatic adrenal lesions [104,105]. There was insufficient evidence to determine the best local treatment modality for isolated and limited adrenal metastases [106]. While surgery is a curative modality option for isolated adrenal metastasis, it has often been contraindicated in the presence of more extensive disease, in elderly patients, and in those with other significant co-morbidities [103,107,108]. Additionally, the recovery time of these procedures usually requires lengthy hospital stays [103]. SBRT is a valid alternative when surgery is not feasible [106,109–111]. However, patients have historically presented significantly worse tumor control, as compared to adrenalectomy [108]. This has likely been due to dose limitations in conventional CT-based SBRT because of the interfractional movement of OARs [112,113], which can be up to 3 cm for local radiosensitive gastrointestinal organs, as well as intrafractional respiratory-induced movement [114]. However, a BED₁₀ of >100 Gy was associated with tumor control approaching that of a resection [111,115]. SMART was capable of respiratory-motion management and online plan adaptation for positional changes in local OARs, making it feasible for the delivery of ablative doses. The early data supported the feasibility and the efficacy of SMART in these tumors [86,116]. The recent data has supported this approach by demonstrating 1-year local control rates of 100% in a limited series [117]. The MRL Dana–Farber master trial (NCT04115254) and the SMART-ONE trial (NCT03878485) will help define the feasibility and the role of SMART for adrenal SBRT.

2.7. Kidney Cancer

The role of radiotherapy and SBRT has been limited in the treatment of primary kidney cancer [118]. SBRT could offer a benefit in large tumors (>4 cm) that are not suitable for surgical resection [119]. SBRT appeared to demonstrate exponential cell death in renal cell carcinoma, as compared to conventional fractionation [120]. However, CT-based SBRT often must use large margins [121] to account for movements during therapy [122]. MRL-based SBRT had an advantage over CT-based SBRT by eliminating the need for ITVs, one of the reasons for large margins [123]. The early data has suggested that SMART could be well tolerated with clinically meaningful disease control [124,125]. Therefore, if currently active trials establish a larger role of SBRT [126,127], SMART could play an important part in kidney cancer radiotherapy in the future.

2.8. Breast Cancer

Breast conservation is important to many people with breast cancer, and treatment strategies to avoid mastectomies have been developed that are effective and widely adopted for early-stage breast cancer. RT played an integral role in this treatment design to ensure the clinical outcomes were similar to that of mastectomy [128]. Due to concerns of normal tissue exposure and the inconvenience of 5–6 weeks of daily RT in traditional post-partial mastectomy whole-breast RT, accelerated partial-breast irradiation (APBI) was explored as a potential alternative in specially selected patients with favorable patient and

tumor characteristics [129,130]. APBI focuses solely on the areas surrounding the surgical bed and is typically delivered within 1–2 weeks. Both brachytherapy and external beam techniques were explored to determine their unique advantages and drawbacks [131,132]. Brachytherapy offers excellent conformality but is a more invasive procedure. External beam radiotherapy (EBRT) is non-invasive but requires larger margins due to the uncertainties in the daily design and the intrafractional motion management. The high dose per fraction for EBRT APBI could have contributed to late cosmetic toxicity, although evidence for this has been mixed [131,133,134], with a larger percentage of treated breast volume being a predictor for adverse cosmetic outcomes [135]. SMART could be an excellent external beam APBI modality to improve clinical outcomes. SMART could improve upon existing external beam APBI due to its superior soft-tissue visualization of the resected cavity and online plan adaptation for the daily design that could allow for a smaller PTV, or even a zero-margin PTV, without sacrificing coverage.

A single institution prospective trial of a 10-fraction with zero-margin PTV APBI on a 0.35 T MRL in 30 patients reduced treatment volumes by 52%, as compared to conventional APBI [136]. These data supported the exploration of APBI delivered with SMART. An early dosimetric analysis demonstrated that 88.5% of the possible dosimetric objectives were fulfilled during planning [137]. The early evidence of APBI delivered with MRLs demonstrated dosimetric advantages over traditional CT-based strategies. If long-term clinical and cosmetic outcome data for APBI delivered with SMART are favorable, this could become an important modality for elderly people with early-stage breast cancer, as approximately 40% of these patients are unable to complete their 5-year hormone therapy, which significantly increases the risk of disease recurrence [138]. However, the clinical benefit of SMART APBI remains unclear, as long-term outcomes for CT-based APBI are excellent. Therefore, whether the dosimetric advantages translate into clinically meaningful improvements over existing APBI techniques is not yet known. The phase-II trial, Real-Time MRI-Guided Three-Fraction Accelerated Partial-Breast Irradiation in Early Breast Cancer (MAPBI) (NCT03936478), is exploring cosmetic and clinical outcomes with SMART APBI.

2.9. Prostate Cancer

There has been an increased utilization of SBRT to reduce the length of treatment and take advantage of the low α/β ratio in prostate cancer [139,140]. The early studies demonstrated significant gastrointestinal and genitourinary toxicity [141,142]. Recent large phase-III trials have had conflicting evidence regarding toxicity [143,144]. MR-guided SBRT (Non-MRL based) is one strategy that has been employed to reduce toxicity. MRI is regularly used in the diagnosis, staging, and management of prostate cancer [145,146] due to its excellent visualization of lesions in both the prostate and the normal surrounding tissue [147]. MRI has been used during treatment planning to better visualize the critical OARs [148], to aid in contouring, and more recently, to help guide boosters to high-risk foci [149]. Therefore, nonadaptive MRL-SBRT and SMART appear to be a logical evolution in prostate SBRT [150,151].

SMART and nonadaptive MRL-SBRT offer multiple advantages over CT-based prostate SBRT, which includes include inter- and intra-fractional rectal motion management and proper daily alignment for urethral-sparing techniques. In addition, SMART and nonadaptive MRL-SBRT do not require the invasive implantation of fiducial markers for daily alignment, which is often a transrectal procedure that has been associated with complications that impacted the quality of life in up to one-third of patients [152,153]. SMART feasibility for prostate cancer is well established [154–156]. Urethral-sparing techniques demonstrated significantly low rates of acute genitourinary toxicity [157]. The results from the SCIMITAR trial, a phase-II, dual-center, single-arm trial that treated post-operative prostate cancer at high-risk for recurrence, with SBRT, demonstrated worse gastrointestinal toxicity of up to 6 months in patients treated with CT-based SBRT, as compared to MRL-SBRT [158].

The MIRAGE trial (NCT04384770) was the first phase-III trial to compare SMART with CT-based SBRT [159]. MIRAGE sought to evaluate if the aggressive margin reduction that

had been made feasible with MRL-based treatment would significantly reduce acute grade-2 or higher genitourinary toxicity, as compared to CT-guided treatment [159]. MRL-based MRgSBRT demonstrated a significant reduction in grade-2 or higher acute genitourinary (24.4% (95% CI, 15.4–35.4%) vs. 43.4% (95% CI, 32.1–55.3%); $p = 0.01$) and gastrointestinal (0.0% (95% CI, 0–4.6%) vs. 10.5% (95% CI, 4.7–19.7%); $p = 0.003$) toxicity [159]. This first prospective head-to-head study of CT-based SBRT and MRL-based MRgSBRT clearly demonstrated how MRL capabilities could translate into improved clinical outcomes.

There are multiple current phase-II trials exploring SMART in prostate cancer. The European Stereotactic MRI-Guided Radiation Therapy for Localized Prostate Cancer (SMILE) trial (NCT04845503) is exploring SMART feasibility within an estimated cohort of 68 males. In addition, a phase-II trial (NCT05183074) is exploring the utilization of an MRL to deliver SMART with simultaneously integrated boosters for MR-prominent tumor foci. Another phase-II trial (NCT04984343) is exploring SMART hypofractionation, reducing the standard 5 fractions to 2, to continue reducing treatment time in this very common cancer.

2.10. Spinal Metastases

Spine RT is an important part of metastatic disease management to improve pain, prevent pathological fractures, and prevent neurological morbidity. SBRT had improved efficacy, as compared to conventional forms of radiotherapy [160]. MRIs have been used in spine SBRT to accurately delineate the spinal cord and create a 1–2 mm planning OAR volume (PRV) to decrease disease coverage [160]. Bony structures act as surrogates for the daily design in conventional CBCT image guidance, but CBCTs are not reliable for the accurate visualization of the spinal cord. Therefore, a spinal cord PRV is created during treatment planning to account for daily motion management. MRLs could provide a benefit due to their superior demarcation of the spinal cord and other soft-tissue OAR positions with daily MRIs, as compared to CBCTs [10]. Dosimetric feasibility studies suggested that design improvements with MRI could reduce the dose to the spinal cord [161]. Daily MRIs allow for direct plan registration of the spinal cord, thereby eliminating the need for cord PRVs and allowing for greater tumor coverage. Additionally, the comparatively low fields of the MRLs, as compared to many diagnostic MRIs, have also decreased the artifact and geometric distortions caused by metal hardware [162]. Utilizing an MRL for spine SBRT also improved the integration of the CT treatment planning scan because the radiation oncologist was able to ensure the same patient position [163,164]. These advantages could allow for reduced margins and safe dose escalation. However, it remains unclear if these dosimetric advantages will be clinically meaningful, as compared to CBCT-based spine SBRT. The results of a current phase-I/II trial treating all sites of disease with SMART, including the spine (NCT04115254), and the Pilot Study of Same-Session MR-Only Simulation and Treatment with SMART for Oligometastases of the Spine (NCT03878485) could help determine the feasibility of this technique.

2.11. Oligometastatic Cancer

The increasing data have demonstrated that patients with limited metastases who were treated in a definitive manner at all sites of disease had increased overall survival [165]. This limited metastatic state is termed oligometastatic, and it blurs the line between localized and incurable systemic disease. Recent clinical trials have demonstrated the benefit of SBRT for patients with oligometastatic cancer, typically defined as between one and five metastatic lesions. Randomized phase-II studies of oligometastatic NSCLC [166] and prostate cancer [167] showed improved outcomes with SBRT at all metastatic sites. The phase-II SABR-COMET trial demonstrated that SBRT had improved overall and progression-free survival for various histologies, as compared to standard palliative therapy [168]. However, multi-site SBRT has a significant risk of increased toxicity. The NRG BR-001 trial that delivered SBRT to all sites of metastatic disease demonstrated a rate of late grade-3 or higher toxicity to be 20% at 2 years [169]. Similarly, SABR-COMET reported a 29% rate of grade-2 or higher toxicity, including 3 treatment-related deaths, in the SBRT group, as

compared to only 9% in the control group. SMART was uniquely suited for delivering high-dose SBRT to multiple sites concurrently due to its excellent therapeutic window [170]. In addition, SMART has also enabled safe isotoxic dose escalation [82,86], with increased local control and overall survival rates.

Data have been limited concerning the use of SMART in an oligometastatic setting, but SMART has been well tolerated [86,102,171]. Several ongoing clinical trials are evaluating the use of MRgRT in the management of oligometastatic disease. Notably, the SMART-ONE trial is a single-arm trial that is investigating the feasibility of delivering single-fraction MR-guided SBRT to up to 10 sites of disease (NCT04939246). The Washington University School of Medicine is exploring the use of SMART in oligometastatic disease of the spine (NCT03878485). We eagerly await the results of these trials to establish the feasibility, efficacy, and safety of MRgRT in an oligometastatic setting.

2.12. Ablative Dose Re-Irradiation

Re-irradiation (reRT) has historically been limited due to the increased risk of severe toxicity due to cumulatively high OAR doses; however, it also could provide a significant benefit in carefully selected patients with locally recurrent or progressive cancer [172,173]. Therefore, dose selection in reRT is a delicate balance between prioritizing tumor control and patient safety that usually results in modest dose delivery. Historically, these doses did not offer robust local control, especially in patients who did not proceed to surgery [174]. However, dose escalation could improve long-term local control and overall survival in reRT [174–176]. The improved therapeutic ratio of SMART could allow for the safe delivery of dose-escalated reRT.

SMART reRT data have been limited, but the treatment has been well tolerated. SMART reRT in the abdomen and pelvis demonstrated a 1-year local control rate approaching 90% [177]. With a median follow-up of 14 months, there was no acute or late grade-3 or higher toxicity, demonstrating the safety of this modality. Another recent report focused only on prostate reRT and demonstrated a 1-year disease progression-free survival rate that also approached 90%, while maintaining minimal toxicity [178]. SMART reRT appears to be associated with strong local disease control and minimal toxicity, which could warrant further investigation in clinical trials.

3. Future Directions

SMART has enabled the delivery of greater doses to tumors surrounded by some of the most radiosensitive normal tissue within the body, and this has indicated potential dose-escalated treatments that were previously thought to be infeasible, as discussed. Although this has been primarily achieved with MR-guided anatomic adaptation, we believe that the future of SMART may lie in advanced adaptation techniques. This requires the immense data stored in daily MRIs to better understand the tumoral response to treatment throughout the course of radiotherapy, and then these daily insights must be used to adjust both the dosage and fractions throughout the treatment. This would represent major a paradigm shift in the field of radiation oncology. Traditionally, dosage and fractionations were determined prior to and during treatment planning. Even with the current advances in SMART, we continue to use this approach and merely adapt to improve the delivery of a predetermined dose and fractionation. However, studying the tumor changes in response to treatment via daily MRI could provide deeper insights into the nature of a specific tumor and how it will ultimately respond to the current dose and fractionation plan.

Two novel studies, Adaptive Radiation for Locally Advanced Rectal Adenocarcinoma (NCT05108428) and Theragnostic Utilities for Neoplastic Diseases of the Rectum by MRI-Guided Radiotherapy (THUNDER2; NCT04815694), are already utilizing MRL to explore plan adaptation based on tumoral response. They are relying on the tumoral volumetric changes to identify which rectal tumors would benefit the most from sequential booster-dose escalation. Guiding treatment planning based upon volumetric response for certain

cancers is clinically feasible when using MRL in longer treatment courses of conventional and minimally hypofractionated radiotherapy. However, utilizing this same technique with SMART is far more difficult due to the significantly shorter treatment course that often does not allow enough time for tumors to demonstrate a clinically obvious volumetric response. Therefore, the more subtle and less well-understood peri- and intra-tumoral changes during therapy should be utilized to guide physiologically and biologically adaptive radiotherapy. The multiparametric MRI (mpMRI) allows for a wider breadth of imaging data to better investigate these often-imperceptible changes.

MRL-Based Multiparametric MRI

MRL adaptation has traditionally been employed for the management of interfractional tumoral and OAR changes in shape and position. However, MRI has also been used for assessing biological and physiological information [179–181], as well as for MRI techniques termed mpMRI [182]. One such technique is diffusion-weighted imaging [183] which enabled the detection of changes in water mobility [184]. These changes were correlated with tumor growth [185] and necrosis [186]. This was facilitated by mapping a parameter known as the apparent diffusion coefficient (ADC), which was then used to track the response to radiation therapy [187]. ADC mapping is particularly attractive in adaptive radiotherapy since the changes in ADC could be noted before morphological changes in the tumor [188], and these changes in diffusion could be used to guide dose-escalation strategies and biologically guided radiation plan adaptation [189,190]. Diffusion-weighted imaging has been applied using a 1.5 T linear accelerator [191–193]. Although technical challenges have been reported [194], DWI was included as an option in this simulation [35]. DWI was initially applied using the 0.35 T tri-⁶⁰Co system [195,196] and was shown to be predictive of tumor histology [197] and, in combination with deep learning, therapeutic response [198]. Technical challenges were reported [199] when the 0.35 T MRgRT system had transitioned from the tri-⁶⁰Co system to MRL, but recent applications using DWI with a 0.35 T MRL have appeared promising [200].

A potential application of MRL-based adaptive radiotherapy is the use of metabolic changes to guide RT, as this has been utilized in the recently developed PET/CT-guided radiotherapy delivery systems [201]. Cancer metabolism is severely dysregulated [202], and this dysregulation is reflected downstream, as the concentrations of many metabolites are modulated in cancer cells [203]. While positron-emission tomography (PET) [204–206] has traditionally been applied to observe the metabolic accumulation in tumor cells, MR-based techniques, such as magnetic resonance spectroscopic imaging (MRSI) [207], chemical exchange saturation transfer (CEST) [208,209], and hyperpolarized dynamic magnetic resonance spectroscopy [210], were able to interrogate metabolic processes further downstream [211]. MRSI allowed for the noninvasive mapping of a number of metabolite concentrations by simultaneously acquiring MR data in the spatial frequency and temporal domains [212]. It was applied to produce high-resolution metabolite maps in gliomas [213], and lactate mapping of glioblastoma has been performed using deuterium [214]. Additionally, using phosphorus-based MRSI, the mapping of intra- and extra-cellular pH in tumors was demonstrated [215]. The technical limitations concerning the online incorporation of MRSI with MRL as a work flow have persisted due to the relatively long scan times [216] and low sensitivity in conventional magnetic-field-strength systems [217]. Sensitivity could be counteracted by hyperpolarizing the nucleus, which has resulted in a large increase in sensitivity for a short period of time [218]. The main application has been to observe the dynamic conversion of pyruvate into lactate in tumors [219]. Lastly, CEST allowed for the indirect detection of low concentration solutes via their effect on the water MR signal [220]. CEST has been shown to predict the chemo-radiotherapeutic response of tumors [221,222].

While these MR-based metabolic-imaging techniques have yet to be incorporated into online MRgRT due to the technical challenges, they have significant potential for assessing biological behavior in adaptive RT. The additional incorporation of artificial

intelligence into the interpretation of mpMRI data could facilitate biologically driven RT plan adaptation [223,224].

4. Barriers and Limitations

Although MRLs represent one of the most exciting advancements within the field of radiation oncology, these combined linear accelerators have limitations. This novel technology is resource intensive, requiring considerable financial and time investments for operation. The commissioning of MRL requires the development of departmental MR-safety protocols similar to those for diagnostic MRIs, which include MRI safety questionnaires for all patients and thorough MRI safety training for all users with an emphasis on ferrous-material awareness [225]. MRL uses a different workflow, as compared to other linear accelerators; thus, all members of the treatment team, including the physician, physicists, and therapists, must learn to properly operate MRLs [226]. Furthermore, the daily time requirement for online adaptive radiotherapy can be substantial, from 30 to 60 min per treatment, to allow for adequate plan evaluation, adaptation, and treatment delivery, even with an experienced team. This limits total patient throughput and can often require considerable time-at-machine for physicians and physicists.

MRLs also have physical limitations due to the special physics of concurrent MRI with external beam radiotherapy. Lorentz forces have resulted in overdosing hollow organs and required an advanced treatment planning system [227]. MRI geometric distortion, the uncertainty associated with MRI regarding radiation isocenter distance, the multi-leaf collimator position error, and the uncertainties in voxel size and tracking have presented additional physical limitations [101]. Therefore, the familiarity and expertise of physicians, dosimetrists, and physicists regarding these special physics were required for optimal treatment planning and establishing more robust quality assurance methods [86]. MRIs lack electron density and attenuation coefficient information. Therefore, CT images are still required for treatment planning. Additionally, there is a lack of a six-degree couch for adjustments due to the confined space of the MRLinac system.

Patient selection is critical for a successful MRL program. Special attention is required for patients with claustrophobia, large body habitus, and MRI-incompatible implanted devices. Patients with claustrophobia may require pre-treatment anxiolytic therapy or may not be able to tolerate it at all. Patients with large body habitus may not be able to fit within the geometric dimensions of the machine. Even if the patient physically fits into the machine, they may exceed the maximal field-of-view, which can result in aliasing artifacts. This is especially important when using special devices, such as coils, depending on the treatment site.

Diligent screening for all potentially implanted ferromagnetic devices is required for all patients, and alternative treatment options should be considered in these cases.

MRL has many advantages over CT-based linear accelerators. However, MRL was not designed to be a replacement for CT-based linear accelerators. We found that MRL was best suited in cases where its unique advantages were required to deliver a treatment that would be too dangerous in a CT-based linear accelerator.

5. Conclusions

MRL is rapidly becoming an integral instrument for personalized radiotherapy. SMART represents the next generation of SBRT by expanding the therapeutic window due to its vastly improved precision through enhanced soft-tissue resolution and daily MR-guided online adaptation, along with real-time gating in MRIdian. Safe dose escalation using isotoxic approaches with SMART appears to be improving disease outcomes across multiple tumor sites. There are a multitude of cutting-edge clinical trials currently in progress to establish this new modality's role in many types of cancer. Looking forward, MRL and mpMRI appear to have significant synergistic potential, in conjunction with SMART, in personalized cancer therapy.

Author Contributions: Conceptualization, J.M.B. and S.A.R.; methodology, J.M.B.; writing—original draft preparation, J.M.B. and J.W.; writing—review and editing, J.M.B., J.W., E.K., R.C.-C., M.L.S., I.M.O., J.A., G.R., K.L.; visualization, J.M.B.; supervision, S.A.R. and V.F.; project administration, J.M.B. and S.A.R.; funding acquisition, S.A.R. All authors have read and agreed to the published version of the manuscript.

Funding: Submission fees were paid by ViewRay, Inc., Oakwood, OH, USA.

Data Availability Statement: The data presented in this study are available in this article.

Acknowledgments: We thank the ViewRay and Elekta team members who provided us with an MRL installation and treatment data.

Conflicts of Interest: Stephen Rosenberg has received research grants from ViewRay, Inc. He also received an honorarium and has served on the Lung Research Consortium Advisory Board for ViewRay, Inc. Vladimir Feygelman and Kujtim Latifi have received consulting fees from ViewRay, Inc. No other authors have any conflict of interest to declare.

References

1. Sung, H.; Ferlay, J.; Siegel, R.L.; Laversanne, M.; Soerjomataram, I.; Jemal, A.; Bray, F. 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. [\[CrossRef\]](#) [\[PubMed\]](#)
2. Abdel-Wahab, M.; Gondhowiardjo, S.S.; Rosa, A.A.; Lievens, Y.; El-Haj, N.; Polo Rubio, J.A.; Prajogi, G.B.; Helgadottir, H.; Zubizarreta, E.; Meghzifene, A.; et al. Global Radiotherapy: Current Status and Future Directions-White Paper. *JCO Glob. Oncol.* **2021**, *7*, 827–842. [\[CrossRef\]](#) [\[PubMed\]](#)
3. Atun, R.; Jaffray, D.A.; Barton, M.B.; Bray, F.; Baumann, M.; Vikram, B.; Hanna, T.P.; Knaul, F.M.; Lievens, Y.; Lui, T.Y.; et al. Expanding global access to radiotherapy. *Lancet Oncol.* **2015**, *16*, 1153–1186. [\[CrossRef\]](#)
4. Onishi, H.; Shirato, H.; Nagata, Y.; Hiraoka, M.; Fujino, M.; Gomi, K.; Niibe, Y.; Karasawa, K.; Hayakawa, K.; Takai, Y.; et al. Hypofractionated stereotactic radiotherapy (HypoFXST) for stage I non-small cell lung cancer: Updated results of 257 patients in a Japanese multi-institutional study. *J. Thorac. Oncol.* **2007**, *2*, S94–S100. [\[CrossRef\]](#)
5. Jaffray, D.A. Image-guided radiotherapy: From current concept to future perspectives. *Nat. Rev. Clin. Oncol.* **2012**, *9*, 688–699. [\[CrossRef\]](#)
6. Letourneau, D.; Martinez, A.A.; Lockman, D.; Yan, D.; Vargas, C.; Ivaldi, G.; Wong, J. Assessment of residual error for online cone-beam CT-guided treatment of prostate cancer patients. *Int. J. Radiat. Oncol. Biol. Phys.* **2005**, *62*, 1239–1246. [\[CrossRef\]](#)
7. Thomas, D.H.; Santhanam, A.; Kishan, A.U.; Cao, M.; Lamb, J.; Min, Y.; O’Connell, D.; Yang, Y.; Agazaryan, N.; Lee, P.; et al. Initial clinical observations of intra- and interfractional motion variation in MR-guided lung SBRT. *Br. J. Radiol.* **2018**, *91*, 20170522. [\[CrossRef\]](#) [\[PubMed\]](#)
8. Byun, D.J.; Gorovets, D.J.; Jacobs, L.M.; Happersett, L.; Zhang, P.; Pei, X.; Burleson, S.; Zhang, Z.; Hunt, M.; McBride, S.; et al. Strict bladder filling and rectal emptying during prostate SBRT: Does it make a dosimetric or clinical difference? *Radiat. Oncol.* **2020**, *15*, 239. [\[CrossRef\]](#) [\[PubMed\]](#)
9. Loi, M.; Magallon-Baro, A.; Suker, M.; van Eijck, C.; Sharma, A.; Hoogeman, M.; Nuytens, J. Pancreatic cancer treated with SBRT: Effect of anatomical interfraction variations on dose to organs at risk. *Radiother. Oncol.* **2019**, *134*, 67–73. [\[CrossRef\]](#)
10. Noel, C.E.; Parikh, P.J.; Spencer, C.R.; Green, O.L.; Hu, Y.; Mutic, S.; Olsen, J.R. Comparison of onboard low-field magnetic resonance imaging versus onboard computed tomography for anatomy visualization in radiotherapy. *Acta Oncol.* **2015**, *54*, 1474–1482. [\[CrossRef\]](#)
11. Casamassima, F.; Cavedon, C.; Francescon, P.; Stancanelli, J.; Avanzo, M.; Cora, S.; Scalchi, P. Use of motion tracking in stereotactic body radiotherapy: Evaluation of uncertainty in off-target dose distribution and optimization strategies. *Acta Oncol.* **2006**, *45*, 943–947. [\[CrossRef\]](#) [\[PubMed\]](#)
12. Yousaf, T.; Dervenoulas, G.; Politis, M. Advances in MRI Methodology. *Int. Rev. Neurobiol.* **2018**, *141*, 31–76. [\[CrossRef\]](#)
13. Weygand, J.; Fuller, C.D.; Ibbott, G.S.; Mohamed, A.S.; Ding, Y.; Yang, J.; Hwang, K.P.; Wang, J. Spatial Precision in Magnetic Resonance Imaging-Guided Radiation Therapy: The Role of Geometric Distortion. *Int. J. Radiat. Oncol. Biol. Phys.* **2016**, *95*, 1304–1316. [\[CrossRef\]](#) [\[PubMed\]](#)
14. Chang, J.H.; Lim Joon, D.; Nguyen, B.T.; Hiew, C.Y.; Esler, S.; Angus, D.; Chao, M.; Wada, M.; Quong, G.; Khoo, V. MRI scans significantly change target coverage decisions in radical radiotherapy for prostate cancer. *J. Med. Imaging Radiat. Oncol.* **2014**, *58*, 237–243. [\[CrossRef\]](#) [\[PubMed\]](#)
15. Dhermain, F. Radiotherapy of high-grade gliomas: Current standards and new concepts, innovations in imaging and radiotherapy, and new therapeutic approaches. *Chin. J. Cancer* **2014**, *33*, 16–24. [\[CrossRef\]](#)
16. Lagendijk, J.J.; Raaymakers, B.W.; van Vulpen, M. The magnetic resonance imaging-linac system. *Semin. Radiat. Oncol.* **2014**, *24*, 207–209. [\[CrossRef\]](#)

17. Acharya, S.; Fischer-Valuck, B.W.; Kashani, R.; Parikh, P.; Yang, D.; Zhao, T.; Green, O.; Wooten, O.; Li, H.H.; Hu, Y.; et al. Online Magnetic Resonance Image Guided Adaptive Radiation Therapy: First Clinical Applications. *Int. J. Radiat. Oncol. Biol. Phys.* **2016**, *94*, 394–403. [\[CrossRef\]](#) [\[PubMed\]](#)
18. Carr, H.Y. Steady-State Free Precession in Nuclear Magnetic Resonance. *Phys. Rev.* **1958**, *112*, 1693–1701. [\[CrossRef\]](#)
19. De Mol van Otterloo, S.R.; Christodouleas, J.P.; Blezer, E.L.A.; Akhlat, H.; Brown, K.; Choudhury, A.; Eggert, D.; Erickson, B.A.; Daamen, L.A.; Faivre-Finn, C.; et al. Patterns of Care, Tolerability, and Safety of the First Cohort of Patients Treated on a Novel High-Field MR-Linac within the MOMENTUM Study: Initial Results from a Prospective Multi-Institutional Registry. *Int. J. Radiat. Oncol. Biol. Phys.* **2021**, *111*, 867–875. [\[CrossRef\]](#) [\[PubMed\]](#)
20. De Leon, J.; Woods, A.; Twentyman, T.; Meade, M.; Sproule, V.; Chandran, S.; Christiansen, J.; Kennedy, N.; Marney, M.; Barooshian, K.; et al. Analysis of data to Advance Personalised Therapy with MR-Linac (ADAPT-MRL). *Clin. Transl. Radiat. Oncol.* **2021**, *31*, 64–70. [\[CrossRef\]](#)
21. Menard, C.; van der Heide, U.A. Introduction: Magnetic resonance imaging comes of age in radiation oncology. *Semin. Radiat. Oncol.* **2014**, *24*, 149–150. [\[CrossRef\]](#) [\[PubMed\]](#)
22. Mutic, S.; Dempsey, J.F. The ViewRay system: Magnetic resonance-guided and controlled radiotherapy. *Semin. Radiat. Oncol.* **2014**, *24*, 196–199. [\[CrossRef\]](#) [\[PubMed\]](#)
23. Wachowicz, K.; De Zanche, N.; Yip, E.; Volotovskyy, V.; Fallone, B.G. CNR considerations for rapid real-time MRI tumor tracking in radiotherapy hybrid devices: Effects of B0 field strength. *Med. Phys.* **2016**, *43*, 4903. [\[CrossRef\]](#)
24. Hori, M.; Hagiwara, A.; Goto, M.; Wada, A.; Aoki, S. Low-Field Magnetic Resonance Imaging: Its History and Renaissance. *Investig. Radiol.* **2021**, *56*, 669–679. [\[CrossRef\]](#) [\[PubMed\]](#)
25. Shultz, D.C. High Field MR Guided Using the Unity Platform. In Proceedings of the 9th MR in RT Symposium, Los Angeles, CA, USA, 7 February 2023.
26. Gillies, R.J.; Bhujwala, Z.M.; Evelhoch, J.; Garwood, M.; Neeman, M.; Robinson, S.P.; Sotak, C.H.; Van Der Sanden, B. Applications of magnetic resonance in model systems: Tumor biology and physiology. *Neoplasia* **2000**, *2*, 139–151. [\[CrossRef\]](#) [\[PubMed\]](#)
27. Tomaszewski, M.R.; Gillies, R.J. The Biological Meaning of Radiomic Features. *Radiology* **2021**, *299*, E256. [\[CrossRef\]](#)
28. Tomaszewski, M.R.; Latifi, K.; Boyer, E.; Palm, R.F.; El Naqa, I.; Moros, E.G.; Hoffe, S.E.; Rosenberg, S.A.; Frakes, J.M.; Gillies, R.J. Delta radiomics analysis of Magnetic Resonance guided radiotherapy imaging data can enable treatment response prediction in pancreatic cancer. *Radiat. Oncol.* **2021**, *16*, 237. [\[CrossRef\]](#)
29. Park, S.I.; Guenette, J.P.; Suh, C.H.; Hanna, G.J.; Chung, S.R.; Baek, J.H.; Lee, J.H.; Choi, Y.J. The diagnostic performance of CT and MRI for detecting extranodal extension in patients with head and neck squamous cell carcinoma: A systematic review and diagnostic meta-analysis. *Eur. Radiol.* **2021**, *31*, 2048–2061. [\[CrossRef\]](#) [\[PubMed\]](#)
30. Sumi, M.; Nakamura, T. Extranodal spread in the neck: MRI detection on the basis of pixel-based time-signal intensity curve analysis. *J. Magn. Reson. Imaging* **2011**, *33*, 830–838. [\[CrossRef\]](#) [\[PubMed\]](#)
31. Boeke, S.; Monnich, D.; van Timmeren, J.E.; Balermipas, P. MR-Guided Radiotherapy for Head and Neck Cancer: Current Developments, Perspectives, and Challenges. *Front. Oncol.* **2021**, *11*, 616156. [\[CrossRef\]](#) [\[PubMed\]](#)
32. Chuter, R.W.; Pollitt, A.; Whitehurst, P.; MacKay, R.I.; van Herk, M.; McWilliam, A. Assessing MR-linac radiotherapy robustness for anatomical changes in head and neck cancer. *Phys. Med. Biol.* **2018**, *63*, 125020. [\[CrossRef\]](#)
33. Fischer-Valuck, B.W.; Henke, L.; Green, O.; Kashani, R.; Acharya, S.; Bradley, J.D.; Robinson, C.G.; Thomas, M.; Zoberi, I.; Thorstad, W.; et al. Two-and-a-half-year clinical experience with the world's first magnetic resonance image guided radiation therapy system. *Adv. Radiat. Oncol.* **2017**, *2*, 485–493. [\[CrossRef\]](#)
34. Chen, A.M.; Cao, M.; Hsu, S.; Lamb, J.; Mikaelian, A.; Yang, Y.; Agazaryan, N.; Low, D.A.; Steinberg, M.L. Magnetic resonance imaging guided reirradiation of recurrent and second primary head and neck cancer. *Adv. Radiat. Oncol.* **2017**, *2*, 167–175. [\[CrossRef\]](#)
35. McDonald, B.A.; Vedam, S.; Yang, J.; Wang, J.; Castillo, P.; Lee, B.; Sobremonte, A.; Ahmed, S.; Ding, Y.; Mohamed, A.S.R.; et al. Initial Feasibility and Clinical Implementation of Daily MR-Guided Adaptive Head and Neck Cancer Radiation Therapy on a 1.5T MR-Linac System: Prospective R-IDEAL 2a/2b Systematic Clinical Evaluation of Technical Innovation. *Int. J. Radiat. Oncol. Biol. Phys.* **2021**, *109*, 1606–1618. [\[CrossRef\]](#) [\[PubMed\]](#)
36. Chen, A.M.; Hsu, S.; Lamb, J.; Yang, Y.; Agazaryan, N.; Steinberg, M.L.; Low, D.A.; Cao, M. MRI-guided radiotherapy for head and neck cancer: Initial clinical experience. *Clin. Transl. Oncol.* **2018**, *20*, 160–168. [\[CrossRef\]](#) [\[PubMed\]](#)
37. Malik, N.H.; Kim, M.S.; Chen, H.; Poon, I.; Husain, Z.; Eskander, A.; Boldt, G.; Louie, A.V.; Karam, I. Stereotactic Radiation Therapy for De Novo Head and Neck Cancers: A Systematic Review and Meta-Analysis. *Adv. Radiat. Oncol.* **2021**, *6*, 100628. [\[CrossRef\]](#)
38. Strom, T.; Wishka, C.; Caudell, J.J. Stereotactic Body Radiotherapy for Recurrent Unresectable Head and Neck Cancers. *Cancer Control* **2016**, *23*, 6–11. [\[CrossRef\]](#) [\[PubMed\]](#)
39. Sebastian, N.T.; Xu-Welliver, M.; Williams, T.M. Stereotactic body radiation therapy (SBRT) for early stage non-small cell lung cancer (NSCLC): Contemporary insights and advances. *J. Thorac. Dis.* **2018**, *10*, S2451–S2464. [\[CrossRef\]](#)
40. Wulf, J.; Hädinger, U.; Oppitz, U.; Thiele, W.; Ness-Dourdoumas, R.; Flentje, M. Stereotactic radiotherapy of targets in the lung and liver. *Strahlenther. Onkol.* **2001**, *177*, 645–655. [\[CrossRef\]](#)

41. Palma, D.A.; Olson, R.; Harrow, S.; Gaede, S.; Louie, A.V.; Haasbeek, C.; Mulroy, L.; Lock, M.; Rodrigues, G.B.; Yaremko, B.P.; et al. Stereotactic ablative radiotherapy versus standard of care palliative treatment in patients with oligometastatic cancers (SABR-COMET): A randomised, phase 2, open-label trial. *Lancet* **2019**, *393*, 2051–2058. [\[CrossRef\]](#) [\[PubMed\]](#)
42. Videtic, G.M.M.; Donington, J.; Giuliani, M.; Heinzerling, J.; Karas, T.Z.; Kelsey, C.R.; Lally, B.E.; Latzka, K.; Lo, S.S.; Moghanaki, D.; et al. Stereotactic body radiation therapy for early-stage non-small cell lung cancer: Executive Summary of an ASTRO Evidence-Based Guideline. *Pract. Radiat. Oncol.* **2017**, *7*, 295–301. [\[CrossRef\]](#) [\[PubMed\]](#)
43. Timmerman, R.; Paulus, R.; Galvin, J.; Michalski, J.; Straube, W.; Bradley, J.; Fakiris, A.; Bezjak, A.; Videtic, G.; Johnstone, D.; et al. Stereotactic Body Radiation Therapy for Inoperable Early Stage Lung Cancer. *JAMA* **2010**, *303*, 1070–1076. [\[CrossRef\]](#) [\[PubMed\]](#)
44. Timmerman, R.D.; Hu, C.; Michalski, J.M.; Bradley, J.C.; Galvin, J.; Johnstone, D.W.; Choy, H. Long-term Results of Stereotactic Body Radiation Therapy in Medically Inoperable Stage I Non-Small Cell Lung Cancer. *JAMA Oncol.* **2018**, *4*, 1287–1288. [\[CrossRef\]](#) [\[PubMed\]](#)
45. Timmerman, R.; McGarry, R.; Yiannoutsos, C.; Papiez, L.; Tudor, K.; DeLuca, J.; Ewing, M.; Abdulrahman, R.; DesRosiers, C.; Williams, M.; et al. Excessive toxicity when treating central tumors in a phase II study of stereotactic body radiation therapy for medically inoperable early-stage lung cancer. *J. Clin. Oncol.* **2006**, *24*, 4833–4839. [\[CrossRef\]](#) [\[PubMed\]](#)
46. Bezjak, A.; Paulus, R.; Gaspar, L.E.; Timmerman, R.D.; Straube, W.L.; Ryan, W.F.; Garces, Y.I.; Pu, A.T.; Singh, A.K.; Videtic, G.M.; et al. Safety and Efficacy of a Five-Fraction Stereotactic Body Radiotherapy Schedule for Centrally Located Non-Small-Cell Lung Cancer: NRG Oncology/RTOG 0813 Trial. *J. Clin. Oncol.* **2019**, *37*, 1316–1325. [\[CrossRef\]](#)
47. Fakiris, A.J.; McGarry, R.C.; Yiannoutsos, C.T.; Papiez, L.; Williams, M.; Henderson, M.A.; Timmerman, R. Stereotactic body radiation therapy for early-stage non-small-cell lung carcinoma: Four-year results of a prospective phase II study. *Int. J. Radiat. Oncol. Biol. Phys.* **2009**, *75*, 677–682. [\[CrossRef\]](#) [\[PubMed\]](#)
48. Chaudhuri, A.A.; Tang, C.; Binkley, M.S.; Jin, M.; Wynne, J.F.; von Eyben, R.; Hara, W.Y.; Trakul, N.; Loo, B.W., Jr.; Diehn, M. Stereotactic ablative radiotherapy (SABR) for treatment of central and ultra-central lung tumors. *Lung Cancer* **2015**, *89*, 50–56. [\[CrossRef\]](#)
49. Lindberg, K.; Grozman, V.; Karlsson, K.; Lindberg, S.; Lax, I.; Wersall, P.; Persson, G.F.; Josipovic, M.; Khalil, A.A.; Moeller, D.S.; et al. The HILUS-Trial-a Prospective Nordic Multicenter Phase 2 Study of Ultracentral Lung Tumors Treated With Stereotactic Body Radiotherapy. *J. Thorac. Oncol.* **2021**, *16*, 1200–1210. [\[CrossRef\]](#)
50. Henke, L.; Kashani, R.; Yang, D.; Zhao, T.; Green, O.; Olsen, L.; Rodriguez, V.; Wooten, H.O.; Li, H.H.; Hu, Y.; et al. Simulated Online Adaptive Magnetic Resonance-Guided Stereotactic Body Radiation Therapy for the Treatment of Oligometastatic Disease of the Abdomen and Central Thorax: Characterization of Potential Advantages. *Int. J. Radiat. Oncol. Biol. Phys.* **2016**, *96*, 1078–1086. [\[CrossRef\]](#)
51. Regnery, S.; Buchele, C.; Weykamp, F.; Pohl, M.; Hoegen, P.; Eichkorn, T.; Held, T.; Ristau, J.; Rippke, C.; Konig, L.; et al. Adaptive MR-Guided Stereotactic Radiotherapy is Beneficial for Ablative Treatment of Lung Tumors in High-Risk Locations. *Front. Oncol.* **2021**, *11*, 757031. [\[CrossRef\]](#) [\[PubMed\]](#)
52. Ligtens, H.; Hackett, S.L.; Merckel, L.G.; Snoeren, L.; Kontaxis, C.; Zachiu, C.; Bol, G.H.; Verhoeff, J.J.C.; Fast, M.F. Towards mid-position based Stereotactic Body Radiation Therapy using online magnetic resonance imaging guidance for central lung tumours. *Phys. Imaging Radiat. Oncol.* **2022**, *23*, 24–31. [\[CrossRef\]](#) [\[PubMed\]](#)
53. Finazzi, T.; Haasbeek, C.J.A.; Spoelstra, F.O.B.; Palacios, M.A.; Admiraal, M.A.; Bruynzeel, A.M.E.; Slotman, B.J.; Lagerwaard, F.J.; Senan, S. Clinical Outcomes of Stereotactic MR-Guided Adaptive Radiation Therapy for High-Risk Lung Tumors. *Int. J. Radiat. Oncol. Biol. Phys.* **2020**, *107*, 270–278. [\[CrossRef\]](#) [\[PubMed\]](#)
54. Henke, L.E.; Olsen, J.R.; Contreras, J.A.; Curcuro, A.; DeWees, T.A.; Green, O.L.; Michalski, J.; Mutic, S.; Roach, M.C.; Bradley, J.D.; et al. Stereotactic MR-Guided Online Adaptive Radiation Therapy (SMART) for Ultracentral Thorax Malignancies: Results of a Phase 1 Trial. *Adv. Radiat. Oncol.* **2019**, *4*, 201–209. [\[CrossRef\]](#) [\[PubMed\]](#)
55. Bryant, J.M.; Sim, A.J.; Feygelman, V.; Latifi, K.; Rosenberg, S.A. Adaptive hypofractionated and stereotactic body radiotherapy for lung tumors with real-time MRI guidance. *Front. Oncol.* **2023**, *13*, 1061854. [\[CrossRef\]](#)
56. Sandoval, M.L.; Sim, A.J.; Bryant, J.M.; Bhandari, M.; Wuthrick, E.J.; Perez, B.A.; Dilling, T.J.; Redler, G.; Andreozzi, J.; Nardella, L.; et al. MR-Guided SBRT/Hypofractionated RT for Metastatic and Primary Central and Ultracentral Lung Lesions. *JTO Clin. Res. Rep.* **2023**, 100488. [\[CrossRef\]](#)
57. Reardon, M.J.; Walkes, J.C.; Benjamin, R. Therapy insight: Malignant primary cardiac tumors. *Nat. Clin. Pract. Cardiovasc. Med.* **2006**, *3*, 548–553. [\[CrossRef\]](#)
58. Hudzik, B.; Miszalski-Jamka, K.; Glowacki, J.; Lekston, A.; Gierlotka, M.; Zembala, M.; Polonski, L.; Gasior, M. Malignant tumors of the heart. *Cancer Epidemiol.* **2015**, *39*, 665–672. [\[CrossRef\]](#)
59. Goldberg, A.D.; Blankstein, R.; Padera, R.F. Tumors metastatic to the heart. *Circulation* **2013**, *128*, 1790–1794. [\[CrossRef\]](#)
60. Wolchok, J.D.; Chiarion-Sileni, V.; Gonzalez, R.; Rutkowski, P.; Grob, J.J.; Cowey, C.L.; Lao, C.D.; Wagstaff, J.; Schadendorf, D.; Ferrucci, P.F.; et al. Overall Survival with Combined Nivolumab and Ipilimumab in Advanced Melanoma. *N. Engl. J. Med.* **2017**, *377*, 1345–1356. [\[CrossRef\]](#)
61. Murphy, M.C.; Sweeney, M.S.; Putnam, J.B., Jr.; Walker, W.E.; Frazier, O.H.; Ott, D.A.; Cooley, D.A. Surgical treatment of cardiac tumors: A 25-year experience. *Ann. Thorac. Surg.* **1990**, *49*, 612–617; discussion 617–618. [\[CrossRef\]](#)
62. Cham, W.C.; Freiman, A.H.; Carstens, P.H.; Chu, F.C. Radiation therapy of cardiac and pericardial metastases. *Radiology* **1975**, *114*, 701–704. [\[CrossRef\]](#)

63. Bonomo, P.; Livi, L.; Rampini, A.; Meattini, I.; Agresti, B.; Simontacchi, G.; Paiar, F.; Mangoni, M.; Bonucci, I.; Greto, D.; et al. Stereotactic body radiotherapy for cardiac and paracardiac metastases: University of Florence experience. *Radiol. Med.* **2013**, *118*, 1055–1065. [[CrossRef](#)] [[PubMed](#)]
64. Sim, A.J.; Palm, R.F.; DeLozier, K.B.; Feygelman, V.; Latifi, K.; Redler, G.; Washington, I.R.; Wuthrick, E.J.; Rosenberg, S.A. MR-guided stereotactic body radiation therapy for intracardiac and pericardial metastases. *Clin. Transl. Radiat. Oncol.* **2020**, *25*, 102–106. [[CrossRef](#)] [[PubMed](#)]
65. Katz, M.H.G.; Shi, Q.; Meyers, J.P.; Herman, J.M.; Choung, M.; Wolpin, B.M.; Ahmad, S.; Marsh, R.d.W.; Schwartz, L.H.; Behr, S.; et al. Alliance A021501: Preoperative mFOLFIRINOX or mFOLFIRINOX plus hypofractionated radiation therapy (RT) for borderline resectable (BR) adenocarcinoma of the pancreas. *J. Clin. Oncol.* **2021**, *39*, 377. [[CrossRef](#)]
66. Chang, D.T.; Schellenberg, D.; Shen, J.; Kim, J.; Goodman, K.A.; Fisher, G.A.; Ford, J.M.; Desser, T.; Quon, A.; Koong, A.C. Stereotactic radiotherapy for unresectable adenocarcinoma of the pancreas. *Cancer* **2009**, *115*, 665–672. [[CrossRef](#)] [[PubMed](#)]
67. Hammel, P.; Huguet, F.; van Laethem, J.L.; Goldstein, D.; Glimelius, B.; Artru, P.; Borbath, I.; Bouche, O.; Shannon, J.; Andre, T.; et al. Effect of Chemoradiotherapy vs Chemotherapy on Survival in Patients with Locally Advanced Pancreatic Cancer Controlled after 4 Months of Gemcitabine with or without Erlotinib: The LAP07 Randomized Clinical Trial. *JAMA* **2016**, *315*, 1844–1853. [[CrossRef](#)]
68. Koong, A.C.; Le, Q.T.; Ho, A.; Fong, B.; Fisher, G.; Cho, C.; Ford, J.; Poen, J.; Gibbs, I.C.; Mehta, V.K.; et al. Phase I study of stereotactic radiosurgery in patients with locally advanced pancreatic cancer. *Int. J. Radiat. Oncol. Biol. Phys.* **2004**, *58*, 1017–1021. [[CrossRef](#)]
69. Koong, A.C.; Christofferson, E.; Le, Q.T.; Goodman, K.A.; Ho, A.; Kuo, T.; Ford, J.M.; Fisher, G.A.; Greco, R.; Norton, J.; et al. Phase II study to assess the efficacy of conventionally fractionated radiotherapy followed by a stereotactic radiosurgery boost in patients with locally advanced pancreatic cancer. *Int. J. Radiat. Oncol. Biol. Phys.* **2005**, *63*, 320–323. [[CrossRef](#)]
70. Hoyer, M.; Roed, H.; Sengelov, L.; Traberg, A.; Ohlhuis, L.; Pedersen, J.; Nellesmann, H.; Kiil Berthelsen, A.; Eberholst, F.; Engelholm, S.A.; et al. Phase-II study on stereotactic radiotherapy of locally advanced pancreatic carcinoma. *Radiother. Oncol.* **2005**, *76*, 48–53. [[CrossRef](#)]
71. Schellenberg, D.; Goodman, K.A.; Lee, F.; Chang, S.; Kuo, T.; Ford, J.M.; Fisher, G.A.; Quon, A.; Desser, T.S.; Norton, J.; et al. Gemcitabine chemotherapy and single-fraction stereotactic body radiotherapy for locally advanced pancreatic cancer. *Int. J. Radiat. Oncol. Biol. Phys.* **2008**, *72*, 678–686. [[CrossRef](#)]
72. Schellenberg, D.; Kim, J.; Christman-Skieller, C.; Chun, C.L.; Columbo, L.A.; Ford, J.M.; Fisher, G.A.; Kunz, P.L.; Van Dam, J.; Quon, A.; et al. Single-fraction stereotactic body radiation therapy and sequential gemcitabine for the treatment of locally advanced pancreatic cancer. *Int. J. Radiat. Oncol. Biol. Phys.* **2011**, *81*, 181–188. [[CrossRef](#)]
73. Zhu, X.; Ju, X.; Cao, Y.; Shen, Y.; Cao, F.; Qing, S.; Fang, F.; Jia, Z.; Zhang, H. Patterns of Local Failure after Stereotactic Body Radiation Therapy and Sequential Chemotherapy as Initial Treatment for Pancreatic Cancer: Implications of Target Volume Design. *Int. J. Radiat. Oncol. Biol. Phys.* **2019**, *104*, 101–110. [[CrossRef](#)] [[PubMed](#)]
74. Bernard, V.; Herman, J.M. Pancreas SBRT: Who, What, When, Where, and How. *Pract. Radiat. Oncol.* **2020**, *10*, 183–185. [[CrossRef](#)] [[PubMed](#)]
75. Arcelli, A.; Guido, A.; Buwenge, M.; Simoni, N.; Mazzarotto, R.; Macchia, G.; Deodato, F.; Cilla, S.; Bonomo, P.; Scotti, V.; et al. Higher Biologically Effective Dose Predicts Survival in SBRT of Pancreatic Cancer: A Multicentric Analysis (PAULA-1). *Anticancer Res.* **2020**, *40*, 465–472. [[CrossRef](#)]
76. Krishnan, S.; Chadha, A.S.; Suh, Y.; Chen, H.C.; Rao, A.; Das, P.; Minsky, B.D.; Mahmood, U.; Delclos, M.E.; Sawakuchi, G.O.; et al. Focal Radiation Therapy Dose Escalation Improves Overall Survival in Locally Advanced Pancreatic Cancer Patients Receiving Induction Chemotherapy and Consolidative Chemoradiation. *Int. J. Radiat. Oncol. Biol. Phys.* **2016**, *94*, 755–765. [[CrossRef](#)] [[PubMed](#)]
77. Ma, S.J.; Prezzano, K.M.; Hermann, G.M.; Singh, A.K. Dose escalation of radiation therapy with or without induction chemotherapy for unresectable locally advanced pancreatic cancer. *Radiat. Oncol.* **2018**, *13*, 214. [[CrossRef](#)]
78. Reyngold, M.; O'Reilly, E.M.; Varghese, A.M.; Fiasconaro, M.; Zinovoy, M.; Romesser, P.B.; Wu, A.; Hajj, C.; Cuaron, J.J.; Tuli, R.; et al. Association of Ablative Radiation Therapy with Survival Among Patients with Inoperable Pancreatic Cancer. *JAMA Oncol.* **2021**, *7*, 735–738. [[CrossRef](#)] [[PubMed](#)]
79. Tchelebi, L.T.; Zaorsky, N.G.; Rosenberg, J.C.; Sharma, N.K.; Tuanquin, L.C.; Mackley, H.B.; Ellis, R.J. Reducing the Toxicity of Radiotherapy for Pancreatic Cancer With Magnetic Resonance-guided Radiotherapy. *Toxicol. Sci.* **2020**, *175*, 19–23. [[CrossRef](#)]
80. Bohoudi, O.; Bruynzeel, A.M.E.; Senan, S.; Cuijpers, J.P.; Slotman, B.J.; Lagerwaard, F.J.; Palacios, M.A. Fast and robust online adaptive planning in stereotactic MR-guided adaptive radiation therapy (SMART) for pancreatic cancer. *Radiother. Oncol.* **2017**, *125*, 439–444. [[CrossRef](#)]
81. Rudra, S.; Jiang, N.; Rosenberg, S.A.; Olsen, J.R.; Roach, M.C.; Wan, L.; Portelance, L.; Mellon, E.A.; Bruynzeel, A.; Lagerwaard, F.; et al. Using adaptive magnetic resonance image-guided radiation therapy for treatment of inoperable pancreatic cancer. *Cancer Med.* **2019**, *8*, 2123–2132. [[CrossRef](#)]
82. Chuong, M.D.; Bryant, J.; Mittauer, K.E.; Hall, M.; Kotecha, R.; Alvarez, D.; Romaguera, T.; Rubens, M.; Adamson, S.; Godley, A.; et al. Ablative 5-Fraction Stereotactic Magnetic Resonance-Guided Radiation Therapy with On-Table Adaptive Replanning and Elective Nodal Irradiation for Inoperable Pancreas Cancer. *Pract. Radiat. Oncol.* **2021**, *11*, 134–147. [[CrossRef](#)]

83. Hassanzadeh, C.; Rudra, S.; Bommireddy, A.; Hawkins, W.G.; Wang-Gillam, A.; Fields, R.C.; Cai, B.; Park, J.; Green, O.; Roach, M.; et al. Ablative Five-Fraction Stereotactic Body Radiation Therapy for Inoperable Pancreatic Cancer Using Online MR-Guided Adaptation. *Adv. Radiat. Oncol.* **2021**, *6*, 100506. [\[CrossRef\]](#) [\[PubMed\]](#)
84. Bryant, J.; Palm, R.F.; Herrera, R.; Rubens, M.; Hoffe, S.E.; Kim, D.W.; Kaiser, A.; Ucar, A.; Fleming, J.; De Zarraga, F.; et al. Multi-Institutional Outcomes of Patients Aged 75 years and Older with Pancreatic Ductal Adenocarcinoma Treated with 5-Fraction Ablative Stereotactic Magnetic Resonance Image-Guided Adaptive Radiation Therapy (A-SMART). *Cancer Control* **2023**, *30*, 10732748221150228. [\[CrossRef\]](#) [\[PubMed\]](#)
85. Heerkens, H.D.; van Vulpen, M.; Erickson, B.; Reerink, O.; Intven, M.P.; van den Berg, C.A.; Molenaar, I.Q.; Vleggaar, F.P.; Meijer, G.J. MRI guided stereotactic radiotherapy for locally advanced pancreatic cancer. *Br. J. Radiol.* **2018**, *91*, 20170563. [\[CrossRef\]](#) [\[PubMed\]](#)
86. Henke, L.; Kashani, R.; Robinson, C.; Curcuru, A.; DeWees, T.; Bradley, J.; Green, O.; Michalski, J.; Mutic, S.; Parikh, P.; et al. Phase I trial of stereotactic MR-guided online adaptive radiation therapy (SMART) for the treatment of oligometastatic or unresectable primary malignancies of the abdomen. *Radiother. Oncol.* **2018**, *126*, 519–526. [\[CrossRef\]](#) [\[PubMed\]](#)
87. Hall, W.A.; Straza, M.W.; Chen, X.; Mickevicius, N.; Erickson, B.; Schultz, C.; Awan, M.; Ahunbay, E.; Li, X.A.; Paulson, E.S. Initial clinical experience of Stereotactic Body Radiation Therapy (SBRT) for liver metastases, primary liver malignancy, and pancreatic cancer with 4D-MRI based online adaptation and real-time MRI monitoring using a 1.5 Tesla MR-Linac. *PLoS ONE* **2020**, *15*, e0236570. [\[CrossRef\]](#)
88. Bryant, J.M.; Palm, R.F.; Liveringhouse, C.; Boyer, E.; Hodul, P.; Malafa, M.; Denbo, J.; Kim, D.; Carballido, E.; Fleming, J.B.; et al. Surgical and Pathologic Outcomes of Pancreatic Adenocarcinoma (PA) After Preoperative Ablative Stereotactic Magnetic Resonance Image Guided Adaptive Radiation Therapy (A-SMART). *Adv. Radiat. Oncol.* **2022**, *7*, 101045. [\[CrossRef\]](#) [\[PubMed\]](#)
89. Parikh, P.J.; Lee, P.; Low, D.; Kim, J.; Mittauer, K.E.; Bassetti, M.F.; Glide-Hurst, C.; Raldow, A.; Yang, Y.; Portelance, L.; et al. Stereotactic MR-Guided On-Table Adaptive Radiation Therapy (SMART) for Patients with Borderline or Locally Advanced Pancreatic Cancer: Primary Endpoint Outcomes of a Prospective Phase II Multi-Center International Trial. *Int. J. Radiat. Oncol.* **2022**, *114*, 1062–1063. [\[CrossRef\]](#)
90. Benson, A.B.; D’Angelica, M.I.; Abbott, D.E.; Anaya, D.A.; Anders, R.; Are, C.; Bachini, M.; Borad, M.; Brown, D.; Burgoyne, A.; et al. Hepatobiliary Cancers, Version 2.2021, NCCN Clinical Practice Guidelines in Oncology. *J. Natl. Compr. Cancer Netw.* **2021**, *19*, 541–565. [\[CrossRef\]](#)
91. Adam, R.; Chiche, L.; Aloia, T.; Elias, D.; Salmon, R.; Rivoire, M.; Jaeck, D.; Saric, J.; Le Treut, Y.P.; Belghiti, J.; et al. Hepatic resection for noncolorectal nonendocrine liver metastases: Analysis of 1452 patients and development of a prognostic model. *Ann. Surg.* **2006**, *244*, 524–535. [\[CrossRef\]](#) [\[PubMed\]](#)
92. Nordlinger, B.; Sorbye, H.; Glimelius, B.; Poston, G.J.; Schlag, P.M.; Rougier, P.; Bechstein, W.O.; Primrose, J.N.; Walpole, E.T.; Finch-Jones, M.; et al. Perioperative FOLFOX4 chemotherapy and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC 40983): Long-term results of a randomised, controlled, phase 3 trial. *Lancet Oncol.* **2013**, *14*, 1208–1215. [\[CrossRef\]](#)
93. Smith, J.J.; D’Angelica, M.I. Surgical management of hepatic metastases of colorectal cancer. *Hematol. Oncol. Clin. N. Am.* **2015**, *29*, 61–84. [\[CrossRef\]](#)
94. Ruers, T.; Van Coevorden, F.; Punt, C.J.; Pierie, J.E.; Borel-Rinkes, I.; Ledermann, J.A.; Poston, G.; Bechstein, W.; Lentz, M.A.; Mauer, M.; et al. Local Treatment of Unresectable Colorectal Liver Metastases: Results of a Randomized Phase II Trial. *JNCI J. Natl. Cancer Inst.* **2017**, *109*, dxj015. [\[CrossRef\]](#)
95. Rim, C.H.; Lee, J.S.; Kim, S.Y.; Seong, J. Comparison of radiofrequency ablation and ablative external radiotherapy for the treatment of intrahepatic malignancies: A hybrid meta-analysis. *JHEP Rep.* **2023**, *5*, 100594. [\[CrossRef\]](#) [\[PubMed\]](#)
96. Dawson, L.A.; Winter, K.A.; Knox, J.J.; Zhu, A.X.; Krishnan, S.; Guha, C.; Kachnic, L.A.; Gillin, M.; Hong, T.S.; Craig, T.; et al. NRG/RTOG 1112: Randomized Phase III Study of Sorafenib vs. Stereotactic Body Radiation Therapy (SBRT) Followed by Sorafenib in Hepatocellular Carcinoma (HCC) (NCT01730937). In Proceedings of the ASTRO’s 64th Annual Meeting, San Antonio, TX, USA, 23–26 October 2022; p. 1057.
97. Ohri, N.; Tome, W.A.; Mendez Romero, A.; Miften, M.; Ten Haken, R.K.; Dawson, L.A.; Grimm, J.; Yorke, E.; Jackson, A. Local Control After Stereotactic Body Radiation Therapy for Liver Tumors. *Int. J. Radiat. Oncol. Biol. Phys.* **2021**, *110*, 188–195. [\[CrossRef\]](#)
98. Pan, C.C.; Kavanagh, B.D.; Dawson, L.A.; Li, X.A.; Das, S.K.; Miften, M.; Ten Haken, R.K. Radiation-associated liver injury. *Int. J. Radiat. Oncol. Biol. Phys.* **2010**, *76*, S94–S100. [\[CrossRef\]](#) [\[PubMed\]](#)
99. Sterzing, F.; Brunner, T.B.; Ernst, I.; Baus, W.W.; Greve, B.; Herfarth, K.; Guckenberger, M. Stereotactic body radiotherapy for liver tumors: Principles and practical guidelines of the DEGRO Working Group on Stereotactic Radiotherapy. *Strahlenther. Onkol.* **2014**, *190*, 872–881. [\[CrossRef\]](#) [\[PubMed\]](#)
100. Feldman, A.M.; Modh, A.; Glide-Hurst, C.; Chetty, I.J.; Movsas, B. Real-time Magnetic Resonance-guided Liver Stereotactic Body Radiation Therapy: An Institutional Report Using a Magnetic Resonance-Linac System. *Cureus* **2019**, *11*, e5774. [\[CrossRef\]](#) [\[PubMed\]](#)
101. Rosenberg, S.A.; Henke, L.E.; Shaverdian, N.; Mittauer, K.; Wojcieszynski, A.P.; Hullett, C.R.; Kamrava, M.; Lamb, J.; Cao, M.; Green, O.L.; et al. A Multi-Institutional Experience of MR-Guided Liver Stereotactic Body Radiation Therapy. *Adv. Radiat. Oncol.* **2019**, *4*, 142–149. [\[CrossRef\]](#) [\[PubMed\]](#)

102. Boldrini, L.; Cellini, F.; Manfredi, S.; Chiloire, G.; Teodoli, S.; Cusumano, D.; Fionda, B.; Mattiucci, G.C.; De Gaetano, A.M.; Azario, L.; et al. Use of Indirect Target Gating in Magnetic Resonance-guided Liver Stereotactic Body Radiotherapy: Case Report of an Oligometastatic Patient. *Cureus* **2018**, *10*, e2292. [\[CrossRef\]](#)
103. Moreno, P.; de la Quintana Basarrate, A.; Musholt, T.J.; Paunovic, I.; Puccini, M.; Vidal, O.; Ortega, J.; Kraimps, J.L.; Bollo Arocena, E.; Rodriguez, J.M.; et al. Adrenalectomy for solid tumor metastases: Results of a multicenter European study. *Surgery* **2013**, *154*, 1215–1222; discussion 1222–1223. [\[CrossRef\]](#) [\[PubMed\]](#)
104. Planchard, D.; Popat, S.; Kerr, K.; Novello, S.; Smit, E.F.; Faivre-Finn, C.; Mok, T.S.; Reck, M.; Van Schil, P.E.; Hellmann, M.D.; et al. Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann. Oncol.* **2018**, *29*, iv192–iv237. [\[CrossRef\]](#) [\[PubMed\]](#)
105. Yaney, A.; Stevens, A.; Monk, P.; Martin, D.; Diaz, D.A.; Wang, S.J. Radiotherapy in Oligometastatic, Oligorecurrent and Oligoprogressive Prostate Cancer: A Mini-Review. *Front. Oncol.* **2022**, *12*, 932637. [\[CrossRef\]](#) [\[PubMed\]](#)
106. Scorsetti, M.; Alongi, F.; Filippi, A.R.; Pentimalli, S.; Navarria, P.; Clerici, E.; Castiglioni, S.; Tozzi, A.; Reggiori, G.; Mancosu, P.; et al. Long-term local control achieved after hypofractionated stereotactic body radiotherapy for adrenal gland metastases: A retrospective analysis of 34 patients. *Acta Oncol.* **2012**, *51*, 618–623. [\[CrossRef\]](#) [\[PubMed\]](#)
107. Alexandrescu, S.T.; Croitoru, A.E.; Grigorie, R.T.; Tomescu, D.R.; Droc, G.; Grasu, M.C.; Popescu, I. Aggressive surgical approach in patients with adrenal-only metastases from hepatocellular carcinoma enables higher survival rates than standard systemic therapy. *Hepatobiliary Pancreat. Dis. Int.* **2021**, *20*, 28–33. [\[CrossRef\]](#)
108. Gunjur, A.; Duong, C.; Ball, D.; Siva, S. Surgical and ablative therapies for the management of adrenal ‘oligometastases’—A systematic review. *Cancer Treat. Rev.* **2014**, *40*, 838–846. [\[CrossRef\]](#) [\[PubMed\]](#)
109. Holy, R.; Piroth, M.; Pinkawa, M.; Eble, M.J. Stereotactic body radiation therapy (SBRT) for treatment of adrenal gland metastases from non-small cell lung cancer. *Strahlenther. Onkol.* **2011**, *187*, 245–251. [\[CrossRef\]](#) [\[PubMed\]](#)
110. Rudra, S.; Malik, R.; Ranck, M.C.; Farrey, K.; Golden, D.W.; Hasselle, M.D.; Weichselbaum, R.R.; Salama, J.K. Stereotactic body radiation therapy for curative treatment of adrenal metastases. *Technol. Cancer Res. Treat.* **2013**, *12*, 217–224. [\[CrossRef\]](#)
111. Chance, W.W.; Nguyen, Q.N.; Mehran, R.; Welsh, J.W.; Gomez, D.R.; Balter, P.; Komaki, R.; Liao, Z.; Chang, J.Y. Stereotactic ablative radiotherapy for adrenal gland metastases: Factors influencing outcomes, patterns of failure, and dosimetric thresholds for toxicity. *Pract. Radiat. Oncol.* **2017**, *7*, e195–e203. [\[CrossRef\]](#)
112. Wysocka, B.; Kassam, Z.; Lockwood, G.; Brierley, J.; Dawson, L.A.; Buckley, C.A.; Jaffray, D.; Cummings, B.; Kim, J.; Wong, R.; et al. Interfraction and respiratory organ motion during conformal radiotherapy in gastric cancer. *Int. J. Radiat. Oncol. Biol. Phys.* **2010**, *77*, 53–59. [\[CrossRef\]](#)
113. Knybel, L.; Cvek, J.; Otahal, B.; Jonszta, T.; Molenda, L.; Czerny, D.; Skacelikova, E.; Rybar, M.; Dvorak, P.; Felzl, D. The analysis of respiration-induced pancreatic tumor motion based on reference measurement. *Radiat. Oncol.* **2014**, *9*, 192. [\[CrossRef\]](#) [\[PubMed\]](#)
114. Chen, B.; Hu, Y.; Liu, J.; Cao, A.N.; Ye, L.X.; Zeng, Z.C. Respiratory motion of adrenal gland metastases: Analyses using four-dimensional computed tomography images. *Phys. Med.* **2017**, *38*, 54–58. [\[CrossRef\]](#) [\[PubMed\]](#)
115. Desai, A.; Rai, H.; Haas, J.; Witten, M.; Blacksburn, S.; Schneider, J.G. A Retrospective Review of CyberKnife Stereotactic Body Radiotherapy for Adrenal Tumors (Primary and Metastatic): Winthrop University Hospital Experience. *Front. Oncol.* **2015**, *5*, 185. [\[CrossRef\]](#) [\[PubMed\]](#)
116. Palacios, M.A.; Bohoudi, O.; Bruynzeel, A.M.E.; van Sorsen de Koste, J.R.; Cobussen, P.; Slotman, B.J.; Lagerwaard, F.J.; Senan, S. Role of Daily Plan Adaptation in MR-Guided Stereotactic Ablative Radiation Therapy for Adrenal Metastases. *Int. J. Radiat. Oncol. Biol. Phys.* **2018**, *102*, 426–433. [\[CrossRef\]](#)
117. Michalet, M.; Bettaieb, O.; Khalfi, S.; Ghorbel, A.; Valdenaire, S.; Debuire, P.; Ailleres, N.; Draghici, R.; De Meric De Bellefon, M.; Charissoux, M.; et al. Stereotactic MR-Guided Radiotherapy for Adrenal Gland Metastases: First Clinical Results. *J. Clin. Med.* **2022**, *12*, 291. [\[CrossRef\]](#)
118. Motzer, R.J.; Jonasch, E.; Agarwal, N.; Alva, A.; Baine, M.; Beckermann, K.; Carlo, M.I.; Choueiri, T.K.; Costello, B.A.; Derweesh, I.H.; et al. Kidney Cancer, Version 3.2022, NCCN Clinical Practice Guidelines in Oncology. *J. Natl. Compr. Cancer Netw.* **2022**, *20*, 71–90. [\[CrossRef\]](#)
119. Siva, S.; Correa, R.J.M.; Warner, A.; Staehler, M.; Ellis, R.J.; Ponsky, L.; Kaplan, I.D.; Mahadevan, A.; Chu, W.; Gandhidasan, S.; et al. Stereotactic Ablative Radiotherapy for $\geq T1b$ Primary Renal Cell Carcinoma: A Report from the International Radiosurgery Oncology Consortium for Kidney (IROCK). *Int. J. Radiat. Oncol. Biol. Phys.* **2020**, *108*, 941–949. [\[CrossRef\]](#)
120. Siva, S.; Ali, M.; Correa, R.J.M.; Muacevic, A.; Ponsky, L.; Ellis, R.J.; Lo, S.S.; Onishi, H.; Swaminath, A.; McLaughlin, M.; et al. 5-year outcomes after stereotactic ablative body radiotherapy for primary renal cell carcinoma: An individual patient data meta-analysis from IROCK (the International Radiosurgery Consortium of the Kidney). *Lancet Oncol.* **2022**, *23*, 1508–1516. [\[CrossRef\]](#)
121. Sonier, M.; Chu, W.; Lalani, N.; Erler, D.; Cheung, P.; Korol, R. Implementation of a volumetric modulated arc therapy treatment planning solution for kidney and adrenal stereotactic body radiation therapy. *Med. Dosim.* **2016**, *41*, 323–328. [\[CrossRef\]](#) [\[PubMed\]](#)
122. Prins, F.M.; Stemkens, B.; Kerkmeijer, L.G.W.; Barendrecht, M.M.; de Boer, H.J.; Vonken, E.P.A.; Lagendijk, J.J.W.; Tijssen, R.H.N. Intrafraction Motion Management of Renal Cell Carcinoma With Magnetic Resonance Imaging-Guided Stereotactic Body Radiation Therapy. *Pract. Radiat. Oncol.* **2019**, *9*, e55–e61. [\[CrossRef\]](#) [\[PubMed\]](#)
123. Keller, B.; Bruynzeel, A.M.E.; Tang, C.; Swaminath, A.; Kerkmeijer, L.; Chu, W. Adaptive Magnetic Resonance-Guided Stereotactic Body Radiotherapy: The Next Step in the Treatment of Renal Cell Carcinoma. *Front. Oncol.* **2021**, *11*, 634830. [\[CrossRef\]](#)

124. Rudra, S.; Fischer-Valuck, B.; Pachynski, R.; Daly, M.; Green, O. Magnetic Resonance Image Guided Stereotactic Body Radiation Therapy to the Primary Renal Mass in Metastatic Renal Cell Carcinoma. *Adv. Radiat. Oncol.* **2019**, *4*, 566–570. [\[CrossRef\]](#)
125. Tetar, S.U.; Bohoudi, O.; Senan, S.; Palacios, M.A.; Oei, S.S.; Wel, A.M.V.; Slotman, B.J.; Moorselaar, R.; Lagerwaard, F.J.; Bruynzeel, A.M.E. The Role of Daily Adaptive Stereotactic MR-Guided Radiotherapy for Renal Cell Cancer. *Cancers* **2020**, *12*, 2763. [\[CrossRef\]](#) [\[PubMed\]](#)
126. Lalani, A.-K.A.; Swaminath, A.; Pond, G.R.; Morgan, S.C.; Azad, A.; Chu, W.; Winkquist, E.; Kapoor, A.; Bonert, M.; Bramson, J.L.; et al. Phase II trial of cytoreductive stereotactic hypofractionated radiotherapy with combination ipilimumab/nivolumab for metastatic kidney cancer (CYTOSHRINK). *J. Clin. Oncol.* **2022**, *40*, TPS398. [\[CrossRef\]](#)
127. Siva, S.; Chesson, B.; Bressel, M.; Pryor, D.; Higgs, B.; Reynolds, H.M.; Hardcastle, N.; Montgomery, R.; Vanneste, B.; Khoo, V.; et al. TROG 15.03 phase II clinical trial of Focal Ablative STereotactic Radiosurgery for Cancers of the Kidney—FASTRACK II. *BMC Cancer* **2018**, *18*, 1030. [\[CrossRef\]](#)
128. Early Stage Breast Cancer. Consent Statement. 1990. Available online: <https://consensus.nih.gov/1990/1990earlystagebreastcancer081html.htm> (accessed on 12 March 2023).
129. Acharya, S.; Hsieh, S.; Michalski, J.M.; Shinohara, E.T.; Perkins, S.M. Distance to Radiation Facility and Treatment Choice in Early-Stage Breast Cancer. *Int. J. Radiat. Oncol. Biol. Phys.* **2016**, *94*, 691–699. [\[CrossRef\]](#) [\[PubMed\]](#)
130. Joo, J.H.; Ki, Y.; Jeon, H.; Kim, D.W.; Jung, J.; Kim, S.S. Who are the optimal candidates for partial breast irradiation? *Asia Pac. J. Clin. Oncol.* **2021**, *17*, 305–311. [\[CrossRef\]](#) [\[PubMed\]](#)
131. Meattini, I.; Marrazzo, L.; Saieva, C.; Desideri, I.; Scotti, V.; Simontacchi, G.; Bonomo, P.; Greto, D.; Mangoni, M.; Scoccianti, S.; et al. Accelerated Partial-Breast Irradiation Compared With Whole-Breast Irradiation for Early Breast Cancer: Long-Term Results of the Randomized Phase III APBI-IMRT-Florence Trial. *J. Clin. Oncol.* **2020**, *38*, 4175–4183. [\[CrossRef\]](#) [\[PubMed\]](#)
132. Galalae, R.; Hannoun-Levi, J.M. Accelerated partial breast irradiation by brachytherapy: Present evidence and future developments. *Jpn. J. Clin. Oncol.* **2020**, *50*, 743–752. [\[CrossRef\]](#)
133. Livi, L.; Meattini, I.; Marrazzo, L.; Simontacchi, G.; Pallotta, S.; Saieva, C.; Paier, F.; Scotti, V.; De Luca Cardillo, C.; Bastiani, P.; et al. Accelerated partial breast irradiation using intensity-modulated radiotherapy versus whole breast irradiation: 5-year survival analysis of a phase 3 randomised controlled trial. *Eur. J. Cancer* **2015**, *51*, 451–463. [\[CrossRef\]](#)
134. Whelan, T.J.; Julian, J.A.; Berrang, T.S.; Kim, D.H.; Germain, I.; Nichol, A.M.; Akra, M.; Lavertu, S.; Germain, F.; Fyles, A.; et al. External beam accelerated partial breast irradiation versus whole breast irradiation after breast conserving surgery in women with ductal carcinoma in situ and node-negative breast cancer (RAPID): A randomised controlled trial. *Lancet* **2019**, *394*, 2165–2172. [\[CrossRef\]](#) [\[PubMed\]](#)
135. Kennedy, W.R.; Roach, M.C.; Thomas, M.A.; Ochoa, L.; Altman, M.B.; Hernandez-Aya, L.F.; Cyr, A.E.; Margenthaler, J.A.; Zoberi, I. Long-Term Outcomes with 3-Dimensional Conformal External Beam Accelerated Partial Breast Irradiation. *Pract. Radiat. Oncol.* **2020**, *10*, e128–e135. [\[CrossRef\]](#) [\[PubMed\]](#)
136. Acharya, S.; Fischer-Valuck, B.W.; Mazur, T.R.; Curcuru, A.; Sona, K.; Kashani, R.; Green, O.; Ochoa, L.; Mutic, S.; Zoberi, I.; et al. Magnetic Resonance Image Guided Radiation Therapy for External Beam Accelerated Partial-Breast Irradiation: Evaluation of Delivered Dose and Intrafractional Cavity Motion. *Int. J. Radiat. Oncol. Biol. Phys.* **2016**, *96*, 785–792. [\[CrossRef\]](#) [\[PubMed\]](#)
137. Price, A.T.; Kennedy, W.R.; Henke, L.E.; Brown, S.R.; Green, O.L.; Thomas, M.A.; Ginn, J.; Zoberi, I. Implementing stereotactic accelerated partial breast irradiation using magnetic resonance guided radiation therapy. *Radiother. Oncol.* **2021**, *164*, 275–281. [\[CrossRef\]](#)
138. Crivellari, D.; Sun, Z.; Coates, A.S.; Price, K.N.; Thurlimann, B.; Mouridsen, H.; Mauriac, L.; Forbes, J.F.; Paridaens, R.J.; Castiglione-Gertsch, M.; et al. Letrozole compared with tamoxifen for elderly patients with endocrine-responsive early breast cancer: The BIG 1-98 trial. *J. Clin. Oncol.* **2008**, *26*, 1972–1979. [\[CrossRef\]](#) [\[PubMed\]](#)
139. Schaeffer, E.; Srinivas, S.; Antonarakis, E.S.; Armstrong, A.J.; Bekelman, J.E.; Cheng, H.; D’Amico, A.V.; Davis, B.J.; Desai, N.; Dorff, T.; et al. NCCN Guidelines Insights: Prostate Cancer, Version 1.2021. *J. Natl. Compr. Cancer Netw.* **2021**, *19*, 134–143. [\[CrossRef\]](#) [\[PubMed\]](#)
140. Baker, B.R.; Basak, R.; Mohiuddin, J.J.; Chen, R.C. Use of stereotactic body radiotherapy for prostate cancer in the United States from 2004 through 2012. *Cancer* **2016**, *122*, 2234–2241. [\[CrossRef\]](#)
141. Widmark, A.; Gunnlaugsson, A.; Beckman, L.; Thellenberg-Karlsson, C.; Hoyer, M.; Lagerlund, M.; Kindblom, J.; Ginman, C.; Johansson, B.; Bjornlinder, K.; et al. Ultra-hypofractionated versus conventionally fractionated radiotherapy for prostate cancer: 5-year outcomes of the HYPO-RT-PC randomised, non-inferiority, phase 3 trial. *Lancet* **2019**, *394*, 385–395. [\[CrossRef\]](#) [\[PubMed\]](#)
142. Katz, A.; Ferrer, M.; Suarez, J.F.; Multicentric Spanish Group of Clinically Localized Prostate Cancer. Comparison of quality of life after stereotactic body radiotherapy and surgery for early-stage prostate cancer. *Radiat. Oncol.* **2012**, *7*, 194. [\[CrossRef\]](#) [\[PubMed\]](#)
143. Brand, D.H.; Tree, A.C.; Ostler, P.; van der Voet, H.; Loblaw, A.; Chu, W.; Ford, D.; Tolan, S.; Jain, S.; Martin, A.; et al. Intensity-modulated fractionated radiotherapy versus stereotactic body radiotherapy for prostate cancer (PACE-B): Acute toxicity findings from an international, randomised, open-label, phase 3, non-inferiority trial. *Lancet Oncol.* **2019**, *20*, 1531–1543. [\[CrossRef\]](#)
144. Nicosia, L.; Mazzola, R.; Rigo, M.; Figlia, V.; Giaj-Levra, N.; Napoli, G.; Ricchetti, F.; Corradini, S.; Ruggieri, R.; Alongi, F. Moderate versus extreme hypofractionated radiotherapy: A toxicity comparative analysis in low- and favorable intermediate-risk prostate cancer patients. *J. Cancer Res. Clin. Oncol.* **2019**, *145*, 2547–2554. [\[CrossRef\]](#)

145. Kasivisvanathan, V.; Rannikko, A.S.; Borghi, M.; Panebianco, V.; Mynderse, L.A.; Vaarala, M.H.; Briganti, A.; Budaus, L.; Hellawell, G.; Hindley, R.G.; et al. MRI-Targeted or Standard Biopsy for Prostate-Cancer Diagnosis. *N. Engl. J. Med.* **2018**, *378*, 1767–1777. [\[CrossRef\]](#)
146. Sidaway, P. MRI improves diagnosis. *Nat. Rev. Clin. Oncol.* **2018**, *15*, 345. [\[CrossRef\]](#) [\[PubMed\]](#)
147. Wibmer, A.G.; Vargas, H.A.; Hricak, H. Role of MRI in the diagnosis and management of prostate cancer. *Future Oncol.* **2015**, *11*, 2757–2766. [\[CrossRef\]](#)
148. Teunissen, F.R.; Wortel, R.C.; Hes, J.; Willigenburg, T.; de Groot-van Breugel, E.N.; de Boer, J.C.; van Melick, H.H.; Verkooijen, H.M. Adaptive magnetic resonance-guided neurovascular-sparing radiotherapy for preservation of erectile function in prostate cancer patients. *Phys. Imaging Radiat. Oncol.* **2021**, *20*, 5–10. [\[CrossRef\]](#) [\[PubMed\]](#)
149. Kerkmeijer, L.G.; Groen, V.H.; Pos, F.J.; Haustermans, K.; Monninkhof, E.M.; Smeenk, R.J.; Kunze-Busch, M.C.; den Boer, J.C.; Zijp, J.V.; Vulpen, M.V.; et al. Focal Boost to the Intraprostatic Tumor in External Beam Radiotherapy for Patients with Localized Prostate Cancer: Results from the FLAME Randomized Phase III Trial. *J. Clin. Oncol.* **2021**, *39*, 787–796. [\[CrossRef\]](#)
150. Tocco, B.R.; Kishan, A.U.; Ma, T.M.; Kerkmeijer, L.G.W.; Tree, A.C. MR-Guided Radiotherapy for Prostate Cancer. *Front. Oncol.* **2020**, *10*, 616291. [\[CrossRef\]](#)
151. Cuccia, F.; Corradini, S.; Mazzola, R.; Spiazzi, L.; Rigo, M.; Bonu, M.L.; Ruggieri, R.; Buglione di Monale, E.B.M.; Magrini, S.M.; Alongi, F. MR-Guided Hypofractionated Radiotherapy: Current Emerging Data and Promising Perspectives for Localized Prostate Cancer. *Cancers* **2021**, *13*, 1791. [\[CrossRef\]](#)
152. Fawaz, Z.S.; Yassa, M.; Nguyen, D.H.; Vavassiss, P. Fiducial marker implantation in prostate radiation therapy: Complication rates and technique. *Cancer Radiother.* **2014**, *18*, 736–739. [\[CrossRef\]](#)
153. Gill, S.; Li, J.; Thomas, J.; Bressel, M.; Thursky, K.; Styles, C.; Tai, K.H.; Duchesne, G.M.; Foroudi, F. Patient-reported complications from fiducial marker implantation for prostate image-guided radiotherapy. *Br. J. Radiol.* **2012**, *85*, 1011–1017. [\[CrossRef\]](#) [\[PubMed\]](#)
154. Dunlop, A.; Mitchell, A.; Tree, A.; Barnes, H.; Bower, L.; Chick, J.; Goodwin, E.; Herbert, T.; Lawes, R.; McNair, H.; et al. Daily adaptive radiotherapy for patients with prostate cancer using a high field MR-linac: Initial clinical experiences and assessment of delivered doses compared to a C-arm linac. *Clin. Transl. Radiat. Oncol.* **2020**, *23*, 35–42. [\[CrossRef\]](#)
155. Tetar, S.U.; Bruynzeel, A.M.E.; Oei, S.S.; Senan, S.; Fraikin, T.; Slotman, B.J.; Moorselaar, R.; Lagerwaard, F.J. Magnetic Resonance-guided Stereotactic Radiotherapy for Localized Prostate Cancer: Final Results on Patient-reported Outcomes of a Prospective Phase 2 Study. *Eur. Urol. Oncol.* **2021**, *4*, 628–634. [\[CrossRef\]](#) [\[PubMed\]](#)
156. Alongi, F.; Rigo, M.; Figlia, V.; Cuccia, F.; Gaj-Levra, N.; Nicosia, L.; Ricchetti, F.; Sicignano, G.; De Simone, A.; Naccarato, S.; et al. 1.5 T MR-guided and daily adapted SBRT for prostate cancer: Feasibility, preliminary clinical tolerability, quality of life and patient-reported outcomes during treatment. *Radiat. Oncol.* **2020**, *15*, 69. [\[CrossRef\]](#) [\[PubMed\]](#)
157. Bruynzeel, A.M.E.; Tetar, S.U.; Oei, S.S.; Senan, S.; Haasbeek, C.J.A.; Spoelstra, F.O.B.; Piet, A.H.M.; Meijnen, P.; Bakker van der Jagt, M.A.B.; Fraikin, T.; et al. A Prospective Single-Arm Phase 2 Study of Stereotactic Magnetic Resonance Guided Adaptive Radiation Therapy for Prostate Cancer: Early Toxicity Results. *Int. J. Radiat. Oncol. Biol. Phys.* **2019**, *105*, 1086–1094. [\[CrossRef\]](#) [\[PubMed\]](#)
158. Ma, T.M.; Ballas, L.K.; Wilhalme, H.; Sachdeva, A.; Chong, N.; Sharma, S.; Yang, T.; Basehart, V.; Reiter, R.E.; Saigal, C.; et al. Quality-of-Life Outcomes and Toxicity Profile among Patients with Localized Prostate Cancer after Radical Prostatectomy Treated with Stereotactic Body Radiation: The SCIMITAR Multicenter Phase 2 Trial. *Int. J. Radiat. Oncol. Biol. Phys.* **2023**, *115*, 142–152. [\[CrossRef\]](#)
159. Kishan, A.U.; Ma, T.M.; Lamb, J.M.; Casado, M.; Wilhalme, H.; Low, D.A.; Sheng, K.; Sharma, S.; Nickols, N.G.; Pham, J.; et al. Magnetic Resonance Imaging-Guided vs Computed Tomography-Guided Stereotactic Body Radiotherapy for Prostate Cancer: The MIRAGE Randomized Clinical Trial. *JAMA Oncol.* **2023**. [\[CrossRef\]](#) [\[PubMed\]](#)
160. Redmond, K.J.; Robertson, S.; Lo, S.S.; Soltys, S.G.; Ryu, S.; McNutt, T.; Chao, S.T.; Yamada, Y.; Ghia, A.; Chang, E.L.; et al. Consensus Contouring Guidelines for Postoperative Stereotactic Body Radiation Therapy for Metastatic Solid Tumor Malignancies to the Spine. *Int. J. Radiat. Oncol. Biol. Phys.* **2017**, *97*, 64–74. [\[CrossRef\]](#) [\[PubMed\]](#)
161. Redler, G.; Stevens, T.; Cammin, J.; Malin, M.; Green, O.; Mutic, S.; Pitroda, S.; Aydogan, B. Dosimetric Feasibility of Utilizing the ViewRay Magnetic Resonance Guided Linac System for Image-guided Spine Stereotactic Body Radiation Therapy. *Cureus* **2019**, *11*, e6364. [\[CrossRef\]](#)
162. Stradiotti, P.; Curti, A.; Castellazzi, G.; Zerbi, A. Metal-related artifacts in instrumented spine. Techniques for reducing artifacts in CT and MRI: State of the art. *Eur. Spine J.* **2009**, *18* (Suppl. 1), 102–108. [\[CrossRef\]](#) [\[PubMed\]](#)
163. Paulson, E.S.; Erickson, B.; Schultz, C.; Allen Li, X. Comprehensive MRI simulation methodology using a dedicated MRI scanner in radiation oncology for external beam radiation treatment planning. *Med. Phys.* **2015**, *42*, 28–39. [\[CrossRef\]](#)
164. Spieler, B.; Samuels, S.E.; Llorente, R.; Yechieli, R.; Ford, J.C.; Mellon, E.A. Advantages of Radiation Therapy Simulation with 0.35 Tesla Magnetic Resonance Imaging for Stereotactic Ablation of Spinal Metastases. *Pract. Radiat. Oncol.* **2020**, *10*, 339–344. [\[CrossRef\]](#) [\[PubMed\]](#)
165. Weichselbaum, R.R.; Hellman, S. Oligometastases revisited. *Nat. Rev. Clin. Oncol.* **2011**, *8*, 378–382. [\[CrossRef\]](#) [\[PubMed\]](#)
166. Gomez, D.R.; Tang, C.; Zhang, J.; Blumenschein, G.R., Jr.; Hernandez, M.; Lee, J.J.; Ye, R.; Palma, D.A.; Louie, A.V.; Camidge, D.R.; et al. Local Consolidative Therapy vs. Maintenance Therapy or Observation for Patients with Oligometastatic Non-Small-Cell Lung Cancer: Long-Term Results of a Multi-Institutional, Phase II, Randomized Study. *J. Clin. Oncol.* **2019**, *37*, 1558–1565. [\[CrossRef\]](#) [\[PubMed\]](#)

167. Phillips, R.; Shi, W.Y.; Deek, M.; Radwan, N.; Lim, S.J.; Antonarakis, E.S.; Rowe, S.P.; Ross, A.E.; Gorin, M.A.; Deville, C.; et al. Outcomes of Observation vs Stereotactic Ablative Radiation for Oligometastatic Prostate Cancer: The ORIOLE Phase 2 Randomized Clinical Trial. *JAMA Oncol.* **2020**, *6*, 650–659. [\[CrossRef\]](#) [\[PubMed\]](#)
168. Palma, D.A.; Olson, R.; Harrow, S.; Gaede, S.; Louie, A.V.; Haasbeek, C.; Mulroy, L.; Lock, M.; Rodrigues, G.B.; Yaremko, B.P.; et al. Stereotactic Ablative Radiotherapy for the Comprehensive Treatment of Oligometastatic Cancers: Long-Term Results of the SABR-COMET Phase II Randomized Trial. *J. Clin. Oncol.* **2020**, *38*, 2830–2838. [\[CrossRef\]](#)
169. Chmura, S.; Winter, K.A.; Robinson, C.; Pisansky, T.M.; Borges, V.; Al-Hallaq, H.; Matuszak, M.; Park, S.S.; Yi, S.; Hasan, Y.; et al. Evaluation of Safety of Stereotactic Body Radiotherapy for the Treatment of Patients With Multiple Metastases: Findings from the NRG-BR001 Phase 1 Trial. *JAMA Oncol.* **2021**, *7*, 845–852. [\[CrossRef\]](#)
170. Derynda, B.R.; Liveringhouse, C.L.; Bryant, J.M.; Rosenberg, S.A. MR-Guided Radiation Therapy for Oligometastatic Malignancies. *Appl. Rad. Oncol.* **2021**, *10*, 25–32.
171. Tyran, M.; Cao, M.; Raldow, A.C.; Dang, A.; Lamb, J.; Low, D.A.; Steinberg, M.L.; Lee, P. Stereotactic Magnetic Resonance-guided Online Adaptive Radiotherapy for Oligometastatic Breast Cancer: A Case Report. *Cureus* **2018**, *10*, e2368. [\[CrossRef\]](#)
172. Haque, W.; Crane, C.H.; Krishnan, S.; Delclos, M.E.; Javle, M.; Garrett, C.R.; Wolff, R.A.; Das, P. Reirradiation to the abdomen for gastrointestinal malignancies. *Radiat. Oncol.* **2009**, *4*, 55. [\[CrossRef\]](#)
173. Valentini, V.; Morganti, A.G.; Gambacorta, M.A.; Mohiuddin, M.; Doglietto, G.B.; Coco, C.; De Paoli, A.; Rossi, C.; Di Russo, A.; Valvo, F.; et al. Preoperative hyperfractionated chemoradiation for locally recurrent rectal cancer in patients previously irradiated to the pelvis: A multicentric phase II study. *Int. J. Radiat. Oncol. Biol. Phys.* **2006**, *64*, 1129–1139. [\[CrossRef\]](#)
174. Hunt, A.; Das, P.; Minsky, B.D.; Koay, E.J.; Krishnan, S.; Herman, J.M.; Taniguchi, C.; Koong, A.; Smith, G.L.; Holliday, E.B. Hyperfractionated abdominal reirradiation for gastrointestinal malignancies. *Radiat. Oncol.* **2018**, *13*, 143. [\[CrossRef\]](#) [\[PubMed\]](#)
175. Koom, W.S.; Choi, Y.; Shim, S.J.; Cha, J.; Seong, J.; Kim, N.K.; Nam, K.C.; Keum, K.C. Reirradiation to the pelvis for recurrent rectal cancer. *J. Surg. Oncol.* **2012**, *105*, 637–642. [\[CrossRef\]](#)
176. Tao, R.; Tsai, C.J.; Jensen, G.; Eng, C.; Kopetz, S.; Overman, M.J.; Skibber, J.M.; Rodriguez-Bigas, M.; Chang, G.J.; You, Y.N.; et al. Hyperfractionated accelerated reirradiation for rectal cancer: An analysis of outcomes and toxicity. *Radiother. Oncol.* **2017**, *122*, 146–151. [\[CrossRef\]](#)
177. Chuong, M.D.; Bryant, J.M.; Herrera, R.; McCulloch, J.; Contreras, J.; Kotecha, R.; Romaguera, T.; Alvarez, D.; Hall, M.D.; Rubens, M.; et al. Dose-Escalated Magnetic Resonance Image-Guided Abdominopelvic Reirradiation With Continuous Intrafraction Visualization, Soft Tissue Tracking, and Automatic Beam Gating. *Adv. Radiat. Oncol.* **2022**, *7*, 100840. [\[CrossRef\]](#) [\[PubMed\]](#)
178. Cuccia, F.; Rigo, M.; Figlia, V.; Gaj-Levra, N.; Mazzola, R.; Nicosia, L.; Ricchetti, F.; Trapani, G.; De Simone, A.; Gurrera, D.; et al. 1.5T MR-Guided Daily Adaptive Stereotactic Body Radiotherapy for Prostate Re-Irradiation: A Preliminary Report of Toxicity and Clinical Outcomes. *Front. Oncol.* **2022**, *12*, 858740. [\[CrossRef\]](#) [\[PubMed\]](#)
179. Wang, J.; Weygand, J.; Hwang, K.P.; Mohamed, A.S.; Ding, Y.; Fuller, C.D.; Lai, S.Y.; Frank, S.J.; Zhou, J. Magnetic Resonance Imaging of Glucose Uptake and Metabolism in Patients with Head and Neck Cancer. *Sci. Rep.* **2016**, *6*, 30618. [\[CrossRef\]](#)
180. Salzillo, T.C.; Mawoneke, V.; Weygand, J.; Shetty, A.; Gumin, J.; Zacharias, N.M.; Gammon, S.T.; Piwnica-Worms, D.; Fuller, G.N.; Logothetis, C.J.; et al. Measuring the Metabolic Evolution of Glioblastoma throughout Tumor Development, Regression, and Recurrence with Hyperpolarized Magnetic Resonance. *Cells* **2021**, *10*, 2621. [\[CrossRef\]](#) [\[PubMed\]](#)
181. Dutta, P.; Perez, M.R.; Lee, J.; Kang, Y.; Pratt, M.; Salzillo, T.C.; Weygand, J.; Zacharias, N.M.; Gammon, S.T.; Koay, E.J.; et al. Combining Hyperpolarized Real-Time Metabolic Imaging and NMR Spectroscopy to Identify Metabolic Biomarkers in Pancreatic Cancer. *J. Proteome Res.* **2019**, *18*, 2826–2834. [\[CrossRef\]](#)
182. Maziero, D.; Straza, M.W.; Ford, J.C.; Bovi, J.A.; Diwanji, T.; Stoyanova, R.; Paulson, E.S.; Mellon, E.A. MR-Guided Radiotherapy for Brain and Spine Tumors. *Front. Oncol.* **2021**, *11*, 626100. [\[CrossRef\]](#) [\[PubMed\]](#)
183. Le Bihan, D.; Breton, E.; Lallemand, D.; Grenier, P.; Cabanis, E.; Laval-Jeantet, M. MR imaging of intravoxel incoherent motions: Application to diffusion and perfusion in neurologic disorders. *Radiology* **1986**, *161*, 401–407. [\[CrossRef\]](#) [\[PubMed\]](#)
184. Sugahara, T.; Korogi, Y.; Kochi, M.; Ikushima, I.; Shigematu, Y.; Hirai, T.; Okuda, T.; Liang, L.; Ge, Y.; Komohara, Y.; et al. Usefulness of diffusion-weighted MRI with echo-planar technique in the evaluation of cellularity in gliomas. *J. Magn. Reson. Imaging* **1999**, *9*, 53–60. [\[CrossRef\]](#)
185. Ellingson, B.M.; Malkin, M.G.; Rand, S.D.; Connelly, J.M.; Quinsey, C.; LaViolette, P.S.; Bedekar, D.P.; Schmainda, K.M. Validation of functional diffusion maps (fDMs) as a biomarker for human glioma cellularity. *J. Magn. Reson. Imaging* **2010**, *31*, 538–548. [\[CrossRef\]](#) [\[PubMed\]](#)
186. Hein, P.A.; Eskey, C.J.; Dunn, J.F.; Hug, E.B. Diffusion-weighted imaging in the follow-up of treated high-grade gliomas: Tumor recurrence versus radiation injury. *AJNR Am. J. Neuroradiol.* **2004**, *25*, 201–209.
187. Decker, G.; Murtz, P.; Gieseke, J.; Traber, F.; Block, W.; Sprinkart, A.M.; Leitzen, C.; Buchstab, T.; Lutter, C.; Schuller, H.; et al. Intensity-modulated radiotherapy of the prostate: Dynamic ADC monitoring by DWI at 3.0 T. *Radiother. Oncol.* **2014**, *113*, 115–120. [\[CrossRef\]](#) [\[PubMed\]](#)
188. Bains, L.J.; Zweifel, M.; Thoeny, H.C. Therapy response with diffusion MRI: An update. *Cancer Imaging* **2012**, *12*, 395–402. [\[CrossRef\]](#) [\[PubMed\]](#)
189. McGarry, S.D.; Hurrell, S.L.; Kaczmarowski, A.L.; Cochran, E.J.; Connelly, J.; Rand, S.D.; Schmainda, K.M.; LaViolette, P.S. Magnetic Resonance Imaging-Based Radiomic Profiles Predict Patient Prognosis in Newly Diagnosed Glioblastoma before Therapy. *Tomography* **2016**, *2*, 223–228. [\[CrossRef\]](#) [\[PubMed\]](#)

190. Park, J.E.; Kim, H.S.; Jo, Y.; Yoo, R.E.; Choi, S.H.; Nam, S.J.; Kim, J.H. Radiomics prognostication model in glioblastoma using diffusion- and perfusion-weighted MRI. *Sci. Rep.* **2020**, *10*, 4250. [[CrossRef](#)] [[PubMed](#)]
191. Kooreman, E.S.; van Houdt, P.J.; Nowee, M.E.; van Pelt, V.W.J.; Tijssen, R.H.N.; Paulson, E.S.; Gurney-Champion, O.J.; Wang, J.; Koetsveld, F.; van Buuren, L.D.; et al. Feasibility and accuracy of quantitative imaging on a 1.5 T MR-linear accelerator. *Radiother. Oncol.* **2019**, *133*, 156–162. [[CrossRef](#)]
192. Thorwarth, D.; Ege, M.; Nachbar, M.; Monnich, D.; Gani, C.; Zips, D.; Boeke, S. Quantitative magnetic resonance imaging on hybrid magnetic resonance linear accelerators: Perspective on technical and clinical validation. *Phys. Imaging Radiat. Oncol.* **2020**, *16*, 69–73. [[CrossRef](#)] [[PubMed](#)]
193. Habrich, J.; Boeke, S.; Nachbar, M.; Nikolaou, K.; Schick, F.; Gani, C.; Zips, D.; Thorwarth, D. Repeatability of diffusion-weighted magnetic resonance imaging in head and neck cancer at a 1.5 T MR-Linac. *Radiother. Oncol.* **2022**, *174*, 141–148. [[CrossRef](#)] [[PubMed](#)]
194. Kooreman, E.S.; van Houdt, P.J.; Keesman, R.; Pos, F.J.; van Pelt, V.W.J.; Nowee, M.E.; Wetscherek, A.; Tijssen, R.H.N.; Philippens, M.E.P.; Thorwarth, D.; et al. ADC measurements on the Unity MR-linac—A recommendation on behalf of the Elekta Unity MR-linac consortium. *Radiother. Oncol.* **2020**, *153*, 106–113. [[CrossRef](#)] [[PubMed](#)]
195. Yang, Y.; Cao, M.; Sheng, K.; Gao, Y.; Chen, A.; Kamrava, M.; Lee, P.; Agazaryan, N.; Lamb, J.; Thomas, D.; et al. Longitudinal diffusion MRI for treatment response assessment: Preliminary experience using an MRI-guided tri-cobalt 60 radiotherapy system. *Med. Phys.* **2016**, *43*, 1369–1373. [[CrossRef](#)] [[PubMed](#)]
196. Shaverdian, N.; Yang, Y.; Hu, P.; Hart, S.; Sheng, K.; Lamb, J.; Cao, M.; Agazaryan, N.; Thomas, D.; Steinberg, M.; et al. Feasibility evaluation of diffusion-weighted imaging using an integrated MRI-radiotherapy system for response assessment to neoadjuvant therapy in rectal cancer. *Br. J. Radiol.* **2017**, *90*, 20160739. [[CrossRef](#)]
197. Kalbasi, A.; Kamrava, M.; Chu, F.I.; Telesca, D.; Van Dams, R.; Yang, Y.; Ruan, D.; Nelson, S.D.; Dry, S.M.; Hernandez, J.; et al. A Phase II Trial of 5-Day Neoadjuvant Radiotherapy for Patients with High-Risk Primary Soft Tissue Sarcoma. *Clin. Cancer Res.* **2020**, *26*, 1829–1836. [[CrossRef](#)] [[PubMed](#)]
198. Gao, Y.; Ghodrati, V.; Kalbasi, A.; Fu, J.; Ruan, D.; Cao, M.; Wang, C.; Eilber, F.C.; Bernthal, N.; Bukata, S.; et al. Prediction of soft tissue sarcoma response to radiotherapy using longitudinal diffusion MRI and a deep neural network with generative adversarial network-based data augmentation. *Med. Phys.* **2021**, *48*, 3262–3372. [[CrossRef](#)]
199. Lewis, B.; Guta, A.; Mackey, S.; Gach, H.M.; Mutic, S.; Green, O.; Kim, T. Evaluation of diffusion-weighted MRI and geometric distortion on a 0.35T MR-LINAC at multiple gantry angles. *J. Appl. Clin. Med. Phys.* **2021**, *22*, 118–125. [[CrossRef](#)]
200. Weygand, J.; Armstrong, T.; Bryant, J.M.; Andreozzi, J.; Oraiqat, I.M.; Liveringhouse, C.L.; Latifi, K.; Yamoah, K.; Costello, J.R.; Frakes, J.M.; et al. Accurate, repeatable, and geometrically precise diffusion-weighted imaging on a 0.35 T MRI-guided linear accelerator. In Proceedings of the Annual European Society for Radiotherapy and Oncology (ESTRO) Meeting, Vienna, Austria, 24–28 March 2023.
201. Oderinde, O.M.; Shirvani, S.M.; Olcott, P.D.; Kuduvalli, G.; Mazin, S.; Larkin, D. The technical design and concept of a PET/CT linac for biology-guided radiotherapy. *Clin. Transl. Radiat. Oncol.* **2021**, *29*, 106–112. [[CrossRef](#)]
202. Warburg, O. The Metabolism of Carcinoma Cells. *J. Cancer Res.* **1925**, *9*, 148–163. [[CrossRef](#)]
203. Sullivan, L.B.; Gui, D.Y.; Vander Heiden, M.G. Altered metabolite levels in cancer: Implications for tumour biology and cancer therapy. *Nat. Rev. Cancer* **2016**, *16*, 680–693. [[CrossRef](#)]
204. Phelps, M.E.; Hoffman, E.J.; Mullani, N.A.; Ter-Pogossian, M.M. Application of annihilation coincidence detection to transaxial reconstruction tomography. *J. Nucl. Med.* **1975**, *16*, 210–224.
205. Ter-Pogossian, M.M.; Phelps, M.E.; Hoffman, E.J.; Mullani, N.A. A positron-emission transaxial tomograph for nuclear imaging (PETT). *Radiology* **1975**, *114*, 89–98. [[CrossRef](#)] [[PubMed](#)]
206. Phelps, M.E.; Huang, S.C.; Hoffman, E.J.; Selin, C.; Sokoloff, L.; Kuhl, D.E. Tomographic measurement of local cerebral glucose metabolic rate in humans with (F-18)2-fluoro-2-deoxy-D-glucose: Validation of method. *Ann. Neurol.* **1979**, *6*, 371–388. [[CrossRef](#)] [[PubMed](#)]
207. Posse, S.; Otazo, R.; Dager, S.R.; Alger, J. MR spectroscopic imaging: Principles and recent advances. *J. Magn. Reson. Imaging* **2013**, *37*, 1301–1325. [[CrossRef](#)]
208. Van Zijl, P.C.; Yadav, N.N. Chemical exchange saturation transfer (CEST): What is in a name and what isn't? *Magn. Reson. Med.* **2011**, *65*, 927–948. [[CrossRef](#)]
209. Wu, B.; Warnock, G.; Zaiss, M.; Lin, C.; Chen, M.; Zhou, Z.; Mu, L.; Nanz, D.; Tuura, R.; Delso, G. An overview of CEST MRI for non-MR physicists. *EJNMMI Phys.* **2016**, *3*, 19. [[CrossRef](#)] [[PubMed](#)]
210. Ardenkjaer-Larsen, J.H.; Fridlund, B.; Gram, A.; Hansson, G.; Hansson, L.; Lerche, M.H.; Servin, R.; Thaning, M.; Golman, K. Increase in signal-to-noise ratio of >10,000 times in liquid-state NMR. *Proc. Natl. Acad. Sci. USA* **2003**, *100*, 10158–10163. [[CrossRef](#)]
211. Salzillo, T.C.; Hu, J.; Nguyen, L.; Whiting, N.; Lee, J.; Weygand, J.; Dutta, P.; Pudakalakatti, S.; Millward, N.Z.; Gammon, S.T.; et al. Interrogating Metabolism in Brain Cancer. *Magn. Reson. Imaging Clin. N. Am.* **2016**, *24*, 687–703. [[CrossRef](#)] [[PubMed](#)]
212. Bogner, W.; Gruber, S.; Trattinig, S.; Chmelik, M. High-resolution mapping of human brain metabolites by free induction decay (1)H MRSI at 7 T. *NMR Biomed.* **2012**, *25*, 873–882. [[CrossRef](#)] [[PubMed](#)]
213. Hangel, G.; Cadrien, C.; Lazen, P.; Furtner, J.; Lipka, A.; Heckova, E.; Hingerl, L.; Motyka, S.; Gruber, S.; Strasser, B.; et al. High-resolution metabolic imaging of high-grade gliomas using 7T-CRT-FID-MRSI. *Neuroimage Clin.* **2020**, *28*, 102433. [[CrossRef](#)]

214. De Feyter, H.M.; Behar, K.L.; Corbin, Z.A.; Fulbright, R.K.; Brown, P.B.; McIntyre, S.; Nixon, T.W.; Rothman, D.L.; de Graaf, R.A. Deuterium metabolic imaging (DMI) for MRI-based 3D mapping of metabolism in vivo. *Sci. Adv.* **2018**, *4*, eaat7314. [\[CrossRef\]](#)
215. Korzowski, A.; Weinfurter, N.; Mueller, S.; Breitling, J.; Goerke, S.; Schlemmer, H.P.; Ladd, M.E.; Paech, D.; Bachert, P. Volumetric mapping of intra- and extracellular pH in the human brain using (31) P MRSI at 7T. *Magn. Reson. Med.* **2020**, *84*, 1707–1723. [\[CrossRef\]](#) [\[PubMed\]](#)
216. Bogner, W.; Otazo, R.; Henning, A. Accelerated MR spectroscopic imaging—a review of current and emerging techniques. *NMR Biomed.* **2021**, *34*, e4314. [\[CrossRef\]](#) [\[PubMed\]](#)
217. Henning, A.; Fuchs, A.; Murdoch, J.B.; Boesiger, P. Slice-selective FID acquisition, localized by outer volume suppression (FIDLOVS) for (1)H-MRSI of the human brain at 7 T with minimal signal loss. *NMR Biomed.* **2009**, *22*, 683–696. [\[CrossRef\]](#) [\[PubMed\]](#)
218. Hovener, J.B.; Schwaderlapp, N.; Lickert, T.; Duckett, S.B.; Mewis, R.E.; Highton, L.A.; Kenny, S.M.; Green, G.G.; Leibfritz, D.; Korvink, J.G.; et al. A hyperpolarized equilibrium for magnetic resonance. *Nat. Commun.* **2013**, *4*, 2946. [\[CrossRef\]](#)
219. Nelson, S.J.; Kurhanewicz, J.; Vigneron, D.B.; Larson, P.E.; Harzstark, A.L.; Ferrone, M.; van Criekinge, M.; Chang, J.W.; Bok, R.; Park, I.; et al. Metabolic imaging of patients with prostate cancer using hyperpolarized[1-(1)(3)C]pyruvate. *Sci. Transl. Med.* **2013**, *5*, 198ra108. [\[CrossRef\]](#) [\[PubMed\]](#)
220. Zhou, J.; van Zijl, P.C. Chemical exchange saturation transfer imaging and spectroscopy. *Prog. Nucl. Magn. Reson. Spectrosc.* **2006**, *48*, 109–136. [\[CrossRef\]](#)
221. Meissner, J.E.; Korzowski, A.; Regnery, S.; Goerke, S.; Breitling, J.; Floca, R.O.; Debus, J.; Schlemmer, H.P.; Ladd, M.E.; Bachert, P.; et al. Early response assessment of glioma patients to definitive chemoradiotherapy using chemical exchange saturation transfer imaging at 7 T. *J. Magn. Reson. Imaging* **2019**, *50*, 1268–1277. [\[CrossRef\]](#) [\[PubMed\]](#)
222. Regnery, S.; Adeberg, S.; Dreher, C.; Oberhollenzer, J.; Meissner, J.E.; Goerke, S.; Windschuh, J.; Deike-Hofmann, K.; Bickelhaupt, S.; Zaiss, M.; et al. Chemical exchange saturation transfer MRI serves as predictor of early progression in glioblastoma patients. *Oncotarget* **2018**, *9*, 28772–28783. [\[CrossRef\]](#)
223. Cusumano, D.; Boldrini, L.; Dhont, J.; Fiorino, C.; Green, O.; Gungor, G.; Jornet, N.; Kluter, S.; Landry, G.; Mattiucci, G.C.; et al. Artificial Intelligence in magnetic Resonance guided Radiotherapy: Medical and physical considerations on state of art and future perspectives. *Phys. Med.* **2021**, *85*, 175–191. [\[CrossRef\]](#)
224. Bryant, J.M.; Saghand, P.G.; Latifi, K.; Frakes, J.; Hoffe, S.A.; Moros, E.; Mittauer, K.E.; Kotecha, R.; El Naqa, I.; Rosenberg, S.A. A novel multi-task hybrid deep neural network (DNN) predicts tumor progression during MRgRT. In Proceedings of the Annual European Society for Radiotherapy and Oncology (ESTRO) Meeting, Vienna, Austria, 24 March–28 March 2023.
225. Botman, R.; Tetar, S.U.; Palacios, M.A.; Slotman, B.J.; Lagerwaard, F.J.; Bruynzeel, A.M.E. The clinical introduction of MR-guided radiation therapy from a RTT perspective. *Clin. Transl. Radiat. Oncol.* **2019**, *18*, 140–145. [\[CrossRef\]](#)
226. Mittauer, K.; Paliwal, B.; Hill, P.; Bayouth, J.E.; Geurts, M.W.; Baschnagel, A.M.; Bradley, K.A.; Harari, P.M.; Rosenberg, S.; Brower, J.V.; et al. A New Era of Image Guidance with Magnetic Resonance-guided Radiation Therapy for Abdominal and Thoracic Malignancies. *Cureus* **2018**, *10*, e2422. [\[CrossRef\]](#) [\[PubMed\]](#)
227. Kueng, R.; Guyer, G.; Volken, W.; Frei, D.; Stabel, F.; Stampanoni, M.F.M.; Manser, P.; Fix, M.K. Development of an extended Monte Carlo method for efficient and accurate dose calculation in magnetic fields. *Med. Phys.* **2020**, *47*, 6519–6530. [\[CrossRef\]](#) [\[PubMed\]](#)

Disclaimer/Publisher’s Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.