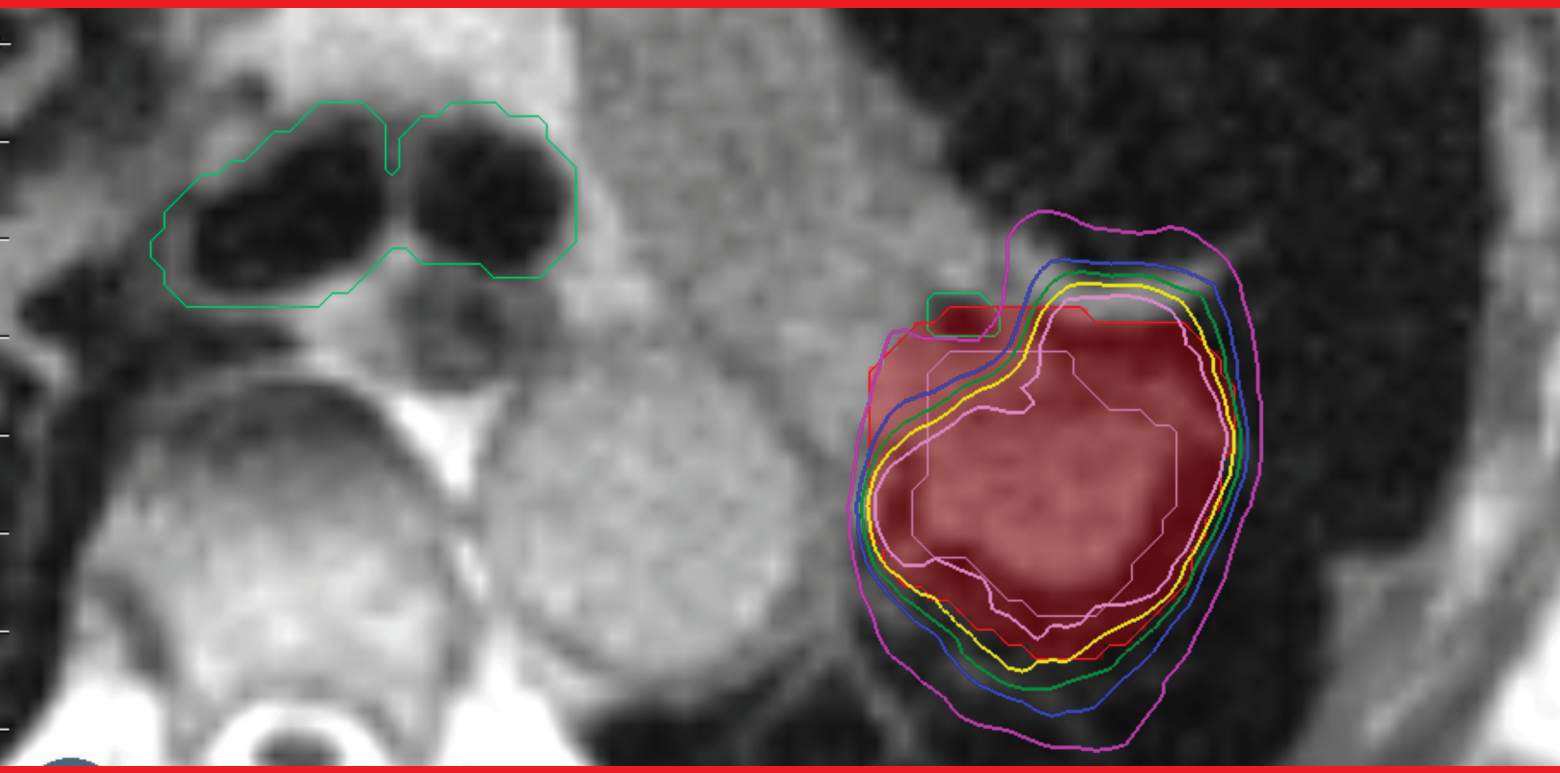
September 2021
Volume 10, Number 3

Applied Radiation Oncology™

10 YEARS



SA-CME
Actualizing Risk-Adapted Thoracic SBRT With MR Guidance

SA-CME
Integrating MRgRT into Clinical Practice: Clinical Advantages and Practical Limitations

SA-CME
MRgRT for Oligometastatic Malignancies

Research
Time-Driven Activity-Based Costing of CT-Guided vs. MR-Guided Prostate SBRT

www.appliedradiationoncology.com

Meet Elekta Harmony: The perfect balance

Designed to meet the daily challenges faced by healthcare professionals and hospitals, Elekta Harmony provides the perfect balance of productivity, precision and versatility—without compromise.

Elekta

Scan to find out more

AppliedRadiationOncology™

Anderson Publishing, Ltd.
180 Glenside Avenue,
Scotch Plains, NJ 07076
Tel: 908-301-1995
Fax: 908-301-1997
info@appliedradiology.com
ESSN: 2334-5446 (online)

CIRCULATION, COVERAGE and ADVERTISING RATES: Details regarding circulation, coverage, advertising rates, space sizes, and similar information are available to prospective advertisers. Closing date is 30 days preceding date of issue. View our media planner at appliedradiationoncology.com/advertise.

EDITORIAL CONTRIBUTIONS: Applied Radiation Oncology accepts clinical review articles, research papers, and case reports that pertain to radiation oncology and related oncologic imaging procedures that will be of interest to radiation oncologists. Author guidelines are available at https://appliedradiationoncology.com/Author-Guidelines. Every precaution is taken to ensure accuracy, but the publishers cannot accept responsibility for the correctness or accuracy of the information supplied or for any opinion expressed. Before using procedures or treatments discussed or suggested by authors, clinicians should evaluate their patients' conditions, compare the recommendations of other authorities, consider possible contraindications or dangers, and review applicable manufacturer's product information. Review articles and cases should be geared to the practitioner and should reflect practical everyday clinical applications rather than research activity. Articles and cases may pertain to clinical management, administration, fiscal, technical, and medico-legal issues. All review articles, research articles and case reports undergo a double-anonymized peer review process.

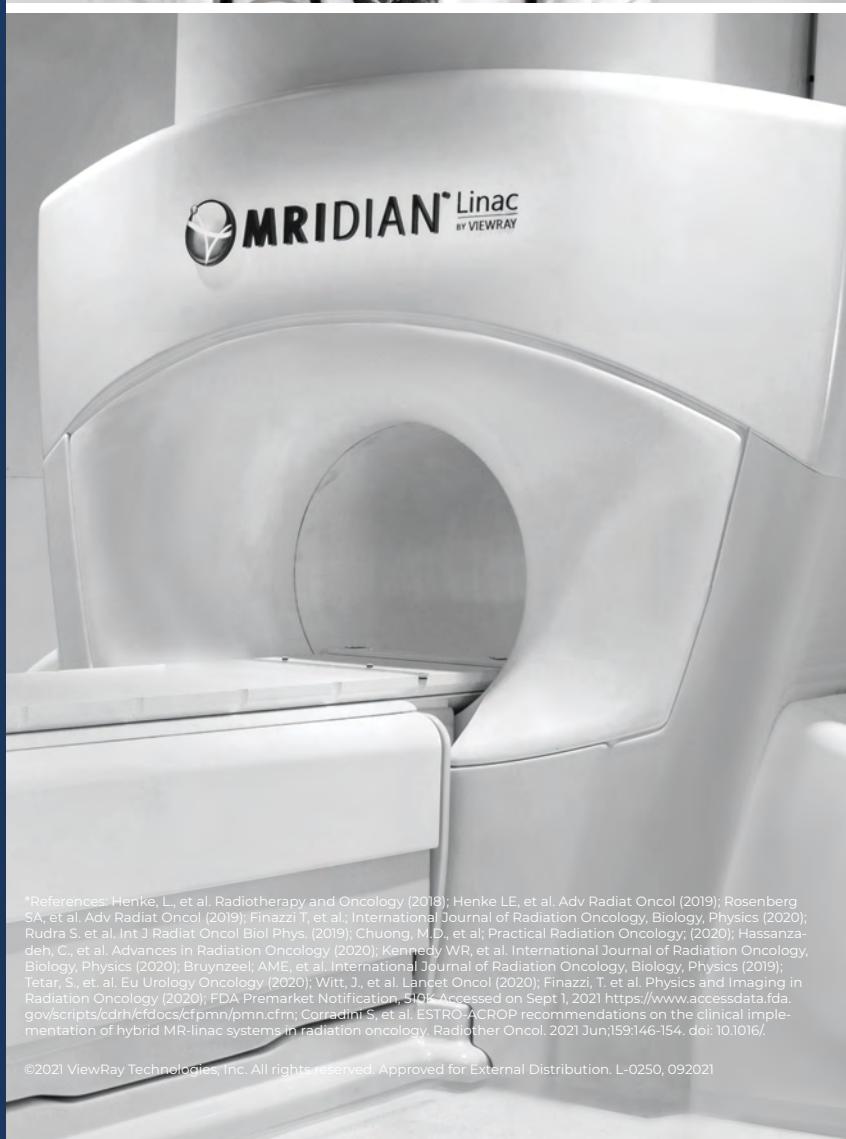
Editorial Advisory Board

Applied Radiation Oncology™

FOCUS: MR-GUIDED RADIATION THERAPY (MRgRT)

Applied Radiation Oncology (ISSN: 2334-5446) is published quarterly by Anderson Publishing, Ltd.,180 Glenside Avenue, Scotch Plains, NJ 07076. Subscription is free of charge to all medical professionals. To update your subscription preferences, visit appliedradiationoncology.com/subscribe. Complaints concerning non-receipt of this journal should be made via email to our publisher, Kieran Anderson at kieran@appliedrradiology.com.

MRIDIAN® SMART



ABLATIVE DOSES.
TIGHTER MARGINS.
FEWER FRACTIONS.

MRIdian Stereotactic MRI-Guided Adaptive Radiotherapy (SMART) is the *only* treatment that integrates diagnostic-quality MR imaging, streamlined on-table adaptive replanning, and continuous, real-time, soft tissue tracking and automated beam gating. MRIdian SMART allows clinical teams to define tighter treatment margins, deliver ablative doses in five or fewer fractions, while avoiding unwanted dose to OARs, and minimizing toxicities without relying on implanted markers.*

Join the community conducting breakthrough research while delivering unmatched clinical results today. Discover how MRIdian SMART enables teams to *treat and prove what others can't.*

www.viewray.com

VIEWRAY®
VISIBLY BETTER™

*References: Henke, L., et al. Radiotherapy and Oncology (2018); Henke LE, et al. Adv Radiat Oncol (2019); Rosenberg SA, et al. Adv Radiat Oncol (2019); Finazzi T, et al.; International Journal of Radiation Oncology, Biology, Physics (2020); Rudra S. et al. Int J Radiat Oncol Biol Phys. (2019); Chuong, M.D., et al; Practical Radiation Oncology; (2020); Hassanzadeh, C., et al. Advances in Radiation Oncology (2020); Kennedy WR, et al. International Journal of Radiation Oncology, Biology, Physics (2020); Bruynzeel; AME, et al. International Journal of Radiation Oncology, Biology, Physics (2019); Tetar, S., et. al. Eu Urology Oncology (2020); Witt, J., et al. Lancet Oncol (2020); Finazzi, T. et al. Physics and Imaging in Radiation Oncology (2020); FDA Premarket Notification, 5104 Accessed on Sept 1, 2021 https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm; Corradini S, et al. ESTRO-ACROP recommendations on the clinical implementation of hybrid MR-linac systems in radiation oncology. Radiother Oncol. 2021 Jun;159:146-154. doi: 10.1016/.

Dr. Suh is the editor-in-chief of *Applied Radiation Oncology*, and professor and chairman, Department of Radiation Oncology at the Taussig Cancer Institute, Rose Ella Burkhardt Brain Tumor and Neuro-oncology Center, Cleveland Clinic, Cleveland, OH.

Celebrating 10 Years

John Suh, MD, FASTRO, FACR

Ten years ago this October marked an exciting event for *ARO*: the launch of our inaugural issue! Thanks to a tremendous team of board members, peer reviewers, managing editor, and dedicated supporters like yourselves, we have expanded from an online-only publication to both a print and web-based journal, offering numerous new features and improvements over the years. These updates include free webinars and SA-CME opportunities, introduction of research articles, a double-blind peer review system with an ever-growing panel of vetted peer reviewers, the Resident Voice editorial from ARRO leadership, biweekly enewsletters summarizing industry news, the *ARO* Insights blog, a climbing social media presence thanks to your support, and much more. We are very proud and grateful of how *ARO* has evolved over the past decade!

To commemorate our 10-year milestone, *ARO* has updated its look, enhancing readability with artful uses of white space, color, and a modernized layout. We hope you enjoy the fresh new design, which is also featured in our sister publication, *Applied Radiology*, celebrating a whopping 50 years of service.

MRgRT: Magnetic Appeal

While change is good and enlists its share of excitement, dependability strengthens trust. In every issue, *ARO* provides a steadfast array of quality editorial content to aid in the management and treatment of cancer patients. In this issue, which focuses on the promising field of MR-guided radiation therapy, we owe a special thanks to Stephen Rosenberg, MD, director of MRgRT at Moffit Cancer Center, for developing a fantastic lineup on the topic. Included are three comprehensive, SA-CME-accredited review articles on: MR guidance in SBRT for lung cancer treatment, advantages and limitations of integrating MRgRT into practice, and MRgRT for oligometastatic cancer. The issue also features a well-written research article comparing provider costs of MRgRT with CTgRT for prostate SBRT delivery at a single institution. Adding to the theme is a Technology Trends article in which industry/clinical experts discuss the two primary MRgRT systems, time and workload needs, ablative doses, and future directions.

We are also delighted to present the webinar, *MR-Guided Radiotherapy: Patient Selection and New Opportunities,* which is moderated by Dr. Rosenberg and will complement the issue theme. This will be held on September 29th and archived afterward at https://appliedradiationoncology.com/webinars/on-demand. The webinar is free and features four expert panelists. We hope you can join us!

In addition to the MRgRT focus, this issue also features: *Analysis of the Radiation Oncology In-Training Examination Content Using a Clinical Care Path Conceptual Framework,* an excellent research article that challenges the current approach to residency education; the Resident Voice column, *Improving Cancer Equity Through Advocacy,* which amplifies the critical need to address disparities in our healthcare system; and two interesting case reports: *Efficacy of Stereotactic Radiotherapy in Recurrent Intrahepatic Cholangiocarcinoma* and *Radiation Therapy in the Treatment of Plantar Fibromatosis.*

We hope you enjoy this issue and greatly appreciate your loyal support over the past decade! We look forward to your continued readership and hope to influence and optimize the use of radiation oncology, a highly effective treatment for many patients.

Actualizing Risk-Adapted Thoracic SBRT with MR Guidance

Description

While traditionally CT- and x-ray based, lung stereotactic body radiation therapy (SBRT) practices will likely be impacted by the emerging availability of MR guidance. This review provides an overview of the role of MR guidance in SBRT for the treatment of lung cancers. Limitations, data, and future directions for treatments are reviewed with a focus on peripheral, central, and ultracentral lung cancers.

Learning Objectives

Upon completing this activity, the readers should be able to:

- classify lung cancers using accepted definitions of peripheral, central, and ultracentral;
- describe limitations of CT-based treatment of lung cancers in peripheral, central, and ultracentral locations and understand the potential for MR-guidance in these settings; and
- identify and summarize at least two previously published studies in MR-guided lung SBRT.

Accreditation/ Designation Statement

The Institute for Advanced Medical Education is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians. The Institute for Advanced Medical Education designates this journal-based CME activity for a maximum of 1 AMA PRA Category 1 Credit.™

Physicians should only claim credit commensurate with the extent of their participation in the activity. These credits qualify as SA-CME credits.

Authors

Lisa Singer, MD, PhD; Benjamin H. Kann, MD; Daniel N. Cagney, MD; Jonathan E. Leeman, MD; Sue S. Yom, MD, PhD; David Kozono, MD, PhD;

Harvard Medical School, Brigham and Women's Hospital and Dana-Farber Cancer Institute, Boston, MA (Drs. Singer, Kann, Cagney, Leeman, Kozono); University of California, San Francisco (Drs. Yom and Singer); Artificial Intelligence in Medicine Program, Mass General, Brigham, MA (Dr. Kann); Mater Private Hospital, Dublin, Ireland (Dr. Cagney).

Target Audience

- Radiation Oncologists
- Related Oncology Professionals

Instructions

To successfully earn credit, participants must complete the activity during the valid credit period.

1. Review this article in its entirety.
2. Visit www.appliedradiology.org/SAM.
3. Login to your account or (new users) create an account.
4. Complete the post test and review the discussion and references.
5. Complete the evaluation.
6. Print your certificate.

Estimated time for completion:
1 hour

Date of release and review:
September 1, 2021

Expiration date:
August 31, 2023

Disclosures

Dr. Singer received funding from Viewray, outside the scope of this project. Dr. Yom has received research grants from Genentech, Bristol-Myers Squibb, Merck, and BioMimetix, outside the scope of this work. Dr. Leeman works on research in MRI sponsored by NH TherAguix, related to work outlined in this review, and from Viewray, outside the scope of this work. Dr. Casey works on research in MRI sponsored by NH TherAguix, related to work outlined in this review, and from Viewray, outside the scope of this work.

No other authors, faculty, or any individuals at IAME or *Applied Radiation Oncology* who had control over the content of this program have any relationships with commercial supporters.

Actualizing Risk-Adapted Thoracic Stereotactic Body Radiation Therapy with MR Guidance

Lisa Singer, MD, PhD; Benjamin H. Kann, MD; Daniel N. Cagney, MD; Jonathan E. Leeman, MD; Sue S. Yom, MD, PhD; David Kozono, MD, PhD

Lung cancer is the leading cause of cancer death in both men and women in the US.[1] Although most lung cancers are stage IV at the time of diagnosis,[2] lung cancer screening enables the diagnosis of earlier lesions and reduces mortality.[3] Thoracic stereotactic body radiation therapy (SBRT) is a noninvasive alternative to surgery for patients with early stage lung cancers, and its use is supported by multiple studies including the randomized trial CHISEL, which compared SBRT to radiation therapy delivered with standard fractionation and demonstrated improved local control with SBRT.[4] Based on available data to date, 5-year tumor control with SBRT is considered around 90%.[5,6]

Randomized data comparing surgery with SBRT is more limited. Two randomized trials, STARS and ROSEL, which compared lobectomy to SBRT, were closed early due to slow accrual. A secondary unplanned combined analysis showed excellent outcomes with SBRT, with 3-year overall survival (OS) of 95%, 3-year recurrence-free survival of 86%, and grade 3 toxicity of 10%, with no grade 4 or 5 toxicities.[7] After expansion of the SBRT arm of the STARS trial to a single-arm study with longer follow-up, 5-year OS was 87% and 5-year progression free survival (PFS) was 77%, comparing favorably to a matched cohort of patients treated with surgery, with no differences in PFS or cumulative incidence of local, regional, or distant failures. Three- and 5-year OS were higher with SBRT.[8] Given the caveats of these analyses, further data are needed. Additional trials including the randomized studies STABLE-MATES (NCT02468024) and VALOR (NCT02984761) are underway.

Despite the excellent local control seen with SBRT, severe toxicities have been reported in tumors near the airways and mediastinal structures, leading to classification of tumors as peripheral (noncentral), or central (within 2 cm of the proximal bronchial tree including the distal 2 cm of the trachea and lobar bronchi).[9] Within central tumors, ultracentral has emerged as a higher risk category of tumors.[10] While the definition of ultracentral has differed across studies, ultracentral generally refers to abutment of the tumor or planning target volume (PTV) with critical organs at risk (OARs) such as the proximal bronchial tree, esophagus, or great vessels. In the SUNSET trial, ultracentral tumors were defined as those with a PTV touching or overlapping the central bronchial tree, esophagus, pulmonary vein or pulmonary artery.[10] Various SBRT regimens have been tested prospectively for peripheral,[9,11,12] central,[13-15] and ultracentral[16-19] lung tumors. These classifications and regimens are summarized in **Table 1**.

Reports of excess toxicity for tumors in high-risk locations have also led to risk-adapted approaches to SBRT, which balance tumor coverage at adequate biologic effective dose for alpha/beta of 10 (BED_{10}) with OAR sparing. An example of an institutional approach using a conventional linear accelerator is shown in **Figure 1**. In this example, if OARs cannot be spared without compromising tumor coverage, further fractionation is pursued. Based on data from Onishi et al,[20] local control

Affiliations: Dr. Singer is an assistant professor and **Dr. Yom** is a professor, radiation oncology, University of California, San Francisco. **Dr. Kann** is an assistant professor, **Dr. Leeman** is an instructor, and **Dr. Kozono** is an assistant professor, radiation oncology, Brigham and Women's Hospital and Dana-Farber Cancer Institute, Boston, MA. **Dr. Cagney** is a consultant radiation oncologist, Mater Private, Dublin, Ireland. **Disclosures:** Dr. Singer received funding from ViewRay, outside the scope of this project. Dr. Yom has received research grants from Genentech, Bristol-Myers Squibb, Merck, and BioMimetix, outside the scope of this work. Dr. Leeman works on research in MRI sponsored by NH TherAguix, related to work outlined in this review, and from ViewRay, outside the scope of this work. Dr. Casey works on research in MRI sponsored by NH TherAguix, related to work outlined in this review, and from ViewRay, outside the scope of this work. The remaining authors have no conflicts of interest. None of the authors received outside funding for the production of this original manuscript and no part of this article has been previously published elsewhere.

Table 1. Overview of Peripheral, Central, and Ultracentral Lung Cancer Definitions and Treatment Regimens

LOCATION	DESCRIPTION	REGIMENS PROSPECTIVELY EVALUATED (DOSE/FRACTIONATION)	PROSPECTIVE STUDIES
Peripheral	More than 2 cm from proximal bronchial tree and with PTV not abutting mediastinal OARs	54 Gy in 3 fractions 34 Gy in 1 fraction 48 Gy in 4 fractions	RTOG 0236 (Timmeran, 2006) RTOG 0915 (Videtic, 2015) JCOG 0403 (INagata, 2015)
Central	Within 2 cm of proximal bronchial tree	50-60 Gy in 5 fractions 60 Gy in 8 fractions 70 Gy in 10 fractions	RTOG 0813 (Bezjak, 2019) Ongoing EORTC 221133 (Adebahr, 2015) Xia, 2006
Ultracentral	PTV abutting or overlapping tree or mediastinal OAR	50 Gy in 5 fractions 70 Gy in 10 fractions 60 Gy in 8 fractions 60 Gy in 15 fractions	Washington University (Henke, 2019) Prospective registry at MDA (Li, 2014) HILUS (Lindberg, 2021) NCIC CTG Br.25 (Cheung, 2014)

Key: PTV = planning target volume, RTOG = Radiation Therapy Oncology Group, JCOG = Japan Clinical Oncology Group, EORTC = European Organization for Research and Treatment of Cancer, OARs = organs at risk, MDA = MD Anderson, NCIC CTG = Canadian Cancer Trials Group

and OS are inferior below a BED_{10} of 100; thus, in the example approach in **Figure 1**, rather than compromising adequate tumor coverage to meet OARs, alternate regimens are considered to maximize BED_{10} to the extent possible.

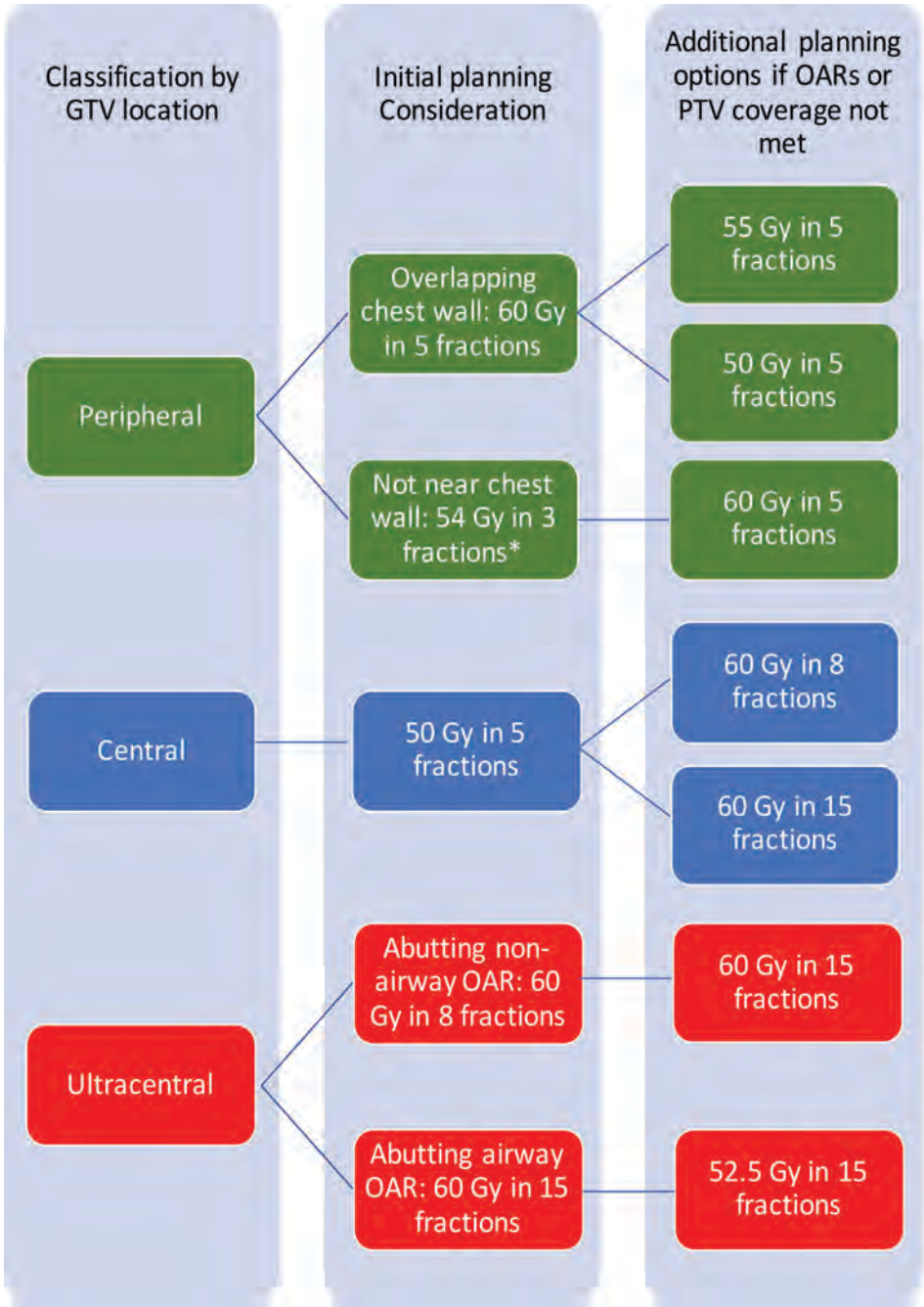
The risk-adapted approach shown in **Figure 1** is impacted by the additional options afforded by MR-linacs. An MR-linac is a device combining an MRI scanner with a linear accelerator, currently available as FDA-approved devices from Elekta, as the Unity, and from ViewRay, as the MRIdian.[21] MR-linacs allow for MR-guided tumor setup and real-time MRI monitoring during treatment for tumor tracking. Importantly, these technologies permit online adaptive radiation therapy, the replanning of radiation treatment with the patient on the treatment table, accounting for daily differences in tumor and OAR location and morphology. Online adaptive radiation therapy is also possible on non-MR-linacs through systems such as Ethos (Varian).[22] OARs contoured for initial and adaptive MR-linac plans are similar to OARs contoured for conventional non-MR guided, nonadaptive radiation therapy.[23] In the absence of new data, dose constraints for MR-guided SBRT are generally based on accepted constraints used for non-MR linac SBRT. Due to the dose fall-off with SBRT and time required for recontouring, MR-guided online adaptive recontouring may focus on the recontouring of structures within a high-dose region (2 to 3 cm from the target) on treatment day. Outside of this high-dose region, the dose is unlikely to violate OAR metrics. When delivered using an MR-linac, adaptive SBRT is often referred to as stereotactic MR-guided adaptive radiation therapy (SMART), with various workflows previously described.[24,25] SMART is available for both Elekta[26] and ViewRay[27] MR-linacs. Although the specific steps for SMART differ by vendor, SMART requires steps to be implemented on treatment day including acquisition of a new MRI on the day of treatment, recontouring on the MRI acquired at treatment, plan reoptimization, plan approval, and quality assurance checks prior to delivery. Lung lesions have been treated with both systems.[28,29] Major differences between the Elekta Unity and ViewRay MRIdian MR-linacs are shown in **Table 2**.[30-33] Currently, there is no consensus on clinical indications for utilizing an adaptive replan; thresholds for requiring SMART vary by center and disease site. MR-linacs can be used to treat lung cancer in peripheral, central, and ultracentral locations, with relevant data and considerations reviewed. Due to the ability of SMART to account for daily changes in target and OARs, and the potential for reduced PTV margins with real-time MR guidance, SMART may also be beneficial for thoracic reirradiation in these locations.

Peripheral Lesions

Peripheral thoracic tumors are more than 2 cm from the proximal bronchial tree, not involving the central pleura or mediastinum. They can be further classified by their proximity to the chest wall. Chest wall proximity is important to recognize due to the association of chest wall dose with severe chest wall pain and rib fracture.[34] V30 < 30 cc is a constraint used for 3-fraction regimens.[34] Optimized V37, the 5-fraction BED_3 equivalent of V30, was associated with reduced toxicity in a retrospective study of 5-fraction regimens.[35]

Safety and efficacy of single-fraction SBRT for peripheral tumors was demonstrated in the prospective trial RTOG 0915.[11,36] In data from Cleveland Clinic, which included a review of patients treated on RTOG 0915, chest wall toxicity with single-fraction regimens was increased with abutment or proximity of the chest wall, with grade 2 to 4 toxicity 5.7% in tumors >2 cm from the chest wall and 30.6% for tumors abutting the chest wall.[37] Proximity to the chest wall or to central structures remains a challenge for

FIGURE 1. Risk-adapted approach to lung stereotactic body radiation therapy using a conventional linac. *Consider 34 Gy in 1 fraction. GTV = gross tumor volume, OARs = organs at risk, PTV = planning target volume



the safe implementation of single-fraction regimens in peripheral tumors.

Peripheral tumors close to the diaphragm may also experience significant respiratory motion, leading to larger volume internal target volumes (ITVs) when motion reduction techniques are not used. Use of breath-hold gating, which has also been performed on conventional linacs, can mitigate this effect. The availability of MR imaging during treatment for real-time breath hold monitoring may be an advantage of MR-guided SBRT for the treatment of peripheral tumors susceptible to motion (**Figure 2A-2B**). In addition, the daily adaptive replanning enabled by MR-linac treatment may be useful for rapidly growing, or shrinking, tumors abutting the chest wall due to the ability of adaptive replanning to account for daily changes in the relationship between tumor position and chest wall. An important consideration for the treatment of peripheral tumors with SMART is that arms are typically positioned at the sides due to the time on table. An arms-down position may limit beam angles and may also bring the inframammary fold into the field.

In a report of 23 patients with peripheral lung tumors treated with SMART in the Netherlands, online adaptation improved PTV coverage.[38] For the subset of patients who also underwent free-breathing 4-dimensional computed tomography (4DCT), SMART breath-hold PTVs were 53.7% the volume of PTVs generated from an ITV. In a subsequent study of 17 patients simulated at the same center for planned single-fraction MR-guided SBRT,[39] 7 patients were unable to undergo single-fraction SBRT (because of difficulty in gross tumor volume [GTV] tracking due to tumor size in 1 patient, difficulty in GTV tracking due to blood vessels in 4, proximity to chest wall in 1 patient, and difficulty in breath holds in 1 patient). Of the 10 undergoing single-fraction SBRT, 9 completed treatment in one session, and median total in-room procedural time was 120 minutes. Online adaptive replanning improved PTV coverage but did not impact GTV coverage. These studies provide support for the use of SMART in peripheral tumors. The phase I trial SMART ONE (NCT04939246) is assessing the feasibility of single-fraction SMART in tumors in the lung as well as other sites.

Due to the limited availability of simulation appointments at many centers, and the difference in immobilization required for MR-guided vs non-MR-guided simulation, additional research is also needed

Table 2. Summary of Key Differences Between Two Commercially Available MR-linacs

PARAMETERS	VIEWRAY MRIDIAN	ELEKTA UNITY
Static magnetic field strength	0.35 Tesla	1.5 Tesla
Magnet configuration	Split	Closed
Bore diameter	70 cm	70 cm
Cine orientation for intrafraction tumor tracking	Sagittal	Multiple planes
Commercially available beam gating based on tumor motion	Automated pausing of beam	Manual pausing of beam
Treatment beam, relative to static magnetic field	Perpendicular	Perpendicular
Photon energy	6 MV	7 MV
Availability of online adaptive replanning	Yes	Yes
Maximum field size, superior to inferior	24 cm	22 cm

FIGURE 2. Example cases utilizing MR-guided radiation therapy. Left lower lobe lung tumor is seen on MR-linac simulation scan performed with breath hold (A). Maximum intensity projection (MIP) created from 4D-CT for the same tumor shows tumor motion, leading to a larger internal target volume for stereotactic body radiation therapy (SBRT) performed with free breathing (B). The treatment plan for an ultracentral lung tumor treated with SMART, 50 Gy in 5 fractions is shown, superimposed on an axial MR image acquired with True Fast Imaging with Steady State Precession (TRUFI). The 40 Gy line is seen curving around tree (green); 52.5 Gy line is seen carving out great vessel (C).

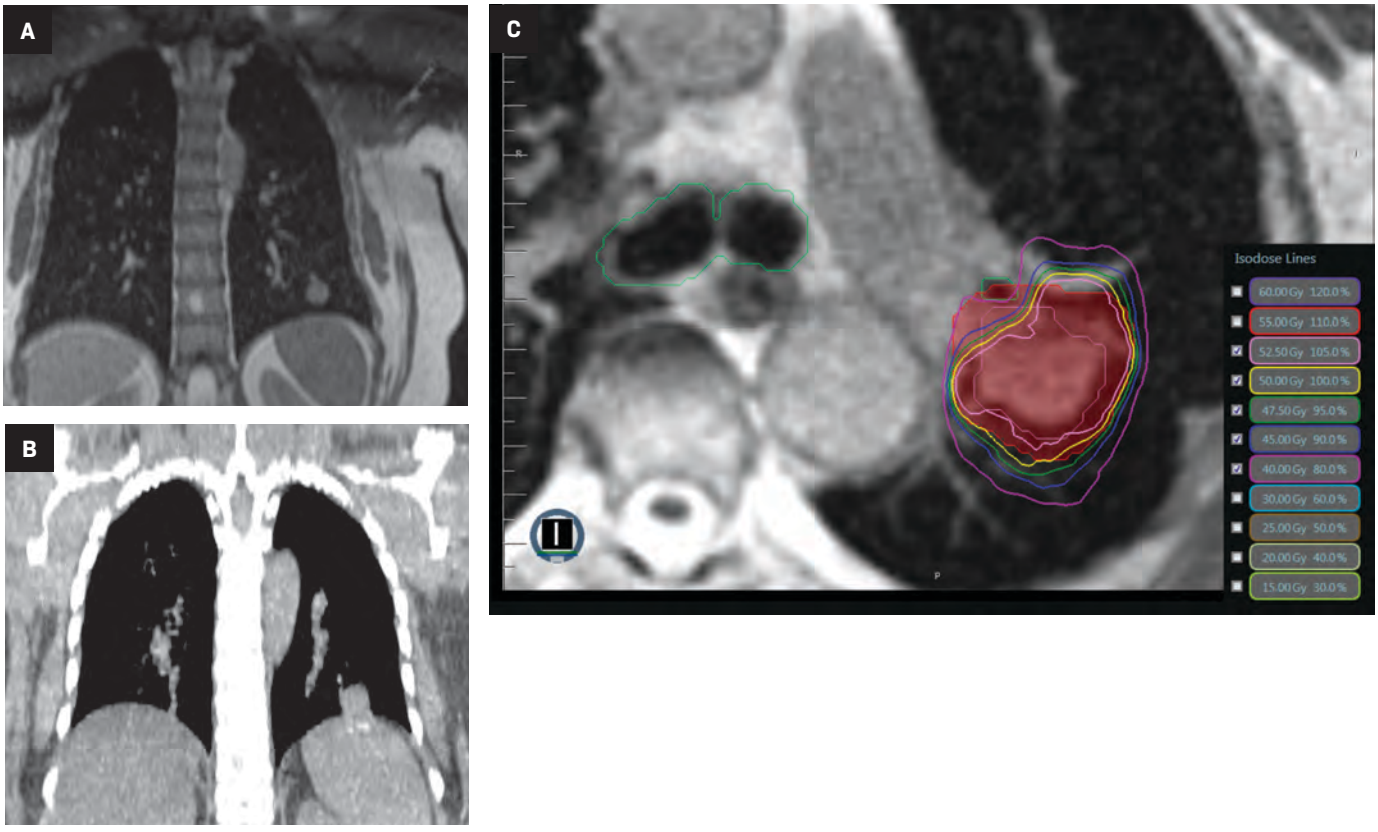
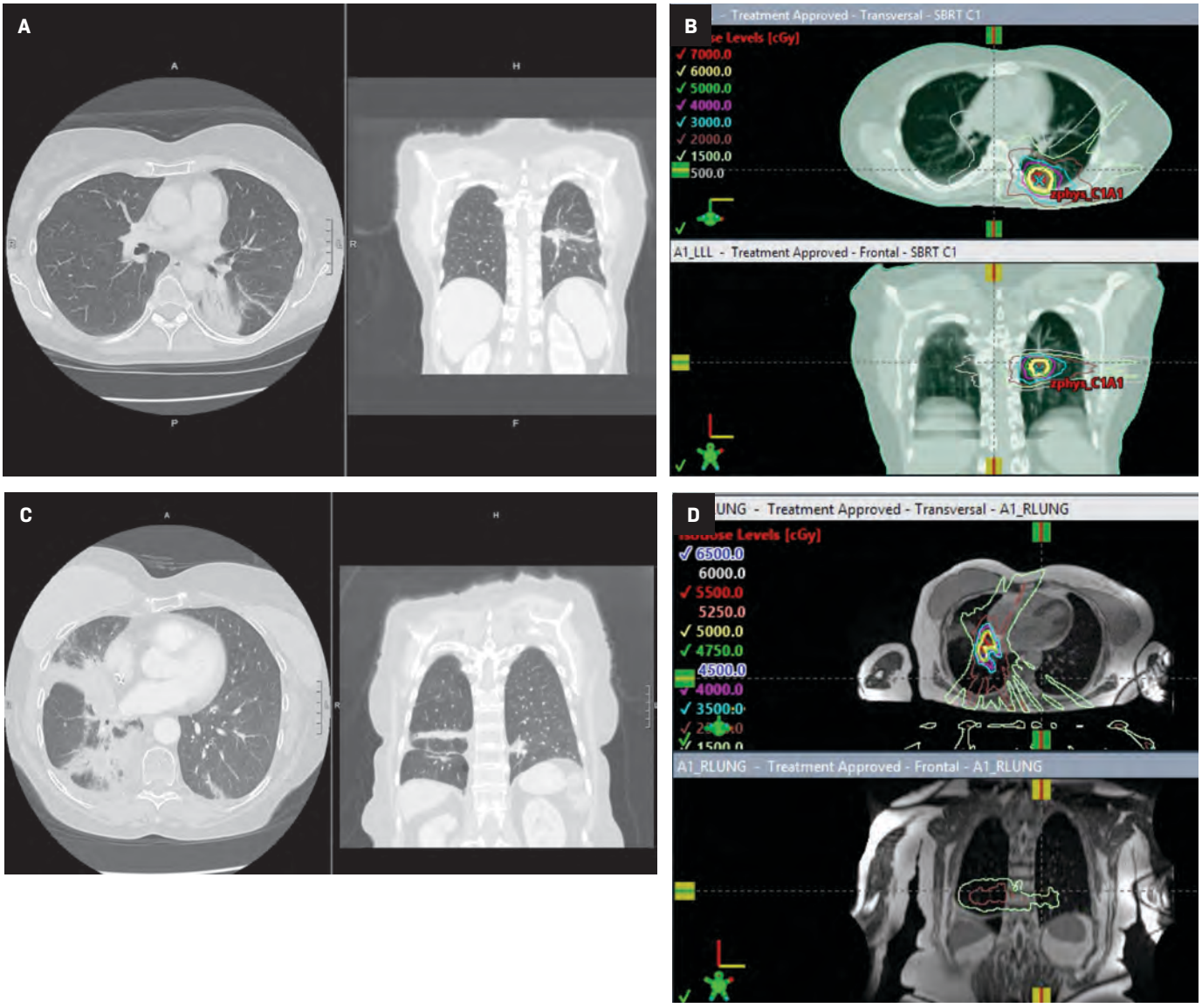


FIGURE 3. Radiation pneumonitis (RP) following treatment with volumetric-modulated arc therapy (VMAT) vs MR-guided intensity-modulated radiation therapy (IMRT). Axial (left) and coronal (RT) chest computed tomography (CT) for a patient with Grade 1 RP treated with VMAT (A). Corresponding VMAT plan, with 15-20 Gy isodose lines conforming to the tumor shape and correlating with consolidation seen at CT (B). Axial (left) and coronal (right) CT chest for a patient with grade 1 RP treated with MR-guided IMRT (C). Corresponding IMRT plan, showing 15-20 Gy isodose lines correlating with consolidation in contralateral and ipsilateral lung (D).

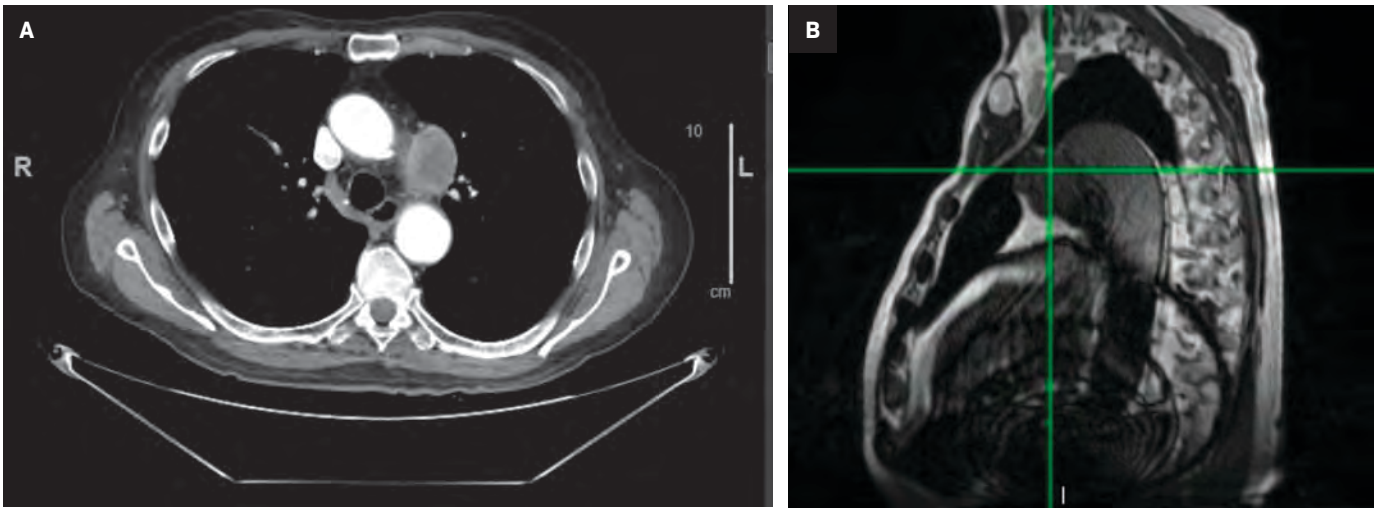


to better identify optimal candidates for MR-guided RT. A recent case report, which did not require online adaptive replanning, noted a reduced treatment time for single-fraction lung SBRT.[40] The ability to better predict which tumors do not benefit from online adaptive replanning could also further reduce on-table time.

Central Lesions

Central tumors are within 2 cm of the proximal bronchial tree, with further subclassification of tumors touching the tree as ultracentral. Due to the proximity of the proximal bronchial tree, these tumors are at increased risk for OAR toxicity as seen on the phase II prospective study reported by Timmerman et al.[9] The online adaptive replanning workflows utilized in MR-guided SBRT may be promising for central tumors due to the ability to account for daily changes in OAR location and morphology. In addition, MR-linacs allow for real-time tumor tracking during treatment, which may be helpful in decreasing appropriate PTV margin. A decreased PTV margin

FIGURE 4. Example of artifact from an aortic stent interfering with tracking for MR-guided stereotactic body radiation therapy (SBRT). Contrast-enhanced pre-radiation therapy chest computed tomography shows an ultracentral lung tumor (A). MR-linac artifact is seen inferior and cosagittal to tumor, with tumor denoted by green crosshairs, impairing tracking during treatment (B).



could enable improved target coverage while sparing OARs.

In a retrospective analysis from VU Medical Center in the Netherlands of 25 patients with central lung tumors treated with SMART in 5 or 8 fractions, the reoptimized plan was selected in 92% of cases.[41] SMART also reduced the number of OAR violations. The feasibility of SMART for central lung tumors is being studied on a prospective, phase I trial in the US (NCT04115254). The prospective phase II trial LUNG STAAR (NCT04917224) is assessing SMART in central lung cancers.

Ultracentral Lesions

Although ultracentral tumors have been defined variably across studies, definitions generally consider these tumors as touching, close to (≤ 1 cm) or overlapping critical OARs. The SUNSET trial categorized PTVs abutting the tree or mediastinal OARs as ultracentral.[10] SBRT for ultracentral tumors requires careful consideration of tumor location and motion. Retrospective data from Memorial Sloan Kettering Cancer Center identified an increased risk of grade 5 toxicity (hazard ratio 16.9, confidence interval 3.2-88%) in ultracentral tumors treated with SBRT in the setting of antiangiogenic agents. The recent prospective HILUS trial reported grade 5 toxicity in 10 of 65 patients (15%) using a regimen of 60 Gy in 8 fractions, with dose to the hottest 0.2 cc of main bronchi and trachea as the strongest predictor for grade 5 bronchopulmonary hemorrhage.[42] In this trial, dose was prescribed to the 67% isodose line, with hot spots of 150%. The protocol did not specify OAR dose guidelines for the lobar and segmental bronchi.

MR-guided SBRT holds promise for ultracentral tumors due to the potential for MR-guided setup and tumor tracking with real-time MRI during treatment, as well as the potential for online adaptive replanning to ensure sparing of OARs based on daily geometry and morphology (**Figure 2C**). Online adaptive replanning can also ensure that absolute dose constraints are met daily. In a prospective feasibility study from Washington University in St. Louis, 5 patients with ultracentral tumors were treated with 50 Gy in 5 fractions, with 10 of 25 fractions requiring adaptive replanning to improve PTV coverage or reverse OAR violations.[16] Case reports and case series describe the safety and feasibility of MR-guided SBRT for cardiac lesions, which are ultracentral by definition due to their location in the heart.[43-46]

Challenges for MR-guided SBRT for ultracentral tumors include identification and contouring of structures that may be better defined on CT such as the proximal bronchial tree, the limited spatial resolution of MR and challenge in tracking very small tumors, and the use of IMRT on MR-linacs, which may have a less favorable distribution of low dose compared to VMAT. In **Figure 3**, a case of CTCAE (Common Terminology Criteria for Adverse Events) grade 1 (asymptomatic) pneumonitis is shown for a patient treated with SBRT on a non-MR linac using volumetric-modulated arc therapy (VMAT). A case of CTCAE grade 1 pneumonitis is also shown for a patient with an ultracentral tumor treated with MR-guided SBRT using static field, coplanar (intensity-modulated radiation therapy) IMRT on an MR-linac. The low dose is more diffuse in the MR-linac case, leading to radiation changes

even in the contralateral lung.

Despite the potential of MR-guided SBRT for the treatment of peripheral, central, and ultracentral primary and secondary lung cancers, challenges to the broad application of this technique remain. Evidence to date has largely been in the form of retrospective or prospective phase I trials, motivating the need for additional phase II or III data. In addition, patients with primary lung cancer may have comorbidities such as chronic obstructive pulmonary disease, limiting ability to breath-hold or to lay flat for the 1 hour or more duration of SMART. Careful assessment of patients prior to simulation is needed. MR-unsafe pacemakers or other devices may preclude the use of MR-guided SBRT for some patients. Artifacts can also be associated with MR conditional implants, impairing the ability to contour or safely track. For example, in **Figure 4**, the sagittal cine obtained at MR simulation is shown for a patient with an ultracentral lung metastasis and an MR conditional aortic stent. The artifact from the stent was inferior to the target, but cosagittal, and precluded safe tracking on sagittal cine during treatment. This patient was treated with non-MR-guided SBRT with an excellent response. This case illustrates the need for both MR-guided and non-MR-guided SBRT options for patients.

Future Directions

In light of the toxicity seen on HILUS and other studies, additional research is needed to ensure the safe and effective treatment of central and ultracentral lung cancers. Use of radiosensitizers could improve the therapeutic window by allowing for the utilization of lower radiation treatment doses, which when combined with a radiosensitizer localizing to tumor, could allow for simultaneous local control of the tumor and improved normal tissue sparing. Given the promise of MR-guided radiation therapy for the treatment of central and ultracentral lung tumors, gadolinium-based nanoparticles may be especially useful due to their ability to localize the tumor and serve as radiosensitizers. Such agents that provide both therapeutic and diagnostic information are also known as theranostics.[47]

The Nano-Rad study in France recently demonstrated the safety of combining gadolinium-based nanoparticles with whole-brain radiation in patients with multiple brain metastases.[48] The selective distribution of the nanoparticle in brain metastases was also demonstrated. A similar preferential distribution in lung tumors would be particularly beneficial for the treatment of central and ultracentral cancers in close proximity to normal tissues if doses lower than standard ablative SBRT doses could be utilized. A clinical trial is currently open studying the use of gadolinium-based nanoparticles in the MR-guided treatment of central lung cancers (NCT04789486). Because the clinical efficacy of gadolinium-based nanoparticles in this setting is unknown, the trial utilizes an ablative prescription dose of 50 Gy in 5 fractions. In the future, it would be particularly advantageous for ultracentral tumors if radiosensitizers could enable treatment of these cancers to doses of 40 Gy in 5 fractions, or lower, facilitating sparing of more sensitive normal tissues.

Artificial intelligence (AI) may help accelerate efficiency and facilitate the adoption of MR-guided radiation therapy. Currently, there is a daily, time-intensive process of manual recontouring required for daily online adaptive replanning. Due to the proximity of nearby normal tissues, central, ultracentral, and peripheral lung tumors frequently require recontouring of dose-limiting OARs. AI algorithms, including deep learning, have shown the ability to produce highly accurate OARs within seconds on both CT and MR images.[49,50] AI has also shown promise in tumor auto-contouring, which can be coupled with online dose optimization to limit time for adaptive replanning.[51] Because radiation therapists, radiographers, and physicists also participate in recontouring at some centers,[52,53] AI has the potential to improve workflows for the interdisciplinary team. As SBRT options for patients broaden, AI may also be able to accelerate development of mock plans,[54] allowing for comparison plans to be generated proactively, assisting in selection of fractionation scheme and MR-linac vs non-MR linac for each patient. This will allow for truly individualized, risk-adaptive SBRT.

Conclusions

MR-linacs expand options for the treatment of thoracic tumors with SBRT by offering excellent soft-tissue contrast compared with CT, as well as additional advantages including MR-guided setup, online adaptive replanning, and real-time MRI-based monitoring of breath-hold treatments. For peripheral tumors, MR-guided SBRT may be advantageous in minimizing dose to the chest wall, and in minimizing normal lung treated with MR-guided breath-hold treatment. MR-guided setup may help with the visualization and sparing of OARs in the treatment of central and ultracentral tumors with SBRT. Disadvantages of MR-guided SBRT for peripheral, central, and ultracentral lung tumors include the potential for longer times on the treatment table and incompatibility of this technology with MR unsafe implants. Future work evaluating MR-guided lung SBRT on prospective studies is needed. By allowing OAR sparing with the potential for dose escalation, MR-guidance holds

promise in improving risk-adapted SBRT for the treatment of thoracic malignancies.

References

1) Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. *CA Cancer J Clin.* 2020;70(1):7-30. doi:10.3322/caac.21590

2) Cancer of the lung and bronchus – cancer stat facts. NIH National Cancer Institute Surveillance, Epidemiology, and End Results Program. Accessed June 6, 2021. https://seer.cancer.gov/statfacts/html/lungb.html

3) Sands J, Tammemägi MC, Couraud S, et al. Lung screening benefits and challenges: a review of the data and outline for implementation. *J Thorac Oncol.* 2021;16(1):37-53. doi:10.1016/j.jtho.2020.10.127

4) Ball D, Mai GT, Vinod S, et al. Stereotactic ablative radiotherapy versus standard radiotherapy in stage 1 non-small-cell lung cancer (TROG 09.02 CHISEL): a phase 3, open-label, randomised controlled trial. *Lancet Oncol.* 2019;20(4):494-503. doi:10.1016/S1470-2045(18)30896-9

5) Timmerman RD, Hu C, Michalski J, et al. Long-term results of RTOG 0236: A phase II trial of stereotactic body radiation therapy (SBRT) in the treatment of patients with medically inoperable stage I non-small cell lung cancer. *Rad Oncol Biol.* 2014;90(Supplement):S30. doi:10.1016/j.ijrobp.2014.05.135

6) Senthi S, Lagerwaard FJ, Haasbeek CJA, Slotman BJ, Senan S. Patterns of disease recurrence after stereotactic ablative radiotherapy for early stage non-small-cell lung cancer: a retrospective analysis. *Lancet Oncol.* 2012;13(8):802-809. doi:10.1016/S1470-2045(12)70242-5

7) Chang JY, Senan S, Paul MA, et al. Stereotactic ablative radiotherapy versus lobectomy for operable stage I non-small-cell lung cancer: a pooled analysis of two randomised trials. *Lancet Oncol.* 2015;16(6):630-637. doi:10.1016/S1470-2045(15)70168-3

8) Chang JY, Mehran RJ, Feng L, et al. Stereotactic ablative radiotherapy in operable stage I NSCLC patients: long-term results of the expanded STARS clinical trial. *J Clin Oncol.* 2021;39(15 supplement):Abstract8506. doi:10.1200/JCO.2021.39.15_suppl.8506

9) Timmerman R, McGarry R, Yiannoutsos C, 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(30):4833-4839. doi:10.1200/JCO.2006.07.5937

10) Giuliani M, Mathew AS, Bahig H, et al. SUNSET: Stereotactic Radiation for Ultracentral Non-Small-Cell Lung Cancer – Safety and Efficacy Trial. *CLLC.* 2018;19(4):e529-e532. doi:10.1016/j.cllc.2018.04.001

11) Videtic GMM, Hu C, Singh AK, et al. A randomized phase 2 study comparing 2 stereotactic body radiation therapy schedules for medically inoperable patients with stage i peripheral non-small cell lung cancer: NRG Oncology RTOG 0915 (NCCTG N0927). *Int J Radiat Oncol Biol Phys.* 2015;93(4):757-764. doi:10.1016/j.ijrobp.2015.07.2260

12) Nagata Y, Hiraoka M, Shibata T, et al. A phase II trial of stereotactic body radiation therapy for operable T1N0M0 non-small cell lung cancer; Japan Clinical Oncology Group (JCOG0403); long term follow-up results. *Radiat Oncol Biol.* 2018;102(3):S9. doi:10.1016/j.ijrobp.2018.06.115.

13) 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.* April 2019:JCO.18.00622–15. doi:10.1200/JCO.18.00622

14) Adebahr S, Collette S, Shash E, et al. LungTech, an EORTC Phase II trial of stereotactic body radiotherapy for centrally located lung tumours: a clinical perspective. *BJR.* 2015;88(1051):20150036. doi:10.1259/bjr.20150036

15) Xia T, Li H, Sun Q, et al. Promising clinical outcome of stereotactic body radiation therapy for patients with inoperable stage I/II non-small-cell lung cancer. *Radiation Oncology Biology.* 2006;66(1):117-125. doi:10.1016/j.ijrobp.2006.04.013

16) Henke L, Olsen JR, Contreras JA, et al. Stereotactic MR-guided online adaptive radiation therapy (SMART) for ultracentral thorax malignancies: results of a phase 1 trial. 2019;4(1):201-209. doi:10.1016/j.adro.2018.10.003

17) Li Q, Swanick CW, Allen PK, Gomez DR, Welsh JW, Liao Z. Stereotactic ablative radiotherapy (SABR) using 70Gy in 10 fractions for non-small cell lung cancer: Exploration of clinical indications. *Radiother Oncol.* 2014;112(2):256-261. doi:10.1016/j.radonc.2014.07.010

18) Lindberg K, Grozman V, Karlsson K, et al. The HILUS-Trial-a prospective Nordic multicenter phase 2 study of ultracentral lung tumors treated with stereotactic body radiotherapy. *J Thorac Oncol.* April 2021:1-11. doi:10.1016/j.jtho.2021.03.019

19) Phase II study of accelerated hypofractionated three-dimensional conformal radiotherapy for stage T1-3 N0 M0 non-small cell lung cancer: NCIC CTG BR.25. *J Nat Cancer Inst.* 2014;106(8):dju164-dju164. doi:10.1093/jnci/dju164

20) Onishi H, Araki T, Shirato H, et al. Stereotactic hypofractionated high-dose irradiation for stage I nonsmall cell lung carcinoma: clinical outcomes in 245 subjects in a Japanese multiinstitutional study. *Cancer.* 2004;101(7):1623-1631. doi:10.1002/cncr.20539

21) Sim AJ, Kaza E, Singer L, Rosenberg SA. A review of the role of MRI in diagnosis and treatment of early stage lung cancer. *Clin Transl Radiat Oncol.* 2020;24:16-22. doi:10.1016/j.ctro.2020.06.002

22) Sibolt P, Andersson LM, Calmels L, et al. Clinical implementation of artificial intelligence-driven cone-beam computed tomography-guided online adaptive radiotherapy in the pelvic region. *Phys Imag Radiat Oncol.* 2021;17:1-7. doi:10.1016/j.phro.2020.12.004

23) Kong F-MS, Ritter T, Quint DJ, et al. Consideration of dose limits for organs at risk of thoracic radiotherapy: atlas for lung, proximal bronchial tree, esophagus, spinal cord, ribs, and brachial plexus. *Int J Radiat Oncol Biol Phys.* 2011;81(5):1442-1457. doi:10.1016/j.ijrobp.2010.07.1977

24) Green OL, Henke LE, Hugo GD. Practical clinical workflows for online and offline adaptive radiation therapy. *Sem Radiat Oncol.* 2019;29(3):219-227. doi:10.1016/j.semradonc.2019.02.004.

25) Boyle PJ, Huynh E, Boyle S, et al. Use of a healthy volunteer imaging program to optimize clinical implementation of stereotactic MR-guided adaptive radiotherapy. *Tech Innov Patient Support Radiat Oncol.* 2020;16:70-76. doi:10.1016/j.tipsro.2020.10.004

26) Alongi F, Rigo M, Figlia V, 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. March 2020:1-9. doi:10.1186/s13014-020-01510-w

27) Chuong MD, Bryant J, Mittauer KE, 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(2):134-147. doi:10.1016/j.prro.2020.09.005

28) de Mol van Otterloo SR, Christodouleas JP, Blezer ELA, 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.* July 2021. doi:10.1016/j.ijrobp.2021.07.003

29) Crockett CB, Samson P, Chuter R, in MDF, 2021. Initial clinical experience of MR-guided radiotherapy (MRgRT) for non-small cell lung cancer (NSCLC). *Front Oncol.* 2021;11. doi:10.3389/fonc.2021.617681/full

30) Corradini S, Alongi F, Andratschke N, et al. ESTRO-ACROP recommendations on the clinical implementation of hybrid MR-linac systems in radiation oncology. *Radiother Oncol.* 2021;159:146-154. doi:10.1016/j.radonc.2021.03.025

31) Tocco BR, Kishan AU, in TMF, 2020. MR-guided radiotherapy for prostate cancer. *Front Oncol.* 2020;10. doi:10.3389/fonc.2020.616291/full

32) Chin S, Eccles CL, McWilliam A, et al. Magnetic resonance-guided radiation therapy: a review. *J Med Imaging Radiat Oncol.* 2020;64(1):163-177. doi:10.1111/1754-9485.12968

33) Kurz C, Buizza G, Landry G, et al. Medical physics challenges in clinical MR-guided radiotherapy. *Radiat Oncol.* 2020;15(1):93–16. doi:10.1186/s13014-020-01524-4

34) Dunlap NE, Cai J, Biedermann GB, et al. Chest wall volume receiving >30 Gy predicts risk of severe pain and/or rib fracture after lung stereotactic body radiotherapy. *Int J Radiat Oncol Biol Phys.* 2010;76(3):796-801. doi:10.1016/j.ijrobp.2009.02.027

35) Jumeau R, Filion E, Bahig H, et al. A dosimetric parameter to limit chest wall toxicity in SABR of NSCLC. *BJR.* 2017;90(1075):20170196. doi:10.1259/bjr.20170196

36) Videtic GM, Paulus R, Singh AK, et al. Long-term follow-up on NRG oncology RTOG 0915 (NCCTG N0927): a randomized phase 2 study comparing 2 stereotactic body radiation therapy schedules for medically inoperable patients with stage I peripheral non-small cell lung cancer. I*nt J Radiat Oncol Biol Phys.* 2019;103(5):1077-1084. doi:10.1016/j.ijrobp.2018.11.051

37) Manyam BV, Videtic GMM, Verdecchia K, Reddy CA, Woody NM, Stephans KL. Effect of tumor location and dosimetric predictors for chest wall toxicity in single-fraction stereotactic body radiation therapy for stage I non-small cell lung cancer. *Pract Radiat Oncol.* 2019;9(2):e187-e195. doi:10.1016/j.prro.2018.11.011

38) Finazzi T, Palacios MA, Haasbeek CJA, et al. Stereotactic MR-guided adaptive radiation therapy for peripheral lung tumors. *Radiother Oncol.* 2020;144:46-52. doi:10.1016/j.radonc.2019.10.013

39) Finazzi T, van Sörnsen de Koste JR, Palacios MA, et al. Delivery of magnetic resonance-guided single-fraction stereotactic lung radiotherapy. *Phys Imag Radiat Oncol.* 2020;14:17-23. doi:10.1016/j.phro.2020.05.002

40) Chuong MD, Kotecha R, Mehta MP, et al. Case report of visual biofeedback-driven, magnetic resonance-guided single-fraction SABR in breath hold for early stage non-small-cell lung cancer. *Med Dosim.* 2021;46(3):247-252. doi:10.1016/j.meddos.2021.01.003

41) Finazzi T, Palacios MA, Spoelstra FOB, et al. Role of on-table plan adaptation in mr-guided ablative radiation therapy for central lung tumors. Int J Radiat Oncol Biol Phys. 2019;104(4):933-941. doi:10.1016/j.ijrobp.2019.03.035

42) Lindberg K, Grozman V, Karlsson K, et al. The HILUS-Trial: a prospective Nordic multicenter phase 2 study of ultracentral lung tumors treated with stereotactic body radiotherapy. *J Thorac Oncol.* April 2021. doi:10.1016/j.jtho.2021.03.019.

43) Pomp J, van Asselen B, Tersteeg RHA, et al. Sarcoma of the heart treated with stereotactic MR-guided online adaptive radiation therapy. *Case Rep Oncol.* 2021;14(1):453-458. doi:10.1159/000513623

44) Shi DD, Liu KX, Hacker F, et al. Development and implementation of an online adaptive stereotactic body radiation therapy workflow for treatment of intracardiac metastasis. *Pract Radiat Oncol.* February 2021. doi:10.1016/j.prro.2021.01.009

45) Corradini S, Bestenbostel von R, Romano A, et al. MR-guided stereotactic body radiation therapy for primary cardiac sarcomas. *Radiat Oncol.* 2021;16(1):60-68. doi:10.1186/s13014-021-01791-9

46) Sim AJ, Palm RF, DeLozier KB, et al. MR-guided stereotactic body radiation therapy for intracardiac and pericardial metastases. *Clin Transl Radiat Oncol.* 2020;25:102-106. doi:10.1016/j.ctro.2020.10.006

47) Mauro N, Utzeri MA, Varvarà P, Cavallaro G. Functionalization of metal and carbon nanoparticles with potential in cancer theranostics. *Molecules.* 2021;26(11):3085. doi:10.3390/molecules26113085

48) Verry C, Dufort S, Villa J, et al. Theranostic AGuIX nanoparticles as radiosensitizer: a phase I, dose-escalation study in patients with multiple brain metastases (NANO-RAD trial). *Radiother Oncol.* 2021;160:159-165. doi:10.1016/j.radonc.2021.04.021

49) Elguindi S, Zelefsky MJ, Jiang J, et al. Deep learning-based auto-segmentation of targets and organs-at-risk for magnetic resonance imaging only planning of prostate radiotherapy. *Phys Imag Radiat Oncol.* 2019;12:80-86. doi:10.1016/j.phro.2019.11.006

50) Amjad A, Xu J, Thill D, et al. Deep learning-based auto-segmentation on CT and MRI for abdominal structures. *Radiat Oncol Biol.* 2020;108(3, Supplement):S100-S101.

51) Rigaud B, Anderson BM, Yu ZH, et al. Automatic segmentation using deep learning to enable online dose optimization during adaptive radiation therapy of cervical cancer. *Int J Radiat Oncol Biol Phys.* 2021;109(4):1096-1110. doi:10.1016/j.ijrobp.2020.10.038

52) McNair HA, Wiseman T, Joyce E, Peet B, Huddart RA. International survey; current practice in on-line adaptive radiotherapy (ART) delivered using Magnetic Resonance Image (MRI) guidance. *Tech Innov Patient Support Radiat Oncol.* 2020;16:1-9. doi:10.1016/j.tipsro.2020.08.002

53) McNair HA, Joyce E, O'Gara G, et al. Radiographer-led online image guided adaptive radiotherapy: a qualitative investigation of the therapeutic radiographer role. *Radiography.* June 2021. doi:10.1016/j.radi.2021.04.012

54) McIntosh C, Conroy L, Tjong MC, et al. Clinical integration of machine learning for curative-intent radiation treatment of patients with prostate cancer. *Nat Med.* June 2021:1-7. doi:10.1038/s41591-021-01359-w

Integrating MR-Guided Radiation Therapy Into Clinical Practice: Clinical Advantages and Practical Limitations

Description

While MR-guided radiation therapy (MRgRT) offers many benefits, it is a costly and resource-intensive investment that can strain radiation oncology clinics not adequately prepared to incorporate this treatment. This work reviews clinical advantages and practical limitations of MRgRT, and suggests ideal patients for this technology. The authors also provide a practical guide for centers acquiring MRI-based linear accelerators to foster seamless integration.

Learning Objectives

Upon completing this activity, the readers should be able to:

- learn and apply the advantages of MRgRT over more conventional CT-based treatment techniques;
- understand the practical limitations of MRgRT; and
- become familiar with the disease sites that may benefit most from this new technology.

Accreditation/ Designation Statement

The Institute for Advanced Medical Education is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians. The Institute for Advanced Medical Education designates this journal-based CME activity for a maximum of 1 AMA PRA Category 1 Credit.™ Physicians should only claim credit commensurate with the extent of their participation in the activity. These credits qualify as SA-CME credits.

Authors

Leila T. Tchelebi, MD; Nicholas G. Zaorsky, MD, MPH; Jennifer Rosenberg, MD; Kujtim Latifi, PhD; Sarah Hoffe, MD

Affiliations: Penn State Cancer Institute, Hershey, PA (Drs. Tchelebi, Zaorsky, Rosenberg), Moffitt Cancer Center, Tampa, FL (Drs. Latifi and Hoffe)

Target Audience

- Radiation Oncologists
- Related Oncology Professionals

Instructions

To successfully earn credit, participants must complete the activity during the valid credit period.

1. Review this article in its entirety.
2. Visit www.appliedradiology.org/SAM.
3. Login to your account or (new users) create an account.
4. Complete the post test and review the discussion and references.
5. Complete the evaluation.
6. Print your certificate.

Estimated time for completion:
1 hour

Date of release and review:
September 1, 2021

Expiration date:
August 31, 2023

Disclosures

No authors, faculty, or any individuals at IAME or *Applied Radiation Oncology* who had control over the content of this program have any relationships with commercial supporters.

Integrating MR-Guided Radiation Therapy Into Clinical Practice: Clinical Advantages and Practical Limitations

Leila T. Tchelebi, MD; Nicholas G. Zaorsky, MD, MS; Jennifer Rosenberg, MD; Kujtim Latifi, PhD; Sarah Hoffe, MD

MR-guided radiation therapy (MRgRT) has emerged as a promising radiation treatment modality for a variety of solid malignancies. This technology is being increasingly adopted at practices across the US and abroad. ViewRay, the company to introduce the first MRgRT system into clinical practice at Washington University in 2014,[1] now has 45 treatment units installed at practices around the world. Meanwhile, Elekta developed the Unity system which first came into clinical practice at UMC Utrecht in the Netherlands in 2017,[2] and is now installed in 25 practices worldwide. While there are a number of benefits to MRgRT, it is a costly and resource-intensive investment that can strain radiation oncology clinics not adequately prepared to incorporate this new treatment modality into practice. The purpose of the present work is to review both the clinical advantages and the practical limitations of MRgRT, and to suggest which patients are likely to derive the greatest benefit from this technology. We aim to provide a practical guide for centers acquiring MRI-based linear accelerators (MR-linacs) to incorporate the technology more seamlessly into clinical practice.

Clinical Advantages of MRgRT

There are several advantages to MRgRT over conventional computed tomography (CT)-guided treatment techniques. Among these advantages are superior target visualization through improved soft-tissue imaging, real-time tumor tracking, real-time image-guided gating, and real-time plan adaptation (**Table 1**).[3-5] Improved soft-tissue imaging has been cited as a primary reason patients are treated on an MR-linac rather than a CT-based machine.[6] A comparison of pelvic anatomy acquired on a CT-simulator vs an MR-simulator is shown in **Figure 1**.

Daily MRI acquisition on an MR-linac allows for superior organ-at-risk and target-volume visualization, which, in turn, allows for plan adaptation.[5] Online adaptive radiation therapy can improve planning target volume (PTV) coverage and reduce treatment toxicity.[7-9] In their study of 10 patients undergoing pancreas stereotactic body radiation therapy (SBRT), El-Bared et al showed that adaptive replanning resulted in a 10% improvement in the volume of the PTV receiving 100% of the prescribed dose (90% vs 80%, $P < 0.01$) compared with nonadaptive plans.[7] The maximum dose to the duodenum was achieved more frequently in the adaptive vs nonadaptive plans.[7]

By allowing for improved target volume coverage with reduced toxicity, online adaptive replanning permits dose escalation. In their trial of MR-guided online adaptive radiation therapy (SMART) for abdominal malignancies, Henke et al found that plan adaptation resulted in improved PTV coverage in 64 of 97 delivered fractions, with zero Grade 3 or higher toxicity.[10] Ablative doses of radiation could only be delivered with adaptive replanning, permitting the delivery of higher radiation doses than has historically been possible to tumors within the abdomen.[11] The ability to dose escalate using adaptive replanning on an MR-linac for inoperable pancreatic cancer has also been demonstrated.[12] Henke et al also conducted a phase I trial of SMART for ultracentral thoracic malignancies and found that PTV

Affiliations: Dr. Tchelebi is an assistant professor, **Dr. Zaorsky** is a tenure-track assistant professor, and **Dr. Rosenberg** is an assistant professor, all in the Department of Radiation Oncology, Penn State Cancer Institute, Hershey, PA. Dr. Zaorsky is also an assistant professor in the Department of Public Health Sciences, Penn State College of Medicine. **Dr. Latifi** is an assistant professor, and **Dr. Hoffe** is a professor and section head of GI radiation oncology, both in the Department of Radiation Oncology, Moffitt Cancer Center, Tampa, FL. **Disclosure:** The authors have no conflicts of interest to disclose. None of the authors received outside funding for the production of this original manuscript and no part of this article has been previously published elsewhere.

Table 1. Advantages and Limitations of the Distinguishing Features of MRgRT With Examples of Cancer Sites Deriving the Most Benefit From Each Feature

FEATURE	ADVANTAGE	LIMITATION	DISEASE SITES THAT MAY BENEFIT
Improved soft-tissue visualization with MRI	Enhanced contouring of target and OARs	Time-consuming Requires physician training in MRI interpretation as well as additional personnel (radiologists) to assist with contours	All could potentially benefit
Real-time tracking and gating	Smaller set-up margins required Enhanced target accuracy Decreased dose to OARs No need for fiducials	Time-consuming	Lung cancer Pancreas cancer Liver cancer Prostate cancer
Functional imaging	Imaging biomarkers provide quantitative information regarding changes in tumor tissue for more targeted therapy	Functional imaging sequences not available on units in clinical use	Rectal cancer Pancreas cancer Liver cancer
Online adaptive replanning	Ability to assess anatomy of the day to make plan modifications to maximize dose to tumor and minimize dose to OARs Allows for dose escalation withoutconcomitant increase in toxicity	Challenging to contour anatomy of the day without IV/oral contrast Time-consuming Requires physician and physics presence	Pancreas cancer Ultracentral lung cancer Liver cancer

Key: MRgRT = MR-guided radiation therapy, OARs = organs at risk

coverage was improved in 30% of fractions with adaptive replanning.[13] The authors found they were able to reverse potentially life-threatening severe toxicities observed in historical trials of SBRT for ultracentral thoracic malignancies, which has precluded the use of ablative SBRT for many of these cases.

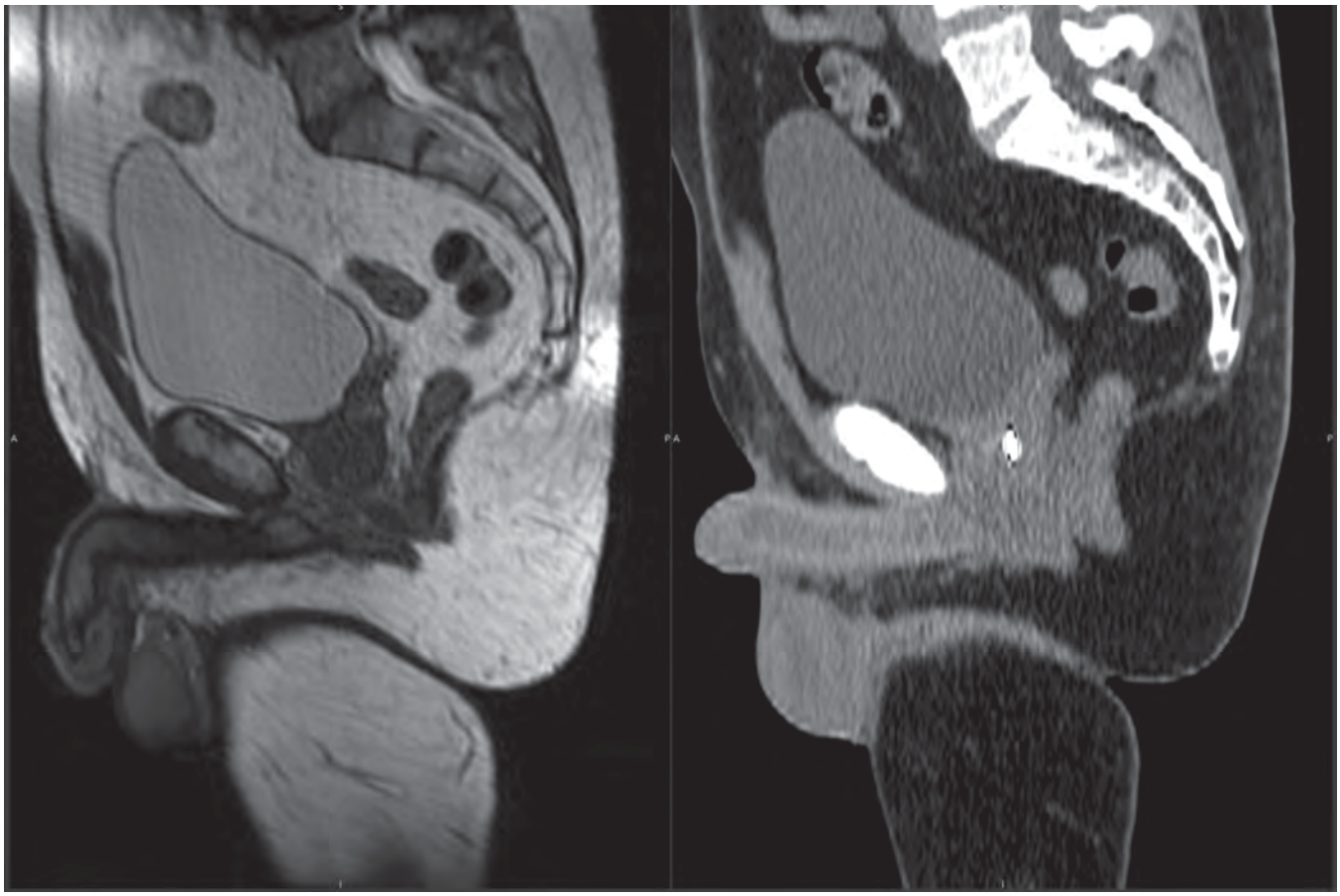
While online adaptive radiation therapy is an attractive feature of the MR-linac, it is not utilized for every patient treated on these machines. Reporting on their first 2.5 years of treating patients on the world's first MR-linac, Fischer-Valuk et al note that only about 25% of patients were treated with online adaptive radiation therapy.[6] The majority of these patients had abdominal malignancies. Among the patients treated with 5-fraction SBRT adaptive radiation, the incidence of plan adaption was 84%, which is in keeping with other reports in the literature.[14]

Additional advantages of the MR-linac include real-time tumor tracking and gating. Unlike gating on a conventional linac, gating on an MR-linac does not require fiducials or increase radiation exposure to the patient. The two-dimensional cine imaging on an MR-linac provides real-time live cine MRI frames that can be deformably registered to a preview cine MRI scan acquired right before the start of treatment.[15] A boundary is created to identify the tracking margin and radiation is halted whenever the anatomy of interest moves outside the boundary. This allows for a reduction in the margin typically added for setup uncertainty and intrafraction motion, allowing for improved target accuracy and decreased doses to adjacent organs at risk.[13,16-18]

MRI-based radiation treatment delivery also can provide functional imaging to guide radiation treatment. Diagnostic diffusion-weighted MRI, for example, has been shown to predict response to radiation therapy for a number of disease sites.[19-23] Diffusion-weighted MRI images can be used to create apparent diffusion coefficients (ADC), which provide quantitative information regarding changes in tumor tissue, such as development of necrosis, to guide therapy.[24] Dynamic contrast-enhanced (DCE) MRI sequences measure tissue perfusion and vascularity, and can serve as another biomarker for radiation delivery.[25] These imaging biomarkers can assist in patient selection for dose escalation or de-escalation, allowing for more individualized patient treatment.[26,27] While the feasibility of obtaining functional imaging on MR-linac units has been demonstrated, it is not available for commercial use at this time.[26,28,29] The modifications necessary to adapt MRI scanners for use in radiation treatment systems, such as a low field strength in the case of ViewRay's MRIdian or the split gradient coil system in the case of Elekta's Unity, may degrade the quality of the quantitative MRI data provided.[30] Efforts are ongoing to overcome these challenges such that functional imaging can one day be widely available on MR-linac systems in use.

The many advantages of MRgRT make this an attractive technology to adopt in radiation therapy practices. The cancers seen most in radiation oncology clinics – cancers of the

FIGURE 1. Comparison of MRI- and CT-based imaging of soft tissue. The MRI of the pelvis (left) reveals improved soft-tissue contrast relative to the CT of the pelvis (right).



breast, lung, colorectum, and prostate – all appear to derive benefit from treatment on an MR-linac (**Table 2**). In the case of breast cancer, MRgRT has been proposed as a valuable treatment technique for patients receiving partial-breast irradiation, given that the postoperative tumor bed is more clearly visualized on MRI than on CT.[31,32] Further, chest wall movement requires additional margins to account for setup uncertainty, which can be avoided with MRgRT's real-time tumor tracking and gating.[31] MRgRT has also been proposed as a solution to overcoming the challenges encountered when treating lung cancer patients by allowing for dose escalation, functional imaging, and reduced toxicity, particularly in the case of centrally located tumors.[13,31,33] In the case of rectal cancer, MRgRT is an enticing solution for patients wishing to undergo organ preservation, owing to its improved soft-tissue visualization, ability for adaptive replanning, functional imaging capabilities, and tumor gating, allowing for dose escalation.[27,34-36] Prostate cancer patients also appear to derive benefit from the implementation of MRgRT, given the high doses of radiation needed to treat prostate cancer while sparing the adjacent rectum and bladder, which are subject to significant variability in daily positioning.[31,37,38]

While there are potential advantages to treating these common malignancies with MRgRT over more conventional treatment techniques, the rarer cancers appear to derive the most benefit from this treatment (**Table 2**). Abdominal malignancies are challenging to treat on CT-based radiation therapy delivery systems. These cancers, including those of the pancreas and liver, are proximal to the bowel, which is intolerant of the ablative doses needed for treatment with curative intent. Moreover, abdominal organs are subject to constant fluctuations in position due to respiratory motion, gastric filling, and bowel distention. As a result, larger margins are needed to ensure adequate dose delivery to the tumor targets. A number of not only retrospective, but also prospective studies, demonstrate the safety and potential efficacy of MRgRT in managing abdominal malignancies.[10,12,39-48] Recently, Hassanzadeh et al published their experience treating 44 patients with inoperable pancreatic cancer to 50 Gy in 5 fractions on an

Table 2. Potential Role of MRgRT in Select Disease Sites

SITE	SITE-SPECIFIC ADVANTAGES	SITE-SPECIFIC LIMITATIONS	CLINICAL SCENARIO THAT MAY BENEFIT
Brain	Enhanced contouring of target and OARs	Time-consuming Requires physician training in MRI interpretation as well as additional personnel (radiologists) to assist with contours	All could potentially benefit
Head and neck	Smaller set-up margins required Enhanced target accuracy Decreased dose to OARs No need for fiducials	Time-consuming	Lung cancer Pancreas cancer Liver cancer Prostate cancer
Breast	Imaging biomarkers provide quantitative information regarding changes in tumor tissue for more targeted therapy	Functional imaging sequences not available on units in clinical use	Rectal cancer Pancreas cancer Liver cancer
Lung	Ability to assess anatomy of the day to make plan modifications to maximize dose to tumor and minimize dose to OARs Allows for dose escalation without concomitant increase in toxicity	Challenging to contour anatomy of the day without IV/oral contrast Time-consuming Requires physician and physics presence	Pancreas cancer Ultracentral lung cancer Liver cancer
Upper abdominal malignancies (pancreas, liver)	Improved soft-tissue visualization Tracking and gating Ability for adaptive replanning	Longer treatment times and resource utilization for adaptive cases Complexity of contouring on MRI	Most sites appear to derive benefit given current dose escalation limitations for primary abdominal malignancies with CT-based planning
Rectum	Improved soft-tissue visualization Ability for adaptive replanning	6 MV only Longer treatment times and resource utilization for adaptive cases Complexity of contouring on MRI Large field sizes needed to treat subclinical disease Long treatment course (ie, 5-6 weeks)	Retreatment Nonoperative cases – potential for tumor boost
Uterus	Improved soft-tissue visualization Tracking and gating	6 MV only Large field sizes needed to treat subclinical disease Long treatment course (ie, 5-6 weeks)	Limited Potential for tumor boost in inoperable patients
Prostate	Improved soft-tissue visualization Tracking and gating	6 MV only No VMAT Longer treatment time resulting in more variability in tumor position	SBRT cases
Anus	Improved soft-tissue visualization	6 MV only No VMAT Large field sizes needed to treat subclinical disease Long treatment course (ie, 5-6 weeks)	Limited Potential for retreatment of locally recurrent disease
Sarcoma	Improved soft-tissue visualization Functional imaging can show areas of necrosis	Large field sizes needed No VMAT	Limited

Key: MRgRT = MR-guided radiation therapy, CT = computed tomography; VMAT = volumetric-modulated arc therapy, OARs = organs at risk, MV = megavoltage, SBRT = stereotactic body radiation therapy

MR-linac. Local control and overall survival rates at 1 year were 84% and 68%, respectively, with low rates of late toxicity.[12]

Practical Limitations of MRgRT

While there are a number of advantages to MRgRT, clinicians should also consider several limitations when seeking to adopt this technology in daily practice (**Table 1**). Some inherent limitations associated with coupling an MRI to radiation treatment are geometric distortion, electron density disruption, susceptibility artifacts, and the inability to treat patients with contraindications to MRI, such as metal implants.[18] In addition, the features that distinguish MR-based from CT-based radiation treatment – including the acquisition of MR-imaging, adaptive replanning, and gating – result in significantly longer on-table times for patients.[2,10,49] MR-linacs also deliver fewer monitor units per minute and are only capable of delivering static step-and-shoot radiation plans, rather than volumetric-modulated arc therapy (VMAT), increasing beam-on time, thus further lengthening each treatment.[50]

There are several disadvantages to longer treatment times for cancer patients. For patients with claustrophobia, being in an enclosed space for prolonged periods can be intolerable.[6,31] Patients needing to maintain a full bladder to minimize dose to organs at risk, such as rectal and prostate cancer patients, may struggle if treatment times are lengthened. Further, as treatment time is prolonged, intrafraction motion increases, which in turn increases the need for adaptive replanning, further lengthening treatment time.[51] In their trial of MRgRT for patients with thoracic malignancies, Henke et al did not meet their primary endpoint of feasibility, defined as a treatment session lasting less than 80 minutes.[13] The authors note they have since improved their institution's online adaptive process to reduce treatment times. Thus, lengthy treatment times are a limitation new MR-linac users should be aware of and prepared to address.

In addition to the patient inconveniences associated with longer treatment times, lengthier treatments limit the number of patients who can be treated daily on an MR-linac. As a result, patients seen in consultation for MRgRT may have to wait several weeks for availability to start treatment. This limitation can be problematic for patients with fast-growing tumors, tumors in which prolonged treatment time results in inferior outcomes, or in patients on a strict treatment timeline involving a scheduled surgery following radiation.[52,53] In addition, given the complexity of this technology and it being relatively nascent, machine downtime is not infrequent, resulting in further delays or the need to transfer patients to standard linacs.[54]

Several planning limitations associated with MRgRT may further restrict which patients are ideally suited for treatment on these machines. One such limitation is treatment energy. The MR-linac can only deliver 6 to 7 MV treatments, which may not be ideally suited for larger patients undergoing treatment to the abdomen or pelvis. Another limitation is the field size (22 to 24 cm).[18,55] Size limitations may preclude the treatment of certain malignancies, such as sarcomas, and make it impractical to treat malignancies requiring coverage of large elective volumes, such as cancers of the head and neck. Since MRgRT treatment can only be done using step-and-shoot static fields, as opposed to VMAT, multiple fields are required to optimize treatment plans. This can be arduous for dosimetrists and physicists to plan and for radiation therapists to deliver, in addition to being lengthy. In their study on use of MRgRT for prostate cancer, for example, Tetar et al found that 15 beams were required to deliver the optimal treatment plan.[56] The increased time to deliver a 15-field, step-and-shoot plan can create the very problem an MR-linac is intended to solve, given the increased time for fluctuations in target positioning.

Perhaps the most significant limitation to implementing MRgRT in clinical practice is the heavy resource utilization. Due to complex treatment planning and delivery, which differs significantly from conventional CT-based radiation therapy, a team trained specifically in the plan design and delivery of MR-based radiation therapy is needed.[18,57-59] This team involves physicians, radiologists, and physicists.[18,57] Henke et al discuss the need to also hire advanced radiation therapists to assist with recontouring to make treatment delivery feasible.[13] The time required for personnel to be stationed at MR-linacs during treatment delivery makes them unavailable to perform other duties in the clinic, which can result in serious constraints on physician and physicist staffing. However, not all cases require adaptation on a daily basis.[60]

It is particularly important for physicians to consider the extended time required at the treatment machine for cases requiring daily plan adaptation. The process for an adaptive case requires an initial isocenter verification check, followed by contouring of the normal organs to review the original plan on the anatomy of the day. This can result in significant time delays given the complexity of defining the interface between normal tissues and target volumes, particularly for abdominal malignancies.[61] If an adaptive plan is needed, the physician must remain at the MR-linac while the new plan is run, and then evaluate the new plan to determine acceptability for treatment. In some circumstances, additional iterations of the planning process are required to meet the objectives of the normal tissue

constraints and the desired target coverage.[47] These situations challenge our physics colleagues, whose expertise is needed to determine how best to adjust the cost functions and which constraints to prioritize. The physician time involved can extend to up to 45 minutes per adaptive plan. After multiple iterations of the planning process, it will then be up to the physician to determine whether gross tumor volume (GTV) coverage should be sacrificed to keep the normal tissue constraints within appropriate limits.

Additional personnel may also be required due to the complexity of this treatment technique. A radiologist with expertise in MRI may need to be recruited to the program to aid the transition of the physician practice to MR-based contouring, which differs substantially from CT-based planning.[62,63] For some sites, such as the pancreas, additional fusion of the diagnostic CT scan, which has intravenous and oral contrast, may be necessary to delineate the GTV. For moving targets, such as thoracic and abdominal malignancies, breath-hold techniques may be needed to manage the tumor motion due to respiration. Fusion of the planning MR images with the planning CT images, all obtained with a technique such as deep inspiration breath hold, can pose challenges when these planning images must also be fused with diagnostic images, such as PET (positron emission tomography) and CT images, to verify the target and its position at the time of treatment. Careful attention must be paid to the appearance of the GTV on the MRI images relative to the CT images, because the MR volumes will often appear smaller than on CT.[62,63] For sites such as the pancreas, optimizing target delineation is essential to avoid a marginal miss.[64]

Another consideration for practices newly adopting MRgRT is lack of prospective data to guide use. Several trials are underway investigating the clinical benefits of MRgRT for cancer patients (eg, NCT04075305, NCT04351204). However, limited prospective data are available to indicate which outcomes are improved, and for which cancer patients, relative to treatment on a conventional CT-based system.[65] The theoretical benefits of this technology may not translate into real-world benefits.[65] Treating patients with a therapy not evaluated in a randomized controlled trial can, in the worst case, be harmful to patients. Clinics with limited resources should consider this lack of data when justifying the resource expenditure for MRgRT.

Future Directions

As MRgRT is increasingly used and newer technology becomes available, many clinical limitations described above may be improved. Improvements in the workflow through automatic reconstruction of the daily delivered dose, implementation of an MRI-only workflow, and the creation of consortiums to allow for a more coordinated, evidence-based introduction of MRgRT into clinical practice, are being explored.[66-68] Artificial intelligence is also being explored as a means of automating aspects of treatment planning, such as contouring and plan optimization, to decrease treatment time and resource utilization.[69] The need for clinical trials to better address which patients would benefit most from treatment on an MR-linac is also being actively addressed.[65] These improvements should eventually allow for more seamless integration of MRgRT into daily clinical practice, reducing the current burden on treatment facilities and patients.

Conclusions

The practical limitations of MRgRT limit the number of cancer patients who would derive the most benefit from this technology. Given the current capabilities of MR-linacs and the limited prospective data, careful patient selection is critical for appropriate resource allocation in practices adopting this technology. Centers seeking to adopt MRgRT into their clinical practices should carefully consider the limitations of this therapy to prepare for its successful implementation.

References

1) Mutic S, Dempsey JF. The ViewRay system: magnetic resonance-guided and controlled radiotherapy. *Semin Radiat Oncol.* 2014;24(3):196-199.

2) Raaymakers BW, Jürgenliemk-Schulz IM, Bol GH, et al. First patients treated with a 1.5 T MRI-Linac: clinical proof of concept of a high-precision, high-field MRI guided radiotherapy treatment. *Phys Med Biol.* 2017;62(23):L41-l50.

3) Hall WA, Paulson ES, van der Heide UA, et al. The transformation of radiation oncology using real-time magnetic resonance guidance: a review. *Euro J Cancer.* 2019;122:42-52.

4) Winkel D, Bol GH, Kroon PS, et al. Adaptive radiotherapy: the Elekta Unity MR-linac concept. *Clin Transl Radiat Oncol.* 2019;18:54-59.

5) Noel CE, Parikh PJ, Spencer CR, et al. Comparison of onboard low-field magnetic resonance imaging versus onboard computed tomography for anatomy visualization in radiotherapy. *Acta Oncol.* 2015;54(9):1474-1482.

6) Fischer-Valuck BW, Henke L, Green O, 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(3):485-493.

7) El-Bared N, Portelance L, Spieler BO, et al. Dosimetric benefits and practical pitfalls of daily online adaptive MRI-guided stereotactic radiation therapy for pancreatic cancer. *Pract Radiat Oncol.* 2019;9(1):e46-e54.

8) Palacios MA, Bohoudi O, Bruynzeel AME, et al. Role of daily plan adaptation in MR-guided stereotactic ablative radiation therapy for adrenal metastases. *Int J Radiat Oncol Biol Phys.* 2018;102(2):426-433.

9) Tchelebi LT, Zaorsky NG, Rosenberg JC, et al. Reducing the toxicity of radiotherapy for pancreatic cancer with magnetic resonance-guided radiotherapy. *Toxicol Sci.* 2020.

10) Henke L, Kashani R, Robinson C, 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(3):519-526.

11) Crane CH. Hypofractionated ablative radiotherapy for locally advanced pancreatic cancer. *J Radiat Res.* 2016;57(S1):i53-i57.

12) Hassanzadeh C, Rudra S, Bommireddy A, et al. Ablative five-fraction stereotactic body radiation therapy for inoperable pancreatic cancer using online MR-guided adaptation. *Adv Radiat Oncol.* 2021;6(1):100506.

13) Henke LE, Olsen JR, Contreras JA, et al. Stereotactic MR-guided online adaptive radiation therapy (SMART) for ultracentral thorax malignancies: results of a phase 1 trial. *Adv Radiat Oncol.* 2018;4(1):201-209.

14) Henke L, Kashani R, Robinson C, 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(3):519-526.

15) Green OL, Rankine LJ, Cai B, et al. First clinical implementation of real-time, real anatomy tracking and radiation beam control. *Med Phys.* 2018;45(8):3728-3740.

16) Massaccesi M, Cusumano D, Boldrini L, et al. A new frontier of image guidance: organs at risk avoidance with MRI-guided respiratory-gated intensity modulated radiotherapy: Technical note and report of a case. *J Appl Clin Med Phys.* 2019;20(6):194-198.

17) Boldrini L, Cusumano D, Cellini F, Azario L, Mattiucci GC, Valentini V. Online adaptive magnetic resonance guided radiotherapy for pancreatic cancer: state of the art, pearls and pitfalls. *Radiat Oncol.* 2019;14(1):71.

18) Chin S, Eccles CL, McWilliam A, et al. Magnetic resonance-guided radiation therapy: a review. *J Med Imag Radiat Oncol.* 2020;64(1):163-177.

19) Eccles CL, Haider EA, Haider MA, Fung S, Lockwood G, Dawson LA. Change in diffusion weighted MRI during liver cancer radiotherapy: preliminary observations. *Acta Oncol.* 2009;48(7):1034-1043.

20) Weiss E, Ford JC, Olsen KM, et al. Apparent diffusion coefficient (ADC) change on repeated diffusion-weighted magnetic resonance imaging during radiochemotherapy for non-small cell lung cancer: a pilot study. *Lung Cancer.* 2016;96:113-119.

21) King AD, Thoeny HC. Functional MRI for the prediction of treatment response in head and neck squamous cell carcinoma: potential and limitations. *Cancer Imag.* 2016;16(1):23.

22) Foltz WD, Wu A, Chung P, et al. Changes in apparent diffusion coefficient and T2 relaxation during radiotherapy for prostate cancer. *J Magn Reson Imag.* 2013;37(4):909-916.

23) Pasquier D, Hadj Henni A, Escande A, et al. Diffusion weighted MRI as an early predictor of tumor response to hypofractionated stereotactic boost for prostate cancer. *Sci Rep.* 2018;8(1):10407.

24) Tsien C, Cao Y, Chenevert T. Clinical applications for diffusion magnetic resonance imaging in radiotherapy. *Semin Radiat Oncol.* 2014;24(3):218-226.

25) Cao Y. The promise of dynamic contrast-enhanced imaging in radiation therapy. *Semin Radiat Oncol.* 2011;21(2):147-156.

26) Boldrini L, Cusumano D, Chiloiro G, et al. Delta radiomics for rectal cancer response prediction with hybrid 0.35 T magnetic resonance-guided radiotherapy (MRgRT): a hypothesis-generating study for an innovative personalized medicine approach. *Radiol Med.* 2019;124(2):145-153.

27) Tchelebi LT, Romesser PB, Feuerlein S, et al. Magnetic resonance guided radiotherapy for rectal cancer: expanding opportunities for non-operative management. *Cancer Control.* 2020;27(1):1073274820969449.

28) Yang Y, Cao M, Sheng K, et al. Longitudinal diffusion MRI for treatment response assessment: preliminary experience using an MRI-guided tri-cobalt 60 radiotherapy system. *Med Phys.* 2016;43(3):1369-1373.

29) Kooreman ES, van Houdt PJ, Nowee ME, et al. Feasibility and accuracy of quantitative imaging on a 1.5 T MR-linear accelerator. *Radiother Oncol.* 2019;133:156-162.

30) van Houdt PJ, Yang Y, van der Heide UA. Quantitative magnetic resonance imaging for biological image-guided adaptive radiotherapy. *Front Oncol.* 2021;10(3190).

31) Corradini S, Alongi F, Andratschke N, et al. MR-guidance in clinical reality: current treatment challenges and future perspectives. *Radiat Oncol.* 2019;14(1):92.

32) Groot Koerkamp ML, Vasmel JE, Russell NS, et al. Optimizing MR-guided radiotherapy for breast cancer patients. *Front Oncol.* 2020;10(1107).

33) Crockett CB, Samson P, Chuter R, et al. Initial clinical experience of MR-guided radiotherapy for non-small cell lung cancer. *Front Oncol.* 2021;11(157).

34) Boldrini L, Intven M, Bassetti M, Valentini V, Gani C. MR-guided radiotherapy for rectal cancer: current perspective on organ preservation. *Front Oncol.* 2021;11(530).

35) Intven MPW, de Mol van Otterloo SR, Mook S, et al. Online adaptive MR-guided radiotherapy for rectal cancer; feasibility of the workflow on a 1.5T MR-linac: clinical implementation and initial experience. *Radiother Oncol.* 2021;154:172-178.

36) Chiloiro G, Boldrini L, Meldolesi E, et al. MR-guided radiotherapy in rectal cancer: first clinical experience of an innovative technology. *Clin Transl Radiat Oncol.* 2019;18:80-86.

37) Tocco BR, Kishan AU, Ma TM, Kerkmeijer LGW, Tree AC. MR-guided radiotherapy for prostate cancer. *Front Oncol.* 2020;10:616291-616291.

38) Bruynzeel AME, Tetar SU, Oei SS, et al. A prospective single-arm phase II study of stereotactic magnetic-resonance-guided adaptive radiotherapy for prostate cancer: early toxicity results. *Int J Radiat Oncol Biol Phys.* 2019.

39) Luterstein E, Cao M, Lamb JM, et al. Clinical outcomes using magnetic resonance–guided stereotactic body radiation therapy in patients with locally advanced cholangiocarcinoma. *Adv Radiat Oncol.* 2020;5(2):189-195.

40) Klüter S, Katayama S, Spindeldreier CK, et al. First prospective clinical evaluation of feasibility and patient acceptance of magnetic resonance-guided radiotherapy in Germany. *Strahlenther Onkol.* 2020;196(8):691-698.

41) Hal WA, Straza MW, Chen X, et al. 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(8):e0236570.

42) Bohoudi O, Bruynzeel AME, Senan S, et al. Fast and robust online adaptive planning in stereotactic MR-guided adaptive radiation therapy (SMART) for pancreatic cancer. *Radiother Oncol.* 2017;125(3):439-444.

43) Feldman AM, Modh A, Glide-Hurst C, Chetty IJ, Movsas B. Real-time magnetic resonance-guided liver stereotactic body radiation therapy: an institutional report using a magnetic resonance-linac system. *Cureus.* 2019;11(9):e5774.

44) Rosenberg SA, Henke LE, Shaverdian N, et al. A multi-institutional experience of MR-guided liver stereotactic body radiation therapy. *Adv Radiat Oncol.* 2019;4(1):142-149.

45) Rudra S, Jiang N, Rosenberg SA, et al. Using adaptive magnetic resonance image-guided radiation therapy for treatment of inoperable pancreatic cancer. *Cancer Med.* 2019;8(5):2123-2132.

46) Chuong MD, Springett GM, Freilich JM, et al. Stereotactic body radiation therapy for locally advanced and borderline resectable pancreatic cancer is effective and well tolerated. *Int J Radiat Oncol Biol Phys.* 2013;86(3):516-522.

47) Hall WA, Small C, Paulson E, et al. Magnetic resonance guided radiation therapy for pancreatic adenocarcinoma, advantages, challenges, current approaches, and future directions. *Front Oncol.* 2021;11(867).

48) Boldrini L, Corradini S, Gani C, et al. MR-guided radiotherapy for liver malignancies. *Front Oncol.* 2021;11(1053).

49) Hehakaya C, Van der Voort van Zyp JR, Lagendijk JJW, Grobbee DE, Verkooijen HM, Moors EHM. Problems and promises of introducing the magnetic resonance imaging linear accelerator into routine care: the case of prostate cancer. *Front Oncol.* 2020;10(1741).

50) Ding S, Li Y, Liu H, et al. Comparison of intensity modulated radiotherapy treatment plans between 1.5T MR-linac and conventional linac. *Technol Cancer Res Treat.* 2021;20:1533033820985871-1533033820985871.

51) Sevak PR, Nejad-Davarani S, Kim J, Weiss S, Elshaikh MA, Glide-Hurst CK. Intrafractional motion of target volumes and organs at risk due to bladder filling: implications for MR-only prostate radiation therapy. *Int J Radiat Oncol Biol Phys.* 2017;99(2):E720-E721.

52) Perez RO, Habr-Gama A, Gama-Rodrigues J, et al. Accuracy of positron emission tomography/computed tomography and clinical assessment in the detection of complete rectal tumor regression after neoadjuvant chemoradiation: long-term results of a prospective trial (National Clinical Trial 00254683). *Cancer.* 2012;118(14):3501-3511.

53) Shaikh T, Handorf EA, Murphy CT, Mehra R, Ridge JA, Galloway TJ. The impact of radiation treatment time on survival in patients with head and neck cancer. *Int J Radiat Oncol Biol Phys.* 2016;96(5):967-975.

54) Keller BM, Campbell M, Ruschin ME, et al. MR-linac radiotherapy in year one: experience's in imaging, patient treatment and data collection. *Int J Radiat Oncol Biol Phys.* 2020;108(3):e249-e250.

55) Chuter RW, Whitehurst P, Choudhury A, van Herk M, McWilliam A. Technical note: investigating the impact of field size on patient selection for the 1.5T MR-linac. *Med Phys.* 2017;44(11):5667-5671.

56) Tetar SU, Bruynzeel AME, Lagerwaard FJ, Slotman BJ, Bohoudi O, Palacios MA. Clinical implementation of magnetic resonance imaging guided adaptive radiotherapy for localized prostate cancer. *Phys Imag Radiat Oncol.* 2019;9:69-76.

57) van Herk M, McWilliam A, Dubec M, Faivre-Finn C, Choudhury A. Magnetic resonance imaging-guided radiation therapy: a short strengths, weaknesses, opportunities, and threats analysis. *Int J Radiat Oncol Biol Phys.* 2018;101(5):1057-1060.

58) Murray J, Tree AC. Prostate cancer – advantages and disadvantages of MR-guided RT. *Clin Transl Radiat Oncol.* 2019;18:68-73.

59) Eccles CL, Campbell M. Keeping up with the hybrid magnetic resonance linear accelerators: how do radiation therapists stay current in the era of hybrid technologies? *J Med Imaging Radiat Sci.* 2019;50(2):195-198.

60) Sandoval ML, Youssef I, Latifi K, et al. Non-adaptive MR-Guided radiotherapy for prostate sbrt: less time, equal results. *J Clin Med.* 2021;10(15):3396.

61) Tyran M, Jiang N, Cao M, et al. Retrospective evaluation of decision-making for pancreatic stereotactic MR-guided adaptive radiotherapy. *Radiother Oncol.* 2018;129(2):319-325.

62) Hall WA, Heerkens HD, Paulson ES, et al. Pancreatic gross tumor volume contouring on computed tomography (CT) compared with magnetic resonance imaging (MRI): results of an international contouring conference. *Pract Radiat Oncol.* 2018;8(2):107-115.

63) Heerkens HD, Hall WA, Li XA, et al. Recommendations for MRI-based contouring of gross tumor volume and organs at risk for radiation therapy of pancreatic cancer. *Pract Radiat Oncol.* 2017;7(2):126-136.

64) Barrord M, Ahmad S, Patel S, et al. Patterns of failure after neoadjuvant stereotactic body radiation therapy or fractionated chemoradiation in resectable and borderline resectable pancreatic cancer. *Pancreas.* 2020;49(7):941-946.

65) Verkooijen HM, Henke LE. Sensible introduction of MR-guided radiotherapy: a warm plea for the RCT. *Front Oncol.* 2021;11(872).

66) Menten MJ, Mohajer JK, Nilawar R, et al. Automatic reconstruction of the delivered dose of the day using MR-linac treatment log files and online MR imaging. *Radiother Oncol.* 2020;145:88-94.

67) Johnstone E, Wyatt JJ, Henry AM, et al. Systematic review of synthetic computed tomography generation methodologies for use in magnetic resonance imaging-only radiation therapy. *Int J Radiat Oncol Biol Phys.* 2018;100(1):199-217.

68) Verkooijen HM, Kerkmeijer LGW, Fuller CD, et al. R-IDEAL: a framework for systematic clinical evaluation of technical innovations in radiation oncology. *Front Oncol.* 2017;7:59.

69) Wang C, Zhu X, Hong JC, Zheng D. Artificial intelligence in radiotherapy treatment planning: present and future. *Technol Cancer Res Treat.* 2019;18:1533033819873922.

MR-Guided Radiation Therapy for Oligometastatic Malignancies

Description

This review article describes technical advantages for MR-guided radiation therapy (MRgRT) that lead to the rationale for use in the oligometastatic setting. The authors summarize existing data demonstrating the feasibility, safety, and efficacy of MRgRT for various disease sites. Finally, the authors discuss ongoing clinical trials utilizing MRgRT, which will continue to define and expand its role.

Learning Objectives

Upon completing this activity, the readers should be able to:

- understand the evolving treatment of oligometastatic disease and the role of stereotactic body radiation therapy (SBRT) across anatomical disease sites;
- comprehend the pros/cons of MRgRT in the treatment of oligometastatic disease across anatomical disease sites; and
- implement the treatment of oligometastatic disease with SBRT with appropriate understanding of the potential benefits/pitfalls of MRgRT vs. CT-based radiation therapy.

Accreditation/ Designation Statement

The Institute for Advanced Medical Education is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians. The Institute for Advanced Medical Education designates this journal-based CME activity for a maximum of 1 AMA PRA Category 1 Credit.™ Physicians should only claim credit commensurate with the extent of their participation in the activity. These credits qualify as SA-CME credits.

Authors

*Brittany R. Derynda, BA, *Casey L. Liveringhouse, MD, John M. Bryant, MD, Stephen A. Rosenberg, MD, MS (*contributed equally to this work)

Affiliations: H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL (all authors)

Target Audience

- Radiation Oncologists
- Related Oncology Professionals

Instructions

To successfully earn credit, participants must complete the activity during the valid credit period.

1. Review this article in its entirety.
2. Visit www.appliedradiology.org/SAM.
3. Login to your account or (new users) create an account.
4. Complete the post test and review the discussion and references.
5. Complete the evaluation.
6. Print your certificate.

Estimated time for completion:
1 hour

Date of release and review:
September 1, 2021

Expiration date:
August 31, 2023

Disclosures

Dr. Rosenberg reports: Novocure: consulting (honoraria); ViewRay: consulting medical advisory board, Lung Research Consortium (noncompensated), research grants. No other authors, faculty, or any individuals at IAME or *Applied Radiation Oncology* who had control over the content of this program have any relationships with commercial supporters.

MR-Guided Radiation Therapy for Oligometastatic Malignancies

*Brittany R. Derynda, BA; *Casey L. Liveringhouse, MD; John M. Bryant, MD; Stephen A. Rosenberg, MD, MS

A considerable body of evidence is emerging to support the existence of an oligometastatic state, in which patients with limited metastases may experience prolonged overall survival (OS),[1] blurring the line between a localized disease state and what was previously considered incurable metastatic cancer. Recent clinical trials demonstrate the benefit of stereotactic body radiation therapy (SBRT) for patients with oligometastatic cancer, typically defined as 1-5 metastatic lesions. Randomized phase II studies of oligometastatic non-small cell lung cancer (NSCLC)[2] and prostate cancer[3,4] showed improved outcomes with SBRT to all metastatic sites. The SABR-COMET study was a phase II trial of patients with up to 5 sites of metastatic disease of various histologies, in which SBRT improved OS and progression-free survival (PFS) as compared to standard palliative therapy.[5]

The promising results of these trials have spawned further trials evaluating SBRT for oligometastatic disease. The NRG has opened phase II/III trials investigating SBRT for patients with oligometastatic breast cancer (BR-002; NCT02364557) and NSCLC (LU-002; NCT03137771). SABR-COMET-10 (NCT03721341) is an ongoing phase III trial investigating the benefit of SBRT for patients with 4 to 10 metastases,[6] potentially expanding the definition of oligometastatic cancer. A search of the national clinical trials database [clinicaltrials.gov] for the term "oligometastatic" reveals 182 studies either active or completed without results, as of the time of this writing. Clearly, there is prominent interest in this paradigm, with large cooperative groups bringing the concept to the international stage.

While the utilization of SBRT for oligometastatic disease is gaining prominence, the potential toxicity should be carefully considered. In the recently published NRG BR-001 trial in which patients with oligometastatic cancer received SBRT to all sites of metastatic disease, the rate of late grade ≥ 3 toxicity was 20% at 2 years.[7] Similarly, the authors of SABR-COMET reported a 29% rate of grade ≥ 2 toxicity in the SABR arm (including 3 treatment-related deaths), compared with 9% in the control arm. Studies of SBRT for central NSCLC tumors also bring to attention the potential for severe treatment-related toxicity.[8,9] Therefore, the potential toxicity associated with delivering SBRT to multiple sites necessitates caution to ensure the burden of late toxicity is minimized, especially in this population who may experience prolonged survival.

With accumulating evidence supporting the use of SBRT in oligometastatic disease, there is increasing interest toward leveraging technologies such as MR-guided radiation therapy (MRgRT) for this purpose. In the context of adaptive SBRT or hypofractionated radiation therapy, the use of MRI guidance has been labeled stereotactic MR-guided adaptive radiation therapy (SMART). SMART represents a novel modality for SBRT delivery in the oligometastatic setting to improve therapeutic efficacy and safety, especially in anatomically constrained sites or in patients who may require SBRT to multiple sites. Early evidence supports the safety and feasibility of utilizing MRgRT (and/

Affiliations: *Ms. Derynda is a medical student at the Nova Southeastern University, Dr. Kiran C. Patel College of Osteopathic Medicine – Tampa Bay Regional Campus, Clearwater, FL. ***Dr. Liveringhouse** is a PGY3 radiation oncology resident; **Dr. Bryant** is a PGY2 radiation oncology resident; and **Dr. Rosenberg** is the director of MRI Guided Radiation Therapy, Department of Radiation Oncology, all at H. Lee Moffitt Cancer Center and Research Institute, Department of Radiation Oncology Tampa, FL. *contributed equally to this work. **Disclosure:** Dr. Rosenberg reports: Novocure: consulting (honoraria); ViewRay: consulting medical advisory board, Lung Research Consortium (noncompensated), research grants. No other authors have conflicts of interest to disclose. None of the authors received outside funding for the production of this original manuscript and no part of this article has been previously published elsewhere. **Acknowledgement:** The authors thank Paul V. Strong, PhD, for his assistance with this manuscript.

or SMART),[10] and it is being implemented into clinical practice at many centers. These findings have served as the basis for ongoing prospective trials utilizing MRgRT/SMART. In this review, we will discuss the rationale for SMART in the treatment of oligometastases and summarize existing literature describing its use in various disease sites. Finally, we will discuss the future of SMART and ongoing prospective clinical trials evaluating this treatment paradigm.

Rationale for MRgRT

While achieving increased biologically effective dose (BED)[11] may improve tumor control probability (TCP), dose constraints for organs at risk (OARs) may limit the dose that can safely be delivered.[12] Thanks to enhanced soft-tissue imaging resolution, workflows allowing for efficient online daily adaptive re-planning and real-time tumor tracking, MRgRT has distinct advantages compared with conventional radiation therapy technologies in the delivery of SBRT. Of note, real-time adaptive radiation therapy (RTT) may be achieved in different ways depending on the type of MR-linac utilized. For example, daily adaptive replanning on MRIdian (ViewRay) differs from Elekta Unity's "adapt-to-position" or "adapt-to-shape" approach. The "adapt-to-position" allows for repositioning of the isocenter for better target coverage during daily set-up while "adapt-to-shape" is a tool that automatically propagates contours onto the online planning MRI and can be edited with electron densities (ED) being assigned based on the average ED value of the corresponding contour on the pre-treatment CT.[13] In comparison, the MRIdian system utilizes a couch with 3 degrees of freedom to position anatomy and tumor appropriately with online adaptive therapy focused on tumor/anatomical changes to ensure target coverage and decreased dose to OARs.[14]

One aspect complicating delivery of SBRT is the uncertainty in OAR location due to daily variation in position and filling[15-17] as well as uncertainty of target location due to respiratory motion. While the use of image-guided radiation therapy with cone-beam commuted tomography (CT) provides localization of soft-tissue anatomy and is commonly utilized prior to each SBRT fraction in conventional linac-based delivery, most workflows do not allow for daily plan adaptation. The enhanced imaging visualization with MRI guidance and workflow for many available MRgRT platforms allows for daily online adaptive re-planning, in which target volumes and OARs are recontoured and a reoptimized dose distribution is generated based on the day's anatomy,[18-20] which thus may facilitate dose escalation.[21] Further, variation in target location due to respiratory motion necessitates the use of motion management strategies for SBRT. The use of RTT with gated treatment delivery with MRgRT in some MR-linac systems allows for smaller PTV margins and may be advantageous over other commonly used motion management strategies such as use of internal target volumes (ITVs), which increase the size of the target volume and may lead to difficulty in achieving dose escalation. Further advantages of MRgRT over CT-based SBRT include improved soft-tissue visualization for precise delineation of target and normal tissues on both planning and daily imaging. Serial MRI imaging during treatment may also provide insight into treatment response.

Overview of Evidence for Site-Specific MRgRT

Abdomen and Retroperitoneum

Common targets for SBRT in the abdomen include primary and metastatic tumors of the liver, pancreas, adrenal glands, kidney, and lymph nodes. OARs including the stomach, duodenum, small bowel, and uninvolved liver are radiosensitive organs subject to positional uncertainty due to respiratory motion and variable daily filling. Therefore, abdominal oligometastases represent an ideal setting for MRgRT and SMART and available data support excellent clinical outcomes with low rates of radiation-therapy-related toxicity.

The MOMENTUM study is a multi-institutional prospective registry conducted by the MRI Linac Consortium, enrolling patients treated with high-field (1.5 Tesla) MRgRT to a variety of disease sites.[22] In MOMENTUM, 17% of liver, 76% of pancreas, 70% of rectum, and 82% of lymph node fractions were treated with online adaptation, and the rate of grade ≥ 3+ acute toxicity was only 4%. A phase I trial including 20 patients with oligometastatic or unresectable primary intra-abdominal tumors treated with SBRT demonstrates the importance of the SMART approach in this setting, where adaptive plans were created for 81 of 97 fractions and in which PTV coverage was increased in 64 of 97 fractions.[23] Of the 81 adapted fractions, 75% were adapted primarily because the initial plan violated OAR dose constraints. Notably, the authors reported 0% grade ≥ 3 acute toxicity. Authors from the University of California, Los Angeles (UCLA), published their institutional experience of 106 patients treated with SMART to abdominal or pelvic primary or oligometastatic tumors to a median dose of 40 Gy in 5 fractions. In contrast to MOMENTUM and Henke et al, only 13.9% of the UCLA fractions were adapted. The 2-year local control was 74%, including 96% with those achieving BED >100 Gy vs 69% for BED < 100 Gy, while < 1% experienced grade 3+ acute toxicity and 7.3% experienced late grade 3+ late toxicity.[24]

For liver and hepatobiliary lesions specifically, MRgRT is associated with excellent local control and low

TABLE 1. LIST OF ONGOING US CLINICAL TRIALS FOR MR-GUIDED RADIATION THERAPY

Study Title	Sponsor	Condition/Disease	URL
SMART-ONE: Stereotactic MRI-guided Adaptive Radiation Therapy (SMART) in One Fraction	Baptist Health South Florida	Oligometastatic cancer, up to 10 sites of disease	https://clinicaltrials.gov/ct2/show/NCT04939246
Real-Time MRI-Guided 3-Fraction Accelerated Partial Breast Irradiation in Early Breast Cancer	University of Wisconsin, Madison	Breast cancer DCIS LCIS	https://ClinicalTrials.gov/show/NCT03936478
CONFIRM: Magnetic Resonance Guided Radiation Therapy	Dana-Farber Cancer Institute	Gastric cancer Invasive breast cancer In situ breast cancer	https://ClinicalTrials.gov/show/NCT04368702
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	Oligometastases of the spine	https://clinicaltrials.gov/ct2/show/NCT03878485
Stereotactic MRI-Guided On-table Adaptive Radiation Therapy (SMART) for Locally Advanced Pancreatic Cancer	ViewRay	Pancreatic cancer	https://clinicaltrials.gov/ct2/show/NCT03621644
MRI-Guided Adaptive RadioTHerapy for Reducing XerostomiA in Head and Neck Cancer (MARTHA-trial)	Panagiotis Balermpas, University of Zurich	Head and neck cancer Xerostomia due to radiation therapy	https://clinicaltrials.gov/ct2/show/NCT03972072
Three Fraction Accelerated Partial Breast Irradiation as the Sole Method of Radiation Therapy for Low-Risk Stage 0 and I Breast Carcinoma	Washington University School of Medicine	Breast carcinoma Breast cancer	https://clinicaltrials.gov/ct2/show/NCT03612648
Stereotactic MR-Guided Radiation Therapy	Dana-Farber Cancer Institute	Pancreas cancer Lung cancer Renal cancer	https://clinicaltrials.gov/ct2/show/NCT04115254

Key: DCIS = ductal carcinoma in situ, LCIS = lobular carcinoma in situ, PET = positron emission tomography, CT = computed tomography, SBRT = stereotactic body radiation therapy

rates of toxicity. A systematic review of 16 studies including 973 patients with 1034 liver lesions treated with MRgRT demonstrated local control rates of 93% at 3 years with a 5.3% risk of grade 3 or higher toxicity.[25] Similarly, in a multi-institutional retrospective study of 26 patients with unresectable primary or metastatic liver tumors treated with MRgRT, freedom from local progression (FFLP) at 21 months was 80.4% overall, including 100% for hepatocellular carcinoma vs 75% for colorectal metastases. This excellent local control was accompanied by minimal toxicity, as only 7.7% of patients developed late grade 3 gastrointestinal (GI) toxicity and no patient had grade 4 or 5 GI toxicity.[26] Luterstein et al published the UCLA experience of MRgRT for 17 patients with locally advanced cholangiocarcinoma. The 2-year local control was 73.3%, and only 1 patient (6%) experienced late grade 3 toxicity.[27]

While there is no defined standard of care for patients with locally advanced or borderline resectable pancreatic cancer, SBRT has emerged as an improvement over conventionally fractionated regimens.[28] Given close proximity to radiosensitive intra-abdominal structures, the rate of severe toxicity with pancreas SBRT approaches 10%.[29] In a phase I trial of 20 patients with inoperable pancreatic cancer treated with MRgRT to 24 Gy in 3 fractions, no patient experienced grade 3+ toxicity.[30] Rudra et al described a series of 44 patients with unresectable pancreatic cancer treated with conventionally fractionated radiation therapy, hypofractionated radiation therapy, or SBRT with an MRgRT approach and demonstrated that patients with BED >70 Gy were associated with improved OS with a nonsignificant trend toward improved local control (77% vs 57%), with only 3 patients experiencing grade 3+ toxicity.[31] Chuong et al from Miami Cancer Institute reported their institutional experience with MRgRT for 35 patients with pancreatic cancer treated with MRgRT to a median dose of 50 Gy in 5 fractions with 1 year local control of 87.8% and risk of late grade 3 toxicity of 2.9%.[32] Similarly, the application of SMART for reirradiation for recurrent pancreatic cancer is being explored.[33]

Given proximity to critical organs (eg, stomach, bowel), adrenal and renal tumors also represent promising targets for SMART. In a multi-institu-

Study Title	Sponsor	Condition/Disease	URL
Stereotactic Body Radiotherapy and Focal Adhesion Kinase Inhibitor in Advanced Pancreas Adenocarcinoma	Washington University School of Medicine	Pancreas cancer	https://clinicaltrials.gov/ct2/show/NCT04331041
Nivolumab, Ipilimumab and Chemoradiation in Treating Patients With Locally Advanced Pancreatic Cancer	Herlev Hospital	Locally advanced pancreatic cancer	https://clinicaltrials.gov/ct2/show/NCT04247165
Study of PSMA PET/MR-Guided Stereotactic Body Radiation Therapy With Simultaneous Integrated Boost (SBRT-SIB) for High-Intermediate and High Risk Prostate Cancer	Weill Medical College of Cornell University	Prostate cancer	https://clinicaltrials.gov/ct2/show/NCT04402151
CT-Guided Stereotactic Body Radiation Therapy and MRI-guided Stereotactic Body Radiation Therapy for Prostate Cancer, MIRAGE Study	Jonsson Comprehensive Cancer Center	Prostate adenocarcinoma	https://clinicaltrials.gov/ct2/show/NCT04384770
Adaptative MR-Guided Stereotactic Body Radiotherapy of Liver Tumors	Centre Georges Francois Leclerc	Liver cancer	https://clinicaltrials.gov/ct2/show/NCT04242342
Preoperative MR-Guided Radiation Therapy in Gastric Cancer	Washington University School of Medicine	Gastric adenocarcinoma	https://clinicaltrials.gov/ct2/show/NCT04162665
Immune Checkpoint Inhibitor and MR-guided SBRT for Limited Progressive Metastatic Carcinoma	Baptist Health South Florida	Metastatic carcinoma	https://clinicaltrials.gov/ct2/show/NCT04376502
Randomized Phase II Trial of Salvage Radiotherapy for Prostate Cancer in 4 weeks v. 2 weeks	Weill Medical College of Cornell University	Prostate cancer	https://clinicaltrials.gov/ct2/show/NCT04422132

Key: DCIS = ductal carcinoma in situ, LCIS = lobular carcinoma in situ, PET = positron emission tomography, CT = computed tomography, SBRT = stereotactic body radiation therapy

tional retrospective study including 13 metastatic adrenal lesions treated with RTT radiation therapy with gold fiducial markers and 8 adrenal lesions treated with conventional linac-based SBRT without RTT, no grade 2 or higher reactions were reported for either group. However, the group treated with RTT had 100% local control at 1 year, compared with 50% local control in the group treated without RTT, highlighting the importance of accounting for tumor motion and pointing toward the potential utility of MRgRT in this setting. Similarly, Palacios et al published an institutional experience of patients treated with MRgRT for adrenal tumors at VU Medical Center in Amsterdam, Netherlands. They noted significant daily positional variation for bowel, duodenum, and stomach, resulting in up to one-third of baseline plans not meeting dose constraints for each fraction. Further, they noted that online reoptimization improved target coverage in 63% of fractions. Similarly, emerging data support the feasibility and utility of SMART for primary or secondary kidney tumors[34-37] with a similar rationale to that for adrenal tumors.

Pelvis

Pelvic SBRT is most frequently utilized for prostate tumors and pelvic lymph node recurrences. Radiosensitive intrapelvic organs (ie, bladder, rectum, small bowel) are subject to daily variation in location and filling, making this an ideal setting for MRgRT. The use of hypofractionated radiation therapy and SBRT is increasingly being utilized and now represents a standard-of-care option for localized prostate cancer.[38] While high-quality evidence supports the use of prostate SBRT, there is concern for potentially increasing the risk of urinary and GI toxicity compared with conventionally fractionated regimens,[39-42] leading to interest in utilization of MRgRT in this context. The benefit of MRgRT for prostate cancer lies in the ability to account for daily variation in bladder and rectal filling as well as RTT of the prostate,[43] and the ability to treat without implanted fiducial markers. A prospective single-arm phase II trial of 101 patients treated with SMART to 36.25 Gy in 5 fractions over 2 weeks with daily adaptation

demonstrated minimal GI and genitourinary (GU) toxicity.[44,45] Similarly, 25 patients treated with SMART to 35 Gy in 5 fractions on a prospective observational protocol had only 12% grade 2 GU toxicity and no grade 3 toxicity.[46] Although SMART may be helpful for prostate SBRT, much of the benefit may be derived from RTT and gating secondary to bowel/bladder changes. This was most recently seen in a nonadaptive, MR-guided prostate SBRT series by our group showing minimal toxicity and excellent PSA (prostate-specific antigen) response.[47] Treating the primary tumor (as well as limited sites of spread) in the setting of oligometastatic prostate cancer may significantly improve patient outcomes and quality of life.[48] Additionally, the broad published experience of prostate SBRT can inform the utilization of MRgRT for pelvic nodal oligometastases and oligorecurrences as directed by newer imaging agents such as prostate-specific membrane antigen (PSMA) to improve the early detection of oligometastatic disease. As many pelvic malignancies such as prostate cancer, bladder cancer, rectal cancer, and gynecologic cancers are managed primarily with radiation therapy, treatment of recurrent pelvic lymph node metastases in the re-irradiation setting presents a challenging clinical scenario that might be ideally addressed with MRgRT. Small retrospective series have demonstrated the feasibility of the SMART workflow for pelvic nodal metastases, in which online adaptive replanning may decrease the dose to OARs and facilitate the use of smaller margins[49,50,51] for definitive management of pelvic oligometastatic disease.

Thorax

SBRT is the standard of care for early stage, unresectable or medically inoperable NSCLC. Outcomes with SBRT have demonstrated excellent local control with limited toxicity for peripheral lesions with 1-,[52,53] 3-[54-57]or 5-[58] fraction SBRT regimens. However, the potential for severe or life-threatening toxicity associated with SBRT to central or ultracentral lung tumors, necessitates caution.[59-62] The most recent example of this is the Nordic-HILUS trial. HILUS is a prospective, single-arm phase 2 trial including 65 patients with ultracentral lung tumors (defined as within < 1cm of the proximal bronchial tree without endobronchial invasion)[63] treated with 7 Gy x 8 fractions in which 15% of patients experienced treatment-related death (grade 5 toxicity). In total, the rate of grade 3 to 5 toxicity in HILUS was 34%.[64] These sobering results illustrate that even with modern dose constraints and treatment planning techniques, the potential for grave toxicity remains for ultracentral lung tumors. Opposing this concern for toxicity is the understanding that dose-escalation is often required for durable control in NSCLC, with patients achieving BED >100 Gy associated with improved OS.[65] Due to the necessity for dose-escalation and the high risk of severe toxicity, SBRT for ultracentral tumors should optimally be delivered with appropriate motion management strategies to treat with the smallest possible margin. Due to respiratory motion, the use of ITVs with 4D CT is often utilized to ensure accurate localization.

Early experiences with MRgRT show promise for treatment of central lung tumors. In a small phase I trial, 5 patients with oligometastatic or unresectable primary ultracentral thorax tumors received MRgRT to 50 Gy in 5 fractions. Four of 5 patients and 10 of 25 total fractions were planned with daily online adaptation. No patients had grade ≥ 3 acute toxicity while 2 patients had late grade 3 or 4 toxicity. In a phase II clinical trial in which 41 patients with central lung tumors received SBRT, the rate of grade ≥ 3 toxicity was 14.6%, including 1 case of fatal hemoptysis.[66] A retrospective series of 50 patients with 54 primary or metastatic lung tumors treated with SMART showed excellent outcomes, where 93% were able to achieve BED >100 Gy, and grade 3 toxicity was seen in only 8% without any grade 4 or 5 toxicity.[67] In a separate series of 25 patients with central lung tumors treated with SMART to 60 Gy in 8 fractions or 55 Gy in 5 fractions, Finazzi et al illustrated the benefit of daily adaptation, as PTV coverage was improved in 61% of fractions and reduced the number of OAR constraint violations.[66] Thus, patients with central or ultracentral lung tumors may be ideal for treatment with MRgRT, in which gated delivery with RTT can avoid the use of larger ITVs[68] and optimize dose-escalation, and should be tested in prospective trials (NCT 04917224). MRgRT could have important implications for the treatment of both primary and metastatic lesions to the lung to allow for dose escalation with decreasing the risk of toxicity.

With evidence pointing to the effectiveness of single-fraction SBRT for peripheral lung tumors,[51,70] there has also been interest in adopting MRgRT for this approach. Finazzi et al reported a series of 23 patients with peripheral lung tumors treated with SMART with breath-hold gated delivery. The SMART-PTVs were estimated to be less than 54% of the volume of ITVs generated for the same tumor, while adaptation facilitated improved PTV coverage and allowed all patients to achieve BED >100 Gy. Only 1patient experienced grade 3 toxicity, and there were no cases of grade 4 or 5 toxicity.[69]

The Future of MR-Guided Radiation Therapy: Ongoing Clinical Trials

A number of ongoing clinical trials are evaluating the use of MRgRT in the management of primary or oligometastatic disease. Notably, the

SMART-ONE trial, which will open at the Miami Cancer Institute, is a single-arm trial investigating the feasibility of delivering single-fraction, MR-guided SBRT to up to 10 disease sites (NCT04939246). Additional active clinical trials include patients being treated with MRgRT for breast, prostate, pancreas, liver, and spine tumors, among others **(Table 1)**. Isotoxic dose escalation has potential to improve local control and may even impact OS; early reports are encouraging but this needs to be tested in prospective trials.[53,71] As of yet, no prospective comparisons have been reported to determine the benefit of MRgRT over CT-based SBRT. As evidence begins to accumulate supporting the feasibility of MRgRT for various disease sites, direct comparison with CT-based SBRT will be necessary to optimize patient selection for this advanced treatment modality. MRgRT also has potential to incorporate diffusion-weighted (DWI) imaging into its daily scans to assess for intra-treatment tumor changes before tumor size or morphology changes appear on traditional imaging methods.[72]

Barriers and Limitations of MR-Guided Radiation Therapy

While the use of MRgRT is growing, broad adoption is limited by cost, availability, practical factors, and technical aspects. Commissioning, treatment delivery, and maintenance of MR-linac systems are resource intensive, requiring multidisciplinary cooperation and expertise from physicists, therapists, dosimetrists, and physicians.[73] The use of MR systems also requires standardized MRI safety protocols in addition to typical radiation safety protocols, and staff must be appropriately trained to ensure safety for all involved. The use of online adaptation with MRgRT may require up to 45-120 minutes of total treatment time, requiring extended physician and physicist presence at the machine. Patients must be able to tolerate appropriate positioning and immobilization, and potential anxiety or claustrophobia must be managed proactively. In patients with oligometastatic disease who may receive MRgRT or SMART to multiple sites, this lengthy treatment time may be multiplied. Physical limitations of MRgRT may include Lorentz forces, which may potentially lead to overdosing hollow organs; MRI geometric distortion; uncertainty associated with MRI to radiation isocenter distance; multileaf collimator position error; and uncertainties with voxel size and tracking.[26] Similarly, the lack of electron density and attenuation coefficient information on MRI requires fusion to CT images for dose-calculations in treatment planning. Due to these additional technical factors, physicist and dosimetrist experience and expertise with these issues is essential to ensure appropriate treatment planning and delivery.

Conclusion

MRgRT represents a promising treatment modality for patients with oligometastases. An accumulating body of evidence supports the feasibility of MRgRT and SMART for various disease sites. Thanks to enhanced soft-tissue resolution and workflows allowing for daily online-adaptation and RTT, MRgRT can facilitate dose-escalation to optimize TCP and minimize normal tissue complication probability. Ongoing clinical trials will continue to define and potentially expand the role of MRgRT for primary and oligometastatic disease.

References

1) Hellman S, Weichselbaum RR. Oligometastases. *J Clin Oncol.* 1995;13(1):8-10. doi:10.1200/JCO.1995.13.1.8

2) Gomez DR, Tang C, Zhang J, 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(18):1558-1565. doi:10.1200/JCO.19.00201

3) Phillips R, Shi WY, Deek M, et al. Outcomes of observation vs stereotactic ablative radiation for oligometastatic prostate cancer: the ORIOLE phase 2 randomized clinical trial. *JAMA Oncol.* 2020;6(5):650–659. doi:10.1001/jamaoncol.2020.0147

4) Ost P, Reynders D, Decaestecker K, et al. Surveillance or metastasis-directed therapy for oligometastatic prostate cancer recurrence: a prospective, randomized, multicenter phase II trial. *J Clin Oncol.* 2018;36(5):446-453. doi:10.1200/JCO.2017.75.4853

5) Palma DA, Olson R, Harrow S, 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(10185):2051-2058. doi:10.1016/S0140-6736(18)32487-5

6) Palma DA, Olson R, Harrow S, et al. Stereotactic ablative radiotherapy for the comprehensive treatment of 4-10 oligometastatic tumors (SABR-COMET-10): study protocol for a randomized phase III trial. *BMC Cancer.* 2019;19(1):816. doi:10.1186/s12885-019-5977-6

7) Chmura S, Winter KA, Robinson C, 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(6):845-852. doi:10.1001/jamaoncol.2021.0687

8) Timmerman R, McGarry R, Yiannoutsos C, 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(30):4833-4839. doi:10.1200/JCO.2006.07.5937

9) Lindberg K, Grozman V, Karlsson K, 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(7):1200-1210. doi:10.1016/j.jtho.2021.03.019

10) van Otterloo SRM, Christodouleas JP, Blezer ELA, 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 [published online ahead of print, 2021 Jul 12]. *Int J Radiat Oncol Biol Phys.* 2021;S0360-3016(21)00872-5. doi:10.1016/j.ijrobp.2021.07.003

11) Onishi H, Shirato H, Nagata Y, et al. Hypofractionated stereotactic radiotherapy (HypoFXSRT) for stage I non-small cell lung cancer: updated results of 257 patients in a Japanese multi-institutional study. *J Thorac Oncol.* 2007;2(7 Suppl 3):S94-S100.

doi:10.1097/JTO.0b013e318074de34

12) Gerhard SG, Palma DA, Arifin AJ, et al. Organ at risk dose constraints in SABR: a systematic review of active clinical trials. *Pract Radiat Oncol*. 2021;11(4):e355-e365. doi:10.1016/j.prro.2021.03.005

13) Winkel D, Bol GH, Kroon PS, et al. Adaptive radiotherapy: the Elekta Unity MR-linac concept. *Clini Transl Radiat Oncol. 2019*;18:54-59.

14) Mittauer K, Paliwal B, Hill P, et al. A new era of image guidance with magnetic resonance-guided radiation therapy for abdominal and thoracic malignancies. *Cureus*. 2018;10(4):e2422. doi:10.7759/cureus.2422

15) Thomas DH, Santhanam A, Kishan AU, et al. Initial clinical observations of intra- and interfractional motion variation in MR-guided lung SBRT. *Br J Radiol*. 2018;91(1083):20170522. doi:10.1259/bjr.20170522

16) Byun DJ, Gorovets DJ, Jacobs LM, et al. Strict bladder filling and rectal emptying during prostate SBRT: Does it make a dosimetric or clinical difference? *Radiat Oncol*. 2020;15(1):239. doi:10.1186/s13014-020-01681-6

17) Loi M, Magallon-Baro A, Suker M, et al. Pancreatic cancer treated with SBRT: effect of anatomical interfraction variations on dose to organs at risk. *Radiother Oncol*. 2019;134:67-73. doi:10.1016/j.radonc.2019.01.020

18) Raaymakers BW, Jürgenliemk-Schulz IM, Bol GH, et al. First patients treated with a 1.5 T MRI-linac: clinical proof of concept of a high-precision, high-field MRI guided radiotherapy treatment. *Phys Med Biol*. 2017;62(23):L41-L50. doi:10.1088/1361-6560/aa9517

19) Wu QJ, Li T, Wu Q, Yin FF. Adaptive radiation therapy: technical components and clinical applications. *Cancer J*. 2011;17(3):182-189. doi:10.1097/PPO.0b013e31821da9d8

20) Hales RB, Rodgers J, Whiteside L, et al. Therapeutic radiographers at the helm: moving towards radiographer-led MR-guided radiotherapy. *J Med Imaging Radiat Sci*. 2020;51(3):364-372. doi:10.1016/j.jmir.2020.05.001

21) Noel CE, Parikh PJ, Spencer CR, et al. Comparison of onboard low-field magnetic resonance imaging versus onboard computed tomography for anatomy visualization in radiotherapy. *Acta Oncol*. 2015;54(9):1474-1482. doi:10.3109/0284186X.2015.1062541

22) van Otterloo SRM, Christodouleas JP, Blezer ELA, 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 [published online ahead of print, 2021 Jul 12]. *Int J Radiat Oncol Biol Phys*. 2021;S0360-3016(21)00872-5. doi:10.1016/j.ijrobp.2021.07.003

23) Henke L, Kashani R, Robinson C, 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(3):519-526. doi:10.1016/j.radonc.2017.11.032

24) Yoon SM, Luterstein E, Chu FI, et al. Clinical outcomes of stereotactic magnetic resonance image-guided adaptive radiotherapy for primary and metastatic tumors in the abdomen and pelvis [published online ahead of print, 2021 Jul 20]. *Cancer Med*. 2021;10.1002/cam4.4139. doi:10.1002/cam4.4139

25) Dobrzycka M, Spychalski P, Rostkowska O, et al. Stereotactic body radiation therapy for early-stage hepatocellular carcinoma - a systematic review on outcome. *Acta Oncol*. 2019;58(12):1706-1713. doi:10.1080/0284186X.2019.1657942

26) Rosenberg SA, Henke LE, Shaverdian N, et al. A multi-institutional experience of MR-guided liver stereotactic body radiation therapy. *Adv Radiat Oncol*. 2018;4(1):142-149. doi:10.1016/j.adro.2018.08.005

27) Luterstein E, Cao M, Lamb JM, et al. Clinical outcomes using magnetic resonance-guided stereotactic body radiation therapy in patients with locally advanced cholangiocarcinoma. *Adv Radiat Oncol*. 2019;5(2):189-195. doi:10.1016/j.adro.2019.09.008

28) Tchelebi LT, Lehrer EJ, Trifiletti DM, et al. Conventionally fractionated radiation therapy versus stereotactic body radiation therapy for locally advanced pancreatic cancer (CRiSP): An international systematic review and meta-analysis. *Cancer*. 2020;126(10):2120-2131. doi:10.1002/cncr.32756

29) Petrelli F, Comito T, Ghidini A, Torri V, Scorsetti M, Barni S. Stereotactic body radiation therapy for locally advanced pancreatic cancer: a systematic review and pooled analysis of 19 trials. *Int J Radiat Oncol Biol Phys*. 2017;97(2):313-322. doi:10.1016/j.ijrobp.2016.10.030

30) Heerkens HD, van Vulpen M, Erickson B, et al. MRI guided stereotactic radiotherapy for locally advanced pancreatic cancer. *Br J Radiol*. 2018;91(1091):20170563. doi:10.1259/bjr.20170563

31) Rudra S, Jiang N, Rosenberg SA, et al. Using adaptive magnetic resonance image-guided radiation therapy for treatment of inoperable pancreatic cancer. *Cancer Med*. 2019;8(5):2123-2132. doi:10.1002/cam4.2100

32) Chuong MD, Bryant J, Mittauer KE, et al. Ablative 5-fraction stereotactic magnetic resonance-guided radiation therapy with on-table adaptive replanning and elective nodal irradiation for inoperable pancreas cancer [published correction appears in *Pract Radiat Oncol*. 2021 May-Jun;11(3):e354]. *Pract Radiat Oncol*. 2021;11(2):134-147. doi:10.1016/j.prro.2020.09.005

33) Doty DG, Chuong MD, Gomez AG, et al. Stereotactic MR-guided online adaptive radiotherapy reirradiation (SMART reRT) for locally recurrent pancreatic adenocarcinoma: a case report [published online ahead of print, 2021 Jun 10]. *Med Dosim*. 2021;S0958-3947(21)00047-9.

34) Kutuk T, McCulloch J, Mittauer KE, et al. Daily online adaptive magnetic resonance image (MRI) guided stereotactic body radiation therapy for primary renal cell cancer [published online ahead of print, 2021 Apr 1]. *Med Dosim*. 2021;S0958-3947(21)00022-4. doi:10.1016/j.meddos.2021.02.008

35) Kerkhof EM, Raaymakers BW, van Vulpen M, et al. A new concept for non-invasive renal tumour ablation using real-time MRI-guided radiation therapy. *BJU Int*. 2011;107(1):63-68. doi:10.1111/j.1464-410X.2010.09458.x

36) Prins FM, Stemkens B, Kerkmeijer LGW, et al. Intrafraction motion management of renal cell carcinoma with magnetic resonance imaging-guided stereotactic body radiation therapy. *Pract Radiat Oncol*. 2019;9(1):e55-e61. doi:10.1016/j.prro.2018.09.002

37) 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(4):566-570. doi:10.1016/j.adro.2019.04.002

38) Morgan SC, Hoffman K, Loblaw DA, et al. Hypofractionated radiation therapy for localized prostate cancer: executive summary of an ASTRO, ASCO, and AUA evidence-based guideline. *Pract Radiat Oncol*. 2018;8(6):354-360. doi:10.1016/j.prro.2018.08.002

39) Fransson P, Nilsson P, Gunnlaugsson A, et al. Ultra-hypofractionated versus conventionally fractionated radiotherapy for prostate cancer (HYPO-RT-PC): patient-reported quality-of-life outcomes of a randomised, controlled, non-inferiority, phase 3 trial. *Lancet Oncol*. 2021;22(2):235-245. doi:10.1016/S1470-2045(20)30581-7

40) Widmark A, Gunnlaugsson A, Beckman L, 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(10196):385-395. doi:10.1016/S0140-6736(19)31131-6

41) Brand DH, Tree AC, Ostler P, 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(11):1531-1543. doi:10.1016/S1470-2045(19)30569-8

42) Gonzalez-Motta A, Roach M 3rd. Stereotactic body radiation therapy (SBRT) for high-risk prostate cancer: Where are we now? *Pract Radiat Oncol*. 2018;8(3):185-202. doi:10.1016/j.prro.2017.11.008

43) de Muinck Keizer DM, Kerkmeijer LGW, Willigenburg T, et al. Prostate intrafraction

motion during the preparation and delivery of MR-guided radiotherapy sessions on a 1.5T MR-linac. *Radiother Oncol*. 2020;151:88-94. doi:10.1016/j.radonc.2020.06.044

44) Bruynzeel AME, Tetar SU, Oei SS, 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(5):1086-1094. doi:10.1016/j.ijrobp.2019.08.007

45) Tetar SU, Bruynzeel AME, Oei SS, et al. Magnetic resonance-guided stereotactic radiotherapy for localized prostate cancer: final results on patient-reported outcomes of a prospective phase 2 study [published online ahead of print, 2020 Jun 11]. *Eur Urol Oncol*. 2020;S2588-9311(20)30061-4. doi:10.1016/j.euo.2020.05.007

46) Alongi F, Rigo M, Figlia V, et al. 1.5T 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(1):69. doi:10.1186/s13014-020-01510-w

47) Sandoval ML, Youssef I, Latifi K, et al. Non-adaptive MR-guided radiotherapy for prostate SBRT: less time, equal results. *J Clin Med*. 2021;10(15):3396. doi:10.3390/jcm10153396

48) Ost P, Reynders D, Decaestecker K, et al. Surveillance or metastasis-directed therapy for oligometastatic prostate cancer recurrence: a prospective, randomized, multicenter phase II trial. *J Clin Oncol*. 2018;36(5):446-453. doi:10.1200/JCO.2017.75.4853

49) Winkel D, Kroon PS, Werensteijn-Honingh AM, Bol GH, Raaymakers BW, Jürgenliemk-Schulz IM. Simulated dosimetric impact of online replanning for stereotactic body radiation therapy of lymph node oligometastases on the 1.5T MR-linac. *Acta Oncol*. 2018;57(12):1705-1712. doi:10.1080/0284186X.2018.1512152

50) Werensteijn-Honingh AM, Kroon PS, Winkel D, et al. Feasibility of stereotactic radiotherapy using a 1.5 T MR-linac: multi-fraction treatment of pelvic lymph node oligometastases. *Radiother Oncol*. 2019;134:50-54. doi:10.1016/j.radonc.2019.01.024

51) Winkel D, Werensteijn-Honingh AM, Kroon PS, et al. Individual lymph nodes: "See it and Zap it." *Clin Transl Radiat Oncol*. 2019;18:46-53. doi:10.1016/j.ctro.2019.03.004

52) Videtic GM, Hu C, Singh AK, et al. A randomized phase 2 study comparing 2 stereotactic body radiation therapy schedules for medically inoperable patients with stage I peripheral non-small cell lung cancer: NRG Oncology RTOG 0915 (NCCTG N0927) [published correction appears in *Int J Radiat Oncol Biol Phys*. 2016 Mar 1;94(3):638. Timmerman, Robert D [added]]. *Int J Radiat Oncol Biol Phys*. 2015;93(4):757-764. doi:10.1016/j.ijrobp.2015.07.2260

53) Chuong MD, Kotecha R, Mehta MP, et al. Case report of visual biofeedback-driven, magnetic resonance-guided single-fraction SABR in breath hold for early stage non-small-cell lung cancer. *Med Dosim*. *2021*;46(3):247-252.

54) Timmerman R, Papiez L, McGarry R, et al. Extracranial stereotactic radioablation: results of a phase I study in medically inoperable stage I non-small cell lung cancer. *Chest*. 2003;124(5):1946-1955. doi:10.1378/chest.124.5.1946

55) Timmerman RD, Hu C, Michalski J, et al. Long-term results of RTOG 0236: a phase II trial of stereotactic body radiation therapy (SBRT) in the treatment of patients with medically inoperable stage i non-small cell lung cancer. *Int J Radiat Oncol*. 2014;90(1, Supplement):S30. doi:https://doi.org/10.1016/j.ijrobp.2014.05.135

56) Timmerman R, Paulus R, Galvin J, et al. Stereotactic body radiation therapy for inoperable early stage lung cancer. *JAMA*. 2010;303(11):1070-1076. doi:10.1001/jama.2010.261

57) Timmerman RD, Paulus R, Pass HI, et al. Stereotactic body radiation therapy for operable early-stage lung cancer: findings from the NRG Oncology RTOG 0618 trial. *JAMA Oncol*. 2018;4(9):1263-1266. doi:10.1001/jamaoncol.2018.1251

58) Bezjak A, Paulus R, Gaspar LE, 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(15):1316-1325. doi:10.1200/JCO.18.00622

59) Lindberg K, Grozman V, Karlsson K, 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(7):1200-1210. doi:10.1016/j.jtho.2021.03.019

60) Timmerman R, McGarry R, Yiannoutsos C, 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(30):4833-4839. doi:10.1200/JCO.2006.07.5937

61) Tekatli H, Duijm M, Oomen-de Hoop E, et al. Normal tissue complication probability modeling of pulmonary toxicity after stereotactic and hypofractionated radiation therapy for central lung tumors. *Int J Radiat Oncol Biol Phys*. 2018;100(3):738-747. doi:10.1016/j.ijrobp.2017.11.022

62) Chen H, Laba JM, Zayed S, Boldt RG, Palma DA, Louie AV. Safety and effectiveness of stereotactic ablative radiotherapy for ultra-central lung lesions: a systematic review. *J Thorac Oncol*. 2019;14(8):1332-1342. doi:10.1016/j.jtho.2019.04.018

63) Timmerman R, McGarry R, Yiannoutsos C, 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(30):4833-4839. doi:10.1200/JCO.2006.07.5937

64) Lindberg K, Grozman V, Karlsson K, 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(7):1200-1210. doi:10.1016/j.jtho.2021.03.019

65) Onishi H, Shirato H, Nagata Y, et al. Hypofractionated stereotactic radiotherapy (HypoFXSRT) for stage I non-small cell lung cancer: updated results of 257 patients in a Japanese multi-institutional study. *J Thorac Oncol*. 2007;2(7 Suppl 3):S94-S100. doi:10.1097/JTO.0b013e318074de34

66) Thompson M, Rosenzweig KE. The evolving toxicity profile of SBRT for lung cancer. *Transl Lung Cancer Res*. 2019;8(1):48-57. doi:10.21037/tlcr.2018.10.06

67) Finazzi T, Haasbeek CJA, Spoelstra FOB, et al. Clinical outcomes of stereotactic MR-guided adaptive radiation therapy for high-risk lung tumors. *Int J Radiat Oncol Biol Phys*. 2020;107(2):270-278. doi:10.1016/j.ijrobp.2020.02.025

68) Finazzi T, Palacios MA, Spoelstra FOB, et al. Role of on-table plan adaptation in MR-guided ablative radiation therapy for central lung tumors. *Int J Radiat Oncol Biol Phys*. 2019;104(4):933-941. doi:10.1016/j.ijrobp.2019.03.035

69) Finazzi T, Palacios MA, Haasbeek CJA, et al. Stereotactic MR-guided adaptive radiation therapy for peripheral lung tumors. *Radiother Oncol*. 2020;144:46-52. doi:10.1016/j.radonc.2019.10.013

70) Videtic GM, Paulus R, Singh AK, et al. Long-term follow-up on NRG Oncology RTOG 0915 (NCCTG N0927): a randomized phase 2 study comparing 2 stereotactic body radiation therapy schedules for medically inoperable patients with stage I peripheral non-small cell lung cancer. *Int J Radiat Oncol Biol Phys*. 2019;103(5):1077-1084. doi:10.1016/j.ijrobp.2018.11.051

71) Chuong MD, Alvarez D, Romaguera T, et al. Case report of ablative magnetic resonance-guided stereotactic body radiation therapy for oligometastatic mesenteric lymph nodes from bladder cancer. *Ther Radiol Oncol.* 2020;4:20-20.

72) Lewis B, Guta A, Mackey S, et al. 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(2):118-125.

73) Botman R, Tetar SU, Palacios MA, Slotman BJ, Lagerwaard FJ, Bruynzeel AME. The clinical introduction of MR-guided radiation therapy from a RTT perspective. *Clin Transl Radiat Oncol*. 2019;18:140-145. doi:10.1016/j.ctro.2019.04.01

Time-Driven Activity-Based Costing of CT-Guided vs MR-Guided Prostate SBRT

Neil R. Parikh, MD, MBA; Mary Ann Clark, MHA; Parashar Patel, MPA; Kayla Kafka-Peterson, RN, BSN; Lalaine Zaide, PA; Ting Martin Ma, MD, PhD; Michael L. Steinberg, MD; Minsong Cao, PhD; Ann C. Raldow, MD, MPH; James Lamb, PhD; Amar U. Kishan, MD

Abstract

Background and Purpose: Stereotactic body radiation therapy (SBRT) has become a standard-of-care option for localized prostate cancer. While prostate SBRT has traditionally been delivered using computed-tomography-guided radiation therapy (CTgRT), MR-imaging-guided radiation therapy (MRgRT) is now available. MRgRT offers real-time soft-tissue visualization and ease of adaptive planning, obviating the need for fiducial markers, and potentially allowing for smaller planning target volume (PTV) margins. Although prior studies have focused on evaluating the cost-effectiveness of MRgRT vs CTgRT from a payor perspective, the difference in provider costs to deliver such treatments remains unknown. This study thus used time-driven activity-based costing (TDABC) to determine the difference in provider resources consumed by delivering prostate SBRT via MRgRT vs CTgRT.

Methods: Data was collected from a single academic institution where prostate SBRT is routinely performed using both CTgRT and MRgRT. Five-fraction SBRT (40 Gy total dose) was assumed to be delivered through volumetric-modulated arc therapy for CTgRT patients, and through step-and-shoot, fixed-gantry intensity-modulated radiation therapy for MRgRT patients. Process maps were constructed for each portion of the radiation delivery process via interviews/surveys with departmental personnel and by measuring CTgRT and MRgRT treatment times. Prior to simulation, only CTgRT patients underwent placement of three gold fiducial markers. Personnel capacity cost rates were calculated by dividing total personnel costs by the annual minutes worked by a given personnel. Equipment costs included both an annualized purchase price and annual maintenance costs. Ultimately, the total costs of care encompassing personnel, space/equipment, and materials were aggregated across the entire chain of care for both CTgRT and MRgRT patients in a base case.

Results: Direct costs associated with delivering a 5-fraction course of prostate SBRT were $1,497 higher with MRgRT than with CTgRT – comprised of personnel costs ($210 higher with MRgRT), space/equipment ($1,542 higher with MRgRT), and materials ($255 higher with CTgRT). Only CTgRT patients underwent fiducial placement, which accounted for $591. MRgRT patients were assumed to undergo both CT simulation (for electron density calculation) and MRI simulation, with the former accounting for $168. Mean time spent by patients in the treatment vault per fraction was 20 minutes (range 15-26 minutes) for CTgRT, and 31 minutes (range 30-34 minutes) for MRgRT. Patient time spent during fiducial placement (CTgRT only) was 60 minutes. Modifying the number of fractions treated would result in the cost difference of $1,497 (5 fractions) changing to $441 (1 fraction) or to $2,025 (7 fractions).

Conclusion: This study provides an approximate comparison of the direct resources required for a radiation oncology provider to deliver prostate SBRT with CTgRT vs MRgRT. We await findings from the currently accruing phase III MIRAGE trial, which is comparing these modalities, and will subsequently measure acute and late genitourinary/gastrointestinal (GU/GI) toxicities, temporal change in quality-of-life outcomes, and 5-year biochemical, recurrence-free survival. Results from studies comparing the efficacy and safety of MRgRT vs CTgRT will ultimately allow us to put this cost difference into context.

Ultrahypofractionation or stereotactic body radiation therapy (SBRT) has now become a standard-of-care option for localized prostate cancer.[1] While SBRT has traditionally been delivered using linear accelerators (linacs) employing computed-tomography-guided radiation therapy (CTgRT), recent technological advances have allowed for MR-imaging-guided radiation therapy (MRgRT) to treat patients with radiation. Initially pioneered for use in thoracic and gastrointestinal malignancies, MRgRT has recently been highlighted in prostate cancer,[2,3] offering several advantages including real-time, soft-tissue visualization and ease of adaptive planning, obviating the need for fiducial markers, and potentially allowing for smaller planning target volume (PTV) margins.

Although prior studies have focused on evaluating the cost-effectiveness of MRgRT vs CTgRT from a payor perspective,[4,5] this study aimed to determine the difference in provider resources consumed by delivering prostate SBRT via MRgRT vs CTgRT. This study used time-driven activity-based costing (TDABC), an accounting technique conceptualized by Kaplan and Anderson in 2004,[6] to quantify the overall personnel, space/equipment, and material costs associated with SBRT delivered with MRgRT vs with CTgRT. Accounting for numerous processes and variation in key inputs, TDABC lends itself well to radiation oncology, where in recent years it has increasingly been utilized – including notable studies in prostate cancer.[7,8] In addition to quantifying resources utilized at discrete steps, the granular nature of TDABC may also lead to insights that may be used to improve care processes and gain efficiencies.

Methods

Building Process Maps to Define the Intervention

To inform this TDABC model, data were collected from a single academic institution where prostate SBRT is routinely performed using both CTgRT and MRgRT. Process maps were initially constructed for each portion of the radiation delivery process: initial consultation, simulation, treatment planning, treatment delivery over 5 SBRT fractions, 1 on-treatment visit (OTV), and 1 follow-up visit. The amount of time spent during individual processes of care was obtained by interviews/surveys with departmental personnel (physicians, nurses, dosimetrists, physicists, front office personnel, and radiation therapists), with the exception of CTgRT and MRgRT treatment times, which were measured from patients undergoing prostate SBRT from April 2021 to June 2021. A map overlooking the entire flow of care, including notable differences between CTgRT vs MRgRT, is seen in **Figure 1**.

Technology Utilized

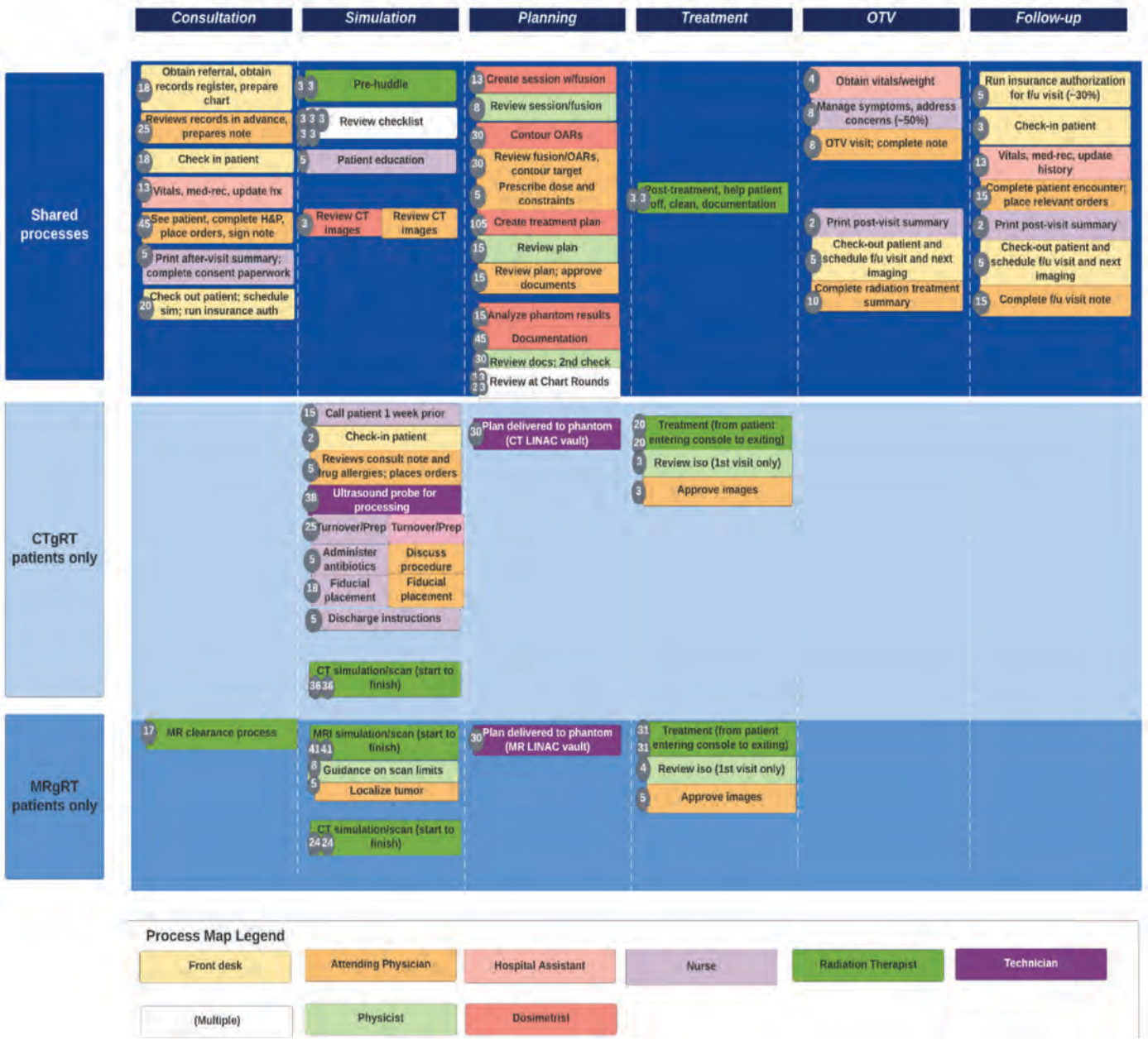
Prior to simulation, CTgRT patients underwent placement of 3 gold fiducial markers by a radiation oncologist that was done in a perineal fashion using transrectal ultrasound, lithotomy position, and local lidocaine block – all in the outpatient setting. CTgRT patients were then assumed to be treated on TrueBeam STx (Varian) with on-table position management involving the ExacTrac patient positioning system (BrainLab), which utilizes kV orthogonal x-rays with fiducial matching. Treatment was performed via volumetric-modulated arc therapy (VMAT). During treatment, CTgRT patients initially underwent ExacTrac (matched to fiducials) and cone-beam CT (CBCT) (to ensure appropriate bladder filling and rectum emptiness) prior to the first arc, with ExacTrac only performed between the first and second arc.

MRgRT patients were assumed to be treated on MRIdian linac (ViewRay), a platform that integrates a linac with split-magnet MRI technology and provides continuous soft-tissue imaging during treatment. Patients were treated with step-and-shoot, fixed-gantry intensity-modulated radiation therapy (IMRT) involving 10-17 beams. Image-guidance was performed by fine tuning localization with MRI to the prostate itself. Our institutional protocol did not routinely utilize adaptive planning in the treatment of localized prostate cancer; therefore, estimates pertaining to the additional time and resources for adaptive planning were not included.

Both groups of patients were to receive prostate SBRT in 40 Gy over 5 fractions, every other day, approximately over 1.5 weeks. Preparation prior to simulation and treatment in both groups included obtaining full

Affiliations: Dr. Parikh is an attending physician at the San Antonio Cancer Center, San Antonio, TX. **Ms. Clark** is senior director, health economics, and **Mr. Patel** is senior vice president, government affairs and market access, both at ViewRay Inc., Oakwood Village, OH. **Ms. Kafka-Peterson** is a registered nurse, **Ms. Zaide** is a physician assistant, **Dr. Ma** is a PGY4 resident physician, **Dr. Steinberg** is a professor and chair of radiation oncology, **Dr. Cao** is a professor of medical physics, **Dr. Raldow** is assistant professor of radiation oncology, **Dr. Lamb** is an associate professor of medical physics, and **Dr. Kishan** is an associate professor of radiation oncology and vice chair of clinical and translational research, all in the Department of Radiation Oncology, University of California Los Angeles. **Disclosures:** Dr. Parikh is a consultant for Radiopharm Theranostics. Ms. Clark is an employee and shareholder of ViewRay Inc. Mr. Patel is an employee and shareholder of ViewRay Inc. Dr. Steinberg is on the strategic advisory board for ViewRay Inc. Dr. Raldow is the local principal investigator for the SMART trial sponsored by ViewRay Inc., and serves as a consultant, product tester, and member of the Gastrointestinal Consortium. Dr. Lamb has received consulting fees from ViewRay Inc. Dr. Kishan has received consulting fees and research support from ViewRay Inc., grant support from the Prostate Cancer Foundation and the American Society for Radiation Oncology, and consulting fees from Varian. This study was supported by grant P50CA09213 from the Prostate Cancer National Institutes of Health (NIH) Specialized Programs of Research Excellence (Dr. Kishan) and a grant from ViewRay. The research data supporting the findings of this study are stored in an institutional repository and will be shared upon reasonable request to the corresponding author, Dr. Kishan (AUKishan@mednet.ucla.edu).

Figure 1. Process map outlining steps shared between computed-tomography-guided radiation therapy (CTgRT) and MR-guided radiation therapy (MRgRT), as well as unique steps in each. The box color of each step represents the personnel involved. The number inside the left-handed oval represents the average number of minutes a step takes.



bladder (patients asked to fully void and then drink 16-24 ounces of water approximately 30 minutes before simulation/treatment), and empty rectum (obtained by using two fleet enemas before treatment). If simulation/treatment was scheduled prior to 2 pm, the patient was instructed to do one enema the night before, and another enema the morning of treatment upon waking up. If simulation/treatment was instead scheduled after 2 pm, the patient was instructed to do an enema that day upon waking up, and another enema at 12 pm.

Estimating the Cost of Supplying Patient Care Resources

Personnel capacity cost rates (CCRs) were calculated by dividing total personnel costs (including salary, bonuses, benefits, cost of administrative support, malpractice insurance for physicians, educational funds, information technology, and office expenses) by the annual minutes worked by a given personnel member. These estimates were obtained from the department chief financial officer. Ultimately personnel

CCRs were found to be $5.16/minute for attending radiation oncologists, $1.32/minute for technologists, $2.56/minute for physicists, $2.27/minute for dosimetrists, $2.11/minute for radiation therapists, $2.42/minute for nurses, $1.09/minute for hospital assistants, $0.97/minute for front desk staff, and $0.70/minute for environmental services staff members.

The cost of equipment included both the average sales price amortized over a useful life of 10 years, as well as annual maintenance costs. The combined sales price of TrueBeam STx with ExacTrac was estimated to be $4,750,000, with estimated annual maintenance costs of $417,500. Sales price for MRIdian linac was estimated to be $7,800,000, with estimated annual maintenance costs of $550,000. Each of these estimates was provided by company representatives as typical sales prices; actual sales prices vary and are subject to change.

Space costs were made on a dollar per square foot ($/sq ft) basis. New construction costs based on institutional estimates were $1,000/sq ft for the CTgRT linac vault, $1,265/sq ft for the MRgRT linac vault (higher due to additional radiofrequency shielding and considerations involving a superconductor magnet with helium), and $420/sq ft for all other spaces; useful life of all spaces was assumed to be 25 years. All space and equipment were assumed to be available for clinical use 5 days per week (except for 10 holidays per year and 2 days per year for maintenance); during each working day, all linacs and the CT simulator were available for clinical use for 9.5 hours (machine-specific quality assurance [QA] assumed to occur outside this window) and all other spaces made available 8 hours per day.

The overwhelming majority of materials costs incurred were related to fiducial placement (associated with CTgRT delivery only), and were obtained from the lead nurse overseeing such procedures. The invoice cost of a 3-pack of gold fiducial markers was $210 each. Additionally, per-patient material costs associated with room turnover, draping the patient and preparing a sterile field, and medicating the patient were also included. Both groups of patients were assumed to have not undergone hydrogel placement.

Also included in this estimate was machine-specific QA for each linac computed by amortizing these costs across the percentage of a linac's clinically available minutes spent on an individual treatment. The CT-guided linac and MR-guided linac were estimated to have daily QA of 20 minutes/day vs 40 minutes/day, monthly QA of 240 minutes/month vs 360 minutes/month, and yearly QA of 900 minutes/year vs 1,380 minutes/year, respectively.

Calculating Total Cost of Care

Ultimately, the total costs of care encompassing personnel, space/equipment, and materials were aggregated across the entire chain of care for both CTgRT and MRgRT patients in a base case. A synopsis of major assumptions used in calculating CTgRT and MRgRT costs is presented in **Table 1**. Additional sensitivity analysis is found in subsequent sections of the manuscript.

Results

Base Case Scenario

Given the baseline models as discussed above, the direct costs associated with delivering a 5-fraction course of prostate SBRT were $1,497 higher with MRgRT than with CTgRT – comprised of personnel ($210 higher with MRgRT), space/equipment ($1,542 higher with MRgRT), and materials ($255 higher with CTgRT). Differences in costs are broken down by phase of care **(Table 2)**, with the largest differences seen in treatment delivery ($1,303 higher for MRgRT).

At simulation, both personnel and materials costs were higher with CTgRT ($169 and $256, respectively) than with MRgRT given the need for fiducial placement (only necessary for CTgRT and accounting for $591 overall). During simulation, however, space/equipment costs were $410 higher in MRgRT given the need for CT simulation to be performed (for electron density calculations) in addition to the utilization of the high-cost MRI linac vault for simulation scans.

During treatment delivery, MRgRT resulted in $1,303 higher costs per course mainly due to $1,018 higher space/equipment costs from both increased time in the vault (171 minutes for MRgRT vs 115 minutes for CTgRT during treatment delivery), as well as higher space/equipment CCR ($9.62/minute vs $6.43/minute). When estimating the time spent from a patient entering to exiting the room (mean 20 minutes [range 15-26 minutes] for CTgRT-based treatment on 5 patient encounters; mean 31 minutes [range 30 to 34 minutes] for MRgRT-based on 6 patient encounters) these estimates intentionally excluded patients who required additional waiting in the room for bladder filling. For MRgRT, the possibility of adaptive treatment was not included in this analysis.

Regarding patient time, CTgRT patients spent 30 additional minutes during simulation largely due to fiducial placement, which occupied 60 minutes (excluding the variable wait time between fiducial placement and same-day simulation). This was only partially offset by the dual CT and MRI simulation scans that MRgRT patients underwent. During treatment delivery, MRgRT patients spent 56 more minutes across the entire treatment course.

Additional Sensitivity Analyses

Instead of performing SBRT over 5 fractions, the study also compared

Table 1. Major Assumptions for CTgRT vs MRgRT in Prostate SBRT

ASSUMPTION	CT-GUIDED LINAC SBRT	MR-GUIDED LINAC SBRT	SHARED BY CTGRT AND MRGRT
Machine (Manufacturer)	TrueBeam STx (Varian) with ExacTrac (BrainLab)	MRIdian Linac (ViewRay)	
Real-time imaging of soft tissue	No	Yes	
Type of simulation required	CT simulation only (Diagnostic MRI may be done prior)	CT simulation and MR simulation	
Technique	VMAT	Fixed-gantry, step-and-shoot IMRT	
Fiducials placed	Yes - for image guidance	No	
Annual time spent on machine QA (minutes)	8,760	15,660	
Construction costs for linac vault	$1,000 / sq ft	$1,265 / sq ft	
List price of machine	$4,750,000	$7,800,000	
Annual maintenance costs of machine	$417,500	$550,000	
Space of linac vault	686 sq ft	1134 sq ft	
Space/equipment cost of linac vault	$6.43/minute	$9.62/minute	
Number of fractions			5
Dose per fraction			8 Gy
Time machine is clinically available during year, excluding QA (minutes)			141,930
Personnel CCR (Attending Physician)			$5.16/minute
Personnel CCR (Technologist)			$1.32/minute
Personnel CCR (Physicist)			$2.56/minute
Personnel CCR (Dosimetrist)			$2.27/minute
Personnel CCR (Radiation Therapist)			$2.11/minute
Personnel CCR (Nurse)			$2.42/minute
Personnel CCR (Hospital Assistant)			$1.09/minute
Personnel CCR (Front Desk Staff)			$0.97/minute

Key: CTgRT = computed-tomography-guided radiation therapy, MRgRT = MR-guided radiation therapy, SBRT = stereotactic body radiation therapy, linac = linear accelerator, VMAT = volumetric-modulated arc therapy, QA = quality assurance, CCR = capacity cost rates

how decreasing treatment to a single fraction (as in PROSINT)[9] or increasing to 7 fractions (as in HYPO-RT-PC)[10,11] would influence costs for both modalities. The overall cost increase from CTgRT to MRgRT would change from $1,497 (5 fractions) to $441 (1 fraction) or to $2,025 (7 fractions).

By decreasing the amount of time machines were clinically available by 20%, the cost difference from CTgRT to MRgRT went from $1,497 to $1,893; when increasing clinically available time by 20%, the cost difference decreased to $1,233. Decreasing the list price for each linac 20%, the CTgRT-MRgRT cost difference declined from $1,497 to $1,328. By decreasing the list price for only MRgRT by 20%, the cost difference declined from $1,497 to $1,231.

Currently, CT simulation is still performed for MRgRT patients to aid with electron density calculations. However, if synthetic CT images were used instead – similar to a process outlined in MR-OPERA[12] – this would result in savings of $168.

Discussion

This study provides an approximate comparison of the direct resources required for a radiation oncology provider to deliver prostate SBRT with CTgRT vs MRgRT. For context, this $1,497 increase in direct costs from utilizing MRgRT for 5-fraction prostate SBRT instead of CTgRT is comparable to a $1,316 increase seen with MRgRT in an analysis previously conducted for patients with unresectable

Table 2. Difference in Cost Between CT-Guided and MR-Linac SBRT

MAP	PROCESS STEP	PERSONNEL	SPACE + EQUIPMENT	MATERIALS	TOTAL
1	New Patient	-$41	-$1	$0	-$42
2	Simulation	$169	-$410	$256	$15
3	Treatment Planning	-$13	-$114	$0	-$126
4	Treatment (total)	-$285	-$1,018	$0	-$1,303
5	On Treatment Visit (total)	$0	$0	$0	$0
6	Follow-Up Visit (total)	$0	$0	$0	$0
7	Machine-specific QA	-$40	$0	$0	-$41
	Total	-$210	-$1,542	$255	-$1,497

CTgRT higher *MRgRT higher*

Key: SBRT = stereotactic body radiation therapy, CTgRT = computed-tomography-guided radiation therapy, MRgRT = MR-guided radiation therapy , QA = quality assurance

hepatocellular carcinoma receiving liver SBRT.[13]

Notably, this analysis does not include radiology resources utilized in obtaining a diagnostic prostate MRI that may be ordered for planning purposes in CTgRT patients. While many CTgRT and MRgRT patients alike may receive diagnostic MRI at initial staging, a subset of CTgRT patients undergoing neoadjuvant androgen deprivation therapy will require an additional MRI (for planning purposes) around the time of CT planning to account for prostate size. Although TDABC estimates from this step are not available, 2021 Medicare Physician Fee Schedule reimbursements total approximately $462 for prostate MRI – with national payment amounts (nonfacility price) for CPT codes 72197 (MRI pelvis with-without contrast) and 76377 (3D rendering with interpretation) at $389 and $73, respectively.

Also not included in this analysis is the possibility of adaptive planning. While a couple of studies involving MRgRT in prostate cancer have utilized adaptive planning, [14,15] the incremental benefit, if any, of such an approach has not yet been elucidated. Because our institution does not routinely utilize adaptive planning for MRgRT, the nontrivial increased time and resources associated with such an effort were not included.

Lastly, not included in this analysis is the placement of a hydrogel spacer. While randomized data have shown placement of a rectal spacer resulting in improved rectal toxicity and sexual function,[16,17] it is not covered by all payors and may also result in rare grade 3 toxicity (including rectum perforation and urethral damage).[18] As a result, its utilization often depends on physician experience, patient preference, and clinical factors. Although our analysis did not account for spacer hydrogel placement, it is worth noting that the cost differential between a CTgRT patient receiving fiducials plus hydrogel vs an MRgRT patient receiving hydrogel alone would be significantly smaller than $591 (the cost currently attributed to doing fiducial placement alone in CTgRT patients). Because most steps are shared in a combined fiducial plus hydrogel placement, the additional cost from placing fiducials in this setting mainly comes from materials costs of the fiducials themselves.

Although this study focuses exclusively on the resources associated with processes, personnel, space/equipment, and materials involved in performing prostate SBRT with CTgRT vs MRgRT, we currently await data comparing the safety/efficacy of the two modalities. While single-arm prospective data by Tetar et al has illustrated a favorable safety profile with MRgRT prostate SBRT (no grade 3-plus toxicity reported; symptoms returning to baseline by 12 months),[2] the currently accruing phase III MIRAGE trial aims to formally compare these modalities in a randomized fashion, and will subsequently measure acute and late GU/GI toxicities, temporal change in quality-of-life outcomes, and 5-year biochemical recurrence-free survival.[3] While real-time image guidance may allow for smaller PTV margins with MRgRT, it is unclear how this will compare to the difference in dosimetry achieved by VMAT with CTgRT vs step-and-shoot IMRT with MRgRT.

Given comorbidities and clinical situations, it is likely that certain patients may be suitable for one modality. For example, patients with extreme claustrophobia or with nonpacemaker-compatible implanted devices may not be suitable candidates for MRgRT. On the other hand, patients with an excessive bleeding risk or who cannot easily come off anticoagulants may not be suitable for CTgRT given the need for fiducial placement.

Finally, one must acknowledge the following caveats to the analysis when interpreting this study's results,

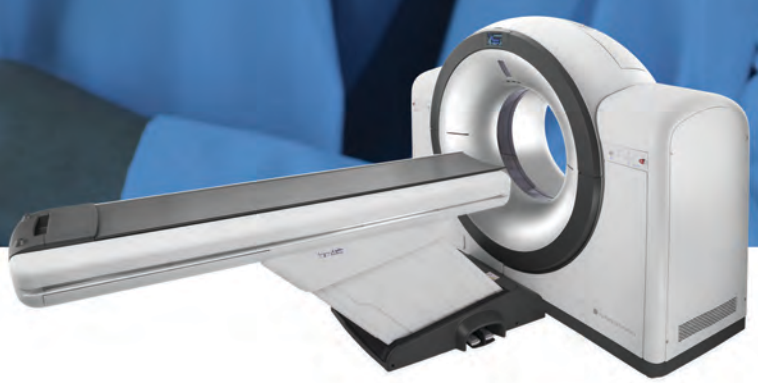
FUJIFILM
Value from Innovation

Reliability in Action.

For the Radiology Director, who oversees everything, reliability matters.

Persona CT delivers clinical and operational excellence with consistent dependability for your bottom line.

Be visionary.



#VisionaryCT

Persona CT

and especially when extrapolating findings to other centers. First, the data used to inform process times, personnel costs, and materials costs comes from a single academic department, where protocols and processes may vary compared with other institutions. For example, while our institution utilized fiducials for CTgRT SBRT delivery, this practice is not universal, as 27% of SBRT patients treated in PACE-B did not receive fiducials.[19] In addition, our institution utilized both CBCT and orthogonal kV x-rays before treatment as well as orthogonal kV x-rays during treatment, whereas other centers may have only used CBCT prior to treatment – thereby resulting in lower treatment times. Second, the equipment costs used in this analysis were taken from sales representatives and may be subject to variation depending on specific contract agreements. Third, when accounting for different fractionation regimens (eg, 1 fraction or 7 fractions vs 5 fractions), the approximate cost per fraction was kept constant and did not explicitly account for the variable length of treatment time depending on nominal dose delivered.

Conclusion

In conclusion, the base case of this TDABC analysis estimates $1,497 in increased direct costs utilized by delivering prostate SBRT with MRgRT instead of CTgRT, although as seen in sensitivity analyses above, modifications to key model inputs may change this result. Results from studies comparing the efficacy and safety between MRgRT vs CTgRT will ultimately allow us to put this cost difference into context.

References

1) National Comprehensive Cancer Network. Prostate Cancer (Version 2.2021). Accessed July 1, 2021. https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf

2) Tetar SU, Bruynzeel AME, Oei SS, et al. Magnetic resonance-guided stereotactic radiotherapy for localized prostate cancer: final results on patient-reported outcomes of a prospective phase 2 study. *Eur Urol Oncol.* 2020.

3) Ma TM, Lamb JM, Casado M, et al. Magnetic resonance imaging-guided stereotactic body radiotherapy for prostate cancer (mirage): a phase III randomized trial. *BMC Cancer.* 2021;21:538.

4) Schumacher LD, Dal Pra A, Hoffe SE, et al. Toxicity reduction required for MRI-guided radiotherapy to be cost-effective in the treatment of localized prostate cancer. *Br J Radiol.* 2020;93:20200028.

5) Hehakaya C, van der Voort van Zyp JRN, Vanneste BGL, et al. Early health economic analysis of 1.5 T MRI -guided radiotherapy for localized prostate cancer: decision analytic modelling. *Radiother Oncol.* 2021;161:74-82.

6) Kaplan RS, Anderson SR. Time-driven activity-based costing. *Harv Bus Rev.* 2004;82:131-8,150.

7) Laviana AA, Ilg AM, Veruttipong D, et al. Utilizing time-driven activity-based costing to understand the short- and long-term costs of treating localized, low-risk prostate cancer. *Cancer.* 2016;122:447-455.

8) Dutta SW, Bauer-Nilsen K, Sanders JC, et al. Time-driven activity-based cost comparison of prostate cancer brachytherapy and intensity-modulated radiation therapy. *Brachytherapy.* 2018;17:556-563.

9) Greco C, Pares O, Pimentel N, et al. Safety and efficacy of virtual prostatectomy with single-dose radiotherapy in patients with intermediate-risk prostate cancer: results from the prosint phase 2 randomized clinical trial. *JAMA Oncol.* 2021;7:700-708.

10) Widmark A, Gunnlaugsson A, Beckman L, 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.

11) Fransson P, Nilsson P, Gunnlaugsson A, et al. Ultra-hypofractionated versus conventionally fractionated radiotherapy for prostate cancer (HYPO-RT-PC): patient-reported quality-of-life outcomes of a randomised, controlled, non-inferiority, phase 3 trial. *Lancet Oncol.* 2021;22:235-245.

12) Persson E, Gustafsson C, Nordstrom F, et al. MR-opera: a multicenter/multivendor validation of magnetic resonance imaging-only prostate treatment planning using synthetic computed tomography images. *Int J Radiat Oncol Biol Phys.* 2017;99:692-700.

13) Parikh NR, Lee PP, Raman SS, et al. Time-driven activity-based costing comparison of ct-guided versus mr-guided sbrt. *JCO Oncol Pract.* 2020;16:e1378-e1385.

14) Alongi F, Rigo M, Figlia V, 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.

15) Bruynzeel AME, Tetar SU, Oei SS, 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.

16) Hamstra DA, Mariados N, Sylvester J, et al. Sexual quality of life following prostate intensity modulated radiation therapy (IMRT) with a rectal/prostate spacer: secondary analysis of a phase 3 trial. *Pract Radiat Oncol.* 2018;8:e7-e15.

17) Hamstra DA, Mariados N, Sylvester J, et al. Continued benefit to rectal separation for prostate radiation therapy: final results of a phase III trial. *Int J Radiat Oncol Biol Phys.* 2017;97:976-985.

18) Schorghofer A, Drerup M, Kunit T, et al. Rectum-spacer related acute toxicity – endoscopy results of 403 prostate cancer patients after implantation of gel or balloon spacers. *Radiat Oncol.* 2019;14:47.

19) Brand DH, Tree AC, Ostler P, 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.

Analysis of the Radiation Oncology In-Training Examination Content Using a Clinical Care Path Conceptual Framework

Kevin R. Rogacki, MD; Stanley Gutiontov, MD; Chelain R. Goodman, MD, PhD; Elizabeth Jeans, MD, MEd; Yasmin Hasan, MD; Daniel W. Golden, MD, MHPE

Abstract

Hypothesis: The American College of Radiology (ACR) Radiation Oncology In-Training Examination (TXIT) is an assessment administered by radiation oncology training programs to assess resident performance against national benchmarks. Results are currently reported using a disease site conceptual framework. The clinical care path framework was recently proposed as a complementary view of resident education. This study assesses distribution of 2016-2019 TXIT questions using the clinical care path framework with the hypothesis that questions are unequally distributed across the clinical care path framework, leading to underassessment of fundamental clinical skills.

Methods and Materials: Using a clinical care path framework, 1,200 questions from the 2016-2019 TXITs were categorized into primary categories and subcategories. The distribution of questions was evaluated.

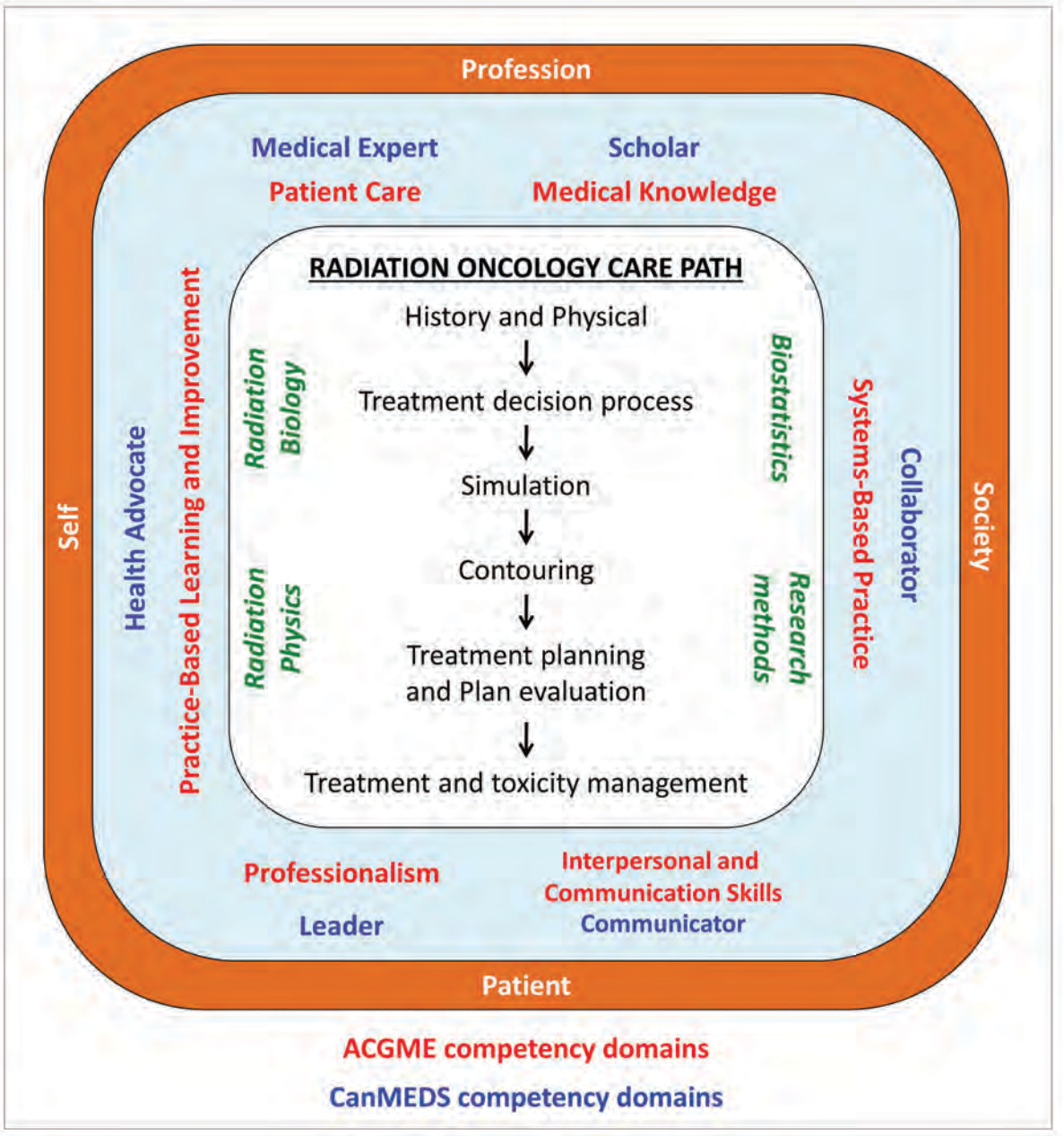
Results: Primary categorization was achieved for 98.7% of questions. Where applicable, subcategorization was achieved for 96.6% of questions. There was substantial inter-rater reliability (primary category $\kappa = 0.78$, subcategory $\kappa = 0.79$). Distribution of TXIT content by the clinical care path framework was: treatment decision (35%), diagnosis (16%), radiation biology (12%), radiation physics (12%), treatment planning (9%), biostatistics (4%), cancer biology (4%), toxicity and management (4%), brachytherapy (2%), quality assurance (1%), and research methods (1%). Of the 419 questions within the treatment decision primary category, knowledge from randomized clinical trials was most frequently evaluated (43%).

Conclusions: TXIT question items are unequally distributed across clinical care path categories, emphasizing treatment decision over other categories such as treatment planning and toxicity and management. Reporting examination data by both clinical care path and disease site conceptual frameworks may improve assessment of clinical competency.

Affiliations: Dr. Rogacki is a PGY5 resident in the Department of Radiation Oncology, Northwestern University Feinberg School of Medicine, Chicago, IL. **Dr. Gutiontov** is a former resident, **Dr. Hasan** is an associate professor, and **Dr. Golden** is an associate professor, all in the Department of Radiation and Cellular Oncology, University of Chicago. **Dr. Goodman** is an assistant professor in the Department of Radiation Oncology, MD Anderson Cancer Center, Houston, TX, and was a resident at Northwestern University when contributing to this study. **Dr. Jeans** is a PGY 5 resident in the Department of Radiation Oncology, Mayo Clinic, Rochester, MN. **Disclosure:** Dr. Golden reports grants from the National Institutes of Health, the Radiation Oncology Institute, and the Bucksbaum Institute for Clinical Excellence, as well as manager of RadOncQuestions LLC, outside the scope of this work. None of the authors received outside funding for the production of this original manuscript. The data in this manuscript were presented as an abstract at the American Society for Radiation Oncology (ASTRO) Annual Meeting in 2020 (Rogacki K, Gutiontov S, Goodman CR, Jeans E, Hasan Y, Golden DW. Analysis of the Radiation Oncology In-Training Exam content using a care path conceptual framework [abstract]. In: Proceedings of the American Society for Radiation Oncology; 2020 Oct 24-28; Miami, FL [virtual meeting]; Poster Q&A Session. Int J Radiat Oncol Biol Phys. 2020; 108(3)e439,2988.). This manuscript, however, has not been previously published. The data supporting the findings of this study are available from the corresponding author, Dr. Golden (dgolden@radonc.uchicago.edu), upon reasonable request.

The American of College of Radiology (ACR) Radiation Oncology In-Training Examination (TXIT) is a standardized assessment used to assess radiation oncology trainees' acquisition of knowledge necessary for independent practice. By providing "mean norm-referenced scores at the national, institutional, and individual levels," the TXIT serves as a formative assessment to inform

Figure 1. Radiation oncology education clinical care path conceptual framework. From Perez and Brady's Principles and Practice of Radiation Oncology, 7th ed (p. 2243), by D.W. Golden and P. Ingledew, 2018, Lippincott, Williams & Wilkins. Printed with permission.

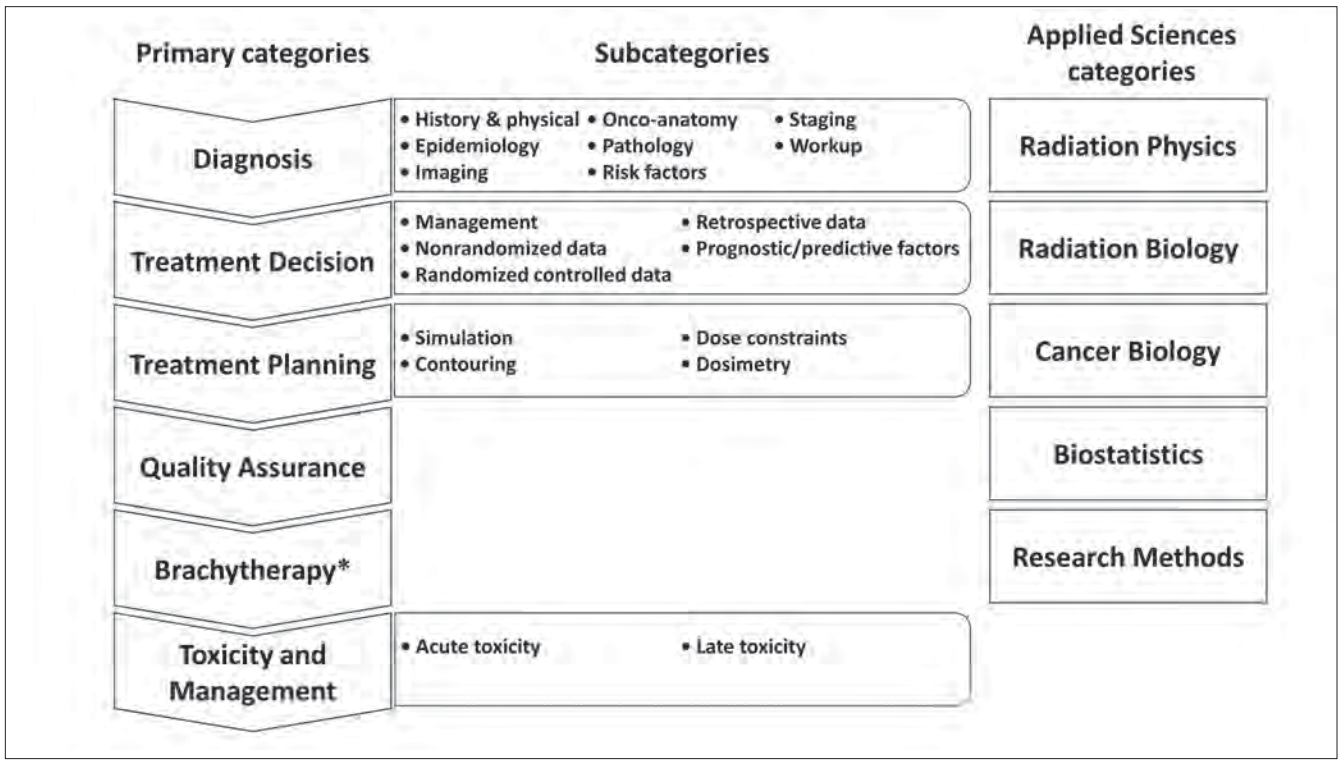


trainees and training programs on content areas that may require additional attention for self-study or formal didactics.[1-4]

The annual TXIT examination consists of 300 single-answer, multiple-choice questions and is sponsored by the ACR Commission on Publications and Lifelong Learning.[3] Examination content is organized into 13 sections according to a disease site conceptual framework (eg, thoracic, breast, lung), or by basic science subject (biology, physics, statistics).

In medical education, a conceptual framework facilitates organization and perception of educational content. A conceptual framework can also "represent [a] way of thinking about a problem" and influence how interrelated topics may be considered.[5] Traditionally, the field of radiation oncology has used a disease site conceptual framework to organize resident education. The use of a disease site framework is reflected in didactic

Figure 2. Clinical care path primary categories (A), subcategories (B), and applied sciences categories (C) used to classify TXIT in-training exam questions. *Brachytherapy included as a primary category to emphasize its unique position within the clinical care path.



curricula, clinical rotations, case logs, textbooks, and board examination categories.[6,7] This prevailing conceptual framework also underlies development of assessment tools such as the TXIT examination.[4]

A conceptual framework based on the radiation oncology clinical care path was recently proposed and represents an alternative and complementary lens through which to view radiation oncology education (**Figure 1**).[8] The clinical care path conceptual framework represents the stepwise clinical activities involved in providing care to a patient receiving radiation therapy. These steps begin at the initial consultation and encompass the treatment decision, simulation, contouring, treatment planning, quality assurance, toxicity management, and long-term follow-up. For medical specialties with a technical component, such a framework may better encompass the spectrum of professional activities in which a physician must demonstrate proficiency to be considered competent for independent practice. As a result, the clinical care path framework may provide a more direct link to competency-based medical education.[9-11]

The extent to which the TXIT assesses competency in the clinical activities central to the practice of radiation oncology as defined by the clinical care path conceptual framework is unknown. The purpose of this study was to assess the distribution of questions in the 2016-2019 TXIT examinations using the clinical care path framework. We hypothesized that the TXIT content is unequally distributed across the clinical care path framework, leading to underassessment of fundamental clinical skills.

Methods and Materials

Category Definition

The clinical care path framework was adapted to derive clinical care path primary categories and subcategories (**Figure 2**) along with definitions to guide categorization by independent coders (**Table 1**). Subjects outside of the clinical care path but fundamental to the practice of radiation oncology including radiation biology, cancer biology, radiation physics, biostatistics, and research methods were included as separate applied sciences primary categories (**Figure 2**).

Coding of Question Items

Two independent coders categorized 1,200 questions from the 2016-2019 TXIT examinations based on the content of the question stem, answer choices, and associated rationale. Inter-rater reliability was assessed with Cohen's kappa coefficient test statistic. Items with discordant categorizations were independently reconciled by a third coder. If reconciliation was not achieved, the question was deemed uncategorizable

Table 1. Definitions Guide for Question Categorization

PRIMARY CATEGORIES AND SUBCATEGORIES	DEFINITION
Clinical Care Path Categories	
Diagnosis	**Questions relating to the diagnosis and integration of clinicopathologic data during initial consultations**
▪History and physical	History and exam findings pertinent to a diagnosis of cancer
▪Epidemiology	Epidemiological facts relating to cancer incidence, prevalence, and population level data
▪Imaging	Imaging modalities or imaging findings
▪Onco-anatomy	Anatomy questions, patterns of spread, and questions about loss or alteration of function due to tumor involvement
▪Pathology	Histological diagnosis and principles
▪Risk factors	Predisposing factors to cancer development
▪Staging	TNM staging, clinical group staging, pathological group staging, and risk groups
▪Workup	Catch-all category for utilization or interpretation of other studies performed during diagnosis (ie, laboratory tests)
Treatment Decision	**Questions relating to treatment principles or medical knowledge informing treatment decision making**
▪Management	General treatment principles (often derived from consensus guidelines)
▪Nonrandomized data	Phase I, phase II, and observational studies
▪Prognostic/predictive factors	Clinical, pathological and treatment factors that are prognostic for outcome or predictive for treatment effect
▪Randomized control data	Phase III, randomized control studies, including meta-analyses
Treatment Planning	**Questions relating to radiation treatment planning**
▪Contouring	Tumor volumes, normal volumes, field placement, and field borders
▪Dose constraints	QUANTEC data, dosimetric studies, dose constraints utilized in clinical trials
▪Dosimetry	Radiation planning and dosimetry concepts (ie, measurement of dose)
▪Simulation	Simulation modalities, patient setup, and skills employed during simulation
Quality Assurance	**Questions pertaining to QA activities performed as part of treatment verification and/or delivery (ie, IGRT)**
Brachytherapy	**Questions relating to brachytherapy**
Toxicity and Management	**Questions relating to identification, mitigation, and management of treatment-related toxicities**
▪Acute	Acute toxicity occurring during and just after completion of treatment (ie, fatigue, dermatitis, mucositis, proctitis, cystitis, etc.)
▪Late	Late toxicity occurring because of delayed radiation effects (i.e. secondary malignancy, fertility, chronic organ dysfunction, etc.)
Applied Sciences Categories	
Biostatistics	**Questions employing statistical principles**
Research Methods	**Questions pertaining to the research process and trial design**
Cancer Biology	**Questions about tumor biology, cellular physiology, and molecular mechanisms in the absence of radiation effects (ie, mutations, genomic alterations, cell receptors, downstream effectors, systemic therapy mechanism of action)**
Radiation Physics	**Questions pertaining to fundamental physics concepts and material commonly taught in radiation physics courses or discussed in radiation physics texts**
Radiation Biology	**Questions about the biological action of radiation treatment and fundamental radiobiological concepts commonly taught in a radiation biology course or discussed in radiobiology texts**

**Bold indicates primary category †Bullets indicate subcategory within a primary category if applicable*
Key: TNM = tumor, nodes, metastases; QUANTEC = Quantitative Analyses of Normal Tissue Effects in the Clinic; QA = quality assurance; IGRT = image-guided radiation therapy

Table 2. Examples of Reconciled or Uncategorized Question Items

EXAMPLE	QUESTION ITEM	ANSWER AND RATIONALE	CATEGORIZATION BY CODER†	FINAL CATEGORIZATION
Primary Category – Reconciled	Which tumor markers can be used as adjunctive studies to assess for disease progression in metastatic breast cancer? A. CEA, CA 15-3, CA 19.9 B. CEA, CA 15-3, CA 27.29 C. CEA, CA 19.9, CA 27.29 D. CA 15-3, CA 19.9, CA 27.29	Key: B. Solution/Rationale: NCCN breast cancer guidelines include optional use of CEA, CA 15-3, CA 27.29 in the assessment of metastatic breast cancer. The ASCO guidelines on biomarkers to guide systemic therapy for metastatic breast cancer state that CEA, CA 15-3, and CA 27.29 may be used to assist in treatment decision-making; however, they should not be used alone for monitoring disease response. CA 19.9 is not used in breast cancer; more often in pancreatic cancer. Van Poznak C, Somerfield MR, Bast RC, et al. Use of biomarkers to guide decisions on systemic therapy for women with metastatic breast cancer: American Society of Clinical Oncology Clinical Practice Guideline. *J Clin Oncol*. 2015;33:2695-2704.	1: Diagnosis - Workup 2: Treatment Decision-Management 3: Diagnosis - Workup	Diagnosis - Workup
Subcategory – Reconciled	For pleomorphic adenoma of the parotid gland, which feature increases the risk of local recurrence? A. Patient age B. Tumor size C. Male gender D. Tumor spillage	Key: D. Solution/Rationale: Surgical excision with a superficial or complete parotidectomy and facial nerve preservation is the recommended treatment for pleomorphic adenoma. Tumor spillage, residual disease, and recurrent disease after initial surgery are risk factors for additional recurrence. With a margin-negative surgical excision, size is not an independent risk factor for recurrence of a pleomorphic adenoma. Liu FF, Rotstein L, Davison AJ, et al. Benign parotid adenomas: a review of the Princess Margaret Hospital experience. *Head Neck*. 1995;17(3):177-183.	1: Retrospective data 2: Prognostic/predictive factors 3: Prognostic/predictive factors	Treatment Decision – Prognostic/ predictive factors
Primary Category – Uncategorized	What is the MOST common radiation technique for treatment of pterygium? A. Electrons with bolus B. IMRT C. Orthovoltage photons D. Beta emitter brachytherapy	Key: D. Solution/Rationale: Contact brachytherapy with strontium-90 is commonly utilized in the postoperative treatment of pterygium. Other methods are less focal. Pashtan I, Oh KS, Loeffler JS. Radiation therapy in the management of pituitary adenomas. *Int J Radiat Oncol Biol Phys*. 1994;28(1):101-103.	1: Radiation Physics 2: Treatment Decision 3: Treatment Planning	Uncategorized (primary category)
Subcategory – Uncategorized	What is the approximate 5-year local regional failure rate of T4, node positive anal cancer after definitive chemoRT? A. 20% B. 40% C. 60% D. 80%	Key: C. Solution/Rationale: According to the secondary analysis of RTOG 98-11 stratified by TN staging, for patients with T4, N1-3 cancer, the rate of 5-year LRF was 60%. Gunderson LL, Moughan J, Ajani JA, et al. Anal carcinoma: impact of TN category of disease on survival, disease relapse, and colostomy failure in US Gastrointestinal Intergroup RTOG 98-11 phase 3 trial. *Int J Radiat Oncol Biol Phys*. 2013;87(4):638-645.	1: Randomized control data 2: Nonrandomized data 3: Prognostic factors	Treatment Decision – Uncategorized (subcategory)

† Coder 1: SG; Coder 2: KRR; Coder 3: CRG
Key: NCCN = National Comprehensive Cancer Network, ASCO = American Society of Clinical Oncology, IMRT = intensity-modulated radiation therapy, RTOG = Radiation Therapy Oncology Group, LRF = locoregional failure

Table 3. Patterns of Disagreement in TXIT Question Items Requiring Reconciliation

Disagreement by Subcategory

SCENARIO	N (215 TOTAL)	PATTERN OF DISAGREEMENT IN CATEGORIZATION
Disagreement between all coders	16	No pattern
Disagreement between initial coders, reconciled by third coder	199	Most common disagreements by primary categorization*: ▪ diagnosis & treatment decision (34) ▪ treatment decision & treatment planning (28) ▪ cancer biology & radiation biology (23) ▪ radiation physics & quality assurance (12) ▪ treatment planning & radiation physics (12) ▪ treatment planning & toxicity and management (12) ▪ biostatistics & research methods (10)

Disagreement by Subcategory

SCENARIO	N (128 TOTAL)	PATTERN OF DISAGREEMENT IN CATEGORIZATION
Disagreement between all coders	18	▪ 16 of 18 disagreements at level of subcategory within treatment decision primary category (ie, management, nonrandomized data, randomized data, retrospective data, prognostic/predictive factors)
Disagreement between initial coders, unreconciled by third coder (different primary category)	25	▪ 23 of 25 were categorized by initial coders in primary category of treatment decision ▪ 16 of these 23 were labelled by the third coder as diagnosis (6) or treatment planning (10)
Disagreement between initial coders, reconciled by third coder	85	Most common primary categories for which subcategories were reconciled: ▪ treatment decision (53) ▪ diagnosis (22) ▪ treatment planning (7)

n indicates number of questions
**Most frequent pairwise disagreements listed in descending order from most to least common (≥ 10 occurrences)*
†Number of disagreements by category or category pairs provided in parentheses

at the primary or subcategorization level. Examples of reconciled and uncategorized questions are provided in **Table 2**. A single coder categorized questions according to disease site and content area. At the time of question categorization, all coders were radiation oncology residents at accredited US residency programs.

Institutional review board review of this study was not obtained as no human subjects were researched.

Results

Question Classification

Initial question categorization was achieved with substantial agreement between two independent coders (primary category, $\kappa = 0.78$; subcategory, $\kappa = 0.79$). In total, 343 questions (28.6%) required categorization by a third coder. Of the 1,200 question items, 1184 (99%) were successfully categorized by primary category. Of 199 questions for which reconciliation of the primary category was achieved, items were most commonly labeled as treatment decision by one coder and either diagnosis (n = 34, 17%) or treatment planning (n = 28, 14%) by the second coder. Of the 762 question items with a subcategory, 719 (94%) were successfully subcategorized. Of 85 questions for which reconciliation of the subcategory was achieved, most were within the treatment decision (n = 55, 65%), diagnosis (n = 22, 25%), or treatment planning primary categories (n = 7, 8%). Additional details of reconciled questions are available in **Table 3.**

TXIT Content by the Clinical Care Path Framework

The distribution of question items from the 2016-2019 TXIT examinations according to the clinical care path framework is reported in **Table 4**. A total of 796 (66%) question items were classified using the clinical care path, with the remaining 404 (34%) categorized as applied sciences. Clinical care path questions assessing treatment decisions were most prevalent, representing approximately 35% of all items (n = 435). These questions most frequently evaluated data

Table 4. TXIT Question Categorization by a Clinical Care Path Framework for Examination Years 2016-2019

PRIMARY CATEGORIES AND SUBCATEGORIES	N (%)
Clinical Care Path Categories	***796 (66)***
Diagnosis	**186 (16)**
Epidemiology	18 (2)
Imaging	10 (1)
Onco-anatomy	44 (4)
Pathology	20 (2)
Risk factors	10 (1)
Staging	57 (5)
Workup	10 (1)
Uncategorized subcategory	14 (1)
Treatment Decision	**419 (35)**
Management	103 (9)
Nonrandomized data	32 (3)
Prognostic/predictive factors	37 (3)
Randomized control data	182 (15)
Retrospective data	15 (1)
Uncategorized subcategory	50 (4)
Treatment Planning	**112 (9)**
Contouring	37 (3)
Dose constraints	34 (3)
Dosimetry	25 (2)
Simulation	5 (<1)
Uncategorized subcategory	11 (1)
Quality Assurance	**11 (1)**
Brachytherapy	**23 (2)**
Toxicity and Management	**45 (4)**
Acute	9 (1)
Late	34 (3)
Uncategorized subcategory	2 (<1)
Applied Sciences Categories	***404 (34)***
Biostatistics	**46 (4)**
Research Methods	**14 (1)**
Cancer Biology	**48 (4)**
Radiation Physics	**140 (12)**
Radiation Biology	**140 (12)**
Uncategorized Primary Category	16 (1)
TOTAL	**1200 (100)**

**Bold items indicate primary categories with subcategories listed beneath if applicable*
†Percentages rounded to nearest whole number
Key: TXIT = Radiation Oncology In-Training Exam

derived from randomized clinical trials (n = 182). Questions assessing diagnosis were the second most common (n = 186, 16%) and most frequently assessed tumor staging. Approximately 10% of questions assessed treatment planning (n = 112), of which approximately two-thirds were related to contouring and dose constraints. Questions evaluating treatment toxicity represented approximately 4% of items. Questions assessing brachytherapy included 23 questions within a 4-year testing period (2%).

For the applied sciences questions, radiation and cancer biology represented approximately 16% of all question items (n = 188), followed by radiation physics (n = 140, 12%), and biostatistics/research methods (n = 60, 5%).

TXIT Content by a Disease Site Framework

When classifying questions other than those defined as applied sciences according to a disease site framework, disease sites were represented approximately equally, with 6% to 8% of total questions dedicated to most sites (**Table 5**). Breast (n = 95, 8%) and head and neck (n = 93, 8%) were most frequently assessed, followed by lymphoma, pediatrics, genitourinary, and gynecologic disease sites (n = 73 to 83, 7%).

Discussion

Content analysis of the TXIT using a clinical care path framework demonstrates an uneven distribution in the number of questions allocated to the different steps of the clinical care path. Specifically, the exam most frequently assesses knowledge used to guide treatment decisions with fewer questions assessing treatment planning skills and management of treatment-related toxicity. This uneven distribution is not apparent when evaluating question content through a disease site framework.

Table 5. TXIT Question Categorization by a Disease Site Framework for Examination Years 2016-2019

DISEASE SITE	TXIT YEAR, N (%)				
	2016	2017	2018	2019	2016-2019 Average
Breast	24 (8)	23 (8)	25 (8)	23 (8)	24 (8)
Central Nervous System	14 (5)	21 (7)	19 (6)	16 (5)	18 (6)
Gastrointestinal	20 (7)	18 (6)	21 (7)	17 (6)	19 (6)
Genitourinary	22 (7)	19 (6)	17 (6)	22 (7)	20 (7)
Gynecology	19 (6)	21 (7)	19 (6)	19 (6)	20 (7)
Head and neck	23 (8)	22 (7)	24 (8)	24 (8)	23 (8)
Lymphoma	19 (6)	23 (8)	20 (7)	21 (7)	21 (7)
*Other	2 (1)	1 (<1)	0	0	1 (<1)
Palliative	4 (1)	7 (2)	5 (2)	9 (3)	6 (2)
Pediatrics	19 (6)	22 (7)	21 (7)	19 (6)	20 (7)
Sarcoma	3 (1)	3 (1)	4 (1)	4 (1)	4 (1)
Skin	4 (1)	1 (<1)	0	1 (<1)	2 (<1)
Thorax	21 (7)	16 (5)	21 (7)	16 (5)	19 (6)
Statistics	16 (5)	15 (5)	15 (5)	15 (5)	15 (5)
Biology	41 (14)	45 (15)	42 (14)	47 (16)	44 (15)
Physics	49 (16)	43 (14)	47 (16)	47 (16)	47 (16)

**Other contains 2 questions about heterotopic ossificans prophylaxis and 1 question about general cardiac dose constraints*
†Numbers and percentages rounded to nearest whole number
Key: TXIT = Radiation Oncology In-Training Exam

Table 6. Strategies to Improve Representation of Clinical Care Path Content on TXIT Examinations

SUGGESTION	COMMENT	PERCEIVED EFFORT OF IMPLEMENTATION
Report scores using a clinical care path framework in addition to scoring reports by a disease site framework	Provides feedback regarding acquisition of clinical competencies represented by the clinical care path framework	Low
Rebalance question content for better distribution across the clinical care path	Keep the number of questions fixed, but adjust the question content to increase underrepresented clinical care path content	Intermediate
Add questions to increase underrepresented content	▪ TXIT previously contained as many as 510 question items[1] ▪ Trainees will not welcome a longer testing session	Intermediate
Employ case-based questions to facilitate assessment across the clinical care path using a single clinical vignette	▪ Case-based questions are commonly employed by other medical licensing exams such as the USMLE ▪ Case-based questions have previously been included on the in-training exam in very limited capacity[2]	High
Restructure the administration of the in-training exam to end-of-rotation subject exams	▪ Structure subject exams like NBME shelf exams administered during required clinical rotations in medical school ▪ Permits more frequent, longitudinal testing of material ▪ Allows for cumulatively more questions over the course of a year, as number of questions are not constrained by one testing session	Very High

1. Paulino AC, Kurtz E. American College of Radiology In-Training Examination for Residents in Radiation Oncology (2004-2007). Int J Radiat Oncol Biol Phys. *2008;70(3):666-670. doi:10.1016/j.ijrobp.2007.09.049*
2. Coia LR, Wilson JF, Bresch JP, Diamond JJ. Results of the in-training examination of the American College of Radiology for Residents in Radiation Oncology. Int J Radiat Oncol Biol Phys. *1992;24(5):903-905. doi:10.1016/0360-3016(92)90472-t*
Key: TXIT = Radiation Oncology In-Training Exam, USMLE = United States Medical Licensing Examination, NBME = National Board of Medical Examiners

In considering this uneven distribution, it is important to note that the TXIT never intended to serve as a comprehensive trainee assessment. The first chairman of the ACR Committee on Professional Testing established at the outset that "factors of clinical judgment, diagnostic skills and general sophistication in selecting a treatment program for a patient are not assessed in the in-training examination."[1] Moreover, the ACR has emphasized that the TXIT is not to be used as the principle method of assessing performance in residency, predicting success on the American Board of Radiology (ABR) written board examinations, or as a criterion for employment.[5] As a result, relying on the TXIT as a measure of resident competency across all entrustable professional activities in radiation oncology is a task for which the TXIT was not designed.

Underassessment of certain competencies may be inherent to written examinations in medical education, as evidenced by content analysis of the plastic surgery and orthopedic surgery in-training examinations, which showed unequal distributions of in-training exam content relative to the Accreditation Council for Graduate Medical Education (ACGME) Milestones and competencies.[12] In particular, there appears to be a bias for test-makers with regard to the type of questions included on written in-training examinations with respect to available published evidence on which those questions are based. A content analysis of the plastic surgery in-training examination found there were significantly more Level III (decision-making questions) compared to Level I (fact recall) or Level II (interpretation questions). In addition, Level III questions more frequently justified the correct answer by referencing a journal article, with an overall higher mean number of journal references cited for these questions compared with other question types.[13] One possible explanation for this finding is that decision-making questions may be easier to develop because consensus exists due to the availability of supporting data.

When extrapolating this to the TXIT exam, and our own finding that treatment decision questions are predominant, we hypothesize there may be fewer questions from underrepresented clinical care path categories because there are fewer data on which to base single best answers. In other words, an acceptable range of choices exists. As an example, the preferred method to position a patient for set-up during computed tomography (CT) simulation may vary among radiation

oncologists. Multiple set-up positions may be considered correct, so developing a multiple-choice question to assess a trainee's CT simulation knowledge may be challenging. Our analysis of the TXIT exam content is unable to support or refute this hypothesis as an explanation for the bias toward treatment decision questions. To remedy this, exam item writers may benefit from training on how to develop a multiple-choice question assessing knowledge that is not based on journal publications, but that is required to function as a competent radiation oncologist.

Nevertheless, the TXIT continues to serve a singular and influential role in formative assessment of radiation oncology trainees as it is the only assessment tool that allows residency programs to benchmark their trainees against national metrics. Acknowledging the prominence of the TXIT in resident assessment, residency programs should encourage realignment of the exam to better assess underrepresented radiation oncology clinical care path competencies. Although changes to the TXIT as suggested in **Table 6** may accomplish this goal, the effort and resources required to do so may be prohibitive.

Alternatively, instead of retrofitting the TXIT to improve assessment of specific competencies, a better strategy may be to develop new assessment methods that target specific components of the radiation oncology clinical care path in which trainees are underassessed. For example, residents in the US and Canada have identified a general absence of formal instruction and assessment in treatment planning that impedes transition to independent clinical practice.[14-16] To address this curricular deficiency, radiation oncology educators could make a concerted effort to create teaching resources and assessment tools to promote and measure acquisition of treatment planning skills. Potential advantages of this approach include removing constraints imposed by a multiple-choice format, incorporating performance-based assessment, and using multiple assessment tools to triangulate trainee competency.[17,18]

Finally, it would be of interest to analyze the ABR Clinical Radiation Oncology Qualifying Exam according to the radiation oncology clinical care path framework. If current formative and summative assessments in the US do not assess for clinical competency across the entire clinical care path, then practicing clinicians may be deficient in specific areas. Further inquiry is needed into the development of comprehensive assessment methods to ensure clinical competency across the clinical care path.

This study has several limitations. First, the categorization of questions is inherently subjective despite utilizing multiple coders to avoid incorrect or inconsistent categorization. Among questions in which the initial two coders disagreed there was frequent overlap between the diagnosis, treatment decision, and treatment planning categories. This likely stems from the abundance of treatment decision questions and the inherent overlap of content with adjacent clinical care path primary categories of diagnosis and treatment planning. The small number of quality assurance questions may be due to significant overlap with the radiation physics category, making it difficult to conclude whether this is an underrepresented content area based on our analysis. Furthermore, the level of agreement between initial categorization by two coders is only moderate and not all question items were categorized through our reconciliatory process. These findings suggest there are other conceptualizations of a clinical care path framework that may improve categorization and better facilitate analysis of exam content.

Conclusions

Radiation oncology ACR TXIT questions are unequally distributed along the radiation oncology clinical care path conceptual framework. The exam contains a higher proportion of questions pertaining to treatment decisions than questions assessing other clinical skills such as treatment planning, toxicity management, and brachytherapy. To the extent that the TXIT reflects national licensing exams and, more broadly, content prioritized in radiation oncology education, deficiencies in education and assessment within specific areas of the radiation oncology clinical care path may manifest as deficiencies in clinical competency among radiation oncology trainees. Acknowledging there is no singular assessment that can holistically measure trainees' preparedness for independent practice, radiation oncologists in training and their future patients would benefit from additional assessment tools to comprehensively assess knowledge and skills fundamental to all aspects of the practice of radiation oncology.

References

1) Wilson JF, Diamond JJ. Summary results of the ACR (American College of Radiology) experience with an in-training examination for residents in radiation oncology. *Int J Radiat Oncol Biol Phys*. 1988;15(5):1219-1221. doi:10.1016/0360-3016(88)90207-6

2) Coia LR, Wilson JF, Bresch JP, Diamond JJ. Results of the in-training examination of the American College of Radiology for Residents in Radiation Oncology. *Int J Radiat Oncol Biol Phys*. 1992;24(5):903-905. doi:10.1016/0360-3016(92)90472-t

3) DXIT™ and TXIT™ In-Training Exams. Accessed January 20, 2020. https://www.acr.org/Lifelong-Learning-and-CME/Learning-Activities/In-Training-Exams. Published 2020.

4) Hatch SS, Vapiwala N, Rosenthal SA, et al. Radiation Oncology Resident In-Training examination. *Int J Radiat Oncol Biol Phys*. 2015;92(3):532-535. doi:10.1016/j.ijrobp.2015.02.038

5) Bordage G. Conceptual frameworks to illuminate and magnify. *Med Educ*. 2009;43(4):312-319. doi:10.1111/j.1365-2923.2009.03295.x

6) Accreditation Council for Graduate Medical Education (ACGME). ACGME Program Requirements for Graduate Medical Education in Radiation Oncology; 2020. Accessed January 2021. https://www.acgme.org/Portals/0/PFAssets/ProgramRequirements/430_RadiationOncology_2020.pdf?ver=2020-02-20-135340-140

7) American Board of Radiology Study Guide for Clinical (General and Radiation Oncology). Accessed July 1, 2020. https://www.theabr.org/radiation-oncology/initial-certification/the-qualifying-exam/studying-for-the-exam/clinical-radiation-oncology. Published 2020.

8) Golden DW, Ingledew P-A. Radiation Oncology Education. In: *Perez and Bradys Principles and Practice of Radiation Oncology*. 7th ed. Lippincott, Williams & Wilkins; 2018:2220-2252.

9) Accreditation Council for Graduate Medical Education (ACGME). Common Program Requirements (Residency). 2020:1-55. Accessed July 1, 2020. https://www.acgme.org/Portals/0/PFAssets/ProgramRequirements/CPRResidency2020.pdf

10) The radiation oncology milestone project. *J Grad Med Educ*. 2014;6(1s1):307-316. doi:10.4300/jgme-06-01s1-27

11) Carraccio C, Englander R, Van Melle E, et al. Advancing competency-based medical education: a charter for clinician-educators. *Acad Med*. 2016;91(5):645-649. doi:10.1097/ACM.0000000000001048

12) Ganesh Kumar N, Benvenuti MA, Drolet BC. Aligning in-service training examinations in plastic surgery and orthopaedic surgery with competency-based education. *J Grad Med Educ*. 2017;9(5):650-653. doi:10.4300/JGME-D-17-00116.1

13) Silvestre J, Bilici N, Serletti JM, Chang B. Low levels of evidence on the plastic surgery in-service training exam. *Plast Reconstr Surg*. 2016;137(6):1943-1948. doi:10.1097/PRS.0000000000002164

14) Moideen N, de Metz C, Kalyvas M, Soleas E, Egan R, Dalgarno N. Aligning requirements of training and assessment in radiation treatment planning in the era of competency-based medical education. *Int J Radiat Oncol Biol Phys*. 2020;106(1):32-36. doi:10.1016/j.ijrobp.2019.10.005

15) Best LR, Sengupta A, Murphy RJL, et al. Transition to practice in radiation oncology: mind the gap. *Radiother Oncol J Eur Soc Ther Radiol Oncol*. 2019;138:126-131. doi:10.1016/j.radonc.2019.06.012

16) Wu SY, Sath C, Schuster JM, et al. Targeted needs assessment of treatment planning education for united states radiation oncology residents. *Int J Radiat Oncol Biol Phys*. 2020;106(4):677-682. doi:10.1016/j.ijrobp.2019.11.023

17) Van Der Vleuten CPM, Schuwirth LWT, Driessen EW, et al. A model for programmatic assessment fit for purpose. *Med Teach*. 2012;34(3):205-214. doi:10.3109/0142159X.2012.652239

18) Miller GE. The assessment of clinical skills/competence/performance. *Acad Med*. 1990;65(9 Suppl):S63-7. doi:10.1097/00001888-199009000-00045

The Use of PSMA Targeted Therapy and Hormone Therapy in Renally Impaired Patient

Nat Lenzo, MMed MSc(Oncol) EMBA FRACP FAANMS[1]; Jaideep S. Sohi, MD[2]

Affiliations: [1]Nuclear Medicine and Internal Medicine Physician, GenesisCare Theranostics, Clinical Professor in Medicine, Notre Dame University Australia; [2]President, American Molecular Imaging, Inc., Assistant Professor of Nuclear Medicine, California Northstate University School of Medicine

CASE SUMMARY

An 82-year-old man presented with rising PSA of 21 ng/ml in July 2015. Prior to this time, in 2008, he received androgen deprivation therapy (ADT) and prostatic bed radiation (74 Gy). Patient was in Grade III renal failure with an eGFR of 30-40 ml/min and had previously undergone a laminectomy along with a history of osteoarthritis and lumbar stenosis.

In August 2015, the patient underwent a bone scan, which only detected degenerative changes. A CT scan found no evidence of metastatic disease. However, slightly prominent pelvic nodes of uncertain significance were noted and further evaluated with a 68-gallium (^{68}Ga) PSMA-11 PET scan in September 2015. At the time of the PSMA PET scan, his PSA had risen to 29 ng/ml; it increased to 40 ng/ml the following month. At this time, the eGFR was 35 ml/min.

IMAGING FINDINGS

Results of the ^{68}Ga PSMA-11 PET scan indicated prostate cancer recurrence with nodal involvement of the left supraclavicular, mediastinal, retrocrural, para-aortic and aortocaval, pelvic and inguinal regions (Figure 1).

Given the patient's prior treatment and co-morbidities, he was offered peptide receptor radionuclide therapy (PRRT) as per institutional protocol with signed informed consent. Treatment consisted of three cycles of 177-Lutetium (^{177}Lu) PSMA imaging and therapy (I&T): 6.77 GBq, 6.5 GBq and 4.9 GBq. Administered activities were decreased to take into account patients' renal impairment.

Post Lu-177 PSMA treatment, the patient's PSA fell to a nadir of 1.2 ng/ml with significant reduction in PSMA-avid lesions within the pelvis (Figures 2 and 3). Side effects of treatment included mild (grade 1) dry mouth and short-term lethargy. There was no significant change to complete blood count (CBC) or liver function tests (LFTs), and eGFR improved to 41 ml/min, likely secondary to reduction of obstructive uropathy from previous bulky adenopathy and reduction of recurrent disease at the prostatic bed.

In late 2017, the PSA increased to 6.5 ng/ml with a second prostate cancer recurrence. At this time, the patient remained in renal failure (eGFR 30-40 ml/min). In early February 2018, the patient received an additional 5.98 GBq ^{177}Lu PSMA-I&T treatment. While his PSA fell for seven months, it began to rise again, reaching 7.5 ng/ml by February 2019. The patient was initiated on intermittent low-dose enzalutamide (80 mg daily) which was well tolerated; the eGFR remained between 25-30 ml/min and other than mild anemia (hemoglobin 11.7 g/dl) his CBC, LFTs, electrolytes and lactate dehydrogenase were otherwise normal. PSA decreased to a nadir of 0.39 ng/ml by November 2019 with persistent stable biochemical profile. A PSMA PET scan prior to enzalutamide (Figure 4) revealed several small volume osseous metastases and persistent disease at the prostatic bed.

In early 2020, the patient's PSA started rising (1.6 ng/ml) and a repeat PSMA PET scan (Figure 4) revealed resolution of most osseous PSMA avid metastases but persistence of prostatic bed disease and progressive disease in the right

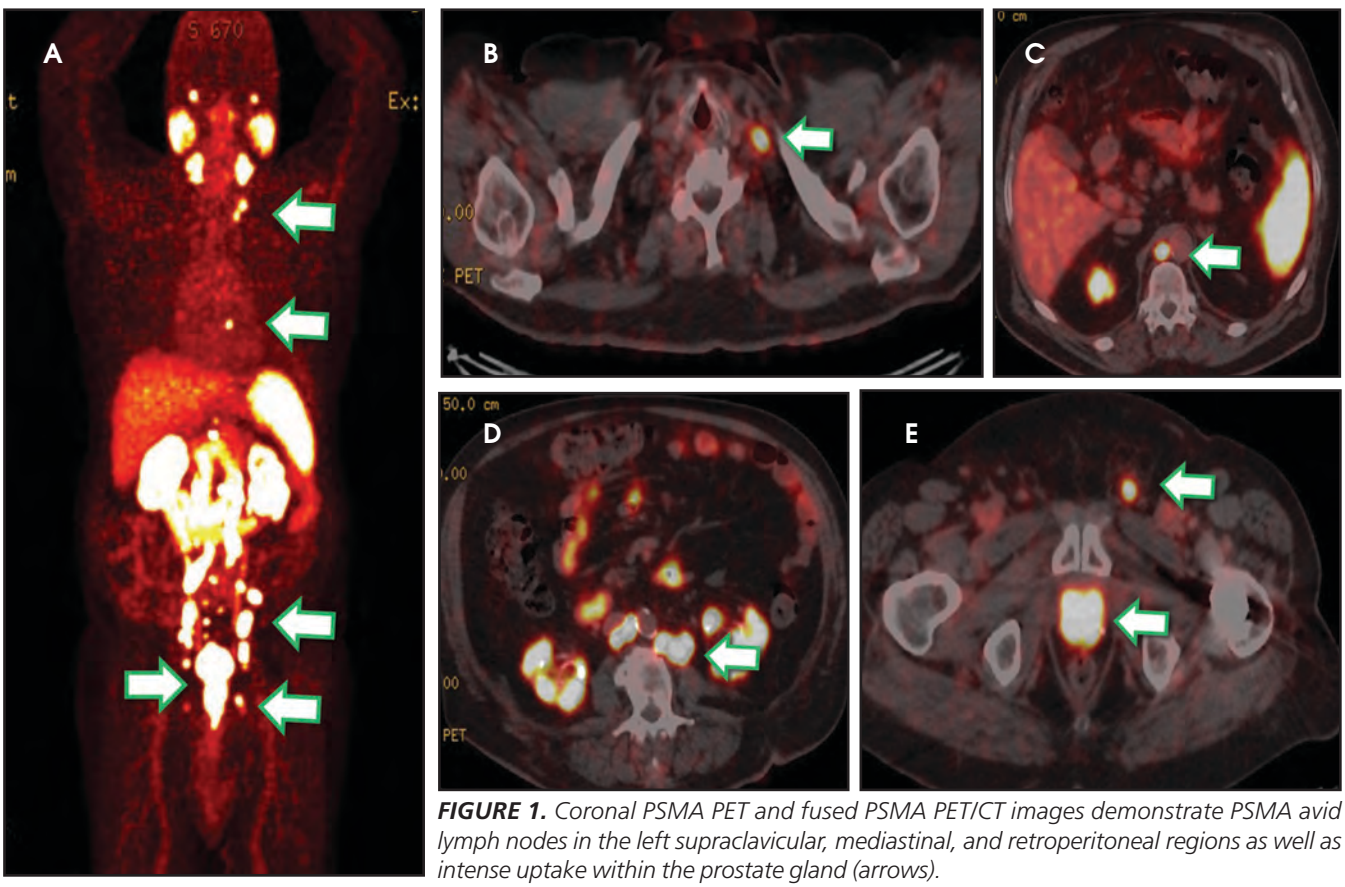


FIGURE 1. *Coronal PSMA PET and fused PSMA PET/CT images demonstrate PSMA avid lymph nodes in the left supraclavicular, mediastinal, and retroperitoneal regions as well as intense uptake within the prostate gland (arrows).*

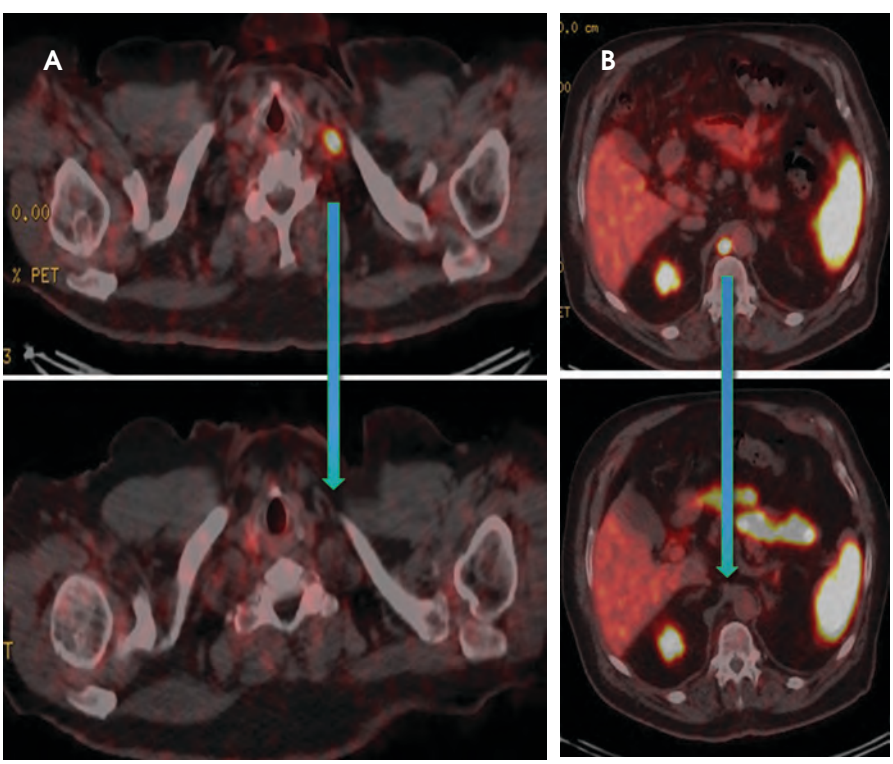


FIGURE 2. *Pretherapy images (upper rows) demonstrate PSMA avid lymph nodes within the left supraclavicular and right retrocrural regions. Resolution of these lymph nodes is noted on the post therapy images (lower rows).*

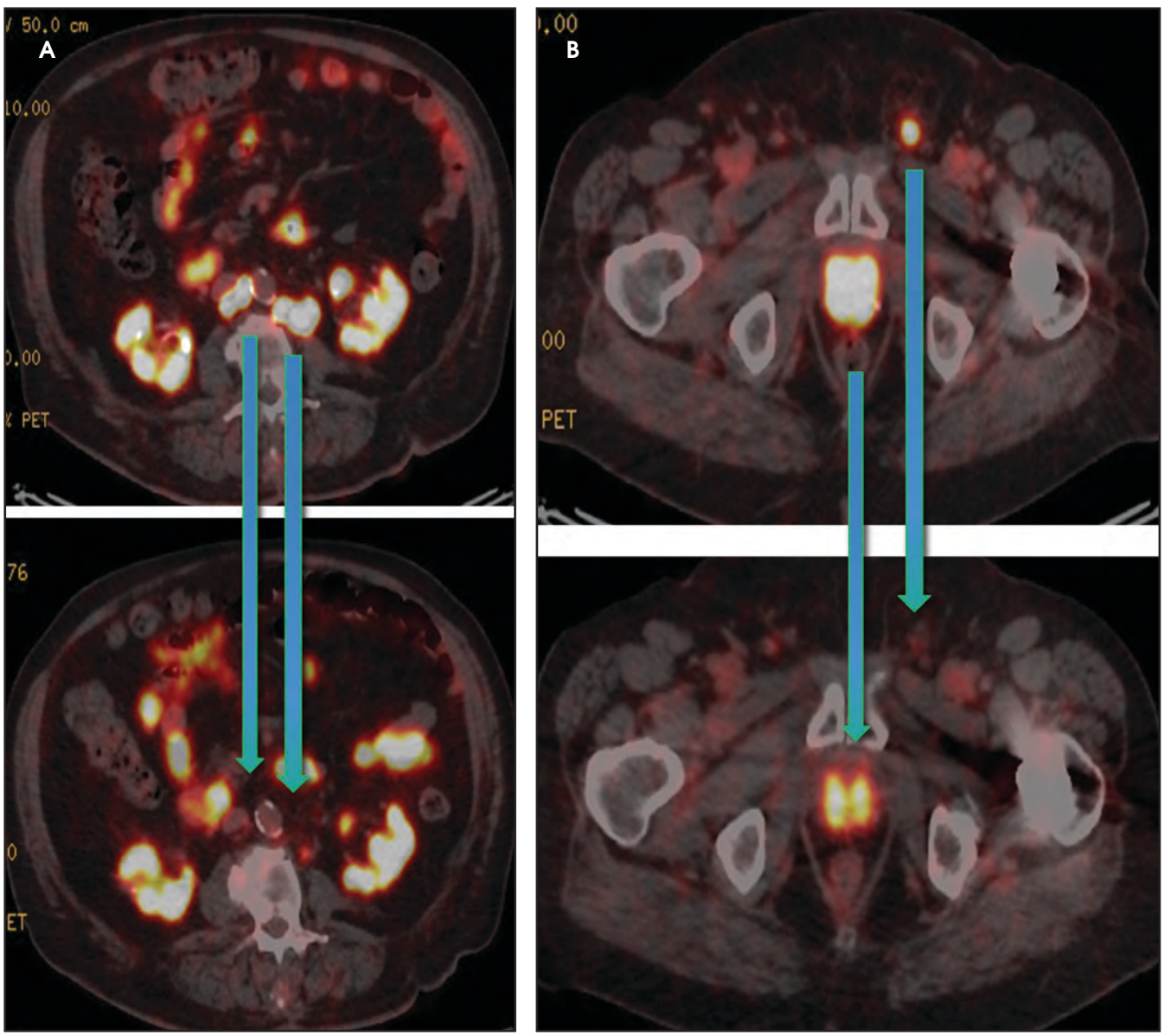


FIGURE 3. *Pretherapy images (upper rows) demonstrate PSMA avid lymph nodes within the aortocaval, left paraaortic and left inguinal regions. Also seen is focal intense uptake localizing to the prostate. Resolution of these lymph nodes is noted on the post therapy images (lower rows). In addition, there is improvement in the level of PSMA uptake localizing to the prostate.*

posterior ilium. This has been managed with an increasing dose of enzalutamide (to 120 mg daily). The latest status from May 2021 is asymptomatic from prostate cancer with stable biochemical profile and PSA of 3.5 ng/ml (PSA doubling time of greater than 12 months).

DISCUSSION

As shown with this case and as described in the literature, ^{177}Lu PSMA therapy provides a good response in patients with nodal predominant disease[1,2]. ^{177}Lu PSMA therapy is well tolerated by elderly patients and is not particularly nephrotoxic, therefore, it can be given judiciously to patients with renal impairment[3,4]. This treatment can be repeated safely and successfully[5].

Also important, the use of novel anti-androgen therapy as an additive treatment post-radionuclide therapy may offer additional options to elderly and renal impaired patients who may not be able to tolerate chemotherapy[2,6].

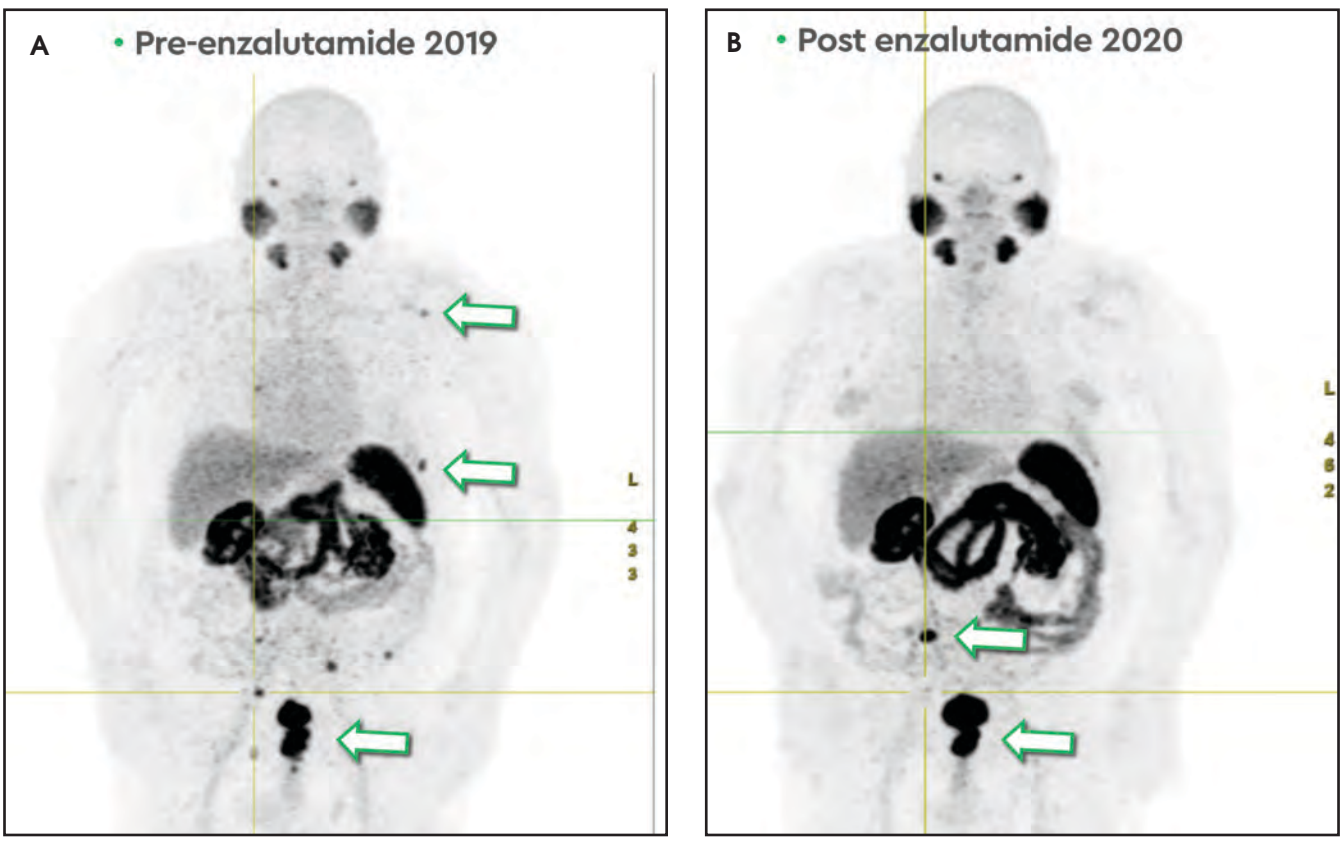


FIGURE 4. *PSMA PET in 2019 prior to introduction of the novel androgen receptor blocker enzalutamide showing multiple small volume PSMA avid osseous metastases and persistent disease in the prostatic bed. In 2020 in the setting of a newly rising PSA while on low dose enzalutamide a repeat PSMA PET revealed persistent disease at the prostatic bed, improvement in almost all previously noted PSMA avid osseous metastases apart from the right posterior ilium, indicating resistant disease to low dose enzalutamide at those sites.*

PSMA PET may also be an aid to help delineate disease not responding to therapeutic interventions[7].

CONCLUSION

PSMA PET can help monitor disease progression and treatment management, as shown in this case. The combination of therapies such as Lu-177 PSMA and enzalutamide may improve efficacy and survival.

REFERENCES

1. von Eyben FE, Singh A, Zhang J, et al. ^{177}Lu-PSMA radioligand therapy of predominant lymph node metastatic prostate cancer. ***Oncotarget***. 2019;10(25):2451-2461. Published 2019 Mar 29. doi:10.18632/oncotarget.26789
2. Emmett L, Willowson K, Violet J, Shin J, Blanksby A, Lee J. Lutetium ^{177} PSMA radionuclide therapy for men with prostate cancer: a review of the current literature and discussion of practical aspects of therapy. ***J Med Radiat Sci***. 2017;64(1):52-60. doi:10.1002/jmrs.227
3. Yordanova A, Becker A, Eppard E, Kürpig S, Fisang C, Feldmann G, Essler M, Ahmadzadehfar H. The impact of repeated cycles of radioligand therapy using [^{177}Lu]Lu-PSMA-617 on renal function in patients with hormone refractory metastatic prostate cancer. Eur J Nucl Med Mol Imaging. 2017 Aug;44(9):1473-1479. doi: 10.1007/s00259-017-3681-9. Epub 2017 Mar 23. PMID: 28337529.
4. Gallyamov M, Meyrick D, Barley J, Lenzo N. Renal outcomes of radioligand therapy: experience of [^{177}Lu]lutetium-prostate-specific membrane antigen ligand therapy in metastatic castrate-resistant prostate cancer. Clin Kidney J.2019 Aug: 14;13(6):1049-1055. doi: 10.1093/ckj/sfz101. PMID: 33391748
5. Aghdam RA, Amoui M, Ghodsirad M, et al. Efficacy and safety of 177Lutetium-prostate-specific membrane antigen therapy in metastatic castration-resistant prostate cancer patients: First experience in West Asia - A prospective study. World J Nucl Med. 2019;18(3):258-265. doi:10.4103/wjnm.WJNM_66_18.
6. Meyrick D, Gallyamov M, Sabarimurugan S, Falzone N, Lenzo N. Real-World Data Analysis of Efficacy and Survival After Lutetium-177 Labelled PSMA Ligand Therapy in Metastatic Castration-Resistant Prostate Cancer. Target Oncol. 2021 May;16(3):369-380. doi: 10.1007/s11523-021-00801-w. Epub 2021 Mar 9. PMID: 33687624.
7. Grubmüller B, Rasul S, Baltzer P, et al. Response assessment using [^{68}Ga]Ga-PSMA ligand PET in patients undergoing systemic therapy for metastatic castration-resistant prostate cancer. Prostate. 2020 Jan;80(1):74-82. doi:10.1002/pros.23919. Epub 2019 Oct 15. PMID: 31614001.

Magnetic Appeal: Changing Treatment Paradigms with MR-Guided Radiation Therapy

Mary Beth Massat

With an armamentarium of nearly every state-of-the-art radiation therapy technology under one roof, Baptist Health's Miami Cancer Institute was one of the first sites to implement an MR-guided linac in April 2018. Michael Chuong, MD, medical director of the Proton Therapy Center, physician director of the MRI-Guided Radiation Therapy Program, and director of Radiation Oncology Clinical Research, was one of the first physicians to treat patients using the new technology.

"The ability to visualize the internal anatomy of patients, not just prior to, but also continuously during treatment, and perform on-table adaptive replanning as needed, is really unique among our other advanced radiation therapy technologies," says Dr. Chuong. "We've tried to push the envelope to benefit patients and that is through significant dose escalation for a large percentage of our patients."

MR-guided radiation therapy (MRgRT), offered through two primary companies – ViewRay (MRIdian) **(Figure 1)** and Elekta (Elekta Unity) **(Figure 2)** – allows users to adjust radiation dose in real-time based on live MR images of the tumor and surrounding anatomy. This MR guidance is "a fundamental paradigm shift that will be more broadly adopted in the future," says Dr. Chuong, "especially as costs and treatment times decrease."

Ms. Massat is a freelance health care writer based in Crystal Lake, IL.

Early Adopters

At Miami Cancer Institute, which uses MRIdian, pancreatic cancer is the primary disease site treated, specifically to escalate dose to an ablative range; the most common dose fractionation schedule is 50 Gy/5 fractions. At the 2021 annual congress of the European Society for Radiotherapy and Oncology (ESTRO), Dr. Chuong presented results of an analysis of 50 patients treated at the institute suggesting that ablative MRgRT could improve long-term local tumor control and overall survival. While the median overall survival after chemotherapy and conventional radiation therapy is about 12 to 15 months, patients in the study achieved median overall survival of 21 months, with a 50% survival rate after 2 years.[1]

Sunnybrook's Odette Cancer Centre was one of the first users of Elekta Unity, initially installing a prototype, says Arjun Sahgal, MD, director of the MR-linac program and deputy chief of radiation oncology. In August 2019, Sunnybrook enrolled its first patient in the MOMENTUM (The Multiple OutcoMe EvaluatioN of radiation Therapy Using the MR-linac) study, which aims to accelerate the technical and clinical development of anatomic and functional MRgRT and facilitate the evidence-based introduction of the MR-linac into clinical practice.[2] Sunnybrook is a founding member of the Elekta MR-Linac Consortium, a collaborative industrial-academic partnership developed to support advancement of the technology) and 1 of

Figure 1. MRIdian MR linac. Photo courtesy of ViewRay

8 international centers involved in MOMENTUM. Although the center is focused on central nervous system tumors, they have treated prostate cancer and will soon treat pancreatic cancer and head and neck patients.

Time and Workload Needs

A disadvantage of current MRgRT therapies is the added time required for treatment. That's primarily because while the patient is on the MR-linac table, the images are acquired, then the tumor is contoured from those daily images, and the treatment plan is adapted as needed. Following treatment plan generation and physics quality checks, the patient is treated. Auto-contouring, faster systems for computation, and migrating to volumetric-modulated radiation therapy (VMAT) should help reduce that time, Dr. Sahgal says.

However, with MRgRT, part of the weakness is also a strength. "The key is you want to be able to treat the tumor of the day," he says. "Even in the brain, we have observed and reported on tumor migration.[3] Understanding that migration during treatment is key to building that next phase of radiation oncology, which is clinical target volume (CTV) margin reduction. The only way we are going to achieve that is by imaging each day prior to radiation delivery with MR. Understanding where the microscopic disease is and how we can shrink the margin safely will lead to less normal tissue being irradiated."

After treating more than 150 brain tumors with the MR-linac, this is precisely what Sunnybrook is doing with the UNITED study: evaluating the safety of reducing CTV margins for glioblastoma patients from 1.5 cm to 5 mm with weekly adaption of the treatment plan.[4] If successful, the next step is incorporating metabolic imaging and voxel-based dose escalation to areas of resistant tumor.

Physician workload also expands with use of the technology. "We no longer work in the background, contouring and reviewing plans for approval, and seeing the patient weekly in review clinics," Dr. Sahgal adds. "We are there in the treatment room, doing the procedure even multiple times during a patient's course of therapy and essentially creating personalized treatments much akin to what a surgeon does. Our role is becoming more complex and in the moment."

Two Systems, Different Approaches

The development of Elekta Unity followed a concept originally proposed by Jan Lagendijk, PhD, and Bas W. Raaymakers, PhD, at University Medical Center (UMC) Utrecht (Netherlands): integrating a linac and MRI by creating a "donut"-type gap

Figure 2. Elekta Unity MR linac by Elekta. Photo courtesy of Sunnybrook Health Sciences Center

within the magnetic field, thus creating a magnetic-field-free zone where the linac is then placed.[5] Elekta collaborated with UMC Utrecht and Philips Healthcare to commercialize that concept, says John Christodouleas, MD, senior vice president of medical affairs and clinical research at Elekta, and a radiation oncologist at the Hospital of the University of Pennsylvania.

The inclusion of a 1.5T MR "opens up the field to a larger breadth of technologies already developed in the diagnostic realm, where 70% of all MRIs are 1.5T," Dr. Christodouleas says. He notes that online-guided radiation therapy represents less than 1% of the global radiation therapy market. Elekta has 42 systems installed or about to go live, 11 of which are in the US.

A benefit of using a higher-field-strength MR system is a greater signal-to-noise ratio, which can increase image quality, reduce background noise and shorten scanning time. "These devices are meant to support adaptive paradigms," he adds. "[MRgRT] is being used anywhere the clinician needs ultraprecision or the capability to adapt to changes in anatomy or biology."

The Elekta Unity delivers 3 distinct adaptive paradigms, explains Dr. Christodouleas. Most people will think about adapting to the anatomy, including the shape and position of the tumor in relationship to surrounding healthy tissue. However, the ability to image the patient in real time during treatment also enables the clinician to see and adapt the actual dosimetry delivered to the patient. Additionally, the clinician can see the biology and adapt treatment to the patient's response.

"We've been adjusting for changes in shape, but dose adaptive and response adaptive are concepts that have been hard to act upon," he says. These are areas of enormous interest in the MR-Linac Consortium and Elekta expects to see a pipeline of clinical trials exploring both concepts.

The MRIdian has a 0.35T MR scanner. While low-field MR systems are not typically used in diagnostic radiology, the lower field strength is advantageous in RT because it avoids the influence of a strong magnetic field on the radiation dose distribution. With a lower-field MR system, users can avoid most of the unavoidable interaction of the strong magnetic field's influence on the radiation dose distribution, explains Martin Fuss, MD, chief medical officer of ViewRay and an oncologist with Radiation Oncology Specialists PC in Portland, OR. Rather than use an existing diagnostic MR scanner,

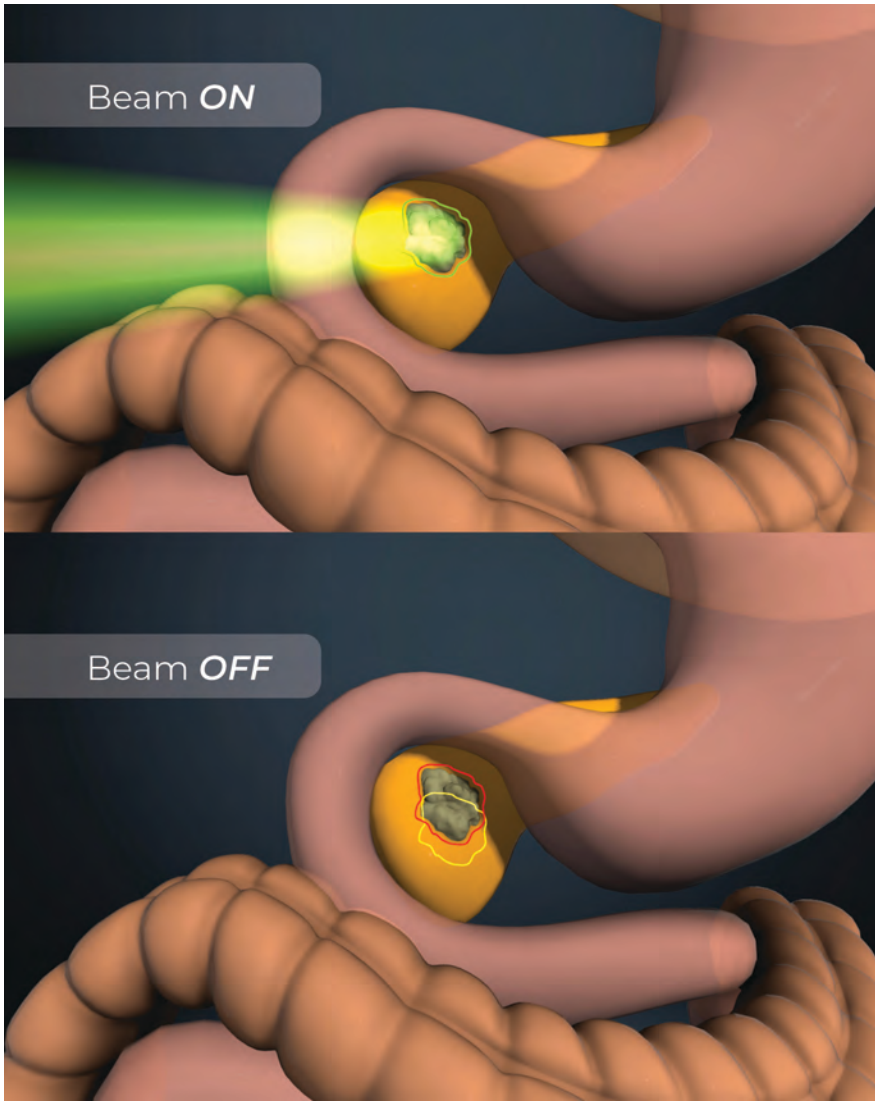


Figure 3. Using MR imaging to detect slight intrafraction motion during beam delivery, MRIdian allows oncologists to visualize this pancreas tumor's edge and surrounding organ position in real time; when tumors move or organs at risk change position, the beam reacts automatically turning radiation beams on and off, to ensure the prescribed doses reach the target while avoiding critical structures. This feature is only available on the MRIdian MR linac. Photo courtesy of ViewRay

ViewRay designed an MRI magnet and integrated it with a linac for the explicit purpose of delivering radiation therapy. It's a compromise, Dr. Fuss adds, between good image quality and maintaining the capabilities of the MRI scanner to enable imaging while the radiation beam is on.

Of the 45 installed and operational MRIdian systems treating patients globally, 18 are in the US. More than 14,300 patients have been treated on MRIdian with clinically reported outcomes in over 3,200 patients. In 2020 in the US, 87% of all treatment courses on MRIdian systems were delivered by stereotactic body radiation therapy (SBRT). Nearly 1 in 4 (23%) of these patients received treatment for pancreatic cancer with 96% of the SBRT fractions adjusted daily using on-table or online adaptive replanning. By comparison, only 12% of plans for treating prostate cancer (18% of patients) are adapted on the day of treatment. For liver lesions (16% of patients) and lung tumors (10% of patients), 41% and 33%, respectively, of all delivered fractions were adapted with the patient on the table.

Routinely Delivering Ablative Doses

The use of ablative doses with MRgRT has become fairly routine at Miami Cancer Institute. Dr. Chuong says patients with no other options after enduring many lines of systemic therapy are now disease free thanks to the higher doses enabled by MRgRT.[6]

Dr. Chuong and colleagues published a retrospective analysis of 35 pancreatic cancer patients,

most with locally advanced disease, who were treated with 5-fraction stereotactic MR-guided adaptive radiation therapy (SMART) in consecutive days. Approximately 91% received induction chemotherapy for several months prior to SMART.[7]

"The 2-year median survival control and progression-free survival numbers are all significantly higher than historical control and approaching the range of what you would expect from surgical resection," says Dr. Chuong.

Dr. Chuong and his colleagues are also evaluating single-fraction ablative radiation therapy for patients with oligometastatic disease in the SMART ONE trial.[8] This prospective trial aims to confirm the feasibility of using MRI guidance to complete ablative treatment to tumors in the chest, abdomen, and pelvis in only 1 fraction vs several, which would be especially beneficial for treatment of multiple oligometastases.

"MR guidance offers significant benefits for treating some oligometastatic tumors, especially given that the randomized data showing the addition of SBRT to systemic therapy improves overall survival," Dr. Chuong says. Considering that oligometastatic lesions may be near radiosensitive organs (eg, the bowel) that are intolerant of high doses, he believes MRgRT will help widen the population cohort eligible for ablative radiation therapy and provide safe, effective outcomes.

An important differentiator of MRIdian is the ability to perform on-table adaptive radiation therapy along with the system's real-time, soft-tissue tracking and automated beam gating features. "With the integration of an MR scanner into a radiation dose delivery device, clinicians now have the ability to keep looking at the target while they deliver the dose," says Dr. Fuss. "That is critical, because for the first time we don't have to assume that the target resides in the right location relative to the damaging radiation beam. We can confirm that location multiple times a second."

This capability changes the decades-old paradigm that nearby normal tissues limit the ability to deliver dose. "Now, we are able to break that paradigm and stay away from normal tissue during treatment," he says. "We can now control depositing damaging doses to tumor tissue without causing toxicities to nearby organs at risk. This is only possible due to the integrated soft-tissue tracking and associated automated beam gating to either switch the radiation beam on or pause it." **(Figure 3)**

Although the capability to perform on-table adaptive RT requires direct physician and physicist involvement during treatment, it has enabled Dr. Chuong to safely prescribe ablative doses. Over time, Miami Cancer Institute has become more efficient with this new workflow, which initially could take up to 90 minutes but now is routinely completed in 60 minutes. To help address the need for replanning, Miami Cancer Institute has extensively trained senior therapists on anatomy to aid the contouring process, which is then reviewed by the physician.

In pancreatic cancer patients treated with MRgRT, nearly all have had their plans reoptimized while on the table because critical organ constraints would otherwise have been exceeded if using the original treatment plan. "The ability to adapt is important," Dr. Chuong explains. "Even if you don't adapt, the confidence that the dose is safe to deliver and the understanding of how those changes in anatomy can affect the plan are key."

For example, he prescribed 50 Gy/5 fractions to a metastatic lymph node next to the brachial plexus because he had the ability to adapt and contour the dose each day based on the shoulder position. "If I was treating this patient on any other machine, I almost certainly would not have prescribed that dose because I wouldn't have had the certainty and confidence to do so. That patient had a complete response and remains disease free 3 years later," he says.

Advancing MRgRT

Dr. Sahgal and co-authors recently demonstrated the feasibility of using a 1.5T MR-linac for in vivo chemical exchange saturation transfer (CEST), a type of metabolic imaging, of central nervous system tumors during radiation therapy to monitor treatment response. Changes were observed in individual patients over time, including between treatment fractions, as well as differences between high- and low-grade tumors. The authors also reported significant CEST signal contrast between the tumor and contralateral normal-appearing white matter (cNAWM) regions.[9]

"We are getting to the point of incorporating functional metabolic imaging beyond diffusion," says Dr. Sahgal. "Metabolic imaging, in addition to high-quality diffusion imaging, will allow us to really drill down to the cellular level of what is happening in these tumors [during treatment] to create a biologically based adaptive MRgRT paradigm."

Currently, hundreds of technical or clinical projects on Elekta Unity are in progress. These include the

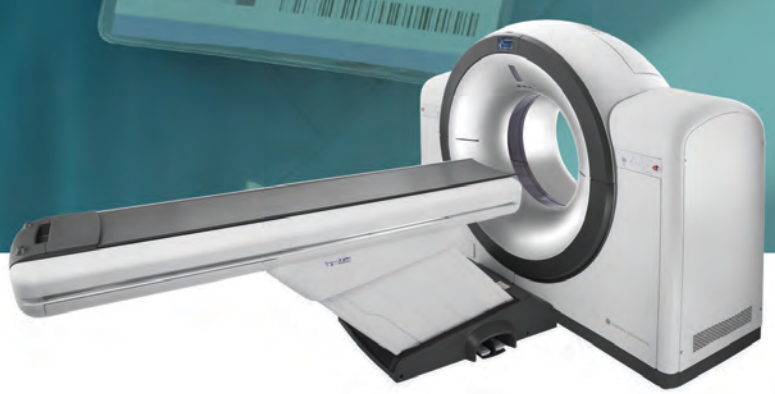
FUJIFILM
Value from Innovation

People-First Design.

For the Radiation Therapist, your patient's positive experience builds trust during treatment.

Persona CT delivers an intuitive design, 64 slice, 85cm big bore, for optimized speed, comfort and accuracy.

Be Visionary.



#VisionaryCT

Persona CT

Hermes study at the Royal Marsden NHS Foundation Trust investigating the safety of using SBRT to deliver 2 fractions over 8 days vs 5 fractions over 10 days for localized prostate cancer,[10] and the MR Adaptor at MD Anderson to compare the use of weekly adapted intensity-modulated radiation therapy (IMRT) to standard nonadapted IMRT in patients with low-risk human-papilloma-virus-positive oropharyngeal cancer.[11]

In addition to implementing MR safety policies and procedures, clinicians can expect a learning curve regarding tracking structures or boundaries with MR instead of CT images. To assist, ViewRay and Miami Cancer Institute are launching an advanced user group and training course for MRIdian focused on workflow, efficiency, and improvements for on-table adaptive therapy.

According to Dr. Fuss, two areas where ViewRay is enhancing the system are in improving workflow and developing site-specific coils. The company is also working with clinical partners to further extend functional imaging capabilities, such as recently licensing diffusion-weighted imaging capabilities from UCLA that enable b values up to 800.

"Many of the current system enhancements were first brought to us or had been requested by our clinical partners," says Dr. Fuss. "For example, the team at UCLA first demonstrated the ability to acquire DWI data on the MRIdian. The associated clinical data was so compelling, that we licensed the sequence and made it available to our install base."

Elekta will be adding enhancements to its MR protocol library with 7 new sequences intended to address specific clinical problems, says Dr. Christodouleas. These include an 18-second T2 with breath hold for thoracic imaging that leverages Philips Healthcare's Compressed SENSE acceleration technique. The next software upgrade will also support gating functionality for motion management in 3 dimensions.

References

1) Chuong M. Long-term outcomes of MR-guided SABR & on-table adaptive replanning for unresectable pancreas cancer. ESTRO 2021. Presentation Number: OC-0415. Accessed August 31, 2021. https://www.estro.org/Congresses/ESTRO-2021/502/profferedpapers25-uppergi/3760/long-termoutcomesofmr-guidedsabr-on-tableadaptiver

2) NIH U.S. National Library of Medicine. The MOMENTUM Study: The Multiple Outcome Evaluation of Radiation Therapy Using the MR-Linac Study (MOMENTUM). Accessed August 30, 2021. https://clinicaltrials.gov/ct2/show/NCT04075305

3) Stewart J, Sahgal A, Lee Y, et al. Quantitating interfraction target dynamics during concurrent chemoradiation for glioblastoma: a prospective serial imaging study. *Int J Radiat Oncol Biol Phys.* 2021 Mar 1;109(3):736-746. doi:10.1016/j.ijrobp.2020.10.002

4) UNIty-Based MR-Linac Guided AdapTive RadiothErapy for High GraDe Glioma: a phase 2 trial (UNITED). Accessed August 30, 2021. https://clinicaltrials.gov/ct2/show/NCT04726397

5) Lagendijk JJ, Raaymakers BW, Raaijmakers AJ, et al. MRI/linac integration. *Radiother Oncol.* 2008 Jan;86(1):25-9. doi:10.1016/j.radonc.2007.10.034

6) Chuong M, Alvarez D, Romaguera T, et al. (2020). Case report of ablative magnetic resonance-guided stereotactic body radiation therapy for oligometastatic mesenteric lymph nodes from bladder cancer. *Ther Radiol Oncol.* 2020;4:20.

7) Chuong MD, Bryant J, Mittauer KE, 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 Mar-Apr;11(2):134-147. doi: 10.1016/j.prro.2020.09.005. Epub 2020 Sep 16. Erratum in: *Pract Radiat Oncol.* 2021;11(3):e354.

8) NIH U.S. National Library of Medicine. Stereotactic MRI-guided Adaptive Radiation Therapy (SMART) in One Fraction (SMART ONE). Accessed August 30, 2021. https://clinicaltrials.gov/ct2/show/NCT04939246?term=SMART&cond=cancer&cntry=US&state=US%3AFL&draw=2&rank=5

9) Chan RW, Lawrence LSP, Oglesby RT, et al. Chemical exchange saturation transfer MRI in central nervous system tumors on a 1.5 T MR-Linac. *Radiother Oncol.* 2021;162:140-149. doi:10.1016/j.radonc.2021.07.010. Epub ahead of print.

10) NIH U.S. National Library of Medicine. Hypofractionated Expedited Radiotherapy for Men With localisEd proState Cancer (HERMES). Accessed August 30, 2021. https://clinicaltrials.gov/ct2/show/NCT04595019

11) NIH U.S. National Library of Medicine. Trial of Magnetic Resonance Imaging Guided Radiotherapy Dose Adaptation in Human Papilloma Virus Positive Oropharyngeal Cancer. Accessed August 30, 2021. https://www.clinicaltrials.gov/ct2/show/NCT03224000

Radiation Therapy in the Treatment of Plantar Fibromatosis – Two Clinical Cases of Recurrent Disease

Sara Couto Gonçalves, MD; Bruno Fernandes, MD; João Casalta-Lopes, MD; Maria Corbal, MD; Margarida Borrego, MD

Case Summary

Case 1

A 49-year-old woman diagnosed with right plantar fibromatosis underwent surgery in 2010. She presented with recurrence in 2018 and was treated with local betamethasone injections due to pain, without improvement. In December 2019, she underwent surgery with gross total excision and closure with skin graft. The postoperative course was complicated with dehiscence of the graft and closure by secondary intention. In September 2020, the patient presented with pain that impaired walking and had progressive growth of the lesion on the right plantar region (**Figure 1A**). She was referred to the radiation therapy (RT) department for evaluation.

Case 2

A 63-year-old woman diagnosed with left plantar fibromatosis underwent local excisions in 2017, 2018 and 2019. The last surgical excision revealed focal involvement of the lateral and deep margins by the lesion. In September 2020, the patient presented with worsening of the pain (patient rated as 10/10), without relief with physiotherapy. She was referred to the RT department for evaluation (**Figure 2A**).

A planning computed tomography (CT) was done in both patients in a ventral decubitus position with adequate immobilization using a thermoplastic mask (**Figures 3A and 3B**) connected to a base plate. Under the treated foot was a foam support individually adapted to the patient's anatomy for stability and comfort. External marks were placed on the mask for laser alignment. Both treatments were done with 6-Mv photons and a 5-mm bolus covering the plantar region, with a gross tumor volume (GTV) to clinical target volume (CTV) margin of 5 to 10 mm, and CTV to planning target volume (PTV) margin of 3 mm (**Figure 4**). The CTV was delineated to encompass all possible disease, both microscopic disease and disease that might have been mistaken for fibrosis and postsurgical changes. In an ideal planning, with MRI images, or in a patient without previous surgery, the planning would be done with only a margin from the GTV to the PTV. A total dose of 30 Gy was prescribed in 2 courses of 15 Gy/ 5 fractions/ 1 week separated by 6 weeks. The patients underwent treatment without relevant side effects during treatment. However, the first patient reported acute plantar pain 3 weeks after completing the total treatment, which improved after a few days without the need for pain treatment. On the first appointment after 3 months of treatment, both presented with almost complete resolution of the initial complaints of pain and walking impairment, and diminution of the visible lesions. At follow-up appointments 6 months after the end of treatment, both patients presented with maintenance of clinical response, without worsening of pain, and stable lesions with drier skin (**Figures 1B and 2B**).

Discussion

Plantar fibromatosis (PF), also known as Morbus Ledderhose or Ledderhose disease, is a rare benign hyperproliferative disorder of the plantar fascia. It is histologically and clinically identical to Dupuytren's disease of the hand, and the two conditions may coexist in up to 25%

Affiliations: Dr. Goncalves and **Dr. Fernandes** are residents, **Dr. Casalta-Lopes** and **Dr. Corbal** are specialists, and **Dr. Borrego** is a specialist and head, all in the Department of Radiation Oncology, Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal. **Disclosure:** The authors have no conflicts of interest to disclose. None of the authors received outside funding for the production of this original manuscript and no part of this article has been previously published or presented elsewhere. The patients have provided informed consent for the publication of this case report.

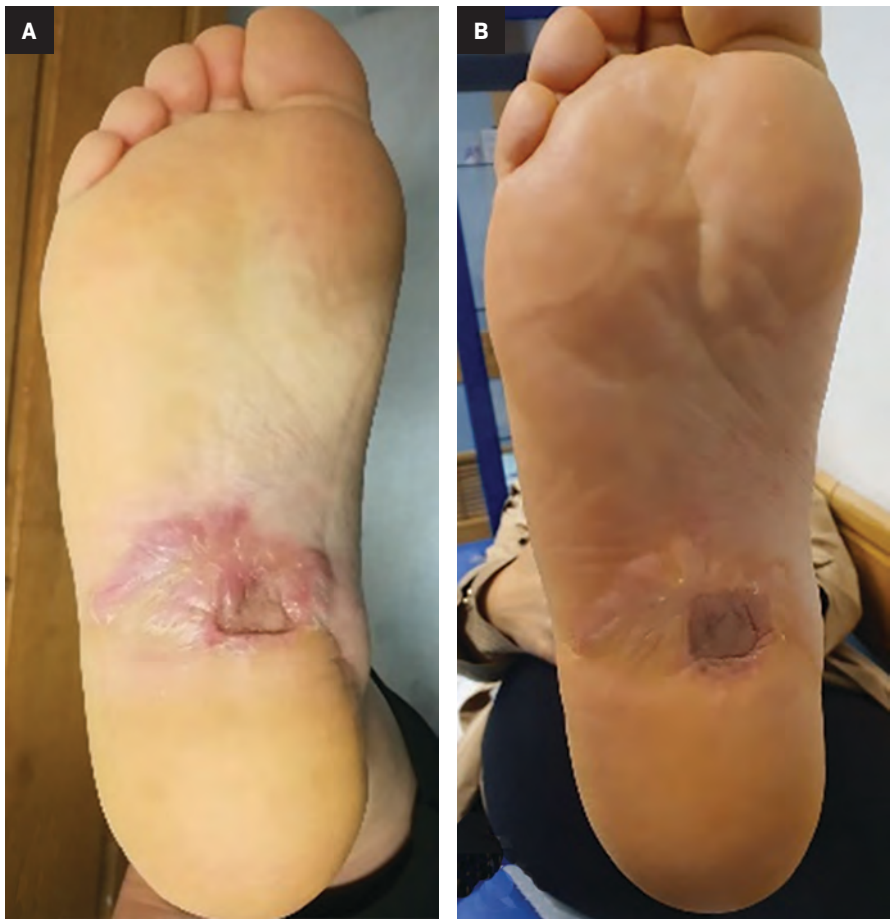


Figure 1. Case 1: Plantar fibromatosis visible lesions on the first appointment (A) and 6 months after treatment (B).

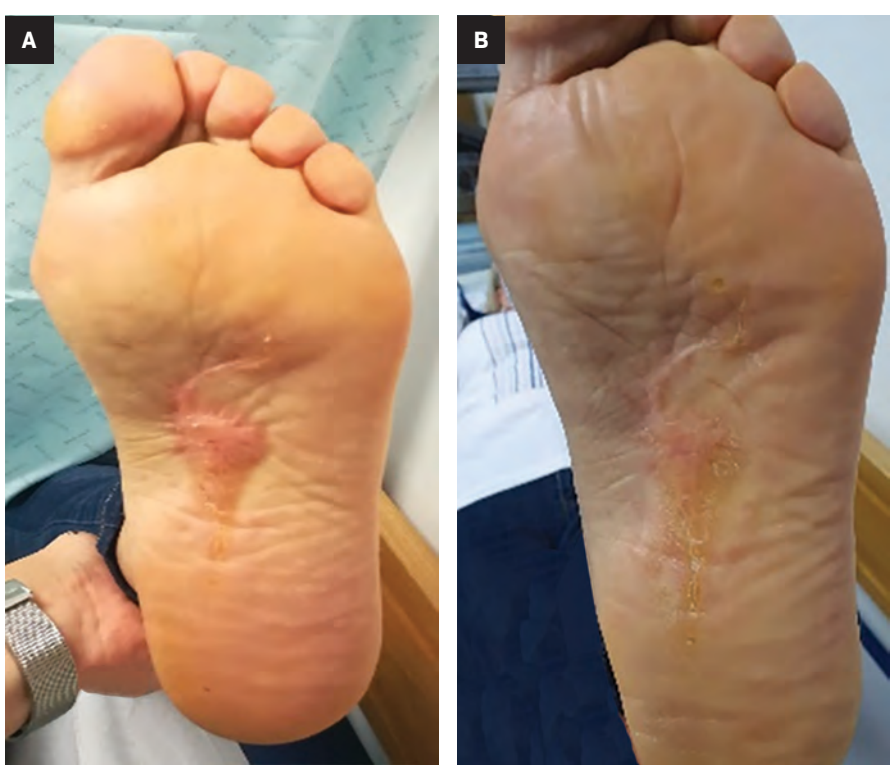


Figure 2. Case 2: Plantar fibromatosis visible lesions on the first appointment (A) and 6 months after treatment (B).

Figure 3. Immobilization with a thermoplastic mask for extremities used in planning computed tomography (CT) in both cases.

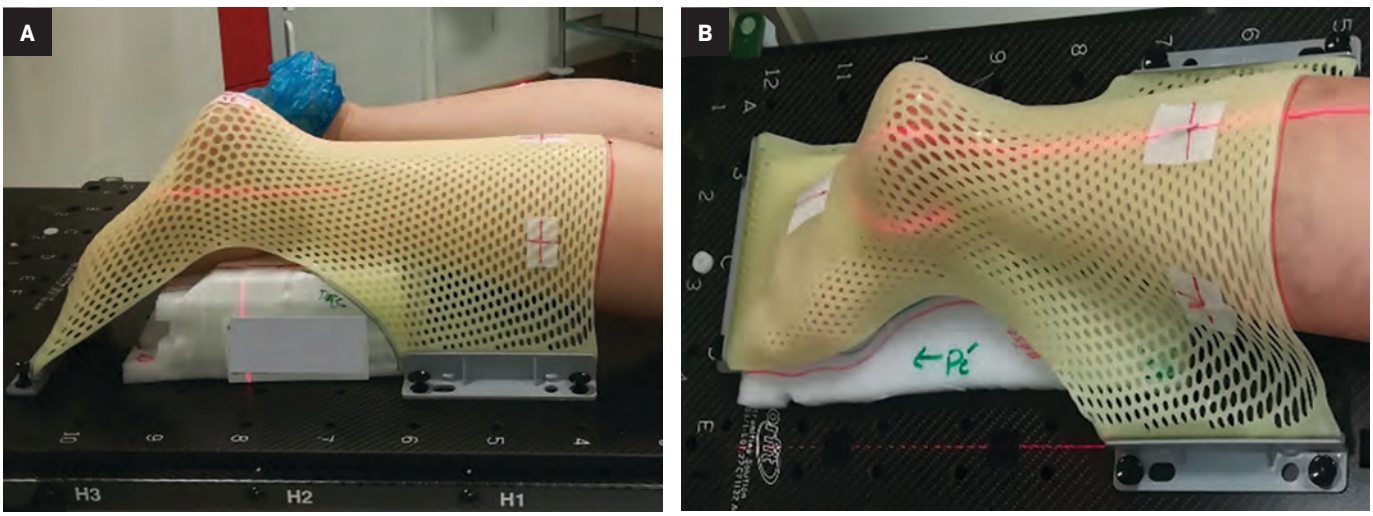
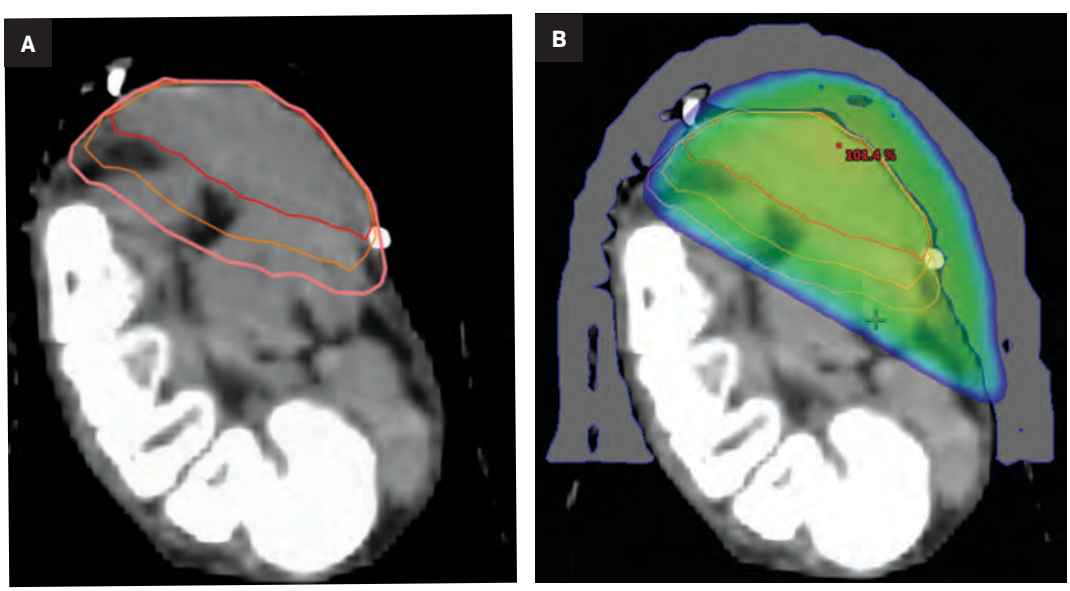


Figure 4. Gross tumor volume (GTV) (red), clinical target volume (CTV) (orange), and planning tumor volume (PTV) contouring (A). Treatment planning with bolus, with 95% of the prescribed dose represented in color wash (B).



to 35% of cases.[1,3-5] The underlying cause is unknown, but there is an association with nicotine and alcohol abuse, diabetes mellitus, anti-epileptic use and genetic factors.[1,4] Additionally, a hereditary role has been suggested as familial occurrence of the disease has been reported.[2] It appears to be more common among Caucasians and some reports suggest that it affects males up to twice as often. Bilateral disease can be observed in approximately 25% of cases.[3-5]

The pathogenesis of PF can be divided into three phases: 1) the initial proliferative phase, with proliferation of fibroblasts and development of nodules and cords; 2) the involutional phase, with differentiation of fibroblasts into myofibroblasts; and 3) the residual phase, with a predominance of collagen fibers, in which the normal type I collagen is replaced by type III collagen.[3,6]

The symptoms usually start in the third to fourth decade of life,[1,4,5] and it presents as single or multiple nodules on the central and medial part of the plantar fascia that may cause tension with pain, and disability in walking and fitting shoes. PF contractures of the toes occur less often.[1,3,4]

The main conservative options for treatments are symptom-oriented and include physiotherapy, orthotic devices, and local steroid injections. Weight loss may also be beneficial.[1,3-5] If symptomatic, surgical treatment is frequently recommended, and may range from local

Table 1. Studies Reporting the Use and Outcomes of Radiation Therapy in Plantar Fibromatosis

AUTHOR(S), YEAR	PATIENTS / SITES	DOSE FRACTIONATION	FOLLOW-UP	CINICAL OUTCOME
Seegenschmiedt et al,[4,5] 2003	25 / 36	2 RT courses of 5 x 3 Gy, total dose of 30 Gy	38 months (median)	No progression; 78% clinical improvement; 22% clinical stability
De Bree et al,[2] 2004	9 / 11	Surgery vs surgery+RT (total 60 Gy) on the recurrent disease	unknown	Recurrence rate: 67% with surgery vs 17% with surgery+RT
Heyd et al,[3] 2010	24 / 33	2 RT courses of 5 x 3 Gy, total dose of 30 Gy, 6-8-week break (28 sites); 2 single courses of 4 Gy repeated at 4-week intervals, total 24-32 Gy (5 sites)	22.5 months (median)	33.3% complete response; 54.5% partial response; 12.1% stable disease
Seegenschmiedt et al,[4] 2012	158 / 270	2 RT courses of 5 x 3 Gy, total dose of 30 Gy, 12-week break vs non-irradiated	68 months (mean)	With RT: 92% complete or partial response (vs 62%), 8% progressive disease (vs 38%), 5% salvage surgery (vs 21%), 79% symptom improvement (vs 19%)

or wide excision with a recommended resection margin of 2 to 3 cm, to subtotal or radical fasciectomy with or without skin grafting.[1,3,4] Recurrence rates after surgery are high, and surgery is also associated with significant morbidity such as delayed wound healing, chronic pain, and poor functional outcomes.[1,2,4]

There are data that report the use and outcomes of RT in the treatment of PF (**Table 1**), mainly from Europe. In some regions, such as North America, the use of RT for this and other benign disease are generally frowned upon, in part due to fear of litigation, and in part because patients typically have surgical consultations before any others.

One study analyzed retrospectively the results of 25 patients (36 affected feet) following 2 RT courses of 5 x 3 Gy for a total dose of 30 Gy. With a median follow-up of 38 months (range: 12 to 67), none presented with disease progression, and 28 feet had regression of pain and tenderness, with stable symptoms in 8 feet.[4,5]

A small Dutch retrospective study reviewed the outcomes of 9 patients (11 feet) with PF. In all, the primary treatment was surgery alone, with a total of 26 operations and a recurrence rate of 90%. In the recurrent disease treated with surgery alone, the recurrence rate was 6/9 (67%) and in the patients treated with the combination of surgery and adjuvant RT (total of 60 Gy), the rate was 1/6 (17%). Two patients in the surgery with RT group became dystrophic, with foot pain and impaired walking.[1,2]

A German multicenter retrospective study reported results from 24 patients (33 feet), treated with 2 RT courses of 5 x 3.0 Gy separated by 6 weeks for a total dose of 30.0 Gy (n = 20) or 2 single fractions of 4.0 Gy on consecutive days, repeated at intervals of 4 weeks to cumulative doses ranging from 24 to 32 Gy (n = 4). Only 2 patients had previously undergone surgery and presented with recurrent disease. All of the others had been prescribed orthotics or oral anti-inflammatory drugs. With a median follow-up of 22.5 months (range: 6 to 76), no clinical progression was observed in the number or size of the lesions or in subjective associated clinical symptoms; 33% showed a complete response, 54.5% a partial response and 12.1% stable disease.[3]

More recently, a single-institution, prospective, nonrandomized cohort study reported results of 158 patients (270 feet) with symptomatic progressive disease. Of these, 91 patients (136 feet) underwent RT and 67 patients (134 feet) did not. The PTV was defined as palpable disease with a 2 cm margin. The dose delivered was 2 courses of 15 Gy / 5 fractions over 1 week, with a 12-week break between courses, for a total dose of 30 Gy / 10 fractions. With a mean follow-up of 68 months (range: 24 to 160), 92% of the irradiated group had stable clinical gross disease or reduction of the lesion size (complete or partial response) (vs 62% in the nonirradiated [NI] group). Eight percent developed progressive disease (vs 38% in the NI group) and 5% underwent salvage surgery (vs 21% in the NI group). Improvement of symptoms was seen in 79% following RT (vs 19% in the NI group). Acute side effects occurred in 26.5%, with slight erythema and/or dry desquamation (21.3%), a diffuse erythema with areas of moist desquamation (5.0%), and late effects with dryness or fibrosis (16.2%).[4]

The suggested radiobiological mechanism of RT is based mostly on the inhibition of the proliferation of the fibroblasts and myofibroblasts, known to be the cause of the symptoms and progression of the disease. Thus, the optimal time for the use of RT is in actively progressing disease.[3,4,6]

The RT target volume should include all of the detectable or palpable gross lesions with a minimum margin of 3 to 5 mm[5] to 10 mm,[6,7] and the treatment can be delivered using orthovoltage photons or electrons.[1,5,6,7] Individual shielding with protection of the surrounding normal soft tissues is advised.[5,6]

Different dose schemes are described, such as: a single dose of 2 to 3 Gy,[5] and 2 single fractions of 4.0 Gy on consecutive days, repeated at intervals of 4 weeks to cumulative doses from 24 to 32 Gy.[3] Also described is the use of a total dose of 15 to 21 Gy,[5,6] or 60 Gy,[2] in 5 fractions per week. However, the scheme with a total dose of 30 Gy in 2 separated courses of 15 Gy in 5 fractions/ week is the most reported. The interval between courses varies among authors, with most describing a 6-[3,6] to 12-week break.[1,4]

The described acute side effects of RT are generally mild, including mainly radiation dermatitis, hyperpigmentation and edema.[3] Dryness and fibrosis are reported as late side effects.[1,3,4,6] There is a theoretical risk of radiation-induced skin cancer, which decreases with the age of the patient at the time of treatment; however, this has not been formally demonstrated.[1,4,6] The risk of irradiated bone fracture and foot dystrophia appears to be associated with higher RT doses.[2]

Conclusions

The underlying cause of PF remains unknown. Although there is no standardized treatment approach, surgical management is often recomended when conservative local therapies fail. However, surgery is rarely effective and often leads to poor functional outcomes and wound complications. In the reported data available, RT seems to be a well-tolerated and effective treatment modality, with good local control and symptomatic benefit. Our results, while anecdotal, coincide with the RT data reviewed. RT should be a first consideration for failure of initial conservative management.

References

1) Taylor R, Hatfield P, McKeown S, et al. A review of the use of radiotherapy in the UK for the treatment of benign clinical conditions and benign tumours. The Royal College of Radiologists. *Clin Oncol.* 2015;1:115.

2) De Bree E, Zoetmulder F, Keus R, et al. Incidence and treatment of recurrent plantar fibromatosis by surgery and postoperative radiotherapy. *Am J Surg.* 2004;187(1):33-38.

3) Heyd R, Dorn A, Herkströter M, et al. Radiation therapy for early stages of morbus Ledderhose. *Strahlenther Onkol* 2010;186(1):24-29.

4) Seegenschmiedt MH, Wielpuetz M, Hanslian M, et al. Long-term outcome of radiotherapy for primary and recurrent Ledderhose disease (chapter 50). In: Eaton C, Seegenschmiedt MH, Bayat A, Gabbiani G, Werker P, Wach W, eds. Dupuytren's disease and related hyperproliferative disorders. Springer-Verlag; 2012; 409-27.

5) Seegenschmiedt MH, Micke O, Niewald M, et al. DEGRO guidelines for radiotherapy on non-malignant disorders. Part III: hyperproliferative disorders. *Strahlenther Onkol.* 2015;191:541-548.

6) Grenfell S, Borg M. Radiotherapy in fascial fibromatosis: a case series, literature review and considerations for treatment of early-stage disease. *J Med Imag Radiat Oncol.* 2014;58 641-647.

7) Seegenschmiedt MH, Micke O, Muecke R. Radiotherapy for non-malignant disorders: state of the art and update of the evidence-based practice guidelines. *Br J Radiol.* 2015;88:20150080.

Efficacy of Stereotactic Body Radiation Therapy in Recurrent Intrahepatic Cholangiocarcinoma

Marina Amorim, MD; Catarina Silva, MD; Carlos Fardilha, MD; Carolina Carneiro, MD; Sónia Vilaça, MD; Guilherme Campos, MD; Cármen Costa, MD; Paulo Costa, MD

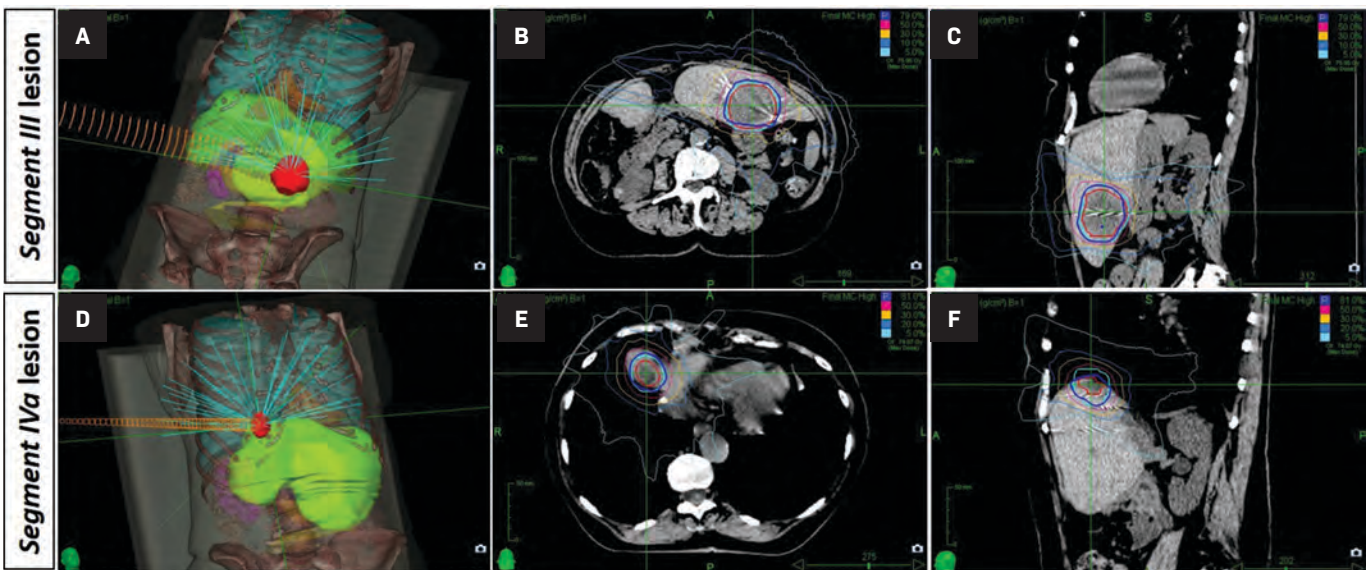
Case Summary

An 81-year-old woman was referred to the hospital in January 2017 with nausea, progressive worsening anorexia, and weight loss of about 6 kg in one year. A computed tomography (CT) scan showed a 9-×-6.5-cm mass in the right hepatic lobe involving the right branch of the portal vein, and a slight ectasia of the intrahepatic bile ducts. Hepatic biopsy revealed a histological diagnosis of cholangiocarcinoma. The patient underwent percutaneous portal embolization in February 2017 followed by right hepatectomy extended to segment I in April 2017. Histopathological examination revealed a diagnosis of intrahepatic cholangiocarcinoma (ICC), stage *p*T2G2N0R0 (AJCC 8th edition staging manual).[1] She remained asymptomatic and with no signs of recurrence until January 2019 when she appeared with anorexia, nausea and weight loss of about 3 kg over a month. Laboratory study revealed an elevation of the tumor marker carbohydrate antigen (CA 19-9) (109.30 U/mL) and gamma-glutamyltransferase (GGT) (80 U/L). Carcinoembryonic antigen (CEA) was not altered. Abdominal MRI showed two focal hepatic lesions, one measuring 4.2 cm in segment III, and the other measuring 1.7 cm in segment IVa. At this point, the patient refused systemic treatment with palliative chemotherapy and, after a multidisciplinary board meeting, it was decided to locally treat both lesions with stereotactic body radiation therapy (SBRT). Two weeks after ultrasound-guided placement of fiducial markers, the patient underwent SBRT with a Cyberknife system (Accuray Incorporated) directed to the segment III liver lesion, at a dose of 60 Gy in 5 fractions of 12 Gy each, on alternate days. Five days after concluding treatment of segment III, she initiated SBRT of the segment IVa lesion, at a dose of 60 Gy, in 3 fractions of 20 Gy each, on alternate days (**Figure 1**). A 5-fractionation scheme was adopted for the segment III lesion to fulfill radiation dose constraints for adjacent normal tissues, according to *UK Consensus on Normal Tissue Dose Constraints for Stereotactic Radiotherapy*.[2] Planning target volume (PTV) for the segment III lesion was 84.87 cm^3 and for segment IVa was 17.09 cm^3. Radiation plans were prescribed to the isodose line that provided greater than 95% coverage of the PTV. The prescription isodose line was 79% and 81%, for segment III and IV lesions, respectively. The Cyberknife Synchrony Respiratory Tracking System was used to continuously monitor respiratory movements and correlate the data with movements of a fiducial-marked target lesions.

The patient concluded SBRT treatment in April 2019 uneventfully and with good tolerance. Subsequently, she maintains 6-monthly imaging and laboratory surveillance. Total follow-up time since SBRT was 23 months. At the last follow-up date (March 2021), the patient had no signs of gastrointestinal, skin or hematologic toxicity, with evidence of gradual remission of the hepatic segment III lesion and total disappearance of the hepatic segment IVa lesion. Furthermore, she has no signs of local recurrence or metastasis,

Affiliations: Dr. Amorim and **Dr. Silva** are residents in the Department of Radiation Oncology, Hospital de Braga, Portugal. **Dr. Fardilha** is a board-certified specialist in the Department of Radiation Oncology, Hospital de Braga, and Department of Radiation Oncology – Júlio Teixeira SA at CUF Institute of Porto, Portugal. **Dr. Carneiro** is a board-certified specialist in the Department of Radiology, Hospital de Braga, Portugal. **Dr. Vilaça** is a board-certified specialist in the Department of General Surgery at Hospital de Braga, Portugal. **Mr. Campos** is a medical dosimetrist in the Department of Radiation Oncology – Júlio Teixeira SA at CUF Institute of Porto, Portugal. **Dr. Cármen Costa** is a board-certified specialist and **Dr. Paulo Costa** is the department chair, both in the Department of Radiation Oncology at Hospital de Braga, and Department of Radiation Oncology – Júlio Teixeira SA at CUF Institute of Porto, Portugal.
Disclosure/informed consent: The authors have no conflicts of interest to disclose. None of the authors received outside funding for the production of this original manuscript and no part of this article has been previously published elsewhere. The patient has provided informed consent for the publication of this case report.

Figure 1. Three-dimensional reconstruction of beam geometries of a Cyberknife treatment plan for hepatic segment III (A) and segment IVa (D) lesions, and 2-dimensional axial (B and E) and sagittal (C and F) images of a Cyberknife treatment plan with isodose curves.



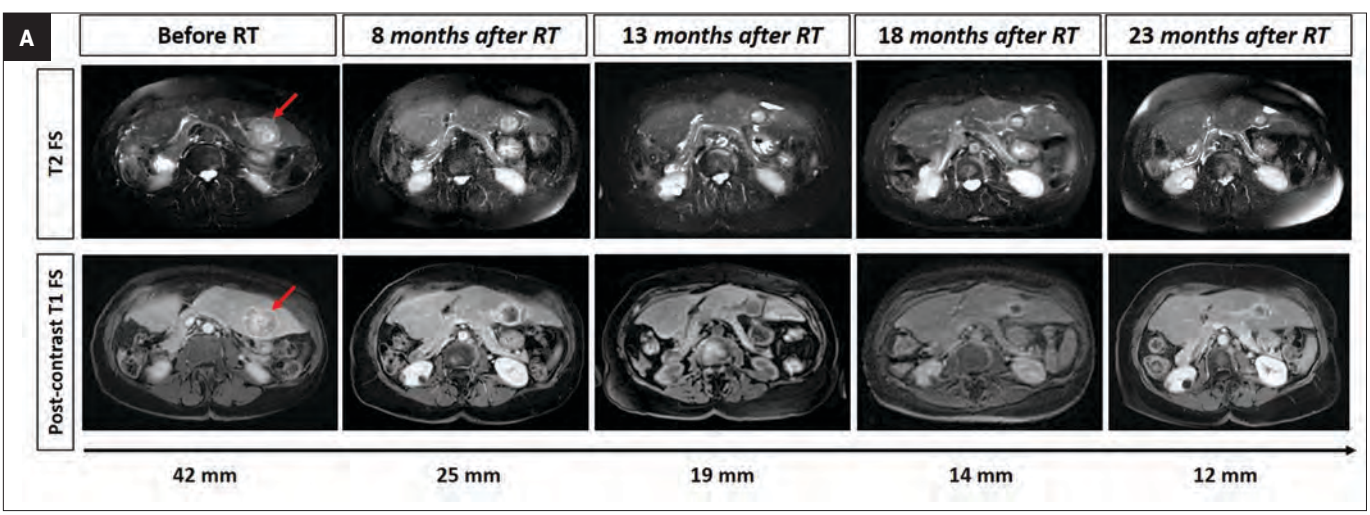


Figure 2. Abdominal MRI images depicting the two liver lesions before and after radiation therapy (segment III liver lesion [A]; segment IVa liver lesion [B]). Both lesions were easily detected in pre-RT MRI. After treatment, the largest lesion (A) showed a progressive volumetric reduction and the smallest lesion (B) disappeared. Note the dysmorphic liver due to previous hepatectomy with the usual hypertrophy of the remaining parenchyma. (Red arrow – lesion identifier, red dashed circle – previous lesion location, FS – fat saturation technique).

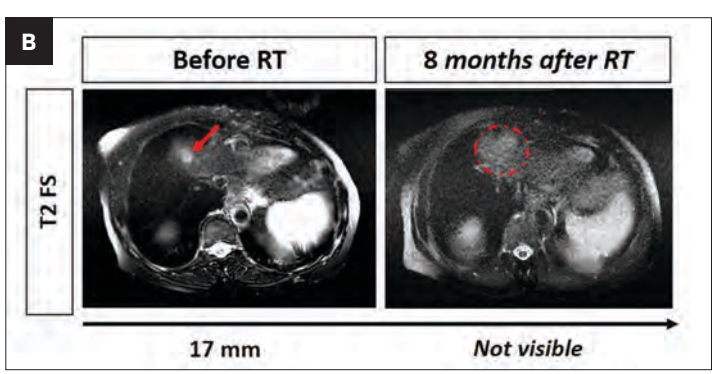
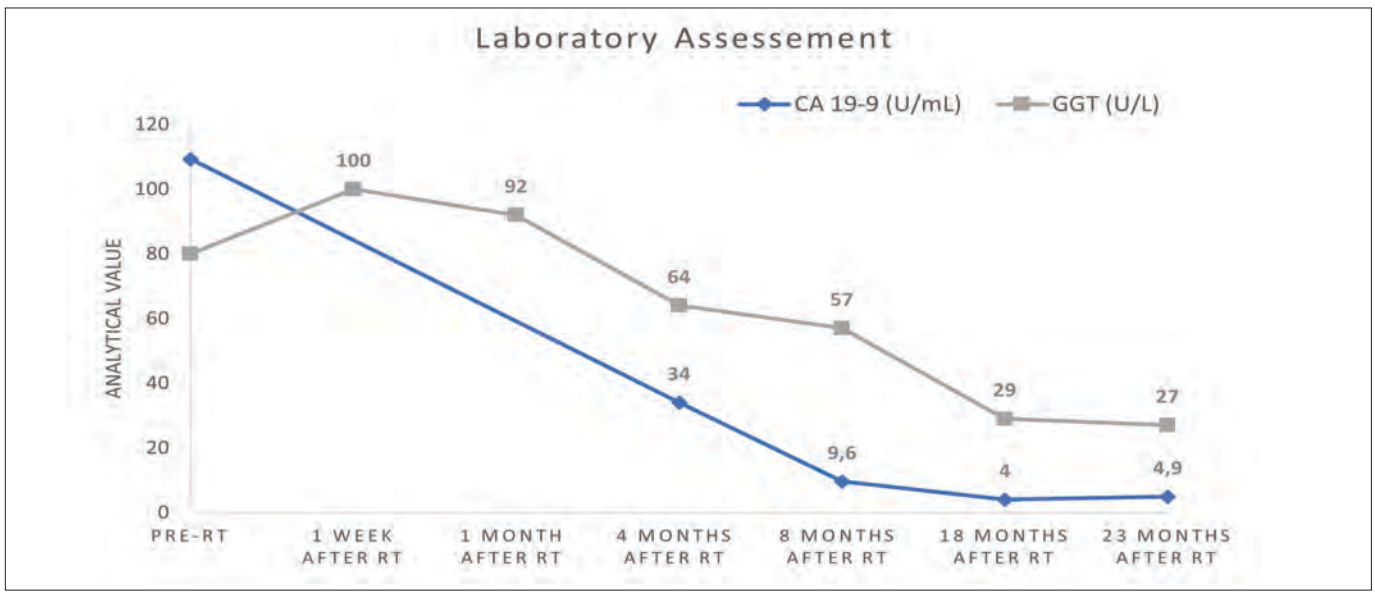


FIGURE 3. Graphic demonstration of gradual decreasing of tumoral marker carbohydrate antigen 19-9 (CA 19-9) and gamma glutamyltransferase (GGT) – Previous to RT and at 1 week and 1, 4, 8, 18 and 23 months after RT. Reference levels for CA 19-9 and GGT are < 37 U/mL and 5-55 U/L, respectively.



even though she has not undergone any systemic treatment (**Figures 2, 3**).

Imaging Findings

Abdominal MRI revealed a 4.2 cm nodular formation at the lower/medial limit of hepatic segment III, with low uptake of contrast product and accentuated filling in the late phase, suggesting metastatic cholangiocarcinoma. It also revealed another 1.7-cm nodular lesion on the cranial margin of the segment VIa with the same characteristics. Macrovascular invasion has not been observed. Follow-up with abdominal MRI every 6 months after SBRT has revealed gradual volumetric reduction of the segment III lesion over time (**Figure 2A**) and disappearance of segment IVa lesion (**Figure 2B**).

CT scan during follow-up excluded other sites of secondary disease such as lungs, lymph nodes or bone metastasis.

Diagnosis

Intrahepatic cholangiocarcinoma previously resected — stage *p*T-2G2N0R0, with subsequent appearance of two liver metastasis

Discussion

ICC is a rare entity with an incidence increasing worldwide, probably due to improved ability to establish the diagnosis.[3] Surgical resection is considered the only treatment with curative intent for localized ICC. However, negative margin resection is challenging in patients with locally advanced tumors, and extended hepatic resection has been demonstrated as an independent risk factor for major postoperative complications.[4] Approximately 70% of patients are unresectable at diagnosis due to multiple intrahepatic tumors, vascular invasion or distant metastases. For these patients, who are unable to achieve optimal resection and are mainly treated with palliative chemotherapy, the median survival ranges 2.3 to 9 months.[3]

The use of RT in intrahepatic malignancies was traditionally limited by concerns over hepatic tolerance and the resulting inability to deliver a sufficient treatment dose, particularly in patients who may have compromised hepatic function. The delivery of tumoricidal doses of RT has become feasible with the development of modern techniques, including charged particles and SBRT; however, evidence is scarce about its applicability in ICC. Studies regarding robotic radiosurgery of liver metastasis have shown that a total dose of 45 to 60 Gy administered in 3 to 5 fractions, with a fraction dose of 9 to 20 Gy was safe and effective as a local treatment option for secondary liver tumors.[5] Moreover, a prospective dose-escalation study that used different doses (30 Gy in 3 fractions, 50 Gy in 5 fractions, and 60 Gy in 6 fractions) determined that the rate of complete and partial response (at 6 and 12 months), as well as the local control rate at 12 months, were significantly higher in the 60 Gy group.[6]

In this work, we present a case of a patient diagnosed with ICC 52 months ago, who underwent total resection of the tumor, with subsequent appearance of two liver metastases effectively and safely treated with SBRT, without any type of systemic treatment. After a follow-up period of 23 months, the patient remains with no signs of disease recurrence or progression. In fact, she has a survival superior to the overall survival (OS) reported in the vast majority of ICC metastatic cancer patients without extrahepatic disease.[7]

Some studies have been published in the last decade about the role of RT as locoregional therapy in patients with unresectable or metastatic ICC without extrahepatic disease.[8-10] A single-institution retrospective study carried out by Tao and colleagues included 79 patients with localized inoperable ICC, treated with 3D-conformal intensity-modulated RT photon beam or passive scatter proton beam techniques, with doses ranging 35 to 100 Gy in 3 to 30 fractions, for a median biologic equivalent dose (EQD2) of 80.5 Gy.[8] Median OS after the first diagnosis was 30 months. Authors concluded that higher EQD2 (> 80.5 Gy) correlated with an improved 3-year OS (73% vs 38%) and 3-year local control (78% vs 45%).[8] However, an important factor could have highly contributed to the observed 3-year OS and local control, as the great majority of patients included in that study (89%) received systemic chemotherapy prior to RT, unlike the patient described in this case report.

A prospective phase II multi-institutional trial including 37 patients with unresectable ICC showed that hypofractionated proton therapy (median EQD2 of 58 Gy) resulted in a median progression-free survival (PFS) rate of 8.4 months, and 1-year and 2-year PFS rates of 41.4% and 25.7%, respectively.[9] The median OS was 22.5 months, with 1-year and 2-year OS rates of 69.7% and 46.5%, respectively.[9] Also, in this study 61.5% of patients underwent chemotherapy before RT. Based on these results, a recent NRG study (NRG-GI001) attempted to evaluate the use of hypofractionated external-beam RT (EBRT) in this patient population; however, this trial closed due to poor accrual. Last year, Smart and colleagues reported 2-year results of a cohort of 66 patients with unresectable or locally recurrent cholangiocarcinoma treated with hypofractionated proton or photon RT, with a median dose of 58.05 Gy (median of biologically effective dose of 80.52 Gy) in 15 fractions.[10] Note that 42% of patients included in this study received prior chemotherapy, and 70% of patients presented with only one tumor lesion before RT. The median OS from the date of diagnosis was 25 months for the entire cohort, and 2-year OS and 2-year local control rates were 58% and 84%, respectively, with a relatively low severe toxicity rate (grade 3 <11%).[10] These studies suggest that ablative doses of radiation allow for a high local control rate and encouraging results in terms of survival outcomes.

SBRT remains an option for the treatment of all primary and metastatic liver cancers. In fact, local control rates reported in a recently published phase III randomized trial for recurrent hepatocellular carcinoma were 70% to 80% at 3 years, with proton beam therapy shown to be noninferior to radiofrequency.[11] SBRT consists of a noninvasive and well-tolerated treatment that may allow patients sustained QOL benefits. Our patient did not require systemic treatment and tolerated SBRT excellently. Furthermore, SBRT in monotherapy was able to sustain good systemic disease control, prompting us to hypothesize about a potential abscopal response.

Conclusion

This case report is about a patient diagnosed with ICC 52 months ago. The patient was initially submitted for right hepatectomy; however, there was subsequent appearance of two liver metastases. She rejected systemic therapy and proceeded with SBRT of liver metastasis. After a total follow-up of 23 months since SBRT, the patient not only retains an excellent survival, but also has no signs of disease recurrence or progression.

Management of cholangiocarcinoma is often difficult, with limited options for salvage treatment. Although radiation has an established role in the treatment of cholangiocarcinoma, SBRT remains an option. This case report highlights the potential efficacy of SBRT in monotherapy for treating multiple intrahepatic metastases of ICC. Future randomized control trials attempting SBRT of the liver are needed for better management of advanced ICC.

References

1) Lee AJ, Chun YS. Intrahepatic cholangiocarcinoma: the AJCC/UICC 8th edition updates. *Chin Clin Oncol*. 2018;7(5):9-11. doi:10.21037/cco.2018.07.03

2) Hanna GG, Murray L, Patel R, et al. UK consensus on normal tissue dose constraints for stereotactic radiotherapy. *Clin Oncol*. 2018;30(1):5-14. doi:10.1016/j.clon.2017.09.007

3) Endo I, Gonen M, Yopp AC, et al. Intrahepatic cholangiocarcinoma: rising frequency, improved survival, and determinants of outcome after resection. *Ann Surg*. 2008;248(1):84-96. doi:10.1097/SLA.0b013e318176c4d3

4) De Jong MC, Nathan H, Sotiropoulos GC, et al. Intrahepatic cholangiocarcinoma: an international multi-institutional analysis of prognostic factors and lymph node assessment. *J Clin Oncol*. 2011;29(23):3140-3145. doi:10.1200/JCO.2011.35.6519

5) García R, Santa-Olalla I, Lopez Guerra JL, Sanchez S, Azinovic I. Robotic radiosurgery for the treatment of liver metastases. *Rep Pract Oncol Radiother*. 2017;22(2):111-117. doi:10.1016/j.rpor.2016.10.002

6) Rule W, Timmerman R, Tong L, et al. Phase i dose-escalation study of stereotactic body radiotherapy in patients with hepatic metastases. *Ann Surg Oncol*. 2011;18(4):1081-1087. doi:10.1245/s10434-010-1405-5

7) Kang SH, Hwang S, Lee YJ, et al. Prognostic comparison of the 7th and 8th editions of the American Joint Committee on Cancer staging system for intrahepatic cholangiocarcinoma. *J Hepatobiliary Pancreat Sci*. 2018;25(4):240-248. doi:10.1002/jhbp.543

8) Tao R, Krishnan S, Bhosale PR, et al. Ablative radiotherapy doses lead to a substantial prolongation of survival in patients with inoperable intrahepatic cholangiocarcinoma: a retrospective dose response analysis. *J Clin Oncol*. 2016;34(3):219-226. doi:10.1200/JCO.2015.61.3778

9) Hong TS, Wo JY, Yeap BY, et al. Multi-institutional phase II study of high-dose hypofractionated proton beam therapy in patients with localized, unresectable hepatocellular carcinoma and intrahepatic cholangiocarcinoma. *J Clin Oncol*. 2016;34(5):460-468. doi:10.1200/JCO.2015.64.2710

10) Smart AC, Goyal L, Horick N, et al. Hypofractionated radiation therapy for unresectable/locally recurrent intrahepatic cholangiocarcinoma. *Ann Surg Oncol*. 2020;27(4):1122-1129. doi:10.1245/s10434-019-08142-9

11) 11. Kim TH, Koh YH, Kim BH, et al. Proton beam radiotherapy vs. radiofrequency ablation for recurrent hepatocellular carcinoma: a randomized phase III trial. *J Hepatol*. 2021;74(3):603-612. doi:10.1016/j.jhep.2020.09.026

Dr. Vidal is a PGY4 resident physician at University of Oklahoma Health Sciences Center - Stephenson Cancer Center.

Improving Cancer Equity Through Advocacy

Gabriel S. Vidal, MD

Residency is a transformative and demanding period in the life of a physician. Learning and attaining proficiency within the field comes from a variety of sources, including professors, clinical staff, scientific literature, and research. However, most is gleaned from the patients we treat daily who bring their fears, anxieties, insecurities, and concerns to the clinic.

Unfortunately, the ongoing COVID-19 pandemic has only heightened emotions we see in clinic and further exposed disparities in our health care system. As an example, COVID-19 hospitalization rates among non-Hispanic Black people and Hispanic or Latino people were about 4.7 times the rate of non-Hispanic White people.[1,2] Only 4.7% of the US oncology workforce is Hispanic, 3% is Black or African American, and 0.1% is American Indian or Alaska Native, according to a recent report by the American Society of Clinical Oncology (ASCO).[3]

Organizations such as ASCO and the American Society for Radiation Oncology (ASTRO) continue to advocate for equitable cancer care and workforce diversity. Lori Pierce, MD, FASTRO, FASCO, focused her ASCO presidency around equity with the theme, "Equity: Every patient. Every day. Everywhere." And every year, ASTRO hosts a Congressional Advocacy Day. Due to the pandemic, the last two meetings were virtual. The most recent Advocacy Day was in late July 2021 and had a record-breaking number of resident physicians in radiation oncology. Thirty residents were among the 100-plus participants from 32 states. In total, more 150 meetings took place with staff members and lawmakers pertaining to the proposed Radiation Oncology Alternative Payment Model (RO-APM), ongoing prior authorization struggles, and increasing federal funding in cancer research.

During my meetings, I reviewed important parts of the RO-APM and how this model would impact my patients and communities in rural Oklahoma. I shared with patients that I was meeting with members of Congress to discuss proposed changes that have a real chance of impacting radiation therapy services in Oklahoma. I told their stories and those of previous patients throughout my meetings, including their enduring struggles due to lack of resources. We also discussed the anxiety experienced from treatment delays due to prior authorization processes in the midst of a pandemic.

As a resident, we are often on the frontlines of medical care. We spend countless hours with our patients in face-to-face interactions or coordinating care. We do more than take their history, perform a physical exam, and review a treatment plan. Most often, we become an integral member of their medical team and oncology journey. Let us amplify their voices and stories by continuing to advocate for more equitable health care, the health of our patients, and our profession overall.

References

1) Webb Hooper M, Nápoles AM, Pérez-Stable EJ. COVID-19 and racial/ethnic disparities. *JAMA*. 2020;323(24):2466-2467. doi:10.1001/jama.2020.8598

2) Garg S, Kim L, Whitaker M, et al. Hospitalization rates and characteristics of patients hospitalized with laboratory-confirmed coronavirus disease 2019 – COVID-NET, 14 United States, March 1-30, 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69(15):458-464.

3) 2020 snapshot: state of the oncology workforce in America. *JCO Oncol Pract*. 2021;17(1):30.

thermoscientific

Got radiation?
See what you've been missing

Imaging in radiation environments just got easier

With superior capabilities for operating in radiation environments, the MegaRAD cameras provide excellent image quality well beyond dose limitations of conventional cameras, and are well suited for radiation hardened imaging applications

MegaRAD3 produce color or monochrome video up to 3 x 10^6 rads total dose

MegaRAD1 produce monochrome video up to 1 x 10^6 rads total dose

KiloRAD PTZ radiation resistant camera with Pan/Tilt/Zoom

In the United States:
For customer service, call 1-800-888-8761
To fax an order, use 1-315-451-9421
Email: sales.cidtec@thermofisher.com

International:
For customer service, call [01) 315-451-9410
To fax an order, use [01) 315-451-9410
Email: sales.cidtec@thermofisher.com

Find out more at **thermofisher.com/cidtec**

ThermoFisher SCIENTIFIC

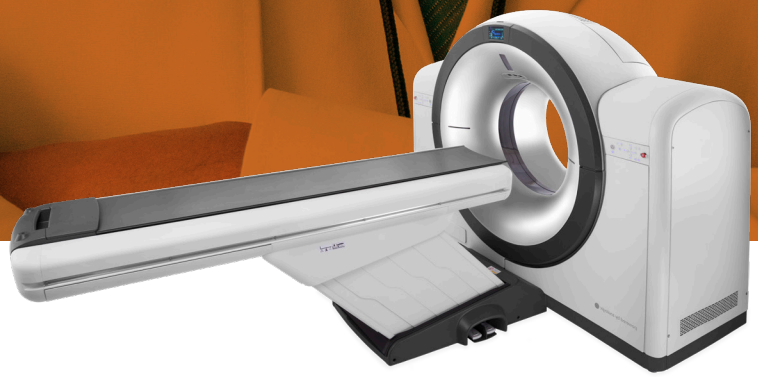
FUJIFILM
Value from Innovation

Visionary Performance.

For the Radiation Oncologist, precision and ease of diagnosis streamlines the care of your patients.

Persona CT is a scalable solution, designed to simplify every step in treatment for your oncology patients of every size.

Be visionary.



#VisionaryCT

Persona CT