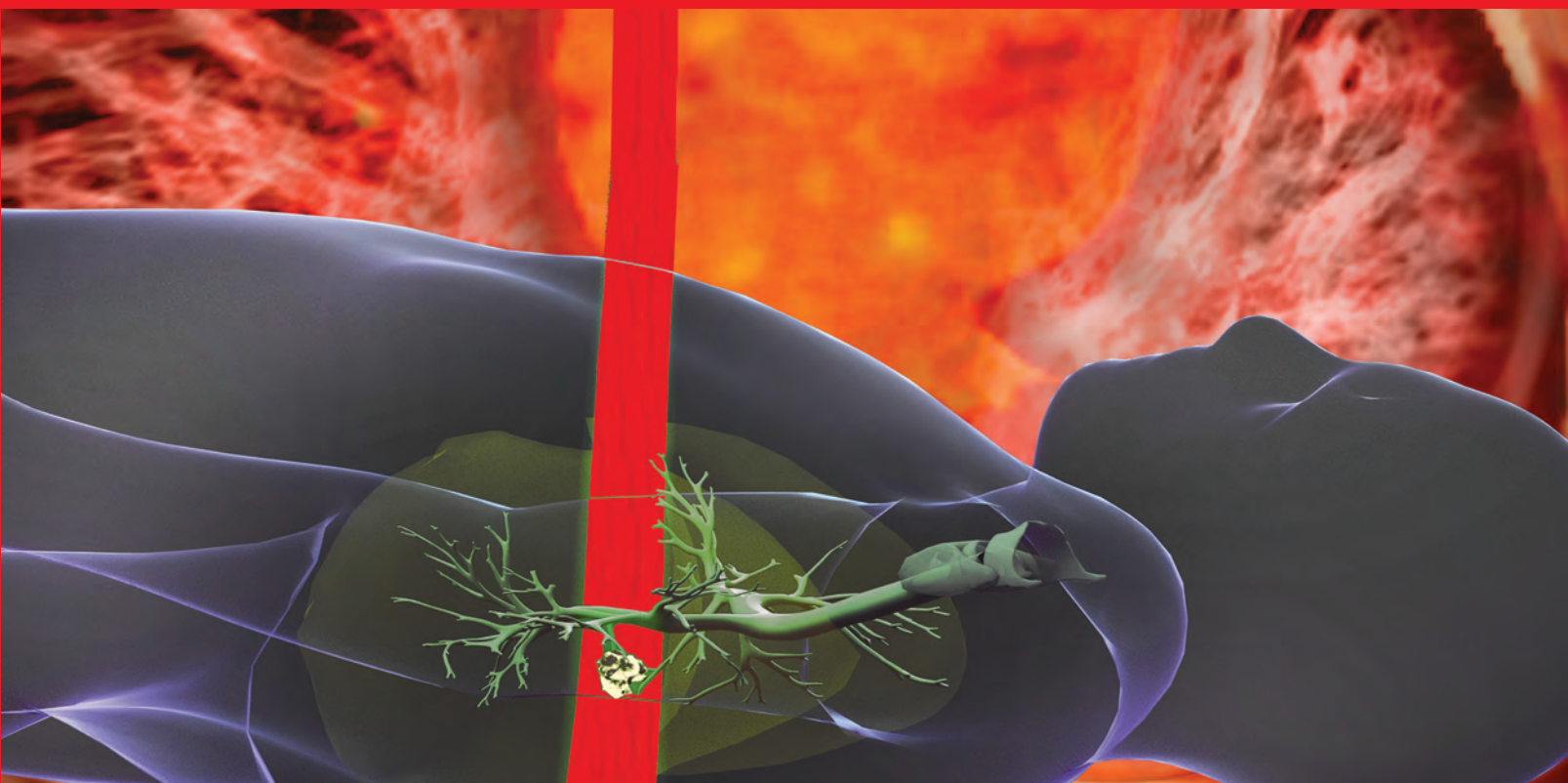


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Applied Radiation Oncology™



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Considerations for Implementing
a Cone Beam Computed
Tomography-Guided Adaptive
Radiotherapy Program

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Disease Characteristics,
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Stent Migration and Fistula
Formation Following Stereotactic
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Pancreatic Cancer

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John Suh, MD, FASTRO, FACR

Professor and Chairman of the Department of Radiation Oncology, at the Taussig Cancer Institute, Rose Ella Burkhardt Brain Tumor and Neuro-oncology Center, Cleveland Clinic, Cleveland, OH

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Chipo Raranje, MS; Ryan Mueller, MD; Alex T. Price, PhD; Lauren E. Henke, MD; Xiaodong Zhao, PhD; Hyun Kim, MD; Eric Laugeman, MS; Joshua P. Schiff, MD

In this review, the authors discuss their experience with delivering cone-beam computed tomography-guided adaptive radiotherapy (CTgART) to a wide variety of disease sites. They highlight the benefits of using treatment planning templates to create a standardized workflow, as well as planning considerations for CTgART delivery to the thorax, abdomen, prostate, and bladder.

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Lan Lu, PhD; Zhexuan Zhang, PhD; Peng Qi, PhD

Online adaptive radiotherapy (ART) makes it possible adjust therapeutic objectives to address the anatomical changes that can occur between the planning and treatment phases of therapy, especially in the management of head and neck, lung, prostate, and gastrointestinal cancers. The authors review online and offline ART technologies, such as cone-beam computed tomography (CBCT) and magnetic resonance imaging (MRI), while examining considerations such as workflow, cost, advantages, and limitations in the context of an ART program.

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This retrospective study examined 340 patients with oropharyngeal cancer (OPC) treated curatively with modern modalities over 10 years at a single institution. The analyses provide a detailed snapshot of the disease characteristics, treatment tolerance, and survival outcomes for patients aged 65 years or older relative to younger patients for both HPV subtypes. Findings highlight the need for enhanced multidisciplinary supportive care for this group of patients who now form the majority of newly diagnosed OPC.

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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.

Advancing Adaptive RT and Patient-Centered Care

John H. Suh, MD, FACP

Welcome to the December issue of *Applied Radiation Oncology*! As the year draws to a close, our field continues to advance with exciting developments in adaptive radiation therapy (ART), personalized care, and a renewed focus on health equity. This issue offers a rich collection of reviews, research, case reports, and commentary that reflect these themes and provide insights to enhance your clinical practice.

Our review articles spotlight ART, a transformative approach to treatment delivery. *Treatment Planning Considerations for Implementing a Cone-Beam Computed Tomography-Guided Adaptive Radiation Therapy Program* provides practical workflows and disease-specific strategies for implementing cone-beam CT-guided ART across various sites such as the thorax, abdomen, prostate, and bladder. Complementing this article, *A Review of Online Adaptive Radiation Therapy* explores the growing feasibility of online ART using CBCT and MRI, accelerated by AI and machine learning. Together, these informative reviews demonstrate the increasing accessibility of ART and its potential to personalize patient care.

The research article *Disease Characteristics, Treatment Toxicity in Older Patients With Oropharyngeal Cancer* highlights important findings on treatment tolerance. While survival outcomes between older and younger patients are similar, older patients experience greater toxicity, underscoring the need for multidisciplinary supportive care and geriatric assessment in treatment planning.

In the commentary *Radiate and Educate: Empowering Future Physicians Through an International Radiation Oncology Student Newsletter*, medical students take a front-seat role in increasing awareness of the radiation oncology field. The article details how the *RadOnc Student Scan* helps bridge the gap between students and medical professionals by offering publishing and networking opportunities, while fostering engagement in our specialty's future. We are extremely proud of the work presented in this article and in the quarterly newsletters developed by talented members of ARO's Future Content Student Committee.

Also featured in the issue are case reports that offer compelling clinical insights. In *Hyperacute Necrosis of a Trigeminal Schwannoma After Gamma Knife Radiosurgery*, a case of immediate tumor necrosis following radiosurgery underscores the unpredictability of clinical outcomes. Additionally, *The Use of Adaptive Radiation in Retroperitoneal Seminoma Patients* demonstrates how ART can optimize outcomes for patients unsuitable for chemotherapy by reducing toxicity while maintaining tumor control.

The Resident Voice column, *Building Barriers or Bridges? How Health and Public Policy Modulate Access to Care*, is an excellent editorial addressing the persistent health disparities driven by discriminatory policies. It is a powerful reminder of our role as advocates for equitable health care and the need to support policies that dismantle barriers to care.

Finally, I would like to sincerely thank Sharon Breske, managing editor for ARO since 2014, for her passion, dedication, and diligence over the past decade! Her leadership, focus, and grit have allowed this journal to grow and transform over the last decade and allowed us to obtain COPE membership and application status with PubMed Central. We wish her the very best with her semi-retirement! Please welcome our new managing editor, Claudia Stahl!

Thank you for being part of the *Applied Radiation Oncology* community. We wish you a joyful new year of peace, hope, health, and continued learning!

Treatment Planning Considerations for Implementing a Cone-Beam CT-Guided Adaptive Radiation Therapy Program

Description

The authors describe practical treatment planning considerations for implementing a cone-beam CT-guided adaptive radiation therapy (CTgART) program with a specific focus on a template-based treatment planning methodology. The article discusses disease-site-specific treatment planning considerations for the delivery of CTgART to the thorax, abdomen, prostate, and bladder, and examines future directions for this technology, which is becoming increasingly accessible and utilized in radiation oncology.

Learning Objectives

Upon completing this activity:

1. Clinicians will develop knowledge of simulation, treatment planning, and treatment delivery techniques utilizing CTgART.
2. Clinicians will learn important steps for implementing CTgART workflows for the thorax, abdomen, prostate, and bladder.
3. Clinicians will understand the future directions of this rapidly advancing technology.

Authors

Chipo Raranje, MS¹; Ryan Mueller, MD¹; Alex T. Price, PhD²; Lauren E. Henke, MD²; Xiaodong Zhao, PhD¹; Hyun Kim, MD¹; Eric Laugeman, MS¹; Joshua P. Schiff, MD¹

Affiliations: ¹Department of Radiation Oncology, Washington University School of Medicine, St. Louis, MO; ²Department of Radiation Oncology, University Hospitals/Case Western Reserve University, Cleveland, OH.

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- Related oncology professionals.

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Workflow Considerations for Implementing a Cone-Beam CT-Guided Adaptive Radiation Therapy Program

Chipo Raranje, MS;¹ Ryan Mueller, MD;¹ Alex T. Price, PhD;² Lauren E. Henke, MD;² Xiaodong Zhao, PhD;¹ Hyun Kim, MD;¹ Eric Laugeman, MS;¹ Joshua P. Schiff, MD^{3*}

Abstract

Cone-beam CT-guided adaptive radiation therapy (CTgART) is an emerging treatment paradigm that enables the delivery of online adaptive radiation therapy (ART) using CT-based onboard imaging. Our department installed and implemented a CTgART system in 2019 and has since developed workflows for the delivery of CTgART to a wide variety of disease sites. Herein we describe workflow considerations for implementing a CTgART program with a specific focus on the template-based treatment planning methodology that drives online adaptive plan creation on our department's CTgART platform (Ethos; Varian Medical Systems, Palo Alto, CA). We describe disease-site-specific information for the delivery of CTgART to the thorax, abdomen, prostate, and bladder, and discuss future directions for this technology, which is becoming increasingly accessible and utilized in radiation oncology.

Keywords: adaptive radiation therapy, image-guided radiation therapy, stereotactic body radiation therapy, treatment planning, gastrointestinal malignancies, thoracic malignancies, genitourinary malignancies

Introduction

Online adaptive radiation therapy (ART) utilizes advanced imaging systems and treatment planning techniques to develop a new treatment plan based on the patient's anatomy of the day while the patient is on the treatment table. The development of stereotactic MR-guided adaptive radiation therapy (MRgART) and cone-beam CT-guided adaptive

radiation therapy (CTgART) have allowed for dosimetric improvements, which have led to improved local control and decreased toxicity rates across numerous disease sites.¹⁻³ While MRgART has been demonstrated to be an effective tool in the treatment of numerous disease sites, this technology's wide availability has been limited by resource requirements. More recently, a CTgART platform has been developed and

may improve the dosimetric and therapeutic index of radiation therapy in a variety of disease sites.⁴⁻⁶ Additionally, one study demonstrated significant cost-savings when using CT-guided stereotactic body radiation therapy (SBRT) compared with stereotactic MRgART (SMART).⁷

Our department installed a CTgART platform in 2019 and has since developed and tested CTgART workflows in a variety of disease

Affiliations: ¹Department of Radiation Oncology, Washington University School of Medicine in St. Louis, St. Louis, MO. ²Department of Radiation Oncology, University Hospitals/Case Western Reserve University, Cleveland, OH. ³Department of Radiation Oncology, Keck School of Medicine of USC, Norris Comprehensive Cancer Center, Los Angeles, CA.

Corresponding author: *Joshua P. Schiff, MD, 1441 Eastlake Ave., Ground Floor, Los Angeles, CA 90033. (joshuapschiff@gmail.com)

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sites. The components of the linear accelerator at our institution (Ethos; Varian Medical Systems, Palo Alto, CA) have been described elsewhere. This platform consists of a ring gantry linear accelerator unit and a dedicated treatment planning system (TPS) that utilizes an Acuros XB, dose-to-medium-based calculation algorithm. The system is capable of intensity-modulated radiation therapy (IMRT) sliding window and volumetric-modulated arc therapy (VMAT) beam delivery. The TPS also utilizes an artificial intelligence (AI)-driven intelligent optimization engine (IOE), which allows users to set hierarchical priorities that define the objective function.⁸ Use of the IOE is required for all cases by the Ethos system. Once optimization begins, the TPS monitors the plan optimization on its own. Due to the inability to manually change goals during optimization, template-based planning is highly useful in generating clinically acceptable treatment plans.

Onboard image guidance is accomplished using a cone-beam CT (CBCT) system. The rapid nature of CBCT acquisition on this unit paired with the dedicated treatment planning software allows for effective delivery of CTgART.⁹⁻¹² The CTgART workflow includes traditional CT simulation, CBCT-based simulation depending on disease site, traditional treatment planning processes, plan adaptation, and treatment delivery. Once the initial treatment plan has been developed and approved, patients present for adaptive treatment. The online adaptive portion of the workflow includes image acquisition, contouring and online adaptive plan optimization, plan selection, quality assurance (QA), and treatment delivery. Our institution has successfully developed disease site-specific CTgART treatment workflows for pancreatic tumors, abdominal

metastases, ultra-central lung tumors, and pelvic malignancies, amongst others.¹³

In the remainder of this article, we describe simulation, treatment planning, and treatment delivery techniques utilizing CTgART as well as future directions of this rapidly advancing technology.

General CTgART Workflow

Traditional CT Simulation

Figure 1 depicts our institution's CTgART workflow. All patients undergo a traditional CT simulation with various disease site-specific institutional order set protocols with appropriate custom immobilization devices. As ART cases can be fairly time consuming, it is critical that the patient be comfortable in the treatment position for an extended period. For example, for CTgART pancreatic cases, we often simulate with one arm up and one arm down. While traditionally pancreatic radiation therapy is conducted with both arms over head, the one arm up one arm down position is more comfortable for patients to maintain for prolonged online adaptive treatments. Most patients can now be treated with high-quality plans with both arms at their side. Of note, patients are generally scanned (and treated) at breath-hold for thoracic and abdominal CTgART cases.

CBCT Simulation

We often subsequently perform a CBCT simulation on our CTgART treatment machine using the same patient positioning and custom immobilization devices. The CBCT simulation is performed to evaluate the patient's suitability for ART, primarily focusing on the ability to delineate the target and surrounding organs at risk (OARs), and the patient's ability to perform end-exhale breath-hold in a reliable and

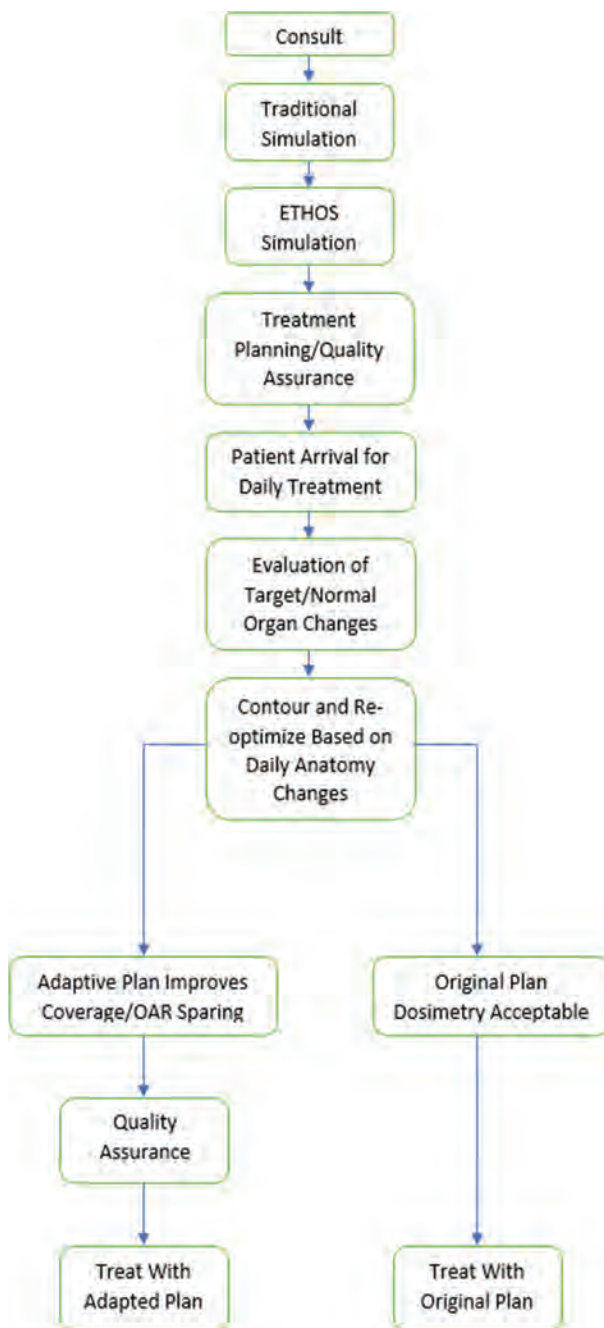
reproducible fashion for breath-hold-gated treatments. This is performed for abdominal CTgART SBRT cases, as diaphragmatic motion, abdominal fluid, and breath-hold quality, among other factors, significantly determine CBCT quality and the subsequent ability to perform CTgART. Alternatively, this is not often done for genitourinary and gynecological cases as image quality in the pelvis is not as strongly tied to those factors. Ultimately, the decision to obtain a CBCT simulation in addition to a traditional CT simulation is at the discretion of the treating radiation oncologist and medical physicist as it is specific to each patient's individual anatomy, regardless of disease site.

Figure 2 demonstrates the potential benefits that breath-hold can provide in target and OAR visualization.

Treatment Planning

Once simulation imaging has been obtained and contours are complete, a contour ring structure that consists of a site- and patient-specific axial and superior/inferior expansion of the planning target volume (PTV) will be constructed.^{14,15} The CT image data set is then shortened to only include image data that spans 5 cm superior and inferior to the contour ring to limit plan optimization time during adaptive treatments, which also assists in minimizing patient time on the table (**Figure 3**). When examining 10 pancreas SBRT patient plans, we found that the mean VMAT optimization time was 641.53 seconds (~10.7 min) for the full-length CT image data set and only 404.62 seconds (~6.7 min) using the shortened CT. For comparison, IMRT optimization for the same 10 patients took 72.34 seconds and 61.42 seconds for the full data set and shortened data set. Despite the faster optimization time, the mean MU ratio was 8.8 and 4.5 for IMRT and VMAT, respectively. Assuming 800 MU/min

Figure 1. Adaptive workflow. An overview of the workflow described for treatment with CT-guided adaptive radiation therapy.



dose rate, the mean beam-on time for IMRT and VMAT plans would be approximately 11 minutes and 5.6 minutes, respectively. The choice to use of IMRT or VMAT is site-specific and addressed below.

Throughout the history of ART, the goals of adaptation have taken on

various forms and today 2 primary strategies exist for ART planning: conventional planning and isotoxic planning.¹⁶ In adaptive conventional planning, the goal is to find a balance between coverage and OAR sparing and keep this balance the same throughout treatment.¹⁷ In adaptive

isotoxic planning, the goal is to dose escalate portions of the PTV that are achievable based on the anatomy of the day while limiting OAR doses to a maximum acceptable constraint. Both account for daily anatomy changes and maintain a level of target coverage, but isotoxic planning target coverage will vary depending on anatomy of the day. For CTgART cases using SBRT dosing (ie, 50 Gy/5 fx), we always use an isotoxic planning strategy to limit normal tissue toxicity.

Template-based planning is the only method for CTgART planning on the Ethos system. During treatment planning, the clinical goals of each structure and their priority are set during the initial template-based planning and cannot be adjusted or edited during an online adaptive session. Therefore, it is imperative that templates be standardized and vetted with a large variety of clinical scenarios to ensure the template (or minor patient-specific changes) can reproducibly provide high-quality, clinically appropriate plans throughout the course of treatment. To verify the quality of a newly constructed template, it is crucial to test the template *in silico* on a wide variety of previously treated patients.¹⁸⁻²⁰ Our process for implementing a new template, which has previously been described, involves rigorous testing of institutionally created templates in prospective *in silico* imaging studies.^{9,13,19} In these studies, the templates, which are based on adaptive treatment planning procedures and constraints from prior ART and non-ART SBRT treatment planning procedures, are tested within emulated CTgART treatments using images collected from patients being treated with non-CTgART radiation therapy within our department. These *in silico* studies are typically performed on 7 to 10 emulated patients and are ideally done prior to

Figure 2. Impact of breath-hold on cone-beam CT (CBCT) quality. (A) Nonbreath-hold CBCT demonstrating significant artifact. (B) Breath-hold CBCT with resultant reduction in artifact.

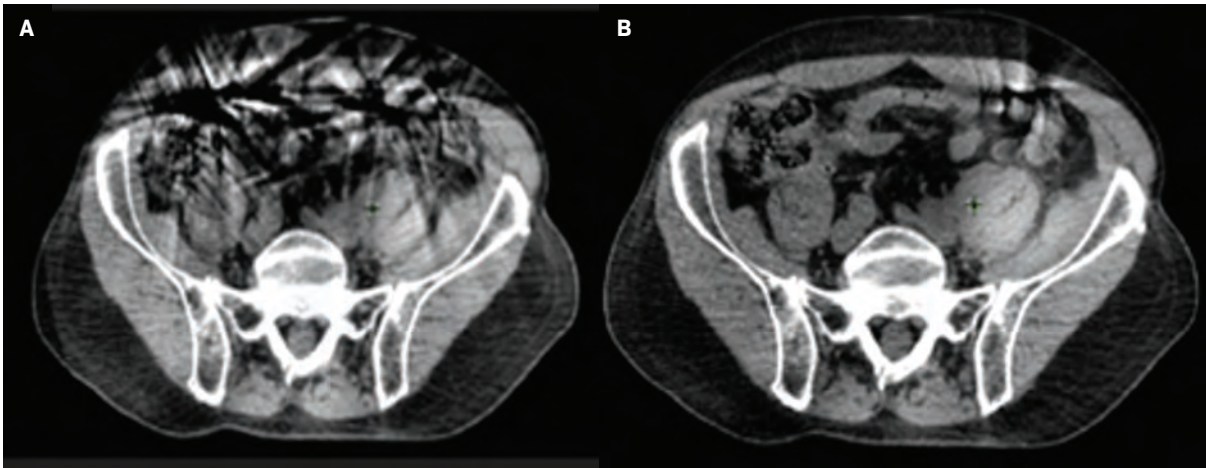
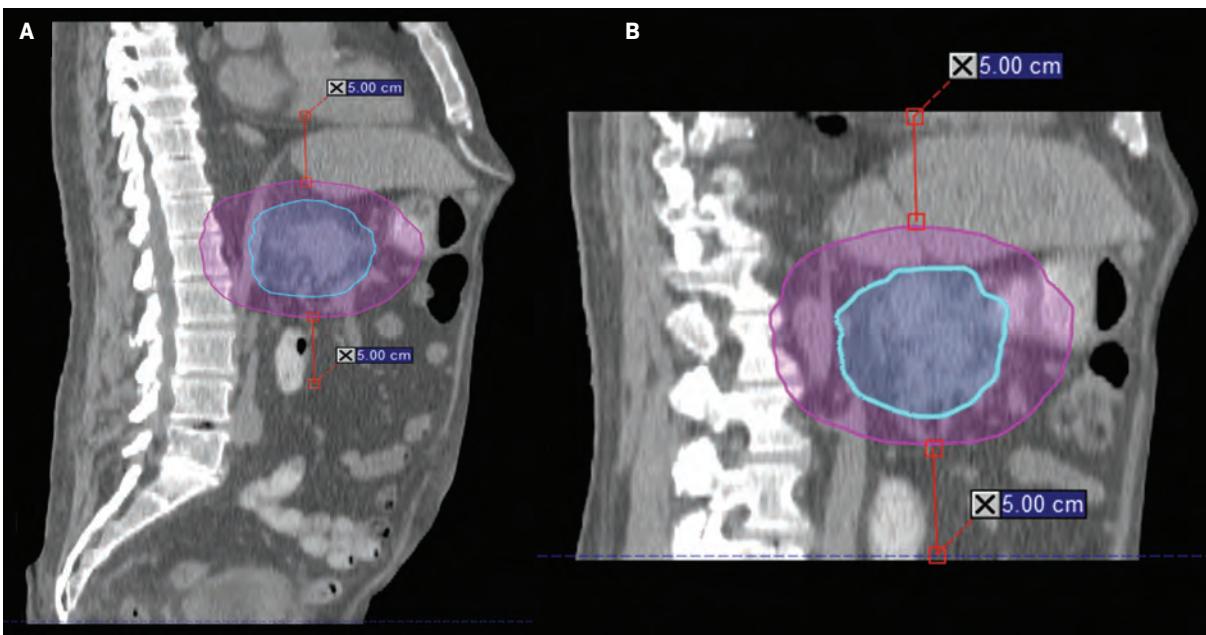


Figure 3. Example of shortened scan for treatment planning. (A) Sagittal view of full-length scan and (B) shortened-scan length. Using a shortened scan for treatment planning minimizes optimization time and patient time on the table.



implementing a new ART workflow of any modality. If the template can construct quality plans among a variety of patients with different anatomies, it will generally be robust when adapting to daily changes in the same patient's anatomy. To construct robust templates for all disease sites, the prescribing physician must concretely define OAR

hard constraints that reflect clinical scenarios in which the oncologist would halt patient treatment if those hard constraints were not met, as well as minimum target coverage goals.

Conventional Approach

When performing CTgART, a conventional treatment planning approach may employ elements such

as mean dose constraints to drive plan optimization or have significant OAR and PTV overlap in which a balance of PTV coverage and OAR sparing must be struck. However, the black box nature of the Ethos optimizer limits the usefulness of using generic or conflicting clinical goals (eg, plugging in clinical goals directly from a non-ART trial).

In a phantom study, we found that the optimized Dmean dose to OARs overlapping with a PTV does not change monotonically with the Dmean constraints specified in plan directives.⁸ In simple terms, the IOE can ensure a patient-specific ideal balance of target coverage and OAR sparing for overlapping structures with conflicting constraints using nonoverlapping optimization structures and optimization clinical goals.

Oftentimes conventional planning target prioritizes coverage. However, if the target coverage objective is the topmost priority, OAR sparing will suffer. Commonly in clinical trials, target coverage has 2 levels per protocol and within variation. Variation acceptable allows for cases where a balance can be struck between coverage and sparing. Therefore, in CTgART planning it is helpful to separate the ideal PTV coverage goal and the variation acceptable or minimum target coverage into individual clinical goals. A similar approach can be done with the OARs, with a clinical goal for both an ideal metric and a hard constraint. From here, the clinical goals can be prioritized as follows: (1) minimum PTV coverage, (2) hard OAR constraint, (3) ideal PTV coverage, and (4) ideal OAR constraint. This order allows the optimizer to first prioritize achieving necessary target coverage followed by meeting any hard OAR constraints. To ensure plan robustness, the first 2 goals should never conflict with each other. In cases where they do, the higher priority will trump the lower so that the goal is not met. In general, if the minimum coverage and hard OAR constraint do not conflict, the order should not matter.

Isotoxic Approach

Our clinical implementation of isotoxic treatment planning prioritizes sparing of OARs over PTV

Table 1. Optimizations Structures for Template: A Nonexhaustive List of Optimization Structures used in CT-Guided Adaptive Radiation Therapy Treatment Planning, How They Are Created, and Their Purposes		
STRUCTURE NAME	STRUCTURE CREATION	PURPOSE
ContourRing	An axial and superior/inferior margin from PTV	Defines area where OARs should be recontoured based on daily anatomy
PTV_OPT Σ^a	PTV cropped out of overlapping OARs + margin	Allows for dose escalation away from critical OARs
GTV_OPT Σ	GTV – OARs + margin	Allows for clinically desirable hot spots within the tumor
PTV_OPT_InnerRing Σ	PTV_OPT – GTV_OPT	Limits hot spots outside of the GTV and promotes dose fall off
Control Ring 1 Σ	3-5 cm ring around PTV	Helps control low-dose spill and verifies no high dose outside of contour ring for safety purposes
NS_TPS_PTV	GTV + radiation oncologist-defined margin	Verifies that derived Ethos PTV structure is consistent with PTV contoured in ARIA (Varian Medical Systems, Palo Alto, CA) and tracks drastic changes in target volume
^a Σ refers to derived structures that are not hand contoured but rather automatically generated from applying predefined operators on pre-existing additional contours. Abbreviations: GTV, gross tumor volume; NS, normal structure; OARs, organs at risk; PTV, planning target volume; TPS, treatment planning system.		

coverage through the utilization of treatment planning templates. Our SBRT templates typically include structures such as a PTV_OPT and gross tumor volume (GTV)_OPT in addition to several other ancillary structures, further described in **Table 1**. The Opt structures play a key role in plan optimization as they allow for the unique ability to reproduce the optimal plan even in the setting of significant anatomic change. When creating clinical templates for isotoxic treatment planning, it is useful to normalize all plans to meet all priority 1 goals for OARs. By doing so, we can ensure that all OAR hard constraints are met at every fraction when adapting online. To obtain appropriate coverage to the PTV, Opt structures are then set as priority 2 goals. **Table 2** depicts sample templated priority 1 and 2 goals that can be utilized when generating adaptive single-dose-level abdominal SBRT plans. Our clinic

typically utilizes priority 3 and 4 goals to improve plan quality and optimize structures beyond their hard constraints, if possible. Lastly, “Report Value Only” goals can be set for metrics in which the value is of interest but is not an optimization goal such as PTV V100%Rx.

Plan Optimization and Evaluation

The Dose Preview workspace can be utilized to evaluate potential conflicting objectives that could result in suboptimal plans. This workspace uses a 9 static field fluence-only fast optimization and dose calculation to evaluate the effects of changing clinical goals and their priorities. In CTgART treatments, it can be useful to generate a plan in a standard departmental TPS with a more desirable beam geometry and export the plan to the CTgART TPS for optimization.

CTgART quantitative plan evaluation examines 2 key features of the plan: Does the plan

Table 2. Abdominal CT-Guided Adaptive Radiation Therapy (CTgART) Template: A Nonexhaustive List of Priority 1 and 2 Goals for the Delivery of Stereotactic Body Radiation Therapy Using a CTgART Platform

STRUCTURE	GOAL	PRIORITY
Stomach	$V3300 \text{ cGy} \leq 0.50 \text{ cm}^3$	1
Small bowel	$V3300 \text{ cGy} \leq 0.50 \text{ cm}^3$	1
Duodenum	$V3300 \text{ cGy} \leq 0.50 \text{ cm}^3$	1
Large bowel	$V3300 \text{ cGy} \leq 0.50 \text{ cm}^3$	1
Spinal canal	$D0.50 \text{ cm}^3 \leq 2 \text{ 500 cGy}$	1
PTV_OPT	$D95\% \geq 100\%$	2
GTV_OPT	$V105\% \geq 95\%$	2
	$V120\% \geq 20\%$	
Both kidneys	$D_{\text{mean}} \leq 1500 \text{ cGy}$	2
ContourRing	$D_{\text{max}} \leq 7500 \text{ cGy}$	2
PTV_OPT_InnerRing	$D5\% \leq 110\%$	2
PTV_5000	$D95\% \geq 2500 \text{ cGy}$	2
Liver-GTV	$V2500 \text{ cGy} < 33\%$	2

PTV, planning target volume.

meet all OAR constraints and has sufficient coverage been obtained? The features that influence the quantitative performance of CTgART plans are of the utmost importance and serve as the baseline for assessing plan and template performance. These features include templated OAR constraints and coverage goals defined by the radiation oncologist with knowledge of what is clinically achievable given the clinical patient population. Although these elements should generally remain rigid, user adjustments to these values may be necessary for special patient anatomical consideration.

In addition to quantitative performance, it is imperative to assess the plan's qualitative performance. A robust template should be able to yield a plan that meets clinical constraints; however, meeting clinical constraints alone may not reflect a high-quality plan. The template should include elements that drive the qualitative plan performance where users can adjust the parameters to accommodate patient-specific

concerns to obtain improved dose distributions. For example, **Figure 4** reflects the impact on plan quality when optimizing with templated goals designed to drive overall plan quality. Notably, both plans meet OAR and PTV_OPT goals; however, additional structures and goals are required to generate SBRT-like dose distributions.

Online Adaptive Treatment Delivery Workflow

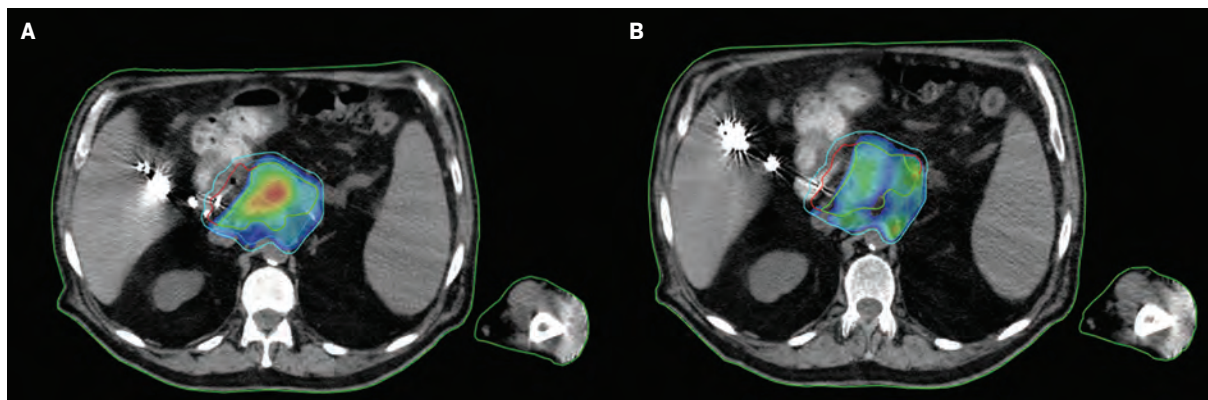
Our clinical CTgART system is equipped with the HyperSight (Varian Medical Systems, Palo Alto, CA) CBCT technology, which enables the acquisition of CBCT images in 6 seconds with image quality comparable to those acquired from CT simulation.²¹ Prior to the installation of the HyperSight, all initial CBCTs were taken in breath-hold due to potential motion artifacts to improve image quality, even in pelvic sites which were treated free breathing. With the more advanced imaging hardware, motion artifacts are less of a concern for pelvic treatment sites and initial CBCTs are acquired in the same state as

simulation and treatment delivery (free-breathing vs breath-hold).

During daily treatments, CTgART utilizes a serial adaptive workflow in which the default setting is for the initial simulation CT and treatment plan contours to be propagated onto the CBCT anatomy of the day as a means of avoiding propagation of systematic errors that may have been created during previous ART fractions.¹⁵ Plan development and reoptimization are performed on the CBCT images.¹⁶ If permanent changes need to be saved for further fractions, such as tumor growth, an offline replanning process is required.

When constructing CTgART plans, it is also important to consider isocenter placement to avoid out-of-field artifacts that may arise on the CBCT. The CTgART system will attempt to deform the target volume based on the influencers and deformable registration from simulation CT to online CBCT. In our clinical experience, we do not utilize the deformed target but instead rigidly propagate the target onto the image. The covering physician

Figure 4. Pancreas CT-guided adaptive radiation therapy plan dose distribution. (A) Shown here is the pancreas plan dose distribution when the template includes goals for structures such as GTV_OPT, which are designed to contain the hotspot within the gross tumor volume (GTV) compared with (B) the pancreas plan dose distribution without any GTV_OPT goals. The hotspots exist more peripherally, which may be of concern when treating near organs at risk.



then makes changes to the target as needed. Initial target contours are created offline with the assistance of abundant clinical information such as diagnostic imaging and surgical pathology reports that are not always readily available when performing online adaptation, and therefore rigidly propagating the initial target volumes helps preserve the initial clinical intent of the prescribing radiation oncologist. In addition, target deformation is variable in quality and may add increased target delineation uncertainty.

To avoid unnecessarily long treatment times, only the portions of OARs that lie in the ContourRing are adjusted in the online adaptive workflow. These are done by an advanced practice radiation therapist to offset the time a radiation oncologist needs to be contouring OARs.^{15,22} Due to potential partial contouring of structures and to facilitate more robust template planning, it is often best practice to utilize absolute volume constraints when possible. This will avoid issues caused by partially contoured structures. Following the final approval of the contour changes from the radiation oncologist and the medical physicist, the plan is then reoptimized. It should be noted,

in Ethos v1.1, when generating a CTgART plan at the treatment console on the day of treatment, the user can only evaluate the performance of priority 1 and 2 goals.

Patient-specific QA is performed via the MobiusAdapt module of Mobius3D (Varian). Mobius3D analyzes plan DICOM files and performs an independent dose calculation and compares the calculated dose to the dose in the TPS plan.²³ Additionally, Mobius3D will perform a 3D gamma analysis. Prior to treatment, an additional verification CBCT is acquired to verify patient positioning. Small rigid shifts can be applied in the event of minor patient movement.²³⁻²⁶

Intrafraction Motion Management

Due to the length of adaptive treatment times, intrafraction motion management is an important aspect of CTgART delivery. Our clinic utilizes several different intrafraction motion management techniques driven by site-specific motion management needs. For some abdominal cases, we implement a breath-hold technique that involves the patient holding their breath on end exhale to limit tumor motion.²⁷ A surface guidance system is utilized to

monitor breath-hold motion and has been shown to reduce tumor motion to clinically acceptable ranges.²⁶ For sites containing more mobile anatomy, acquisition of a midtreatment CBCT is recommended. Additionally, a post-treatment CBCT may be acquired to assess final patient positioning. To limit breath-holds during treatment, VMAT beam geometry is often preferred due to the reduction in MU ratio compared with IMRT, as illustrated in the Treatment Planning section.

Disease-Site-Specific CTgART Workflow Considerations

Thoracic Malignancies

The role of ART in thoracic malignancies has primarily been explored as an avenue to reduce toxicity for patients receiving SBRT for early stage ultracentral lung malignancies.^{3,28,29} To date, only in silico data have been published on the role of CTgART for patients with ultracentral thoracic malignancies, and all patients treated clinically with early stage ultracentral non-small cell lung cancer with CTgART at our institution are treated with 55 Gy/5 fx on trial

(NCT05785845).⁹ When performing CTgART for thoracic malignancies, the primary image data set for treatment planning is the breath-hold simulation CT scan. Treatment plans are generated from templates where the priority 1 OARs are selected based on the proximity of the target to the OARs. When planning thoracic sites, our clinic will typically utilize arc geometries. Although it has been shown that the CTgART TPS takes longer to optimize VMAT plans compared with IMRT optimization times,⁸ the decision to utilize VMAT geometries comes from the motivation to minimize the number of monitor units in the plan, the time required to deliver treatment, and patient breath-holds.

Abdominal Malignancies

ART has a role in the treatment of abdominal malignancies as ART allows for interfraction motion management to account for the mobile luminal gastrointestinal tract during abdominal SBRT delivery. There are published experiences on the benefits of ART for patients with pancreatic cancer, liver cancers, and abdominal oligometastases, among other disease processes.³⁰⁻³² Limited clinical data are available on the safety of CTgART for patients with abdominal malignancies, and the results of an ongoing phase 2 trial evaluating CTgART study evaluating 50 Gy/5 fx for patients with pancreatic cancer are eagerly awaited (NCT05764720). In abdominal CTgART planning, the end-exhale breath-hold CT image is typically the primary data set utilized for treatment planning, and patients are treated end-exhale breath-hold if they can tolerate the technique. For patients treated with a free-breathing technique, planning organ at risk volumes (PRV) are derived from CT imaging from the 0 phase (maximal inhalation) and 50 phase (maximal exhalation) data acquired from the 4DCT at the

time of simulation, thus creating motion PRVs. For the treatment of abdominal malignancies, arc path is determined based on simulation position. Partial arcs are utilized if the patient is simulated with an arm down, which is sometimes done for patient comfort.

Intrafraction bowel motion is a challenge with abdominal CTgART, particularly for pancreas stereotactic CTgART cases, which can be quite long. Data show that intrafraction bowel motion can cause discrepancies between the dose delivered to OARs as intended with the adapted plan and what is actually treated based on bowel placement at the time of treatment delivery.^{33,34} To mitigate this, we often have patients lie in the treatment position for 20 minutes prior to initiating the adaptive process to allow the bowels to settle into a more stable position. A verification CBCT is also acquired prior to treatment delivery, and if bowel has entered the PTV_OPT structure, the treating physician and medical physicist may reinitiate the adaptive contouring and planning process. With regard to contouring within the online adaptive environment, the contour ring is patient-specific and dependent on target size.

Genitourinary Malignancies

The role of ART for genitourinary malignancies is evolving. SMART has an established role in the management of prostate malignancies.^{35,36} There is significant intrigue in implementing CTgART workflows for patients with prostate cancer as ART may allow for dose escalation while minimizing rectal and bladder toxicities.³⁷ At our institution, individuals with prostate cancer who receive CTgART are typically unfavorable intermediate- or high-risk patients treated in the study (NCT05628363). Prostate CTgART may be time consuming

if the plan requires contouring of all the bowel in the pelvis. Intrafraction bladder filling is also a concern that must be accounted for during treatment planning. Discretion should be used for which portions of the plan require contouring (ie, contour ring extent) as certain OARs may never exceed the provided dose constraints given the lower prescription for elective nodal volumes. The use of IMRT beams is advantageous for prostate CTgART given the shorter optimization time.

Adaptive radiation therapy may also confer significant advantages for patients with bladder cancer as a method of mitigating the deleterious dosimetric effects of changes in bladder filling. Two ongoing studies are evaluating CTgART for patients with bladder cancer (NCT05700227, NCT05295992). When performing CTgART for patients with bladder cancer at our institution, a CT data set acquired with the bladder empty functions as the primary treatment planning data set. Additionally, CT simulation imaging is acquired 30 minutes after the initial CT and is fused to the primary data set. The internal target volume (ITV) margin is constructed such that the ITV structure created from the primary data set also covers the entire bladder in the CT scan acquired after 30 minutes of bladder filling. Treatment planning for the bladder is unique because the organ will change in volume over the course of treatment. Our treatment planning technique for bladder treatments considers the anticipated displacement of OARs away from the target because of bladder filling over the course of treatment by generating OAR minus ITV structures. These structures include the bowel, sigmoid, and rectum minus the ITV and can be used as an assessment of the final dosing to these structures during plan delivery. Adaptive bladder treatment plans can utilize static IMRT beam

geometries or VMAT beams; however, static fields are preferred due to the decrease in plan optimization time compared with VMAT plans.

Discussion and Future Directions

Herein we have reviewed in detail our departmental workflow for CTgART as well as specific technical considerations for CTgART workflows in a variety of disease sites. These insights have enabled the development of a robust ART program, treating more than 200 patients with ART per year including 70 patients with CTgART per year.¹³ This review highlights critical lessons for departments installing their own CTgART programs in hopes of enabling more widespread adoption of CTgART.

The original Ethos CTgART platform had a high-quality CBCT scanner capable of acquiring a scan for contouring over the course of a 17-second breath-hold. The recently upgraded CBCT scanner can obtain a high-quality scan in 6 seconds with an increased field of view and reconstruction algorithm that decreases artifacts from implanted devices, all of which further improve image quality with increased spatial and contrast resolution.²¹ These improvements provide CBCT images that can rival traditional CT simulation scanners. Critically for the adaptive process, improved imaging quality improves contour delineation and reduces uncertainty. CTgART, and ART in general, is vulnerable to contouring mistakes as adaptive contouring is performed with onboard imaging under time constraints; as such, improved onboard image quality is critical to minimize contouring errors. In addition, with improved onboard imaging hardware and online treatment planning software capable of performing dose calculations on

CBCT images,^{38,39} CTgART technology may allow for safer and easier implementation of simulation-free treatment workflows.^{40,41}

Timing studies across numerous disease sites and institutions in both simulated and clinical CTgART suggest that patients remain on the treatment table for 19 to 100 minutes depending on the disease site.^{13,42-44} Adaptive times outside of the US may be shorter than local experiences due to US requirements for physician plan approval prior to delivering treatment. In Europe, some experiences report therapists and other providers proceeding with the adaptive plan with a post-treatment review by the supervising physician.⁴⁵ Methods to reduce prolonged treatment times may decrease patient discomfort and reduce the possibility of intrafraction motion that can mitigate the advantages of ART. Possible advancements in the integration of AI-contouring as well as additional optimization of the ART workflow may reduce patient time on the table, resulting in more tolerable treatments and a potential reduction in intrafraction motion of both internal and external patient anatomy. Moreover, further CTgART research may include exploring methods to increase patient comfort during treatment to mitigate discomfort during extended treatment times.

Intrafraction respiratory motion management in stereotactic cases treated on the current CTgART machine platform is limited to breath-hold techniques, whereas traditional linear accelerators have triggered imaging such as automated acquisition of KV x-rays and fluoroscopy. As advanced onboard imaging is combined with traditional C-arm linear accelerator capabilities, it is possible that the optimal interfraction motion management potential of CTgART may intersect with more advanced forms of intrafraction motion management,

further reducing uncertainty for high-dose-per-fraction CTgART treatments in the thorax and upper abdomen.

Although a secondary dose calculation algorithm for QA is provided by the vendor, the online ART process has the potential for high-risk errors that cannot be detected by secondary dose calculations alone. For example, 4 out of the top 5 high-risk failure modes identified by Wang et al for CTgART occurred in the online contouring step.⁴⁶ Therefore, efforts to develop and integrate more sophisticated online QA tools are instrumental in the safe widespread implementation of CTgART. Despite the potential for dose accumulation to enable assessment of dose delivered across adapted plans, our clinical implementation of CTgART does not make use of the Ethos dose accumulation given the vendor recommendations of AAPM TG-132.

Conclusion

CTgART is a powerful tool to improve the therapeutic ratio for radiation therapy but the implementation of CTgART requires a highly standardized workflow. Through the creation of robust treatment planning templates and detailed CTgART processes, it is possible to implement CTgART workflows for a variety of disease sites.

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A Review of Online Adaptive Radiation Therapy

Lan Lu, PhD; Zhexuan Zhang, PhD; Peng Qi, PhD*

Abstract

Advances in cone-beam CT (CBCT) and MRI, together with rapid and accurate tissue segmentation and treatment planning accelerated by artificial intelligence and machine learning, have made online adaptive radiation therapy (ART) feasible on commercial radiation therapy systems. In this review, we examine the status of CBCT- and MRI-based online ART in light of their recent increase in clinical adoption.

Keywords: adaptive radiation therapy, CBCT, MRI

Introduction

With technology advancements and contour standardization, errors in imaging, contouring, and treatment setup have been reduced over the last decades. However, errors occur when a singular treatment plan is used over the course of therapy without adjustment for the patient's anatomical changes during that time. Yan proposed the concept of adaptive radiation therapy (ART) to reduce the impact of anatomical changes during therapy and summarized ART as “a closed loop radiation treatment process where the treatment plan can be modified (including re-optimized) using systematic feedback of measurements (e.g., onboard imaging).”¹ The goal of ART is to maintain objectives of the initial planning over the course of treatment, during which anatomical change may occur.

Anatomical variations between the initial planning and treatment phases are common in radiation therapy for cancers such as head and neck (HN), lung, prostate, and gastrointestinal cancers. Such variations present in different formats (e.g., tumor shrinkage or progression) and timescale (days to weeks). For example, Kishan et al studied 12 patients with HN and observed a median increase of 16% in the gross target volume between treatment planning and the first treatment (a median of 13 d).² Other anatomical changes, such as bladder or rectal filling, peristalsis, and uterus motion, may occur over minutes to hours. Importantly, anatomical variations are often patient-specific and cannot be accurately predicted from population models, warranting the need for ART approaches that can

respond to an individual patient's evolving anatomy.

A critical component of ART is onboard imaging (OBI). Ideally, the image quality of OBI should be comparable to that of simulation to ensure accurate adaptation. However, compared with simulation CT (SIM-CT), OBI on a regular linear accelerator (linac), cone-beam CT (CBCT) system produces inferior images that can be characterized by lower soft tissue contrast, greater susceptibility to artifacts, and inaccurate electron density-to-Hounsfield Unit (HU) calibration.

CBCT technology has been improving due to hardware and software advancements. For example, the gantry speed of a Halcyon linac (Varian Medical Systems, Palo Alto, CA) can reach up to 4 rotations per minutes (RPM), which is 4 times faster than that of a Varian TrueBeam linac. This fast rotation allows for a CBCT acquisition within a single breath-hold (BH).³ The rapid image acquisition, along with an advanced iterative CBCT (iCBCT) reconstruction algorithm, improved

Affiliations: Department of Radiation Oncology, Taussig Cancer Center, Cleveland Clinic, Cleveland, OH.

Corresponding author: *Peng Qi, PhD, Department of Radiation Oncology, Taussig Cancer Center, Cleveland Clinic 9500 Euclid Ave. CA50, Cleveland, OH 44195. (qip@ccf.org)

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image quality and consistency of BH-CBCTs.³ Most recently, Varian introduced the HyperSight CBCT system, making the imaging quality of OBI closer to that of SIM-CT.^{4,5} The HyperSight is available for the Varian Ethos system (developed based on the Halcyon system), a platform specifically designed for online ART.

CBCT produces inferior soft tissue contrast compared to MRI. Therefore, a radiation therapy machine equipped with onboard MRI is more desirable for ART, despite the many technical challenges involved in operating the machine in the presence of a strong magnetic field. The first commercial MRI-guided radiation therapy (MRgRT) machine was developed by ViewRay (ViewRay Inc, Oakwood, USA), combining a 0.35 T MRI scanner and 3 Co-60 sources mounted on a ring gantry.⁶ In its later design, the Co-60 sources were replaced by a linac for improved treatment efficiency.⁷ The Elekta Unity MRI-linac (Elekta, Stockholm, Sweden), FDA cleared in 2023, integrates a 1.5 T MRI scanner with a linac.

In this review, we begin with an overview of offline and online ART before focusing on CBCT- and MRI-based online ART. For CBCT-based online ART, we discuss the workflow, advantages, as well as limitations and futures of the Ethos system. For MRI-based online ART or adaptive MRgRT, we also cover its workflow, advantages and limitations, and conclude with our perspectives on the future of online adaptive MRgRT.

Offline and Online ART

Onboard CBCT may capture progressive anatomical changes, such as tumor progression or shrinkage or those caused by weight loss, enabling the use of offline ART when these changes exceed certain thresholds.¹

Offline ART requires replanning between treatment fractions. Because CBCT lacks the image quality (e.g., artifacts, small field of view, inaccurate HU) needed for treatment planning, repeat simulation is required for offline ART. After resimulation, the workflow of offline ART is similar to that of the initial treatment planning: contouring, planning, physician and physicist review, patient-specific quality assurance (PSQA), pretreatment CBCT verification and correction, and treatment delivery.⁸⁻¹⁰ By combining the delivered fractions with the offline-adapted plans, the overall quality of the radiation therapy can be evaluated. Institutional studies and clinical trials, especially in the treatment of prostate cancer and HN cancer, have shown the benefits of offline ART.¹¹⁻¹⁴ Additionally, repeated functional imaging can be acquired and used to guide dose adjustments based on tumor responses.¹⁵⁻¹⁸ The frequency of offline ART depends on the timescale and magnitude of anatomical variations.

Online ART involves replanning while patients remain in the treatment position. This approach can be further divided into 2 subcategories: plan-of-the-day (PotD) and daily replanning. The PotD method involves creating a library of plans to accommodate potential daily anatomical variations.¹⁹⁻²³ The physician then selects one plan from the library based on the “daily” anatomy of the pretreatment CBCT. The ART using the PotD strategy is also called hybrid ART because the adaptive plan is created offline but the decision for ART is made online. The method of daily replanning requires potential replanning before treatment.⁹ The replanning is triggered if target coverage and/or doses to organs-at-risk (OARs) exceed clinically acceptable errors (mostly by physician’s decision). By default, daily

replanning strategy is referred to as online ART, which we will focus on in this review.

Despite potentially better patient outcomes, online ART is more time-consuming and resource-intensive than conventional RT or offline ART.^{10,23-31} A dedicated team is required to quickly and accurately review and approve daily contours and new plans, and to conduct QAs.

Appropriate patient selection is critical to the success of online ART, which is well suited for cases with noticeable inter-fractional but few intra-fractional anatomical variations. Real-time ART,^{32,33} beyond the scope of this review, could be useful for mitigating the impacts of fast intra-fractional tissue variations.

CBCT-Based Online ART

The Varian Ethos system provides a platform to perform online ART in as little as 15 minutes, which is achieved by using rapid, high-quality CBCT, as well as artificial intelligence (AI) and machine learning (ML).³⁴⁻³⁷

The Ethos system uses a fast gantry (4 RPM) and a novel iterative (iCBCT) reconstruction method to generate high-quality CBCT.^{37,38} It employs AI and ML to expedite tissue segmentation and plan optimization and GPUs to accelerate dose calculations. The Ethos system is an O-ring linac equipped with a 6 MV Flattening Filter Free beam at a maximum dose rate of 800 monitor units per minute (MU/min).³⁷ A dual-layer multileaf collimator allows for the delivery of both intensity-modulated radiation therapy and volumetric-modulated arc therapy.

Workflow

The workflow of online ART on the Ethos system starts with an approved treatment plan called the “reference plan.” At each treatment

session, a CBCT is acquired that can be reconstructed using iCBCT or a conventional Feldkamp-Davis-Kress (FDK) algorithm. For adaptive, or “intent” planning, a certain set of contours called “influencers” are automatically generated using either an AI-based or deformable image registration (DIR)-based method. The influencer structures are typically structures near or within the target. A structure-guided DIR is applied from the planning CT to the CBCT to create a synthetic CT (sCT) for dose calculation. After the influencer review, target volumes may be propagated onto the pretreatment CBCT and reviewed by the physician. The Ethos system then generates 2 types of plans: a “scheduled plan” by calculating the fluence from the reference plan onto the sCT and an “adaptive plan” using an intelligent optimization engine with the “daily” contours. The physician compares the scheduled and adaptive plans in terms of dose-volume histogram (DVH) metrics and dose distributions, and decides which plan is used for treatment. Subsequently, a qualified medical physicist performs the MU verification using Varian Mobius3D. An optional CBCT can be acquired to verify the final treatment position and evaluate for changes in internal anatomy. **Table 1** provides the summary of the workflow of nonadaptive and adaptive planning after the acquisition of SIM-CT.

Advantages

The Ethos system uses onboard CBCT for ART. Because CBCT is widely used for image-guided radiation therapy, the implementation of Ethos online ART may not require major changes to the existing infrastructure or necessitate staff training on a completely new technology like MRI-based online ART.

The Ethos iCBCT offers a higher contrast-to-noise ratio than

conventional CBCT, enabling an improved accuracy in soft tissue delineation and dose calculation. The Ethos 2.0 with HyperSight CBCT further enhances its iCBCT performance with faster acquisition time (6 s), a larger field of view (up to 70 cm), and a newly designed kV detector. Users may directly replan on HyperSight iCBCT, eliminating the need for sCT.

Many centers have implemented online ART using the Ethos system for many disease sites^{14,26,27,29,35-44} and have shown improved target and/or OAR sparing. For a study in advanced pancreatic cancer, Schiff found that 100% of adapted fractions (40) met the OAR constraints while only 1 out of 40 nonadapted fractions met all OAR constraints.⁴⁴ In addition, the Ethos system allows for safe dose escalation in certain cases, which could potentially lead to improved tumor control rates. For online ART, the Ethos system is more cost-effective and offers shorter treatment than MRI-based systems.

Current Challenges and Future Perspectives

The implementation of online ART using the Ethos system is different from conventional CBCT-guided RT in terms of software, hardware, and workflows. The new approach requires considerable resources (especially in personnel) and thus presents a great challenge for its adoption.³⁷ Because online ART requires skilled staff to rapidly and accurately assess a patient's daily anatomical changes, make appropriate plan adjustments, and ensure QA during the treatment session, at least one dedicated medical physicist should be present for the majority of the workday to accommodate patient load.^{37,43} A physician needs to be present for plan and contour review and approval.

Although AI and automation improve the efficiency of online

ART on Ethos, the treatment can take more than 30 minutes for certain disease sites and for specific patients. The prolonged time on the couch may result in changes to the patient's anatomy, requiring the process to be restarted in the worst scenario.

The Ethos system operates as a black box, and some QA methods for regular linacs are not available. Many built-in QA tools are from Varian (e.g., Mobius3D). Although, retrospectively, the dosimetric and contouring accuracy has been verified,^{43,45} there is a need for independent and quick QA solutions for plan checks and secondary dose calculations to guarantee patient safety and treatment accuracy.⁴⁶

Although several studies have demonstrated the dosimetric advantages of online ART in terms of improved target coverage and reduced dose to OARs, more robust prospective clinical trials are needed to establish the impact of online ART on treatment outcomes. Future research also needs to focus on identifying which patient populations and disease sites would benefit most from online ART to optimize resource allocation and ensure cost-effectiveness.⁴⁷

MRI-Based Online Adaptation

Recent technology advancements have made MRgRT a reality by integrating an MRI scanner with a linac or a Co-60 machine.⁴⁸ The first commercial MRgRT system, the ViewRay MRIdian system, was installed at Washington University in St. Louis, and the treatment of patients started in January 2014.⁶ This machine combined a 0.35 T superconducting MRI scanner with 3 Co-60 heads mounted on a ring gantry, with MRI and RT system sharing the same isocenter. Later models of the MRIdian replaced the Co-60 design with

Table 1. Workflows of Nonadaptive and Adaptive Planning

	NONADAPTIVE	ADAPTIVE
Image registration	Rigid registration between the daily CBCT and the SIM-CT	DIR-based registration between the daily CBCT and the SIM-CT
Contour updates	DIR- or AI-based daily contours	DIR- or AI-based daily contours
Optimization	NO	Plan is reoptimized based on the updated “daily contours”
Plan adaptation	Plan is calculated using the fluence of the original plan on the sCT	Plan is recalculated on the sCT after optimization
Abbreviations: AI, artificial intelligence; CBCT, cone beam CT; DIR, deformable image registration; sCT, synthetic CT; SIM-CT, simulation CT.		

a linac for enhanced treatment capabilities. In 2017, the first person was treated using the MRIdian linac system.⁷ Another commercial MRgRT system, the Elekta Unity, was developed by Elekta in partnership with Philips (Philips, Amsterdam, the Netherlands).⁴⁹ It integrates a 1.5 T MRI scanner with a linac equipped with 6 MV beams. The higher magnetic field strength produces diagnostic-quality imaging. With other systems in the development phase,^{50,51} MRgRT introduces a new paradigm in treatment planning, real-time monitoring, and online ART.^{52,53}

Workflow

An efficient workflow is essential for implementing online adaptive MRgRT. After the target and OAR delineation on CT or MR simulation, a reference plan is created to meet the dosimetric criteria. At each treatment session, a daily MRI is acquired prior to the treatment. According to the anatomy changes in the target and OARs between the pretreatment MRI and simulation image, one of the two workflows can be executed. If the anatomy of target and OAR is sustained, the “adapt to position” workflow is applied. The daily MRI is first aligned with the simulation image based on rigid

registration, and an isocenter shift is implemented. The couch is then translated for the ViewRay system or a virtual couch shift is utilized for the Unity system. If necessary, an adaptive plan can be generated by applying segment adaptation or optimization to further enhance plan dosimetry. These adaptive plans are still based on the simulation images. However, if the anatomical changes are significant, the second method, “adapt to shape,” is applied.⁵⁴⁻⁵⁶ The daily MRI and simulation images are first aligned using deformable registration. The original ROIs and plan are propagated to the daily MRI, and new contours of the target and OARs are modified or delineated on the daily MRI. The electron density is assigned to each organ on the MRI generated sCT, and an adaptive plan is generated by adjusting or re-optimizing fluence. A summary of the above adaptive workflows is listed in **Table 2**.

Advantages

With superior soft tissue contrast and continuous intrafractional imaging, an MRgRT system could be ideal for online ART.⁵⁴⁻⁵⁸ Studies show that physicians prefer reoptimized plans in over 90% of cases.^{59,60} Unlike CBCT, MRI is nonionizing radiation,

enhancing patient safety for treatments requiring frequent imaging. Moreover, MRgRT enables physicians to directly monitor tumor motion without relying on surrogates, reducing alignment errors particularly in areas prone to movement (e.g., abdomen and thorax). This capability allows more precise dose delivery to the target while sparing surrounding healthy tissues, resulting in fewer side effects. For example, patients with prostate cancer treated with online adaptive MRgRT experienced lower rates of gastrointestinal and genitourinary toxicity than those treated with conventional approaches.⁶¹⁻⁶³ Emerging data suggest that online adaptive MRgRT enables safe dose escalation in the treatment of pancreatic, prostate, and lung cancer.⁶⁴⁻⁶⁸

Because onboard MRI provides accurate volumetric imaging for each treatment, it enables precise calculation of the cumulative dose to organs from each fraction. This detailed volumetric dose mapping allows clinicians to monitor dose constraints and make adjustment if limits are exceeded.^{69,70} Understanding the exact dose distribution of organs and their specific subregions is essential for assessing potential toxicities. Voxel-by-voxel data of daily dose offer valuable insights into normal tissue tolerance.^{71,72}

Beyond current MRgRT, functional MRI on an MRI-linac enables the potential of biological guidance RT. Studies indicate that conventional RT can leave radioresistant portions of the tumor undertreated due to tumor heterogeneity, contributing to recurrence.⁷³ Online adaptive functional MRgRT allows clinicians to obtain biological insights on specific subvolumes within the tumor, facilitating patient-specific, heterogeneous dosing strategies that potentially improve therapeutic outcomes.⁷⁴⁻⁷⁶

Table 2. Workflows of “Adapt to Position” and “Adapt to Shape” in Adaptive MRI-Guided Radiation Therapy

	ADAPT TO POSITION	ADAPT TO SHAPE
Image registration	Align the daily MRI rigidly to the SIM-CT	Align the daily MRI deformably to the SIM-CT
Contour updates	Use original contours with updated ISO	• Use adapted contours • Assign electron density based on the daily MRI
Segment or fluence optimization	• Use the original segments • Adapt the segments • Optimize segments' weights	• Optimize fluence weights • Adjust fluence shape
Plan adaptation	Recalculate or reoptimize the original plan on the SIM-CT	Recalculate or reoptimize the plan on the online MRI

Abbreviations: SIM-CT, simulation CT.

Current Challenges

Implementing an online adaptive MRgRT program demands considerable investment in capital (significantly more than the in the Ethos system) and personnel, which presents a substantial barrier to its adoption.^{61,77}

Integrating an MRI scanner with a linac is complex and comes with inherent limitations. Both components require modification from their conventional forms, resulting in compromised performance compared with their stand-alone counterparts.^{53,78} Commercial MRI-linacs use lower magnetic field strength than diagnostic MRI scanners (1.5 T to 7 T) to mitigate the electron return effect,⁷⁹ resulting in inferior image quality. Because the moving linac gantry disrupts magnetic field homogeneity, most MRI-linacs only allow step-and-shoot delivery.^{49,80} Additionally, beam configuration is restricted to coplanar angles due to system geometry and beam energy is limited to low energies such as Co-60, 6 MV, and 7 MV.

Another critical concern for online adaptive MRgRT is image distortion as accurate volumetric target delineation and precise location mapping are essential for beam positioning.

The MRI scanner in an MRI-linac requires larger volumetric coverage and off-isocenter imaging than a diagnostic scanner, which complicates achieving a homogeneous magnetic field.⁸¹⁻⁸³ Image distortion is less pronounced at 0.35 T,⁵⁶ but in high-field systems like the 1.5 T Elekta Unity, it becomes a greater challenge. Techniques such as field correction, B0 mapping, and local shimming can improve image quality, although shimming becomes particularly challenging with moving components like the gantry.^{7,53}

Online adaptive MRgRT is time-consuming not only because MRI is inherently slow but also due to the multistep adaptation process. Studies indicate that online adaptation can extend RT sessions by 30 to 60 minutes, impacting treatment efficiency and thus throughput.^{84,85} Like CBCT-based ART, the extended duration may also increase patient discomfort and the risk of undesired intra-fractional motion, potentially compromising the accuracy of replanning. Given its low cost-effectiveness, appropriate patient selection is crucial. Patients who are most likely to benefit should be prioritized for MRgRT, such as those with tumors that are difficult to visualize or

delineate using CBCT or are located near critical structures.

Future Perspectives

One promising direction for adaptive MRgRT involves the use of quantitative MRI-derived biomarkers, which can provide valuable insights into treatment response and enable more personalized radiation therapy for potentially improving outcomes. Dynamic contrast-enhanced MRI, which measures tissue perfusion and permeability, allows clinicians to detect microvascular changes that could indicate early responses or resistance to treatment.^{86,87} This technique is valuable in evaluating cancers such as HN and prostate cancer,^{88,89} where early response indicators could be crucial. Quantitative assessment of T1 and T2 relaxation times shows promise in predicting prostate radiation therapy response.⁹⁰ Chemical exchange saturation transfer MRI can quantify chemical components, with amide proton transfer helping distinguish true progression from pseudoprogression in glioma.⁹¹ These quantitative MRI tools provide valuable noninvasive insights into tissue function, structure, and physiology, revealing tumor heterogeneity, hypoxia characteristics, and treatment

response. All this information helps identify heterogeneous targets and support the feasibility of dose escalation in more aggressive or radioresistant disease areas.

Rapid MRI techniques are essential to achieve comprehensive quantitative measurement. Emerging fast MRI techniques significantly reduce imaging acquisition times through advanced reconstruction algorithms for sparsity acquisitions, such as parallel imaging and compressed sensing.^{92,93} MR fingerprinting, a novel, ultrafast quantitative method, enables simultaneous measurement of multiple parameters, demonstrating great potential for distinguishing diverse tissue characteristics.⁹⁴⁻⁹⁷ Moreover, AI and ML are increasingly being adopted to accelerate MRI reconstruction.^{98,99}

Online adaptive MRigRT transforms the conventional workflow in radiation therapy, introducing many intensive tasks requiring AI assistance for time saving without compromising the treatment accuracy during daily treatment.¹⁰⁰⁻¹⁰³ Additionally, accurate dose accumulation over daily treatments requires robust DIR and precise dose-mapping methods, both of which can also benefit from advancements in AI techniques. Real voxel-by-voxel daily dose assessments enable continuous tracking therapeutic doses for targets and normal tissue tolerances, providing valuable data to further guide future treatments.^{69,70}

It is worth mentioning that the true potential of MRgRT is not merely the increase in target coverage and reduction of toxicity, which may likely improve clinical outcomes for local control and survival rate. More importantly, it opens opportunities to address complex scenarios, such as ultra-dose escalation in areas with large motion or cases in close proximity to critical organs, and reirradiated tumors, among others,

that might have otherwise been impossible to treat.^{76,104}

Conclusion

CBCT-based and MRI-based online ART have gained increasing adoption due to their ability to address daily anatomical variations that are difficult to account for with conventional RT. Given the significant efforts from manufacturers and leading academic centers to advance online ART, we anticipate broader adoption of online ART (potentially even real-time ART) in the near future. However, implementing these technologies remains costly and time-intensive. Therefore, a strategic approach for careful patient selection is essential to ensure that the selected patients could benefit most from online ART and that resources are effectively utilized.

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Disease Characteristics, Treatment Tolerance, and Toxicity in Older Patients (≥ 65 y) With Oropharyngeal Cancer and Implications on Outcomes

Ahmed I. Ghanem, MD, PhD;^{1,2*} Marissa Gilbert, BS;¹ Chun-Hui Lin, MS;³ Remonda Khalil-Moawad, MPH;^{1,4} Samantha Tam, MD;⁵ Steven Chang, MD, FACS;⁵ Farzan Siddiqui, MD, PhD¹

Abstract

Objective: To assess and compare tolerability for standard-of-care treatments and evaluate outcomes in older and younger patients with oropharyngeal cancer (OPC).

Methods and Materials: We queried our institutional database for nonmetastatic OPC treated curatively between January 2009 and June 2020, with radiation therapy $\pm$ systemic therapy, or surgery $\pm$ adjuvant radiation therapy $\pm$ systemic therapy. We compared clinicopathological, treatment-related, and therapeutic toxicity features, and survival outcomes between older (≥ 65 y at diagnosis) and younger (< 65 y at diagnosis) patients across human papilloma virus (HPV) subtypes. Multivariate analyses for predictors of survival in all patients were performed.

Results: In this retrospective study, we evaluated 340 patients with OPC: 123 (36%) older and 217 (64%) younger. There were 252 patients (74%) with HPV+ve OPC. The HPV+ve older patients showed an increasing trend over the years studied. Definitive radiation therapy $\pm$ systemic therapy was utilized in 73.2%, while the remainder had surgery $\pm$ adjuvant radiation therapy $\pm$ systemic therapy. After a median follow-up of 5.24 (interquartile range: 3.53) years, no significant differences in treatment received, overall, disease-free, locoregional recurrence-free, or distant metastasis-free survival were seen between age groups, regardless of HPV status. Significantly larger proportions of older patients received cetuximab (25.8% vs 11.9%; $P < .001$), required hospitalization (46.6% vs 26.9%; $P < .001$), required feeding tubes (63.6% vs 49.5%; $P = .02$), and were switched to a less-toxic systemic therapy protocol (18.3% vs 7.7%; $P = .019$). For all patients, factors such as radiation therapy course completion, radiation therapy delays, unplanned hospitalizations, and feeding tubes never removed were independently associated with various survival endpoints.

Conclusion: While survival outcomes were equivalent between older and younger patients with OPC, older patients exhibited lower tolerance and higher toxicity from systemic therapy, suggesting a need for enhanced multidisciplinary supportive care including geriatric assessment, for older patients receiving concomitant radiation and systemic therapy.

Keywords: oropharyngeal cancer in older age, oropharyngeal squamous cell carcinoma, cancer of the oropharynx, head-and-neck squamous cell carcinomas, human papilloma virus related cancer of the oropharynx, drug tolerance, adverse effects, radiation therapy and chemotherapy toxicity, age-specific death rate, disease-free survival, neoplasm recurrence, neoplasm metastasis

Affiliations: ¹Department of Radiation Oncology, Henry Ford Health-Cancer, Detroit, MI. ²Clinical Oncology Department, Faculty of Medicine, University of Alexandria, Alexandria, Egypt. ³Department of Public Health Sciences, Henry Ford Health, Detroit, MI. ⁴College of Human Medicine, Michigan State University, Lansing, MI. ⁵Department of Otolaryngology, Henry Ford Health, Detroit, MI.

Corresponding author: *Ahmed I. Ghanem, MD, PhD, Department of Radiation Oncology, Henry Ford Health-Cancer, 2800 West Grand Blvd., Detroit, MI 48202. (aghanem1@hfhs.org)

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Data sharing statement: Research data are stored in an institutional repository and will be available upon a reasonable request to the corresponding author.

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Introduction

Oropharyngeal squamous cell carcinoma (OPC) is one of the most common head and neck cancers (HNCs), with a median age at diagnosis of 60 to 63 years and over 21,000 new cases expected in 2024, with more than a one-third in adults 65 years or older.^{1,2} Unlike other smoking-related tumors, which are on the decline, OPC incidence has been significantly rising, driven mainly by human papillomavirus-related (HPV+ve) tumors.³ This rising trend is highest in adults > 65 years old, especially white males,⁴ and within the context of an aging population,⁵ over 18,000 cases of OPC in older adults are expected by 2030, forming 60% of total cases, almost double the 9270 cases diagnosed in 2019.^{2,6}

Notably, the profile for an HPV+ve OPC patient as a young, white, fit male^{7,8} has been shifting with the median age at diagnosis recent increases, which means we are currently facing an evolving epidemic of OPC in older adults driven mainly by HPV+ve tumors.^{9,10} It has been demonstrated that older patients with HPV+ve have better prognoses than HPV-unrelated (HPV-ve) OPC.¹¹⁻¹³ With a growing population of survivors, understanding how current OPC therapeutic approaches affect this group in regard to quality of life (QOL) becomes more critical.

Older adults are vastly underrepresented in cancer clinical trials, and there is concern that standard-of-care (SoC) regimens validated in predominantly younger populations may not be directly applicable to older patients with OPC.^{14,15} Thus, considering the rising age of patients with OPC, a critical question remains as to whether older patients may tolerate current SoC therapies differently

than younger patients. This potential disparity underscores the need for tailored approaches that consider age-related physiological changes and comorbidities. Key practice-changing studies have highlighted a nonsignificant survival benefit in older patients from concomitant chemotherapy, in the definitive/adjuvant radiation therapy (RT) settings, and also for concomitant targeted therapy.¹⁶⁻¹⁸ Importantly, the cohorts of these studies contained a low proportion of older adults (< 5%) and were not prospectively powered for age. Other reports have also shown worse outcomes in older patients with OPC, even after accounting for stage and type of treatment.^{3,19,20} While some studies have shown more RT-related hospitalizations, treatment interruptions, and feeding tube dependence for older patients,^{21,22} others have shown equivalent treatment tolerance between age groups.^{23,24} However, many studies have not accounted for HPV status, included non-OPC cases, or used older/nonstandard RT techniques and systemic therapy (ST) protocols.

Intriguingly, more recent reports have shown a survival gain from multimodality treatment in older patients with accepted treatment tolerance.^{13,25-28} Nevertheless, these studies lacked a comparative group with younger patients, highlighting a knowledge gap in our understanding of how OPC therapeutic strategies may affect older adults for outcomes, toxicity, and tolerability.

Considering the conflicting results and variable designs of previous studies, we sought to define the clinicopathological characteristics and treatment tolerability/toxicity profiles of older (≥ 65 y) vs younger (< 65 y) patients with OPC. We aimed to conduct a comprehensive analysis to determine the correlation between age, HPV status, and treatment

approaches, with outcomes in patients with OPC who had been treated curatively.

Methods and Materials

Study Population

Following institutional review board approval, we queried our institutional HNCs database for patients who had nonmetastatic primary OPC diagnosed between January 2009 and June 2020. All patients had HPV status determined via immunohistochemistry p16 protein testing of tumor biopsies.^{29,30} Patients were excluded if they had: HPV+ve tumors in neck lymph nodes (LNs) with no primary OPC; HPV+ve tumors in which the majority of the tumor was in the oral cavity or larynx; or previous RT to the head-and-neck region. Patients who did not receive curative treatment, those referred to another institution, and those with inadequate follow-up were also excluded.

Treatment and Follow-Up

All patients underwent baseline performance and cancer staging assessments, and all were presented and discussed at multidisciplinary HNCs tumor board meetings. Treatment approaches were based on tumor stage, subsite, and HPV status. Curative treatments included definitive RT ($\pm$ concomitant ST) or surgery, mainly transoral resection (TORS) $\pm$ LN dissection followed by adjuvant RT ($\pm$ ST), depending on pathological risk factors.

Patients were assessed weekly during RT and toxicities were graded per CTCAE v4.0. Nutritional assessment was performed by a registered dietitian. Following treatment, patients had follow-up visits every 3-to-4 months for 2 years;

every 4-to-6 months for 3 years; and annually thereafter, with imaging studies ordered as appropriate.

Study Variables and Treatment Groups

Sociodemographic and clinicopathological characteristics, treatment received, recurrence events (local, regional/nodal, distant), and survival status at the last follow-up were recorded. Comorbidity at diagnosis was calculated using Charlson comorbidity index (CCI).³¹ Patients diagnosed before 2018 were re-staged per the criteria of the American Joint Committee on Cancer (AJCC) 8th edition.³²

Patients were divided into 2 groups: an older group (≥ 65 y) and a younger group (< 65 y) based on age at OPC diagnosis. The 65-year cutoff, that allowed robust statistical comparison, was chosen based on the US Census Bureau guidelines⁵ and other important studies.^{6,10,15,27,33,34} Study variables and survival outcomes were compared between older and younger groups stratified by HPV status. Trends for new cases in the study years were also assessed by age.

Survival Endpoints

Primary survival endpoints included overall survival (OS), locoregional recurrence-free survival (LRFS), distant metastases-free survival (DMFS), and disease-free survival (DFS), which was recorded as the date of first recurrence or death. Local and regional/nodal recurrence-free survival was also assessed. The date of biopsy was the starting timepoint for all endpoints.

Treatment Tolerance and Toxicity

RT Duration and Delays

RT interruptions were assessed, including prescribed RT course not completed and unplanned RT delays

beyond 2 days. Treatment package time (TPT), days between surgery dates and last RT fraction for patients receiving adjuvant RT, and total RT duration, days between first and last RT fractions, were calculated.

Acute Toxicity from RT and Nutritional Support

RT toxicity was measured according to factors such as worst grade of acute mucositis, worst pain score, unplanned hospitalization (excluding admission for intravenous hydration), maximum weight loss, and need for feeding tube (percutaneous endoscopic gastrostomy [PEG] and/or nasogastric tube). At our institution, we do not place feeding tubes prophylactically. Patients experiencing severe dysphagia/odynophagia that prevented adequate oral intake, resulting in significant weight loss and/or dehydration, received a feeding tube following a multidisciplinary evaluation by a speech-language pathologist, dietitian, and radiation oncologist. We calculated total days of feeding tube dependency and reported patients who never had their tubes removed (long-term feeding tube until death/last follow-up).

Systemic Therapy Tolerance and Toxicity

ST protocol received, including cumulative cisplatin dose (mg/m^2), was reported. Dose reduction for a received cycle, unplanned delays, febrile neutropenia events, canceled doses, and rates of switching to a less intense ST protocol due to toxicity was compared between age groups.

Statistical Analysis

Descriptive statistics were reported as frequencies (%) for categorical variables and median

(range) for continuous variables. Age groups stratified by HPV status were compared with chi-square test or Fisher exact tests for categorical variables and Wilcoxon rank sum test for continuous variables. Kaplan-Meier curves were plotted, and log-rank tests were conducted to compare survival endpoints. Univariate analysis (UVA) and multivariate (MVA) Cox regression models were used to identify independent predictors for survival. For MVA, if abundant predictors relative to small event numbers were present, backward stepwise selection was applied to minimize potential collinearity and overfitting. All tests were 2-sided, and statistical significance was set to $P \leq .05$. All analyses were performed in R 4.2.1.

Results

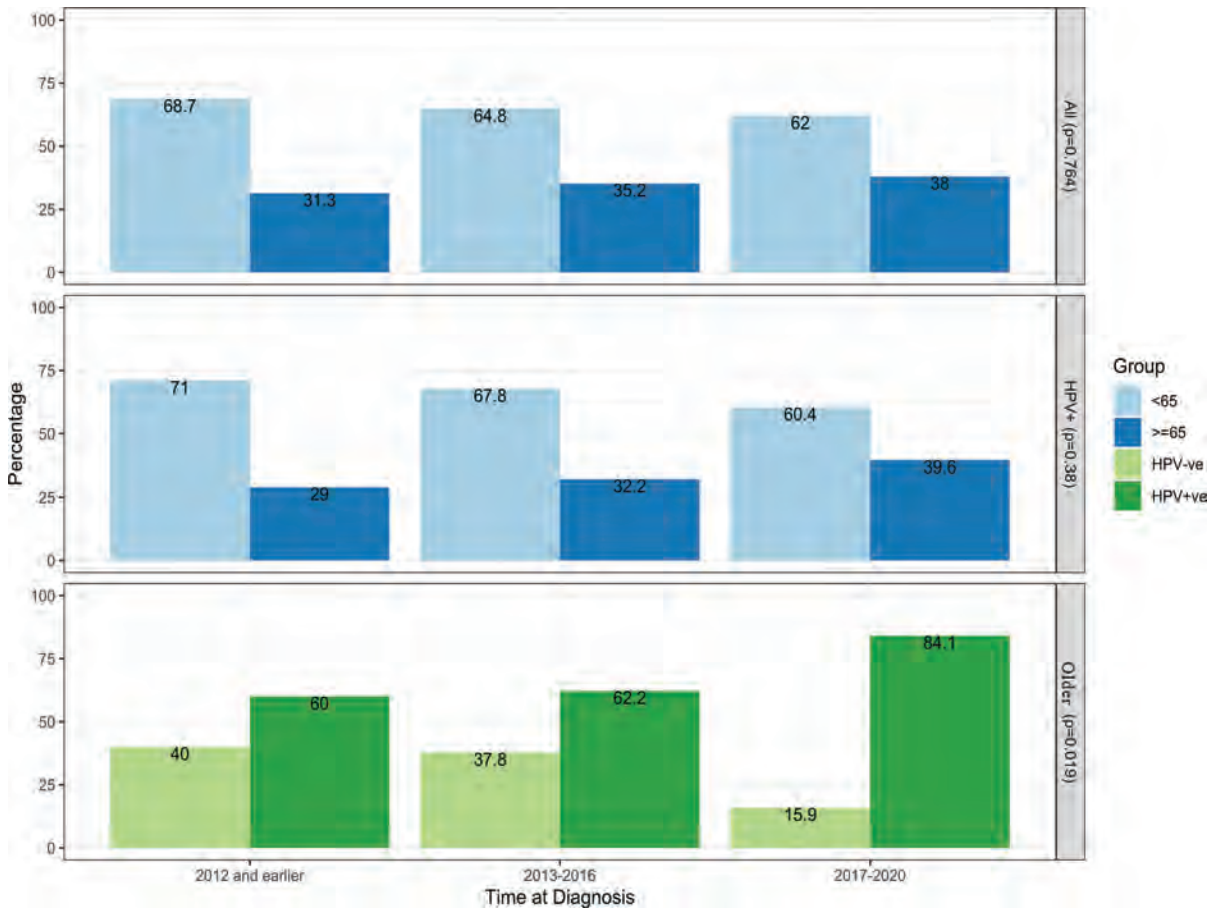
Demographic, Clinicopathological, and Treatment Characteristics

A total of 340 patients with OPC were included: overall median age was 61 (range, 38-91) years; 284 (83.5%) men. There were 252 (74%) patients with HPV+ve and 88 (26%) with HPV-ve OPC. Most tumors were located in the tonsil (44%) or base of tongue (36%), and most patients had stage 1 (43%) or 2 (19%) cancer. The majority of patients ($n = 249$; 73%) received definitive RT $\pm$ ST, and 91 patients (27%) had TORS with or without adjuvant RT $\pm$ ST.

Age Groups and Trends Over Time

A total of 123 patients (36%) were in the older group: 90 with HPV+ve and 33 with HPV-ve OPC. There were 217 (64%) patients in the younger group: 162 with HPV+ve and 55 with HPV-ve OPC. HPV+ve proportion was nonsignificant across age groups. The proportion of older patients increased over time, in

Figure 1. Trends for newly diagnosed patients over the periods of diagnosis for all ($N = 340$), HPV+ve ($N = 252$), and older patients with oropharyngeal cancer ($N = 123$).



which 33% treated from 2009 to 2012 were older compared with 38% for 2017-2020, with a parallel trend for HPV+ve cases (**Figure 1**). There was a significant increase over time in the older group with HPV+ve OPC (60% [2009-2012] vs 84.1% [2017-2020]; $P = .019$).

Age groups were generally similar; however, median CCI was significantly higher in older patients ($P = .033$). The older group had a higher smoking history among HPV-ve and a trend for more base of tongue tumors in HPV+ve patients. All detailed descriptive characteristics by age and HPV status are presented in **Table 1**, and **Supplementary Table 1**

(www.appliedradiationoncology.com).

Survival by Age and HPV Status

After a median follow-up time of 4.9 (interquartile range [IQR]: 3.2) years for older and 5.3 (IQR: 3.8) years for younger patients, $P = 0.35$, 124 died (56.5% with recurrence and 43.5% due to other causes) and 92 recurred: 54 local (16%), 34 nodal/regional (10%), and 46 distant (13.5%) most frequently in the lung (52.2%). No treatment-related deaths during RT occurred.

We observed no significant differences in 3- and 5-year OS, LRFS, or DMFS between older and younger

patients for both HPV subtypes (**Figure 2A-F**). Neither DFS nor local and nodal/regional recurrence-free survival was significantly different between age groups regardless of HPV status (**Supplementary Figure 1A-B, 2A-B, 3A-B**, respectively; (www.appliedradiationoncology.com)). Sites of distant metastases were also not significantly different with age (**Supplementary Figure 1**, www.appliedradiationoncology.com).

Multivariate Analysis: Survival by Age and HPV Status

Based on findings from UVA, Cox regression MVA identified factors associated with survival outcomes

Table 1. Baseline Demographic, Clinicopathological, and Treatment Characteristics for Older (≥ 65 y) vs Younger Patients With Oropharyngeal Cancer Stratified by Human Papillomavirus Status

CHARACTERISTICS	ALL PATIENTS (N = 340)	HPV+VE OP (N = 252)		P VALUE	HPV-VE OPC (N = 88)		P VALUE
		OLDER (≥ 65 Y) (N = 90) (35.7%)	YOUNGER (<65 Y) (N = 162) (64.3%)		OLDER (≥ 65 Y) (N = 33) (37.5%)	YOUNGER (<65 Y) (N = 55) (62.5%)	
Age, y, median (range)	61 (38-91)	70 (65-91)	56 (38-64)	<.001	68 (65-85)	57 (38-64)	<.001
CCI, median (range)	1 (0-8)	1 (0-8)	0 (0-8)	.005	1 (0-6)	1 (0-5)	.033
Sex, N (%)				.377			.765
Male	284 (83.5)	77 (85.6)	146 (90.1)		24 (72.7)	37 (67.3)	
Female	56 (16.5)	13 (14.6)	16 (9.9)		9 (27.3)	18 (32.7)	
Race, N (%)				.89			.286
Black/African American	65 (19.1)	11 (12.2)	23 (14.2)		12 (36.4)	19 (34.5)	
White	261 (76.8)	75 (83.3)	133 (82.1)		18 (54.5)	35 (63.6)	
Other	14 (4.1)	4 (4.4)	6 (3.7)		3 (9.1)	1 (1.8)	
Marital status, N (%)				.028			.001
Married	207 (60.9)	52 (57.8)	112 (60.9)		13 (39.4)	30 (54.5)	
Single	82 (24.1)	19 (21.1)	35 (21.6)		7 (21.2)	21 (38.2)	
Divorced/widowed	51 (34)	19 (21.1)	15 (9.3)		13 (39.4)	4 (7.3)	
Alcohol use, N (%)				.76			.576
Social/occasional	151 (44.4)	43 (47.8)	81 (50)		10 (30.3)	17 (30.9)	
Frequent/alcoholism	93 (27.4)	17 (18.9)	34 (21)		14 (42.4)	28 (50.9)	
Smoking status, N (%)				.652			.007
Current smoker	82 (24.1)	13 (14.4)	28 (17.3)		12 (36.4)	29 (52.7)	
Former smoker	147 (43.2)	43 (47.8)	68 (42)		20 (60.6)	16 (29.1)	
Never smoker	111 (32.6)	34 (37.8)	66 (40.7)		1 (3)	10 (18.2)	
Smoking pack-years, median (range)	30 (1-160)	24 (1-160)	20 (1-150)	.246	40 (10-120)	35 (8-140)	.014
Marijuana use, N (%)	55 (16.2)	10 (11.2)	32 (19.8)	.112	2 (6.1)	11 (20)	.119
Oropharyngeal subsite, N (%)				.061			.939
Tonsil	148 (43.5)	36 (40)	91 (56.2)		9 (27.3)	12 (21.8)	
Base of tongue	122 (35.9)	40 (44.4)	54 (33.3)		10 (30.3)	18 (32.7)	
Soft palate/pharyngeal wall	22 (6.5)	2 (2.2)	5 (3.1)		5 (15.1)	10 (18.2)	
Multiple sites	48 (14.1)	12 (13.3)	12 (7.4)		9 (27.3)	15 (27.3)	
AJCC stage 8th, N (%)				.171			.284
1	146 (42.9)	45 (50)	94 (58)		3 (9.1)	4 (7.3)	
2	63 (18.5)	21 (23.3)	41 (25.3)		0 (0)	1 (1.8)	
3	60 (17.6)	24 (26.7)	27 (16.7)		1 (3)	8 (14.5)	
4A	54 (15.9)	N/A	N/A		24 (72.7)	30 (54.5)	
5B	17 (5)	N/A	N/A		5 (15.2)	12 (21.8)	

Table 1. continued

CHARACTERISTICS	ALL PATIENTS (N = 340)	HPV+VE OP (N = 252)		P VALUE	HPV-VE OPC (N = 88)		P VALUE
		OLDER (≥ 65 Y) (N = 90) (35.7%)	YOUNGER (<65 Y) (N = 162) (64.3%)		OLDER (≥ 65 Y) (N = 33) (37.5%)	YOUNGER (<65 Y) (N = 55) (62.5%)	
Overall treatment, N (%)				.307			.655
Surgery alone	14 (4.1)	3 (3.3)	5 (3.1)		2 (6.1)	4 (7.3)	
Surgery + adjuvant RT	32 (9.4)	10 (11.1)	17 (10.5)		3 (9)	2 (3.6)	
Surgery + adjuvant CRT	45 (13.2)	7 (7.8)	28 (17.3)		2 (6.1)	8 (14.5)	
Definitive RT	33 (9.7)	6 (6.7)	12 (7.4)		6 (18.2)	9 (16.4)	
Definitive CRT	216 (63.5)	64 (71.1)	100 (61.7)		20 (60.6)	32 (58.2)	
Positive final surgical margin, N (%)	23 (25.3)	7 (35)	9 (18)	.224	2 (28.6)	5 (35.7)	.52
Lymphovascular invasion, N (%)	46 (50.5)	9 (45)	24 (48)	>.99	6 (85.7)	7 (50)	.174
Perineural invasion, N (%)	13 (14.3)	1 (5)	7 (14)	.424	0 (0)	5 (35.7)	.124
Extracapsular nodal extension, N (%)	31 (33)	5 (26.3)	16 (30.2)	.98	3 (42.9)	7 (46.7)	> .99
Period of diagnosis, N (%)				.38			.654
2009-2012	46 (13.5)	9 (10)	22 (13.6)		6 (18.2)	9 (16.4)	
2013-2016	128 (37.6)	28 (31.1)	59 (36.4)		17 (51.5)	24 (43.6)	
2017-2020	166 (48.8)	53 (58.9)	81 (50)		10 (30.3)	22 (30.3)	

Bold values are statistically significant values.

Abbreviations: AJCC, American Joint Committee on Cancer; CCI, Charlson Comorbidity Index; CRT, concomitant chemoradiotherapy; HPV+ve, human papilloma virus-related; HPV-ve, human papilloma virus-unrelated; OPC, oropharyngeal squamous cell carcinoma; RT, radiation therapy.

for older patients ($N = 123$) (**Table 2**). Notably, HPV status was associated with all endpoints (HR 1.67-2.97); and CCI and tumor stage were significant predictors for OS. Marital status, OPC subsite, and overall treatment received were prognostic for DFS, while advanced AJCC stage and diagnosis in earlier years were associated with worse DMFS.

We also characterized predictors of survival based on HPV status for the entire cohort ($N = 340$), adjusting for age (**Supplementary Table 2, www.appliedradiationoncology.com**). For patients with HPV+ve OPC, the major predictors for OS included CCI (HR 1.42 [CI: 1.25-1.61]), marijuana use (HR 2.66 [CI: 1.39-5.07]), and AJCC stage 3 vs 1 (HR 2.76 [CI: 1.57-4.84]). AJCC stage, adjuvant vs definitive RT, and period of diagnosis were independently associated with LRFS; smoking pack-years and extracapsular nodal

extension (ENE) were deterministic for DMFS, whereas for HPV-ve patients, smoking status, tumor stage, and ST protocol were associated with OS and DFS. Cetuximab was inferior to platinum protocols for all endpoints for both HPV subgroups.

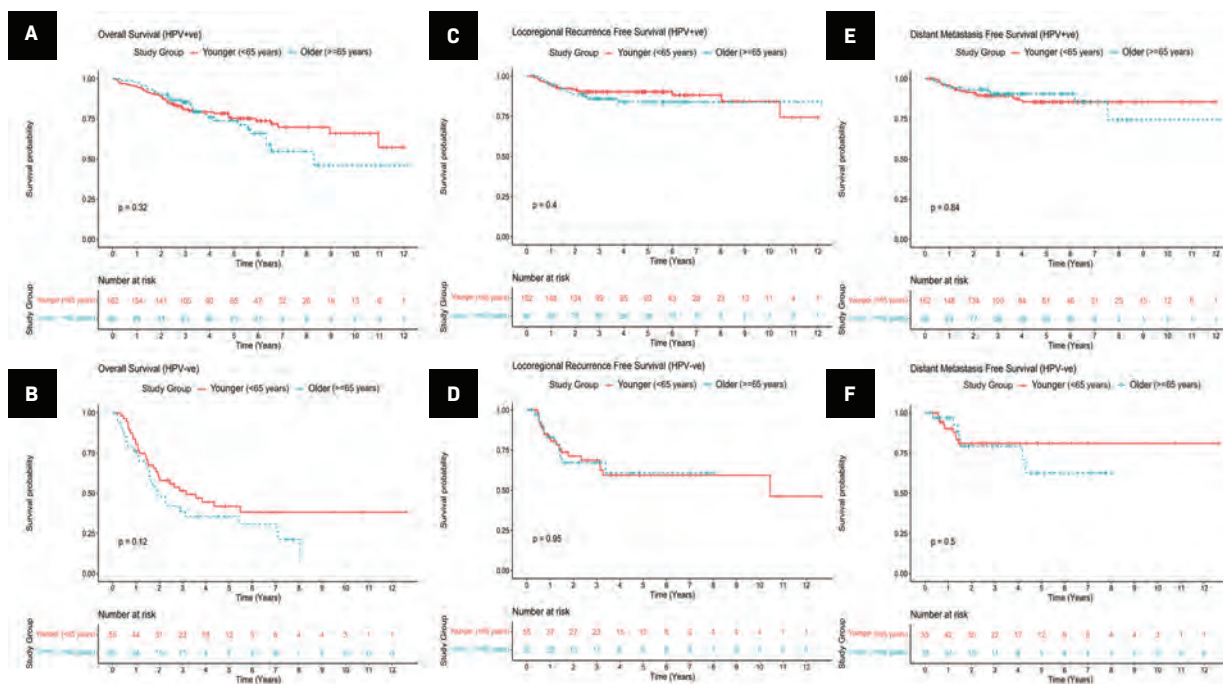
Treatment Tolerability and Acute Toxicity During RT

The central objective of our study was to investigate potential differences in therapeutic details and toxicity outcomes in older vs younger patients who had received RT for OPC ($N = 326$). The age groups were similar for most of these parameters (**Table 3**); however, a significantly higher proportion of older patients were hospitalized during RT (46.6% vs 26.9%; $P < .001$), received a feeding tube during RT (63.6% vs 49.5%; $P = .02$), and had their feeding tube never

removed (19.5% vs 8.7%; $P = .008$). RT interruptions, total RT duration, as well as TPT were nondifferent with age.

Of the 261 patients who had concomitant ST, older patients received more cetuximab, carboplatin, and weekly cisplatin as the primary protocol ($P < .001$) with a trend for more febrile neutropenia ($P = .088$). Older patients were less likely than younger patients to receive cumulative cisplatin $> 200 \text{ mg/m}^2$ (79.6% vs 94.1 %; $P = .006$) and more likely to switch the ST protocol, from cisplatin to carboplatin, cetuximab or cisplatin weekly (after every 3 wk), (18.3% vs 7.7%; $P = .019$). Within older patients, except for more prophylactic feeding tube insertion before RT start in adjuvant compared to definitive CRT patients (44.4% vs 14.3%; $P = .034$), surgery

Figure 2. Kaplan-Meier estimates of survival endpoints for the study cohort ($N = 340$) in older (≥ 65 y) vs younger (< 65 y) patients with log-rank test within HPV+ve and HPV-ve oropharyngeal cancer (OPC).



3- and 5-year overall survival (OS) (A) for older, 85% (95% CI: 78-93) and 74% (CI: 64-85), respectively, vs younger patients, 81% (CI: 75-87) and 75% (CI: 68-83), respectively, for HPV+ve OPC ($P = .32$). 3- and 5-year OS (B) for older, 39% (CI: 25-60) and 36% (CI: 22-57), respectively, vs younger patients, 52% (CI: 40-67) and 42% (CI: 30-58), respectively, for HPV-ve OPC ($P = .12$). 3- and 5-year locoregional recurrence-free survival (LRFS) (C) for older, 86% (CI: 79-94) and 84% (CI: 76-93), respectively, vs younger patients, 90% (CI: 86-95) and 90% (CI: 86-95), respectively, for HPV+ve OPC ($P = .4$). 3- and 5-year LRFS (D) for older, 67% (CI: 52-88) and 61% (CI: 44-85), respectively, vs younger patients, 69% (CI: 57-84) and 59% (CI: 46-77), respectively, for HPV-ve OPC ($P = .95$). 3- and 5-year distant metastases-free survival (DMFS) (E) for older, 91% (CI: 85-97) and 91% (CI: 85-97), respectively, vs younger patients, 90% (CI: 85-95) and 86% (CI: 80-92), respectively, for HPV+ve OPC ($P = .84$). 3- and 5-year DMFS (F) for older, 79% (CI: 64-98) and 63% (CI: 42-92), respectively vs younger patients, 81% (CI: 71-93) and 81% (CI: 71-93), respectively, for HPV-ve OPC ($P = .5$).

was not associated with any added toxicity from RT or ST (**Supplementary Table 3**, www.appliedradiationoncology.com).

Multivariate Analysis: Therapeutic and Toxicity Details as Predictors of Survival

We performed MVA to assess the predictive nature of RT and ST tolerance/toxicity parameters for survival in all patients. Not completing the RT course was significantly associated with worse OS, DFS, and LRFS, with HR 5.54 to 8.12. Unplanned hospitalization (HR 1.71; 95% CI: 1.03-2.84) and RT delays (HR 2.57; 95% CI: 1.45-4.55) were

predictive for OS. Feeding tubes never removed, definitive RT (vs surgery+ RT+/-ST), and diagnosis in earlier years also predicted worse outcomes (**Table 4**).

Discussion

In this retrospective analysis of more than 300 patients treated curatively for OPC over 10 years, we did not observe any significant survival differences between older and younger patients, regardless of HPV status. Interestingly, overall treatment approaches for both groups were similar except for ST protocol. Both RT and ST were

equivalently well tolerated in older and younger patients, although significantly higher proportions of older patients had unplanned hospitalizations and feeding tube insertions, and they were more likely to require switching to a less intense ST protocol.

Thus, we emphasize that more multidisciplinary supportive care may be required for older patients, especially when concomitant ST is used with RT. Importantly, we explored specific RT and ST details, revealing treatment tolerability and toxicity across age groups, shedding light on the clinical consequences of contemporary strategies for treating OPC in an aging population.

Table 2. Multivariate Analysis of Variables Associated With Survival in Older Patients (≥65 y) With Oropharyngeal Cancer

VARIABLE	OLDER PATIENTS ≥ 65 Y WITH OROPHARYNGEAL CANCER (N = 123)							
	OVERALL SURVIVAL		DISEASE-FREE SURVIVAL		LOCOREGIONAL RECURRENCE-FREE SURVIVAL		DISTANT METASTASIS-FREE SURVIVAL	
	HR (95% CI)	P VALUE	HR (95% CI)	P VALUE	HR (95% CI)	P VALUE	HR (95% CI)	P VALUE
HPV status (-ve vs +ve)	1.84 (1.27-2.67) ^a	.001	1.67 (1.23-2.26) ^{b1}	.001	2.97 (1.27-6.92) ^c	.012	**	N/A
Age (continuous)	1.04 (0.98-1.11)	.174	**	N/A	0.91 (0.81-1.01)	.071	**	N/A
CCI (continuous)	1.25 (1.02-1.53)	.028	**	N/A	**	N/A	**	N/A
Marital status (divorced/widowed vs single)	**	N/A	2.7 (1.1-6.57) ^{b1}	.028	**	N/A	**	N/A
Oropharyngeal subsite (soft palate/pharyngeal wall vs tonsil)	2.36 (0.84-6.67)	.105	2.97 (1.05-8.43) ^{b2}	.04	**	N/A	**	N/A
Tumor stage								
T2 vs T1	1.92 (0.71-5.23)	.2	0.93 (0.4-2.16) ^{b1}	.862	**	N/A	**	N/A
T3 vs T1	3.67 (1.07-12.6)	.039	1.79 (0.63-5.07)	.274	**	N/A	**	N/A
T4a/NOS vs T1	3 (1.12-8)	.028	1.33 (0.55-3.25)	.527	**	N/A	**	N/A
T4b vs T1	12.9 (1.95-85)	.008	4.62 (0.98-21.8)	.053	**	N/A	**	N/A
AJCC stage 8th (4B vs 1)	**	N/A	**	N/A	1 (0.13-7.61)	.99	16.9 (2.91-97.6) ^{d1}	.002
Total LN dissected (continuous)	0.98 (0.97-1)	.097	**	N/A	**	N/A	**	N/A
ST received								
Cetuximab vs platinum	1.64 (0.74-3.67)	.224	3.96 (1.89-8.29) ^{b2}	<.001	**	N/A	1.77 (0.48-6.53) ^{d2}	.392
No ST vs platinum	0.91 (0.34-2.43)	.848	1.27 (0.59-2.71)	.543	**	N/A	0.63 (0.13-3.1)	.568
Overall treatment								
Surgery alone vs definitive CRT	**	N/A	4.23 (1.15-15.6) ^{b1}	.03	**	N/A	**	N/A
Surgery + adj RT vs definitive CRT	**	N/A	0.30 (0.1-0.95)	.04	**	N/A	**	N/A

Table 2. continued

VARIABLE	OLDER PATIENTS ≥ 65 Y WITH OROPHARYNGEAL CANCER (N = 123)							
	OVERALL SURVIVAL		DISEASE-FREE SURVIVAL		LOCOREGIONAL RECURRENCE-FREE SURVIVAL		DISTANT METASTASIS-FREE SURVIVAL	
	HR (95% CI)	P VALUE	HR (95% CI)	P VALUE	HR (95% CI)	P VALUE	HR (95% CI)	P VALUE
Surgery + adj CRT vs definitive CRT	**	N/A	0.63 (0.19-2.01)	.432	**	N/A	**	N/A
Definitive RT vs definitive CRT	**	N/A	1.25 (0.47-3.3)	.651	**	N/A	**	N/A
Period of diagnosis (2017-2020 vs 2009-2012)	**	N/A	**	N/A	**	N/A	0.15 (0.03-0.66) ^{d1}	.013

*Bold values are statistically significant values; ** not included in the multivariate analysis model*

Abbreviations: Adj, adjuvant; AJCC, American Joint Committee on Cancer; CCI, Charlson Comorbidity Index; CRT, concomitant chemoradiotherapy; HR, hazard ratio; HPV+ve, human papilloma virus-related; HPV-ve, human papilloma virus-unrelated; LN, lymph node; N/A, not applicable; RT, radiation therapy; ST, systemic therapy.

^aOverall survival for older patients adjusted for alcohol use, smoking status, surgery, RT, and era of diagnosis.

^bDisease-free survival models of older patients: ¹adjusted for surgical margin and oropharyngeal subsite, ²adjusted for HPV status, marital status, overall T stage (excluding overall treatment).

^cLocoregional recurrence-free survival for older patients adjusted for smoking status, total LN dissected, and RT.

^dDistant metastases-free survival models for older patients: ¹adjusted for total positive LN, and HPV status, ²adjusted for period of diagnosis and AJCC stage (8th).

In the years comprising our study period, we observed a steady increase in the number of older patients with OPC and a significant increase in the number of patients with HPV+ve OPC, which aligns with other findings.^{4,6,9,12} Xu et al projected that by 2025, 32.6% of all cases of OPC will occur in patients > 70 years, which approximates the 38% that we saw in our older cohort aged ≥ 65 years between 2017 and 2020.³³

While most previous studies have focused mainly on OS in patients with HPV+ve OPC, our analysis is unique because we evaluated tumor-specific survival endpoints and considered both HPV+ve and HPV-ve status in combination with age. Similar to our findings, a Surveillance, Epidemiology, and End Results (SEER) database study of 355 patients observed no difference in receipt of treatment or 3-year OS in patients with HPV+ve OPC across age groups. Nevertheless, the SEER study did not assess other tumor-specific

endpoints, and it included metastatic patients.³⁴ Dickstein et al evaluated a cohort of 88 older patients with OPC and observed similar survival rates as those in our study; however, they did not include a younger patient comparison group.¹³ In contrast to the findings of a National Cancer Database subgroup analysis of 21,880 patients with HPV+ve OPC, we did not see any differences in disease stage or receipt of surgery in older patients.⁹ In a post hoc analysis of patients with locally advanced OPC treated with definitive RT in the RTOG-0129 and RTOG-0522 randomized trials, older age defined as ≥ 50 years was independently prognostic for DMFS, which was not seen in our analysis, although advanced cancer stage and smoking history were predictive of worse outcomes, similar to our findings. Importantly, that analysis included all-cause mortality in addition to distant metastatic events within the definition of DMFS, unlike

our definition that we believe is more clinically relevant.²⁰ Lastly, in agreement with our results, Windon et al showed a nonsignificant difference in OS between age groups for patients with HPV-ve OPC, although no other endpoints were studied, and no multivariate analysis was performed.¹⁰ Overall, although study designs have varied greatly, a clearer picture of the important features associated with different survival endpoints in older patients with OPC is emerging.

One strength of our study is that we analyzed 91 patients (27%) who had undergone surgery, mainly TORS. In our practice, age is not a major factor for precluding surgery since excellent outcomes have been shown with TORS in older patients,²⁵ and that is why surgery rates were nondifferent with age. Including patients who had surgery gave us the opportunity to compare pathological risk factors by age in this group, and we did not note any distinct features for

Table 3. Radiation Therapy and Systemic Therapy Parameters, and Acute Toxicity Outcomes for Older (≥65 y) vs Younger Patients With Oropharyngeal Cancer Who Received Radiation Therapy (N = 326)

CHARACTERISTIC	OLDER OPC (≥65 Y) (N = 118) (36.2%)	YOUNGER OPC (<65 Y) (N = 208) (63.8%)	P VALUE
RT course not completed	5 (4.2)	9 (4.3)	>.99
Unplanned RT delays ^a	29 (25.7)	42 (21.1)	.434
Total RT duration, days, median (range) ^b	49 (41-71)	49 (36-76)	.311
TPT, days, median (range) ^c	86 (72-128)	81 (65-137)	.265
TPT > 90 d ^c	8 (38.1)	15 (28.3)	.588
TPT > 100 d ^c	4 (19.0)	9 (17.0)	>.99
Acute grade 3 mucositis	52 (44.1)	87 (41.8)	.742
Worst grade of pain during RT, median (range)	7 (0-10)	7 (2-10)	.792
Worst pain grade ≥ 8	38 (32.2)	69 (33.2)	.955
Unplanned hospitalization during RT ^d	55 (46.6)	56 (26.9)	<.001
Unplanned IV hydration during RT ^e	40 (33.9)	70 (33.7)	>.99
Weight loss during RT	107 (90.7)	192 (92.3)	.761
Weight loss during RT > 10%	51 (43.2)	94 (45.2)	.819
Feeding tube during RT	75 (63.6)	103 (49.5)	.02
Feeding tube inserted before RT start ^f	23 (19.5)	23 (11.1)	.28
Feeding tube inserted after RT start (reactive)	52 (44.1)	80 (38.5)	.28
Feeding tube duration, days, median (range) ^g	97 (3-743)	64 (1-760)	.308
Feeding tube never removed	23 (19.5)	18 (8.7)	.008
Concomitant systemic therapy (N = 261)	N = 93 (%)	N = 168 (%)	
Systemic therapy protocol			<.001
Cisplatin every 3 wk	30 (32.3)	96 (57.1)	
Cisplatin every 1 wk	24 (25.9)	40 (23.8)	
Carboplatin ± paclitaxel	15 (16.1)	12 (7.1)	
Cetuximab	24 (25.8)	20 (11.9)	
Total cisplatin received mg/m ² , median (range)	240 (40-300)	240 (40-300)	.12
Cumulative cisplatin > 200 mg/m ²	43 (79.6)	128 (94.1)	.006
ST cycle delayed or cancelled	46 (49.5)	81 (48.2)	.949
ST dose reduction in administered cycle	5 (5.4)	16 (9.5)	.346
Switched ST protocol during RT ^h	17 (18.3)	13 (7.7)	.019

Table 3. continued

CHARACTERISTIC	OLDER OPC (≥65 Y) (N = 118) (36.2%)	YOUNGER OPC (<65 Y) (N = 208) (63.8%)	P VALUE
Febrile neutropenia	8 (8.6)	5 (3)	.088
Data shown as N (%) unless otherwise noted.			
Bold values are statistically significant values.			
Abbreviations: IV, intravenous; OPC, oropharyngeal squamous cell carcinoma; RT, radiation therapy; ST, systemic therapy; TPT, treatment package time.			
^a Delays of 2 or more days during a completed RT course.			
^b Total days elapsed between first to last fraction for a completed course of definitive RT.			
^c Total days from surgery to the date of last fraction for a completed course of adjuvant RT.			
^d Hospitalization during RT other than admission for concomitant systemic therapy or IV hydration.			
^e Admission for IV hydration other than that scheduled in systemic therapy protocol.			
^f Feeding tube inserted prophylactically before start of RT following multidisciplinary decision.			
^g Median time for feeding tubes inserted after RT start date and removed before death.			
^h Switching from cisplatin every 3 wk to a more tolerable ST protocol (cisplatin weekly, carboplatin, cetuximab) due to increased toxicity.			

older patients. Nevertheless, rates of perineural invasion, lymphovascular space invasion (LVSI), and ENE in our older cohort were different from other studies.^{12,13} But similar to our findings, a recent study of 136 patients with HPV+ve OPC who underwent TORS showed that age ≥ 65 years was not associated with ENE, positive final surgical margin, perineural invasion, or LVSI.³⁵ We did not note significantly increased toxicity by surgery for older patients who received adjuvant ($n=9$) compared with definitive CRT ($n=84$), albeit limited number obviates solid conclusions. Thus, more targeted studies of how older patients respond to surgery in combination with RT and ST are needed.

Considering the equivalent survival and good prognoses for older patients observed across numerous studies, especially in patients with HPV+ve OPC, more focus is needed on exploring treatment tolerance and toxicity to leverage the overall therapeutic index. More than half of our older patients received concomitant cisplatin, which is more than the 33% reported by Dickstein et al, and we noted more hospitalizations, grade 3-4 mucositis, and treatment interruptions in our older cohort, although we observed comparable survival rates.¹³ Strom

et al reported more hospitalizations, PEG tube dependence, more frequent use of concomitant cetuximab and carboplatin in older than in younger patients, in agreement with our analysis. However, we did not see more dose reductions.³⁶ In contrast to other studies, we did not observe more RT interruptions in older patients.³⁷

Notably, our study is only one of a few that have reported toxicity rates from RT and ST specifically for patients with OPC, unlike most studies that have encompassed all HNCs. We noted higher rates of feeding tube use, both transient and for life, in the older group, which was also shown by Sachdev et al, who concluded that older age was the only predictor for feeding tube use.³⁸ Of note, in addition to being associated with OS in other studies,³⁹ never removing a feeding tube was also predictive of dismal DMFS in our study. In agreement with our findings, Mayer et al observed that mucositis, weight loss, and leukopenia/infection did not differ with age in a matched-pair analysis of older vs younger patients receiving adjuvant chemoradiotherapy.⁴⁰ Although we did not see differences based on age, we observed that both components

of RT interruptions (incomplete and delayed RT) were independently detrimental for OS, as reported by others.^{40,41} Therefore, our analysis emphasizes that starting with an optimal ST protocol in older patients is advocated as long as treatment providers are flexible and able to reduce doses or switch to a less intense ST protocol once intolerable toxicities are encountered.

With a rising number of older adults being diagnosed with OPC, prospective randomized studies targeting this population are being conducted. Although not exclusive to OPC, the ongoing EGeSOR (NCT02025062), ELAN-FIT (NCT01864772), ELAN-UNFIT (NCT01884623), and ELAN-RT (NCT018648350) trials are dedicated to investigating older adults. The ELAN geriatric evaluation, which takes only 20 minutes to determine patient eligibility for any of the 3 ELAN studies, has been validated and represents an important tool for studying older populations.⁴² The final results of these trials will shed light on the utility of a robust stratification tool for objectively evaluating the fitness of older patients for curative therapies, thereby leveraging survival and QOL

Table 4. Multivariate Analyses of Characteristics and Outcomes, Including Therapeutic Tolerance and Acute Toxicity, Associated With Survival for All Patients With Oropharyngeal Cancer Who Received Radiation Therapy With or Without Systemic Therapy

CHARACTERISTICS AND OUTCOME	ALL PATIENTS WITH OROPHARYNGEAL CANCER WHO RECEIVED RADIATION THERAPY (N = 326)							
	OVERALL SURVIVAL ^A		DISEASE-FREE SURVIVAL ^B		LOCOREGIONAL RECURRENCE-FREE SURVIVAL ^C		DISTANT METASTASIS-FREE SURVIVAL ^D	
	HR (95% CI)	P VALUE	HR (95% CI)	P VALUE	HR (95% CI)	P VALUE	HR (95% CI)	P VALUE
Marital status (married vs single)	0.52 (0.30-0.89)	.018	0.71 (0.42-1.21)	.214	**	N/A	**	N/A
Smoking pack-years (continuous)	1.01 (1.00-1.02)	.028	1.01 (1.00-1.02)	.014	1.00 (0.98-1.01)	.847	1.01 (0.99-1.02)	.344
N stage (N3 vs N0)	**	N/A	**	N/A	**	N/A	20.6 (2.17-195.5)	.008
AJCC stage ^E								
4A vs 1	3.85 (1.24-11.96)	.020	1.74 (0.57-5.30)	.328	0.28 (0.06-1.35)	.112	**	N/A
4B vs 1	3.59 (1.11-11.67)	.033	1.62 (0.49-5.37)	.426	0.92 (0.18-4.71)	.924	**	N/A
Definitive RT (no vs yes) ^F	0.35 (0.18-0.68)	.002	0.44 (0.24-0.81)	.009	0.08 (0.02-0.32)	<.001	**	N/A
RT delays ^G (yes vs no)	2.57 (1.45-4.55)	.001	1.71 (0.99-2.96)	.057	0.95 (0.43-2.11)	.906	**	N/A
RT course completed (no vs yes)	8.12 (2.84-23.21)	<.001	5.54 (2.11-14.55)	.001	7.87 (1.37-45.3)	.021	**	N/A
Unplanned hospitalization during RT ^H (yes vs no)	1.71 (1.03-2.84)	.037	1.04 (0.63-1.72)	.879	**	N/A	3.82 (1.57-9.27)	.003
FT used during RT (no vs yes)	0.93 (0.49-1.77)	.826	0.92 (0.51-1.66)	.776	0.92 (0.36-2.37)	.868	0.52 (0.2-1.4)	.198
FT never removed (yes vs no)	3.55 (1.89-6.67)	<.001	2.60 (1.38-4.93)	.003	**	N/A	3.90 (1.56-9.71)	.004
FT inserted before RT start ^I (yes vs no)	1.74 (0.89-3.42)	.107	1.65 (0.85-3.21)	.139	3.88 (1.53-9.83)	.004	**	N/A
Period of diagnosis	**	N/A	0.58 (0.27-1.23)	.155	0.19 (0.07-0.54)	.002	0.22 (0.06-0.77)	.019

Table 4. continued

CHARACTERISTICS AND OUTCOME	ALL PATIENTS WITH OROPHARYNGEAL CANCER WHO RECEIVED RADIATION THERAPY (N = 326)							
	OVERALL SURVIVAL ^a		DISEASE-FREE SURVIVAL ^b		LOCOREGIONAL RECURRENCE-FREE SURVIVAL ^c		DISTANT METASTASIS-FREE SURVIVAL ^d	
	HR (95% CI)	P VALUE	HR (95% CI)	P VALUE	HR (95% CI)	P VALUE	HR (95% CI)	P VALUE
(2017-2020 vs 2009-2012)								
<i>Bold values are statistically significant values; ** not included in the multivariate analysis model</i> Abbreviations: AJCC, American Joint Committee on Cancer; FT, feeding tube; HPV, human papilloma virus; HR, hazard ratio; RT, radiation therapy; ST, systemic therapy. ^aOverall survival adjusted for HPV status, age, total Charlson Comorbidity Index, alcohol use, oropharyngeal subsite, systemic therapy protocol, cisplatin cumulative dose and weight loss. ^bDisease-free survival adjusted for HPV status, total Charlson Comorbidity Index, systemic therapy protocol and weight loss. ^cLocoregional recurrence-free survival adjusted for HPV status, worst grade of pain during RT, switching systemic therapy protocol during RT and weight loss. ^dDistant metastases-free survival adjusted for HPV status, T stage, systemic therapy protocol and weight loss. ^eAJCC 8th version. ^fDefinitive RT ± ST vs Surgery + RT+/-ST. ^gUnplanned RT delays of > 2 d. ^hHospitalization during radiation therapy other than admission for concomitant systemic therapy or IV hydration. ⁱFT inserted prophylactically before RT start compared with FT inserted after RT.								

outcomes. Nevertheless, recent de-escalation studies for patients with HPV+ve OPC have not stratified for age, and few older patients participated, even though de-escalation is a very desirable option for older groups.⁴³⁻⁴⁶

Our study had several limitations, including the lack of a formal baseline and follow-up QOL measurement, and no formal geriatric assessment (GA) tool for older patients. The clinical integration of GA remains limited in current practice for OPC treatment, highlighting a gap in providing comprehensive, personalized care to older adults with OPC. Partially relevant to GA, we observed that baseline CCI was predictive for worse OS in older patients, with no impact on tumor-specific outcomes that was consistent with others.²⁸

We were also not able to capture all chemotherapy-related toxicities as in other studies,^{13,36,40} although we believe that febrile neutropenia, unplanned hospitalizations, and

dose modifications are all objective surrogate measures for serious toxicity. We did not compare late toxicities/morbidities such as pneumonia and malnutrition that have been associated with increased risk of death.⁴⁵ Of note, we were not able to compare different ST protocols among older patients regarding toxicity. Nevertheless, this comparison is hard, taking into consideration the limited number of patients and the high rates of delayed and cancelled cycles (48%) and the rate of switching to less intense protocols (18%). However, despite having less intense protocols and less cumulative cisplatin doses in the older group, they suffered higher toxicities and more hospitalizations. We observed higher than usual feeding tube use in older patients, partially because temporary nasogastric tubes were included with PEG tubes. Importantly, the definition and survival implications for patients with “feeding tube never removed” should be interpreted with caution

because it included patients who died in the early post-treatment interval with recurrence before removing the tube, while it is not unusual for some fit patients to have feeding tube dependency up to 2 years following RT. TPT was similar with age, suggesting no significant delays due to postoperative complications for older patients managed with surgery. We included only curatively treated patients in our analyses, which may have resulted in selection bias or the confounding effect by indication against older unfit patients with poor overall health status and functional abilities, which might have skewed survival outcomes. Older patients with OPC often present with diverse comorbidities and varying levels of frailty, potentially influencing treatment decisions and outcomes. Limited numbers of patients did not permit a proper matched comparison for age groups based on stage, OPC subsite, treatment category, or ST protocol.

Conclusions

For patients with OPC, older age ≥ 65 years was not associated with any unique clinicopathological characteristics, specific treatment strategies, or worse survival outcomes, regardless of HPV status. Although older patients experienced higher levels of therapeutic toxicity and feeding tube insertions, they did not experience more RT interruptions than younger patients. Our findings underscore the complexities of treatment tolerance and toxicity profiles in this population, often underrepresented in clinical trials. By evaluating functional status, comorbidities, and geriatric syndromes, GA can guide tailored treatment strategies that optimize efficacy outcomes while minimizing treatment-related morbidity in older patients.

Until results from ongoing de-escalation and immunotherapy studies are available, every effort should be made to deliver optimal SoC therapy to patients with OPC regardless of age. Trials dedicated to investigating older patients with OPC are needed to prospectively address treatment tolerability and the key factors affecting QOL in addition to survival.

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Stent Migration and Fistula Formation Following Stereotactic Body Radiation Therapy for Pancreatic Cancer

Sarah Goodchild;^{1*} Ann Nguyen, BS;² Russell Palm, MD;³ Brian Morse, MD;³ Dae Won Kim, MD;³ Pam Hodul, MD;³ J. M. Bryant, MD;³ Sarah Hoffe, MD;³ Aamir Dam, MD;³ Jessica Frakes, MD³

Abstract

Locally advanced pancreatic cancer (LAPC) is associated with a poor prognosis, with rates of eventual surgical resection after neoadjuvant therapies ranging from 10% to 30%. When such tumors are in the pancreatic head, obstructive jaundice is often the presenting symptom, necessitating endoscopic stent placement. Interval stent migration is possible at any time due to several factors, including the mechanical properties of self-expandable metal stents (SEMS), complete sphincterotomy, tumor regrowth, and improved tumor response from chemotherapy and radiation. A 75-year-old woman presented with pancreatic head/neck LAPC who received chemotherapy and stereotactic MR-guided adaptive radiation therapy (SMART) with ablative dose on an MRI linear accelerator. Post-treatment imaging at 6 months incidentally revealed that the previously placed biliary SEMS was dislodged into the duodenum. Endoscopic removal was not performed due to a 10-mm fistulous opening proximal to the major papilla in direct communication with the stent. This case reports stent migration and fistula formation postablative SMART.

Keywords: hepatocellular carcinoma, MRgSBRT, fistula

Case Summary

A 75-year-old woman presented with obstructive jaundice to her primary care physician and was sent to the emergency room for further evaluation. Ultrasound was performed, which showed dilation of the common bile duct, and a proceeding MR cholangiopancreatography displayed a solid mass in the head of the pancreas with a double-duct sign and a CA 19-9 of 1036 U/mL. The patient underwent an endoscopic

ultrasound (EUS) and endoscopic retrograde cholangiopancreatogram (ERCP). Fine-needle biopsy confirmed pancreatic adenocarcinoma. She tolerated 4 cycles of chemotherapy (FOLFIRINOX), starting from February 2022 well, and the CA 19-9 declined to 526 U/mL. She then received stereotactic MR-guided adaptive radiation therapy (SMART) to a dose of 50 Gy in 5 fractions with staging done on August 3, 2022, and treatment delivered from August 18, 2022, to August 24, 2022. Gross

tumor volume (GTV) was contoured on MRI images and checked with the fused contrast-enhanced CT planning images using deep inspiration breath hold. Clinical target volume (CTV) was created using the triangle volumes delineated by Hill et al.¹ The GTV dose was prescribed to a dose of 50 Gy in 5 fractions using a daily adaptive technique with a CTV dose of 30 Gy. Treatment was delivered over consecutive days on the MRIdian (ViewRay Inc.) MRI linear accelerator and an intensity-modulated radiation therapy. The daily max and mean doses respectively to the duodenum for each day were 7.11 Gy and 2.75 Gy for day 1, 7.45 Gy and 2.97 Gy for day 2, 6.68 Gy and 2.69 Gy for day 3, 7.13 Gy and 2.70 Gy for day 4, and 7.47 Gy and 2.67 Gy for day 5. The maximum duodenum dose for

Affiliations: ¹University of South Florida, Tampa, FL. ²University of South Florida Morsani College of Medicine, Tampa, FL. ³Moffitt Cancer Center, Center Tampa, FL.

Corresponding author: *Sarah Goodchild, 2712 E 122nd Ave, Tampa, FL, USA. (sarahg06062@gmail.com)

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Figure 1. Coronal CT image of the migrated stent into the duodenum.



the entire treatment was 35.84 Gy. A follow-up at 5 and 12 weeks showed normal CA 19-9 of 18.1 and 63.5, and no progression on imaging, and she started surveillance. At 7 months post treatment, she was feeling well and had no symptoms related to her cancer. Her pancreas protocol CT scan, however, revealed migration of the biliary stent. Post-treatment scans and endoscopy showed stent migration and fistula formation between the intrapancreatic distal common bile duct and the duodenum lumen. Conservative management was pursued as she was asymptomatic

with adequate biliary decompression and remained symptom free for 11 months thereafter.

Imaging Findings

The ERCP and EUS findings helped confirm a poorly defined irregular pancreas head adenocarcinoma with double-duct sign measuring $3.1 \times 5.6 \times 3.2$ cm confirmed through the pancreas protocol CT scan. The tumor encased the portal vein and superior mesenteric vein by more than 180° and was thus staged as locally advanced. Abnormal

peripancreatic lymphadenopathy was noted. Routine surveillance pancreas protocol CT scan 7 months post SMART completion unexpectedly showed the biliary stent dislodged within the duodenum (**Figure 1**). Endoscopic retrieval was attempted but aborted due to a fistulous opening in the duodenum (**Figure 2**). The proximal aspect of the stent was visualized through the fistulous opening (**Figure 3**).

Diagnosis

At diagnosis, the tumor stage was T4N2M0 and deemed unresectable. The patient's fully covered metal stent made of metal alloy tubular mesh with a synthetic covering was placed 1 month prior to chemotherapy and 7 months prior to SMART.

Gastrointestinal (GI) endoscopy revealed a 10-mm duodenal fistulous opening proximal to the major papilla. The patient's biliary stent was inside the fistula opening and had migrated outward. The stent was not removed in the setting of the contained fistula, and the GI endoscopy team recommended conservative management at the time (**Figure 3**).

A review of the patient's outside endoscopic procedures prior to coming to our center for cancer treatment showed that the initial ERCP had not been successful. The record indicated that the major papilla appeared bulbous and bulging. The papillary orifice could not be visualized, and attempts to achieve biliary cannulation using a conventional technique via the ampulla of Vater were unsuccessful. A precut technique was then successfully employed.

There was mild bleeding in the second portion of the duodenum, which was managed with epinephrine. The procedure was aborted and a percutaneous

Figure 2. Fistulous opening above the major papilla.

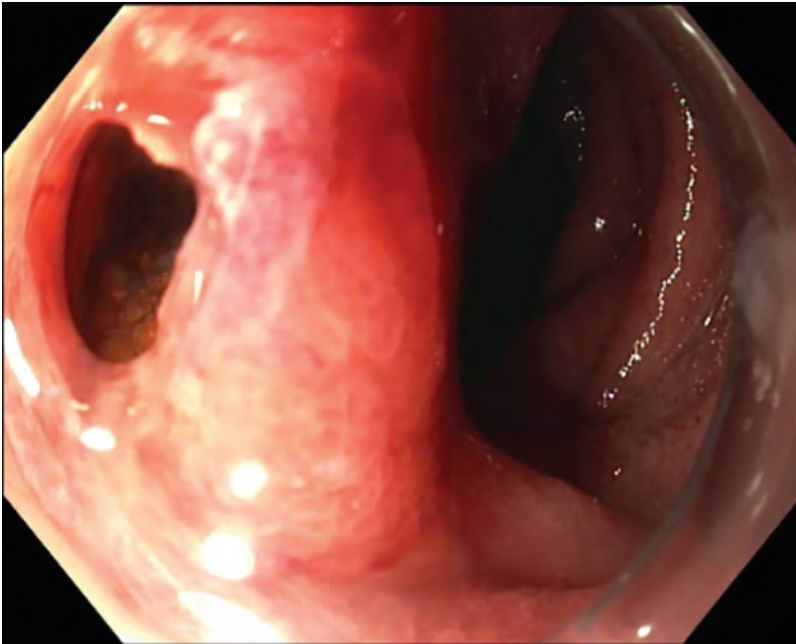
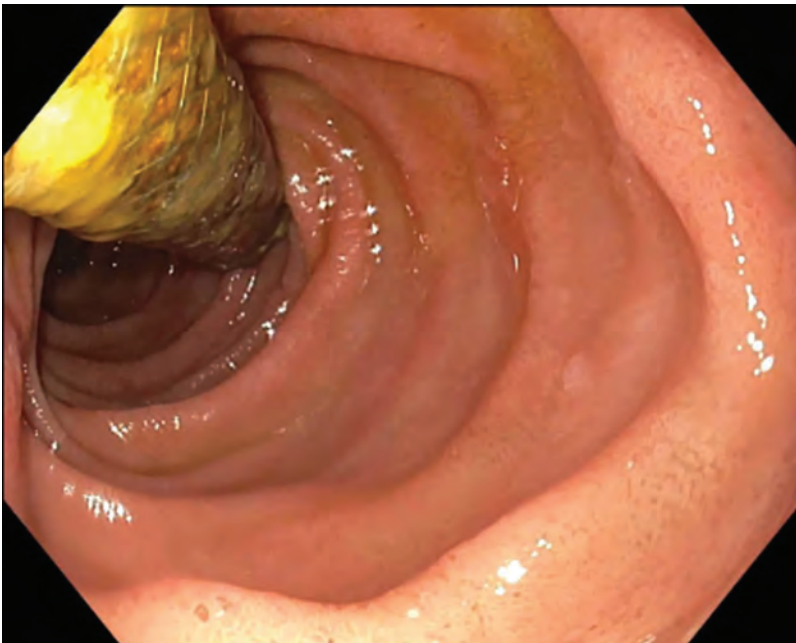


Figure 3. Endoscopic appearance of stent protruding from the fistulous opening proximal to the major papilla.



transhepatic cholangiogram was done instead to place an internal/external stent. Two days later, she had her internal/external drain removed and a fully covered metal stent placed. At the time of the procedure, a

significant hemobilia and blood clots in the bile duct were noted. There was bleeding from the site of the previous papillotomy. A single clip was deployed along the site to successfully stop the bleeding.

Discussion

Locally advanced pancreatic cancer (LAPC) accounts for 30% of newly diagnosed pancreatic cancer, with approximately one-third of the cases becoming resectable after systemic chemotherapy and/or radiation therapy.² Since most of these tumors remain unresectable, survival rates following systemic chemotherapy and traditional radiation therapy have been low.³ Recent studies of systemic therapy, followed by higher biologically effective dose regimens, either alone⁴ or with a tumor modifier,⁵ have reported improved outcomes with low toxicity rates.

In this case, the patient was treated with MRI-guided stereotactic body radiation therapy to a dose of 50 Gy in 5 fractions following 6 months of systemic FOLFIRINOX using daily adaptation. The precision provided by SMART allows for both higher control rates and lower toxicity rates. A recent prospective phase 2 study of both borderline patients and patients with LAPC reported 2-year rates of local control of 78.2% and overall survival of 40.5% following treatment with no acute-grade ≥ 3 acute toxicity and minimal late-grade ≥ 3 toxicity.⁴ While acute-, late-, and high-grade toxicities are minimized using SMART, they can still occur.

The patient had a complicated course following her treatment with chemotherapy and radiation, including stent migration and fistula formation. The location of the fistula was in the precise region where the needle-knife fistulotomy was performed. The antecedent injury to the biliary mucosa was associated with bleeding during and following the procedure, so much so that an endoscopic clip had to be placed to stop the bleeding. Although we cannot be certain as to the exact etiology of the post-treatment-related

fistula, the iatrogenic mucosal defect may have been a predisposing factor in this case. The importance of multidisciplinary evaluation with gastroenterology to individualize risk assessments for each case is important. Specifically, pretreatment endoscopy prior to radiation therapy can provide critical information to the radiation oncologist when tailoring the treatment plan. In this case, the patient is now 18 months post treatment and remains asymptomatic. No endoscopic intervention has been required to date since the identification of the duodenal fistula.

Grade 2 and above rates of GI toxicity postablative radiation therapy have been seen at rates of 2% to 47%, including biliary tract injuries of ulcers, fistulas, and gastric or duodenal mucositis.^{2,3,6,7} Grade 3-4 events such as ulcers, fistulas, and gastric or duodenal mucositis have been seen at rates of 13% to 22.7%.³ For duodenal and other GI fistulas, depending on the severity and containment of the fistula, treatments can vary from conservative management, advanced surgical procedures, and varying endoscopic techniques.^{8,9} In patients with endobiliary stents, there are reported complications associated with radiation therapy. Minimal stent position changes have been described following RT, with stent migration rates of 4.9% proximally and 5.9% distally.¹⁰ However, adverse events such as stent migration and fistula formation occur more frequently in patients who have undergone previous chemoradiotherapy treatment vs those who have undergone stent placement alone.¹¹ The significant interfraction deformation of GI structures, such as the pancreatic head, duodenum, and stomach that may occur during radiation treatment, may affect stent migration.¹⁰ Additionally, a dilated

common bile duct, complete sphincterotomy, prolonged stent insertion, benign strictures, and covered metal stents were the factors associated with stent migration.^{12,13}

Conclusion

This case highlights the potential of significant adverse events despite the evolution of advanced techniques such as SMART. This patient was considered lower risk for adverse events such as stent migration or fistula formation due to her history of no chemoradiation prior to diagnosis. Nonetheless, a fistula still occurs even with the precision and lower toxicity rates of a modern radiation therapy technique. Both gastroenterologists and radiation oncologists should be aware of the potential predisposing factors for fistula formation. In this case, an iatrogenic factor (attempted needle-knife fistulotomy) likely predisposed the patient to develop a fistula post radiation. In the future, knowledge of predisposing endoscopic factors may guide radiation oncologists in modifying from a 5-fraction to a 25-fraction dose plan.¹⁴

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Hyper-Acute Necrosis of a Trigeminal Schwannoma After GKRS: A Case Report

Victor Goulenko, MD;¹ Venkatesh Shankar Madhugiri, MD, FACS;¹ Neil D. Almeida, MD;¹ Elizabeth Mwango Nyabuto, MD;² Katherine Locke, MD;³ Rohil J. Shekher, MD;¹ Assaf Berger, MD;³ Hanna Algattas, MD;³ Kenneth Snyder, MD PhD;^{3,4} Robert Plunkett, MD;^{2,3} Dheerendra Prasad, MD, MCh FACRO^{1,2,3,4*}

Abstract

Trigeminal schwannomas (TS) represent 0.8 to 5% of intracranial schwannomas. Due to their localization, surgery has a high morbidity, with stereotactic radiosurgery being a frequent method of treatment with a high control rate. The main side effects due to radiation are pseudoprogression and worsening of the symptoms related to the affected nerve. Despite tumor necrosis, they tend to be progressive, small, and to spread throughout the tumor. We present a rare case of a 48-year-old woman with trigeminal schwannoma who underwent gamma knife radiosurgery and presented with facial pain immediately after the procedure with significant worsening a few hours later. MRI showed necrosis of the medial part of the extracranial extension of the tumor. This is the first report of hyperacute tumor necrosis after radiation for schwannomas.

Keywords: trigeminal schwannoma, tumor necrosis, gamma knife radiosurgery

Case Summary

A 48-year-old woman with a history of breast cancer 9 years previously (currently in remission), and who had been treated with lumpectomy and radiation, presented with a right-sided headache that had been worsening over 6 months and facial paresthesia at the level of V2, with no trigger points or other neurological complaints or deficits. Symptoms were adequately controlled after starting gabapentin. She was evaluated with an MRI of the brain,

which showed a right-sided mass involving the maxillary division of the trigeminal nerve and extending through the foramen rotundum. The bulk of the tumor was extracranial and displayed a homogeneous contrast enhancement, characteristic of a schwannoma. The patient was evaluated by the neurosurgery team, and due to the risk of morbidity with an extended craniofacial surgical approach, gamma knife radiosurgery (GKRS) was recommended.

The patient underwent GKRS to the tumor using a Vantage

Frame-based fixation on the Esprit model (Elekta AB). Another MRI was obtained on the morning of the procedure. The tumor volume was 5.734 cm³, and a marginal dose of 12 Gy at the 61% isodose line was prescribed in a single fraction (**Figure 1A**). The treatment data are shown in **Table 1**. The maximum dose constraints to the organs at risk used in the treatment plan were 8 Gy to the optic apparatus and 12 Gy to the brainstem.

Immediately after the procedure, the patient reported worsening headache and nausea, which improved with intravenous (IV) steroids and ondansetron, and the patient was discharged. On the same night, the patient presented with a recurrence of these symptoms, including multiple episodes of vomiting and worsening V2 paresthesia. Emergency MRI evaluation within 6 hours of the end

Affiliations: ¹Department of Radiation Medicine, Roswell Park Comprehensive Cancer Center, Buffalo, NY.

²Department of Neurosurgery, Roswell Park Comprehensive Cancer Center, Buffalo, NY. ³Department of Neurosurgery, University at Buffalo, Buffalo, NY. ⁴Jacobs School of Medicine and Biomedical Sciences, University at Buffalo, Buffalo, NY.

Corresponding author: *Dheerendra Prasad, MD, MCh FACRO, 665 Elm St, Buffalo, NY 14203. (dheerendra.prasad@roswellpark.org)

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Figure 1. (A) MRI of the day of the gamma knife radiosurgery (GKRS) treatment showing the extracranial segment of the trigeminal schwannoma, with the yellow line showing the 12 Gy marginal dose at the 61% isodose line (IDL). (B) MRI within 6 h from the GKRS treatment showing tumor necrosis (center of the cursor). (C) MRI contrast-clearance analysis, with the yellow arrow showing the area in blue that corresponds to the viable tumor and the red arrow showing the area of necrosis. (D) PET scan, 1 month after, with lower 18 fluorodeoxyglucose uptake at the extracranial segment of the tumor. (E) 3-month follow-up MRI with collapse of the tumor. (F) 3-month follow-up MRI contrast-clearance analysis, with the yellow arrow showing the area in blue that corresponds to the viable tumor and the red arrow showing the area in red that corresponds to tumor necrosis.

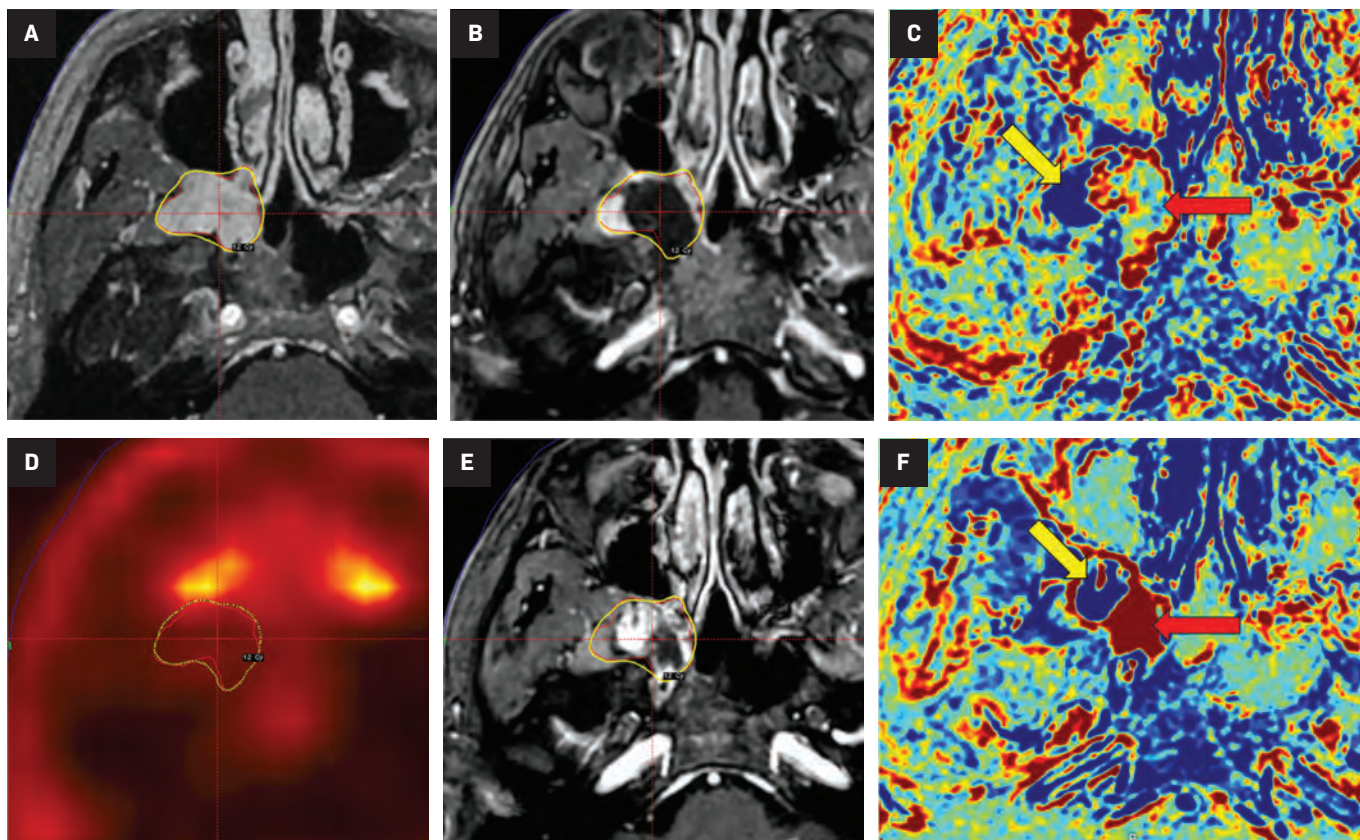


Table 1. Data of Treatment Plan Including Doses for Tumor and Organs at Risk

	VOLUME (cm ³)	MINIMU M DOSE (Gy)	MEAN DOSE (Gy)	MAXIMU M DOSE (Gy)	PRESCRIBED DOSE (Gy)	IDL (%)	COVERAGE	SELECTIVITY	GI	PCI	DELIVERY TIME (min)	DOSE RATE
Tumor	5.734	8.4	15.3	19.7	12	61	0.98	0.83	2.66	0.82	67.37	2.927
Chiasm	0.079	1.1	1.4	1.7	-	-	-	-	-	-	-	-
Left optic nerve	0.329	0.7	1.3	1.9	-	-	-	-	-	-	-	-
Left optic tract	0.069	1	1.2	1.4	-	-	-	-	-	-	-	-
Right optic nerve	0.519	0.5	1.3	2.1	-	-	-	-	-	-	-	-
Right optic tract	0.045	0.9	1.1	1.2	-	-	-	-	-	-	-	-

Abbreviations: GI, gradient index; IDL, isodose line; PCI, Paddick conformity index.

of treatment showed hypo-intensity and absence of perfusion in the medial portion of the extracranial segment of the tumor-characterizing area of tumor necrosis. MRI contrast-clearance analysis was also obtained with the same findings (**Figure 1B**, **Figure 1C**). Dexamethasone was started with an initial bolus of 10 mg IV, followed by a maintenance regimen of 4 mg every 6 hours. By post-admission day 5, the patient had adequate pain control, with only a complaint of V2 paresthesia, and was discharged with tapering of dexamethasone and scheduled follow-up. A 1-month PET scan showed lower fluorodeoxyglucose uptake at the extracranial segment of the tumor, and consecutive MRIs (1-, 3-, and 6-month) had no progression of the necrosis, with collapse of the tumor (**Figure 1D**, **Figure 1E**). Contrast-clear analysis (at 6 hours and 3 months) showed clear delimitation between viable and necrotic tumor (**Figure 1C**, **Figure 1F**).

A review of the delivered treatment plan showed a maximum point dose of 19.7 Gy to the intracranial portion of the tumor, with the area corresponding to the necrotic portion of the tumor receiving a maximum of 18 Gy.

Diagnosis

Hyperacute necrosis of a trigeminal schwannoma post GKRS

Discussion

Schwannomas are mostly benign tumors that arise from the Schwann cells surrounding the nerves and can affect the peripheral and cranial nerves. The 8th cranial nerve complex is the most commonly affected intracranial nerve, corresponding to 90% of all intracranial schwannomas, followed by the trigeminal nerve in 0.8 to

5% of the cases, and less frequently, the other cranial nerves.¹⁻³ These tumors can involve any segment of the nerve and can grow within the intracranial or extracranial spaces; they can extend through the foramina of the skull base and involve multiple compartments.^{2,4} In the modern era, surgical resection and stereotactic radiosurgery (SRS) are the main treatment modalities for these lesions.^{2,5-9}

Gamma knife radiosurgery is a safe and effective treatment for TS, with favorable rates of local control of 77.3 to 94%, making it a popular treatment modality for these benign lesions.^{2,5,7,9} When compared with microsurgery, GKRS has favorable outcomes in terms of cranial nerve preservation, quality of life, and recurrence rates.⁹ Despite its favorable safety profile, the described risks of GKRS include damage to the involved nerve, leading to the aggravation of symptoms, brain edema, hydrocephalus, tumor necrosis, and intratumoral hemorrhage.^{2,7,10} In contrast to vestibular schwannomas, late malignant transformation of TS has not been described, but it is a rare, long-term risk.¹¹ Although necrosis and micro-hemorrhages can be seen as tumor heterogeneity on the pretreatment MRI,¹ their appearance or worsening after radiation, also seen on histopathological analysis,^{10,12} can lead to the formation of cysts, causing a transitory increase in tumor volume and compressive symptoms.⁷

Pseudoprogression is a phenomenon that describes an initial increase in tumor size with subsequent decrease in tumor burden. It has been reported to start approximately a few months following GKRS and has classically been described in the setting of

vestibular schwannomas treated with GKRS.^{2,6-8,13-16} Pseudoprogression can also affect TS treated with SRS/GKRS in 2.2 to 37.5% of the cases.^{2,6-8} In 2020, Nasi et al reported a case with early life-threatening enlargement of a vestibular schwannoma 1 month post GKRS. Surgical pathology showed evidence of extensive radiation-induced coagulative necrosis.¹⁷ Hyperacute necrosis in schwannomas treated with GKRS, occurring within a few hours of treatment, has not been reported in the literature so far.

In the present case, we hypothesize that necrosis within a few minutes to hours of treatment may be due to the obstruction of a supplying artery either due to coagulation or a vascular wall lesion. Damage to the sphenopalatine ganglion affecting the sympathetic or parasympathetic nerves with resulting changes in tumor perfusion would be a less likely cause since no other structure supplied by the ganglion was affected in any manner.

Conclusion

Trigeminal schwannomas are rare tumors that are treated either with surgery, radiation, or a combination of both. Despite high tumor control rates with SRS, adverse radiation effects such as pseudoprogression and worsening of trigeminal symptoms can occur, albeit rarely. While it is common for microscopic areas of necrosis and hemorrhage to form within the tumor soon after treatment, hyperacute necrosis, within hours of treatment, has not been reported. The main hypothesis is that damage to a tumor's penetrating artery caused coagulation and obliteration, leading to the acute lack of blood

supply for a part of the extracranial segment spawning the necrosis. Steroids controlled the patient's symptoms, and no other areas of necrosis were noted on the consecutive scans.

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The Use of Adaptive Radiation in a Retroperitoneal Seminoma Patient with Poor Candidacy for Chemotherapy: A Teaching Case

Michayla B. Brown, MS;¹ Mehran B. Yusuf, MD;² Joseph M. Harms, PhD;² Joel A. Pogue, PhD;² Dennis N. Stanley, PhD;² Andrew McDonald, MD, MS^{2*}

Abstract

Testicular cancers are a common etiology for painless testicular masses occurring in young adult males between the ages of 20 and 34, with 50% diagnosed as seminomas. Seminomas are a malignant germ-cell tumor most commonly confined to the testicles with less frequent de novo involvement of structures outside of the seminiferous tubules. Radiation therapy (RT) has historically been indicated for patients with stage 1-2 seminoma, but its use is declining due to increased uptake of surveillance and modern chemotherapy. However, seminoma is a radiosensitive tumor, and RT may play a role in select cases. This case report describes a nontypical presentation of a large IIC retroperitoneal seminoma measuring 15 cm in an older patient who was a suboptimal candidate for chemotherapy. He was treated with an online adaptive external-beam radiation platform, leading to a significant reduction in body and bowel dose compared with standard-of-care radiation treatment. Clinical regression of tumor was achieved while sparing exposure to significant volumes of bowel and healthy pelvic tissue. The patient had an uneventful recovery and showed no signs of radiation dermatitis or gastrointestinal toxicity.

Keywords: retroperitoneal seminoma, adaptive radiation, cryptorchidism, renal impairment, advanced age

Case Presentation

A 71-year-old man with a history of infantile left-sided cryptorchidism that he believed to have been resolved via left-sided orchiectomy at age 15 brought with him a CT scan from a community hospital revealing ipsilateral retroperitoneal mass to presentation at our

institutional emergency department for evaluation of back pain and a growth in his groin. Scrotal ultrasound revealed one normal right testicle and an apparent left testicle in the left inguinal canal with at least one irregular, hypoechoic mass measuring 1.0 × 1.3 × 1.1 cm. Color Doppler flow was present within this mass. An

additional separate hypoechoic mass inferior to the testicle within the inguinal canal that measured 3.0 × 2.3 × 2.5 cm was also noted. CT of the abdomen and pelvis revealed a large retroperitoneal mass measuring 15.0 × 11.3 × 7.6 cm (**Figure 1**). Of note, the presence of a left testicle in the inguinal canal was unexpected given the patient's report of his past medical history, and he was understandably surprised by its identification. An atrophic left kidney with associated hydro-nephrosis and microlithiasis was also noted. Serum labs, including Complete Metabolic Panel revealed serum creatinine of 1.9 mg/dL (normal: 0.74-1.35 mg/dL), estimated Glomerular Filtration Rate (eGFR)

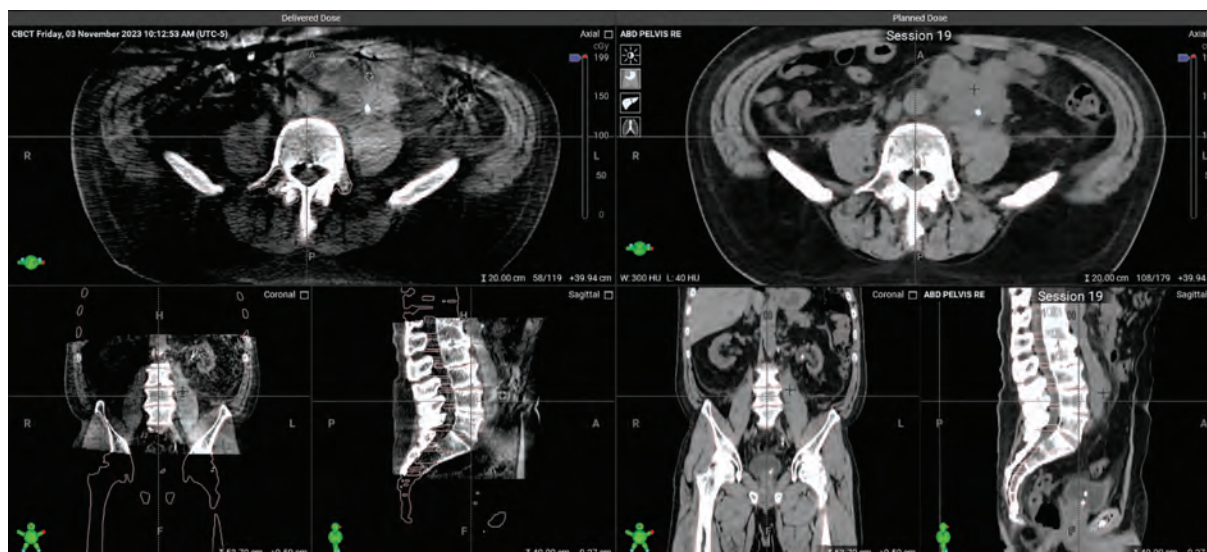
Affiliations: ¹University of Alabama at Birmingham Heersink School of Medicine, Birmingham, AL. ²University of Alabama at Birmingham Hospital Department of Radiation Oncology, Birmingham, AL.

Corresponding author: *Andrew McDonald, MD, MS, Hazelrig-Salter Radiation Oncology Center, 1700 6th Avenue South, Birmingham, AL 35233. (ammcdonald@uabmc.edu)

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Figure 1. CT of the abdomen and pelvis revealing the patient's large retroperitoneal mass



of 37 mL/min/1.73 m² (normal: > 90 mL/min/1.73 m²), consistent with significant renal impairment, as well as alpha-fetoprotein of 1.87 ng/mL (normal: < 10 ng/mL), lactate dehydrogenase of 189 IU/L (normal: 135-225 U/L), and beta-hCG of 4.3 mIU/mL (normal: < 2 mIU/mL), consistent with the criteria for pure seminoma.

Subsequently, the patient underwent left-sided ureteral stent placement and left-sided radical orchiectomy with high ligation of the spermatic cord. Pathology of the testicle and paratesticular mass revealed seminoma measuring 2.7 cm with focal necrosis and confined to the testes. While pathology did identify 4.0 cm of discontinuous spermatic cord involvement, which typically corresponds with stage 3 malignancy, there was no lymphovascular invasion appreciated and margins were negative. The tumor was therefore staged as pT3N0M1, with an overall staging consistent with a bulky stage 2 seminoma. The patient was evaluated by our institutional medical oncology service, and he was determined to be a suboptimal

candidate for cisplatin-based therapy due to advanced age and renal impairment as evidenced by his eGFR. As such, he was referred to the Department of Radiation Oncology, where he was counseled regarding the details of treatment, including adverse effects, risks, and benefits, and gave his consent. After planning, his case was reviewed at our multidisciplinary genitourinary tumor board meeting.

The kilovoltage cone beam CT (kV-CBCT)-guided online adaptive radiation therapy (OART) workflow using Ethos starts by generating a reference plan on the simulation CT image and PET fusion imaging in the supine position prior to an initial treatment course of adaptive external beam radiation (photon- 6X-FFF). Simulation and treatment were in accordance with the previously described institutional workflow by Stanley et al, which includes a comprehensive protocol for integrating kV-CBCT into OART. The implementation process begins with the setup of kV-CBCT systems and the development of standard operating procedures. The workflow involves initial

imaging with kV-CBCT to assess anatomical changes at sequential visits and ensure accurate tumor targeting. The kV-CBCT scan was acquired and influencers, that is, structures critical for guiding image deformation, were automatically contoured (bowel, liver, kidneys, etc.). The influencers were further modified based on real-time data by the qualified medical physicist (QMP) as necessary to account for any deviations from the planned treatment field and reviewed by the treating physician once weekly. This adaptive approach, coupled with regular quality assurance checks, functions to maintain system accuracy and effectiveness. In this patient's case, the primary gross tumor volume (GTVp), low-dose clinical treatment volume (CTV_Low), and other normal tissues were then propagated via a deformable image registration of the simulation CT to the daily kV-CBCT, followed by edits by the QMP or treating physician as necessary. The CTV_High, PTV_Low, and PTV_High were then derived from the GTVp and CTV_Low using prescribed derivations. Two

plans were then generated: a scheduled plan (reference plan recalculated onto daily anatomy) and an adaptive plan (new plan optimized using daily anatomy). The superior of the two was then selected for treatment. Lastly, a verification kV-CBCT was taken after the adaptive planning process and immediately before treatment for patient alignment. IDENTIFY surface monitoring (Varian) was utilized to monitor patient motion throughout the entire treatment session.¹ The process of refining the technology and workflow based on clinical feedback and technical challenges encountered is crucial to the development and success of a quality support system for troubleshooting and optimization during the course of a patient's individualized treatment plan.^{1,2}

For the adaptive therapy in this particular case, GTVp and CTV_Low were drawn each day. CTV_Low consisted of the gross tumor, para-aortic lymph nodes, and ipsilateral lymph nodes extending from the top of the femoral heads inferiorly to the renal vessels superiorly. Note that planning did not include exposure to the inguinal lymph nodes as the rates of primary spread in this setting are low, even in patients with previously violated vascular planes, such as in patients with a surgical history of orchiopexy. The risk of leaving inguinal lymph nodes untreated is further lessened when resection measures include high ligation of the spermatic cord, as was the case with this patient.^{3,4} The CTV_High was a 10 mm expansion of the GTVp_High, excluding the bowel. The CTV-PTV margin for both high- and low-dose volumes was 8 mm. The PTV_Low was prescribed a dose of 2520 cGy in 14 fractions, followed by a sequential 1980 cGy boost in 11 fractions to the PTV_High.

During radiation therapy, a significant reduction in gross tumor volume was appreciated, with reductions in clinical treatment volume from the initial standard plan to the adapted final treatment plan, as shown in **Figure 2**.

The increase in volume treated at fraction 1 compared with reference volume measured during the initial simulation demonstrates rapid neoplastic growth. Initial GTVp had a volume of 713.88 cm³ with treatment volumes of 795.5 ccs, 263.2 cm³, and 217.8 cm³ at fractions 1, 15, and 25, respectively, resulting in a 70% total volume reduction by the end of treatment. Similarly, PTV_High had a reference volume of 1734.4 cm³ with treatment volumes of 1833.4 cm³, 859.4 cm³, and 819.2 cm³ for fractions 1, 14, and 25, respectively, resulting in a 53% total volume reduction. Also noteworthy is the trend for PTV_High volume reduction at fractions 5, 7, and 14, indicating points of the greatest volume reduction. The trend in GTVp volume reduction at fractions 5, 10, and 14 indicates points of the greatest volume reduction. These trends can be similarly appreciated in all measured volumes in **Figure 2**. **Figure 3** shows that without adaption the prescription-level isodose would have been overcovered by 66.3 cm³ and 41.6 cm³ at fractions 15 and 25, respectively. Although not explicitly displayed in **Figure 3**, the prescription-level isodose would have been overcovered by 3.9 cm³ in fraction 21 without adaption. However, with adaption, the size of the radiation treatment field decreased with the targets, sparing the areas where the tumor regressed. Note that the patient was treated with the adaptive plan for 22 out of 25 fractions. The nonadaptive fractions were delivered on fractions 2, 3, and 5.

The patient tolerated treatment well and had an uncomplicated recovery. He was evaluated regularly in an outpatient clinic during the 5-week course of his treatment, and apart from preexisting restriction in physically strenuous activity due to advanced age, he tolerated the treatment well. He showed no signs of radiation dermatitis or gastrointestinal toxicity and thus required no additional pharmacotherapies. After the completion of radiation therapy, MRI and CT scans confirmed clinical regression of disease from 795.5 cm³ at induction of therapy to 217.8 cm³.

Discussion and Conclusions

The optimal management for patients with seminoma is continuing to evolve with increasingly tailored treatment with the dual goals of maintaining excellent oncological outcomes while mitigating potential treatment-related effects of therapy such as secondary malignancy. Considering recent clinical data including SAKK 01/10, there has been renewed interest regarding the addition of focal radiation with reduced intensity chemotherapy for stage 2A/B patients in concordance with the above directives.⁵ Adaptive radiation has the potential to further improve the therapeutic ratio for these patients as well as those who are not able to receive systemic therapy by reducing radiation doses to organs at risk including the bowel.^{3,6}

While seminomas are known to be radiosensitive neoplasms, surgical resection and chemotherapy are both preferred to radiation in most young patients due to the risk of late effects, including secondary malignancy. Given the patient's renal impairment and age, radiation therapy was recommended as the favored curative intent

Figure 2. Absolute and relative target change, with fraction zero showing volumes at simulation

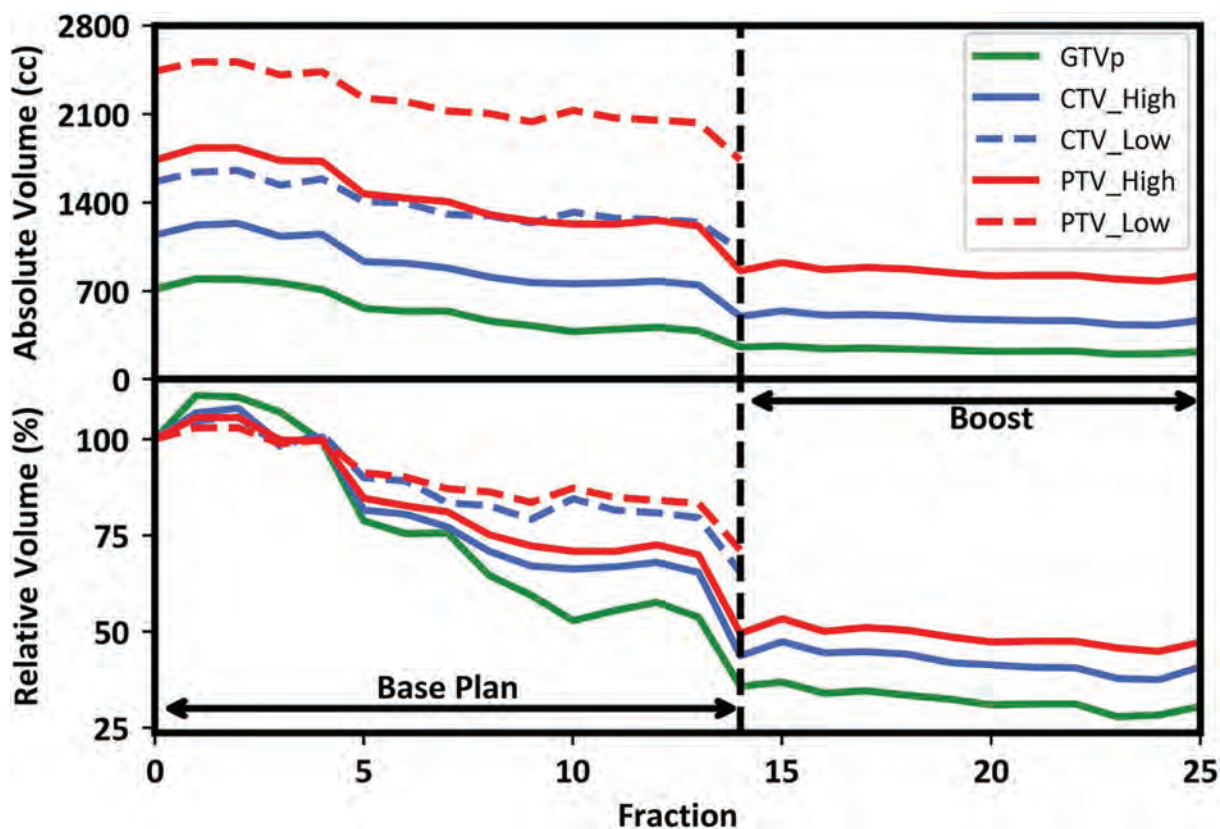
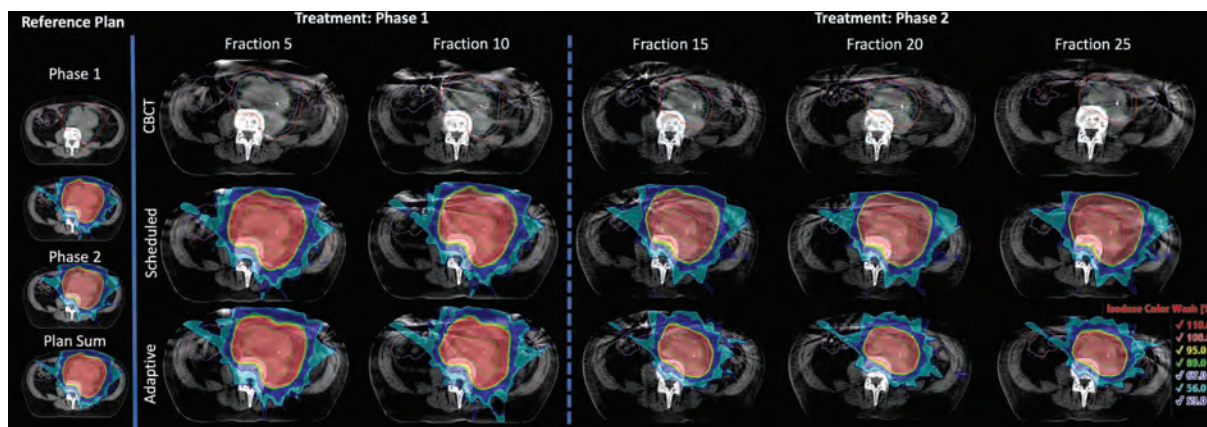


Figure 3. Isodose color wash from reference plans and subsequent fractions as seen on the planning CT and adaptive CBCTs, respectively. The GTVp is shown in green, CTV_High and CTV_Low in blue, PTV_High and PTV_Low in red, and bowel in purple. Starting from fraction 15, which was the first fraction for phase 2, only GTVp, CTV_High, and PTV_High are shown. Relative values for isodose color wash correspond to 49.5, 45, 42.75, 40, 30, 25.2, and 23.9 Gy when shown on the plan sum.

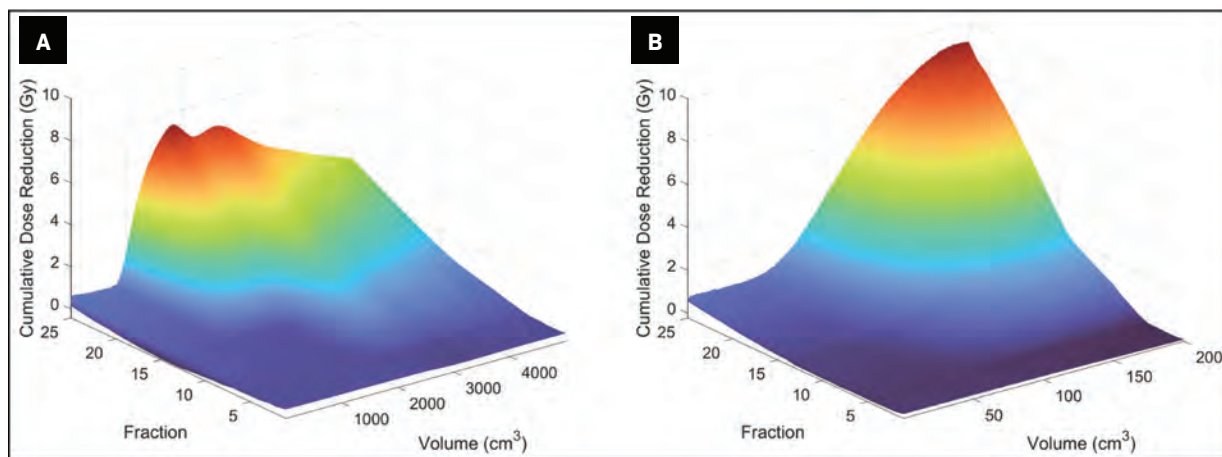


modality⁷. Additional considerations for treatment planning involved implementing a dose of 45 Gy rather than the lower doses of 30 or 36 Gy typically employed for

bulky stage 2B disease and stage 2C disease, with tumors measuring less than 10 cm.⁸ The rationale for escalating beyond 36 Gy was established prior to the development

of modern chemotherapy and lies in the benefit for patients with a larger treatment volume who are ineligible for chemotherapy and old enough that an exposure of 45 Gy to organs at risk

Figure 4. Surface plot of volume receiving cumulative dose reduction equal to cumulative difference between scheduled and adapted — ie, reference plan recalculated on daily anatomy — as a function of fractions for total body (A) and bowel (B)



would pose a low risk of late adverse effects such as secondary malignancy. This dose escalation is similar in practice to lymphoma dosing where escalation beyond 30-36 Gy to 40-50 Gy can be reasonably considered in select patients.^{9,10} However, the most impactful consideration was the prediction that this large mass in close proximity to a significant portion of the bowel would shrink rapidly during treatment, leaving nearby bowel at risk for toxicity from exposure if an adaptive plan were not implemented. Classically, retroperitoneal radiation therapy is associated with severe nausea, and the degree of nausea is thought to have a directly proportional relationship with the amount of bowel exposure. Therefore, the benefit of utilizing adaptive radiation planning in this patient proved to be the dramatic reduction in bowel and body exposure, which might be responsible for the patient's reported absence of nausea. **Figure 4** shows the cumulative dose sparing as a function of volume and fraction number during adaptive therapy. This sparing is calculated as the difference between the scheduled plan, which represents the therapy that the patient

would have had without adaption, and the adapted plan, which was administered to the patient. Note that the tumor enlargement between simulation and the first fraction was anticipated, and fraction 1 was adapted to account for this growth via measurements from CT imaging taken immediately prior. **Figure 4** shows that after about the first week of treatment at fraction 5, sparing was noticed across several volumes of bowel and body. After fraction 25, the dose given to the most exposed 50 cc of the bowel — likely the closest segment of bowel to the PTV — was reduced from approximately 4500 cGy to 3500 cGy. If expanded to the most exposed 200 cc closest to the PTV received, a 9000 cGy exposure to organs at risk could be avoided. Reasonably asserting that this number approximates the 45 Gy prescription dose in the scheduled plan, it follows that this segment of the bowel received approximately 36 Gy with the adaptive plan (**Figure 4**). The use of adaptive radiation in lieu of the standard approach made possible a significantly lower dose delivery to the body, specifically the bowel.

Tumor regression kinetics for neoplasms traditionally treated with

radiation therapy have not been elucidated, so an additional benefit of online adaptive planning is that treatments are continually refined to a shrinking tumor volume. Therefore, when a patient has subpar candidacy for standard treatment methods, adaptive radiation therapy may be a worthwhile option for patients with radiosensitive neoplasms where organs at risk are predicted to accumulate a higher exposure as tumors regress. Further exploration is needed to elucidate trends in the kinetics of tumor regression in radiosensitive neoplasms, which could prove beneficial in an effort for stewardship of the Ethos machine and judicious patient scheduling. Additionally, establishing trends in tumor regression kinetics may justify the addition of an adaptive modification for offline modalities when an online manner is not feasible.

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Radiate and Educate: Empowering Future Physicians Through an International Radiation Oncology Student Newsletter

Anthony L. Alanis, BS;^{1*} Mary Mahoney, MD;² Aseem Panghal, MBBS;³ Laura Maule, BS;⁴ Zachary McSween, MSc;⁵ Colin McNamara, FNP;⁶ Sylvia Choo, BA;⁷ Bahareh Sharafi, MD;⁸ Joshua Qian, MD;⁹ Alexys Gayne, BS;⁶ Drew T. Bergman, MD;⁹ William Tyree, BS;¹⁰ Hamaad Gohar, MHA;¹ Jillian R. Gunther, MD, PhD¹¹

Abstract

Background: The field of radiation oncology (RO) is frequently overlooked by medical students due to limited exposure during traditional medical school curricula. Initiatives aimed at increasing exposure while creating opportunities for medical student engagement are vital. Here, we present the inception, 1.5-year progress, and future goals of a student-led RO newsletter, *RadOnc Student Scan*, published by *Applied Radiation Oncology* (ARO), a quarterly journal for radiation oncologists and clinical specialists who treat cancer patients.

Newsletter Impact on Medical Student Education: The *RadOnc Student Scan* newsletter, crafted by medical student editors, is published quarterly on the ARO website, posted on social media (X, LinkedIn, Facebook, Instagram), and emailed to subscribers. The newsletter's educational impact was measured by social media and email interactions, and participation in publishing and networking opportunities. As of August 28, 2024, a team of 13 medical students from 7 medical schools across 3 countries published 7 issues of the *RadOnc Student Scan* newsletter. Issues included RO key concept reviews, interviews with faculty (7) and residents (3), summaries of recent articles (33), educational resources, and career development opportunities. Since the establishment of the newsletter, 33 unique publishing opportunities were created for student editors. As of February 2024, 3 issues of the newsletter garnered an average viewership of 1296 on X and 591 on Facebook, and 1 issue garnered 145 views on Instagram. For each journal publication emailed to subscribers, there was an average of 6 clicks on the newsletter link.

Discussion: The *RadOnc Student Scan* newsletter is a novel method of potentially increasing medical student exposure to RO. In addition to providing content for readers, the newsletter allowed editors to learn about RO while gaining valuable publishing and networking opportunities. Plans include further medical student recruitment as well as content development and readership analysis using an embedded QR code.

Keywords: radiation oncology, medical education, newsletter, professional development, scholarly activity

Affiliations: ¹University of Texas Rio Grande Valley School of Medicine, Edinburg, TX. ²Department of Radiation Oncology, Fox Chase Cancer Center, Philadelphia, PA. ³Government Medical College and Hospital, Chandigarh, India. ⁴Drexel University College of Medicine, Philadelphia, PA. ⁵Saint George's University School of Medicine, West Indies, Grenada. ⁶Geisel School of Medicine at Dartmouth, Hanover, NH. ⁷University of South Florida Morsani College of Medicine, Tampa, FL. ⁸FIU Herbert Wertheim College of Medicine, Miami, FL. ⁹Memorial Sloan Kettering Cancer Center, New York, NY. ¹⁰LMU-Debusk College of Osteopathic Medicine, Harrogate, TN. ¹¹Department of Radiation Oncology, University of Texas MD Anderson Cancer Center, Houston, TX.

Corresponding author: *Anthony L. Alanis, BS, University of Texas Rio Grande Valley School of Medicine, Edinburg, TX. (anthony.alanis01@utrgv.edu)

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Background

Exposure to radiation oncology (RO) during medical school is limited.^{1,2} In many US medical schools, the preclinical curriculum does not include any substantial exposure to RO.² A decline in applications to RO residency and concurrent record high numbers of unmatched positions compared with historical trends have motivated many in the field to advocate for increased exposure to RO during medical school.³ Educational interventions aimed at supplementing the medical school curriculum have shown promising results.⁴ However, the lack of existing RO departments and faculty at many institutions makes these activities difficult to host.

Stepping outside of institutional limitations, new, successful methods of exposing medical students to RO have been developed. These include educational podcasts, blogs, asynchronous lectures, and small group discussions.^{5,6} While interventions may educate students as an audience, students are also capable of creating educational opportunities of their own.

Inspired by the creativity and positive results of these novel educational resources, we aimed to create the *RadOnc Student Scan* newsletter to engage medical students with RO (**Figure 1**). Unlike previous interventions created for this purpose, the newsletter is crafted by only medical students, and each student learns about RO while creating RO-related content. We used social media and email interaction metrics to assess the educational impact on readers of the newsletter. Publishing and networking opportunities were used to quantify student editor engagement with RO through editing the newsletter. By contributing content for the newsletter, each student editor would engage with RO throughout the editorial process. Student editors networked with faculty and residents by inviting them to participate in the Question and Answer (Q&A) section of the newsletter. We discuss future plans for editor recruitment, content development, and readership analysis using a newly added QR code to the newsletter.

Newsletter Impact on Medical Student Education

Inception, Dissemination, and Impact Assessment

The *RadOnc Student Scan* newsletter, published by the *Applied Radiation Oncology* (ARO) journal,

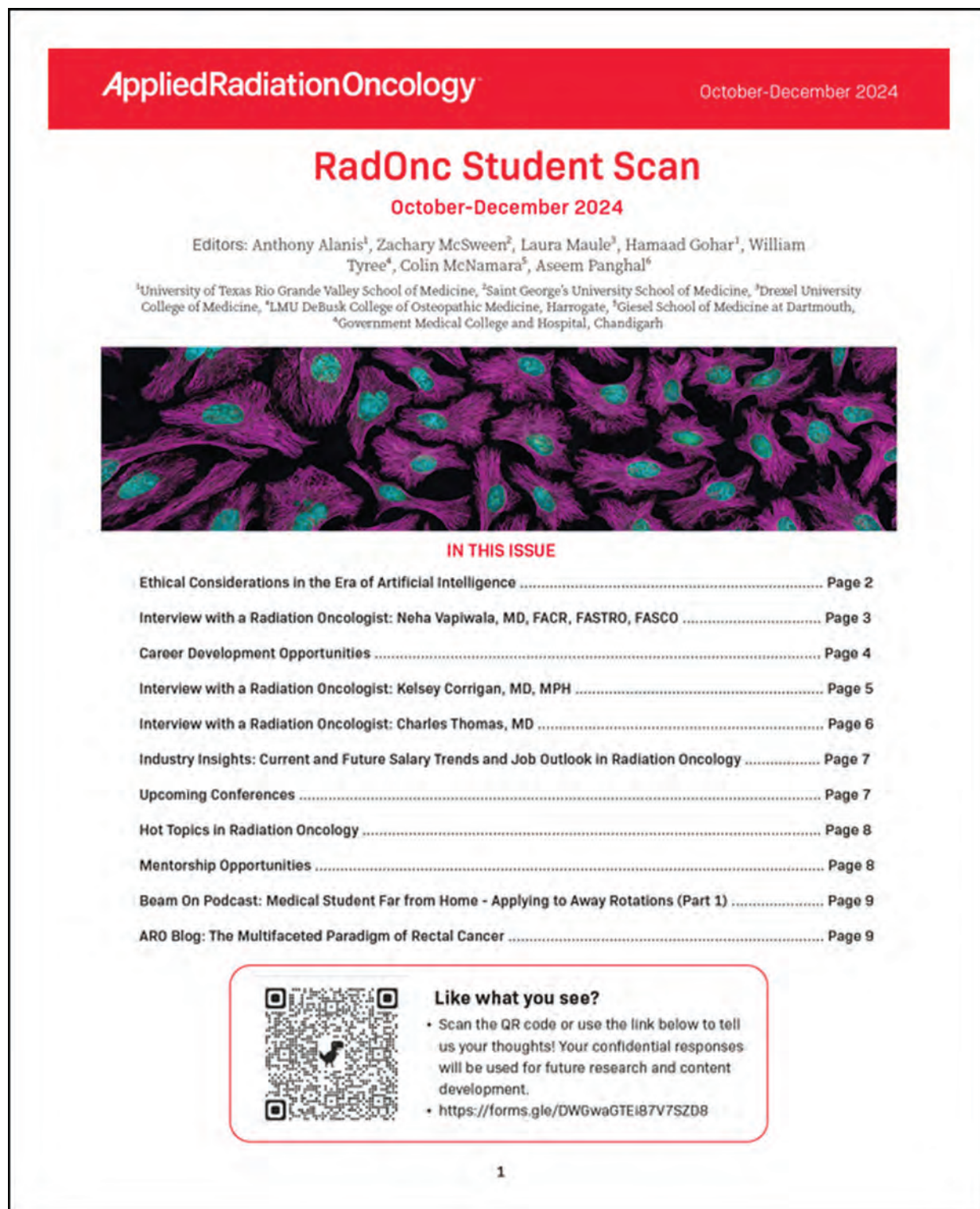
was created by 3 medical students (notably, all without a home RO program), to increase awareness and education about RO among medical students across the country. The founding medical student editors created the outline for the newsletter and a rotating section assignment schedule that provided medical student editors with nearly equal numbers of publishing and networking opportunities per year. Published issues included RO key concept reviews, interviews with RO faculty (7) and residents (3), summaries of recent articles (33), educational resources such as podcasts and blogs, and advertisements for networking opportunities like away rotations, conferences, and society memberships (**Figure 1**). The editors, with approval by ARO, decided on a quarterly publication schedule to maximize publishing opportunities for students and newsletter publicity. After review by the editorial board of ARO, each issue was electronically published on the ARO website, emailed to ARO subscribers, and linked in posts on X (formerly Twitter), Facebook, LinkedIn, and Instagram. The educational impact of the newsletter was assessed by collecting data on social media viewership and engagement (likes, shares, comments), email interactions (opens, clicks), and the publishing and networking opportunities (including Q&A features) created for editors throughout all issues.

Publication and Networking Data

As of August 28, 2024, the *RadOnc Student Scan* newsletter has 7 published issues written by a total of 13 student editors representing 7 schools and 3 countries. In 2023, 4 issues were published, each containing 3 sections that students could edit, yielding a total of 12 publishing opportunities for the year. In 2024, 21 additional publishing opportunities were created for a growing student editor team and expanding newsletter. Since the establishment of the newsletter, there have been 7 interviews with RO faculty and 3 interviews with RO residents. Publishing and networking opportunities were used to assess student engagement with RO. By providing content for the newsletter, each student editor became actively involved in RO through the editorial process. They also connected with faculty and residents by inviting them to contribute to the newsletter's Q&A section.

Newsletter Email Data

ARO, published quarterly, is announced by email to a list of approximately 4400 subscribers. On average, half of those emails are opened, with a

Figure 1. Overview of the *RadOnc Student Scan* newsletter (sixth issue).

click-through rate of 168 on all content and an average of 6 clicks on the *RadOnc Student Scan* newsletter. It is not known whether the viewers of the newsletter are medical students.

Social Media Engagement Data

The engagement data are presented in **Table 1**. For X, the average number of views/impressions per post was 1296 ($n=3$), and the average number of engagements (likes/shares/comments) per post was 24 ($n=1$, 4.22% engagement rate). For Facebook, the average number of reach/impressions per post was 591, and the average number of engagements per post was 6 ($n=3$, 1.81% engagement rate). For Instagram, the number of impressions for 1 post was 145, and the number of engagements was 5 (3.4% engagement rate). Social media data lacked information about whether a user was a medical student or whether they successfully accessed the newsletter via social media.

Discussion

Here, we present the inception, dissemination, and impact of the *RadOnc Student Scan* newsletter. To our knowledge, the *RadOnc Student Scan* newsletter is the world's first international, student-led RO newsletter. The newsletter was written with the primary goal of exposing medical students globally to the field of RO and the secondary goal of fostering a community of student editors engaging with academic RO opportunities early in their career. The student-led nature of this initiative allows authors to break down the complexity of RO to an audience unfamiliar with it, with the intent of increasing student engagement and interest in the field. We observed successful dissemination of the newsletter via email, social media, and publication on the ARO website with student editors engaging with RO content throughout the editing process.

Prior efforts have been made to address the gap in RO education during US medical education. Interventions at the institutional level such as RO-specific lectures have supplemented the standard curriculum.⁶ One study evaluated the feasibility of a 1-day "micro-clerkship" in RO during related clerkships such as medical oncology, palliative care, and radiology.⁴ Of those 97 students across 2 years, 98% found the experience valuable, and nearly half expressed increased interest in pursuing a longer rotation in RO. Similarly, one study reported that 86% of students became interested in

RO after having a single 1-hour introductory lecture by a radiation oncologist.⁷ However, these strategies may be limited by institutional factors, including curricular time restrictions, the availability of a radiation oncologist or department, and the presence of a student interest group.

Innovative educational initiatives in RO that are available to students outside of the traditional medical school curricula are critical. Providing virtual opportunities for medical students to access RO education could help overcome socioeconomic obstacles, including the cost of attending away rotations, or geographic constraints such as proximity to an RO residency program. Podcasts have proven to be a valuable educational tool in medical education, with RO-specific podcasts demonstrating significant engagement and growth.⁵ Within 30 days of initiation, the first educational RO podcast showed a 585% increase in listenership across 53 countries and an 81.4% engagement rate, highlighting a clear demand for supplemental learning resources. Additionally, small group discussions have successfully piqued interest in the field, with one study suggesting that such sessions could triple interest in RO by increasing knowledge of patient care and the critical roles radiation oncologists play in oncology care.⁶ These studies illustrate how unconventional educational resources could boost exposure to RO among medical students. Building on this momentum, we constructed a student-led newsletter to engage students with RO as both readers and content creators, and form a community of aspiring radiation oncologists.

The *RadOnc Student Scan* newsletter generated an abundance of publishing and networking opportunities for the student editors, benefitting both US and international medical students with and without a home RO program. The Q&A section of the newsletter provided opportunities for student editors to meet RO faculty and residents from around the world. We anticipate that this type of networking opportunity could potentially enhance future residency application success for the students through these facilitated introductions with leaders in the RO field.

Planned improvements for the newsletter include expanded readership data collection, content development, and creative editor recruitment strategies. We are gathering readership data and suggestions for content development using a newly added QR code on the front page of our newsletter

Table 1. Social Media Interactions Stratified by Platform

INTERACTIONS BY SOCIAL MEDIA PLATFORM	FACEBOOK (I = 3)	X (I = 3)	INSTAGRAM (I = 1)
Average reach/views (n)	591	1296	145
Average engagements (n)	5.7	14.7	5.0
Average engagement rate (%)	1.8	2.6	3.4
Abbreviation: i, number of issues posted on the source.			

(Figure 1). A challenge we faced was being unable to identify if medical student readers were accessing our newsletter via social media, which limited our ability to report the newsletter's impact on medical student education. With the QR code, we are now able to collect data about the readers' educational background and impression of the newsletter based on their understanding of RO. Importantly, we ask readers about the influence of the newsletter on their decision to pursue a career in RO, something we are excited to report in subsequent studies. Data from the QR code will also guide decisions about future newsletter content with the goal of maximizing reader engagement. In addition to previously used online platforms for editor recruitment and readership expansion, we are seeking to increase the publicity of the newsletter at in-person events such as the American Society for Radiation Oncology (ASTRO) conference and Radiation Oncology Education Collaborative Student Group (ROECG) symposium. We also encourage editors to share the newsletter with their school's student interest groups, research labs, and student affairs offices. To sustain the newsletter moving forward, an editorial board for the newsletter consisting of a copy editor, content coordinator, editor coordinator, and research coordinator was formed to share the responsibilities of drafting each issue. A potential barrier to increasing exposure to RO through the newsletter would be insufficient editors, but so far there are increasing numbers of editors with ties to student interest groups at their schools drawing more attention to RO.

Conclusion

The *RadOnc Student Scan* newsletter, published quarterly since January 2023, has proven to be a novel strategy for engaging medical students

from across the world with RO. This opportunity for medical student editors to learn about RO while gaining valuable publishing and networking opportunities has resulted in an appealing and productive educational intervention. To propel the forward momentum of the newsletter, recruitment of editors, analysis of readership, and creative dissemination methods will continue to be pursued. The newsletter's success can serve as a model for other underrepresented specialties looking to broaden exposure to medical students.

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Building Barriers or Bridges? How Health and Public Policy Modulate Access to Care

Justin M. Barnes, MD, MS



Dr Barnes is a PGY-5 chief resident in the Department of Radiation Oncology, Washington University School of Medicine and Siteman Cancer Center.

Days after moving to St. Louis, I was shocked to see a 20-year difference in life expectancy between neighborhoods just a few miles apart, correlating with drastically different racial and socioeconomic profiles. I have since learned that disparities in health outcomes, including cancer outcomes, exist by race, ethnicity, socioeconomic status, neighborhood, and many other factors, and that these disparities are ubiquitous. Differences in outcomes can be boiled down to discriminatory policies and practices that, downstream, lead to adverse living conditions and unmet social needs, which can impact health directly (eg, pollution), impair healthy behaviors (eg, food deserts), and inhibit access to health care (eg, limited health literacy, time, financial resources).

Without addressing the root of the problem — upstream discriminatory policies and practices — even the most valiant efforts within our institutions and with our community partners will have a blunted impact. We need to fight discriminatory policy with rectifying policy. Unfortunately, we will unlikely be able to fix in one fell swoop all the injustices that have accumulated over centuries, but we can move the needle.

Intelligent health policies that disrupt financial barriers, such as expanding Medicaid eligibility to more low-income adults, limiting insurance plans that offer subpar consumer protections, and other efforts that minimize cost-sharing, have been increasingly shown to improve health care access and even improve survival.¹ However, some patients face high costs that can disincentivize needed care, others face restrictive coverage that can delay or limit needed care, and some lack consistent coverage.² These represent important

issues where advocacy and policy solutions are needed.

Similarly, public policies that more directly address unmet social needs with financial resources (eg, federal and state assistance programs such as food stamps, paid leave, tax credits) are also increasingly linked with improved health care access and survival.³ In addition to optimizing policies that offer immediate aid to individuals facing unmet social needs, efforts to modulate upstream factors that promote upward mobility, such as expanding access to education and improving neighborhood safety and health, will be crucial.

Our patients facing socioeconomic disadvantages need help to overcome barriers to access through policies that impact the social determinants of health. Despite the chaos and tension in the US political system, I hope that we can move the needle to improve health. As physicians — and stewards of health — I feel it is our responsibility to advocate and vote for policies that break down barriers to care and, perhaps, take a seat at the table to shape such policies.

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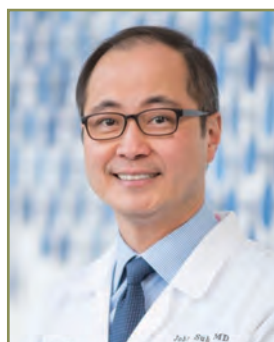
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Corresponding author: Justin M. Barnes, MD, MS, Department of Radiation Oncology, Washington University School of Medicine, 660 S. Euclid Ave, MSC 8224-35-LL, St. Louis, MO 63110. (justinbarnes@wustl.edu)

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