APPLIED RADIATION ONCOLOGY™
VOL 10 NO 1 MARCH 2021

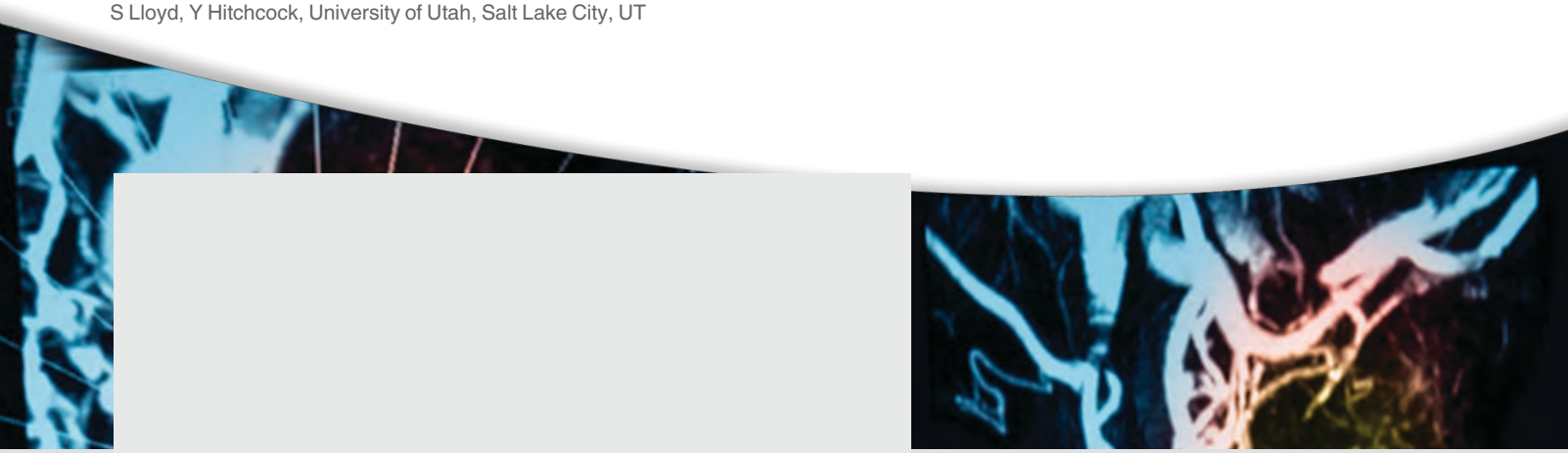
SA-CME CREDIT

Applications of Artificial Intelligence in Head and Neck Radiation Therapy
AC Riegel, Northwell Health, Lake Success, NY

Managing Anxiety and Minimizing Sedation Requirements in the Pediatric Radiation Oncology Population
N Goldman, New York Medical College, Valhalla, NY; M Gallitto, C-C Wu, Columbia University Irving Medical Center, New York, NY

Proliferation Saturation Index to Characterize Response to Radiation Therapy and Evaluate Altered Fractionation in Head and Neck Cancer
MU Zahid, A Rishi, LB Harrison, CD Fuller, EG Moros, JJ Caudell, H Enderling, H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL; ASR Mohamed, K Latifi, The University of Texas MD Anderson Cancer Center, Houston, TX

Upfront Surgery With Adjuvant Radiation Therapy Versus Chemoradiation in HPV-Mediated Oropharyngeal Cancer in Intermediate-Risk Patients
AM Torgeson, Walter Reed National Military Medical Center, Bethesda, MD; KN McComas, Sacred Heart Medical Center, Spokane, WA; G Stoddard, University of Utah Study Design and Biostatistics Center, Salt Lake City, UT; JA Gygi, V Avizonis, Intermountain Medical Center, Murray, UT; S Lloyd, Y Hitchcock, University of Utah, Salt Lake City, UT



LADMSQ200116

MOSAIQ® Plaza

Connecting you to every moment of a patient's journey

MOSAIQ® Plaza transforms cancer care by personalizing every patient's treatment pathway. This integrated suite of digital tools ensures you achieve the highest quality decision-making while delivering value-based care—continuously adapting and optimizing based upon each unique individual patient journey.

Focus where it matters.

elekta.com/mosaiqplaza

Elekta

APPLIED RADIATION ONCOLOGY™

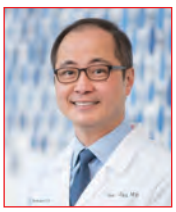
CIRCULATION, COVERAGE and ADVERTISING RATES: Completed details of regarding circulation, coverage, advertising rates, space sizes, and similar information are available to prospective advertisers. Closing date is 30 days preceding date of issue. View our media planner at appliedradiationoncology.com/advertise.

EDITORIAL CONTRIBUTIONS: *Applied Radiation Oncology* accepts clinical-review articles, research papers, and cases that pertain to radiation oncology and related oncologic imaging procedures that will be of interest to radiation oncologists. Manuscripts and cases may be sent electronically to Sharon Breske, Executive Editor for review with our Advisory Board. The opinions and recommendations expressed herein, in articles, columns and cases, are not necessarily those of the publisher. 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. Editorial closing date is the first day of the month 3 months prior to the issue date. 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. Clinical review articles are also solicited by our Editorial Advisory Board. Any editorial submission should be original and unpublished, approximately 1500-2500 words and include the appropriate images, image captions and references. All submissions are to be submitted electronically by emailing a MS Word document, high resolution images, and selected DICOM image data sets to our Editor, Sharon Breske, for review and approval. Authors will be notified by email of acceptance or rejection and of any major recommended revisions. Prior to publication, a PDF of your article or case will be emailed to you for final approval. Manuscripts and cases should be emailed to Sharon Breske, at Sharon@appliedradiationoncology.com.

Anderson Publishing, Ltd
180 Glenside Avenue, Scotch Plains, NJ 07076
(908) 301-1995

ESSN: 2334-5446 (Online)

EDITORIAL ADVISORY BOARD



APPLIED RADIATION ONCOLOGY™

March 2021
Vol. 10, No. 1

FOCUS: HEAD AND NECK CANCER

SA-CME CREDITS

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@appliedradiology.com.

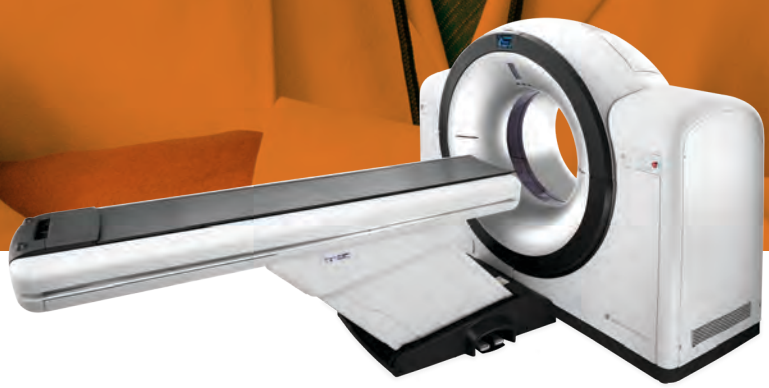
FUJIFILM
Value from Innovation

Visionary Performance.

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

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

Be visionary.

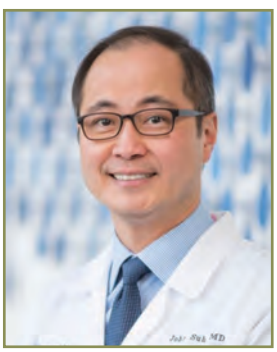


#VisionaryCT

Persona CT

EDITORIAL

Developments in Head and Neck Cancer Treatment



John Suh, MD, FASTRO, FACR
Editor-in-Chief

Welcome to the March 2021 issue of *ARO*! This month's focus is head and neck cancer (HNC), and we are pleased to kick off the issue with a well-written and timely article, *Applications of Artificial Intelligence in Head and Neck Radiation Therapy*. Approved for SA-CME credit, this review delves beyond auto-segmentation to examine the application and clinical impact of AI in dose calculation, adaptive radiation therapy, outcome prediction, quality assurance and more. Better understanding these fundamental concepts will help clinicians maximize the power of machine and deep learning capabilities as AI rapidly advances across numerous specialty areas and fields of medicine, in particular radiation oncology.

Among research presented in the issue, *Proliferation Saturation Index (PSI) to Characterize Response to Radiation Therapy and Evaluate Altered Fractionation in Head and Neck Cancer* discusses an innovative approach toward personalized radiation treatment. Here, the authors show that the PSI model can simulate HNC patient-specific responses to RT and ultimately help identify which patients may most benefit from radiation treatments.

We also present *Upfront Surgery With Adjuvant Radiation Therapy Versus Chemoradiation in HPV-Mediated Oropharyngeal Cancer in Intermediate-Risk Patients: A Multi-Institutional Review*. This informative study underscores the importance of examining a wider range of risks and toxicities when determining primary treatment, especially as more radiation oncologists begin to cautiously consider de-escalated therapy strategies.

Beyond the scope of HNC treatment, we are proud to present a terrific SA-CME accredited review on minimizing anxiety and sedation in pediatric oncology patients, a Technology Trends article summarizing updates in heavy particle ion therapy, the Resident Voice editorial urging development in the essential areas of leadership and advocacy, and noteworthy research findings on how prostate stereotactic body radiation therapy with simultaneous moderate dose escalation to the dominant intraprostatic lesion is feasible.

Ten Years Strong

This issue also marks the journal's 10th year in publication, a milestone we celebrate with immense pride and gratitude. While our mission remains the same – to provide practical applications for the management and treatment of cancer patients – we have evolved in many ways since our inception to better serve you. Highlights include the introduction of original research articles in the journal, free SA-CME credits, webinars, ARRO Resident Voice editorials, monthly enewsletters (soon to be biweekly), exponential social media growth, the transition to a robust double-blind peer review process, our ever-growing panel of expert reviewers, and a talented, dedicated editorial advisory board that has doubled in size.

We are tremendously thankful to all those who have supported *ARO* and contributed to our growth over the last decade and look forward to a better 2021, especially as more of us receive our COVID-19 vaccines. Please stay healthy and safe.

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.*

RESIDENT VOICE

Training in Radiation Oncology: Missing Leadership and Advocacy Development

Justin D. Anderson, MD; Sarah A. Dooley, MD; Austin J. Sim, MD, JD

Justin D. Anderson, MD

Sarah A. Dooley, MD

Austin J. Sim, MD, JD

The Accreditation Council for Graduate Medical Education (ACGME) considers being an "effective member or leader of a health care team or other professional group"[1] an essential milestone for residency training; however, formalized curricula in leadership development in residency training programs across specialties are lacking. Several radiation oncology residency programs have developed independent curricular content surrounding leadership,[2,3] but in general, the greater acquisition of leadership competency remains unmet.

Many specialties in medicine are designed around health care teams that grant residents a gradual increase in leadership responsibilities as they mature from junior to senior residents. However, the apprenticeship model in radiation oncology limits opportunities to develop these skills, including team management and conflict resolution. This increases the need for investments in leadership training in radiation oncology.

Additionally, the ACGME notes that residents should be able to "advocate for quality patient care and optimal patient care systems." One such avenue lies in political advocacy. Recent legislation for prior authorization and reimbursement portends significant changes in our field, but only a few physicians are engaged in this process. A dedicated introduction to the legislative process has shown to increase physician understanding and willingness to participate in political advocacy in other specialties.[4] The American Society for Radiation Oncology (ASTRO) Advocacy Day serves as one opportunity for trainees to engage and participate in political advocacy early in their careers and should be more widely supported.

As the current pandemic has exposed flaws in our health care system and spurred significant change, becoming an effective advocate and leader is more important than ever. Developing these skills in young practitioners is important to ensure our field continues working with legislators to improve patient care and curate positive change. Implementing a standardized core curriculum in radiation oncology that includes education on leadership development and effective advocacy is a great place to start.

References

1. The Radiation Oncology Milestone Project. A Joint Initiative of the Accreditation Council for Graduate Medical Education and the American Board of Radiology. 2015, Accessed December 31, 2020. https://www.acgme.org/Portals/0/PDFs/Milestones/RadiationOncologyMilestones.pdf?ver=2015-11-06-120520-123
2. Berriochoa C, Amarnath S, Berry D, Koyfman SA, Suh JH, Tendulkar RD. Physician leadership development: a pilot program for radiation oncology residents. *Int J Radiat Oncol Biol Phys.* 2018;102(2):254-256.
3. Song E, Frakes JM, Dilling TJ, Quinn JF, Harrison LB, Hoffe SE. A novel radiation oncology residency training leadership curriculum: baseline attitudes and of past and current residents. *Int J Radiat Oncol Biol Phys.* 2019;105(suppl):E157-E158.
4. Joseph N, Huang J, Som A, et al. The impact of physician exposure to organized political advocacy in the Society of Interventional Radiology. *J Vasc Interv Radiol.* 2021;S1051-0443(20)30966-30970. https://doi.org/10.1016/j.jvir.2020.11.004

SA–CME Information

Applications of Artificial Intelligence in Head and Neck Radiation Therapy

Description

The purpose of this article is to review recent advancements in artificial intelligence (AI) as they specifically pertain to head and neck radiation oncology. The main focus will be applications and clinical impact of these techniques. Specifically, this article addresses autosegmentation of organs at risk (OARs), autosegmentation of target volumes, treatment planning and predictive dose calculation, image-guided adaptive radiation therapy, prognosis and outcome prediction, and quality assurance.

Learning Objectives

After completing this activity, participants will be able to:

1. Understand the fundamentals of artificial intelligence
2. Explore how artificial intelligence can be applied to head and neck cancer radiation therapy in the following venues: autosegmentation of organs-at-risk, autosegmentation of target volumes, treatment planning and predictive dose calculation, image-guided adaptive radiation therapy, prognosis and outcome prediction, and quality assurance
3. Recognize limitations to avoid pitfalls in and maximize the potential of artificial intelligence

Authors

Adam C. Riegel, PhD, DABR, *is an associate chief physicist, Department of Radiation Medicine, Northwell Health, Lake Success, NY.*

OBTAINING CREDITS

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.

Date of release and review: March 1, 2021
Expiration date: February 28, 2023
Estimated time for completion: 1 hour

Disclosures: No authors, faculty, or individuals at the Institute for Advanced Medical Education (IAME) or *Applied Radiation Oncology* who had control over the content of this program have relationships with commercial supporters.

Accreditation/Designation Statement: The IAME is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians. The IAME designates this journal-based 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 for ABR diplomates, based on the criteria of the American Board of Radiology.

Commercial Support: None

As part of this CME activity, the reader should reflect on how it will impact his or her personal practice and discuss its content with colleagues.

SA-CME (see page 6)

Applications of Artificial Intelligence in Head and Neck Radiation Therapy

Adam C. Riegel, PhD, DABR

The role of artificial intelligence (AI) in radiation oncology has increased dramatically in the past 5 years, touching nearly every aspect of our field. Artificial intelligence can be broadly defined as "the use of a machine (computer) to perform tasks that typically require human thought."[1] In radiation oncology, these tasks were previously limited to highly repetitive actions that could be scripted in common programming languages. Recently, though, as the widespread accessibility of powerful computing resources has enabled the utilization of machine learning, researchers are finding novel applications for AI in many aspects of radiation oncology previously thought impossible.

Machine learning techniques can be defined as algorithms that yield output from a given input without specific instructions. The algorithms "learn" by detecting underlying patterns in the input data. This period of learning is called model training. Training can be supervised (where the model is generated to produce known output) or unsupervised (where the model determines its own output based on the data itself).[1] Deep learning is a specific type of machine learning that utilizes an artificial neural network that models human neurocognitive design to simulate human thought and understanding. Deep-learning architectures have several hidden layers that process input data through deeper levels of abstraction to learn patterns and produce output.[2] The patterns or "features" are often complex and nonlinear in nature.[2,3] One of the more common types of deep-learning methodologies for image-based tasks is a convolutional neural network (CNN). First introduced to nonmedical image classification by Krizhevsky et al in 2012,[4] CNNs convolve input data with multiple filters or "kernels" to produce progressively more abstract representations of the input data. Many AI applications in radiation oncology utilize some variation of the CNN.

Dr. Riegel *is an associate chief physicist, Department of Radiation Medicine, Northwell Health, Lake Success, NY.* *Disclosure: The author has no conflicts of interest to disclose and has not received outside funding for the production of this original manuscript. No part of this article has been previously published elsewhere.*

The purpose of this article is to review recent advancements in AI as they specifically pertain to head and neck radiation oncology. Although some technical details regarding AI techniques will be discussed, the main focus will be application and clinical impact of these techniques. Specifically, this article will focus on the following applications: autosegmentation of organs at risk (OARs), autosegmentation of target volumes, treatment planning and predictive dose calculation, image-guided adaptive radiation therapy, prognosis and outcome prediction, and quality assurance. For more granular detail about AI methodologies in radiation oncology, the reader is referred to the excellent review articles cited here.[1-3,5,6]

Organ-at-Risk Segmentation

OAR segmentation is an ideal task for automation due to its repetitive nature and the common geometric properties of normal anatomy shared among all members of the population. Furthermore, manual delineation of head and neck OARs is tedious and prone to variation among multiple observers.[7] Early attempts at automatic OAR segmentation involved a posteriori region-growing and edge-detection approaches. Following this early work, automatic OAR segmentation was accomplished with single- or multi-atlas-based techniques that utilized deformable image registration to warp contours from a similar atlas patient to the current patient.[8,9] Such atlas-based approaches are now widely available as commercial products by multiple vendors.

Recently, researchers have assessed the use of machine learning in OAR segmentation with impressive results. Several authors have shown improvements

SA-CME (see page 6)

in volume overlap with "ground truth" contours using models trained on computed tomography (CT) datasets.[10-16] In these studies, "ground truth" contours typically consisted of expert contours or consensus contours from public databases. Metrics to compare automatically segmented volumes with ground truth included variations of the Dice similarity coefficient index (DSC), Hausdorff distance, or average surface distance.[6] Not only were OARs more accurate, they were also generated faster using AI.

Van Dijk et al reported significantly improved results using a deep-learning approach relative to atlas-based autosegmentation for 19 of 22 head and neck OARs.[11] The deep-learning architecture consisted of multiple CNNs trained on a relatively large database of more than 500 CT image sets. Furthermore, human observers found that CNN-based contours generated fewer obvious errors than atlas-based autosegmentation (9% vs 30%, respectively) and, for most OARs, were found to require less correction than atlas-based segmentation. This algorithm is one of the few commercial deep-learning segmentation tools and is known by the brand name DLCExpert (Mirada Medical, Ltd.).

Though less common than CT, researchers have also investigated autosegmentation on other imaging modalities such as MRI. Yang et al focused on segmentation of the parotid gland in pre- and post-treatment treatment MRI to better quantify changes in parotid volume. The authors used support vector machine classification to train the 15-patient model. T1- and T2-weighted postcontrast MRIs were acquired pretreatment and at 3-, 6-, and 12-month intervals after treatment. Overlap with physician-drawn parotid contours was over 90% for both parotid glands in follow-up MRI scans and autosegmented contours highlighted a 25% reduction in parotid volume at 3 months.[17]

Target Segmentation

Automatic segmentation of gross tumor volumes (GTVs) and clinical target volumes (CTVs) is more difficult than that of OARs due to the inherently abnormal nature of the anatomy, but potentially yields benefits in reducing delineation variability and increasing efficiency. Cardenas et al have written several papers on automatic CTV delineation in head and neck cancers.[18-20] In their first 2018 publication, the authors used manually segmented GTVs from 52 node positive and negative oropharyngeal patients to train a deep-learning model to generate high-risk CTVs with a nonuniform margin. The deep-learning model showed good overlap with manually segmented ground truth CTVs (mean DSC range from 0.755 to 0.840 for all pathologies).[20] In their second paper, the authors used a CNN to train a CTV-generating model on 285 oropharyngeal patients and compared its performance to atlas-based segmentation. Overlap DSC was 0.816 for deep learning and 0.739 for atlas-based segmentation.[19] In their most recent paper, the authors focused specifically on nodal CTVs by training a new model with 51 head and neck patients of varying primary site. Node level volumes were contoured and used as input in the CNN deep-learning architecture. The DSC for nodal CTVs ranged from 0.843 to 0.909 compared to ground truth and, qualitatively, more than 99% were scored as acceptable by a panel of 3 experts.[18]

In a study aimed at contouring GTV (split into primary and nodal volumes) and CTV for nasopharyngeal cancer, Men et al set a deep deconvolutional neural network (with an added deconvolution step at the end of the network to restore some high-resolution features) against a conventional CNN.[21] The authors demonstrated significantly better overlap with ground truth for all targets using the experimental architecture (82.6% and 80.9% vs 73.7% and 72.3% for CTV and GTV primary, respectively), but nodal GTV lagged in performance at 62.3%. Although this was better than 33.7% with the conventional CNN, the authors highlighted a few reasons for the deficiency, including lack of clear anatomical boundaries, variable target locations, and poor contrast on CT.[21]

The lack of contrast on CT can be mitigated by adding a second modality with supplementary information such as positron emission tomography (PET)/CT. Guo et al used a 3D CNN to develop a model to segment GTV using CT simulation and registered diagnostic PET/CT. The model was trained using 140 patients with squamous cell carcinoma whose PET was deformably registered to simulation CT. Three models were created: CT alone, PET alone, and CT simulation with registered PET. The combined PET/CT model outperformed CT alone and PET alone by 0.4 and 0.05 in mean overlap metrics, respectively, demonstrating the advantage of incorporating functional information into the model.[22] Berthon et al proposed a decision tree that, through machine learning, would select from multiple automatic segmentation algorithms. The decision tree was tested on 20 oropharyngeal patients and segmented GTVs overlapped with manually drawn ground truth with a DSC of 0.77.[23]

Treatment Planning and Predictive Dose Calculation

The first step of the treatment planning process is CT simulation. For years, physicists have been researching ways to replace CT simulation with MRI simulation because of MRI's superior soft-tissue contrast. The largest hurdle in replacing CT with MRI is arguably the loss of electron density information provided in CT that is used in dose calculation. Like automatic segmentation, earlier approaches to "synthetic" CT generation (electron density

SA-CME (see page 6)

maps produced from MRI) began with thresholding methods and atlas-based deformable image registration. Researchers are now using deep learning to produce synthetic CTs. Dinkla et al rationalize the need for MRI-based planning in head and neck cancer in the context of MR-guided linear accelerators. Thirty-four head and neck cancer patients received CT simulation and large field of view T2-weighted MRI on a 3T scanner. Average absolute errors were 75 ± 9, 214 ± 26, 35 ± 3, and 130 ± 24 HU for body, bone, soft tissue, and air, respectively. The authors speculate that HU values for bone in synthetic CT are slightly lower than actual CTs due to registration errors between CT and MRI. Dose distributions calculated on synthetic CT were within 1% of dose calculated on actual CT voxel by voxel.[24] Klages et al performed a similar study comparing 23 patients in two general adversarial networks to generate synthetic CT. Mean absolute HU errors and dosimetric errors were comparable to Dinkla et al, but the authors found that combining results from three orthogonal views decreased HU errors.[25]

Automated treatment planning is another potential application of AI. Currently, commercial knowledge-based planning systems use the relative geometry of targets and OARs in previously treated patients to predict the dose-volume histograms for de novo patients.[26] Machine learning is being applied to dose prediction as well, with the goal that more accurate dose prediction will yield inverse optimization parameters to speed up the planning process. Chen et al used 70 nasopharyngeal cancer patients who had been treated with 6 MV step-and-shoot intensity-modulated radiation therapy (IMRT) to train a CNN-based dose prediction model. A unique aspect of this model was that the authors tested a general model against a modification that specifically identified out-of-field voxels to potentially increase accuracy near the edges of beams. The model was then tested against 10 additional nasopharyngeal patients and the predicted dose was compared voxel by voxel against the clinical treatment plan. For most regions of interest, the models performed comparably, but the "out-of-field" modification significantly improved agreement for the smaller regions of interest such as chiasm, lenses, and optic nerves.[27] In a more recent paper, the same group compared two CNN-based dose prediction models specifically for helical tomotherapy. The models were CResDevNet and a standard U-Net architecture. Using 136 nasopharyngeal treatment plans and 24 validation plans, the models were tested against 60 patients. The mean absolute error with clinical plans was between 3.2 ± 2.5% and 3.7 ± 2.9% for the CResDevNet and U-Net, respectively. CResDevNet also had a slight advantage with the majority of OARs when the overlap of dose-volume histogram curves was measured.[28]

Adaptive Radiation Therapy

Adaptive radiation therapy is a specialized form of image-guided radiation therapy frequently used in head and neck treatment sites due to the significant anatomical changes that can occur over the course of treatment. Currently, adaptive radiation therapy usually uses an "offline" approach. The physician may set a predefined trigger point, perhaps halfway through treatment, where the plan will be re-evaluated based on localization imaging such as cone-beam CT (CBCT) and adapted to current anatomy if necessary. The physician may also call for ad hoc adaptation based on changes seen in image guidance or on-treatment visits. In offline adaptive therapy, the patient receives a new CT simulation and a new plan is generated for the remaining fractions. This is extremely time-consuming and labor-intensive as the entire treatment planning process must be repeated with the new CT. Although training AI models requires substantial time upfront, increased operational speed yields significant benefit to offline adaptive radiation therapy and opens the possibility of "online" adaptive radiation therapy where the plan is adapted immediately after localization imaging is acquired and the patient remains on the table. Without the increased computational speed that machine learning provides, the feasibility of online adaptation is questionable.

Tong et al investigated the use of adversarial networks for OAR segmentation on both CT simulation and low-field MRI acquired on an MR-guided linear accelerator for online adaptation of image-guided therapy. The CT model was trained on 48 patients from the RTOG 522 dataset and the MRI model was trained on 25 MRI volumes acquired on the MRIdian system (ViewRay). The authors found that the adversarial network that included multiple integrated neural networks (SC-GAN-DenseNet) performed better than other models for both CT and low-field MRI. This is particularly notable given the low signal-to-noise environment of low-field MRI and the short contouring time for the deep-learning model (approximately 14 seconds compared to 30 minutes for the comparable model-based algorithm).[16] Although not currently a focus in head and neck applications, intrafraction motion management may also benefit from fast contour propagation in MR-guided linear accelerators with continuous image monitoring during treatment.[29]

Guidi et al deformably registered daily localization MVCT or kV CBCT to CT simulations to measure the changes in dose due to changing anatomy over time. The authors focused on parotid glands as they are prone to substantial changes during the course of treatment. Using a support vector machine, changes in parotid volume were classified into categories ranging from "Correct Treatment" where planning was not necessary to "Suggested Replanning" where changes indicate

SA-CME (see page 6)

replanning would mitigate suboptimal dosimetric changes. The authors included additional classifications to alert users of abnormal changes in volume data that are either extreme anatomical fluctuations or artifactual. The authors found that, by the fourth week of treatment, approximately 55% of patients required retreatment. The authors validated their approach by comparing their classification to physician judgment and found good concordance between the model and physicians.[30]

One of the few commercial online image-guided adaptive therapy solutions is the Ethos platform by Varian. Built on Halcyon hardware, the Ethos system contains proprietary deep-learning AI that drives online adaptation of the plan from iteratively reconstructed kV CBCT. In a recent publication, the authors (Varian employees) vaguely describe the deep-learning algorithm as CNN-based similar to U-net and DenseNet. After targets and organs at risk are propagated to current anatomy, the plan is reoptimized while the patient is on the treatment table.[31] Though numerous abstracts were presented at recent national meetings about this adaptive platform, few manuscripts on clinical user experiences have yet been published.

Outcome Prediction

Outcome prediction is another application of AI in head and neck radiation therapy. Several authors have explored normal tissue complication probability (NTCP) prediction of xerostomia and dysphagia with machine learning methods.[32-34] Lee et al used quality of life surveys to identify the most influential predictive factors in a multivariable xerostomia model in squamous cell carcinoma and nasopharyngeal carcinoma. Interestingly, the authors found that, in addition to ipsilateral and contralateral parotid dose, features such as age, T-stage, financial status, and education were also significant predictors of xerostomia.[32,33] Dean et al built three dysphagia machine learning models based on prior work[35] with 173 patients for training and 90 patients for validation from a variety of head and neck disease sites and several institutions. Dysphagia was scored using CTCAE version 3 and dose to the pharyngeal mucosa was considered along with other clinical factors. The authors compared models trained with dose-volume data alone vs inclusion of spatial dose information. The authors found that spatial dose information did not improve NTCP modeling of dysphagia and therefore recommended the standard model that includes dose-volume information only, with the caveat that different spatial dose metrics may produce different results.[34]

Research in radiomics, the study of hundreds or thousands of subtle features within regions of interest contoured on diagnostic imaging, has been accelerated by machine learning algorithms.[36] Ren et al developed a model to differentiate between stage I-II and stage III-IV squamous cell carcinoma by extracting 970 radiomic features from multisequence MRI.[37] Van Dijk et al used the 90th percentile of the MRI signal from pretreatment T1-weighted MRI to predict xerostomia.[38] Gabryś et al compared conventional NTCP prediction models of xerostomia with machine learning models that included a variety of user-selected radiomic and dosiomic features. Xerostomia was split into early, late, and long-term time periods, with acceptable predictive success occurring only for long-term toxicity. Small parotids with steep dose gradients in the lateral direction were more prone to xerostomia. The authors suggested this may be caused by the changes in anatomy during treatment, pulling the smaller glands close to high dose regions.[39] If this is true, such a finding would support the need for adaptive therapy as described above.

Quality Assurance

The use of machine learning in medical physics quality assurance procedures is rooted in the idea that physics resources are scarce and should be allocated where they can make the most impact. In other words, tasks that can be automated should be automated so that physicists, like physicians, can concentrate on tasks that truly require expert human judgment. Several authors have investigated the utility of machine learning in identifying plan parameter outliers,[40] finding erroneous contours,[41] calculating output factors in proton therapy,[42] predicting MLC leaf position errors,[43] and predicting gamma index passing rates in IMRT QA.[44-48]

In their 2016 paper, Valdes et al state their intent to create virtual IMRT QA[46] where planners would be able to predict the gamma indices of a given plan before running the QA, potentially avoiding overmodulated plans and ultimately saving time. This is particularly applicable to head and neck treatment plans as they tend to be more complex than other anatomical sites. The authors began by training a generalized linear model with Poisson regression and LASSO regularization on nearly 500 Eclipse-based treatment plans (Varian) for a variety of sites.[46] The authors then augmented this model with portal dosimetry measurements from a different institution[47] and, in their most recent publication, updated their 500-plan model using a CNN called VGG-16. The authors found comparable results between the CNN and their Poisson-regression model, although the CNN yielded several advantages over the Poisson model including calculation speed (after model training) and independence from user-selected features.[48]

Limitations of Artificial Intelligence in Radiation Therapy

There is tremendous potential in AI-based approaches to solving our most pressing problems in head and neck radiation therapy. There are, however, limitations to what AI can currently

SA-CME (see page 6)

accomplish. Image reconstruction parameters, for example, significantly impact the performance of image-based AI algorithms for CT,[49,50] PET,[51] and MRI.[52] Quality of autosegmentation and radiomics analysis is dependent on the accuracy of ground truth contours, which are typically drawn by physicians prone to intra- and interobserver variation.[53] Deep-learning algorithms are abstract by nature and the source of errant results can be difficult to pinpoint.[2,3,54] Large high-quality datasets are required for adequate training and validation of deep-learning algorithms to prevent overfitting.[2,5,54] Even with an adequate sample, deep-learning techniques can be fooled by subtle changes in imaging,[2] which is potentially troubling if imaging artifacts occur. Given the "black box" nature of artificial intelligence, thorough validation procedures are required to ensure models are yielding reasonable results. Regulators are understandably cautious about certifying such powerful and complex tools for clinical use, which may explain the relatively limited number of commercially available AI tools.

Conclusion

Advancements in AI continue at a rapid pace. Given the plethora of digital data generated for patients undergoing head and neck radiation therapy, radiation oncology is well positioned to harness the power of machine learning and deep learning to improve decision-support algorithms, autosegmentation, treatment planning, outcome prediction, and quality assurance. Although few commercial products exist using AI technology, it is only a matter of time until such products are available. It will be incumbent upon us as medical professionals to familiarize ourselves with the basics of AI so we may shine a light in the "black box" and provide the most intelligent care (artificial or otherwise) to our patients.

References

1. Deig CR, Kanwar A, Thompson RF. Artificial intelligence in radiation oncology. *Hematol Oncol Clin North Am*. 2019;33(6):1095-1104. doi:10.1016/j.hoc.2019.08.003
2. Meyer P, Noblet V, Mazzara C, Lallement A. Survey on deep learning for radiotherapy. *Comput Biol Med*. 2018;98:126-146. doi:10.1016/j.compbiomed.2018.05.018
3. Cardenas CE, Yang J, Anderson BM, Court LE, Brock KB. Advances in auto-Segmentation. *Semin Radiat Oncol*. 2019;29(3):185-197. doi:10.1016/j.semradonc.2019.02.001
4. Krizhevsky A, Sutskever I, Hinton GE. ImageNet classification with deep convolutional neural networks. *Adv Neural Inf Process Sys*. 2012;60(6):1097-1105.
5. Wang C, Zhu X, Hong JC, Zheng D. Artificial intelligence in radiotherapy treatment planning: present and future. *Technol Cancer Res Treat*. 2019;18:1-11. doi:10.1177/1533033819873922
6. Vrtovec T, Močnik D, Strojan P, Pernuš F, Ibragimov B. Auto-segmentation of organs at risk for head and neck radiotherapy planning: from atlas-based to deep learning methods. *Med Phys*. 2020;47(9):e929-e950. doi:10.1002/mp.14320
7. Riegel AC, Berson AM, Destian S, et al. Variability of gross tumor volume delineation in head and neck cancer using CT and PET/CT fusion. *Int J Radiat Oncol Biol Phys*. 2006;65(3):726-732. doi:10.1016/j.ijrobp.2006.01.014
8. Lim JY, Leech M. Use of auto-segmentation in the delineation of target volumes and organs at risk in head and neck. *Acta Oncol (Madr)*. 2016;55(7):799-806. doi:10.3109/0284186X.2016.1173723
9. Kosmin M, Ledsam J, Romera-Paredes B, et al. Rapid advances in auto-segmentation of organs at risk and target volumes in head and neck cancer. *Radiother Oncol*. 2019;135:130-140. doi:10.1016/j.radonc.2019.03.004
10. Liang S, Tang F, Huang X, et al. Deep-learning-based detection and segmentation of organs at risk in nasopharyngeal carcinoma computed tomographic images for radiotherapy planning. *Eur Radiol*. 2019;29(4):1961-1967. doi:10.1007/s00330-018-5748-9
11. van Dijk LV, Van den Bosch L, Aljabar P, et al. Improving automatic delineation for head and neck organs at risk by deep learning contouring. *Radiother Oncol*. 2020;142:115-123. doi:10.1016/j.radonc.2019.09.022
12. Ibragimov B, Xing L. Segmentation of organs-at-risks in head and neck CT images using convolutional neural networks: *Med Phys*. 2017;44(2):547-557. doi:10.1002/mp.12045
13. Zhu W, Huang Y, Zeng L, et al. AnatomyNet: Deep learning for fast and fully automated whole-volume segmentation of head and neck anatomy. *Med Phys*. 2019;46(2):576-589. doi:10.1002/mp.13300
14. Chan JW, Kearney V, Haaf S, et al. A convolutional neural network algorithm for automatic segmentation of head and neck organs at risk using deep lifelong learning. *Med Phys*. 2019;46(5):2204-2213. doi:10.1002/mp.13495
15. Tong N, Gou S, Yang S, Ruan D, Sheng K. Fully automatic multi-organ segmentation for head and neck cancer radiotherapy using shape representation model constrained fully convolutional neural networks. *Med Phys*. 2018;45(10):4558-4567. doi:10.1002/mp.13147
16. Tong N, Gou S, Yang S, Cao M, Sheng K. Shape constrained fully convolutional DenseNet with adversarial training for multiorgan segmentation on head and neck CT and low-field MR images. *Med Phys*. 2019;46(6):2669-2682. doi:10.1002/mp.13553
17. Yang X, Wu N, Cheng G, et al. Automated segmentation of the parotid gland based on atlas registration and machine learning: A longitudinal mri study in head and neck radiation therapy. *Int J Radiat Oncol Biol Phys*. 2014;90(5):1225-1233. doi:10.1016/j.ijrobp.2014.08.350
18. Cardenas CE, Beadle BM, Garden AS, et al. Generating high-quality lymph node clinical target volumes for head and neck cancer radiotherapy using a fully automated deep learning-based approach. *Int J Radiat Oncol*. 2021;109(3):801-812. doi:10.1016/j.ijrobp.2020.10.005
19. Cardenas CE, Anderson BM, Aristophanous M, et al. Auto-delineation of oropharyngeal clinical target volumes using 3D convolutional neural networks. *Phys Med Biol*. 2018;63(21). doi:10.1088/1361-6560/aae8a9
20. Cardenas CE, McCarroll RE, Court LE, et al. Deep learning algorithm for auto-delineation of high-risk oropharyngeal clinical target volumes with built-in dice similarity coefficient parameter optimization function. *Int J Radiat Oncol Biol Phys*. 2018;101(2):468-478. doi:10.1016/j.ijrobp.2018.01.114
21. Men K, Chen X, Zhang Y, et al. Deep deconvolutional neural network for target segmentation of nasopharyngeal cancer in planning computed tomography images. *Front Oncol*. 2017;7(DEC):1-9. doi:10.3389/fonc.2017.00315
22. Guo Z, Guo N, Gong K, Zhong S, Li Q. Gross tumor volume segmentation for head and neck cancer radiotherapy using deep dense multi-modality network. *Phys Med Biol*. 2019;64(20). doi:10.1088/1361-6560/ab440d
23. Berthon B, Evans M, Marshall C, et al. Head and neck target delineation using a novel PET automatic segmentation algorithm. *Radiother Oncol*. 2017;122(2):242-247. doi:10.1016/j.radonc.2016.12.008
24. Dinkla AM, Florkow MC, Maspero M, et al. Dosimetric evaluation of synthetic CT for head and neck radiotherapy generated by a patch-based three-dimensional convolutional neural network. *Med Phys*. 2019;46(9):4095-4104. doi:10.1002/mp.13663
25. Klages P, Benslimane I, Riyahi S, et al. Patch-based generative adversarial neural network models for head and neck MR-only planning. *Med Phys*. 2020;47(2):626-642. doi:10.1002/mp.13927
26. Tol JP, Delaney AR, Dahele M, Slotman BJ, Verbakel WFAR. Evaluation of a knowledge-based planning solution for head and neck cancer. *Int J Radiat Oncol Biol Phys*. 2015;91(3):612-620. doi:10.1016/j.ijrobp.2014.11.014
27. Chen X, Men K, Li Y, Yi J, Dai J. A feasibility study on an automated method to generate patient-specific dose distributions for radiotherapy using deep learning. *Med Phys*. 2019;46(1):56-64. doi:10.1002/mp.13262

SA-CME (see page 6)

28. Liu Z, Chen X, Men K, Yi J, Dai J. A deep learning model to predict dose–volume histograms of organs at risk in radiotherapy treatment plans. *Med Phys*. Published online 2020. doi:10.1002/mp.14394
29. Eppenhof KAJ, Maspero M, Savenije MHF, et al. Fast contour propagation for MR-guided prostate radiotherapy using convolutional neural networks. *Med Phys*. 2020;47(3):1238-1248. doi:10.1002/mp.13994
30. Guidi G, Maffei N, Meduri B, et al. A machine learning tool for re-planning and adaptive RT: A multicenter cohort investigation. *Phys Medica*. 2016;32(12):1659-1666. doi:10.1016/j.ejmp.2016.10.005
31. Archambault Y, Boylan C, Bullock D, et al. Making on-line adaptive radiotherapy possible using artificial intelligence and machine learning for efficient daily re-planning. *Med Phys Int J*. 2020;8(2):77-86.
32. Lee TF, Liou MH, Huang YJ, et al. LASSO NTCP predictors for the incidence of xerostomia in patients with head and neck squamous cell carcinoma and nasopharyngeal carcinoma. *Sci Rep*. 2014;4:1-8. doi:10.1038/srep06217
33. Lee TF, Chao PJ, Ting HM, et al. Using multivariate regression model with least absolute shrinkage and selection operator (LASSO) to predict the incidence of xerostomia after intensity-modulated radiotherapy for head and neck cancer. *PLoS One*. 2014;9(2). doi:10.1371/journal.pone.0089700
34. Dean J, Wong K, Gay H, et al. Incorporating spatial dose metrics in machine learning-based normal tissue complication probability (NTCP) models of severe acute dysphagia resulting from head and neck radiotherapy. *Clin Transl Radiat Oncol*. 2018;8:27-39. doi:10.1016/j.ctro.2017.11.009
35. Dean JA, Wong KH, Welsh LC, et al. Normal tissue complication probability (NTCP) modelling using spatial dose metrics and machine learning methods for severe acute oral mucositis resulting from head and neck radiotherapy. *Radiother Oncol*. 2016;120(1):21-27. doi:10.1016/j.radonc.2016.05.015
36. Giraud P, Giraud P, Gasnier A, et al. Radiomics and machine learning for radiotherapy in head and neck cancers. *Front Oncol*. 2019;9(MAR):1-13. doi:10.3389/fonc.2019.00174
37. Ren J, Tian J, Yuan Y, et al. Magnetic resonance imaging based radiomics signature for the preoperative discrimination of stage I-II and III-IV head and neck squamous cell carcinoma. *Eur J Radiol*. 2018;106(March):1-6. doi:10.1016/j.ejrad.2018.07.002
38. van Dijk LV, Thor M, Steenbakkers RJHM, et al. Parotid gland fat related Magnetic Resonance image biomarkers improve prediction of late radiation-induced xerostomia. *Radiother Oncol*. 2018;128(3):459-466. doi:10.1016/ j.radonc.2018.06.012
39. Gabryś HS, Buettner F, Sterzing F, Hauswald H, Bangert M. Design and selection of machine learning methods using radiomics and dosiomics for normal tissue complication probability modeling of xerostomia. *Front Oncol*. 2018;8:1-20. doi:10.3389/fonc.2018.00035
40. Azmandian F, Kaeli D, Dy JG, et al. Towards the development of an error checker for radiotherapy treatment plans: a preliminary study. *Phys Med Biol*. 2007;52(21):6511-6524. doi:10.1088/0031-9155/52/21/012
41. McIntosh C, Svistoun I, Purdie TG. Groupwise conditional random forests for automatic shape classification and contour quality assessment in radiotherapy planning. *IEEE Trans Med Imaging*. 2013;32(6):1043-1057. doi:10.1109/TMI.2013.2251421
42. Sun B, Lam D, Yang D, et al. A machine learning approach to the accurate prediction of monitor units for a compact proton machine. *Med Phys*. 2018;45(5):2243-2251. doi:10.1002/mp.12842
43. Carlson JNK, Park JM, Park SY, Park JI, Choi Y, Ye SJ. A machine learning approach to the accurate prediction of multi-leaf collimator positional errors. *Phys Med Biol*. 2016;61(6):2514-2531. doi:10.1088/0031-9155/61/6/2514
44. Wootton LS, Nyflot MJ, Chaovalitwongse WA, Ford E. Error detection in intensity-modulated radiation therapy quality assurance using radiomic analysis of gamma distributions. *Int J Radiat Oncol Biol Phys*. 2018;102(1):219-228. doi:10.1016/j.ijrobp.2018.05.033
45. Nyflot MJ, Thammasorn P, Wootton LS, Ford EC, Chaovalitwongse WA. Deep learning for patient-specific quality assurance: Identifying errors in radiotherapy delivery by radiomic analysis of gamma images with convolutional neural networks. *Med Phys*. 2019;46(2):456-464. doi:10.1002/mp.13338
46. Valdes G, Scheuermann R, Hung CY, Olszanski A, Bellerive M, Solberg TD. A mathematical framework for virtual IMRT QA using machine learning. *Med Phys*. 2016;43(7):4323-4334. doi:10.1118/1.4953835
47. Valdes G, Chan MF, Lim SB, Scheuermann R, Deasy JO, Solberg TD. IMRT QA using machine learning: a multi-institutional validation. *J Appl Clin Med Phys*. 2017;18(5):279-284. doi:10.1002/acm2.12161
48. Interian Y, Rideout V, Kearney VP, et al. Deep nets vs expert designed features in medical physics: an IMRT QA case study. *Med Phys*. 2018;45(6):2672-2680. doi:10.1002/mp.12890
49. Shafiq-Ul-Hassan M, Zhang GG, Latifi K, et al. Intrinsic dependencies of CT radiomic features on voxel size and number of gray levels. *Med Phys*. 2017;44(3):1050-1062. doi:10.1002/mp.12123
50. Zhao W, Zhang W, Sun Y, et al. Convolution kernel and iterative reconstruction affect the diagnostic performance of radiomics and deep learning in lung adenocarcinoma pathological subtypes. *Thorac Cancer*. 2019;10(10):1893-1903. doi:10.1111/1759-7714.13161
51. Galavis PE, Hollensen C, Jallow N, Paliwal B, Jeraj R. Variability of textural features in FDG PET images due to different acquisition modes and reconstruction parameters. *Acta Oncol (Madr)*. 2010;49(7):1012-1016. doi:10.3109/0284186X.2010.498437
52. Mayerhoefer ME, Szomolanyi P, Jirak D, Materka A, Trattnig S. Effects of MRI acquisition parameter variations and protocol heterogeneity on the results of texture analysis and pattern discrimination: An application-oriented study. *Med Phys*. 2009;36(4):1236-1243. doi:10.1118/1.3081408
53. Pavic M, Bogowicz M, Würms X, et al. Influence of inter-observer delineation variability on radiomics stability in different tumor sites. *Acta Oncol (Madr)*. 2018;57(8):1070-1074. doi:10.1080/0284186X.2018.1445283
54. Thompson RF, Valdes G, Fuller CD, et al. Artificial intelligence in radiation oncology imaging. *Int J Radiat Oncol Biol Phys*. 2018;102(4):1159-1161. doi:10.1016/j.ijrobp.2018.05.070

SA–CME Information

Managing Anxiety and Minimizing Sedation Requirements in the Pediatric Radiation Oncology Population

Description

This review article provides a thorough outline of various modalities to help guide implementation of strategies to reduce anxiety in treatment facilities. Categories include interventions before treatment (psychoeducational interventions, play therapy) and during treatment (specialized staff, environmental modifications, distraction, reward/incentive systems).

Learning Objectives

1. Develop an understanding of the drawbacks of using sedation in the pediatric radiation oncology setting.
2. Identify the various interventions available to reduce the need for sedation.
3. Be able to develop a more nuanced plan for implementing various interventions into practice.

Authors

Nathaniel Goldman, BA,* *is a medical student at New York Medical College, Valhalla, NY.* **Matthew Gallitto, MD,* *is a resident physician, and* ***Cheng-Chia Wu, MD, PhD,* *is an assistant professor, Department of Radiation Oncology, Columbia University Irving Medical Center, New York, NY. *Contributed equally to this work.*

OBTAINING CREDITS

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.

Date of release and review: March 1, 2021
Expiration date: February 28, 2023
Estimated time for completion: 1 hour for each activity

Disclosures: No authors, faculty, or individuals at the Institute for Advanced Medical Education (IAME) or *Applied Radiation Oncology* who had control over the content of this program have relationships with commercial supporters.

Accreditation/Designation Statement: The IAME is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians. The IAME designates this journal-based 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 for ABR diplomates, based on the criteria of the American Board of Radiology.

Commercial Support: None

As part of this CME activity, the reader should reflect on how it will impact his or her personal practice and discuss its content with colleagues.

SA-CME (see page 13)

Managing Anxiety and Minimizing Sedation Requirements in the Pediatric Radiation Oncology Population

Nathaniel Goldman, BA*; Matthew Gallitto, MD*; Cheng-Chia Wu, MD, PhD

The use of radiation therapy (RT) is an integral part of the treatment process in the field of pediatric oncology. RT requires a high degree of precision to successfully target malignant cells while sparing normal tissue. As a result, patients must remain still for extended periods and are frequently required to use immobilization devices during treatment. This, in combination with the need to be isolated in a treatment room, undoubtedly produces considerable anxiety for children.

Due to pediatric distress from the treatment process, general anesthesia is frequently required in RT for sedation purposes. Provider surveys suggest the median age at which anesthesia is no longer required is approximately 6 years.[1] Some institutions routinely use general anesthesia for all patients up until age 7.[2,3] While sedation has benefits regarding ease of immobilization, there are considerable drawbacks to this process. First, sedation is invasive and carries potential health risks including increased risk of sepsis associated with central line placement routinely required for administration of medications.[4] In addition, anesthesia increases total time spent in the treatment center while dictating rigid scheduling restraints for both treatment facilities and patients (eg, fasting before treatment).[1] These requirements may be disruptive to a child's ability to maintain social connection and attend school.

More time in the facility also translates to increased staffing requirements, including individuals capable of handling sedated patients, thus leading to a significant cost burden to treatment facilities. Health care cost savings as high as 36% have already been noted in studies that seek ways to reduce the sedation requirement in RT.[5]

The invasive nature, as well as increased risks and costs have led toward a conscious movement to minimize anesthesia in pediatric RT.[3] Several studies have demonstrated the efficacy of particular interventions to reduce anxiety and sedation in pediatric radiation oncology patients through the facilitation of effective coping methods.[5-14] Adequate implementation of these interventions, however, remains difficult for many facilities. Providers surveyed on this topic have suggested that lack of awareness of available tools and strategies continues to be a leading obstacle to putting these practices into use.[1] As such, this review seeks to provide a thorough outline of various modalities to help guide implementation of strategies to reduce anxiety in treatment facilities.

*__Mr. Goldman__ and __Dr. Gallitto__ contributed equally to this work. __Mr. Goldman__ is a medical student at New York Medical College, Valhalla, NY. __Dr. Gallitto__, is a resident, and __Dr. Wu__ is an assistant professor, Department of Radiation Oncology, Columbia University Irving Medical Center, New York, NY. *Acknowledgment: The authors thank Adeline Li, RTT, a radiation therapist at New York-Presbyterian Hospital, for permission to showcase the decorative masks she created for our pediatric patients. 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.*

Interventions Prior to Initiation of Radiation Therapy Treatment

Psychoeducational Interventions

Psychoeducational interventions are humanistic methods of providing patients and caregivers with resources to cope with an illness. In general, these interventions tend to provide information in a way that addresses the psychological and emotional challenges a patient may face. This ranges from explaining general information about treatment and side effects to providing problem-solving strategies for coping with the disease.[15] Psychoeducational interventions in this review are categorized by noninteractive and interactive methods:

Noninteractive education. This provides passive education by a variety of methods including meeting with the staff/nurses prior to treatment, a tour of the facility, video information about treatment, and information pamphlets.[1,16] These traditional interventions intend to familiarize pediatric patients and caregivers with the medical team and treatment process. Meeting in advance with the treatment team gives patients and caregivers the opportunity to ask questions and plan coping strategies before treatment begins. Seeing the

SA-CME (see page 13)

FIGURE 1. *Select examples of creative mask decorations for pediatric patients receiving radiation therapy at our institution. Permission granted by Adeline Li, RTT, a radiation therapist at New York-Presbyterian Hospital, to showcase the masks she created.*

treatment suite either by video or via in-person tour provides the child an early opportunity to become comfortable with unfamiliar medical equipment.

Interactive education. This allows the patient to relate to the treatment experience at a slower pace and develop effective coping strategies. In medical settings, interactive education has been shown to be more effective than traditional, noninteractive education in terms of promoting information recall and compliance with medical advice.[17] RT facilities use a variety of realistic and virtual interactive tools that mainly work to desensitize the child to the RT process. Realistic tools include practicing laying still at home or at the treatment center and performing a "dry run" of the intended treatment. Virtual interventions utilize web-based tools, apps, and augmented/virtual reality to explore the treatment space. Both methods provide children ample opportunity to develop coping strategies for laying still prior to initiation of treatment. The "dry run" strategy has the additional benefit of allowing children to become comfortable with the imaging and radiation equipment and has been shown to contribute to patient desensitization and reduce sedation needs in pediatric RT.[12]

Play Therapy

Another intervention commonly used before treatment involves the use of play. The therapeutic use of play includes a spectrum of interventions varying by the complexity of problems the child faces.[18] These interventions allow the child to interact with the environment in a way that relieves anxiety and builds familiarity within an unfamiliar setting:

Spontaneous play. This is utilized for less complex problems and allows the child to naturally interact with their surroundings without intervention from others. Methods of this type of play involve animal therapy and use of a children's play area. Although this method of play may not be effective for developing coping around complex problems, spontaneous play can effectively reduce overall anxiety with an unfamiliar environment. For example, simply providing children with toys before undergoing medical procedures has been shown to relieve patient anxiety.[19] These interventions can be effectively implemented in the waiting area so children can relieve stress prior to and even after treatment. In this manner, children will develop a positive association with the treatment facility.

Medical play. This is used for more complex emotional problems and is administered by a trained professional, often a child life specialist (CLS) or social worker, in the health care setting. This type of play involves letting the child interact with medical devices with the goal of developing effective coping methods before treatment. This type of therapy allows children to "play out" their feelings and anxieties.[20] An experienced professional can then help the child build strategies for dealing with these negative emotions. Medical play can be implemented in a way that allows the patient to develop a feeling of agency in their own treatment. For example, playing with teaching dolls and treatment machine models allows the child to play the role of provider. They can then externalize the fears their doll may have, which can be addressed by the CLS. Based on recent provider surveys received by members of the Children's Oncology Group (COG) from 84 institutions, the most common medical play intervention used by providers is mask decoration (71%).[1] Masks can be decorated by the child to depict a favorite superhero or cartoon character to develop a degree of pride. Some creative examples are demonstrated in **Figure 1**. In addition, children can make masks for family and members of the treatment team to create a sense of shared experience. To gain familiarity with

SA-CME (see page 13)

radiation treatment itself, sites also use models of treatment machines, radiology coloring books, and teaching dolls. These interventions allow the child to understand how treatment works and what RT accomplishes. Medical play is among the most researched and efficacious intervention in pediatric RT with multiple studies showing either a reduction in sedation requirement[7,10] or in patient anxiety with this technique.[13] This intervention also produces a significant health care cost reduction largely through decreased anesthesia use.[7]

Interventions During Radiation Therapy Treatment

Specialized Staff

Pediatric patients have unique developmental and psychological needs in the medical setting. Specially trained staff, including CLS staff and social workers, are frequently utilized by RT facilities to care for their pediatric population. CLS staff are reportedly utilized in over half of pediatric RT centers.[1,16] CLSs use developmentally appropriate and individualized strategies to assist children and families with the psychological burden of pediatric illness.[21] In addition, CLS staff are trained in a variety of interventions already mentioned. Integrating a CLS program in RT helps decrease psychological anxiety and sedation needs,[7] as well as reduce overall treatment costs.[7,21,22] In RT facilities that see a smaller volume of pediatric patients, CLSs may not be available. In such cases, regular staff specially trained in various interventions discussed here can be utilized. If special training is not possible, a consistent treatment team can increase a child's familiarity with the staff. Although not specifically studied in pediatric RT, the use of a consistent treatment team is commonly implemented by RT providers[1] and has precedented use for pediatric patients at increased risk of distress in pediatric medical oncology.[23]

Environmental Modifications

The medical environment where a child receives care has been shown to have a significant effect on a patient's anxiety.[24] Therefore, designing interventions aimed at making the medical environment more comforting to pediatric patients can have a significant psychological impact on children undergoing treatment. RT providers have reported using child-friendly décor and allowing patients to ride into the treatment vault on a toy car or airplane. Modifying the environment in this way creates a sense of comfort with the medical setting and has been shown to improve patient satisfaction in comparable pediatric settings.[24]

Distraction

This includes interventions that aim to shift the child's attention away from negative emotion toward more favorable stimuli. This form of intervention is one of the most frequently utilized by pediatric RT providers.[1,16] and serves primarily to alleviate anxiety during treatment. Frequent techniques involve the use of comfort objects for the child to hold, music therapy, aromatherapy, movies, or audiobooks. In the setting of pediatric RT, music therapy has been the most extensively studied with noted benefit during treatment as well as making children potentially open to additional psychosocial support.[6] Music therapy appears to be effective when the child is able to create an individualized playlist beforehand. This method could be imitated for other distraction techniques by allowing the child to select an audiobook or video to watch during treatment.

Another form of distraction involves allowing communication with the caregiver during treatment setup or treatment delivery. Roughly half of pediatric RT providers report using some form of caregiver interaction with the patient once treatment has begun.[1,16] When the child is in the treatment vault, communication with the caregiver can be maintained via two-way audio or video, or by allowing the caregiver to remain in the treatment vault with a lead shield.

Reward/Incentive Systems

Use of a reward system provides incentives for children to complete RT and instills a sense of accomplishment throughout the treatment process. Rewards can be used both after each treatment session as well as at the conclusion of the entire treatment course. Incentives after each RT session include allowing the child to select a prize from a treasure chest and implementing a bravery bead program. Bravery beads are common in pediatric oncology due to the number of procedures/interventions involved. This activity involves the child creating a necklace of different types of beads that are given after various procedures. This necklace becomes a way to commemorate the treatment process and helps children communicate their experience to others.[25] End-of-treatment celebrations are also common in the RT setting, although it is important to note that, in adults, ringing a cancer bell to celebrate treatment completion has been associated with increased levels of overall distress from cancer treatment at follow-up. However, it is unclear if this association is present in the pediatric population.[26]

A unique way to allow children to document and memorialize their treatment is to encourage them to record a video documentary of themselves throughout the process.[11] Children who undergo this movie-making project report increased willingness to undergo treatment since they can record in real-time what RT is like for them. This project also facilitates the ability to communicate their experiences and allows for smoother reintegration back to school. After the fact, a movie-making program could serve as a form of psychoeducation if videos are shared with children who have not yet begun treatment.

Conclusion

This review highlights multiple resources in practice that lead to a reduction

SA-CME (see page 13)

in anxiety and better toleration of RT for children. Anxiety minimization is crucial, especially given increased cost and morbidity associated with the anesthesia requirements. While the types of interventions outlined above are being implemented at several facilities with large pediatric patient volume,[1,14,16] additional research is needed to validate specific practices in pediatric RT and determine which are most effective.

While interventions can be useful for many children to reduce the need for sedation, it is important to determine which patients will be most amenable to this additional support. The use of a screening survey is a valuable tool for RT providers who wish to implement various practices discussed in this review. Screening can be particularly useful in RT facilities with limited resources dedicated to their pediatric population as screening will better direct resources to patients most likely to benefit. Screening can be used to stratify patients into three groups: 1) those likely to require sedation regardless of intervention, 2) those amenable to an intervention (ie, "gray zone"), or 3) those unlikely to require sedation regardless of intervention.[3] Resources can then be targeted toward children in the "gray zone" since they are most likely to benefit from chosen interventions. Various pediatric RT studies describe use of a screening step as part of their intervention process for reducing sedation[3,7,9,10] while others report specific success targeting patients in the "gray zone."[3] Many criteria characterize a child's likelihood of requiring support to avoid sedation but common themes include the child's ability to communicate, physical limitations, level of pain or anxiety, understanding and experience with medical treatment, ability to separate from caregivers, and various other developmental assessments.[3,7,9,10] Additional research is needed to determine the criteria that best stratify patients into these three categories.

It is recognized that RT facilities have different resources and patient populations. Therefore, we hope this review will serve as an outline of tools for centers to use in adopting an individualized approach to their pediatric patients.

References

1. Holt DE, Hiniker SM, Kalapurakal JA, et al. Improving the pediatric patient experience during radiation therapy – a children's oncology group study. *Int J Radiat Oncol Biol Phys*. 2020; 109(2):505-514.
2. McFadyen JG, Pelly N, Orr RJ. Sedation and anesthesia for the pediatric patient undergoing radiation therapy. *Curr Opin Anaesthesiol*. 2011;24(4):433-438. doi:10.1097/ACO.0b013e328347f931
3. Jacques A, Udowicz M, Bayliss Y, Jensen K. Thinking differently about the kids: an innovative approach to improve care provided to pediatric patients undergoing external beam radiation therapy. *J Med Imaging Radiat Sci*. 2014;45(3):269-275. doi:10.1016/j.jmir.2013.12.009
4. Fortney JT, Halperin EC, Hertz CM, Schulman SR. Anesthesia for pediatric external beam radiation therapy. *Int J Radiat Oncol Biol Phys*. 1999;44(3):587-591. doi:10.1016/s0360-3016(99)00058-9
5. Haeberli S, Grotzer MA, Niggli FK, et al. A psychoeducational intervention reduces the need for anesthesia during radiotherapy for young childhood cancer patients. *Radiat Oncol*. 2008;3:17. doi:10.1186/1748-717X-3-17
6. Barry P, O'Callaghan C, Wheeler G, Grocke D. Music therapy CD creation for initial pediatric radiation therapy: a mixed methods analysis. *J Music Ther*. 2010;47(3):233-263. doi:10.1093/jmt/47.3.233
7. Grissom S, Boles J, Bailey K, et al. Play-based procedural preparation and support intervention for cranial radiation. *Support Care Cancer*. 2016;24(6):2421-2427. doi:10.1007/s00520-015-3040-y
8. Klosky JL, Tyc VL, Srivastava DK, et al. Brief report: evaluation of an interactive intervention designed to reduce pediatric distress during radiation therapy procedures. *J Pediatr Psychol*. 2004;29(8):621-626. doi:10.1093/jpepsy/jsh064
9. Mizumoto M, Oshiro Y, Ayuzawa K, et al. Preparation of pediatric patients for treatment with proton beam therapy. *Radiother Oncol*. 2015;114(2):245-248. doi:10.1016/j.radonc.2015.01.007
10. Scott L, Langton F, O'Donoghue J. Minimising the use of sedation/anaesthesia in young children receiving radiotherapy through an elective play preparation programme. *Euro J Oncol Nurs*. 2002;6(1):15-22.
11. Shrimpton BJ, Willis DJ, Tongs CD, Rolfo AG. Movie making as a cognitive distraction for paediatric patients receiving radiotherapy treatment: qualitative interview study. *BMJ Open*. 2013;3(1):e001666. doi:10.1136/bmjopen-2012-001666
12. Slifer KJ. A video system to help children cooperate with motion control for radiation treatment without sedation. *J Pediatr Oncol Nurs*. 1996;13(2):91-97. doi:10.1177/104345429601300208
13. Tsai YL, Tsai SC, Yen SH, et al. Efficacy of therapeutic play for pediatric brain tumor patients during external beam radiotherapy. *Childs Nerv Syst*. 2013;29(7):1123-1129. doi:10.1007/s00381-013-2099-3
14. O'Connor M, Halkett GK. A systematic review of interventions to reduce psychological distress in pediatric patients receiving radiation therapy. *Patient Educ Couns*. 2019;102(2):275-283. doi:10.1016/j.pec.2018.09.023
15. Oncology Nursing Society. Psychoeducation/Psychoeducational Interventions. Accessed October 15, 2020. https://www.ons.org/node/901?display=pepnavigator&sort_by=created&items_per_page=50
16. Boik N, Hall MD. Psychosocial support for pediatric patients at proton therapy institutions. *Int J Part Ther*. 2020;7(1)28-33.
17. Levenson PM, Morrow JR, Signer B. A comparison of noninteractive and interactive video instruction about smokeless tobacco. *J Educ Technol Sys*. 1986;14(3):193-202. doi:10.2190/tpb2-wybe-97q0-qrdb
18. Play Therapy International. The Therapeutic Play Continuum. Accessed October 8, 2020. http://playtherapy.org/Play-Continuum
19. Ghabeli F, Moheb N, Hosseini Nasab SD. Effect of toys and preoperative visit on reducing children's anxiety and their parents before surgery and satisfaction with the treatment process. *J Caring Sci*. 2014;3(1):21-28. doi:10.5681/jcs.2014.003
20. Medical Play. Children's Hospital of Philadelphia. Accessed October 8, 2020. https://www.chop.edu/health-resources/medical-play
21. Boles J. The Value of Certified Child Life Specialists: Direct and Downstream Optimization of Pediatric Patient and Family Outcomes. 2020. Accessed October 14, 2020. https://www.childlife.org/docs/default-source/the-child-life-profession/value-of-cclss-full-report.pdf?sfvrsn=5e238d4d_2
22. Scott MT, Todd KE, Oakley H, et al. Reducing anesthesia and health care cost through utilization of child life specialists in pediatric radiation oncology. *Int J Radiat Oncol Biol Phys*. 10 2016;96(2):401-405. doi:10.1016/j.ijrobp.2016.06.001
23. Kazak AE. Pediatric Psychosocial Preventative Health Model (PPPHM): research, practice, and collaboration in pediatric family systems medicine. *Fam Syst Health*. 2006;24(4):381-395.
24. Hamdan AB. The impact of creating a child-friendly hospital environment in pediatric cancer patients and their families in comprehensive cancer center at King Fahad Medical City. *Curr Pediat Res*. 2016;20(1).
25. What are Bravery Beads? Children's Hospital Foundation. 2020. Accessed October 14, 2020. https://www.youtube.com/watch?v=RnbGfLiHtNA
26. Williams PA, Hu J, Yang D, Cao S, Jennelle RL. The cancer bell: too much of a good thing? *Int J Radiat Oncol Biol Phys*. 10 2019;105(2):247-253. doi:10.1016/j.ijrobp.2019.06.012

Proliferation Saturation Index to Characterize Response to Radiation Therapy and Evaluate Altered Fractionation in Head and Neck Cancer

Mohammad U. Zahid, PhD; Abdallah S.R. Mohamed, MD; Kujtim Latifi, PhD; Anupam Rishi, MD; Louis B. Harrison, MD; Clifton D. Fuller, MD, PhD; Eduardo G. Moros, PhD; Jimmy J. Caudell, MD, PhD; Heiko Enderling, PhD

Abstract

Objective: To personalize radiation therapy dose fractionation protocols, it will be necessary to first quantitatively describe tumor volume reduction dynamics and subsequently simulate the results of alternative fractionation schemes.

Methods and Materials: The proliferation saturation index (PSI) model of tumor volume dynamics was fit to weekly tumor volume data from computed tomography scans of n = 39 head and neck cancer patients who received 66 to 70 Gy in standard daily fractions or with accelerated fractionation. Using the outputs of this model, we additionally simulated how these patients would respond to hyperfractionation with 1.2 Gy fractions twice a day. We identified PSI values that would improve responses and outcomes to hyperfractionation compared to single daily fractions.

Results: The PSI model fit volumetric tumor response dynamics data with high accuracy ($R^2 = 0.92$) using patient-specific PSI values. Simulations of an alternative fractionation protocol demonstrated that a subset of patients with intermediate PSI values could potentially have improved locoregional control by switching to hyperfractionation.

Conclusions: This is the first demonstration of the PSI model fitting data from head and neck cancer patients, and the results suggest a benefit from alternative fractionation schemes for a selected subset of patients.

Dr. Zahid *is a postdoctoral fellow, Department of Integrated Mathematical Oncology, H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL.* ***Dr. Mohamed*** *is an instructor, and* ***Dr. Fuller*** *is an associate professor, both in the Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX.* ***Dr. Latifi*** *is an assistant member,* ***Dr. Rishi*** *is a resident physician,* ***Dr. Harrison*** *is the chair and a senior member,* ***Dr. Moros*** *is a senior member and chief of medical physics, and* ***Dr. Caudell*** *is an associate member, all in the Department of Radiation Oncology, H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL.* ***Dr. Enderling*** *is an associate member, Department of Integrated Mathematical Oncology, and Department of Radiation Oncology, H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL.* *Disclosure: Dr. Caudell reports grants, personal fees and other fees from Varian, outside of the submitted work. Dr. Enderling reports grants from NIH/NCI Physical Sciences in Oncology Network (1 U01 CA244100-01), while conducting the study. Dr. Zahid and Dr. Enderling have a patent "Personalized Radiation Therapy" (63/010,327) pending. Dr. Fuller reports grants from NIH, NIBIB, Elekta, NSF, University of Texas Health Science Center at San Antonio, and the American Association of Physicists in Medicine. Dr. Moros reports grants/payments from Varian outside of the submitted work. No other authors have conflicts of interest to disclose, and no part of this article has been previously published elsewhere.*

Head and neck cancers (HNC) are commonly treated with definitive radiation therapy (RT) with or without systemic therapy, with RT being the single most common oncologic treatment.[1,2] Few inroads have been made to synergize biological and quantitative approaches with radiation biology and radiation oncology methodologies to personalize and optimize RT. Standard treatment is 56 to 70 Gy in 1.8 to 2 Gy fractions once daily with or without concurrent chemotherapy,[1] derived from maximum tolerable dose concepts and dose-escalation trials premised on a "one-size-fits-all" RT dose. Current radiation oncology clinical practice is that every patient receives the same treatment, planned strictly on pre-radiation American Joint Committee on Cancer (AJCC) TNM stage (Tumor size, lymph Node involvement, Metastasis presence), without regard to individual tumor dynamics that may influence RT outcome. Oropharyngeal cancer still represents significant heterogeneity within the same stage group. Thus, it remains unclear why some patients with similar clinical stage, treated with identical RT dose and dose fractionation, are cured while others are not. There is a strong need for personalized RT for individual patients.[3]

Table 1. Patient Characteristics

	Moffitt Cancer Center Cohort n = 17	MD Anderson Cancer Center Cohort n = 22
Primary Site	**n (%)**	**n (%)**
Bilateral	1 (5.9%)	0 (0%)
Base of tongue	0 (0%)	8 (36.4%)
Gum	0 (0%)	1 (4.6%)
Oral cavity	2 (11.8%)	0 (0%)
Oropharynx	14 (82.4%)	0 (0%)
Soft palate	0 (0%)	1 (4.6%)
Tongue	0 (0%)	2 (9.1%)
Tonsil	0 (0%)	10 (45.5%)
T stage		
T1	3 (17.7%)	7 (31.8%)
T2	8 (47.1%)	8 (36.4%)
T3	4 (23.5%)	2 (9.1%)
T4	0 (0%)	5 (22.7%)
TX	2 (11.8%)	0 (0%)
N stage		
N0	1 (5.9%)	0 (0%)
N1	1 (5.9%)	2 (9.1%)
N2	13 (76.5%)	20 (90.9%)
Metastases?		
No	17 (100.0%)	22 (100.0%)
Yes	0 (0%)	0 (0%)
Treatment		
RT alone	0 (0%)	11 (50.0%)
Chemo + RT	17 (100.0%)	11 (50.0%)
p16 status		
Positive	6 (35.3%)	16 (72.7%)
Negative	5 (29.4%)	5 (22.7%)
Unknown	6 (35.3%)	1 (4.6%)

Adaptive RT delivery has been suggested primarily for anatomical and spatial adjustments during the course of treatment.[4] Although alternative fractionation schemes have been tested in clinical trials with modest improvements from altered fractionation, it is possible that these benefits may be offset by increased toxicities across the cohort.[5] This sets up the need to be able to identify specific patients who may benefit from alternative fractionation protocols. To rigorously evaluate every possible radiation dose and dose fractionation is experimentally and clinically unfeasible.[6] However, the burgeoning field of integrated mathematical oncology may make such analyses possible. The integration of quantitative approaches could provide novel, reliable biomarkers based on mathematics and patient-specific disease dynamics to guide RT treatment personalization.[7-9]

Mathematical modeling in radiation oncology has a long history, with the linear-quadratic (LQ) model,[10-14] biologically effective dose (BED),[15-19] tumor control probability,[20–22] and normal tissue complication probability (NTCP)[23-25] being widespread in research and practice. Recent mathematical modeling and simulation studies of the canonical radiobiological principles have led to the concept of temporally feathered radiation therapy (TFRT). In TFRT, different treatment plans are developed for each weekday of fractionated radiation to spare organs at risk in fractionated radiation schedules.[26,27] In close collaboration with experimental biologists, a mathematical model of glioma response to radiation has been calibrated and validated to develop and subsequently experimentally confirm radiation protocols that optimally counteract stem cell dedifferentiation dynamics.[28]

One mainstay of mathematical modeling in radiation oncology is to simulate the volume regression profiles during RT,[29-33] and to predict responses to a variety of dose and dose fractionation protocols.[33-37] Previous analyses revealed that parameters of complex models may

be impossible to determine with limited clinical data,[38] suggesting that the number of patient-specific parameters must be kept to a minimum to avoid overfitting and model uncertainty. To this extent, the novel concept of a proliferation saturation index (PSI) has been previously introduced to simulate non-small cell lung cancer patient-specific response to RT with a single parameter.[39,40] Mathematical analysis revealed that PSI can robustly describe clinical data for a wide range tumor growth models.[41] Here we show that the PSI model can simulate head and neck cancer patient-specific responses to RT with data from two clinical cohorts from Moffitt Cancer Center and MD Anderson Cancer Center. We then use the model to run in silico comparisons of a hyperfractionation protocol to identify which patients may most benefit from hyperfractionated radiation.

Methods and Materials

Patient Data

A total of 39 head and neck cancer patients were treated with 66 to 70 Gy RT with and without concurrent chemotherapy. Seventeen patients were treated at Moffitt Cancer Center where they received a total of 66 to 70 Gy RT in 2 Gy weekday fractions with concurrent chemotherapy, and the remaining 22 patients were treated at MD Anderson Cancer Center where they received a total of 66 to 70 Gy RT (2 or 2.12 Gy weekday fractions or with accelerated fractionation) with half of the patients receiving concurrent chemotherapy. The patient cohort was comprised of different primary sites (oropharyngeal, laryngeal, nasopharyngeal), HPV status, and clinical stage (stage T1-T4). Patient characteristics for the two cohorts are detailed in **Table 1**.

Tumor volumes were delineated on weekly cone-beam computed tomography (CBCT) or CT-on-Rails system combining a GE Smart Gantry CT scanner (GE Healthcare) and a 2100EX linear accelerator (Varian) (256 total CT-scan-derived tumor volumes). It should be noted that contouring tumor volumes from CBCT scans is highly dependent on adequate image quality. Insufficient contrast, obstruction of the tumor by other patient anatomy, and other factors may prevent delineation of tumor volumes. We only included tumor volumes from patients who had contourable images. Nearly 50% of the patients considered for the study had inadequate image quality and were thus excluded. Locoregional control censored up to 5 years was abstracted as outcome measure and determined by biopsy confirmation or imaging sufficient to initiate additional treatments.

Mathematical Model

Tumor growth was modeled as logistic growth as governed by the following differential equation:

$$\frac{dV}{dt} = \lambda V\left(1 - \frac{V}{K}\right)$$

where λ is the intrinsic volumetric growth rate [day^{-1}], V is the gross tumor volume [cc], and K is the tumor carrying capacity [cc], which is defined as the maximum tumor volume that the local tissue can support. We have previously proposed characterizing individual patient tumor growth rates with the PSI, as opposed to the patient-specific growth rates.[41] PSI is defined as the ratio of the initial tumor volume at the start of RT, V_0, to the tumor carrying capacity:

$$PSI \equiv \frac{V_0}{K}$$

PSI is defined between 0 and 1 and PSI represents the fraction of nonproliferative cells in the tumor (**Figure 1**).

Response to radiation was modeled using the linear-quadratic (LQ) model:[13]

$$SF(d) = e^{-\alpha d - \beta d^2}$$

where SF(d) is the surviving fraction of cells after receiving a radiation dose, d [Gy]; and α [Gy^{-1}] and β [Gy^{-2}] are radiosensitivity coefficients. This is connected to the change in tumor volume by assuming that only proliferating cells are killed by radiation, in line with the Norton-Simon hypothesis that the rate of tumor regression under therapy is proportional to the tumor growth rate.[42-44] The change in tumor volume with each radiation fraction is modeled as follows:

$$V_{post-RT-Fx} = V_{pre-RT-Fx} \cdot \gamma\left(1 - \frac{V}{K}\right)$$

where γ is the volumetric death term per radiation fraction that is coupled to the LQ model as follows:

$$\gamma = 1 - SF(d)$$

Implementation and Optimization

Custom scripts were written in MATLAB (Mathworks) to simulate volume trajectories given inputs of fractionation schedule, dose per fraction, λ, PSI, α, and α/β. To evaluate the ability of the model to fit the patient data, an optimization script was written using the particle swarm optimization function from the MATLAB Global Optimization Toolbox to find patient-specific PSI values, given a particular (λ,α) pair for the entire cohort, assuming α/β = 10 Gy. The optimal values for λ and α were found by performing a full grid search over $\lambda \in (0.02, 0.18)$ day^{-1} with a step size of 0.025 and $\alpha \in (0.04, 0.25)$ Gy^{-1} with a step size of 0.01 to find the (λ,α) pair that minimized the mean square error to the patient data across the entire cohort for the first 4 weekly measurements.

Results

The parameter optimization identified that the values of λ = 0.07 day^{-1} and α = 0.09 Gy^{-1} best fit the tumor volume dynamics across the entire patient cohort. Although the values of λ and α were the same for all patients, the patient-specific PSI values allowed the

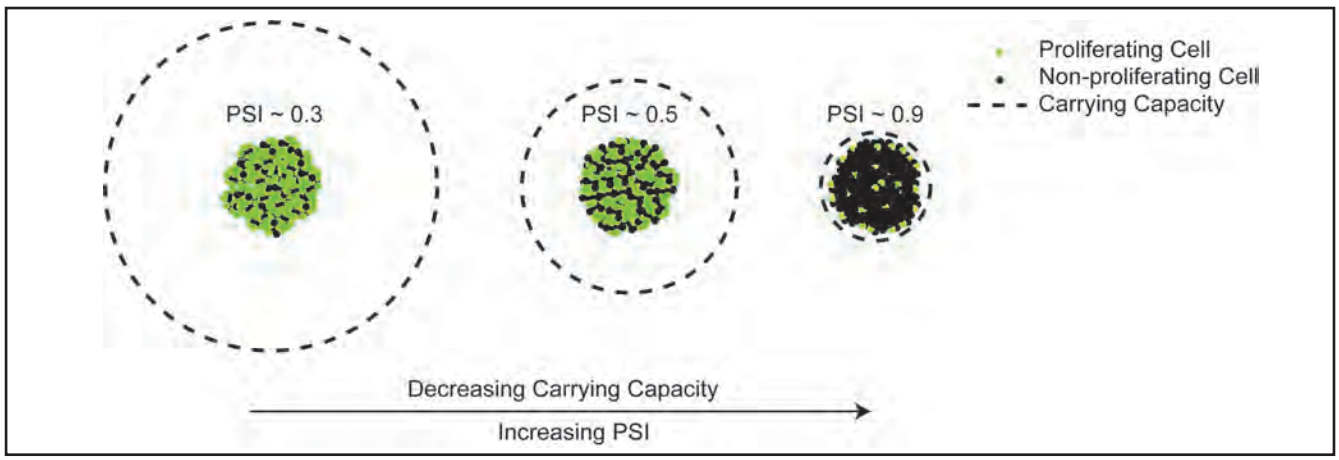


FIGURE 1. *Schematic depiction of proliferation saturation index (PSI). Assuming a fixed growth rate and initial tumor size, an increasing PSI indicates both a decreasing proliferative cell fraction and tumor carrying capacity. Green circles indicate proliferating cells; black circles nonproliferating cells; dashed circle the putative carrying capacity.*

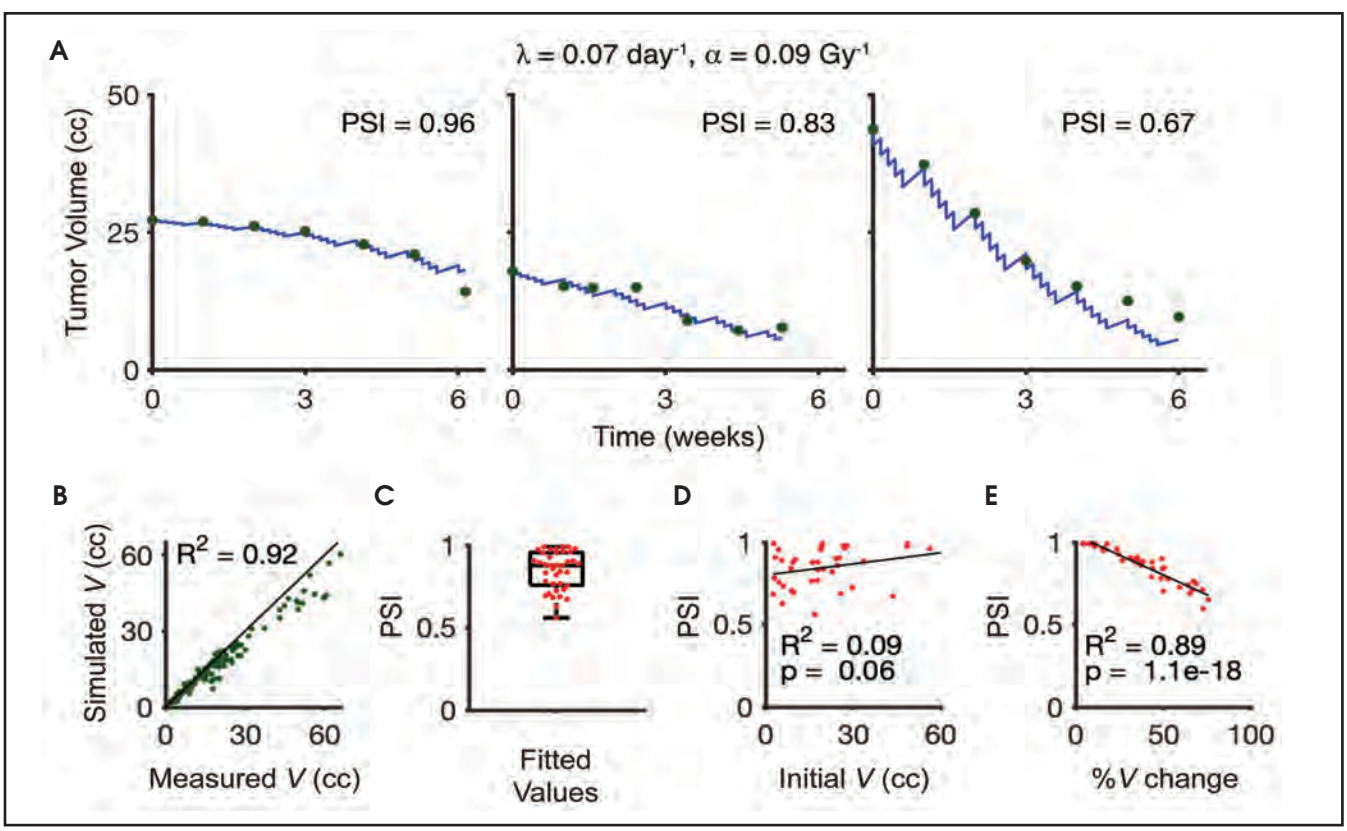


FIGURE 2. *Model fit results with uniform λ and α values across the cohort and patient-specific PSI values. (A) Representative fitting results for 3 patients with 3 different PSI values, using λ = 0.07 day^{-1} and α = 0.09 Gy^{-1}. The green markers indicate weekly tumor volumes at the start of RT; black markers show weekly tumor volumes during RT; blue curves show the model fits. (B) Correlation of simulated volumes (derived from the model fits) to the measured tumor volumes for all 39 patients. Green markers indicate individual weekly time points and the black line has a slope of 1. The R^2 value shows the degree of correlation to this line and thus the accuracy of the simulations. (C) Box plot of fitted PSI values with individual values indicated. The center line indicates the median; the bottom and top edges of the box show the 25th and 75th percentiles, respectively. (D) PSI as a function of initial tumor volume, showing no significant correlation. Black line indicates the best-fit linear regression, with R^2 indicated. P-value is shown for comparison against the null model. (E) PSI as a function of percent tumor volume change by week 4 of RT, showing significant correlation. Black line indicates the best-fit linear regression, with R^2 indicated. P-value is shown for comparison against the null model.*

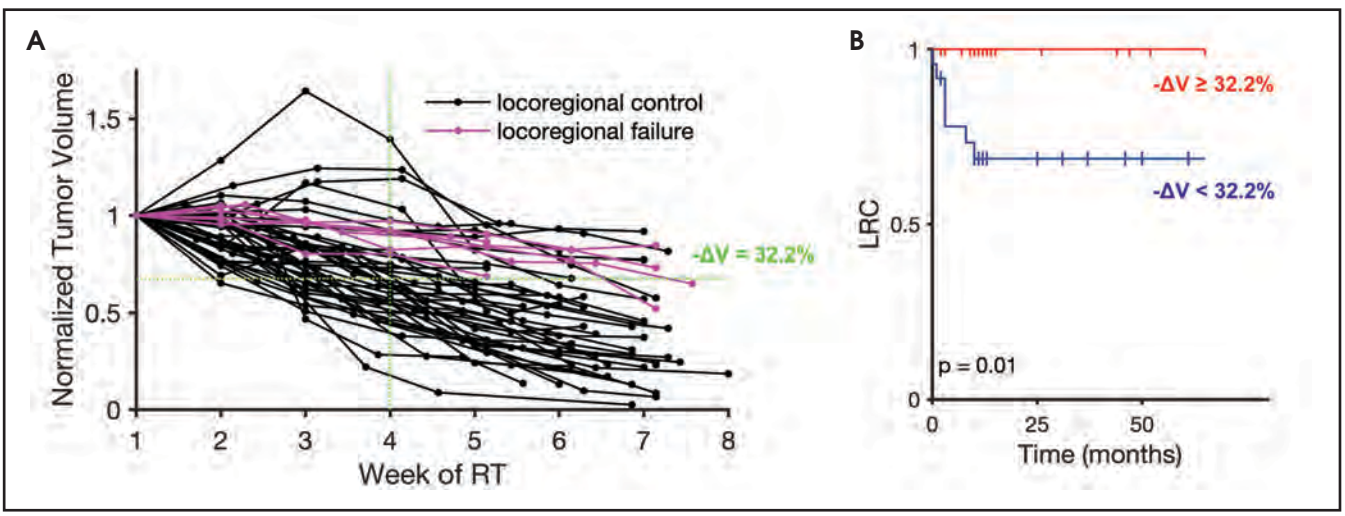


FIGURE 3. *Median tumor volume reduction at week 4 of RT can stratify for locoregional control. (A) Weekly tumor volumes normalized by initial tumor volume before start of RT during the course of treatment. Patients with eventual locoregional failure are highlighted in purple. The indicated median volume reduction at week 4 of RT perfectly separates the locoregional failures at week 4. (B) Kaplan-Meier survival plot for locoregional control (LRC) separated by percent tumor volume reduction at 4 weeks of RT.*

model to fit both shallow-volume regression dynamics (high PSI) and rapid-volume reduction responses (low PSI) with high accuracy (**Figure 2A**). Across the entire cohort, the model fit the weekly tumor volumes with high confidence; $R^2 = 0.92$ (**Figure 2B**). Notably, while PSI was allowed to range from 0 to 1, only values > 0.5 were obtained from the fitting procedure using the optimized λ and α values, which indicates that the model was not overconstrained or overfitting the data (**Figure 2C**).

To assess the clinical significance of the model parameters, we compared patient-specific clinical measures with the fitted model parameters. Initial tumor size did not correlate with PSI (**Figure 2D**), but percent change in tumor volume after 4 weeks of RT showed a strong correlation with PSI (**Figure 2E**).

To translate tumor volume reduction to long-term patient outcomes, we tested midtreatment tumor volume reduction as a predictor for locoregional control (LRC). We found that the median tumor volume reduction at week 4 ($-\Delta V = 32.2\%$) perfectly separates out those patients who had early locoregional recurrence (**Figure 3**). This is comparable to the recent observation that midtreatment nodal decrease ≥ 43% in oropharyngeal cancer is prognostic for locoregional control.[45]

Given that the standard protocol with 2 Gy weekday fractions results in a subset of patients recurring locoregionally, we simulated an alternative hyperfractionation scheme of 1.2 Gy fractions 2 times a day (1.2 Gy BID). These simulations were performed using the previously optimized λ, α values across the cohort, and patient-specific PSI values. As expected, these simulations predicted that all the patients would have increased tumor volume reduction due to the higher total dose (**Figure 4A**). However, only a subset of patients with intermediate PSI ([0.835-0.91], Case II: 12/38 patients, 32%) is predicted to have sufficient marginal increase in tumor volume reduction to cross the previously determined volume-reduction threshold for LRC, indicating a potential to benefit from a switch to hyperfractionation (**Figure 4B**). On the other hand, patients with low PSI values have highly proliferative and radiation-sensitive disease (PSI < 0.835; Case I: 15/38, 39%), with both 2 Gy QD and 1.2 Gy BID yielding midtreatment tumor volume reductions > 32.2% indicating no additional benefit from hyperfractionation. On the other extreme, patients with high PSI values have less proliferative and more radioresistant tumors (PSI > 0.91; Case III: 12/38, 32%), and in this case neither fractionation protocol provides robust midtreatment tumor volume reduction.

Discussion

Herein, we presented a simple mathematical model based on proliferation saturation index, PSI, that was able to characterize head and neck cancer patient-specific volume changes to fractionated RT with only 1 patient-specific parameter with high accuracy. Notably, the growth rate is assumed to be constant across the entire cohort, and all interpatient heterogeneity is captured in the PSI values. Of interest, initial tumor size, and thusly T stage, did not correlate with PSI and midtreatment response. The need to only determine one patient-specific parameter may facilitate future patient-specific modeling and predictions. It may be possible to estimate patient-specific PSI values using midtreatment volume reduction, which was shown to correlate with PSI. Furthermore, these modeling results demonstrate that treatment response dynamics may provide valuable

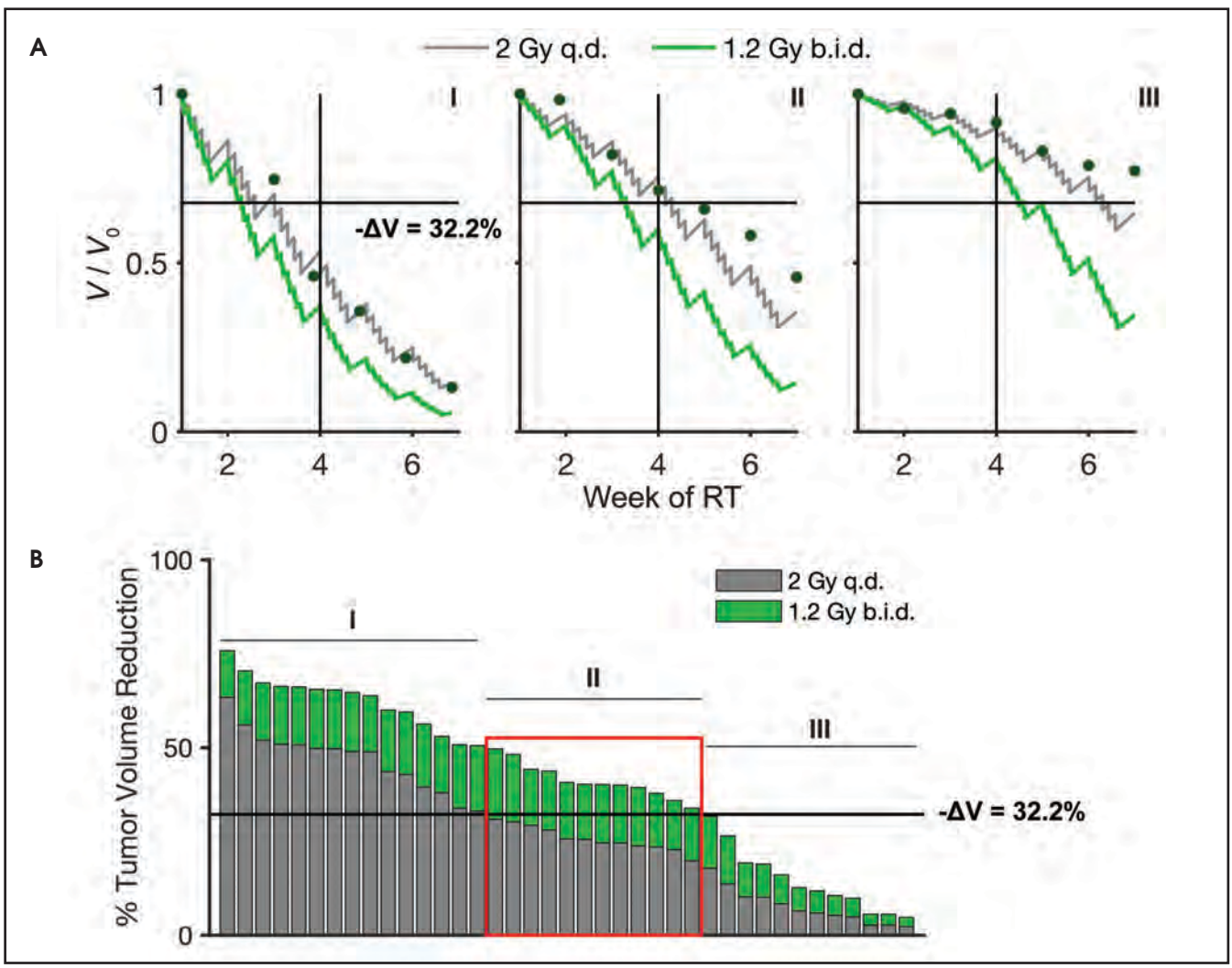


FIGURE 4. *In silico comparison of 2 radiation fractionation schemes for the entire cohort using previously optimized parameters. (A) Normalized tumor volume trajectories for original fractionation scheme (2 Gy QD) compared to an alternative fractionation scheme (1.2 Gy BID) for representative patients from the 3 possible cases (I. Both original and alternate fractionation are below the LRC volume reduction threshold. II. The original fractionation scheme is above the LRC threshold and the alternate fractionation scheme is below the threshold. III. Both fractionation schemes are above the threshold). Black solid lines indicate 32.2% tumor volume reduction at week 4 of RT. (B) Waterfall plot of percent tumor volume reduction for both radiation fraction schemes, sorted by degree of tumor volume reduction. Gray bars indicate percent tumor volume reduction with 2 Gy QD; green bars show percent tumor volume reduction for 1.2 Gy BID; horizontal black line shows the 32.2% tumor volume reduction threshold correlated with LRC; and red box highlights patients calculated to cross the volume reduction threshold correlated with LRC with the alternate fractionation scheme.*

insights to understanding the nature of the disease. These results complement previous analysis of pretreatment tumor volume dynamics associated with outcomes in patients with oropharyngeal cancer.[46]

Additionally, since the tumor volumetric death term was coupled to the LQ model, we were able to simulate the potential response to an alternative fractionation scheme of hyperfractionation with 1.2 Gy BID. Although hyperfractionation is not widely used in clinical practice to treat squamous cell head and neck cancers, large meta-analyses have shown an 8% difference in overall survival at 5 years post-treatment compared with standard fractionation.[5,47] However, this benefit may be offset by long-term toxicities from the increased overall dose and logistical difficulties in delivering multiple fractions a day. Mathematical models of tumor volume dynamics may eventually serve as part of a framework to identify patients who would benefit from hyperfractionation over standard fractionation.

It is important to note that the α values identified in this study are for radiosensitivity for the entire tumor volume

and are not directly comparable to radiosensitivity parameters derived from clonogenic assays in vitro. With the correlation of locoregional control with a volumetric reduction threshold at 4 weeks of RT, we used these simulations to identify which patients could benefit from hyperfractionation to achieve robust midtreatment tumor volume reductions that correlate with locoregional control. This study demonstrates mathematical-modeling-derived PSI as a radioresponse biomarker in head and neck cancer and supports previous findings in non-small cell lung cancer that patients with intermediate PSI values may benefit from hyperfractionation protocols.

Of interest mathematically, it is difficult to accurately identify a unique (λ,α) parameter pair that fits the entire cohort, as other parameter pairs with the same λ/α ratio would yield similar model fits. Thus, it is important to accurately identify either the volumetric growth rate before the start of therapy or tumor radiosensitivity. This can potentially be accomplished with just two pre-treatment CT scans spaced a few weeks apart, such as at diagnosis and at treatment planning or simulation, similar to a previous study of tumor volumetric growth velocity.[46] Radiation sensitivity index, RSI, may be a candidate for radiosensitivity that will be explored in future studies.[3] The alternative fractionation simulations are also limited by the canonical radiobiological assumptions of the LQ model. It will be important to verify whether this method of accounting for different dose sizes holds up in similar data with different doses per fraction.

Notably, our model cannot capture transient increases in tumor volume during the first few weeks of RT. These types of small increases in tumor volume, or pseudo-progression, in early weeks of treatment have been seen in the other studies. In a recent study of 44 node-positive oropharyngeal cancers,[45] the authors saw changes in nodal volume ranging from a 74.3% volume increase to a 73.6% volume decrease at day 10 of chemoradiation; a 48% volume increase to a 94.9.% volume decrease at day 20; and a -18.1% volume increase to a 95.6% volume decrease at day 35. This can potentially be addressed by building a model with a delayed effect of RT.

Conclusion

We acknowledge that this analysis was performed on a small number of patients (n = 39), but we would like to note that our methodology of analyzing longitudinal tumor volumes (6 to 8 CT scans per patient) increases total data points to n = 256 CT scans, significantly strengthening the analysis. The usability of this model in making patient-specific predictions and clinical recommendations still requires independent parameter calibration and validation in independent datasets with larger and more homogenous cohorts.[48] However, the results presented here are important steps in the mathematical modeling of RT response in this cancer type and demonstrate the potential for testing alternative treatment schemes in silico to inform the design of clinical trials for personalizing RT prescriptions.

References

1. Marur S, Forastiere AA. Head and neck cancer: changing epidemiology, diagnosis, and treatment. *Mayo Clin Proc.* 2008;83:489-501.
2. Marur S, Forastiere AA. Head and neck squamous cell carcinoma: update on epidemiology, diagnosis, and treatment. *Mayo Clin Proc.* 2016;91:386-396.
3. Mellon E, Yue B, Strom TS, et al. A genome-based model for adjusting radiotherapy dose (GARD): a retrospective, cohort-based study. *Lancet Oncol.* 2016;18(2):202-211. doi:10.1016/s1470-2045(16)30648-9
4. Veiga C, McClelland J, Moinuddin S, et al. Toward adaptive radiotherapy for head and neck patients: feasibility study on using CT-to-CBCT deformable registration for "dose of the day" calculations. *Med Phys.* 2014;41(3)031703.
5. Bourhis J, Overgaard J, Audry H, et al. Hyperfractionated or accelerated radiotherapy in head and neck cancer: a meta-analysis. *Lancet.* 2006;368(9538):843-854.
6. Enderling H, Kim S, Pilon-Thomas S. The accelerating quest for optimal radiation and immunotherapy combinations for local and systemic tumor control. *Ther Radiol Oncol.* 2018;2:1-3.
7. Enderling H, Alfonso JCL, Moros E, Caudell JJ, Harrison LB. Integrating mathematical modeling into the roadmap for personalized adaptive radiation therapy. *Trends Cancer.* 2019;5(8):467-474. doi:10.1016/*j.trecan.2019.06*.006
8. Aherne NJ, Dhawan A, Scott JG, Enderling H. Mathematical oncology and its application in non melanoma skin cancer--a primer for radiation oncology professionals. *Oral Oncol.* 2020;103:104473.
9. Anderson ARA, Quaranta V. Integrative mathematical oncology. *Nat Rev Cancer.* 2008;8(1):10-19. doi:10.14389/adr.4.10
10. Fowler JF. Fractionated radiation therapy after Strandqvist. *Acta Radiol Oncol.* 1984;23(4):209-216.
11. Dale RG. The application of the linear-quadratic dose-effect equation to fractionated and protracted radiotherapy. *Br J Radiol.* 1985;58(690):515-528.
12. Muller-Runkel R, Vijayakumar S. Equivalent total doses for different fractionation schemes, based on the linear quadratic model. *Radiology.* 1991;179(2):573-577.
13. Fowler JF. The linear-quadratic formula and progress in fractionated radiotherapy. *Br J Radiol.* 1989;62(740):679-694. doi:10.1259/0007-1285-62-740-679
14. Sachs RK, Hlatky LR, Hahnfeldt P. Simple ODE models of tumor growth and anti-angiogenic or radiation treatment. *Math Comput Model.* 2001;33(12-13):1297-1305. doi:10.1016/S0895-7177(00)00316-2
15. Diffey BL. A mathematical model of the biologically effective dose of solar UVA received by patients undergoing oral psoralen photochemotherapy for psoriasis. *Phys Med Biol.* 1981;26(6):1129.
16. Fowler JF. 21 Years of biologically effective dose. *Br J Radiol.* 2010;83(991):554-568. doi:10.1259/bjr/31372149
17. Orton CG. A unified approach to dose-effect relationships in radiotherapy. II: Inhomogeneous dose distributions. *Int J Radiat Oncol Biol Phys.* 1988;14(3):557-560.
18. Dale RG, Jones B. The effect of tumour shrinkage on biologically effective dose, and possible implications for fractionated high dose rate brachytherapy. *Radiother Oncol.* 1994;33(2):125-132.
19. Dahlman EL, Watanabe Y. Evaluating the biologically effective dose (BED) concept using a dynamic tumor simulation model. *Med Phys.* 2020.
20. O'Rourke SFC, McAneney H, Hillen T. Linear quadratic and tumour control probability modelling in external beam radiotherapy. *J Math Biol.* 2009;58(4-5):799.
21. Dhawan A, Kohandel M, Hill R, Sivaloganathan S. Tumour control probability in cancer stem cells hypothesis. *PLoS One.* 2014;9(5):e96093.
22. Chvetsov AV, Stewart RD, Kim M, Meyer J, Rengan R. Volume effects in the TCP for hypoxic and oxygenated tumors. *Med Phys.* 2020;47(9)4626-4633.
23. Colombo F, Francescon P, Cora S, Testolin A, Chierego G. Evaluation of linear accelerator radiosurgical techniques using biophysical parameters (NTCP and TCP). *Int J Radiat Oncol Biol Phys.* 1995;31(3):617-628.

24. Stocks T, Hillen T, Gong J, Burger M. A stochastic model for the normal tissue complication probability (NTCP) and applications. *Math Med Biol.* 2017;34(4):469-492. doi:10.1093/imammb/dqw013
25. Palma G, Monti S, Conson M, Pacelli R, Cella L. Normal tissue complication probability (NTCP) models for modern radiation therapy. *Seminars in Oncology.* 2019(46):210-218.
26. López Alfonso JC, Parsai S, Joshi N, et al. Temporally feathered intensity-modulated radiation therapy: A planning technique to reduce normal tissue toxicity. *Med Phys.* 2018;45(7):3466-3474.
27. Parsai S, Qiu RLJ, Qi P, et al. A step-by-step guide to temporally feathered radiation therapy planning for head and neck cancer. *J Appl Clin Med Phys.* 2020;21(7)209-215.
28. Leder K, Pitter K, LaPlant Q, et al. Mathematical modeling of PDGF-driven glioblastoma reveals optimized radiation dosing schedules. *Cell.* 2014;156(3):603-616.
29. Rockne R, Rockhill JK, Mrugala M, et al. Predicting the efficacy of radiotherapy in individual glioblastoma patients in vivo: a mathematical modeling approach. *Phys Med Biol.* 2010;55(12):3271-3285. doi:10.1088/0031-9155/55/12/001
30. Watanabe Y, Dahlman EL, Leder KZ, Hui SK. A mathematical model of tumor growth and its response to single irradiation. *Theor Biol Med Model.* 2016;13(1):1-20. doi:10.1186/s12976-016-0032-7
31. Wang P, Feng Y. A mathematical model of tumor volume changes during radiotherapy. *Sci World J.* 2013;2013.
32. Chvetsov A V. Tumor response parameters for head and neck cancer derived from tumor-volume variation during radiation therapy. *Med Phys.* 2013;40(3):34101.
33. Kyroudis CA, Dionysiou DD, Kolokotroni EA, Stamatakos GS. Studying the regression profiles of cervical tumours during radiotherapy treatment using a patient-specific multiscale model. *Sci Rep.* 2019;9(1):1-16. doi:10.1038/s41598-018-37155-9
34. Jeong J, Shoghi KI, Deasy JO. Modelling the interplay between hypoxia and proliferation in radiotherapy tumour response. *Phys Med Biol.* 2013;58(14):4897.
35. Jeong J, Oh JH, Sonke J-J, et al. Modeling the cellular response of lung cancer to radiation therapy for a broad range of fractionation schedules. *Clin Cancer Res.* 2017;23(18):5469-5479.
36. Arnesen MR, Hellebust TP, Malinen E. Impact of dose escalation and adaptive radiotherapy for cervical cancers on tumour shrinkage—a modelling study. *Phys Med Biol.* 2017;62(6):N107.
37. Kawahara D, Wu L, Watanabe Y. Optimization of irradiation interval for fractionated stereotactic radiosurgery by a cellular automata model with reoxygenation effects. *Phys Med Biol.* 2020;65(8):85008.
38. Chvetsov AV, Sandison GA, Schwartz JL, Rengan R. Ill-posed problem and regularization in reconstruction of radiobiological parameters from serial tumor imaging data. *Phys Med Biol.* 2015;60(21):8491.
39. Prokopiou S, Moros EG, Poleszczuk J, et al. A proliferation saturation index to predict radiation response and personalize radiotherapy fractionation. *Radiat Oncol.* 2015;10(1):1-8. doi:10.1186/s13014-015-0465-x
40. Sunassee ED, Tan D, Ji N, et al. Proliferation saturation index in an adaptive Bayesian approach to predict patient-specific radiotherapy responses. *Int J Radiat Biol.* 2019;95(10):1421-1426.
41. Poleszczuk J, Walker R, Moros EG, Latifi K, Caudell JJ, Enderling H. Predicting patient-specific radiotherapy protocols based on mathematical model choice for proliferation saturation index. *Bull Math Biol.* 2018;80(5):1195-1206. doi:10.1007/s11538-017-0279-0
42. Norton L, Simon R, others. Tumor size, sensitivity to therapy, and design of treatment schedules. *Cancer Treat Rep.* 1977;61(7):1307-1317.
43. Norton L, Simon R. Growth curve of an experimental solid tumor following radiotherapy. *J Natl Cancer Inst.* 1977;58(6):1735-1741.
44. Simon R, Norton L. The Norton--Simon hypothesis: designing more effective and less toxic chemotherapeutic regimens. *Nat Clin Pract Oncol.* 2006;3(8):406-407.
45. Byun DJ, Tam MM, Jacobson AS, et al. Prognostic potential of mid-treatment nodal response in oropharyngeal squamous cell carcinoma. *Head Neck.* 2020;43(1):173-181.
46. Perni S, Mohamed ASR, Scott J, et al. CT-based volumetric tumor growth velocity: a novel imaging prognostic indicator in oropharyngeal cancer patients receiving radiotherapy. *Oral Oncol.* 2016;63:16-22. doi:10.1016/j.oraloncology.2016.10.022
47. Lacas B, Bourhis J, Overgaard J, et al. Role of radiotherapy fractionation in head and neck cancers (MARCH): an updated meta-analysis. *Lancet Oncol.* 2017;18(9):1221-1237.
48. Brady R, Enderling H. Mathematical Models of Cancer: When to predict novel therapies, and when not to. *Bull Math Biol.* 2019;81(10):3722-3731.

Localized Prostate Cancer Recurrence

R. Jeffrey Karnes, MD, FACS; Mohamed E. Ahmed, MBBCh

Affiliation: Department of Urology, Mayo Clinic, Rochester, MN.

CASE SUMMARY

A 70-year-old man presented with persistent rising prostate specific antigen (PSA) of 3.2ng/mL in July 2020. The patient was post retropubic radical prostatectomy (RRP) for Gleason 3+4=7 in 2006. Subsequently, the patient experienced biochemical recurrences for which he received salvage external beam radiation therapy to the prostate bed in 2007, cryotherapy to the vesicourethral anastomosis in 2015, and external beam radiation therapy to the pelvic lymph nodes in 2016, followed by hormone therapy for approximately one year. In February 2019, the patient's PSA level started to rise to detectable levels at 0.45ng/mL, reaching 1.1ng/mL in July 2019.

A PET/MR scan revealed increased uptake in a perirectal lymph node. In September 2019, the patient underwent MRI-guided cryoablation of this perirectal lymph node. Interestingly, despite treatment, the PSA continued to rise to 2.3 ng/mL in March 2020, and to 3.2 ng/mL in July 2020.

The patient underwent evaluation with MRI of the abdomen and pelvis, C-11 choline PET/CT scan, and Ga-68 PSMA PET/CT scan.

IMAGING FINDINGS

MRI of the abdomen and pelvis revealed a post-ablation defect in the left posterolateral aspect of the vesicourethral anastomosis. However, there was prominent increased signal that could not exclude recurrent tumor in this region. In addition, there was increased activity around the ablated left perirectal lymph node. There were multiple tiny lymph nodes worrisome for nodal metastases within the perirectal and presacral regions. Additionally, there was a 3-mm right internal iliac chain lymph node also worrisome for metastatic involvement.

C-11 choline PET/CT scan revealed a left presacral soft tissue nodule with trace choline uptake. There was no definite choline uptake above background activity along the vesicourethral anastomosis; however, the area was partially obscured by physiologic activity of urine. There was no other choline-avid lymphadenopathy or osseous or visceral metastases.

Ga-68 PSMA PET/CT scan, in comparison, revealed multiple small posterior and left lateral perirectal tracer-avid lymph nodes or soft tissue nodules. There was also another tracer-avid anterior right perirectal soft tissue nodule or lymph node abutting the posterior aspect of the bladder just to the right of midline. In addition, there was intense tracer uptake at the vesicourethral anastomosis as well as minimal tracer activity in a right internal iliac lymph node. There were no tracer-avid bone lesions.

Of interest, both the MRI and C-11 choline PET/CT scan were suspicious for local recurrence as well as perirectal nodal recurrence, however, these lesions were very obvious on Ga-68 PSMA PET/CT scan.

DIAGNOSIS

Localized prostate cancer recurrence

FOLLOW-UP

The patient re-initiated treatment with Lupron hormone therapy of three months' duration. The patient responded very well to the treatment and the PSA decreased rapidly to undetectable levels <0.10ng/mL in one month.

DISCUSSION

Prostate cancer accounts for nearly 33,000 deaths annually, representing the second-most common cause of cancer death among men, ranking only behind lung cancer.[1] While primary prostate cancer can be managed with radical prostatectomy or radiation therapy, 40% of patients will experience disease relapse.[2] Recurrent prostate cancer requires personalized management that depends on the location of disease relapse. In 2013, the US Food and Drug Administration approved C-11 choline PET/CT scanning for detecting prostate cancer relapse after primary treatment failure, with an optimum PSA level of ≥ 2.0ng/mL.[3] Despite the higher sensitivity of the C-11 choline PET/CT scan to disease recurrence compared with conventional imaging, Ga-68 PSMA PET/CT has demonstrated significantly higher sensitivity than C-11 choline PET/CT. In a systematic review

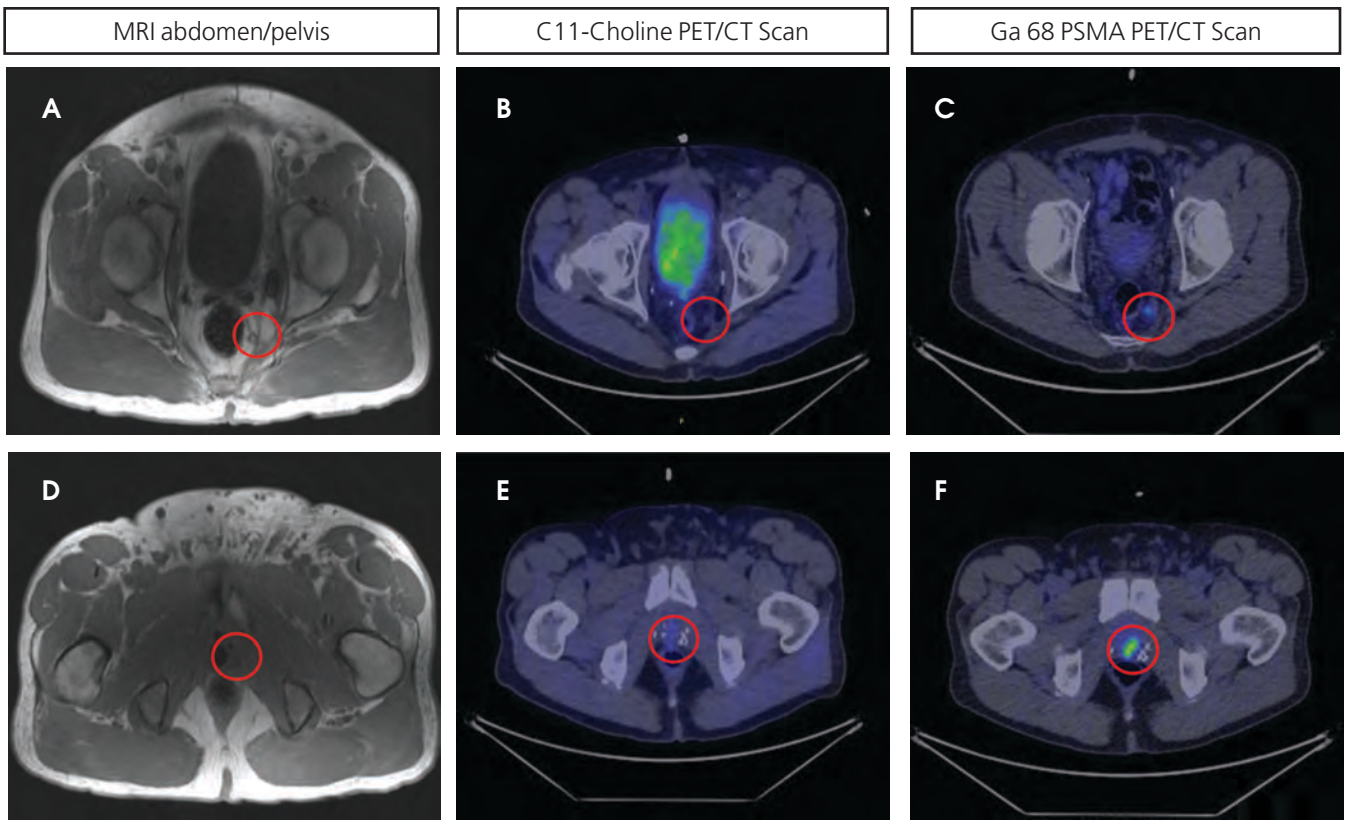


FIGURE 1. *Comparison between MRI abdomen/pelvis, C-11 choline PET/CT and Ga68 PSMA PET/CT in detecting local recurrence.*

and meta-analysis, Eyben et al reported that Ga-68 PSMA PET/CT was able to detect the location of disease relapse after primary radical prostatectomy in half of patients with PSA levels between 0.5 and 1 ng/mL, and in up to 75% of patients with PSA >1 ng/mL.[4,5] Some recent reports suggest that Ga-68 PSMA PET/CT can detect disease recurrence at PSA levels <0.5 ng/mL.[6,7]

This report demonstrates the significant difference in sensitivity between MRI abdomen/pelvis, C-11 choline PET/CT, and Ga-68 PSMA PET/CT in detecting prostate cancer relapse. The higher sensitivity of Ga-68 PSMA PET/CT allows it to detect disease relapse at very small volumes of <8 mm.[8] Despite the fact that Ga-68 PSMA PET/CT is not yet approved by the FDA for this indication, Afaq et al reported that PSMA PET/CT has a significant impact on disease management, with overall changes in 39-76% of cases.[8] The high performance of PSMA PET/CT represents the future of prostate cancer diagnosis and management.

CONCLUSION

This report confirms the important clinical consideration of the high sensitivity of Ga-68 PSMA PET/CT in determining disease recurrence after initial treatment failure, particularly in patients with very low PSA levels.

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer Statistics 2020. *CA Cancer J Clin.* 2020; 70: 7-30. doi:10.3322/caac.21590
2. Mullins JK, Feng Z, Trock BJ, Epstein JI, Walsh PC, Loeb S. The impact of anatomical radical retropubic prostatectomy on cancer control: the 30-year anniversary. *J Urol.* 2012; 188: 2219-2224. doi:10.1016/j.juro.2012.08.028
3. Mitchell CR, Lowe VJ, Rangel LJ, Hung JC, Kwon ED, et al. Operational characteristics of (11)c-choline positron emission tomography/computerized tomography for prostate cancer with biochemical recurrence after initial treatment. *J Urol.* 2013: 189: 1308-1313. doi:10.1016/j.juro.2012.10.069
4. von Eyben FE, Picchio M, von Eyben R, Rhee H, Bauman G. (68)Ga-Labeled Prostate-specific Membrane Antigen Ligand Positron Emission Tomography/Computed Tomography for Prostate Cancer: A Systematic Review and Meta-analysis. *Eur Urol Focus.* 2018; 4: 686-693. doi:10.1016/j.euf.2016.11.002
5. von Eyben FE, Baumann GS, Baum RP. PSMA diagnostics and treatments of prostate cancer become mature. *Clin Transl Imaging.* 2018; 6*:* 145-148. doi:10.1007/s40336-018-0270-2
6. Eissa A, Elsherbiny A, Coelho RF, Rassweiler J, Davis JW, et al. The role of 68Ga-PSMA PET/CT scan in biochemical recurrence after primary treatment for prostate cancer: a systematic review of the literature. *Minerva Urol Nefrol.* 2018; 70: 462-478. doi:10.23736/s0393-2249.18.03081-3
7. Pfister D, Bolla M, Briganti A, Carroll P, Cozzarini C, et al. Early salvage radiotherapy following radical prostatectomy. *Eur Urol.* 2014; 65: 1034-1043. doi:10.1016/j.eururo.2013.08.013
8. Afaq A, Bomanji J. Prostate-specific membrane antigen positron emission tomography in the management of recurrent prostate cancer. *Br Med Bull.* 2018; 128: 37-48. doi:10.1093/bmb/ldy032

Upfront Surgery With Adjuvant Radiation Therapy Versus Chemoradiation in HPV-Mediated Oropharyngeal Cancer in Intermediate-Risk Patients: A Multi-institutional Review

Anna M. Torgeson, MD; Kyra N. McComas, MD; Jesse A. Gygi, MHA, MPH; Shane Lloyd, MD; Greg Stoddard, MBA, MPH; Ying Hitchcock, MD; Vilija Avizonis MD

Abstract

Background: We conducted a multi-institutional retrospective review of patients with HPV-mediated oropharyngeal squamous cell carcinoma (HPV-SCC) to compare outcomes for upfront oncologic surgery plus adjuvant radiation therapy (RT) or chemoradiation therapy.

Methods: We analyzed 281 patients from two institutions treated from 2010 to 2017. The primary outcome was event-free survival (EFS). Secondary outcomes were overall survival (OS), locoregional control and major complications. Univariate (UVA) and multivariate (MVA) Cox proportional hazards models were done, and Kaplan-Meier survival curves generated.

Results: There were 55 surgery and 226 RT patients, median follow-up 37 months. There were fewer locoregional failures (0% vs 11%, $P = 0.04$) but more major complications (18% vs 11%, $P < 0.01$) for surgery patients. Adjuvant chemoradiation therapy was utilized in 44%. On UVA there was a trend for improved EFS in the surgery group (HR 0.48, $P = 0.07$), which did not persist on MVA (HR 1.07, $P = 0.91$).

Conclusion: Upfront surgery did not improve EFS or OS. Local control improved, with more major complications.

Dr. Torgeson *is a radiation oncologist at Walter Reed National Military Medical Center, Bethesda, MD.* ***Dr. Lloyd*** *is an associate professor, and* ***Dr. Hitchock*** *is a professor, both at University of Utah Department of Radiation Oncology, Salt Lake City, UT.* ***Dr. McComas*** *is an intern at Sacred Heart Medical Center, Spokane, WA.* ***Mr. Stoddard*** *is co-director, University of Utah Study Design and Biostatistics Center.* ***Mr. Gygi*** *is the data manager, Department of Oncology, and* ***Dr. Avizonis*** *is the chairperson, Department of Radiation Oncology, Intermountain Medical Center, Murray, UT.*
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. This study was highlighted as a Research Feature Presentation at the Multidisciplinary Head and Neck Cancers Symposium, Scottsdale, AZ, February 27-29, 2020.

The incidence of human-papillomavirus-related squamous cell carcinoma (HPV-SCC) of the oropharynx is increasing internationally.[1-3] Fortunately, the prognosis with treatment is favorable, but at the cost of both acute and late toxicity.[3-6] Efforts are underway to preserve and improve survival outcomes while decreasing toxicity with upfront surgical resection,[7-9] decreasing definitive radiation therapy (RT) doses/volume, or eliminating chemotherapy[10] in certain patients.

Newer surgical techniques are thought to have significantly lower toxicity compared with prior techniques,[11-13] with potential to eliminate RT in lowest-risk patients, decrease the adjuvant RT dose in intermediate-risk patients (T3/T4 tumors, two or more positive lymph nodes, close margins, perineural invasion [PNI], lymphovascular space invasion [LVSI]), eliminate chemotherapy in high-risk patients (positive margins, extranodal extension), and possibly improve survival outcomes for highest-risk patients. When compared with results from previous RT trials,[14] the toxicity profile appears to be improved, although such comparisons between datasets are problematic.

Until recently, no randomized trial had been published comparing outcomes between upfront treatment modality, whether surgery or RT; only a few retrospective series have described outcomes between these patients.[15,16] Despite the paucity of data comparing the effectiveness and/or toxicity of either definitive treatment, the incidence of upfront surgical resection has increased significantly (56% to 82% from 2004 to 2015) in facilities that report to the National Cancer Database (NCDB).[17]

Given this lack of data regarding the most appropriate primary treatment for patients with HPV-SCC, we sought to compare upfront surgical resection vs RT or chemoradiation therapy in a multi-institutional retrospective review.

Methods

Patients treated with RT at Intermountain Healthcare and Huntsman Cancer Hospital from 2010 to 2017 for nonmetastatic HPV-SCC were included in this study. These are independent institutions in the Salt Lake area with independently practicing physicians, and both have an average of two to three head and neck (H&N) radiation oncologists, three H&N fellowship-trained surgeons, and one medical oncologist. This study was exempt from both centers' institutional review boards after initial review (IRB#1051068 and #00012307). To be included, patients could not have another concurrent cancer at diagnosis and had to be treated with curative intent. For primary RT, this required a dose of at least 66 Gray (Gy) to the primary tumor, and treatment of the bilateral neck (or unilateral neck for well-lateralized tonsillar primaries). For surgical patients, this was defined either as a transoral robotic surgery (TORS) or wide local excision with neck dissection of at least the ipsilateral levels II-IV, followed by adjuvant RT. Generally, patients with positive surgical margins or extranodal extension received adjuvant chemoradiation therapy. Occasionally patients with PNI, extensive nodal disease, or other high-risk factors received adjuvant chemoradiation therapy at the discretion of the treating physicians.

Patient data collected included demographic factors: age, gender, performance status, and smoking status (current, former 10 pack-years, former < 10 pack-years, and nonsmoker). Clinical tumor factors included: p16 status; primary tumor size; primary tumor location; location of involved lymph nodes (ipsilateral or bilateral); and the

Table 1. Patient Characteristics for Treatment With Upfront Surgery or Radiation Therapy

Variable	Surgery First	%	Radiation Therapy First	%
Gender				***P* = 0.95**
Male	51	93%	209	92%
Female	4	7%	17	8%
Age Group				***P* = 0.06**
18-65	47	85%	158	70%
66-79	8	15%	65	29%
80+	0	0%	3	1%
KPS/ECOG				***P* = 0.06**
0	46	84%	161	71%
1	9	16%	65	29%
Smoking Status				***P* = 0.37**
Never	23	42%	96	43%
Current	7	13%	32	14%
Former < 10pkyr	3	5%	29	13%
Former > 10pkyr	20	36%	64	29%
unknown	2	4%	5	2%
Primary Site				***P* < 0.01**
Tonsil	41	75%	97	43%
Base of Tongue	14	25%	121	54%
Soft Palate	0	0%	1	<1%
Pharynx NOS	0	0%	7	3%
Tumor Size				***P* < 0.01**
2 cm or less	28	51%	42	19%
2.1-4.0 cm	24	44%	119	53%
> 4.0 cm	3	5%	57	25%
Unknown	0	0%	8	4%
AJCC 7th/8th cT stage				***P* < 0.01**
T0	4	7%	3	1%
T1	27	49%	44	19%
T2	21	38%	100	44%
T3	2	4%	51	23%
T4	1	2%	26	12%
Unknown	0	0%	2	1%
AJCC 7thcN stage				***P* = 0.004**
N0	2	4%	23	10%
N1	8	15%	22	10%
N2a	6	11%	23	10%
N2b	35	64%	98	43%
N2c	1	2%	52	23%
N3	3	5%	8	4%
AJCC 8th cN stage				***P* < 0.01**
N0	2	4%	23	10%
N1	49	89%	143	63%
N2	1	2%	5	23%
N3	3	5%	8	4%

Key: RT = radiation therapy, KPS = Karnofsky Performance Status, ECOG = Eastern Cooperative Oncology Group, pkyr = pack-year, NOS = not otherwise specified, AJCC = American Joint Committee on Cancer, cm = centimeter, c- clinical, Gy = gray, Tx = treatment, LR = local recurrence, DM = distant metastases, PEG = percutaneous endoscopic gastrostomy, ORN = osteoradionecrosis

Table 1 *conitunued on page 30*

Table 1 continued

Variable	Surgery First	%	Radiation Therapy First	%
AJCC 7th cGroup				***P* = 0.56**
Stage I	1	2%	1	< 1%
Stage II	1	2%	13	6%
Stage III	8	15%	26	12%
Stage IVA	42	76%	176	78%
Stage IVB	3	5%	10	4%
AJCC 8th cGroup				***P* < 0.01**
Stage I	48	87%	119	53%
Stage II	4	7%	79	35%
Stage III	3	5%	28	12%
RT Dose Group				***P* < 0.01**
< 60Gy	3	5%	3	1%
60-65.99Gy	39	71%	15	7%
66-70Gy	13	24%	208	92%
Chemotherapy?				***P* < 0.01**
No Chemotherapy	31	56%	2	9%
Chemotherapy	24	44%	203	91%
Chemotherapy Type				***P* < 0.01**
No Chemotherapy	31	56%	21	9%
Cisplatin	16	29%	168	74%
Cetuximab	3	5%	30	13%
Other	5	9%	7	3%
Completed Tx?				***P* = 0.22**
Did Not Complete	4	7%	8	4%
Completed	51	93%	218	96%
Any Recurrence?				***P* = 0.04**
No Recurrence	51	93%	183	81%
LR Only	0	0%	25	11%
DM Only	4	7%	12	5%
LR+DM	0	0%	5	2%
Time to Recurrence?				***P* = 0.19**
No Recurrence	51	93%	183	81%
Within 12 Months	3	5%	27	11%
12-24 Months	1	2%	10	5%
> 24 Months	0	0%	6	2%
Died From Cancer				***P* = 0.48**
Alive	48	87%	182	81%
Dead, Not Cancer	1	2%	9	4%
Dead, Cancer	6	11%	26	12%
Dead, Unknown	0	0%	7	3%
Complication				***P* = 0.003**
None	45	82%	202	89%
PEG >1yr	2	4%	9	4%
ORN	2	4%	12	5%
Other	6	11%	2	1%
Unknown	0	0%	1	< 1%

Key: RT = radiation therapy, KPS = Karnofsky Performance Status, ECOG = Eastern Cooperative Oncology Group, pkyr = pack-year, NOS = not otherwise specified, AJCC = American Joint Committee on Cancer, cm = centimeter, c- clinical, Gy = gray, Tx = treatment, LR = local recurrence, DM = distant metastases, PEG = percutaneous endoscopic gastrostomy, ORN = osteoradionecrosis

American Joint Committee on Cancer (AJCC) 7th and 8th edition tumor (T), node (N), and overall group stage. Treatment factors collected included: upfront treatment (oncologic surgery or RT), RT dose, and whether systemic therapy was given and, if so, type. In patients who underwent upfront surgery, data collected included pathologic tumor size, T stage (8th edition), PNI, LVSI, margin status, number of nodes involved, pathologic N stage (8th edition), whether nodes were ipsilateral or bilateral, and whether extranodal extension (ENE) was present. Time from surgical resection to the start of RT was also collected. Clinical outcomes collected included time from diagnosis to last follow-up, vital status (alive or dead), cause of death if applicable, local recurrence status, distant metastases status, time to local recurrence or distant metastases, salvage method if applicable, and major complications. Major complications included feeding tube dependence > one year, osteoradionecrosis, carotid injury requiring intervention or causing death, spinal cord injury, severe lymphedema requiring ongoing therapy or limiting quality of life, or other major event thought to be related to cancer treatment as documented in the medical record.

Differences between the demographic, clinical, treatment, and outcome factors between treatment groups were compared using chi-square analysis. The primary outcome was event-free survival (EFS), which included death from any cause, locoregional recurrence, or distant recurrences. Secondary outcomes included OS, locoregional failure rate, and major complication rates. Both EFS and OS were examined using Cox-proportional hazards modeling via univariate analysis (UVA) followed by multivariate analysis (MVA). Demographic, clinical, and treatment factors with a *P*-value of ≤ 0.2 were included in the multivariate model and Kaplan-Meier curves were then generated.[18] A *P*-value of ≤ 0.05 was

Table 2: Event Free Survival, Upfront Surgery Versus Radiation Therapy

Variable	UVA HR	P value	MVA HR	*P* value
First Line Tx				
RT	1	1	1	1
Surgery		1.07	0.91	
Age				
18-65	1	1	1	1
66-79	1.63	0.06	1.45	0.20
80+	3.36	0.10	6.45	0.09
Smoking				
Never	1	1	1	1
Current	1.24	0.58	1.08	0.86
Former < 10pkyr	2.44	0.01	2.64	0.02
Former > 10pkyr	1.68	0.08	1.86	0.06
Primary Site				
Tonsil	1	1	1	1
Base of Tongue	1.35	0.239	0.98	0.93
Soft Palate	17.7	0.01	7.25	0.08
Pharynx NOS	1.18	0.82	0.59	0.52
Performance Status				
ECOG 0	1	1	1	1
ECOG 1	1.81	0.02	1.39	0.26
7th/8th T stage				
0	0.75	0.77	0.63	0.68
1	0.91	0.79	0.95	0.90
2	1	1	1	1
3	1.92	0.04	1.14	0.72
4	2.79	< 0.01	1.88	0.11
Unknown T	2.99	0.29	2.14	0.50
8th N				
0	1.05	0.91	0.97	0.96
1	1	1	1	1
2	1.86	0.03	1.54	0.19
3	3.04	0.02	2.50	0.08
RT Dose				
66-70Gy	1	1	1	1
< 60Gy	0.67	0.69	1.20	0.87
60-65.99Gy	0.48	0.07	1.27	0.66
Chemo Group				
No Chemotherapy	1	1	1	1
Cisplatin	2.63	0.04	3.15	0.09
Cetuximab	5.44	< 0.01	6.13	0.02

Key: UVA = univariate analysis, MVA = multivariate analysis, HR = Hazard Ratio, Tx = Treatment, RT = radiation therapy, pkyr = pack-year, NOS = Not Otherwise Specified, ECOG = Eastern Cooperative Oncology Group, Gy = Gray

required for significance. Patients were then stratified into a low-risk group (LR) and a high-risk group (HR) similar to the stratification from RTOG 0129.[19] Patients in the LR group were AJCC 7th edition T0-2, N0-2a, with any smoking status. There were not enough nonsmokers/< 10 pack-year smokers in the low T/N stage RT group to lend statistical significance, so smoking status was not included for low-risk stratification. The HR patients had more advanced disease (N2b-3) and either were current smokers or had a smoking history > 10 pack-years. In these patients, EFS and OS were also examined on UVA.

Results

There were 281 patients who met inclusion criteria for this study, 55 of whom underwent oncologic surgery as their primary treatment and 226 of whom underwent primary RT. Median age was 60 and median follow-up time for all patients was 37 months, 37 for the RT group and 33 for the surgery group. The groups were well-balanced in terms of gender and smoking status (**Table 1**). There was a strong trend toward older age in the RT group (30% over 65 vs 15%, $P = 0.06$) and poorer performance status (29% ECOG 1 vs 16%, $P = 0.06$) (see **Table 1**). Base of tongue location was more common in the RT group (54% vs 25%, $P < 0.01$), as were tumors > 4 cm (25% vs 5%, $P < 0.01$) with subsequently more advanced AJCC 7th/8th edition T stage (64% T0-T2 vs 94%, $P > 0.01$). RT patients also had more advanced nodal disease, with N2c-N3 (7th edition) disease accounting for 27% vs 7% of surgical patients ($P = 0.004$). In patients who underwent upfront surgical resection, all underwent postoperative adjuvant RT, and 24% of patients underwent high-dose RT (66-70 Gy) (**Table 1**). Of the surgical patients, 16% had positive margins, 24% had extranodal extension, and 44% underwent adjuvant chemoradiation therapy. All patients started RT within 8 weeks of surgery. Rates of treatment completion did not differ between the two groups. Surgical patients were less likely to have local recurrences (0% vs 11%, $P = 0.04$), but more likely to have major complications (18% vs 11%, $P = 0.003$), see **Table 1**. Feeding-tube dependence > 1 year and osteoradionecrosis (ORN) rates were comparable (~ 4%), but the rates of carotid, spinal cord, and soft-tissue injury were higher in the surgery arm (11%

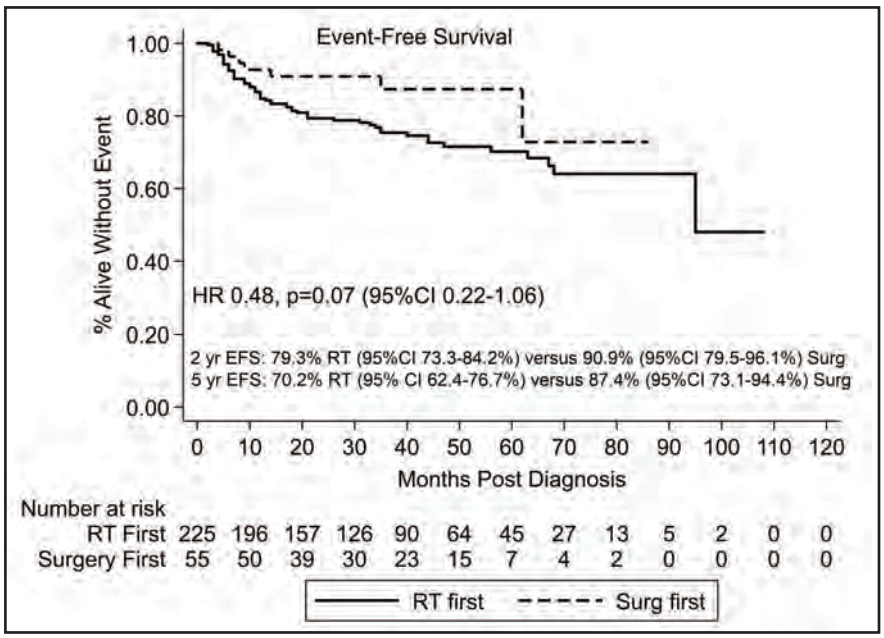


FIGURE 1. *Event-free survival (EFS) for patients treated with upfront surgery plus adjuvant radiation (with or without chemotherapy) vs those treated with primary chemoradiation therapy.*

vs 1%, $P = 0.003$), see **Table 1**. Of that 11%, 5 out of 6 patients received adjuvant RT alone and 2 out of 6 received curative high-dose RT.

On UVA, there was a trend toward improved EFS with surgery compared to RT (HR 0.48, $P = 0.07$), which was lost on MVA (HR 1.07, $P = 0.91$) (see **Table 2**, **Figure 1**). Factors associated with worsened EFS included being a former smoker of < 10 pack-years compared with a never smoker (HR 2.49, $P = 0.02$) and cetuximab compared with no systemic therapy (HR 6.13, $P = 0.02$). There was a trend for decreased EFS for age 80+ compared with age 18 to 65 (HR 6.45, $P = 0.09$), former smokers > 10 pack-years compared with never smokers (HR 1.86, $P = 0.06$), soft palate site compared with tonsil (HR 7.25, $P = 0.08$), cN3 stage compared with cN1 (HR 2.50, $P = 0.08$), and cisplatin compared with no chemotherapy (HR 3.15, $P = 0.09$).

With respect to OS, upfront resection did not affect survival on either univariate (HR 0.75, $P = 0.49$) or multivariate analysis (HR 1.42, $P = 0.57$). There was a trend toward decreased survival for patients aged 66 to 79 compared with 18 to 65 (HR 1.89 $P = 0.07$) and ECOG 1 performance status (HR 1.83, $P = 0.08$) compared with ECOG 0. There was significant detriment for former >10 pack-year smokers (**Table 3**, **Figure 2**) compared with nonsmokers (HR 2.81, $P < 0.01$), patients with T4 disease compared with T2 (HR 3.25, $P > 0.01$), and cetuximab therapy compared with no chemotherapy (HR 5.10, $P = 0.04$).

On subgroup analysis, there were 169 low-risk patients (cT0-T2, cN0-1 AJCC 8th edition). Neither EFS (HR 0.91, $P = 0.84$) nor OS (HR 1.62, $P = 0.35$) were affected by the method of upfront treatment on UVA. Of low-risk surgery patients, 40% underwent adjuvant chemoradiation therapy, 22% underwent high-dose RT, 18% had positive margins, and 10% had ENE. There remained an 11% higher complication rate in surgery patients ($P = 0.02$) with a trend toward improved local control (0% local recurrences vs 8%, $P = 0.06$). There were 88 high-risk patients (cN2b-3 7th edition, >10 pack-year or current smokers). Neither EFS (HR 0.95, $P = 0.92$) nor OS (HR 1.27, $P = 0.62$) were affected by upfront treatment on UVA. Of high-risk surgery patients, 55% underwent adjuvant chemoradiation therapy and 35% underwent high-dose RT. There was a 15% higher rate of major complications for upfront surgery (25% vs 10%, $P = 0.02$) with a 15% decrease in local recurrences ($P = 0.02$).

Discussion

In this study, patients with HPV-SCC of the oropharynx, initial surgical resection was not associated with improved EFS or OS compared to upfront RT. Surgery was associated with a small decrease in rate of local recurrences at the expense of increased rates of major complications, particularly injury to the ipsilateral carotid artery, spinal cord, or skin and soft tissue. Of patients who started with surgery, nearly half received trimodality therapy (surgery, RT, chemotherapy) and nearly a quarter received curative-dose RT. On subgroup analysis, neither the low- nor the high-risk patients benefitted from upfront surgical resection and in the high-risk patients, upfront surgery was associated with a 25% rate of major complications.

Although there was an initial trend toward improved EFS with initial resection, when other factors were considered on MVA, such as stage and performance status, this trend disappeared. The lack of a trend for OS between groups combined with the difference in rates of locoregional control on chi-square analysis suggest that the improvement in EFS was likely driven by locoregional control and that these patients are highly salvageable. In fact, of the 25 patients who failed locally, 70% of them were surgically salvaged. The locoregional control difference was likely secondary to more advanced stage patients in the RT group. Notably, there was no improvement in survival even for the highest-risk subgroup (former smokers with advanced nodal disease), for whom treatment escalation may have been beneficial. The lack of improvement in survival is informative and consistent with pre-

Table 3: Overall Survival, Upfront Surgery Versus Radiation Therapy

Variable	UVA HR	*P* value	MVA HR	*P* value
First Line Tx				
RT	1	1	1	1
Surgery	0.75	0.49	1.42	0.57
Age				
18-65	1	1	1	1
66-79	1.74	0.06	1.89	0.07
80+	2.19	0.44	2.96	0.43
Smoking				
Never	1	1	1	1
Current	1.67	0.25	1.79	0.23
Former < 10pkyr	1.95	0.15	2.43	0.10
Former > 10pkyr	2.38	0.01	2.81	< 0.01
Primary Site				
Tonsil	1	1	1	1
Base of Tongue	1.05	0.88	0.67	0.22
Soft Palate	11.99	0.02	6.67	0.11
Pharynx NOS	1.46	0.61	0.64	0.60
Performance Status				
ECOG 0	1	1	1	1
ECOG 1	2.40	<0.01	1.83	0.08
7th/8th T stage				
0	1.34	0.78	1.12	0.92
1	1.24	0.61	1.32	0.55
2	1	1	1	1
3	2.26	0.03	1.16	0.74
4	4.45	< 0.01	3.25	> 0.01
Unknown T	3.75	0.20	1.60	0.68
8th N				
0	1.37	0.49	1.65	0.34
1	1	1	1	1
2	1.58	0.18	1.49	0.33
3	2.74	0.06	2.60	0.11
RT Dose				
66-70Gy	1	1	1	1
< 60Gy	0.90	0.92	1.12	0.92
60-65.99Gy	0.65	0.32	1.39	0.61
Chemo Group				
No Chemotherapy	1	1	1	1
Cisplatin	2.12	0.16	2.39	0.21
Cetuximab	4.90	< 0.01	5.10	0.04

Key: UVA = univariate analysis, MVA = multivariate analysis, HR = Hazard Ratio, Tx = Treatment, RT = radiation therapy, pkyr = pack-year, NOS = Not Otherwise Specified, ECOG = Eastern Cooperative Oncology Group, Gy = Gray

viously published retrospective data[16] and a recently reported randomized trial,[20] although survival based on upfront treatment was not the primary outcome in either of these studies. The lack of survival benefit was also shown in a meta-analysis of seven published studies that compared both modalities, but these data are limited by poor quality data in the included studies.[15] A recently published NCDB report also found that survival with upfront surgery was not improved with HPV-SCC, but was improved in HPV-negative disease.[21] Interestingly, a recently presented study of 96 patients in Japan found that patients who were locally advanced but resectable had a trend toward improved survival with upfront surgery or induction chemotherapy followed by surgery,[22] something that could not be confirmed in this retrospective study.

The difference in rates of major complications between the two modalities was surprising, especially since more than half of the upfront surgery patients did not receive chemotherapy and only a quarter of them received high-dose RT. Even more surprising was the type of complications these patients suffered (carotid, spinal cord, lymphedema). Similarly, a recently published series of 267 patients treated with upfront surgery over 8 years found that major (ie, PEG tube dependence and tracheostomy) complication rates were low, but other meaningful outcomes, such as aspiration of thin liquids (17% with adjuvant RT, 33% with adjuvant chemoradiation), difficulty with understandable speech (~40%), and diet limited to soft foods (27% to 46%), were present in a significant proportion of patients.[23] This lack of improvement in toxicity outcomes has also been seen in the more commonly discussed toxicities, as upfront surgery was also associated with a nonclinically meaningful worsened swallowing function in the ORATOR trial, although rates of PEG tube dependence were low in both arms. The trial found a clinically meaningful decline in global and emotional functioning at one year in the surgical arm and a trend toward decreased ability to tolerate a normal diet without restrictions at one year (84% vs 100%, $P = 0.055$). Toxicities also differed in quality between groups. Conversely, the same study of 96 locally advanced HPV-SCC patients in Japan also found that those who underwent upfront surgical resection had less aspiration pneumonia and need for supplemental nutrition than patients treated with upfront RT.[22]

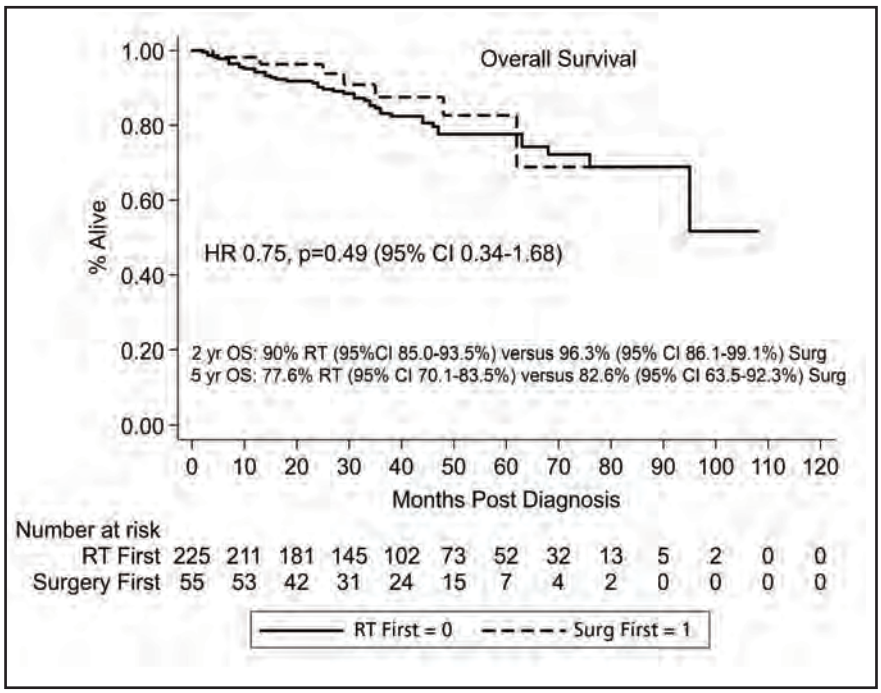


FIGURE 2. *Overall survival for patients treated with upfront surgery plus adjuvant radiation (with or without chemotherapy) vs those treated with primary chemoradiation therapy.*

These studies suggest the importance of considering a wide range and degree of toxicity and complications when comparing data from primary modalities. As we await the final manuscripts for both phase II de-escalation trials (HN-002 and E3311) to better detail acute and long-term toxicities, this data serves as an important reminder that comparing these modalities is not comparing "apples to apples." In other words, toxicities between treatments may not be classified as better, just different.

It is also important to recognize that the purpose of this study was not to assess whether upfront surgical resection could completely negate the need for adjuvant therapy in the lowest-risk patients (ie, T1-T2 primaries, 7th edition N0-1, no PNI/LVSI), as approximately 70% of surgical patients in this study had at least N2b disease. In this largely intermediate risk cohort, 44% of surgery patients underwent chemoradiation therapy (trimodality) and a quarter received high-dose treatment. This is consistent with other retrospective data that included lower-risk patients.[23-25] On ECOG 3311, which assessed the role of surgery in the de-escalation of treatment for HPV-SCC based on pathologic criteria after surgery, approximately 1/3 of patients met the high-risk criteria after surgery (positive margins or > 1mm ENE) and received tri-modality therapy despite a rigorous credentialing and review process.[26] Patients fared slightly better on the ORATOR trial,[20] which compared quality-of-life outcomes after either surgery or RT as initial treatment, with 24% of patients requiring adjuvant chemoradiation therapy. Taken together, these data would suggest that upstaging remains a significant risk for surgical patients even with aggressive staging, with the risk increasing with expanding disease burden on presentation.

This study and others like it may one day become obsolete if de-escalation becomes standard of care, whether through de-escalated primary or adjuvant RT or surgery. However, this study and others like it should serve as a source of caution for de-escalation: Five-year overall survival was only 77% to 82% in a (relatively) young cohort with supposedly favorable disease biology, with most deaths due to cancer progression. While these numbers are excellent compared with more aggressive locally confined cancers (pancreas, glioblastoma), they are still not above 90%. The results of HN-002, a phase II trial that examined the role for reduced-dose RT +/- chemotherapy, recently found that 60 Gy plus chemotherapy may be an acceptable de-escalation option for cancer control; however, combining dose reduction with omission of chemotherapy was not.[27] The 2-plus year survival rate for the RT plus chemotherapy group was excellent (90%), as were the survival rates on E3311 (93% to 95%). Although the vast majority of patients will face recurrence in the first two years, longer follow-up is needed from both a survival and toxicity standpoint for both of these trials. Certainly, RTOG 1016 seemed to urge caution on the replacement of cisplatin with cetuximab.[28]

The major limitation in this retrospective study was that only major complications, such as ORN, PEG tube dependence, and other major injuries, were recorded. These events were fortunately rare, but do not adequately capture a patient's quality of life after treatment. Xerostomia, dysgeusia, trismus, dysarthria, and inability to tolerate a normal diet may not be so severe to require supplemental nutrition or render the patient without understandable speech, but can be quite limiting. Finally, although performance status was included as a part of this study, comorbidity scores were not. This is specifically relevant to the decision on whether to use systemic therapy and which particular agent. Cetuximab was associated with a significantly increased risk of death in this study, and several of these patients were given cetuximab on RTOG 1016, but several of them were also likely given cetuximab due to medical comorbidities or concern for poor tolerance of cisplatin. Despite these limitations, retrospective data continue to play an important role when comparing surgery and RT as primary

treatment options, as those trials can be difficult to fully accrue. This has certainly been seen in the early stage lung cancer setting, and will likely be an issue for the ongoing ORATOR2 trial.

Conclusion

In this retrospective study, surgical resection did not improve survival outcomes. Upfront resection was associated with a lower local recurrence rate at the expense of a higher major complication rate. Subgroup analysis failed to show an effect of surgery (other than the increased complication rate) for either high- or low-risk patients. As we (cautiously) move into an era of de-escalated therapy, a wider range of toxicities and risks should be considered when choosing a primary treatment modality.

References

1. Chaturvedi AK, Anderson WF, Lortet-Tieulent J, et al. Worldwide trends in incidence rates for oral cavity and oropharyngeal cancers *J Clin Oncol*. 2013;31(36):4550-4559.
2. Chaturvedi AK, Engels EA, Pfeiffer RM, et al. Human papillomavirus and rising oropharyngeal cancer incidence in the United States. *J Clin Oncol*. 2011;29(32):4294-4301.
3. American Cancer Society. Key Statistics for Oral Cavity and Oropharyngeal Cancers. Accessed August 15, 2019. https://www.cancer.org/cancer/oral-cavity-and-oropharyngeal-cancer/about/key-statistics.html
4. Ang KK, Harris J, Wheeler R, et al. Human papillomavirus and survival of patients with oropharyngeal cancer. *N Engl J Med*. 2010;363:24-35.
5. Fakhry C, Westra WH, Li S, et al. Improved survival of patients with human papillomavirus-positive head and neck squamous cell carcinoma in a prospective clinical trial. *J Natl Cancer Inst*. 2008;100:261-269.
6. Dayyani F, Etzel CJ, Liu M, et al. Meta-analysis of the impact of human papillomavirus (HPV) on cancer risk and overall survival in head and neck squamous cell carcinomas (HNSCC). *Head Neck Oncol*. 2010;2:15. doi: 10.1186/1758-3284-2-15
7. Post Operative Adjuvant Therapy De-intensification Trial for Human Papillomavirus-related, p16+ Oropharynx Cancer (ADEPT). Accessed August 15, 2019. https://www.clinicaltrials.gov/ct2/show/NCT01687413.
8. Transoral Surgery Followed by Low-Dose or Standard-Dose Radiation Therapy With or Without Chemotherapy in Treating Patients With HPV Positive Stage III-IVA Oropharyngeal Cancer (ECOG 3311). Accessed August 15, 2019. https://www.clinicaltrials.gov/ct2/show/NCT01898494
9. Post-operative Adjuvant Treatment for HPV-positive Tumors (PATHOS). Accessed August 15, 2019. https://www.clinicaltrials.gov/ct2/show/NCT02215265.
10. Reduced-Dose Intensity-Modulated Radiation Therapy With or Without Cisplatin in Treating Patients With Advanced Oropharyngeal Cancer. Accessed August 15, 2019. https://www.clinicaltrials.gov/ct2/show/NCT02254278.
11. Hutcheson KA, Holsinger FC, Kupferman ME, et al. Functional outcomes after TORS for oropharyngeal cancer: a systematic review. *Eur Arch Otorhinolaryngal*. 2015;272:463-471.
12. Haughey BH, Hinni ML, Salassa JR, et al. Transoral laser microsurgery as primary treatment for advanced-stage oropharyngeal cancer: A United States multicenter study. *Head Neck*. 2011;33:1683-1694.
13. Canis M, Martin A, Kron M, et al.Results of transoral laser microsurgery in 102 patients with squamous cell carcinoma of the tonsil. *Eur Arch Otorhinolaryngal*. 2013;270:2299-2306.
14. Machtay M, Moughan J, Trotti A, et al. Factors associated with severe late toxicity after concurrent chemoradiation for locally advanced head and neck cancer: an RTOG analysis. *J Clin Oncol*. 2008;26:3582-3589.
15. Sinha P, Karadaghy OA, Doering, MM, et al. Survival for HPV-positive oropharyngeal squamous cell carcinoma with surgical versus non-surgical treatment approach: a systematic review and meta-analysis. *Oral Oncol*. 2018;86:121-131. doi: 10.1016/j.oraloncology.2018. 09.018.
16. Vawda N, Banerjee RN, Debenham BJ. Impact of smoking on outcomes of HPV-related oropharyngeal cancer treated with primary radiation or surgery. *IJROBP*. 2019;103(5):1125-1131. doi: 10.1016/j.ijrobp.2018.11.046
17. Cracchio JR, Baxi SS, Morris LG, et al. Increase in primary surgical treatment of T1 and T2 oropharyngeal squamous cell carcinoma and rates of adverse pathologic features: National Cancer Data Base. *Cancer*. 2016;122:1523-1532.
18. Hosmer DW, Lemeshow S, Sturdivant RX. *Applied Logistic Regression*. John Wiley and Sons, Inc. 2013.
19. Ang KK, Harris J, Wheeler R, et al. Human papillomavirus and survival of patients with oropharyngeal cancer. *N Eng J Med*. 2010;363:24-35.
20. Nichols AC, Theurer J, Prisman E, et al. Radiotherapy versus trans-oral robotic surgery and neck dissection or oropharyngeal squamous cell carcinoma (ORATOR): an open label, phase 2, randomized trial. *Lancet Oncol*. 2019;20(10)1349-1359. doi: https://doi.org/10.1016/S1470-2045(19)30410-3
21. Mahmoud O, Sung, K, Civantos FJ, et al Transoral robotic surgery for oropharyngeal squamous cell carcinoma in the era of human papillomavirus. *Head Neck*. 2018;40:710-721.
22. Yokota T, Iida Y, Kamijo T, et al. Which treatment strategies are the most promising for locally advanced resectable human papillomavirus-associated oropharyngeal cancers? *J Clin Oncol*. 2019;37:15_suppl. doi:10.1200/JCO.2019.37.15_suppl.e17556
23. Van Abel KM, Quick MH, Graner DE, et al. Outcomes following TORS for HPV-positive oropharyngeal carcinoma: PEGs, tracheostomies, and beyond. *Am J Otolaryngol*. 2019;40(5)729-734. doi 10.1016/j.amjoto.2019.07.003
24. Roden DF, Hobelmann K, Vimawala S, et al. Evaluating the impact of smoking on disease-specific survival outcomes in patients with human-papillomavirus-associated oropharyngeal cancer treated with transoral robotic surgery. *Cancer*. 2020:126;9. doi:10.1002/cncr.32739
25. Dhanireddy B, Burnett NP, Sanampudi S, et al. Outcomes in surgically resectable oropharynx cancer treated with transoral robotic surgery versus definitive chemoradiation. *Am J Otolaryng*. 2019;40(5);673-677. doi: 10.1016/j.amjoto.2019.06.001
26. Ferris RL, Flamand Y, Weinstein GS, et al. Transoral robotic surgical resection followed by randomization to low- or standard dose IMRT in resectable p16+ locally advanced oropharynx cancer: a trial of the ECOG-ACRIN Cancer Research Group (E3311). *J Clin Onc*. 2020;38:suppl; abstr 6500. doi: 10.1200/JCO. 2020. 38.15_suppl.6500
27. Yom SS, Torres-Saavedra P, Caudell JJ, et al. NRG-HN002: A randomized phase ii trial for patients with p16-positive, non-smoking-associated, locoregionally advanced oropharyngeal cancer. *IJROBP* 2020;105(3);684-685.
28. Gillison ML, Trotti, AM, Harris J, et al. Radiation therapy plus cetuximab or cisplatin in human papillomavirus-positive oropharyngeal cancer (NRG Oncology RTOG 1016): a randomized, multicenter, non-inferiority trial. *Lancet* 2019;393(10166):40-50. doi:10.1016/S0140-6736(18)32779-X

Stereotactic Body Radiation Therapy With Integrated Boost to the Dominant Intraprostatic Nodule: Initial Dosimetric and Clinical Outcomes

Suhong Yu, PhD; Daniel Huang, BS; Joseph S. Mathew, MD; Michael A. Dyer, MD; B. Nicolas Bloch, MD; Sean Keohan, BS; Ariel E. Hirsch, MD

Abstract

Purpose: Prostate stereotactic body radiation therapy (SBRT) with dose escalation to the dominant intraprostatic lesion (DIL) is an option to increase local control. We investigated the feasibility and toxicity of a moderate boost to DIL while respecting established dose constraints.

Materials and Methods: Ten patients with prostate cancer who met eligibility criteria for NRG-GU005 were included. T2-weighted MRI and planning pelvis computed tomography (CT) were fused to delineate targets and organs at risk (OARs). SBRT plans (36.25 Gy in 5 fractions) followed GU005 constraints. Paired T-tests were used for analysis of dosimetrics. Early (< 90 days) and late (> 90 days) genitourinary (GU) and gastrointestinal (GI) toxicity were graded by National Cancer Institute Common Terminology Criteria.

Results: Mean prescription dose (36.25 Gy) coverage of the planning target volume (PTV) was 95.4%. The conformity index for all plans was < 1.2, and the dose to 0.03 cc of the PTV was < 120% of the prescription dose (43.50 Gy). The minimum dose (D99%) of the PTV was 35.1 ± 0.4 Gy, whereas the D99% for DIL was 38.6 ± 0.8 Gy. Using an alpha/beta of 1.5, BED was 199.4 Gy for PTV vs. 237.3 Gy for DIL, $P < 0.001$. The incidence of acute grade 1 or 2 GI toxicity was 20%, of which 10% persisted past 90 days. The incidence of acute GU toxicity was 80%, of which 50% persisted past 90 days. No patients developed grade 3 or greater GI or GU toxicity.

Conclusion: Prostate SBRT with simultaneous moderate dose escalation to DIL is feasible and can be accomplished while respecting standard OAR constraints.

Prostate adenocarcinoma is the non-cutaneous cancer with the highest incidence among men in the US; there were 174,650 new prostate cancer cases in the US in 2019.[1] According to the Surveillance, Epidemiology, and End Results (SEER) program, 77% of new prostate cancer cases in 2019 were diagnosed as localized stage.[2]

Based on National Comprehensive Cancer Network (NCCN) guidelines, treatment options for low- to intermediate-risk prostate cancer include active surveillance, surgery, and radiation therapy.[3] Radiation is delivered either via external-beam radiation therapy (EBRT) or brachytherapy (BT), with the potential addition of androgen deprivation therapy for unfavorable intermediate-risk groups. Previous studies have shown that dose escalation in EBRT is associated with improved biochemical control and progression-free survival but is not associated with improved overall survival.[4-7] With dose-escalated EBRT, care must be taken in radiation treatment planning, as there can be greater risk of toxicity from increased dose to organs at risk (OARs), including the rectum and bladder.[8]

Prior research has shown that prostate cancer is characterized by a low alpha/beta ratio of approximately 1.5 Gy.[9-11] This gives rise to a potential benefit of hypofractionated radiation therapy, where radiation is delivered in higher daily doses over fewer total

Dr. Yu *is assistant professor, Department of Radiation Oncology, University of Massachusetts Medical School, Worcester, MA.* ***Mr. Huang*** *is a medical student at Boston University School of Medicine.* ***Dr. Mathew*** *is a former medical student,* ***Dr. Dyer*** *is assistant professor,* ***Mr. Keohan*** *is a senior radiation therapist, and* ***Dr. Hirsch*** *is associate professor, all in Department of Radiation Oncology, Boston University School of Medicine.* ***Dr. Bloch*** *is professor, Department of Radiology, University of Massachusetts Medical School, Worcester, MA. Dr. Bloch and Dr. Yu were formerly with the Department of Radiology and Department of Radiation Oncology, respectively, Boston University School of Medicine, where the research work was performed.*

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.

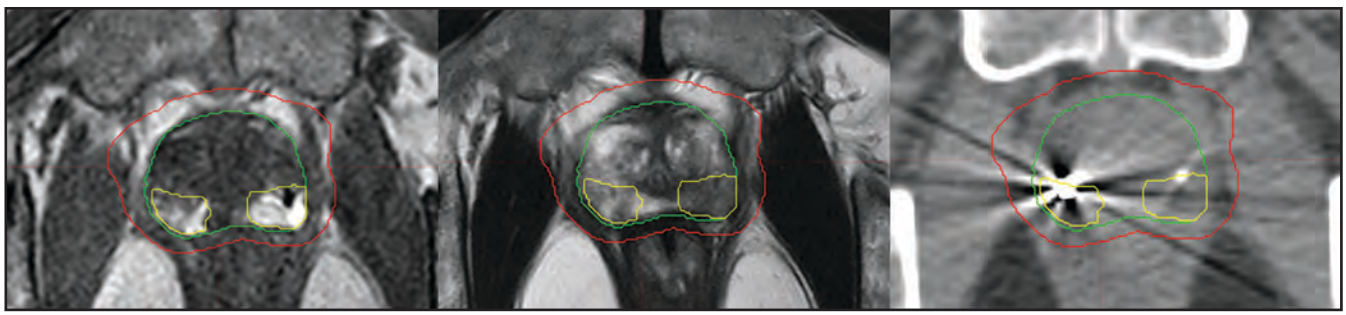


FIGURE 1. *Dominant intraprostatic lesion (DIL) visualization comparisons on MRI THRIVE, T2 and CT axial slice, DIL (yellow), prostate (green), planning target volume (PTV) (red).*

fractions, in terms of achieving greater tumor control while minimizing toxicity. Stereotactic body radiation therapy (SBRT) is a form of extreme hypofractionation; one common regimen used in prostate cancer is 36.25 Gy in 5 fractions (7.25 Gy per fraction), as per the NRG RTOG-0938 trial.[12] Studies suggest that SBRT for treatment of low- to intermediate-risk prostate cancer is associated with improved biochemical relapse-free survival, with an acceptable toxicity profile.[13-15]

Studies of patterns of failure in EBRT with standard fractionation show the area of local recurrence is the dominant intraprostatic lesion (DIL) in approximately 90% to 100% of cases.[16,17] Therefore, the DIL is a favorable target for heterogeneous dose escalation in SBRT. A phase I trial conducted by Herrera et al demonstrated promising anti-tumor activity and minimal toxicities associated with SBRT and simultaneous dose escalation to the DIL up to 50 Gy in 5 fractions.[18]

The objective of this study is to investigate the efficacy and toxicity profile of a moderate boost to the DIL while following NRG-GU005 dose constraints. We hypothesized that it is feasible to boost the DIL during SBRT and that doing so while following established dosimetric constraints would result in a favorable toxicity profile.

Materials and Methods

Subjects

We retrospectively reviewed 10 consecutive patients treated at our institution between October 2017 and December 2018 with definitive SBRT (36.25 Gy in 5 fractions) for intermediate-risk prostate cancer; these patients were treated with SBRT following the dose contouring guidelines and dose constraints from the SBRT arm of NRG-GU005 to guide treatment planning. No patients received hormone therapy. We retrospectively analyzed clinical characteristics, dosimetry, and toxicity of these patients by chart review. This study was approved as exempt by the institutional review board (IRB).

Treatment Planning

All patients had gold fiducial markers (Civco Medical Solutions) placed in the prostate prior to treatment. Four fiducial markers were placed, and they were placed at least 1 cm apart, when possible. For SBRT planning, both a thin slice (1 to 1.5 mm) noncontrast pelvic CT and a high-resolution nonendorectal coil 1.5 T or 3 T MRI were used. Axial T2-weighted turbo spin echo images provided anatomical information, and axial noncontrast T1-weighted gradient-echo images were used for fiducial marker localization, both in the same straight axial orientation as CT slices with slice thickness of 2 to 3 mm. To accurately identify the DIL, MRI THRIVE images (dynamic contrast-enhanced gradient-echo sequences) were also acquired and fused with planning CT.

Specific preparation instructions were given to all patients to minimize prostate motion during SBRT simulation and treatment. Two days prior to CT simulation, patients were advised to follow a low-gas, low-motility diet. The day prior to simulation, patients were instructed to use a mild laxative and a gas relief medication, as well as to change their diet to a clear liquid diet. On the day of the scan, they were instructed to take a gas relief medication 2 hours prior to their appointment time. Patients were also instructed to empty their bladders before scans. All patients were imaged and treated in supine positions with a SBRT body frame (Bionix). A knee cushion was used when necessary for patient comfort. None of the patients had a rectal spacer, such as SpaceOAR, placed. CT and MRI images were fused in MIMVista (MIM Systems).

Per NRG-GU005 protocol, the gross tumor volume (GTV) was the prostate only, as defined on T2-weighted MRI. The clinical target volume (CTV) was the prostate and approximately 1 cm of proximal seminal vesicles, and the planning target volume (PTV) was 5-mm expansion in all directions, except 3 mm posteriorly on the CTV. The DIL and urethras were contoured with the help of a genitourinary radiologist using THRIVE and T2-weighted MRIs (**Figure 1**).

Treatment plans (36.25 Gy in 5 fractions) were generated with MultiPlan 4.6.1 using sequential optimization. Hot spots (< 120% of prescription dose) inside the PTV were intentionally placed in the DIL region by using the objective constraints. Dose-volume histogram (DVH) constraints

Table 1. Patient Characteristics

Patient Characteristics (N = 10)	Number of Patients
Age	70 (50-75)
Race	
White	40%
Black	60%
Stage (by MRI)	
T1c	1
T2a	2
T2b	1
T2c	6
Gleason Score	
3+3	1
3+4	8
4+3	1
Favorable Intermediate Risk	1
Unfavorable Intermediate Risk	9
Baseline PSA	6.2 (4.2-11.5)

Table 2. Dosimetry Constraints and Plan Results,* $P < 0.001$

Organ Name	Dosimetric Parameter	GU005 Constraints		Plan Value
		Per Protocol	Variation Acceptable	Mean ± STD
PTV	D0.03cc[Gy]	< 38.78	< 43.5	42.63 ± 0.70
	D99%[Gy]	> 34.4	> 33.7	35.08 ± 0.44
	D98%[Gy]	> 36.25	> 34.4	35.63 ± 0.32
	Mean [Gy]			38.91 ± 0.42
DIL	Mean [Gy]			40.45 ± 0.87*
	D99%[Gy]			38.59 ± 0.81*
Rectum	D0.03cc[Gy]	< 38.06	< 40	37.80 ± 0.59
	D3cc[Gy]	< 34.4	< 36	33.89 ± 0.60
	D10%[Gy]	< 32.63	< 34	31.54 ± 0.86
	D20%[Gy]	< 29	< 30	26.96 ± 1.09
	D50%[Gy]	< 18.13	< 19	16.14 ± 1.28
Bladder	D0.03cc[Gy]	< 38.06	< 40	38.60 ± 0.76
	D50%[Gy]	< 18.12	< 20	16.74 ± 0.16
Urethra	D0.03[Gy]	< 38.78	< 43.5	39.13 ± 0.59

Key: PTV = planning target volume, DIL = dominant intraprostatic lesion

for the PTV and OARs from protocol NRG-GU005 were followed (**Table 2**).

SBRT Treatment Delivery

The same bowel regimen used prior to simulation was also used prior to treatment delivery, and all patients were treated on an empty bladder to maximize reproducibility. The entire course was completed within two weeks on an every-other-day basis (eg, M, W, F). SBRT was delivered using the CyberKnife Robotic Radiosurgical System (Accuray Inc.). The CyberKnife system is equipped with two orthogonal kV x-ray imaging devices for image guidance. Fiducial markers can be clearly identified in kV x-ray images attributed to its high density. During treatment delivery, the positions (6D) of fiducial markers were tracked based on the paired kV x-ray images. Imaging was every 15 to 30 seconds to ensure submillimeter tracking accuracy. The robotic system automatically corrected for 6D shifts up to 1-cm translational shifts, 5-degree roll, 2-degree pitch, and 3-degree yaw. If the motion was beyond these limits or noted to be excessive, most commonly due to movement of bowel gas, the treatment was paused until the fiducial orientation/position was back within tolerance.

Follow-up and Toxicity Assessment

Patients were seen in follow-up by the treating radiation oncologist every 3 to 6 months after completion of SBRT. Toxicity and PSA measurements were recorded in medical records as part of standard clinical practice. Retrospectively, genitourinary (GU) and gastrointestinal (GI) toxicity were graded by National Cancer Institute Common Terminology Criteria (NCI-CTC) via chart review. Specific GU symptoms evaluated include dysuria, urinary frequency, urgency, retention, and GI symptoms include proctitis, hemorrhoids, rectal pain, and bleeding. Both early (< 90 days from first fraction) and late (> 90 days from first fraction) toxicities were assessed.

Statistical Analysis

Paired T-tests were used to compare the dose to the entire PTV vs the dose to the DIL.

Results

Subjects

Clinical characteristics are listed in **Table 1**.

Dosimetry

Target coverage and normal tissue dose constraints are listed in **Table 2**.

All NRG-GU005 protocol dosimetric constraints were met (**Table 2**). Mean prostate volume was 39 cc (range 26-59 cc), and mean DIL volume was 2 cc (range 0.7 to 4.5 cc). Mean prescription dose (36.25 Gy) coverage of the PTV was 95.4% (range 93.8 to 97.9%). The conformity index for all plans was < 1.2, and the dose to 0.03 cc of

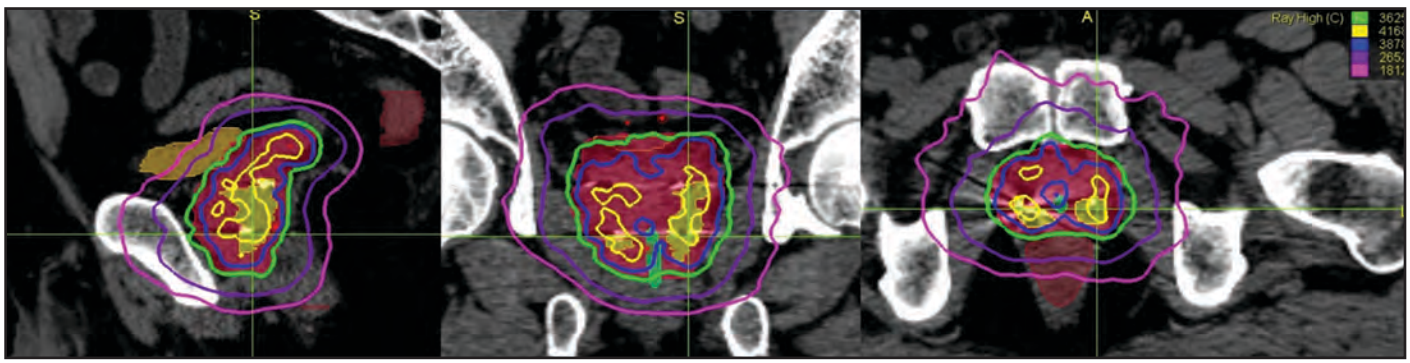


FIGURE 2. *Example of isodose lines (patient #2) in sagittal, coronal and axial planes in which 115% of isodose lines (41.68 Gy) is avoided away from urethra, and it is closely covering the dominant intraprostatic lesion (DIL). Planning target volume (PTV) (red), rectum (brown), bladder (orange), DIL (yellow), urethra (green).*

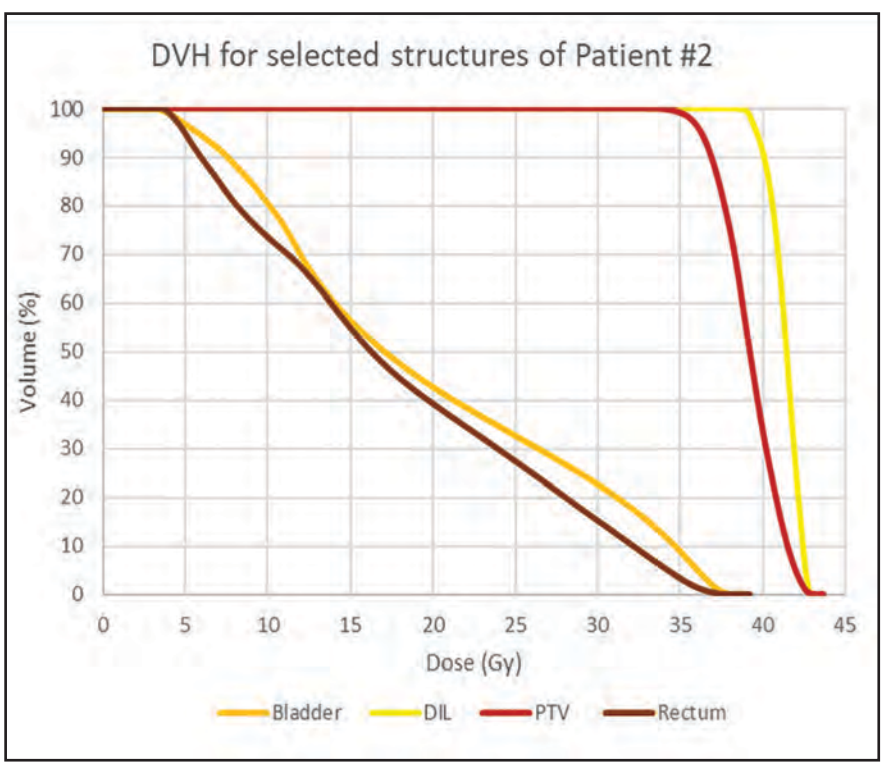


FIGURE 3. *Dose-volume histogram (DVH) for patient #2. DIL = dominant intraprostatic lesion, PTV = planning target volume.*

Table 3. Genitourinary and Gastrointestinal Toxicity by Grade and Time

	Genitourinary Toxicity (dysuria, urinary frequency, urgency, retention)		Gastrointestinal Toxicity (proctitis, hemorrhoids, rectal pain, bleeding)	
Grade	< 90 days % (N = 10)	> 90 days % (N = 10)	< 90 days % (N = 10)	> 90 days % (N = 10)
1	40%	30%	10%	10%
2	40%	20%	10%	0

the PTV was 42.63 Gy (range 41.13 to 43.39 Gy), < 120% of the prescription dose (43.50 Gy). The minimum dose received by 99% of the PTV (D99%) was mean 35.1 ± 0.4 Gy, whereas the mean D99% for the DIL was 38.6 ± 0.8 Gy ($P < 0.001$). Using an alpha/beta of 1.5, this corresponds to a BED of 199.4 Gy for PTV vs. 237.3 Gy for DIL.

For OARs, mean rectum D0.03 cc was 37.8 ± 0.6 Gy, D3cc was 33.89 ± 0.60 Gy, D10% was 31.54 ± 0.86 Gy, and D50% was 16.1 ± 1.3 Gy. Mean bladder D0.03cc was 38.6 ± 0.8 Gy, and mean bladder D50% was 16.7 ± 1.6 Gy (**Table 2**). D0.03cc to the urethra was mean 39.13 ± 0.59 Gy.

Figure 2 shows screenshots of the graphic plan for patient #2, where higher dose lines (115%) are concentrated in and around the DIL. **Figure 3** is the corresponding DVH.

Toxicity

All patients had one on-treatment visit (OTV). The median follow-up time after treatment was 12 months. The incidence of acute grade 1 or 2 GI toxicity was 20%, of which 10% persisted past 90 days. The incidence of acute GU grade 1 or 2 toxicity was 80%, of which 50% persisted past 90 days. No patients developed grade 3 or greater GI or GU toxicity (**Table 3**).

Biochemical Outcomes

The mean pretreatment PSA was 6.2 ng/ml (range 4 to 11.5). After SBRT, the

mean PSA at 3- or 6-month follow-up was 1.5 ng/ml (range 0.7 to 2.4).

Discussion

The motivation for a boost to the DIL has been established, as several studies have shown the DIL to be the main site of tumor recurrence in 90% to 100% of cases.[16,17] Our study investigates both the feasibility and toxicity profile of a moderate boost to the DIL in the context of SBRT for intermediate-risk prostate cancer. The feasibility and accuracy of the treatment planning technique in this work has been investigated using a patient specific 3D-printed prostate phantom and published by Lee et al.[19] The results of our study demonstrate the feasibility of this planning technique in clinical practice, as the DIL received significantly higher doses than the PTV while respecting standard OAR constraints.

While our study is geared toward treatment planning technique and toxicity outcomes, it is important to consider the potential impact on clinical endpoints such as survival and biochemical control. Recently published data from the Focal Lesion Ablative Microboost in Prostate Cancer (FLAME) phase III trial show improved biochemical disease-free survival in the focal boost (up to 95 Gy to the DIL) compared with the standard arm (77 Gy in 35 fractions), with a hazard ratio of 0.45, $P < 0.001$.[20] Although no comparable studies are published for a DIL boost in prostate SBRT, the results from the FLAME trial suggest that delivering a simultaneous integrated boost to the DIL could potentially benefit tumor control in patients with localized prostate cancer.

The efficacy and toxicity profiles associated with a boost to the DIL have also been studied for other modalities such as intensity-modulated radiation therapy (IMRT) and BT.[21-29] For example, Sundahl et al found no significant difference in GU or GI toxicity with median follow-up of 72 months among patients treated with IMRT and 82-Gy simultaneous integrated boost to the DIL.[21] In a prospective phase II trial, Gomez-Iturriaga et al found no grade 3 or greater toxicity at a median follow-up of 18 months among intermediate- or high-risk prostate cancer patients treated with dose escalation to the DIL via combined MRI-transrectal ultrasound fusion high-dose-rate BT.[22]

These results stand in contrast to studies that have investigated toxicity profiles associated with homogeneous dose escalation to the entire prostate. A phase I/II trial by Hannan et al included patients who received homogeneous SBRT of 45, 47.5 and 50 Gy in 5 fractions, and 9.8% of patients who received the 50-Gy dose had late grade 3 or greater GI toxicity.[30] Within this cohort of patients, Kim et al further demonstrated that grade 3 or greater rectal toxicity was associated with > 3 cm^3 volume of rectal wall receiving at least 50 Gy and > 35% rectal wall circumference receiving at least 39 Gy.[31] This highlights the importance of limiting dose escalation only to the DIL and considering methods for reducing radiation dose to the rectal wall such as the use of a rectal spacer. A phase III trial conducted by Hamstra et al showed statistically significant reductions in rectal toxicity among patients undergoing IMRT with SpaceOAR, a hydrogel spacer.[32] Another trial conducted by Hwang et al found that SBRT with periprostatic hydrogel placement was associated with an acute grade 1 or 2 GI toxicity rate of 16% and no recorded grade 3 or greater GI toxicity.[33]

The rationale for administering a moderate boost to the DIL while respecting current SBRT guidelines is to improve efficacy while minimizing toxicity by targeting the area of highest tumor activity, thus improving the therapeutic ratio. In our study, we observed a 20% incidence of acute grade 1 or 2 GI toxicity, of which 10% persisted past 90 days. We also found an 80% incidence of acute grade 1 or 2 GU toxicity, of which 50% persisted past 90 days. None of the patients developed grade 3 or greater GI or GU toxicity. However, an important consideration is the potential underreporting of toxicity data due to the retrospective nature of our study and irregularities in follow-up.

Our results can be compared with existing data on toxicity profiles for SBRT delivered at doses of 35 to 36.25 Gy without DIL dose escalation. Reported rates of acute grade 1 or 2 toxicity associated with SBRT typically fall within about 40% to 80% for GI toxicity and about 60% to 80% for GU toxicity.[34-37] This is in line with the toxicity profiles from our cohort, although our acute GI toxicity rates are relatively favorable at 20%, which is comparable to the acute toxicity rate of 16% from the rectal spacer SBRT trial conducted by Hwang et al.[33] Furthermore, none of the studies report grade 3 or greater GI or GU toxicities associated with SBRT given at standard doses.[34-37] Based on the results of our study and comparison to treatment without dose escalation, providing a moderate boost to the DIL while following established dosimetric constraints does not appear to be associated with increased toxicity to OARs.

A recent phase I trial conducted by Herrera et al studied the toxicity associated with SBRT and simultaneous dose escalation to the DIL up to 50 Gy.[18] In their trial, they found an acute grade 1 or 2 GI toxicity rate of 25%, of which 5% persisted past 90 days, and an acute grade 1 or 2 GU toxicity rate of 70%, of which 40% persisted past 90 days. None of the patients in the trial developed grade 3 or greater GI or GU toxicities. Overall, the toxicity profiles closely mirror our results. While both studies utilized dose escalation to the DIL, only our study incorporated the NRG-GU005 protocol, which establishes dosimetric constraints for SBRT treatment planning.[18] Another difference between the two

studies is that Herrera et al used biodegradable rectal spacers, which may have contributed to the favorable toxicity profile that they observed. However, when considered together, the two studies provide evidence that simultaneous dose escalation to the DIL, with or without the use of rectal spacers, is both safe and feasible.

An additional consideration is the impact of accurate contouring and the delivery of optimal radiation therapy that avoids underdosing the prostate while minimizing toxicity to OARs.[38] This is best achieved with an interdisciplinary team and the contouring input from a diagnostic radiologist. For our study, we recruited a radiologist who assisted with contouring of the DIL for all patients. A study conducted by Dimigen et al found that advice from a consulting radiologist resulted in a change of practice in 45% of cases, ranging from changing target volumes to carrying out further imaging.[39] They argue that radiologists are trained to recognize specific discrepancies from normal anatomy that a radiation oncologist, who is more concerned with encompassing CTVs, may overlook. As such, the assistance of a radiologist with formal training in image interpretation can serve as a beneficial and arguably underutilized resource in radiation therapy planning and contouring.

Limitations to our study include the relatively small sample size of 10 patients, the retrospective nature of toxicity grading, and the short follow-up period, as no patients had follow-up past 12 months. Therefore, our study does not capture radiation-induced toxicities that could potentially arise years after treatment. Future clinical trials, incorporation of larger sample sizes and longer follow-up periods could be performed to not only assess the safety and feasibility of dose escalation to the DIL, but also to examine whether dose escalation is justified by improved clinical outcomes.

Conclusion

Prostate SBRT with simultaneous moderate dose escalation to the DIL is feasible and can be accomplished while still respecting established OAR constraints. The approach to SBRT described in this study results in a favorable toxicity profile comparable to that of standard SBRT regimens without dose escalation. However, such escalation requires more specific MRI-based target delineation and likely would benefit from contouring with a radiologist.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. *CA Cancer J Clin.* 2019;69(1):7-34. doi:10.3322/caac.21551
2. Howlader N, Noone A, Krapcho M, et al. NIH National Cancer Institute. *SEER Cancer Statistics Review,* 1975-2016; 2019. Accessed March 1, 2020. https://seer.cancer.gov/csr/1975_2016/
3. National Comprehensive Cancer Network; 2019. Prostate Cancer (Version 4.2019). Accessed March 1, 2020. https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf
4. Dearnaley DP, Jovic G, Syndikus I, et al. Escalated-dose versus control-dose conformal radiotherapy for prostate cancer: long-term results from the MRC RT01 randomised controlled trial. *Lancet Oncol.* 2014;15(4):464-473. doi:10.1016/S1470-2045(14)70040-3
5. Pasalic D, Kuban DA, Allen PK, et al. Dose escalation for prostate adenocarcinoma: a long-term update on the outcomes of a phase 3, single institution randomized clinical trial. *Int J Radiat Oncol Biol Phys.* 2019;104(4):790-797. doi:10.1016/j.ijrobp.2019.02.045
6. Michalski JM, Moughan J, Purdy J, et al. Effect of standard vs dose-escalated radiation therapy for patients with intermediate-risk prostate cancer: The NRG Oncology RTOG 0126 Randomized Clinical Trial. *JAMA Oncol.* 2018;4(6):e180039. doi:10.1001/jamaoncol.2018.0039
7. Zelefsky MJ, Yamada Y, Fuks Z, et al. Long-term results of conformal radiotherapy for prostate cancer: impact of dose escalation on biochemical tumor control and distant metastases-free survival outcomes. *Int J Radiat Oncol Biol Phys.* 2008;71(4):1028-1033. doi:10.1016/j.ijrobp.2007.11.066
8. Sanda MG, Dunn RL, Michalski J, et al. Quality of life and satisfaction with outcome among prostate-cancer survivors. *N Engl J Med.* 2008;358(12):1250-1261. doi:10.1056/NEJMoa074311
9. Miralbell R, Roberts SA, Zubizarreta E, Hendry JH. Dose-fractionation sensitivity of prostate cancer deduced from radiotherapy outcomes of 5,969 patients in seven international institutional datasets: α/β = 1.4 (0.9-2.2) Gy. *Int J Radiat Oncol Biol Phy* 2012;82(1):e17-24. doi:10.1016/j.ijrobp.2010.10.075
10. Brenner DJ, Martinez AA, Edmundson GK, Mitchell C, Thames HD, Armour EP. Direct evidence that prostate tumors show high sensitivity to fractionation (low alpha/beta ratio), similar to late-responding normal tissue. *Int J Radiat Oncol Biol Phys.* 2002;52(1):6-13. doi:10.1016/s0360-3016(01)02664-5
11. Dasu A, Toma-Dasu I. Prostate alpha/beta revisited — an analysis of clinical results from 14 168 patients. *Acta Oncol.* 2012;51(8):963-974. doi:10.3109/0284186X.2012.719635
12. Lukka HR, Pugh SL, Bruner DW, et al. Patient reported outcomes in NRG Oncology RTOG 0938, evaluating two ultrahypofractionated regimens for prostate cancer. *Int J Radiat Oncol Biol Phys.* 2018;102(2):287-295. doi:10.1016/j.ijrobp.2018.06.008
13. King CR, Brooks JD, Gill H, Pawlicki T, Cotrutz C, Presti JC. Stereotactic body radiotherapy for localized prostate cancer: interim results of a prospective phase II clinical trial. *Int J Radiat Oncol Biol Phys.* 2009;73(4):1043-1048. doi:10.1016/j.ijrobp.2008.05.059
14. King CR, Freeman D, Kaplan I, et al. Stereotactic body radiotherapy for localized prostate cancer: pooled analysis from a multi-institutional consortium of prospective phase II trials. *Radiother Oncol.* 2013;109(2):217-221. doi:10.1016/j.radonc.2013.08.030
15. Freeman DE, King CR. Stereotactic body radiotherapy for low-risk prostate cancer: five-year outcomes. *Radiat Oncol.* 2011;6:3. doi:10.1186/1748-717X-6-3
16. Arrayeh E, Westphalen AC, Kurhanewicz J, et al. Does local recurrence of prostate cancer after radiation therapy occur at the site of primary tumor? Results of a longitudinal MRI and MRSI study. *Int J Radiat Oncol Biol Phys.* 2012;82(5):e787-793. doi:10.1016/j.ijrobp.2011.11.030
17. Cellini N, Morganti AG, Mattiucci GC, et al. Analysis of intraprostatic failures in patients treated with hormonal therapy and radiotherapy: implications for conformal therapy planning. *Int J Radiat Oncol Biol Phys.* 2002;53(3):595-599. doi:10.1016/s0360-3016(02)02795-5
18. Herrera FG, Valerio M, Berthold D, et al. 50-Gy stereotactic body radiation therapy to the dominant intraprostatic nodule: results from a phase 1a/b trial. *Int J Radiat Oncol Biol Phys.* 2019;103(2):320-334. doi:10.1016/j.ijrobp.2018.09.023
19. Lee CL, Dietrich MC, Desai UG, et al. A 3D-printed patient-specific phantom for external beam radiation therapy of prostate cancer. *J Eng Sci Med Diagn Ther.* 2018;1(4). doi:10.1115/1.4040817
20. Kerkmeijer LGW, Groen VH, Pos FJ, et al. Focal boost to the intraprostatic tumor in external beam radiotherapy for patients with localized prostate cancer: results from the FLAME randomized phase iii trial. *JCO.* Published online January 20, 2021: JCO.20.02873. doi:10.1200/JCO.20.02873
21. Sundahl N, De Meerleer G, Villeirs G, et al. Combining high dose external beam radiotherapy with a simultaneous integrated boost to the dominant intraprostatic lesion: analysis of genito-urinary and rectal toxicity. *Radiother Oncol.* 2016;119(3):398-404. doi:10.1016/j.radonc.2016.04.031

22. Gomez-Iturriaga A, Casquero F, Urresola A, et al. Dose escalation to dominant intraprostatic lesions with MRI-transrectal ultrasound fusion high-dose-rate prostate brachytherapy. Prospective phase II trial. *Radiother Oncol.* 2016;119(1):91-96. doi:10.1016/j.radonc.2016.02.004
23. Fonteyne V, Villeirs G, Speleers B, et al. Intensity-modulated radiotherapy as primary therapy for prostate cancer: report on acute toxicity after dose escalation with simultaneous integrated boost to intraprostatic lesion. *Int J Radiat Oncol Biol Phys.* 2008;72(3):799-807. doi:10.1016/j.ijrobp.2008.01.040
24. De Meerleer G, Villeirs G, Bral S, et al. The magnetic resonance detected intraprostatic lesion in prostate cancer: planning and delivery of intensity-modulated radiotherapy. *Radiother Oncol.* 2005;75(3):325-333. doi:10.1016/j.radonc.2005.04.014
25. Singh AK, Guion P, Sears-Crouse N, et al. Simultaneous integrated boost of biopsy proven, MRI defined dominant intra-prostatic lesions to 95 Gray with IMRT: early results of a phase I NCI study. *Radiat Oncol.* 2007;2:36. doi:10.1186/1748-717X-2-36
26. Miralbell R, Mollà M, Rouzaud M, et al. Hypofractionated boost to the dominant tumor region with intensity modulated stereotactic radiotherapy for prostate cancer: a sequential dose escalation pilot study. *Int J Radiat Oncol Biol Phys.* 2010;78(1):50-57. doi:10.1016/j.ijrobp.2009.07.1689
27. Pinkawa M, Piroth MD, Holy R, et al. Dose-escalation using intensity-modulated radiotherapy for prostate cancer - evaluation of quality of life with and without (18)F-choline PET-CT detected simultaneous integrated boost. *Radiat Oncol.* 2012;7:14. doi:10.1186/1748-717X-7-14
28. Ares C, Popowski Y, Pampallona S, et al. Hypofractionated boost with high-dose-rate brachytherapy and open magnetic resonance imaging-guided implants for locally aggressive prostate cancer: a sequential dose-escalation pilot study. *Int J Radiat Oncol Biol Phys.* 2009;75(3):656-663. doi:10.1016/j.ijrobp.2008.11.023
29. Uzan J, Nahum AE, Syndikus I. Prostate dose-painting radiotherapy and radiobiological guided optimisation enhances the therapeutic ratio. *Clin Oncol (R Coll Radiol).* 2016;28(3):165-170. doi:10.1016/j.clon.2015.09.006
30. Hannan R, Tumati V, Xie X-J, et al. Stereotactic body radiation therapy for low and intermediate risk prostate cancer – results from a multi-institutional clinical trial. *Eur J Cancer.* 2016;59:142-151. doi:10.1016/j.ejca.2016.02.014
31. Kim DWN, Cho LC, Straka C, et al. Predictors of rectal tolerance observed in a dose-escalated phase 1-2 trial of stereotactic body radiation therapy for prostate cancer. *Int J Radiat Oncol Biol Phys.* 2014;89(3):509-517. doi:10.1016/j.ijrobp.2014.03.012
32. 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(5):976-985. doi:10.1016/j.ijrobp.2016.12.024
33. Hwang ME, Mayeda M, Liz M, et al. Stereotactic body radiotherapy with periprostatic hydrogel spacer for localized prostate cancer: toxicity profile and early oncologic outcomes. *Radiat Oncol.* 2019;14(1):136. doi:10.1186/s13014-019-1346-5
34. Katz AJ, Santoro M, Ashley R, Diblasio F, Witten M. Stereotactic body radiotherapy for organ-confined prostate cancer. *BMC Urol.* 2010;10:1. doi:10.1186/1471-2490-10-1
35. Chen LN, Suy S, Uhm S, et al. Stereotactic body radiation therapy (SBRT) for clinically localized prostate cancer: the Georgetown University experience. *Radiat Oncol.* 2013;8:58. doi:10.1186/1748-717X-8-58
36. Park Y, Park HJ, Jang WI, Jeong BK, Kim H-J, Chang AR. Long-term results and PSA kinetics after robotic SBRT for prostate cancer: multicenter retrospective study in Korea (Korean radiation oncology group study 15-01). *Radiat Oncol.* 2018;13(1):230. doi:10.1186/s13014-018-1182-z
37. McBride SM, Wong DS, Dombrowski JJ, et al. Hypofractionated stereotactic body radiotherapy in low-risk prostate adenocarcinoma: preliminary results of a multi-institutional phase 1 feasibility trial. *Cancer.* 2012;118(15):3681-3690. doi:10.1002/cncr.26699
38. Salembier C, Villeirs G, De Bari B, et al. ESTRO ACROP consensus guideline on CT- and MRI-based target volume delineation for primary radiation therapy of localized prostate cancer. *Radiother Oncol.* 2018;127(1):49-61. doi:10.1016/j.radonc.2018.01.014
39. Dimigen M, Vinod SK, Lim K. Incorporating a radiologist in a radiation oncology department: a new model of care? *Clin Oncol (R Coll Radiol).* 2014;26(10):630-635. doi:10.1016/j.clon.2014.04.030

APPLIED RADIATION ONCOLOGY™ UPDATE YOUR SUBSCRIPTION PREFERENCES

Launched as an eJournal in 2012, Applied Radiation Oncology (ARO) is now available in print, online or on your mobile device. Published quarterly under the editorial guidance of John Suh, MD, FASTRO, FACR, Chairman of the Department of Radiation Oncology and Associate Director of the Gamma Knife Center at the Brain Tumor and Neuro-Oncology Center at Cleveland Clinic, each issue presents peer-reviewed case presentations and clinical review articles that provide practical, actionable information that radiation oncologists can use to enhance the efficiency and quality of radiotherapy.

Editorial coverage targets imaging, contouring, target delineation, treatment planning, patient immobilization, organ tracking, safety and quality, and other timely topics essential to the discipline.

Please take a moment to update your subscription preferences.

appliedradiationoncology.com/subscribe

Editor's note: *This article was recently published in our sister publication,* Applied Radiology, *Vol 50, Issue 2, p. 30-31, and is included here for potential benefit for a subset of our readers.*

Nuclear Medicine Prepares for Greater ^{68}Ga Demand

Mary Beth Massat

When the US Food and Drug Administration (FDA) approved the use of Gallium-68 prostate-specific membrane antigen (PSMA)-11 (^{68}Ga PSMA-11) PET imaging for prostate cancer in December, nuclear medicine specialists were not the only ones excited by the development.

Several companies aligned with the production and supply chain for ^{68}Ga had been anticipating—and planning for—the FDA's approval and its subsequent expected impact on demand for ^{68}Ga, which can be used diagnostically when paired with PSMA-11, and therapeutically when paired with lutetium-177 or actinium-225.

"We made the investment in a GMP ^{68}Ga generator years before any drugs were approved, betting that the market was going to have a ^{68}Ga drug," says Jay Simon, general manager and managing director of Eckert & Ziegler Radiopharma (Berlin).

In its action, the FDA gave the University of California, San Francisco (UCSF) and University of California, San Diego (UCSD) approval to label the ^{68}Ga isotope with PSMA for PET imaging of the prostate.

Researchers reported that clinical trials comparing PSMA PET imaging .with 18F fluciclovine PET found that ^{68}Ga PSMA-11 PET detected significantly more prostate lesions than 18F fluciclovine PET imaging in cases of cancer recurrence following prostatectomy.[1] Peter Carroll, MD, a professor at the UCSF Helen Diller Family Comprehensive Cancer Center, called the development a "game changer" in a statement issued by UCSF.

In addition, there are nearly 400 clinical trials[2] currently underway involving the use of ^{68}Ga for both diagnosis and therapeutics for prostate and neuroendocrine tumors and other types of cancer. "The market is definitely growing, even beyond PSMA," says Lutz Helmke, PhD, Head of the Medical Radiopharma Segment at Eckert & Zeigler. "We believe there are many more tracers that will come to market and, therefore, we have done our utmost to increase capacity for this product."

Dr. Helmke adds that after the 2017 shortage of germanium, which is used to make ^{68}Ga, Eckert & Ziegler further increased its generator production capacity. He believes the company can meet current world demand for ^{68}Ga generators; however, he said the company is also preparing for the increase in demand resulting from the anticipated regulatory clearance of ^{68}Ga PSMA-11 for general clinical use and will be looking for additional suppliers for its GMP grade germanium.

Dr. Helmke says there is a trend in the US toward developing larger ^{68}Ga generators with higher activities, from 50 mCi to 100 mCi. Eckert & Ziegler has developed a higher activity/higher capacity generator and will be filing for FDA approval in the near future. The company has also opened a new production facility in the Boston area.

"We have a geostrategy to serve our clients regionally but more importantly, we will have CMO capabilities so we can produce our customers' final product," Dr. Helmke says.

Raw Material To Generator Development

IRE ELiT (Fleurus, Belgium), a division of IRE, is also taking action to increase its production of germanium and ^{68}Ga. With respect to the former, IRE is building its own cyclotron to produce germanium; it is also working to increase production of ^{68}Ga generators and higher-quality and capacity ^{68}Ga—up to 100 mCi.

"This is very important for us to have an independent source of germanium," says Jean Bonnet, IRE's head of strategy, sales, and marketing. "We expect that in the future there will be intense competition to source germanium due the anticipated increase in demand for

Ms Massat is a contributing editor to Applied Radiology.

^{68}Ga generators. This will preserve our independence and capacity to maintain our position in the future market."

The higher-capacity generators will offer more flexibility than 50 millicurie generators, Bonnet says.

"We know there will be a burst of demand for several months when there is approval for a new indication, such as with ^{68}Ga PSMA PET," Bonnet says. "So we are preparing for this flexibility with our partners."

Made in the USA

In 2018, after four years as a US distributor of ^{68}Ga generators for German-based Isotopen Technologien München AG (ITM), RadioMedix (Houston, TX) began preparing to manufacture its own ^{68}Ga generators, making it the only US manufacturer of the generators, says Ebrahim S. Delpassand, MD, CEO, founder and chairman of the board.

"Our plan was to … increase the bandwidth, or output, of the ^{68}Ga generators," Dr. Delpassand says. "This was in anticipation that ^{68}Ga usage will only increase."

A secondary goal was to help ITM file a drug master file (DMF) in the US, which occurred in June 2020 for ITM's next generation Germanium-68/Gallium-68 (^{68}Ge/^{68}Ga) generator, GeGant. GeGant generators are available in 30, 50, and 100 mCi.

"Now we have the capability to manufacture five generators every day. This is significant for generator accessibility in the market," Dr. Delpassand says. "We don't anticipate any shortage of ^{68}Ga supply in the market for PSMA, or for future ^{68}Ga-labeled agents that will come to market."

Dr. Delpassand sees other opportunities to label ^{68}Ga with different ligands to address unmet needs in oncology, including targeted therapies for brain tumors, ovarian cancer, pancreatic adenocarcinoma and triple negative breast cancers.

A Solid Approach

Although ^{68}Ga is generally produced in generators, ARTMS (Burnaby, British Columbia) has developed a low-energy cyclotron, QUANTM Irradiation System (QIS), to produce ^{68}Ga from solid zinc-68 targets. ARTMS CEO Charles Conroy explains that the QIS is used to produce decentralized radiopharmaceuticals such as ^{68}Ga on-site at hospitals, radiopharmacies, universities, and the like. The QIS is compatible with existing and new cyclotrons.

"There are hundreds of cyclotrons in North America, and with the QIS we can get the production closer to the end user," says Conroy. "Additionally, we can create large volumes of radioisotopes by utilizing high-purity, solid-metal targets that are then irradiated, significantly amplifying the amount of ^{68}Ga that one can produce. Using that solid target, a non-radioactive material, and a process that results in fewer impurities gives us the ability to produce such large quantities without the need for a generator. It's completely different than what is on the market today."

Compared to ^{68}Ga generators that typically produce 50-100 mCi of ^{68}Ga, Conroy says the QIS can produce five curies each hour, enough for almost 100 patients. In December 2020, ARTMS received Health Canada clearance to use QIS to produce technetium-99m. The QIS can also perform a "split" run, where the beam can be used to make both copper and ^{68}Ga, for example, on a single production run.

"With the QIS, we are able to create enough material in one location, which would usually be a commercial radiopharmacy, to diagnose or treat patients across several different cities," Conroy adds.

"Our customers are really delighted that ARTMS technology gives them more supply chain control and enables them to treat more patients from products being supplied from a single site," Conroy says.

In early January, ARTMS and Telix Pharmaceuticals (Melbourne, Australia) announced the successful preparation of Telix's TLX591-CDx (illumet), a radiopharmaceutical cold kit containing the components needed to prepare ^{68}Ga-PSMA-11 at ambient temperature. The kit is being evaluated at several institutions in the US, including Emory University Hospital, Memorial Sloan Kettering Cancer Center, City of Hope, and Endocyte (Novartis). Further, Telix has established a network of US partners, including approximately 100 nuclear pharmacies, to prepare and distribute the kits for investigational use in qualified clinical trials.

"We anticipate every corner of America, Europe or any country we serve will be able to offer prostate imaging to their patients," says Telix CEO Chris Behrenbruch. It doesn't matter if it's a New York-area hospital or a hospital in a remote area, everybody's going to have access to this diagnostic technology."

References

1. Calais J, Ceci F, Eiber M, et al. 18F-fluciclovine PET-CT and 68Ga-PSMA-11 PET-CT in patients with early biochemical recurrence after prostatectomy: a prospective, single-centre, single-arm, comparative imaging trial. *Lancet Oncol.* 2019 Sep;20(9):1286-1294. doi: 10.1016/S1470-2045(19)30415-2. Epub 2019 Jul 30. Erratum in: *Lancet Oncol.* 2019 Nov;20(11):e613. Erratum in: *Lancet Oncol.* 2020 Jun;21(6):e304. PMID: 31375469; PMCID: PMC7469487.
2. NIH U.S. National Library of Medicine. Available at www.clinicaltrials.gov. (https://www.clinicaltrials.gov/ct2/results?cond=&term=gallium+68&cntry=&state=&city=&dis

From Bullet to Canon? Exploring the Promise of Heavy Particle Ion Therapy

Mary Beth Massat

Cancer deaths continue to decrease due to advancements in screening, early diagnosis and treatment. According to the American Cancer Society, the largest single annual drop in cancer deaths was 2.2 percent from 2016 to 2017.[1] New treatments such as immunotherapy and targeted therapy as well as refinements in existing radiation oncology techniques, such as stereotactic body radiation therapy (SBRT) and 3D or volumetric-modulated arc therapy (VMAT), have contributed to the decline. Unfortunately, patients still suffer the effects of toxicity to normal, healthy tissue. While proton therapy has been shown to reduce acute adverse effects[2] and is generally considered safer in terms of avoiding damage to nearby healthy tissue, another treatment option may offer even more advantages: carbon ion therapy.

The National Institute of Radiological Sciences (NIRS) in Chiba, Japan, is the world's first carbon ion therapy center. Built in in 1994, roughly 12,000 patients have been treated with carbon ion therapy, nearly a quarter of them for localized prostate cancer. Other primary sites include bone and soft tissue, head and neck, and lung cancers.[3] Currently, 12 particle therapy centers in Europe and Asia are in clinical operations using carbon ion.[4]

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

Despite its potential, providing carbon ion therapy is a costly undertaking at $300 million or more to establish a center, with no current reimbursement offered in the US.

In 2015, the University of Texas Southwestern (UTSW) and University of California, San Francisco, were awarded planning grants from the National Cancer Institute (NCI) to support development of a heavy ion treatment center. Hak Choy, MD, FASTRO, professor and chair of the Department of Radiation Oncology at the UTSW Medical Center, led an international symposium on ion therapy at his institution in November 2014 with the goal to determine the direction of future investigation and development. However, while the NCI and the National Institutes of Health (NIH) will fund research, they do not provide funds for building a facility. Globally, all other heavy ion centers – in Germany, Japan, Austria and Italy – were initially funded by their respective governments.

UT Southwestern Medical Center is sponsoring a clinical trial to compare carbon ion to photon radiation therapy for locally advanced, unresectable pancreatic cancer (CIPHER).[5] Led by principal investigator David Sher, MD, the randomized trial seeks to compare overall two-year survival rates. Patients will receive treatment at a center in Japan or Milan and will include American, European and Asian patients.

Coming to America

In November 2019, Mayo Clinic announced plans to build the first carbon ion therapy center in the US on its Jacksonville, Florida, campus. As one of the early US adopters of proton therapy, Mayo is uniquely qualified to add carbon ion therapy to its armamentarium, says Bradford Hoppe, MD, MPH, professor of radiation oncology and the medical director of Particle Therapy at Mayo Clinic Jacksonville.

"Carbon ion therapy is a treatment that was developed in the US 40 years ago but hasn't been used here in 25 years. Mayo Clinic is well positioned to lead this new effort to bring it back to the US," says Dr. Hoppe. "We are going to examine carbon ion therapy for cancer sites where it is known to be effective, but also explore its use in novel situations, much like we have

***FIGURE 1**. An accelerator room at the Osaka Heavy Ion Therapy Center (A). Example of a treatment room at the center (B). photos courtesy Hitachi Ltd.*

done with proton therapy. The potential is there."

The National Comprehensive Cancer Network (NCCN) Guidelines include carbon ion therapy as an appropriate treatment for bone sarcomas and uveal melanomas. Although bone sarcomas are rare, there is a high rate of local recurrence with radiation therapy alone; therefore, surgery is preferred when technically feasible, Dr. Hoppe explains. Yet, some bone sarcomas cannot be safely resected, such as those in lower spine or base of the skull, without causing neurological or functional damage.

"Carbon ions can cause a lot more damage within the tumor [vs photon or proton therapy], so we think it is useful in tumors thought to be more radioresistant," says Dr. Hoppe. These include melanomas, bone sarcomas, soft-tissue sarcomas, carcinomas in the lung, hepatocellular cancer, renal and pancreatic cancer, recurrent rectal cancer, as well as non-squamous head and neck cancers such as adenoid cystic and mucosal melanomas, and recurrent rectal cancer. Similarly, carbon ion therapy may provide additional benefit in patients with local recurrence following conventional radiation, where re-irradiation may be effective.

Carbon ion therapy, in one way, is similar to proton therapy in that there is no exit dose as seen with photons or conventional external-beam radiation therapy; this allows for delivery of a more conformal treatment maximizing dose in the tumor and delivering less dose to surrounding tissue. Yet, different from proton or photon radiation, it more powerfully damages the cancer cell DNA. Dr. Hoppe likens the difference to that of a cannonball (carbon) vs a bullet (proton). Carbon creates more DNA double strand breaks and chromosomal breaks making the cell more susceptible to death.

The Technology

Hitachi, Ltd., has been involved with particle beam therapy solutions since 1994, including at NIRS where the company supplied the magnets, control system, beam monitors and power supply systems for the accelerator. The company's first US-based proton beam therapy center at the University of Texas MD Anderson Cancer Center opened in May 2006. A 2017 acquisition of Mitsubishi Electric's particle therapy equipment business has brought the company back full circle to carbon ion therapy (see **Figure 1A-B** for examples of a heavy ion therapy accelerator system and treatment room). Now, Mayo Clinic is partnering with Hitachi on the carbon ion therapy system in Jacksonville.

The company has also developed a compact, energy-efficient synchrotron accelerator that can power single- or multiple-room systems. This compact, single-room solution is expandable and does not require additional accelerators to power multiple rooms.

A key differentiator of Hitachi's particle therapy system is its capability to perform both proton and carbon ion therapy. According to Sash Matsumoto, vice president of sales and marketing at Hitachi America, this hybrid particle therapy approach allows centers to start with protons and expand to carbon ion.

"Because carbon is 12 times heavier than hydrogen, it requires larger-sized equipment, which increases the construction costs," Matsumoto says. "We believe in this technology and will continue to invest and build these centers."

RaySearch Laboratories also supports and has invested in carbon ion therapy. RayStation Carbon Ion Therapy is a pencil-beam scanning planning system currently used by six centers in Europe and Asia.[6]

With several NCI-funded studies comparing proton therapy with conventional radiation therapy,[7] the next logical step is comparing proton therapy with carbon ion therapy. Mayo Clinic will be well positioned to carry out this research in the US.

Mayo's particle therapy center will have two proton gantries that will move 360 degrees around the patient and one fixed room that can perform both proton and carbon ion therapy. It is also possible that patients may receive a hybrid proton/carbon ion treatment in the fixed room.

"We don't yet fully understand the radiobiologic effect within the target or just outside the target in normal tissue with carbon ion therapy, which means we don't understand it in normal tissue," says Dr. Hoppe. Theoretically, carbon ion therapy could be used to treat the center of the gross tumor volume and then proton used to treat the subclinical disease and margins because of the understanding of the radiobiology and associated toxicity to normal tissue with proton therapy.

Carbon therapy can also shorten treatment times, Dr. Hoppe adds. In unresectable bone sarcomas, the treatment time with carbon ion is half that of photon or protons.

"Carbon ion therapy can reduce treatment times by 25 to 50 percent, which may help offset some of the expense of treatment," he says. However, since the center will not be built until 2025 and likely begin treatments in 2027, many decisions remain on precisely how Mayo Clinic will utilize carbon ion therapy.

Meanwhile, Mayo Clinic is collaborating with other carbon ion centers in Asia and Europe to embark on preclinical and clinical studies before the Jacksonville center is built. With Mayo Clinic having multiple cancer treatment centers across the US, Dr. Hoppe sees an opportunity to initiate early studies through internal referrals. He is hopeful that other US-based cancer centers will invest in carbon ion therapy and collaborate with Mayo in both pre-clinical and clinical studies in part to achieve a baseline of evidence needed for clinical use.

Also on the horizon: particle ion therapy centers exploring the potential of helium – a lighter particle than carbon yet heavier than protons – for cancer treatment. University Hospital Heidelberg, a heavy particle center in Germany, is researching helium as an alternative to proton therapy by comparing treatment plans via computer simulation.[8]

References

1. American Cancer Society. Major cancer types: Lung, breast, prostate, and colorectal cancer. Accessed January 14, 2021. https://www.cancer.org/latest-news/facts-and-figures-2020.html#:~:text=The%2026%2Dyear%20decline%20in,in%20early%20detection%20and%20treatment

2. Baumann BC, Mitra N, Harton JG, et al. Comparative effectiveness of proton vs photon therapy as part of concurrent chemoradiotherapy for locally advanced cancer. *JAMA Oncol.* 2020;6(2):237-246. doi: 10.1001/jamaoncol.2019.4889. PMID: 31876914; PMCID: PMC6990870

3. Mohamad O, Makishima H, Kamada T. Evolution of carbon ion radiotherapy at the National Institute of Radiological Sciences in Japan. *Cancers (Basel).* 2018;10(3):66. doi:10.3390/cancers10030066

4. Particle Therapy Co-Operative Group. Particle therapy facilities in clinical operation (last update: January 2021). Accessed January 20, 2021. https://www.ptcog.ch/index.php/facilities-in-operation

5. NIH, US National Library of Medicine. Trial of Carbon Ion Versus Photon Radiotherapy for Locally Advanced, Unresectable Pancreatic Cancer (CIPHER). Accessed January 20, 2021. https://clinicaltrials.gov/ct2/show/NCT03536182

6. RaySearch Laboratories. RayStation Carbon Ion Therapy. Accessed January 15, 2021. https://www.raysearchlabs.com/carbon-ion-therapy-treatment-planning

7. National Cancer Institute. Is Proton Therapy Safer than Traditional Radiation? Accessed January 20, 2021. https://www.cancer.gov/news-events/cancer-currents-blog/2020/proton-therapy-safety-versus-traditional-radiation

8. Tessonnier T, Mairani A, Chen W, et al. Proton and helium ion radiotherapy for meningioma tumors: a Monte Carlo-based treatment planning comparison. *Radiat Oncol.* 2018;1(2). https://doi.org/10.1186/s13014-017-0944-3

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

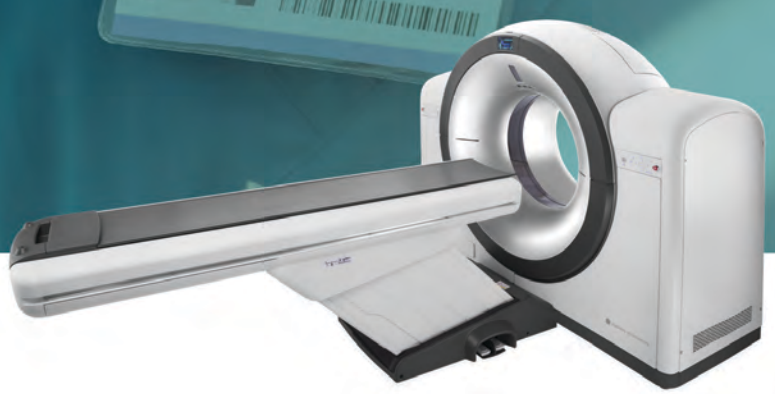
FUJIFILM
Value from Innovation

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