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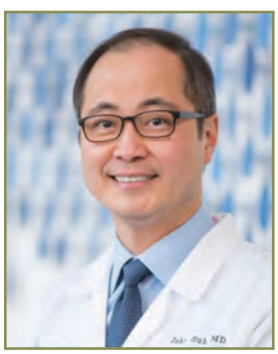

John Suh, MD, FASTRO, FACR

Dear Colleagues:

We are pleased to let you know that our journal and community of registered radiation oncologists have continued to expand over the last several years. We appreciate your support and, as part of our mission to foster a community where peers share practical solutions in the clinical setting, *Applied Radiation Oncology* is issuing a call for clinical cases, review articles and research articles.

We are looking for authors to write and submit on topics that include (but are not limited to): imaging, contouring, target delineation, treatment planning, patient immobilization, organ tracking, safety and quality, and other timely topics essential to the discipline. Important to note is that review articles accepted for publication may be accredited for Continuing Medical Education (CME). Submissions will undergo a double-blind peer review process through our external peer review panel.

If you or your colleagues have an interesting case, review article or research paper for publication consideration in *Applied Radiation Oncology*, please read our Submission Guidelines. As a reference for the types of articles published in *Applied Radiation Oncology*, visit appliedradiationoncology.com and browse our archives.

This is a wonderful opportunity to impart your knowledge to your peers and we look forward to your submissions.

Sincerely,

John Suh, MD, FASTRO, FACR
Editor-in-Chief, Applied Radiation Oncology

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.

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FOCUS: PHYSICIAN WELL-BEING

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The Toll of Burnout on Radiation Oncologist Well-Being

John H. Suh, MD, FASTRO, FACR

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.

For many, December marks a time of joy, with a packed calendar of gatherings and festive traditions. But with a long list of holiday plans and expectations, it can quickly shift to a month of high stress and its unwelcome partner, burnout.

Unfortunately, burnout is a well-known syndrome among physicians regardless of time of year and many of us have witnessed its depleting effects firsthand. Worse, repercussions such as emotional exhaustion and depersonalization can undermine our most important goal—patient care.

Despite being widely documented among physicians, the prevalence of burnout among radiation oncologists is noticeably lacking in the literature. Yet, it is especially needed, particularly given the field's oncology-specific components. Helping to bridge this gap is the CME-approved article, *A Narrative Review on Radiation Oncology Physician Well-being in the United States*. This important article examines burnout in various career stages of the specialty, offering helpful strategies to battle this crippling problem.

Complementing the review is the article *Well-being Within a Radiation Oncology Department: A Single Institution's Experience in Creating a Culture of Well-being*, which chronicles a grassroots effort of the Mayo Clinic residency program that bloomed into a successful department-wide culture of reduced burnout. Backed by funding and strategic planning, they achieved this by mitigating pain points, building camaraderie, and implementing numerous ideas, from fitness challenges to revamped call schedules. We hope you find inspiration from this encouraging work.

This month's Resident Voice editorial, *Pennies to Policy: The Importance of Resident Financial Fluency*, discusses the related topic of financial education during residency and its potential role in reducing aspects of burnout during training and early career. This excellent column also describes how such efforts can promote empathy and advocacy for patients facing financial toxicity in a complicated health care system.

Further exploring clinician well-being is our recent blog, *Virtual Reality and Burnout Prevention: Turning Wellness for Health Care Workers Into a Reality*. This thoughtful write-up shares how a novel technology can reduce burnout, but only when backed by cultural change that embraces its use. Learn more at https://appliedradiationoncology.com/aro-blog (scroll down if needed).

We are also pleased to feature two research articles and a case report in the issue, which discuss insightful findings on the topics of total delivered dose variation in head and neck cancer treatment, prostate brachytherapy, and MR-guided therapy for hepatocellular carcinoma.

In other news, we are excited to welcome Mustafa Basree, DO, MS, as the new Association for Radiation Oncology Residents (ARRO) representative for *ARO*. Dr Basree is a PGY3 radiation oncology resident in the Department of Human Oncology, University of Wisconsin School of Medicine and Public Health, and serves as ARRO's junior chair of Education. In his role with *ARO*, Dr Basree will coordinate the Resident Voice editorial and assist with additional publishing endeavors to elevate resident voices and enhance their overall experience. He succeeds Amishi Bajaj, MD, a radiation oncologist at Northwestern Medicine, and past chair of ARRO, who was a great help to *ARO* and a true pleasure to work with over the last year.

As we move ahead to 2024, we thank you for another year of support and invite you to become involved in *ARO*'s many editorial opportunities, including article submissions, peer reviews, blogs, podcasts, webinars, and more.

We wish you a joyful (but not overbooked!) holiday season and a peaceful, fulfilling new year!

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A Narrative Review on Radiation Oncology Physician Well-Being in the United States

Description

Despite limited studies on burnout among radiation oncologists in the United States, especially when compared with data from other countries, there is a prevalence of burnout among radiation oncologists of all career stages, including trainees, attendings, program directors, and academic chairs. This narrative review summarizes articles reporting on burnout and well-being among attending and resident radiation oncologists in the United States, examines burnout at career stages, discusses the impact of COVID-19, and provides strategies to reduce burnout in the radiation oncology field.

Learning Objectives

Upon completing this activity:

1. Physicians will understand the state of well-being and repercussions of burnout among radiation oncology attendings and trainees in the United States.
2. Physicians will be able to adapt strategies that can reduce burnout, increase personal fulfillment, and create a culture of well-being within the radiation oncology setting.

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Target Audience

- Radiation oncologists
- Related oncology professionals

Commercial Support

None

Accreditation/Designation Statement

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A Narrative Review on Radiation Oncology Physician Well-Being in the United States

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Abstract

Objective: To summarize articles reporting on burnout and well-being among attending and resident radiation oncologists in the United States in a narrative review.

Methods: PubMed was searched for peer-reviewed articles from 2010 through 2023 reporting on burnout and well-being among radiation oncologists in the United States. Each study was critically reviewed and included if it reported primary data utilizing a validated tool to measure burnout among radiation oncologists. A subset of high-quality studies was included.

Results: There are limited studies regarding burnout among radiation oncologists in the United States, especially when compared with data from other countries. Despite these limitations, there is a prevalence of burnout among radiation oncologists of all career stages, with rates of burnout ranging from 30% to 63%. A few smaller studies have explored interventions to decrease burnout and enhance professional fulfillment among radiation oncologists. Best practices to enhance professional fulfillment for radiation oncologists include optimizing support structures to alleviate physicians of administrative duties; including physicians in departmental decisions that affect their work; providing dedicated time for research; promoting work-life balance and job satisfaction; providing support for trainees, including psychological tool-focused approaches and humanities exercises; and encouraging mindfulness.

Conclusions: A large cross-sectional study is warranted to further explore modern burnout rates and causes among radiation oncologists in the United States. This may inform areas of advocacy to improve professional fulfillment among radiation oncologists.

Keywords: radiation oncology; well-being; wellbeing; wellness; burnout, physicians

Introduction

Radiation oncology (RO) is a rewarding yet challenging career, where physicians blend advanced technology and compassionate care to treat patients with cancer. Daily, radiation oncologists make complex decisions, balance treatment effectiveness and side effects, confront mortality, keep pace with rapid technological and medical advancements, and engage in emotionally charged conversations.[1] These oncology-specific elements, combined with recognized stressors of being a physician, including time demands, lack of autonomy, burden of electronic medical records, productivity and reimbursement models, and misalignment of values between providers and practice leadership, can lead to burnout.[2]

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Burnout is characterized by emotional exhaustion (EE), depersonalization (DP) (ie, feeling detached from or callous toward patients), and a sense of reduced personal accomplishment (PA); physicians and physicians-in-training experience burnout at greater rates than the general population.[3,4] Consequences may include inadequate patient care, professional ineffectiveness, and excessive job turnover contributing to financial strain on health care systems. Unfortunately, burnout also contributes to physician harm, including substance abuse, clinical depression, and suicidality.[5] Although physician burnout is widely documented, little is published on its prevalence among radiation oncologists.

Burnout is particularly relevant to the field of RO as additional stressors have recently arisen, including uncertainty regarding future earnings, with government exploration of alternative payment models,[6] declining reimbursements for specialists, and job market concerns.[7,8] Despite efforts to assure alignment between future growth and training,[9] these concerns have presumably contributed to reduced ability to recruit trainees to the field as evidenced by the increased number of unfilled residency positions. In this narrative review, we provide an overview of well-being among RO attendings and trainees in the United States as well as explore potential interventions to improve the state of mental health in the specialty.

Search Strategy and Selection Criteria

We searched PubMed for peer-reviewed, English-language articles published between 2010 and July 2023 using the search terms *oncologist* OR *oncology* AND *radiation* AND *burnout* OR *depression* OR *depressive disorder* OR *mental health* OR *depersonalization* OR *distress* OR *anxiety* OR *emotional exhaustion* OR *well-being* OR *wellbeing* OR *wellness*. We identified additional studies from the reference lists of these articles. Each study was critically reviewed. Studies examining patient mental health were excluded. Of 52 reviewed articles, a total of 20 cross-sectional and 2 prospective interventional studies were included. Of the cross-sectional studies, 7 were thought to be particularly impactful as they included large cohorts that reported primary data utilizing a tool to measure burnout among radiation oncologists in the United States (**Table 1**). The remaining 13 cross-sectional studies included 8 describing burnout among international radiation oncologists, 3 exploring the relationship between burnout in RO with other factors in small cohorts, and 2 describing burnout among medical students and residents of all specialties. We included 2 high-quality prospective studies that were thought to be most pertinent and insightful to describe potential interventions for RO trainees. This article is informed by our narrative review and experience.

Burnout Among Career Stage

Medical school applicants and matriculants are stronger each year with higher Medical College Admission Test scores and Grade Point Averages.[10] Accepted students tend to be highly intelligent, altruistic, and have a strong commitment to the field of medicine. At matriculation, mental health profiles of medical students are similar to, if not more favorable than, those of other college graduates.[11,12] Shortly after orientation, the risk of developing burnout and depression during medical school increases, with rates approaching 50% and 25%, respectively. Contributing factors include personality traits, maladaptive perfectionism, type A personalities, anger suppression, stress, and curricular factors.[11] A large multi-institutional study reported 11.2% of medical students experience suicidal ideation, which is higher than individuals of similar age in the general US population (6.9% among 25-34-year-olds).[13] Unfortunately, the prevalence of distress does not decrease as medical students adapt to the challenges of medical school.[11,13]

In the transition from medical school to residency training, responsibilities increase, leading to increased rates of reported stress and burnout. More than 60% of medical trainees experience burnout in the United States, significantly higher than age-matched individuals in the general population.[12] In residency, trainees often experience inadequate sleep, difficulty with work-life integration, lack of autonomy, time demands, difficulty finding meaning in work, lack of social support (especially for those training at locations away from family and friends), crippling student debt, difficulty caring for sick patients, and future career uncertainty.[1,12] These factors make residents especially vulnerable to burnout.

Although each training program faces unique challenges, burnout has been shown to affect trainees of all specialties.[5] Radiation oncology residents were included in the 2012 Radiation Oncology Workforce Survey conducted by the American Society for Radiation Oncology (ASTRO). Trainee-specific sources of stress included difficulty finding research opportunities and job placement.[14] A survey assessing burnout among RO residents in the United States was performed in 2016 using the Maslach Burnout Inventory

Table 1. Select Cross-Sectional National Studies Including Radiation Oncologists

CITATION	YEAR OF STUDY	INCLUDED SUBJECTS	BURNOUT INSTRUMENT UTILIZED	NO. OF SUBJECTS	NO. OF RESPONDERS (RESPONSE RATE %)	MEAN EE SCORE	HIGH EE (%)	MEAN DP SCORE	HIGH DP (%)	OVERALL BURNOUT*, *N* (%)
Shanafelt[3]	2011	US physicians	MBI	All specialties: 27,276	7288 (26.7)	22.7	37.9	7.1	29.4	3310 (45.5)
				RO: x	RO: 55 (x)	20.5	x	5.2	x	21 (38.2)
Kusano[41]	2012	Academic RO chairs	MBI	87	66 (75.9)	21	25	5.3	10	x (30)
Pohar[14]	2012	RO residents and attendings	Likert scale#	All: 4186	1212 (29)	x	x	x	x	x (47)
				Attendings: 3618	1047 (29)					
				Residents: 568	165 (29)					
Aggarwal[35]	2014	RO program directors	MBI	88	47 (53.4)	21.5	48	7	29	30 (63)
Shanafelt[21]	2014	US physicians	MBI	All specialties: 35,922	6880 (19.2)	25.5	46.9	8.1	34.6	3680 (54.4)
				RO: x	RO: 64 (x)	23.9	x	5.8	x	29 (46)
Ramey[17]	2016	RO residents	MBI	733	232 (31.7)	20.5	28.3	7.1	17.1	x (33.1)
Shanafelt[22]	2017	US physicians	MBI	All specialties: 30,456	5197 (17.1)	23.2	38.7	6.8	27.3	2147 (43.9)
				RO: x	RO: 42 (x)	23.5	x	5.3	x	16 (41)

x Information not available in the manuscript or supplemental materials.

**Defined as high score on the DP or EE subscales of MBI.*

#Not a validated burnout inventory; however, in this review frequency of feeling burned out always, often, or occasionally met the criteria for burnout.

Abbreviations: DP, depersonalization; EE, emotional exhaustion; MBI, Maslach Burnout Inventory; RO, radiation oncology.

—Human Services Survey (MBI-HSS). MBI-HSS is a validated, 22-question survey to measure burnout among those who work in human services; it includes 3 subscales, EE, DP, and PA. The presence of high levels of EE and/or DP has been considered the foundation of burnout in physicians.[3,15,16] In total, 232 of the 733 residents surveyed responded (31.7% response rate). High levels of EE and DP were identified in 28.3% and 17.1%, respectively. Of the responding residents, 33.1% met the criteria for burnout (high EE and/or DP), and 12% had a low sense of PA. Twelve residents (5.9%) responded they felt "at the end of my rope" on a weekly basis or more. There was a statistically significant inverse association between perceived adequacy of work-life balance (odds ratio 0.38; 95% CI 0.17-0.83) and burnout on multivariable analysis.[17] This study was conducted over a decade ago, and current residents likely have additional stressors including variable pass rates on the American Board of Radiology qualifying (written) examinations, perception of job market saturation, future uncertainty, and the coronavirus 2019 (COVID-19) pandemic.[7,8]

Burnout is not specific to students or trainees; attending physicians are at risk of burnout as well. Attending physicians also experience heavy workloads of caring for critically ill oncology patients. Other unique challenges include difficulty finding coverage, productivity targets set by administrators, inefficiency of health care systems, time-consuming documentation requirements, less patient-facing time, lack of autonomy with many treatment decisions dictated by insurance companies, lack of meaning at work, and the fear of malpractice lawsuits.[17–19]

A national study of burnout among US physicians from all specialties was performed in 2011 using the MBI assessment, reporting that 46% of physicians experienced burnout based on either high EE and/or DP levels. Of the physicians surveyed, 55 radiation oncologists responded. Although the percentage of radiation oncologists experiencing burnout was lower than the mean among all participating physicians, the rate was 38% (21 of 55 responders), which is unacceptably high.[3] Burnout rate among radiation oncologists was

higher than the rate of medical and surgical oncologists, 35% and 28% to 36%, respectively.[3,20] The percentage of radiation oncologists reporting burnout increased in follow-up studies by the same group in 2014 and 2017 to 46% (29 of 64 responders) and 41% (16 of 42 responders), respectively, although this increase was not statistically significant.[21,22] The percentage of radiation oncologists satisfied with work-life integration was not statistically different over the years, decreasing from 54.5% (30 of 55 responders) to 44.7% (17 of 42 responders) between 2011 and 2017. Factors contributing to burnout among radiation oncologists could not be identified due to small sample size.

To determine the needs and concerns of the field as well as the prevalence of burnout, radiation oncologists in the United States were surveyed in the 2012 Radiation Oncology Workforce Survey.[14] A 10-point Likert scale was used to assess the frequency that RO attendings and trainees experienced burnout, with a 29% (1047 out of 3618) response rate. Roughly half of radiation oncologists felt burned out always, often, or occasionally. An increasing number of patient consults per year was directly associated with increased frequency of burnout. The top concerns of radiation oncologists in 2011 included documentation, reimbursement, and patients' health insurance coverage.[14] These factors provide areas for which national organizations can advocate on behalf of the workforce; however, concerns have likely changed since this analysis, and the follow-up 2017 Workforce Study and the 2023 ASTRO Workforce Taskforce Review did not address burnout.[9,23]

It is possible that work-life integration is worsening in 2023 compared with when the 2012 Radiation Oncology Workforce Survey was published due to increased at-home demands from the widespread adoption of remote work (eg, tasks involving electronic medical records and contouring), as demonstrated in other fields.[24–26] RO reimbursement is declining while our patients' diseases and treatments are becoming more complex.[27] Recently, there has been increased discussion regarding productivity and reimbursement models, including the new Radiation Oncology Case Rate payment program.[28] Reimbursement changes may put undue pressure on physicians to increase their productivity in other ways.[29–32] Although RO-specific data relating compensation models to burnout have not been reported, compensation plans based on relative value unit (RVU) generation have been significantly associated with high burnout among hematologists and medical oncologists.[33] Physicians may increase their workload when feeling pressure to meet RVU targets, and having more new patients per year has been associated with burnout in RO[14]; in addition, increased patient volume can lead to medical errors.[34] Patient-centered care, including hypofractionation or radiation omission when appropriate, may conflict with financial incentives and departmental expectations for RVU targets. This may lead to slower adoption of evidence-based hypofractionation regimens or overestimating the benefit of radiation or treatments like androgen deprivation therapy, when omission may be appropriate.[30,32] This struggle between financial pressures and patient-centered, up-to-date care can lead to moral injury and decreased professional satisfaction.

Every physician role within an RO department is at risk for burnout, including residency program directors (PDs) and chairs. Radiation oncology residency PDs were surveyed in 2014 using MBI-HSS to assess their rates of stress and burnout,[35] with a response rate of 53.4% (47 out of 88 PDs). Of responders, 11%, 83%, and 6% met the criteria for low, moderate, and high burnout, respectively. Using the burnout definition of high EE and/or DP scores, the rate of PD burnout was 63% (30 of 47 responders), higher than the rate of RO attendings with burnout on the Shanafelt and ASTRO Workforce surveys.[3,14,21,22] Although this is a small study, not having prior experience as a PD correlated with high DP and overall burnout on univariable analysis. Having more years on faculty prior to becoming a PD was correlated with less EE and DP. Dedicated time for PD duties correlated with less EE. There were no significant correlates to burnout on multivariate analysis, likely due to the small sample size. Although 78% reported satisfaction or high satisfaction with being a PD, 85% planned to remain a PD for fewer than 5 years. Major stressors of PDs included Accreditation Council for Graduate Medical Education requirements (47%), administrative duties (30%), and resident morale (28%). As the majority of responders reported planning to remain a PD for fewer than 5 years, this could mean excessive turnover and potential decreased experience or quality of PDs. This study suggests that PDs require additional support, including mentorship and protected time with a goal of increasing professional satisfaction and decreasing burnout. This may lead to enhanced PD retention. This survey was conducted several years ago, and thus did not capture the impact of the sharp decline in medical student applications to RO with many unfilled positions.[36–40] This shift adds additional pressure

for recruitment to their program as a crucial part of the PDs role is to successfully recruit and train future radiation oncologists.

Similar to PDs, members of the Society of Chairs of Academic Radiation Oncology Programs (SCAROP) were surveyed in 2011-2012 using MBI-HSS to determine the prevalence as well as factors contributing to burnout in this cohort.[41] A total of 66 of 87 chairs (76%) responded to this survey, of which 75% and 25% demonstrated moderate and low burnout, respectively. When analyzing the proportion of chairs that had high EE and/or DP scores, 30% met this definition of burnout, which is similar to the rate of RO residents (33%),[17] but lower than the rate of RO attendings (38%-46%)[3,21,22] and RO PDs (60%).[35] On average, responders were working 62.3 hours per week and 79% were satisfied with their current role, which is similar to the PD satisfaction rate.[35] A total of 43% felt their professional roles largely or totally interfered with developing other life goals, and one-quarter felt they were at least moderately likely to step down in the coming 1-2 years; higher EE scores were found among those reporting a moderate likelihood of stepping down. One-quarter of chairs considering stepping down is much lower than the 85% of PDs that planned to stay in their role for at least 5 years; this discrepancy may be attributed to the lower burnout rate among chairs and/or protective factors, such as high rates of emotional intelligence among chairs.[42] Major stressors encountered by academic chairs included budget deficits, faculty recruitment and retention, human resources issues, and balancing the many roles of chair. Chairs have been faced with new financial challenges in recent years as well due to staff shortages during the COVID-19 pandemic, necessitating hiring temporary workers, which is more expensive for departments and not a long-term solution.[43,44] This, coupled with decreased reimbursement rates, leads to chairs making unpopular decisions for departments, such as potential pay cuts or methods to be more financially productive. These financial stressors likely further decrease satisfaction and staff retention.

A follow-up study investigating the relationship between emotional intelligence and burnout among members of SCAROP was performed in 2015.[42] This study utilized the Trait Emotional Intelligence Questionnaire Short Form (TEIQue-SF), a 30-item questionnaire designed to measure global trait intelligence,[45] as well as the abbreviated Maslach Burnout Inventory (a-MBI). Of the 95 academic chairs surveyed, 60 responded (63.2%). The median TEIQue score was found to be 172 out of a possible 210, which is higher than published TEIQue-SF scores of physicians in other specialties, suggesting that RO academic chairs have high emotional intelligence. In this study, higher TEIQue-SF global scores were significantly correlated with lower burnout subscores on a-MBI, including lower EE and DP scores as well as higher PA. This study suggests that emotional intelligence may be protective against burnout.

The Impact of COVID-19

COVID-19 placed unprecedented stress on health care workers across all specialties and practice environments due to work overload, job insecurity, safety concerns, patient deaths, and overall uncertainty.[46] Health care workers of all specialties and roles from 124 institutions across 30 states were surveyed regarding fear of viral exposure or transmission, COVID-19-related anxiety or depression, work overload, burnout, and intentions to reduce hours or leave their jobs between July 1, 2020, and December 31, 2020. Of responding physicians, 1 in 3 intended to reduce work hours and 1 in 5 planned to leave their practice. The University of Texas MD Anderson Cancer Center (MDACC) surveyed their radiation oncologists in May 2020 and found overall decreased burnout using the Qualtrics-based MiniZ burnout survey compared with the year prior.[47] Burnout on the 2020 survey was associated with job-related stress, the COVID-19 pandemic, poor or marginal control over workload, and fears of job security. The majority of employees working from home at least part of the time reported a positive experience, which was associated with reduced burnout.[48] Although MDACC had overall decreased burnout in the early pandemic, institutions' responses to COVID-19 were heterogeneous. The impact of these responses on well-being is underreported.

Strategies to Reduce Burnout and Future Directions

As we have shown, though data are limited, burnout may affect a large portion of radiation oncologists throughout their training and career. Strategic approaches to optimize well-being are needed, and it is important to follow best practices (**Table 2**).[49] The American College of Radiology recently published specific strategies to overcome burnout and enhance professional fulfillment based on existing burnout literature, assigning each category an impact factor reflecting its importance ranked by diverse members of the RO community.[48] The most impactful strategy identified was optimizing support

Table 2. Best Practices for Well-Being in a Radiation Oncology Department

PRACTICE	SOURCE
*Efficiency of Practice**	
Optimize support structures by maintaining adequate multidisciplinary staffing and providing administrative support to alleviate physicians of administrative duties	Beltrán Ponce[49]
*Culture of Wellness**	
Include physicians in departmental decisions that affect their schedules and productivity requirements	Beltrán Ponce[49]
Provide dedicated time for research	Beltrán Ponce[49]
Promote work-life balance and job satisfaction	Beltrán Ponce[49]
Provide support for trainees, including psychological tool-focused approaches and humanities exercises	Gergelis,[48] Khorana[50]
*Personal Resilience**	
Encourage mindfulness	Goodman,[51] Eckstein[52]

**Dimensions of the Stanford Model of Professional Fulfillment.[63]*

structures by maintaining adequate multidisciplinary staffing, providing administrative support to alleviate physicians of administrative duties, including physicians in departmental decisions that affect their schedules and productivity requirements, and providing dedicated time for research to promote recruitment and retention. Other categories with high-impact factors included promoting work-life balance and job satisfaction.

Departmental-level interventions to enhance well-being among radiation oncologists are also warranted. A well-being curriculum combining psychological tool-focused approaches and humanities exercises among residents led to decreased burnout and increased professional fulfillment among residents at 1 institution.[50] Another institution found that narrative-based humanities exercises were well-received by medical and RO trainees, although the effect on burnout was not specifically evaluated.[51] Mindfulness has also been shown to decrease burnout and improve well-being among health care providers[52]; an RO department conducted a survey-based study, which demonstrated that mindfulness was protective against burnout.[53] Providing information on financial well-being was provided as a burnout reduction and wellness strategy for early career and trainee radiation oncologists; however, the impact of this has not been assessed.[54]

Data regarding RO burnout in the United States are lacking compared with other countries[18,55–60] and other oncology disciplines, such as medical and surgical oncology burnout in the United States.[61,62] Due to differences in health care systems and reimbursement models across various countries, international data cannot be a surrogate for the state of well-being for radiation oncologists in the United States. Given the unique pressures facing each specialty, data from medical and surgical oncology in the United States can also not serve as a substitute. In addition, the field of RO has changed greatly over the recent years, suggesting ongoing study is needed. Greater access to work from home offers flexibility, but also results in blurring of professional and personal life, with more work-at-home, after-clinic hours. Declining reimbursement rates, struggles to maintain our workforce, and decreased interest in the field from prospective trainees are all potential contributors to dissatisfaction and burnout. Information regarding radiation oncologist well-being in the United States is outdated and warrants updates to reflect these changes. Current data may serve to squelch inaccurate concerns about the field, which can be amplified on social media and may deter prospective residents.[8]

Future Directions

Surveying the current workforce can inform us of common sticking points across practices to identify the areas we as a field can advocate to change. Having input from current radiation oncologists would guide our professional organizations on which aspects of the specialty to focus their advocacy efforts.

In ASTRO's recently published Workforce Taskforce Review,[9] they note that ASTRO has "a mission to represent and support the success and well-being of RO and its members"; however, as of August 2023, ASTRO does not have a dedicated well-being taskforce. Although creating a taskforce within ASTRO to address the well-being of our physicians would require resources, it is necessary to use the power of our professional organization. The American Society of Clinical Oncology (ASCO) established the Oncology Clinician Well-Being Task Force after the ASCO Ethics Committee held a Burnout and Moral Distress in Oncology Roundtable.[63] This Task Force created a roadmap with 5-year goals to engage in clinician well-being across ASCO activities, broaden clinician resources to support well-being, and promote research to identify clinical and practice needs. We urge our professional organizations to do the

same to advocate for our workforce to improve both professional satisfaction and patient care.

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Well-Being Within a Radiation Oncology Department: A Single Institution's Experience in Creating a Culture of Well-Being

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Abstract

Objective: To summarize the efforts of a single department in addressing burnout among staff and promoting a culture of well-being.

Methods: Surveys from across the department and among individual workgroups were used by leadership to develop methods to address burnout and promote well-being. Committees with members from diverse department roles were also formed to further develop initiatives to create a culture of well-being.

Results: Based on the feedback from surveys, individuals, and committees, we have established a strong culture of well-being within our department. These efforts extend not only to addressing pain points in the work day but also to initiatives creating a sense of camaraderie among staff members across the department.

Conclusion: With the support of institutional and departmental leadership, it is possible to create meaningful improvements in reducing burnout, increasing personal fulfillment, and creating a culture of well-being.

Keywords: well-being, burnout, physician burnout, radiation oncology

Introduction

Burnout is a syndrome resulting from chronic workplace stress that has not been successfully managed, characterized by emotional exhaustion, depersonalization, and a reduced sense of personal accomplishment.[1] Physician burnout has been widely studied and is associated with substance abuse, clinical depression, suicidality, reduced quality of patient care, poor patient outcomes, medical errors, lower patient adherence to physicians' recommendations, and patient dissatisfaction.[2] In addition to physicians, all members of the radiation oncology team are at risk for burnout. A meta-analysis consisting of 11 studies on burnout in radiation therapists found a pooled prevalence of emotional exhaustion, depersonalization, and reduced sense of personal accomplishment for radiation therapists at 38.7%, 21.5%, and 28%, respectively, putting radiation therapists at medium to high risk for burnout.[3] Medical dosimetrists are also at risk for burnout, with staffing shortages and high planning workload being

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associated with reduced feelings of personal accomplishment.[4] Medical physicists have also reported high levels of stress and burnout,[5] with one study reporting rates of 33% to 36% of physicists within their department endorsing burnout symptoms when surveyed over 2 years.[6] Oncology health care workers also face unique challenges that can be incredibly impactful, including frequent exposure to the suffering or death of patients they have cared for. These distinctive stressors have potential to further contribute to burnout.[7]

Recognizing burnout as a crisis in health care, our institution and department have intentionally assessed burnout levels and proactively initiated efforts to improve professional fulfillment and reduce burnout. Well-being has been assessed annually in our department among not only attending physicians, but also residents, advanced practice providers (APPs), nurses, and other staff members using the Maslach Burnout Inventory, which measures burnout as defined by the World Health Organization and in the ICD-11.[1] Although rates of burnout in our department were comparatively low when considering the national average or other departments within our institution, rates were still considered unacceptably high. With a goal to enhance professional fulfillment, which is associated with improved patient outcomes and retention,[7-10] our department has taken initiatives to address burnout across many roles. Here, we report a single institution's approach to assess burnout and implement strategies to intentionally cultivate and sustain a culture of well-being within the department. The grassroots efforts that began within the residency program[11] sparked a department-wide strategy that has resulted in improved community and intention for well-being.

Interventions

Residency

Radiation oncology residency is a stressful experience in which residents are entering a new environment, often away from support networks, coupled with the complex task of caring largely for oncology patients, which comes with a steep learning curve. Imposter syndrome and psychological distress are common.[12] Understanding that well-being is a critical issue for residents, as part of our annual didactics, a clinical psychologist working with the Department of Student Services in a learner support role met with the residents and discussed the topic of isolation in medicine. This prompted an informal needs assessment of the residents, which identified both an interest and a need for a dedicated well-being curriculum. A resident champion with a passion for well-being partnered with a psychologist, a medical humanities professional, and the associate program director to formalize monthly well-being sessions. Residents underwent a formal needs assessment to identify topics associated with burnout, imposter syndrome, depersonalization, work-life balance, financial strain, second victim phenomenon, and coping with anxiety and depression being identified as areas of interest. During the 2019-2020 academic year, the inaugural well-being curriculum consisted of monthly 1-hour small group sessions focused on one of the identified topics of interest. Sessions were held during protected education time and were optional for residents to attend. Optional sessions during protected education time was an intentional part of the design and implementation of the curriculum to avoid further contributing to burnout and feeling overburdened.[11] To provide a balance of topics, sessions alternated between a psychological tool-focused approach and humanities exercises. Incorporation of humanities into medical training has been shown to improve the ability to empathize with patients and promote a more patient-centered approach to care[13,14] Efficacy was evaluated using the Stanford Professional Fulfillment index, which assesses aspects of a culture of wellness, personal resiliency, and efficiency of practice.[15] Survey results were used to modify the well-being curriculum for the next academic year with the goal of continuously refining the sessions and ensuring that residents found them meaningful and useful.

The resident champion and associate program director received grant funding via a competitive educational grant. Following the grant period, the initial results of the first 23 months of the curriculum were presented to the department leadership in the summer of 2021 to obtain an annual budget to sustain the efforts. Costs during the grant period and benchmarking examples from other departments with resident well-being budgets were also utilized to determine an appropriate amount of funding, resulting in a departmental fund allocation of $70/resident per year to be used for quarterly resident wellness events outside of work hours. Events are determined by resident suggestions, with the activity itself or food for the activity being funded by the department allotment. Events have included an annual welcome pool party to start the academic year, sporting event watch parties,

indoor climbing, and paint nights, all of which have been well attended by residents.

To sustain the program, a resident well-being committee was created, led by a senior resident, consisting of residents in different years of training with an interest in well-being to be mentored to continue the program after the original resident well-being champion graduated. The committee selects topics for well-being sessions and coordinates well-being activities to build camaraderie. An award with funding was created for the resident champion to attend an educational conference in recognition of time and efforts. We have also continued to have quarterly humanities-focused activities with the help of the institutional Humanities in Medicine group, such as a focus on narrative writing or a hands-on artistic endeavor. An example of such an exercise includes reviewing a short narrative piece, such as an excerpt from *Art of Oncology*, and then following up with residents writing their own reflections on experiences that relate to the topic being discussed.

Our program also implemented an annual 1-day-long retreat. Residents, the department chair, and program leadership participate in well-being-focused activities, designed by the resident and faculty wellness champions. The structured component of the day consists of a candid group discussion of well-being topics or a pertinent journal article. This is followed by a creative activity, such as painting or photography, and free play with sports and aquatic activities. The retreat occurs early in the academic year to promote team building and engagement.

In addition to tools to build community and camaraderie, our program added structure opportunities for bidirectional feedback about the health of the program and any concerns that may be present. For example, in addition to existing group residency and program leadership meetings, PGY-level-specific meetings with program leadership occur regularly. Research time was enhanced for added flexibility to be used over the PGY3-5, depending on goals. In addition to preferences for research timing, residents were also given the opportunity to submit preferences for rotation timing and mentors. All proposed schedules require final approval by educational leadership; however, added flexibility and input into determining rotation schedules has afforded a welcomed autonomy within the program.

Department

Social and Well-Being Committee: Engagement and Community

The grassroots efforts that began with the residency program sparked a department-wide strategy that has resulted in improved community and intention for well-being. A departmental well-being and social committee was established consisting of members with different departmental roles to ensure the interests of all groups are represented, including attending and resident physicians, nurses, APPs, administrative and desk staff members, and radiation therapists. Members from our satellite locations were included to represent the unique needs of our other locations as well. The committee holds a monthly meeting to discuss ideas, brainstorm activities, plan for future events, review the outcomes of previous events, and implement interventions that may contribute positively to departmental morale. The committee is led by a physician, who has granted protected time for the role. The department provides $12,000 per year to the committee to support initiatives, in addition to $3000 provided from a separate fund that staff physicians contribute to.

Events are chosen with the goals of promoting social connectedness and teamwork, especially across departmental roles. With representatives from diverse departmental roles, locations, and life stages, events are appealing to a broad audience.

Social distancing required early in the COVID-19 pandemic at the inception of many of these initiatives created additional unique challenges, especially in creating a sense of camaraderie within the department. Despite this challenge, we held events that allowed safe social distancing, such as a team trivia night conducted over Zoom, teaming with a private company that specializes in virtual trivia events, Trivia Hub. Our institution developed specific “Joy at Mayo” grants to empower recipients to improve the culture in their local working environments. Department Social and Well-being Committee members were awarded one such grant for Minnesota and Wisconsin state park passes. Group outings with trail hikes, snacks, and activities were planned for those interested as a method to build community outside of work, while including family.

As social distancing restrictions were eased, additional events were organized, including a departmental outing to a local baseball game, community volunteer opportunities, and creating teams to participate in local 5Ks to further promote a sense of community within the department.

A month-long departmental fitness challenge was started in winter 2021, and it has been popular and sustained, with challenges occurring 1 to 2 times annually. Participants choose a team member and are strongly encouraged to choose a partner in a different departmental role to

Table 1. Activities With Goals Used in the Departmental Fitness Challenge

CHALLENGE ACTIVITY	GOAL	MAXIMUM POINTS
Physical activity	30 min per day	30
Water intake	8 cups	1
Meditation/prayer/relaxation	5 min	1
Nightly sleep	7 h	1
Weekly challenge	Specified each week, post photograph	1

build connections across job titles. The goals of the challenge are focused on promoting activities that are evidence-based and associated with improved overall well-being, as noted in **Table 1**. To encourage engagement among participants, weekly challenges for additional points were added, such as posting photos of trying a new fitness activity, recipe, or outdoor activity. For administrative ease, points are tracked using a commercial challenge application, Challenge Runner, where participants are also able to post their weekly challenge photos. At the end of the challenge, participants with the most points are awarded gift cards to local businesses. Prizes are also given in other categories, such as best photo or most creative team name.

To promote social engagement, a department Facebook group was created where people can post about upcoming activities and share exciting personal endeavors. In a recent example, employees have been sharing their senior photos as part of a department-wide scavenger hunt.

A weekly department newsletter was also created. The department was engaged for naming, and ultimately voted on the "HotDish," a reference to the popular Minnesota dish and the process of sharing information. The HotDish consists of a message from the department chair or other appropriate department leader, professional and personal celebratory announcements, a "getting to know you" section featuring 1 to 2 randomly selected department members, and news about upcoming events.

Workplace Optimization

In addition to community building and teamwork, efforts to improve workplace processes have been instrumental in promoting professional fulfillment. Using information from annual well-being surveys, including the Sirota survey, specific departmental surveys, and employee feedback, our department implemented strategies to identify departmental workflow pain points. Groups consisting of representatives of different job roles within the department met to discuss methods of addressing the identified areas, with consideration of how each group would be affected before developing a plan that could be presented to leadership for consideration. Investment from leadership within the department was a high priority. The department leadership encouraged innovative solutions and presented a general openness to optimize workflows. Examples of successful interventions include the creation of new workstreams and roles, several of which we will note below.

One such intervention was the creation of the "dosimetry bridge," which consists of radiation therapists who prepare CT images for contouring and initial imaging fusion that is then approved by the treating physicians. This new therapy role enhanced opportunity and professional satisfaction for radiation therapists, as well as improved efficiency for medical dosimetrists and physicians. The role of the medical dosimetry assistant was also created to assist with normal structure contouring, plan verifications, research protocol submissions, and various other planning-related tasks. This increases the efficiency of physicians and medical dosimetrists, while also providing a strong foundation for radiation therapists with aspirations to train as medical dosimetrists. Together, these roles streamlined the process of completing contours and treatment planning, while providing an avenue for professional development and job satisfaction.

Another minor change with improved satisfaction was adopting a new call schedule. Call physician responsibilities include covering late treatments for the proton facility, which is scheduled to complete treatment at approximately 11 PM, in addition to inpatient call responsibilities and serving as backup physician for covering image checks and new starts at the machine. Recognized challenges with the on-call schedule included handoff of weekend consults and fatigue from the long hours. The attending physicians were surveyed and afforded the opportunity to provide input regarding optimization of the schedule. Proposed options included decoupling late-evening coverage from call, implementing call as a single day, rather than a 1 week, and simply adjusting the timing of call from Monday through Friday to Wednesday through Tuesday. After a review of preferences with stakeholder feedback, the call structure was

Table 2. Departmental Workplace Culture Survey

CATEGORY	QUESTION
Safety culture: mistakes	I feel safe to admit and learn from mistakes
Innovation	I feel encouraged to innovate and come up with new ideas
Safety culture: speak up	I feel free to speak my mind without fear of negative consequences
Decisions	I am involved in decisions that affect my work
Inclusivity	Where I work, efforts are made to make everyone feel like part of the team
Composite score	

adjusted to Wednesday to Tuesday to facilitate improved longitudinal care of weekend on-call patients and for the weekend to break up the week of consecutive late-evening coverage. Call dates for radiation therapists and residents were adjusted in kind to ensure a consistent call team. In addition, a system was implemented for on-call attendings to opt out of late-night coverage if desired.

The inpatient component of call consists of the primary physician covering inpatient consults, while still seeing on-treatment visits and scheduled follow-ups. Inpatient call coverage includes two hospitals, approximately 1 mile apart. Balancing the triage and management of inpatient consults with the needs within the department and seeing scheduled clinic patients was also identified as an area with potential improvement through an institutional Practice Optimization and Acceleration (POA) program designed to increase practice efficiency.[16] Using a POA project structure, the department piloted the creation of an inpatient APP and nurse service to assist with initial inpatient consults during the day. We leveraged the improvement in call physician schedule to enable additional access for follow-up and urgent outpatient consults. The inpatient APP and nurses provide reliable coverage to evaluate urgent consults and facilitate treatments under the supervision of the call physician. The pilot was well received by staff, and the inpatient APP and nurse have now been established as full-time positions within the department. These inpatient APP and nurse roles provided increased autonomy and professional fulfillment, while providing efficient inpatient care with enhanced continuity. The inpatient APP and nurse also rotate in 3-month blocks with an outpatient service, which aids in preventing burnout with the less predictable inpatient call schedule.

The clinical practice committee continually reviews the processes and satisfaction to identify other opportunities for improvement. Two pilots are ongoing within the department to address coverage of high-dose treatment image review and improve communication across the department through standardized processes and platforms.

A department survey was created in 2021 based on the questions previously used in the Sirota survey to assess improvements or declines in department culture. The survey evaluates the workplace culture in the domains of safety culture, innovation, decision-making, and inclusivity, as noted in **Table 2**. A composite score was created based on whether each survey statement was viewed favorably or unfavorably. Compared with 2021 and trending back to 2020, the 2022 results for attending physicians showed an increase in the composite score from 55% to 70%, following the implementation of many of the interventions described above.

Additional efforts have also been made specific to radiation therapists and medical dosimetrists. Radiation therapists were engaged when deciding how to schedule patients with the upgrading of linear accelerators and CT sims as they are most directly affected by the treatment schedule. With this consideration, the ultimate decision was to have an earlier daily treatment start time to prevent therapists from working late each day, as later days had greater potential to overlap with home and childcare responsibilities. This decision impacted other workers, including desk staff, physicians, and physicists. Each group communicated closely, which ultimately allowed for the accommodation of these preferences. With respect to medical dosimetry, a work-from-home option was created as data support that working from home can have a positive effect on reducing burnout.[4,17] An internal survey of medical dosimetrists was conducted, and 100% of the respondents reported maintaining or increasing quality of work, productivity, and well-being while teleworking. Initiatives were explored to maintain quality and continuity of care within department teams, including virtual collaboration avenues, alternative clinic coverage models, and virtual plan review options. With this, team members in many roles collaborated to pilot then standardize the communication platform for remote treatment plan review and processes to ensure consistent, high-quality communication. As on-site dosimetry support continues to be a need in the department, an on-site rotation schedule was developed with dosimetry staff input.

Table 3. Pillars of Well-Being and Initiatives Our Department Used to Address Them

PILLARS OF WELL-BEING	INITIATIVES
Community	Virtual trivia night
	Minnesota and Wisconsin state park passes
	Baseball game
	Volunteering
	Fitness challenge
Engagement	HotDish Newsletter
	Department Facebook group
	Social and Well-being Committee
Workplace	Changes in call schedule
	Adjustments to treatment start times
	Creation of new roles (medical dosimetry assistants, dosimetry bridge, inpatient team)
	Work-from-home option for dosimetry

Discussion

Burnout is a concern not only for physicians but also for the team members with varying roles within a radiation oncology department.[3,4,7,12] This contributes negatively in both the personal and patient care realms of an individual's life.[18] We have worked to create a culture of well-being within our department, approaching opportunities through the lens of social, organizational, and interpersonal commitments to well-being. A key component to the success of our department's initiative has been garnering support across many roles for creating and maintaining this effort. Stakeholder engagement has been important to identify initiatives to pilot, continue, or end. This allows staff across the department of varying roles to feel empowered to actualize change. Departmental leadership has been invested in supporting both social engagement as well as structural and process changes. Constant re-evaluation of department processes with the goal of identification and mitigation of so-called "pain points" has been instrumental.

While personal resilience is an important aspect of avoiding burnout,[19-21] strategies at the organizational level are also needed to prevent burnout and promote well-being. Our department's multifaceted approach has been a key factor in its success. We encourage other departments to approach well-being in their institution through the lens of three pillars of well-being—community, engagement, and workplace—and include representatives from each key role (**Table 3**). Using this approach, we have been able to foster a sustainable culture of well-being within the department that considers the impact of particular changes on each work team and enables meaningful change, while supporting a sense of community. We further attribute the success to considering organization and workstream changes in conjunction with social engagement. For example, if there are numerous activities for community building and engagement outside of work, but the workplace itself has many troublesome areas that remain unaddressed for long periods, it would be difficult to reduce burnout and frustration while at work. Finally, the support of the department chair and clinical practice leaders to allocate time for physician leaders and encourage thoughtful evaluation and implementation of many of the above changes, often leading the efforts to pilot initiatives, has been crucially important.

Conclusion

Burnout continues to be a pervasive problem in health care, across all specialties, levels of training, and roles, including radiation oncology departments. With department and institutional leadership support, meaningful improvements in professional fulfillment and reduced burnout are possible. A multifaceted approach with key stakeholder engagement to identify specific opportunities within individual departments is recommended.

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Unfavorable Intermediate- and High-Risk Prostate Cancer Treated With Predominantly Brachytherapy Alone With Long-Term Follow-Up

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Abstract

Objective: Assess 10-year outcomes of brachytherapy (BT) with or without supplemental external-beam radiation therapy (S-EBRT) for treatment of unfavorable intermediate-risk prostate cancer (U-IRPC) and high-risk prostate cancer (HRPC).

Materials and Methods: Retrospective analysis using multivariable analysis (MVA) and propensity score matching was performed on 156 patients with U-IRPC and HRPC between 2004 and 2016. Favorable HRPC was defined as T1c-T2c, Gleason group 4, and prostate-specific antigen (PSA) < 10.0. In total, 129 patients underwent BT alone using iodine-125 to 145 Gy, while 27 underwent S-EBRT + BT boost to 110 Gy. S-EBRT dose was 45-46 in 1.8-2.0 Gy fractions to the prostate and seminal vesicles. Freedom from biochemical failure (FFBF) was defined by the Phoenix definition of PSA failure. Complications were assessed using the Radiation Therapy Oncology Group grading scale.

Results: Median follow-up was 8.2 vs 8.3 years for BT vs S-EBRT + BT. FFBF for U-IRPC vs HRPC was 80.7% vs 55.6% ($P < .01$), and metastases-free survival (MFS) was 94.5% vs 72.6% ($P < .01$). The S-EBRT + BT group had higher Gleason group ($P = .01$) and higher percent positive biopsy cores >50% ($P < .01$), but also higher use of neoadjuvant androgen deprivation therapy, $P < 0.01$. On MVA, higher clinical stage ($P < .01$) and Gleason group ($P = .04$) independently predicted a lower MFS, whereas higher Charlson score predicted lower overall survival, $P = 0.01$. The adjusted 10-year FFBF and MFS for BT alone vs S-EBRT + BT were 76.8% vs 72.9% ($P = .70$) and 90.8% vs 87.3% ($P = .81$). Favorable HRPC had a 10-year FFBF of 91.7% vs unfavorable HRPC of 31.7%, $P < 0.01$. Prevalence of urinary ($P = .04$) and rectal ($P < .01$) complications was higher using S-EBRT, although this was mostly in grades 1 and 2.

Conclusion: Low-dose-rate BT using iodine-125 alone is a reasonable treatment option for U-IRPC and favorable HRPC, which is effective, convenient, and cost-effective.

Keywords: prostate cancer, brachytherapy, high risk, radiation therapy

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Introduction

Low-dose-rate (LDR) brachytherapy (BT) using radioactive seeds has shown excellent 10-year results in multiple studies.[1–3] However, most patients in these trials were low risk. The National Comprehensive Cancer Network (NCCN) guidelines recommend local therapy for treating patients with unfavorable intermediate-risk prostate cancer (U-IRPC) and high-risk prostate cancer (HRPC), but do not recommend BT as monotherapy without the use of supplemental external-beam radiation therapy (S-EBRT) or neoadjuvant androgen deprivation therapy (NADT).[4] These guidelines tend to emphasize the use of pituitary ablation as opposed to prostate ablation. Our prior experience of patients with favorable IRPC and U-IRPC showed impressive results using predominantly BT alone compared with radical prostatectomy (RP) and external-beam radiation therapy (EBRT) with or without NADT.[5] Our aim was to perform a retrospective analysis of U-IRPC and HRPC, comparing BT with or without S-EBRT, with long-term follow-up.

Materials and Methods

Patient Characteristics

There were 156 patients with U-IRPC and HRPC who underwent BT at our integrated, multifacility health care system between January 2004 and December 2016. Patients were clinically staged, with a digital rectal examination (DRE) for T-stage from the 2002 American Joint Committee Cancer staging.[6] Other tests included initial prostate-specific antigen (PSA) scoring prior to treatment and biopsies of the prostate with a Gleason score (GS) assessment. IRPC was classified as clinical stage T2b-c, GS 3 + 4 or 4 + 3 (group 2 or 3), and/or initial PSA of 10.1-20.0. Percentage positive biopsy core (PPBC < 50%) calculated from the pathology report was also considered an intermediate risk factor. U-IRPC was defined as GS 4 + 3 (group 3) or those with ≥ 2 intermediate-risk factors.[7] HRPC was defined as any patient with GS 8-10 (group 4 or 5), initial PSA >20.0, and/or clinical T3a disease by DRE, but not by MRI.[8] We defined favorable HRPC as ≤ T2c, Gleason group 4, and PSA ≤ 10.0. U-HRPC patients were those with clinical T3a, Gleason group 5, Gleason group 4 with a PSA > 10.0, or Gleason groups 2-5 with a PSA > 20.0. Charlson comorbidity index was assigned to each patient to assess overall health status.[9]

Therapy

Patients underwent S-EBRT using either 3-dimensional conformal therapy with a 6-field approach or intensity-modulated radiation therapy, with 0.8-cm planning target volume around the prostate and seminal vesicles, but a 0.6-cm posterior. The S-EBRT dose prescribed was 45-46 Gy in 1.8-2.0 Gy fractions over 5 weeks covering the prostate and seminal vesicles. The pelvic lymph nodes were not treated. NADT was given using leuprolide, typically for 3-6 months, starting 2-3 months prior to S-EBRT or BT, and concurrently with S-EBRT or BT. For BT, stranded iodine-125 radioactive seeds were inserted transperineally using ultrasound guidance, a stepper-stabilizer unit, and fluoroscopy. Planning ultrasound was done with the placement of a urethral catheter to define the urethra and prostate base. A minimum peripheral dose of 145 Gy to the prostate and proximal seminal vesicles was prescribed using 0.4 mCi per seed with a modified peripheral loading technique, whereas 110 Gy was prescribed for the BT boost patients about 4 weeks after completion of S-EBRT.[10,11] Postimplant dosimetry was performed using CT 1-2 weeks after BT, utilizing the VariSeed 8.0.1 (Varian) fusion program. V100 (percent volume that received ≥ 100% of the prescribed dose) and D90 (percentage of the prescribed dose delivered to 90% of the prostate) were calculated for the prostate.

Follow-Up

Time zero was the date of BT. Freedom from biochemical failure (FFBF) was defined based on the American Society of Therapeutic Radiology and Oncology-Phoenix definition of biochemical failure of PSA nadir + 2 ng/mL threshold.[12] Patients experiencing biochemical failure typically underwent androgen deprivation therapy (ADT). Complications were graded according to the Radiation Therapy Oncology Group grading system for late effects.[13] A minimum of 12 months of follow-up was required for this study.

Statistics

Patient characteristics were delineated with percentages for categorical factors, and median and range were utilized for continuous factors. The Pearson chi-square test was utilized to assess differences in categorical characteristics between larger groups, whereas the Fisher exact test was used for smaller sample size comparisons. The Kruskal-Wallis test was performed to calculate the differences in continuous factors between groups. Kaplan-Meier estimates were performed at 10 years, and the log-rank statistic was performed to estimate the differences between local therapies, using two-sided $P < 0.05$.[14] Multivariable analysis (MVA) using the Cox proportional hazards regression model was utilized to find independent prognostic factors.[15] Outcomes were

then adjusted by weighting the observations according to the inverse probability of treatment, based on the propensity scores, to account for selection bias between treatment groups, based on factors that were independently prognostic on MVA.[16]

Results

Patient Cohort and Prognostic Factors

Median follow-up of BT vs S-EBRT was 8.2 vs 8.3 years, with a range for all patients of 1.4-18.2 years. In total, 124 (79.5%) had U-IRPC, while 32 (20.5%) had HRPC. Also, 129 (82.7%) underwent BT alone, while 27 (17.3%) underwent S-EBRT using BT as a boost (**Tables 1 and 2**).

Median initial PSA for BT alone vs S-EBRT + BT was 9.2 (range, .9-50.0) vs 9.4 (range, 4.2-18.0), $P = 0.87$. The clinical stage was not significantly different between BT alone vs S-EBRT, $P = 0.22$. The S-EBRT group had a higher proportion with higher a Gleason group ($P = .01$) and PPBC > 50% ($P < .01$), but also had a significantly higher percentage of patients undergoing NADT ($P < .01$). Median duration of NADT for BT vs S-EBRT + BT was 3 months (interquartile range [IQR], 3, 6) vs 6 months (IQR, 6, 6), $P = 0.01$, ranging for all patients from 3 to 18 months. NADT using leuprolide was given to 9 (7.0%) vs 16 (59.3%) of BT alone vs S-EBRT, $P < 0.01$. Only 25 patients (16%) underwent NADT, and most received 3-6 months, while only 2 patients received long-term NADT of 12 and 18 months, which were in the S-EBRT group.

On MVA, higher clinical stage ($P < .01$) and higher Gleason group ($P = .04$) independently predicted a lower 10-year MFS, while a higher Charlson score predicted a lower overall survival (OS) ($P = .01$) (**Table 2**).

Dosimetry and Use of MRI

Postimplant dosimetry of BT alone vs S-EBRT + BT revealed a median V100 of 96.8% vs 96.6% ($P = .99$), and a D90 of 115.7% vs 115.9% ($P = .51$). Median prostate size for BT alone vs S-EBRT + BT was 36.9 cm^3 (range, 12.0-72.9 cm^3) vs 29.6 cm^3 (range, 20.4-48.6 cm^3), $P = 0.03$.

Fourteen (8.9%) underwent MRI prior to treatment as part of risk assessment, and 2 of these underwent S-EBRT and had T2 disease on MRI. Twelve underwent BT alone, and 2 of these were upgraded. The first was T2a on DRE and upgraded to T3a on MRI, and their PSA was < 0.1 at 6.7 years. The second patient was upgraded from T2b on DRE to T3a/b on MRI with extracapsular extension and proximal seminal vesicle invasion, and was also biochemically free of disease at 8.7 years.

Main Outcomes

None of the survival outcomes were significantly different between BT alone vs S-EBRT + BT boost. The 10-year FFBF for BT vs S-EBRT was not significant in both unadjusted (77.0% vs 71.6%, $P = .53$) and adjusted models (76.8% vs 72.9%, $P = .70$). The propensity-adjusted 10-year MFS, prostate cancer-specific survival (PCSS), and overall survival (OS) for BT vs S-EBRT were 90.8% vs 87.3% ($P = .81$), 98.4% vs 87.3% ($P = .36$), and 73.4% vs 78.0% ($P = .18$), respectively (**Figure 1**, **Table 3**).

Median follow-up of U-IRPC vs HRPC was 8.5 (1.6-18.2) vs 7.8 years (6.9-8.5), $P = 0.06$. Ten-year FFBF, freedom from salvage therapy (FFST), MFS, PCSS, and OS for U-IRPC vs HRPC were 80.7% vs 55.6% ($P < .01$), 86.0% vs 66.3% ($P = .01$), 94.5% vs 72.6% ($P < .01$), 97.1% vs 100.0% ($P = .55$), and 77.5% vs 60.4% ($P = .60$), respectively.

Subset analysis of 32 patients with HRPC revealed 13 with favorable HRPC and 19 with U-HRPC. The 10-year FFBF for favorable HRPC vs U-HRPC was 91.7% vs 31.7% ($P < .01$), and the 10-year MFS was 100.0% vs 53.7% ($P = .01$). Of those with favorable HRPC, 11 of 13 underwent BT alone.

Salvage Therapy

The 10-year FFST was 83% vs 78% for BT vs S-EBRT + BT, $P = 0.89$. One patient underwent salvage cryotherapy, which failed, and went on to systemic therapy. All other patients underwent ADT as first-line salvage therapy. Three patients who had BT alone received abiraterone and enzalutamide, 1 of whom also received docetaxel. Two patients treated with S-EBRT received docetaxel, 1 of whom also underwent abiraterone and enzalutamide.

Patterns of Failure

FFBF and MFS for U-IRPC were significantly higher than HRPC, with 10-year FFBF of U-IRPC and HRPC being 80.7% vs 55.6%, $P < 0.01$, and MFS of 94.5% vs 72.6%, $P < 0.01$, respectively. Analyzing the patterns of failure, there were few patients with local recurrences: 2 experiencing isolated seminal vesicle recurrence, 1 with seminal vesicle plus prostate recurrence, and 1 with prostate recurrence alone, who later underwent cryotherapy. The patients in this study were in the era prior to prostate-specific membrane antigen PET (PSMA-PET) imaging, while MRI and biopsies were utilized to evaluate patients at the time of biochemical failure (**Table 4**).

Prevalence of Complications

There was a significantly higher prevalence of urinary complications using S-EBRT of 33.3% vs 16.3% for BT alone, $P = 0.04$; however, severe grade 3 and 4 complications for BT vs S-EBRT were not significantly different, 5.4% vs 3.7%,

Table 1. Cohort Patient Characteristics

	BT ALONE (*N* = 129)	S-EBRT + BT (*N* = 27)	TOTAL (*N* = 156)	*P* VALUE
Age, median (IQR)	67.7 (62.3, 73.1)	67.7 (63.6, 70.9)	67.7 (62.4, 73.0)	.90*
Race/ethnicity, *n* (%)				
Asian	12 (9.3%)	4 (14.8%)	16 (10.3%)	
Black	29 (22.5%)	7 (25.9%)	36 (23.1%)	
Hispanic	21 (16.3%)	2 (7.4%)	23 (14.7%)	
White	67 (51.9%)	14 (51.9%)	81 (51.9%)	.56®
Charlson score, median (IQR)	2.0 (1.0, 3.0)	2.0 (1.0, 2.0)	2.0 (1.0, 3.0)	.55*
Clinical T-stage, *n* (%)				
T1c	79 (61.2%)	12 (44.4%)	91 (58.3%)	
T2a	26 (20.2%)	11 (40.7%)	37 (23.7%)	
T2b	20 (15.5%)	4 (14.8%)	24 (15.4%)	
T2c	3 (2.3%)	0 (.0%)	3 (1.9%)	
T3a	1 (.8%)	0 (.0%)	1 (.6%)	.22®
Initial PSA, median (IQR)	9.2 (6.1, 11.7)	9.4 (6.5, 12.7)	9.2 (6.2, 11.8)	.87*
Initial PSA				
≤ 10.0	69 (53.5%)	15 (55.6%)	84 (53.8%)	
10.1-20.0	51 (39.5%)	12 (44.4%)	63 (40.4%)	
> 20.0	9 (7.0%)	0 (.0%)	9 (5.8%)	.54®
Gleason grade group, *n* (%)				
Group 1 (GS 6)	17 (13.2%)	0 (.0%)	17 (10.9%)	
Group 2 (3 + 4)	48 (37.2%)	12 (44.4%)	60 (38.5%)	
Group 3 (4 + 3)	49 (38.0%)	7 (25.9%)	56 (35.9%)	
Group 4 (GS 8)	12 (9.3%)	4 (14.8%)	16 (10.3%)	
Group 5 (GS 9-10)	3 (2.3%)	4 (14.8%)	7 (4.5%)	.01®
PPBC > 50%, *n* (%)	35 (27.1%)	15 (55.6%)	50 (32.1%)	<.01#
Use of NADT, *n* (%)	9 (7.0%)	16 (59.3%)	25 (16.0%)	<.01#

Abbreviations: BT, brachytherapy; GS, Gleason score; IQR, interquartile range; NADT, neoadjuvant androgen deprivation therapy; PPBC, percent positive biopsy cores; PSA, prostate-specific antigen; S-EBRT, supplemental external-beam radiation therapy.

**Kruskal-Wallis P value.*

®*Fisher exact P value.*

#χ^2 *P value.*

P = 0.99. There was also a higher prevalence of rectal complications using S-EBRT vs BT of 22.2% vs 6.2%, *P* < 0.01; most of which were grades 1 and 2, and only 1 severe grade 4 fistula. Most of the severe grade 3 and 4 complications were obstructive urinary symptoms, with 2 transurethral resections of prostate, 2 needing daily clean intermittent catheterization, 1 requiring a daily indwelling urethral catheter, 1 requiring percutaneous nephrostomy tubes, and 1 experiencing grade 3 urinary incontinence (**Table 5**).

Discussion

The NCCN guidelines historically only recommended monotherapy BT for the treatment of low-risk prostate cancer, and only since 2015 recommended its use for favorable IRPC.[4] The NCCN currently only recommends BT as a boost for U-IRPC and HRPC, along with S-EBRT or whole pelvic radiation, and NADT. Whole pelvic radiation is endorsed by the NCCN, along with 6 months of NADT for U-IRPC and a minimum of 18 months of NADT for HRPC, although conflicting

Table 2. Multivariable Analysis of Prognostic Factors

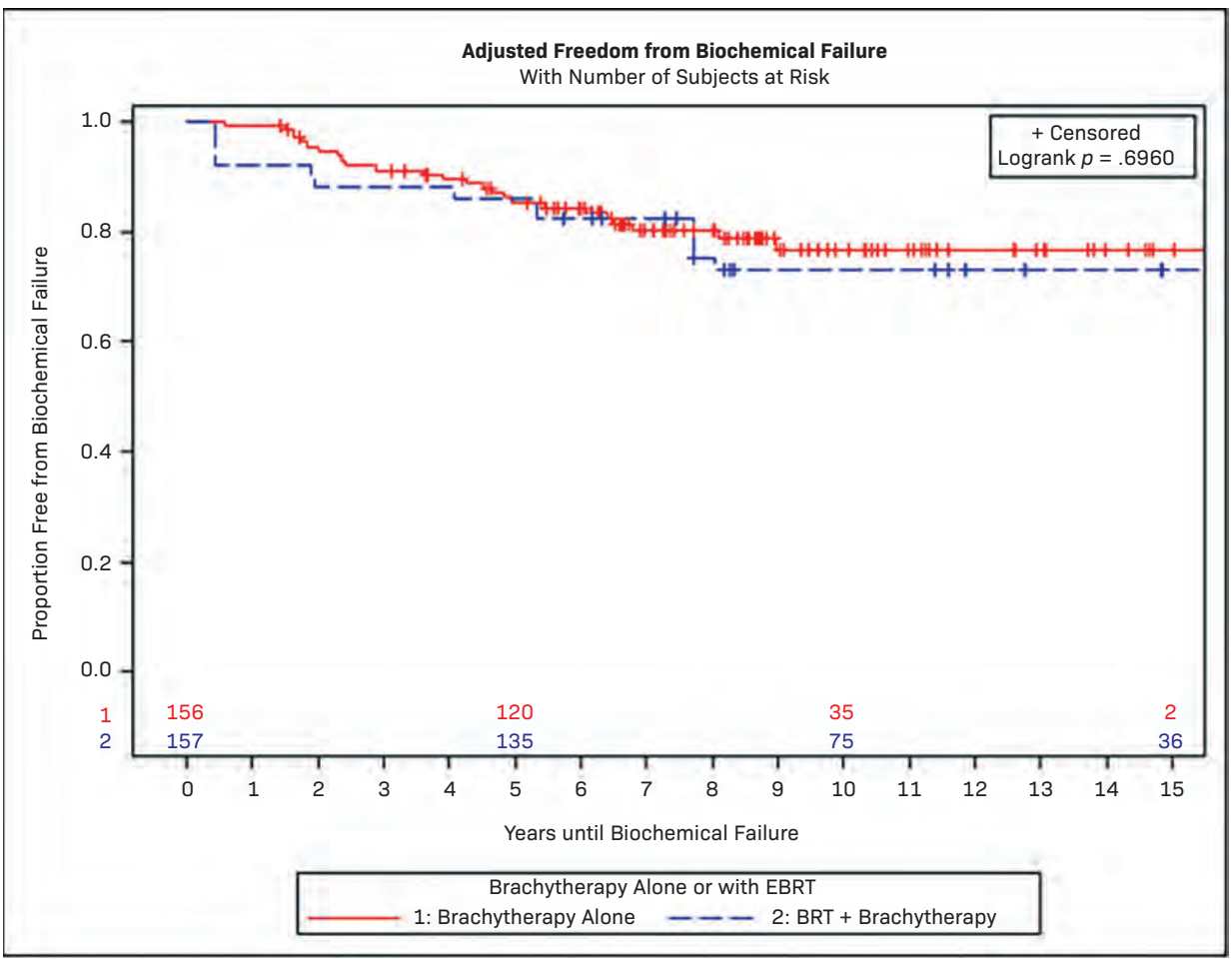
	FFBF	FFST	MFS	PCSS	OS
Age (older vs younger)	HR = .56 *P* = .13	HR = .46 *P* = .08	HR = .62 *P* = .44	HR = .96 *P* = .97	HR = 1.78 *P* = .14
Race (Black vs non-Black)	HR = 1.52 *P* = .31	HR = 1.01 *P* = .98	HR = 1.13 *P* = .87	HR = .31 *P* = .36	HR = .58 *P* = .19
Charlson score (3+ vs 1 and 2)	HR = .97 *P* = .95	HR = 1.65 *P* = .29	HR = 1.51 *P* = .54	HR = .94 *P* = .96	**HR = 2.58** ***P* = .01**
Clinical stage (T2b-3a vs T1c-T2a)	HR = 2.15 *P* = .07	HR = 2.30 *P* = .07	**HR = 6.00** ***P* < .01**	HR = 3.44 *P* = .22	HR = .86 *P* = .72
Initial PSA (>10.0 vs ≤10.0)	HR = 1.23 *P* = .57	HR = 1.38 *P* = .45	HR = 2.36 *P* = .20	HR = .83 *P* = .84	HR = .85 *P* = .65
Gleason group (5,4 vs 3,2,1)	HR = 2.41 *P* = .06	HR = 2.57 *P* = .08	**HR = 4.66** ***P* = .04**	HR = 1.72 *P* = .71	HR = 1.31 *P* = .60
% + cores > 50%	HR = .91 *P* = .82	HR = .60 *P* = .30	HR = .40 *P* = .20	HR = 1.55 *P* = .68	HR = .90 *P* = .79
Use of NADT (N vs Y)	HR = .39 *P* = .07	HR = .84 *P* = .80	HR = .67 *P* = .68	HR = .15 *P* = .14	HR = .56 *P* = .24
Use of S-EBRT (N vs Y)	HR = .72 *P* = .56	HR = 1.12 *P* = .87	HR = 1.01 *P* = .99	HR = .74 *P* = .78	HR = .36 *P* = .07

Abbreviations: FFBF, freedom from biochemical failure; FFST, freedom from salvage therapy; MFS, metastases-free survival; NADT, neoadjuvant androgen deprivation therapy; OS, overall survival; PCSS, prostate cancer-specific survival; PSA, prostate-specific antigen; S-EBRT, supplemental external beam radiation therapy.

Bold values represent statistically significant results.

data exist regarding whole pelvic radiation, and none of these trials used BT.[4,17–19] The most recent trial that was positive for pelvic radiation, but did not use BT, showed an improvement in biochemical failure, disease-free survival, and distant metastases-free survival, and also incorporated the use of PSMA-PET to assess distant disease, which is much more sensitive than prior imaging.[19] Increasing the sensitivity of detecting distant disease will influence oncological outcomes, making MFS closer to a surrogate of FFBF or progression-free survival, and less of a predictor of PCSS. For patients not undergoing RP, the standard recommendation has been long-term NADT with EBRT, considered category 1 by the NCCN. One problem with this recommendation is that patients with HRPC are a heterogeneous mix of patients.[20] One approach could be to segregate HRPC into a favorable vs unfavorable category, in which favorable could represent those with a reasonable probability of having organ-confined disease or disease into the capsule. With the increasing use of MRI and PSMA-PET, selecting U-IRPC and HRPC that may have localized disease should become more feasible, making these patients amenable to BT alone, which provides more ablative doses than EBRT.[5] Our preference would be to offer BT alone to those favorable HRPC with Gleason group 4, PSA ≤ 10.0, T1c-T2c disease, including T3a seen on MRI (not T3a on DRE). Also, it seems that our favorable HRPC patients did just as well as those with U-IRPC, suggesting that these could be merged together as a risk group so that favorable HRPC could be categorized as U-IRPC. However, we recommend excluding those with seminal vesicle invasion and patients with a high risk of systemic disease. The majority of our patients received neither S-EBRT nor NADT, and the patients who did undergo NADT were short-term of 3-6 months. Also, none of our patients underwent whole pelvic radiation. A recent randomized study showed no benefit with the addition of S-EBRT to BT for favorable IRPC, but this study did not include U-IRPC or HRPC.[21] Despite the lack of additional therapies, the BT alone cohort showed excellent FFBF, MFS, and PCSS at 10 years, although for U-HRPC, FFBF and MFS were much lower at 10 years at 31.7% and 43.3%, and no significant difference was found with the addition of S-EBRT, despite 59.3% of S-EBRT + BT boost undergoing NADT vs only 7.0% for the BT-alone group. PCSS remained high for both U-IRPC and HRPC, likely due to the availability of effective salvage therapies that can prolong survival, but are not curative. Although the S-EBRT group did have higher Gleason grouping and higher PPBC > 50%, MVA and propensity score matching did not show any benefit in regards to oncological outcomes with S-EBRT, despite a majority of S-EBRT undergoing NADT. Is it possible that the ablative doses given to the prostate and surrounding capsule are the most important factor in treating U-IRPC and favorable HRPC, while having very high rates of PCSS? The ASCENDE-RT trial treated all patients with NADT of 1 year along with pelvic radiation, comparing high-dose EBRT to the prostate vs BT boost, and this showed improvement of progression-free survival in those who underwent BT, although the BT boost arm did experience more

Figure 1. Adjusted Kaplan-Meier estimates of freedom from biochemical failure, comparing brachytherapy alone vs supplemental external-beam radiation therapy plus brachytherapy.



urinary and rectal toxicities.[22,23] This trial indicates that the ablative doses provided by BT still have an important role in the treatment of U-IRPC and favorable HRPC. A publication of 2 randomized studies by Merrick et al was done on patients with intermediate- and high-risk prostate cancer, which did not show any improvement with the addition of S-EBRT, compared with BT alone.[24] It seems that one difference between the ASCENDE-RT trial vs the Merrick study was that the ASCENDE-RT used pelvic radiation, while the Merrick study may have included only the prostate and seminal vesicles when using S-EBRT. Additionally, a Surveillance, Epidemiology, and End Results Medicare analysis of 5835 patients also confirmed the lack of benefit of S-EBRT in addition to BT in regards to PCSS.[25]

One retrospective study also showed that BT was reasonable for HRPC, which compared 2557 HRPC with a median follow-up of 63.5 months, comparing RP vs EBRT vs BT, with NADT given in 19% vs 93% vs 53%, respectively, $P < 0.0001$.[26] Biochemical relapse-free survival and clinical relapse-free survival (cRFS) were equivalent between BT and EBRT, but both were higher than RP. This may reflect differences on how PSA failures were defined, as the definition for failure is more sensitive for RP compared with EBRT.[12,27] Also, the RP group had more failures in cRFS, as RP patients who underwent adjuvant radiation were counted as failures despite not having failed biochemically.

The main reason for the benefit of BT is that it provides more ablative doses than can be achieved by EBRT with or without NADT by producing a lower PSA nadir of <0.1.[28] Although ablative doses may be effective in eradicating prostate cancer, high doses can cause significant morbidity. However, one can properly select patients who can tolerate these ablative doses by using the American Urological Association urinary score to select

Table 3. Kaplan-Meier Estimates with 95% Confidence at 10 y by Treatment

	# SUBJECTS	OBSERVED EVENTS	10 Y UNADJUSTED PROBABILITY	*P* LOG RANK	10 Y ADJUSTED PROBABILITY	*P* LOG RANK
FFBF						
BT	129	25	77.0% (67.2%, 84.2%)	.53	76.8% (66.9%, 84.0%)	.70
S-EBRT + BT	27	7	71.6% (48.9%, 85.5%)		72.9% (48.7%, 87.1%)	
MFS						
BT	129	11	91.1% (84.1%, 95.1%)	.86	90.8% (83.7%, 94.9%)	.81
S-EBRT + BT	27	3	87.1% (64%, 96%)		87.3% (63%, 96%)	
PCSS						
BT	129	4	98.4% (89.4%, 99.8%)	.94	98.4% (89.3%, 99.8%)	.36
S-EBRT + BT	27	2	93.8% (63.2%, 99.1%)		87.3% (55.0%, 97.0%)	
OS						
BT	129	34	74.1% (63.5%, 82.0%)	.07	73.4% (62.6%, 81.5%)	.18
S-EBRT + BT	27	5	83.7% (56.5%, 94.6%)		78.0% (48.6%, 91.8%)	

Abbreviations: BT, brachytherapy; FFBF, freedom from biochemical failure; MFS, metastases-free survival; OS, overall survival; PCSS, prostate cancer-specific survival; S-EBRT, supplemental external beam radiation therapy.

Table 4. Patterns of Failure

	U-IRPC (*N* = 20)	HRPC (*N* = 12)
Biochemical failure only	14	3
Isolated prostate failure	1	0
Isolated seminal vesicle failure	1	1
Prostate and seminal vesicle failure	0	1
Prostate, seminal vesicle, and pelvic nodal failure	0	1
Positive prostate biopsy	2/5	0/3
Pelvic nodal metastases only	0	2
Peri-rectal nodal metastases only	1	0
Para-aortic and pelvic nodal metastases	2	1
Bone metastases	5	2
Lung metastases	0	1

Abbreviations: HRPC, high-risk prostate cancer; U-IRPC, unfavorable intermediate-risk prostate cancer.

which patients would have a lower probability of long-term urinary effects.[29] In the current study, we had acceptable side effects, and these side effects were more common in those undergoing S-EBRT, although most of these were grades 1 and 2, with severe grade 3 and 4 complications rates being low.

The limitations of this study include that the majority of patients were U-IRPC, with only 20.5% being HRPC. Also, there was an imbalance of GS and PPBC > 50%, with worse patients in the S-EBRT group, showing that the BT-alone patients were subjected to selection bias. We tried to account for these differences by using propensity score matching, although this is a relatively small study with the limitation of being retrospective. Unfortunately, there are few large randomized trials using prostate BT. Low reimbursements, combined with LDR BT requiring more training and skill, give little motivation for physicians to offer LDR BT to their patients.[30–32] This has led to a decline

Table 5. Prevalence of Radiation Therapy Oncology Group Late Complications

	BT (*N* = 129)	S-EBRT + BT (*N* = 27)	*P* VALUE
Urinary complications	21 (16.3%)	9 (33.3%)	.04*
Grade 1 and 2 urinary	14 (10.9%)	8 (29.6%)	.01*
Grade 3 and 4 urinary	7 (5.4%)	1 (3.7%)	.99®
Rectal complications	8 (6.2%)	6 (22.2%)	<.01*
Grade 1 and 2 rectal	7 (5.4%)	6 (22.2%)	<.01*
Grade 3 and 4 rectal	1 (.8%)	0 (.0%)	.99®

Abbreviations: BT, brachytherapy; S-EBRT, supplemental external-beam radiation therapy.

**χ^2 P value.*

®*Fisher exact test P value.*

in the use of LDR BT in clinical practice and residency training, with the potential downstream effect of fewer publications on the role of LDR BT in patients with prostate cancer, and potentially leading to the unavailability to many patients of one of the most successful treatment options for prostate cancer. Thus, we publish our 10-year results on the use of LDR BT on patients with more advanced disease, which, if done properly, can yield favorable oncological outcomes with acceptable rates of side effects, suggesting LDR BT to be a reasonable option in the treatment of U-IRPC and selected HRPC.

Conclusion

LDR BT using iodine-125 alone is a reasonable treatment option for U-IRPC and favorable HRPC, which is effective, convenient, and cost-effective.

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High-Fidelity CT-on-Rails-Based Characterization of Delivered Dose Variation in Conformal Head and Neck Treatments

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Abstract

Objective: This study aims to characterize dose variations from the original plan for a cohort of patients with head and neck cancer (HNC) using high-quality CT on rails (CTOR) datasets and evaluate a predictive model for identifying patients needing replanning.

Materials and Methods: In total, 74 patients with HNC treated on our CTOR-equipped machine were evaluated in this retrospective study. Patients were treated at our facility using in-room, CTOR image guidance—acquiring CTOR kV fan-beam CT images on a weekly to near-daily basis. For each patient, a particular day's treatment dose was calculated by applying the approved, planned beam set to the postimage-guided alignment CT image of the day. Total accumulated delivered dose distributions were calculated and compared with the planned dose distribution, and differences were characterized by comparison of dose and biological response statistics.

Results: The majority of patients in the study saw excellent agreement between planned and delivered dose distribution in targets—the mean deviations of dose received by 95% and 98% of the planning target volumes of the cohort are −0.7% and −1.3%, respectively. In critical organs, we saw a +6.5% mean deviation of mean dose in the parotid glands, −2.3% mean deviation of maximum dose in the brainstem, and +0.7% mean deviation of maximum dose in the spinal cord. Of 74 patients, 10 experienced nontrivial variation of delivered parotid dose, which resulted in a normal tissue complication probability (NTCP) increase compared with the anticipated NTCP in the original plan, ranging from 11% to 44%.

Conclusion: We determined that a midcourse evaluation of dose deviation was not effective in predicting the need for replanning for our patient cohorts. The observed nontrivial dose difference to the parotid gland delivered dose suggests that even when rigorous, high-quality image guidance is performed, clinically concerning variations to predicted dose delivery can still occur.

Keywords: head and neck cancer, intensity-modulated radiation therapy, fan-beam CT

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Introduction

Conformal radiation therapy is a highly effective treatment approach for many cancers. Intensity-modulated radiation therapy allows for a more precise conformation of radiation dose to the targeted tumor volume and increased sparing of surrounding normal tissues.[1-3] Due to the high sensitivity of head and neck tissues and subsequent potential for nontrivial side effects, it is imperative that the high-dose region be delivered with high accuracy and consistency.[4] Advanced image-guided radiation therapy (IGRT) techniques, such as cone-beam CT (CBCT) and in-room CT on rails (CTOR), increase the accuracy of dose delivery, thereby helping to ensure the fidelity of the delivered dose distribution relative to the planned distribution. However, even the best IGRT approach cannot undo anatomical changes, such as weight loss or tumor shrinkage, which occur in patients as the radiation course progresses. These changes can compromise target coverage or increase doses to sensitive structures.

Although dose deviations from planned distributions are known to occur throughout the treatment and have been previously studied,[5] the accuracy of such evaluations is inherently limited by the quality of the in-room, daily imaging modality. Even when 3D imaging is obtained daily via CBCT, the reduced spatial, contrast, and Hounsfield unit (HU) resolution of CBCT, relative to the fan-beam CT (FBCT) simulation dataset, limits the precision with which dose variation can be studied. In particular, the increased scatter component of CBCT imaging influences the relationship between HU, attenuation coefficient, and electron density of patient tissues,[6] resulting in increased uncertainty in dose calculations compared with FBCT images.

In previous studies[7-10] on dose tracking, a limited number of patients (10-18) were included in the study cohorts, which used in-room tomotherapy megavoltage CT,[7] an integrated CT-linear accelerator system,[8] return of patient to the CT simulator, and kV CBCT[10] to image anatomical changes during the treatment course. To address the data deficiency problem and gain a better understanding of potential dose deviation, McCulloch et al[11] built a larger cohort of 100 patients. This added clinical variety and significance to the evaluation; however, the daily imaging modality was still limited to kV CBCT and full 3D dose accumulation was not available, necessitating an approximation to estimate the accumulated dose and thus introducing additional uncertainties into the evaluation.

To improve the accuracy and reliability of recalculated dose distributions, we present accumulated, full-course dose distributions for 74 patients with HNC treated at our facility using in-room, fan-beam CTOR image guidance of identical quality from which the patient was originally simulated and planned. Acquisition of CTOR kV FBCT images on a weekly to near-daily basis for these patients has enabled us to compile a large FBCT dataset for high-quality dose variation investigation. In addition to improved dose-calculation accuracy, the FBCT-to-FBCT image registration employed here facilitates more accurate structure mapping between CT of the day and simulation planning CT. In combination with an FBCT-based, high-fidelity, full-dose recalculation, this allows for improved accuracy in dose tracking and summation that has comparable accuracy to the original plan.

Moreover, such high-accuracy reconstruction of delivered dose ensures improved accuracy in the characterization of dose variations from the original plan. This improved understanding of delivered dose variation, in turn, facilitates improved insights into circumstances leading to observed side effects, along with an evolved rationale for adaptive replanning time points.

Materials and Methods

Patient Data

Our novel dataset consists of 74 patients with HNC treated between 2012 and 2020. The study was approved by the Institutional Review Board. For each patient, there is 1 planning FBCT simulation scan, 1 approved and delivered treatment plan, and 10 to 39 daily FBCT IGRT image sets, with an average of 19.0 daily FBCTs per patient. The frequency of imaging in the patient cohort ranges from 1 to 2.7 days, with more than half of the patients receiving a FBCT at least every second day during the treatment.

All patients were originally planned in the Eclipse treatment planning system (TPS) (version 11.0.42; Varian) and dose was calculated using the anisotropic analytical algorithm. Additional plan details, patient demographics, and clinical characteristics are detailed in **Table 1**. None of these patients received adaptive planning.

Image-Guided Radiation Therapy

Patients were treated on a Siemens Artiste linear accelerator equipped with an in-room Siemens CTOR scanner (SOMATOM Sensation 40; Siemens Healthineers), which was

Table 1. Demographics of Our Patient Cohort

PATIENT COHORT	
Patients, *n*	74
Sex, *n*	
Male	63 (85.1%)
Female	11 (14.9%)
Age, y	
Mean	59.7
Min	23
Max	79
Disease site, *n*	
Oropharynx	49
Thyroid	5
Nasopharynx	4
Sinuses	4
Neck Node (unknown primary)	4
Others	8
Concurrent chemotherapy, *n*	57
Definitive radiation therapy, *n*	64
Fractions, *n*	
30	49 (66.2%)
33	9 (12.2%)
35	9 (12.2%)
39	4 (5.4%)
Others	3 (4.0%)
Prescribed dose, cGy	
6000	8 (10.8%)
6600	23 (31.0%)
6750	29 (39.2%)
7000	9 (12.2%)
7020	4 (5.4%)
Others	1 (1.4%)

used for pretreatment imaging and positioning.

Dose-Tracking Workflow

Dose tracking was carried out using the RayStation TPS[12] (version 10A; RaySearch Laboratories AB) and automated using the built-in scripting application programming interface. Original planned dose distributions were recalculated in RayStation prior to starting dose accumulation. Several scripts were developed to automate the following steps: replicate the registration utilized for image guidance, deformable image registration (DIR), contour propagation, dose calculation on daily images, dose deformation, and dose accumulation.

Rigid registrations utilized for daily image guidance are stored in digital imaging and communications in medicine files as a frame-of-reference transformation matrix and include the operations of translation and rotation. Registrations were loaded into RayStation, along with daily images, then applied to reproduce daily setup and map beams to CTs of the day for daily dose calculation.

Deformable image registration was carried out using a hybrid deformable registration technique (ANACONDA)[13] in RayStation, which combines image intensity and anatomical information (including regions of interest and points of interest together). In our implementation, the anatomical information was not used in the registration technique and the objective function consisted only of image similarity and grid regularization terms.

After calculating the deformation map, the organs at risk (OAR) and target contours were propagated to the daily CT space using the deformation field. Dose was then calculated using the RayStation collapsed cone algorithm[14] on each daily CT image to estimate the actual delivered dose distribution for each treatment session. Subsequently, daily doses were deformed back to the planning CT and accumulated to allow for direct comparison against the planned dose distribution. For treatment days without daily CT images, the most recent prior dose calculation was repeated in the accumulation.

To circumvent potential errors in dose evaluation related to variations of field of view (FOV) in daily images, a sequence of contours that delineated the FOVs in both the planning CT and daily CTs was generated. Deformation mappings computed earlier were then leveraged to map the FOV contours from the daily CT's space to the planning CT space. After all the FOV contours were presented in the same reference space, the intersection was calculated and rendered as the common FOV contour. The intersection of individual target and OAR structures with the common FOV was subsequently calculated to ensure that daily dose volumes encompassed relevant structures.

Image Registration Validation

The image registration procedure in RayStation consists of 2 parts: rigid registration and deformable registration. To verify whether the rigid registration was performing well, we reviewed all planning CT and daily CT pairs and confirmed that the ANACONDA algorithm was performing well in all of the 74 patients' data —ie, the bony structures were well aligned without any visible misalignment. For the deformable registration, we visually verified the resulting deformed daily CT across the dataset and confirmed that the algorithm was manifesting robustness, even when handling large but reasonable anatomical changes. Both of these reviews were performed by a senior medical physicist with extensive expertise in image guidance and registration. We note that the ANACONDA algorithm was previously validated by Weistrand

et al[13] on CBCT data of the head and neck regions and was reported to have performed well in comparison with other algorithms in DIR-LAB. While uncertainties inherently arise in the context of dose deformation and summation, literature quantifying the specific magnitude of the expected error associated with deformation appears lacking.

Dosimetric Evaluation

Dose that was accumulated onto the original simulation planning FBCT was used for all characterizations of the summed, delivered dose. Target coverage was evaluated in terms of dose received by 95% (D95%) and 98% (D98%) of the volume. OAR evaluations include mean dose to the parotid glands, maximum dose to the brainstem, and maximum dose to the spinal cord. Relative deviations for all metrics are reported as below:

$$\text{dose deviation} = \frac{\text{delivered dose} - \text{planned dose}}{\text{planned dose}}$$

Biological Response

With the aim of identifying cases where the parotid gland would experience a high (and subsequently increased) probability of complication due to observed increase in delivered dose, we calculated the normal tissue complication probability (NTCP) for a subset of patients that exceeded planning criteria. Specifically, we filtered out patients with parotid glands where the original planned mean dose was larger than 26 Gy (our planning goal), intersected with those patients where the difference between delivered and planned mean dose was also increased by 4 Gy or more (suggested overdose threshold for replanning by Hunter et al[10]), which was intended to yield insight into the biological manifestations of variations in delivered dose.

Here, we used the RayStation NTCP-Poisson LQ models[15-18] for NTCP evaluation (xerostomia endpoint). For parotid glands' NTCP metric, we set the maximum normalized gradient of the dose-response curve, γ, to 1.8 and the dose giving a 50% response probability D_{50} at 46 Gy.[15] As the NTCP of planned and delivered doses were both evaluated in the same simulation planning CT space, the uncertainty of the biological response deviation stems only from the dose received by each voxel at each fraction.

Results

Deviations of D95/D98 for the 190 planning target volumes (PTV) are shown in **Figure 1**. Note that due to some patients being treated bilaterally or with simultaneous integrated boosts, 1 patient may have more than 1 PTV contour. The mean deviations of D95 and D98 of the PTVs were observed to be −0.7% and −1.3%, respectively. Among patients whose PTVs experienced decreased D95, the maximum deviation was −12.0%, followed by a patient whose D95 variation was −8.7%. With regard to D98 evaluation, 12 patients' PTVs experienced a greater than 10% decrease, the largest followed by the next largest deviations of −28.3% and −16.8%, respectively. We closely investigated the patients whose PTVs experienced more than a 10% decrease in D98 and listed them in **Table 2**. As is shown, patients who saw more than a 10% decrease in D98 of PTVs did not observe the same degree of deviation in D95 due to the relative dose shift being limited to within 10%. In contrast, the PTV of patient HN013 experienced a 12% decrease in D95 but saw a 13.7% increase in D98.

Total delivered dose was evaluated for 147 parotid glands (1 patient had only a right parotid gland), 73 brainstems (1 patient's brainstem contour was not transferred), and 74 spinal cords. The distribution of variation between planned and delivered doses of critical OARs is detailed in **Figure 2**.

We observed an average 6.5% increase in mean dose across all 147 parotid glands for all 74 patients. Of the 147 parotid glands, 71 experienced a ≥ 5% increase

Figure 1. Distribution of D95 and D98 deviation in planning target volumes (PTVs). A positive percentage indicates an increase from the plan and a negative percentage depicts a decrease from the plan.

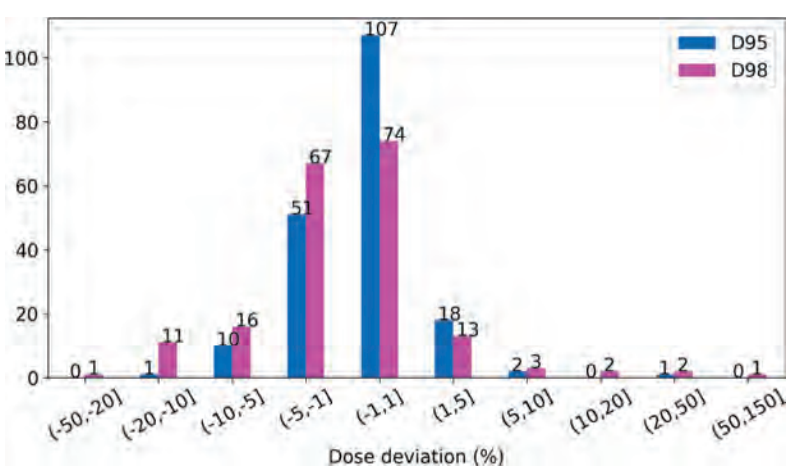


Table 2. Patients with PTVs Where D95 or D98 Decreased by >10% (Bold Font)

	D95				D98			
PATIENT ID	PLANNED DOSE (CGY)	DELIVERED DOSE (CGY)	ABSOLUTE DIFFERENCE	RELATIVE DIFFERENCE (%)	PLANNED DOSE (CGY)	DELIVERED DOSE (CGY)	ABSOLUTE DIFFERENCE	RELATIVE DIFFERENCE (%)
HN089	5798.7	5813.0	14.3	0.3	5653.8	4055.8	−1598.1	**−28.3**
HN021	5880.5	5663.7	−216.8	−3.7	5826.6	4845.7	−980.9	**−16.8**
HN091	5220.2	4832.6	−387.5	−7.4	3883.1	3234.1	−649	**−16.7**
HN068	4929.6	4647.9	−281.7	−5.7	4174.3	3549.7	−624.7	**−15.0**
HN104	6732.2	6719.9	−12.3	−0.2	5039.1	4345.2	−693.9	**−13.8**
HN033	5202.5	5087.9	−114.7	−2.2	5067.2	4452.8	−614.4	**−12.1**
HN010	5800.2	5458.1	−342.1	−5.9	5660.5	4989.7	−670.8	**−11.9**
HN021	5307.7	4949.7	−358	−6.7	5105.9	4511.2	−594.7	**−11.7**
HN046	5310.5	4933.0	−377.5	−7.1	5166.5	4565.6	−601	**−11.6**
HN095	4958.0	4793.3	−164.7	−3.3	4665.7	4123.9	−541.8	**−11.6**
HN057	5184.3	4771.8	−412.5	−8.0	5060.8	4528.8	−532	**−10.5**
HN068	6170.8	5940.7	−230.1	−3.7	5736.3	5154.7	−581.6	**−10.1**
HN013	4502.5	3962.2	−540.3	**−12.0**	2405.7	2734.4	328.7	13.7

A positive percentage indicates an increase from the plan and a negative percentage depicts a decrease from the plan,

Abbreviations: PTV, planning target volume; D95, dose received by 95%; D98, dose received by 95%.

in mean dose, with 10 (13.5%) receiving a 20% to 50% higher mean dose than that was indicated by the original treatment plan. Less frequent increased dosing of the brainstem was observed: the mean and maximum deviation of maximum dose was a 2.3% decrease and a 12.5% increase, respectively. Only 2 patients experienced a 5% to 10% increase in maximum dose to the brainstem, with 1 receiving a cumulated maximum dose that was 12.5% higher than that indicated by the original treatment plan. We note that while the dose to the brainstem increased above what was originally planned, it is well below the known tolerance dose for this structure. For the spinal cord, the mean and maximum deviation of maximum dose was a 0.7% increase and a 13.7% increase, respectively, with 96% of patients receiving a

Figure 2. Distribution of mean dose deviation in parotid glands (A), distribution of maximum dose deviation in brainstems (B), and distribution of maximum dose deviation in spinal cords (C). A positive percentage indicates an increase from the plan and a negative percentage depicts a decrease from the plan.

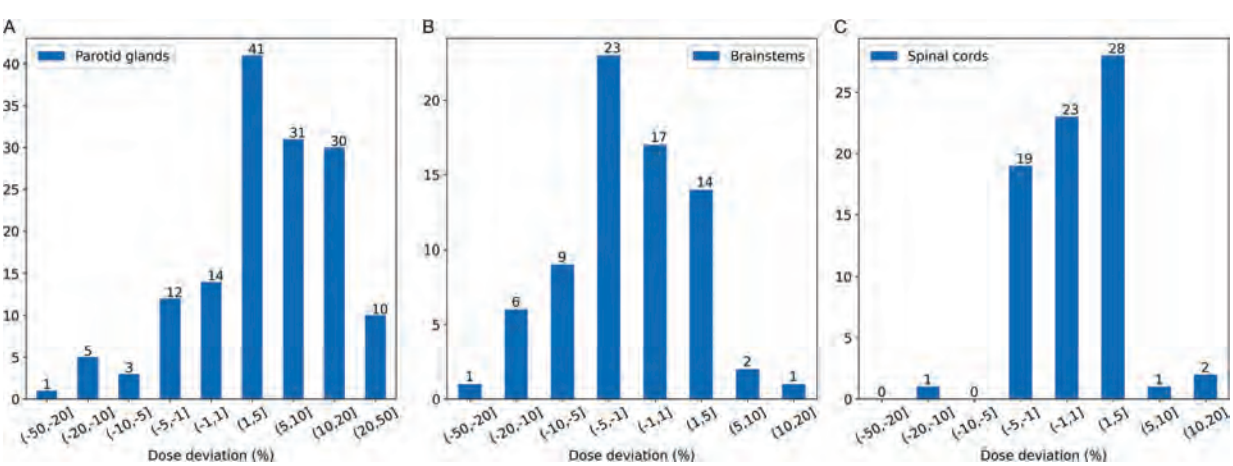


Table 3. Comparison of Mean Dose (cGy) and NTCP of Parotid Glands in Planned and Delivered Doses

	LEFT PAROTID						RIGHT PAROTID					
	PLANNED		DELIVERED		DIFFERENCE		PLANNED		DELIVERED		DIFFERENCE	
PATIENT ID	DOSE	NTCP (%)	DOSE	NTCP (%)	DOSE	NTCP (%)	DOSE	NTCP (%)	DOSE	NTCP (%)	DOSE	NTCP (%)
HN010	2955.9	8	3616.3	31	657.4	**23**	2899.6	13	4197.8	57	1298.2	**44**
HN011	3177.0	28	3638.6	41	461.6	**13**	2094.1	7	2514.7	14	370.7	7
HN022	1956.1	15	2236.0	18	279.9	3	3007.0	36	3514.3	50	507.3	**14**
HN023	2771.6	24	3410.6	38	639.0	**14**	2734.9	16	3261.0	26	526.1	**10**
HN030	2185.1	5	2916.6	16	731.5	**11**	3582.9	25	4213.4	52	630.5	**27**
HN046	5184.3	65	5709.3	82	525.0	**17**	2613.6	13	2823.6	32	210.0	9
HN052	1944.2	2	2116.7	3	172.5	**1**	3544.0	18	4120.9	32	576.9	**14**
HN060	4652.3	62	5378.2	79	725.9	**17**	826.8	0	867.5	0	40.8	0
HN090	3211.7	21	3267.7	24	55.9	3	3678.0	31	4096.8	47	418.9	**16**
HN129	4735.3	64	5207.6	75	472.3	**11**	4004.7	32	4612.6	39	607.9	7

Bold font suggests a more than 10% NTCP increase. A positive percentage indicates an increase from the plan and a negative percentage depicts a decrease from the plan.

Abbreviation: NTCP, normal tissue complication probability.

less than 5% relative increase above the originally planned maximum delivered dose. Again, an increase in delivered dose beyond what was originally predicted does not mean that the structure exceeded its known tolerance dose.

As demonstrated in the central and right panels of **Figure 2**, for maximum dose, only 3 patients' brainstems and 3 patients' spinal cords received ≥ 5% dose than was originally planned and approved. The majority of total dose increases occurred in the parotid glands as priority is typically given to adequate dose coverage of the target, which can subsequently and (sometimes) unavoidably spill dose to the immediately adjacent parotid gland(s).

We next curated a set of patients of interest who had at least 1 parotid gland that was prescribed a greater than 26 Gy mean, initial planning dose, and for which the subsequent delivered mean dose was even higher than the planning goal by more than 4 Gy.[10] The dosimetric difference for parotid glands in this patient subset is listed in **Table 3**.

Of 74 patients, 10 experienced a nontrivial variation of the delivered dose in parotid glands (according to the previously stated criteria), which resulted in NTCP increases compared with the anticipated NTCP in the original plan, ranging from 11% to 44%. **Table 3** lists the planned and delivered NTCPs in parotid glands. Notably, the NTCP in the right parotid glands increased by 44% and 27% in HN010 and HN030, respectively, and the NTCP of HN010 in the left parotid glands increased by 23%, which suggests a potential negative biological response. Further, we found HN010's weight went from 218.9 to 198.2 lb over the course of treatment, representing a loss of 20.7 lb or 9.4% of original weight. The primary gross tumor volume (GTV) was 26.4 cm^3, while the nodal GTV was 51.2 cc. Subject HN030's weight went from 185.7 lb to 163.3 lb over the course of treatment, a loss of 22.4 lb or 12.1% of the original weight. Their primary GTV was 26.0 cc, while the nodal GTV was 33.9 cc. With relatively large primary GTVs that reduced in volume over the course of treatment, along with weight loss, it is not surprising that the parotids migrated closer to the high-dose area of the plan as treatment went on. While these 2 patients were theoretically expected to have a greater than 1 in 2 chance of experiencing grade 2 or higher xerostomia, they were clinically observed to only have grade 1 xerostomia, a very common effect seen in our patient cohort.

Discussion

In this study, we used in-room, CTOR-generated FBCT datasets, equivalent to the high-fidelity fan-beam simulation CT datasets used for the original plan calculation to recalculate daily variations to the dose actually delivered to 74 patients with HNC during more than 2200 treatment fractions, using an average of 19 daily imaging sessions per patient. When daily images were not available for dose calculation, the most recent CT image set and dose calculation were used, with the intent of characterizing dose delivery integrity for each day on which treatment was delivered. While an

average of 19 daily FBCT image sets were acquired per patient, with 14 out of 74 patients having daily FBCTs corresponding to each fraction, 24 patients having an average of 1-2 treatment fractions per validation FBCT, and 36 patients having an average treatment fraction per FBCT greater than 2, we acknowledge this approach as a limitation relative to having verification FBCTs acquired every day for all patients. The use of high-quality fan-beam datasets from in-room CTOR for all daily imaging sessions ensures that the daily dose variations we characterized are equivalent in fidelity to the original, planned dose distributions, overcoming the limitations of other approaches that used less accurate CBCT-generated dose recalculations. Whether by physician directive or due to machine downtime, a minority of patients included in this cohort had images for every day of treatment. Multiple approaches exist to estimate dose metrics at time points that do not have corresponding image data, including averaging metrics over time, using the CT from the date closest to the date missing an image, or using deformation to generate synthetic images of the day, to name but a few. Each approach endeavors to estimate the state of relevant anatomy on days for which the dose was delivered, but imaging was not available, and each approach entails the potential for introduction of uncertainties in the final calculation. Changes in daily imaging can be random or systematic and can occur acutely or progressively over time. In the absence of daily imaging, precise dynamics are ultimately unknown and it remains unclear as to which approach may be best for a particular scenario. In this work, we chose to use the FBCT dataset from the most recently acquired date as the representative daily image since this method has been previously employed.[19] We acknowledge that anything short of daily imaging for all patients represents a limitation of this study.

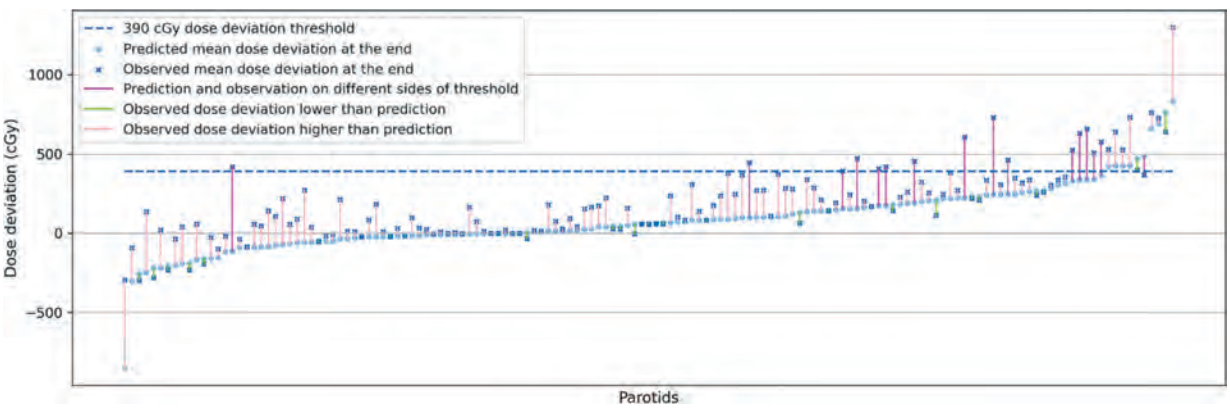
The presented data confirm that the vast majority of patients treated using high-quality daily image guidance receives delivered dose distributions that are very consistent with the originally planned treatment. However, nontrivial variations in delivered dose were still observed for multiple patients. Nontrivial increases to the parotid gland demonstrate that even when rigorous, high-quality image guidance is performed, clinically concerning variations to predicted dose delivery can occur.

With regard to dose variation, significantly more patients experienced increases in delivered dose (vs decreased dose) of the parotid gland, which is reasonable when we consider that typical planning isodose distributions achieve full coverage of the immediately adjacent target area by carefully carving out a narrow window of sparing for the parotid gland. Any variation or change in patient body habitus (eg, weight loss) can easily cause the previously protected parotid gland to shift into the high-dose region, and thus be overdosed.

While significant increases in the delivered dose, relative to the planned dose, are of obvious potential concern, the most important factor to consider is the biological impact. We curated 10 patients (13.5%) as patients of interest to better characterize biological impact, for which we subsequently calculated the NTCP for a xerostomia endpoint. Remarkably, 2 of the 10 patients of interest experienced more than a 25% increase in the original probability of xerostomia (27% and 44%, respectively), which characterizes the clinically significant increase in risk to the patient vs simple quantification of delivered dose variation.

To evaluate the potential need to replan during the treatment course, we also explored the correlation between the dosimetric data at the middle and the end of the treatment, as previously proposed by Hunter et al[10] and McCulloch et al[11] where it was suggested that a midcourse dose deviation is likely to be predictive of the outcome for the entire treatment course. Recently published data from McCulloch et al[11] suggested that a less than 15% deviation between planned and delivered doses for parotid glands would not have a significant toxicity impact on a patient population. While this threshold may be debatable, we endeavored to investigate the validity of this assertion for our own dataset. In **Figure 3**, we plot the deviation from the total planned to total delivered mean dose received by 147 parotid glands of 74 patients. Additionally, we calculated the deviation from accumulated planned dose to accumulated delivered mean dose in the first half of the treatment for each parotid gland and scaled each by 2 to serve as the predicted deviation at the end of the treatment (light blue dots in **Figure 3**). The predicted mean dose deviation at the end of the treatment is connected by color-coded segments to the actual observed total mean dose deviation at the end of the treatment. We ordered the parotid gland data by the predicted mean dose deviation for improved illustration and understanding. We defined the dose deviation threshold (dark blue dashed line) for the entire treatment course at 15% of the prescribed mean dose of 26 Gy for the parotid glands, resulting

Figure 3. Correlation between predicted mean dose deviation and observed total mean dose deviation. Parotid glands are sorted ascendingly from left to right by predicted mean dose deviation at the end of the treatment (light blue points). The corresponding observed total mean dose deviations (dark blue crossmark) are connected by color-coded segments to predicted mean dose. For the parotids that saw decreases from predicted deviation to observed deviation, we use light green to color the segments. For the parotids that saw increases from predicted deviation to observed deviation, but prediction and observation are on the same side of the threshold (dashed line), we use light pink to color the segment. For the parotids that saw increases from predicted deviation to observed deviation, where prediction and observation are on the different sides of the dashed line, we use dark pink to color the segment to underscore the significance of the subject.



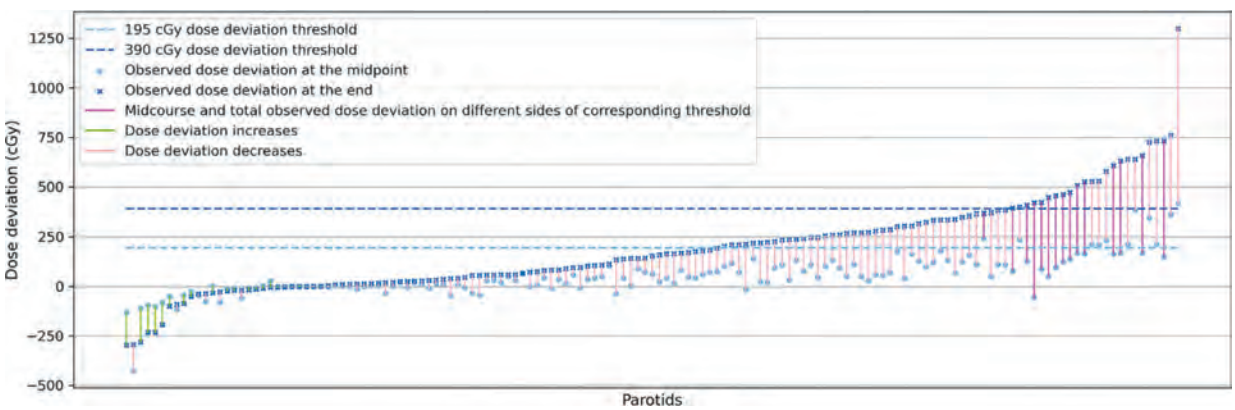
in a value of 3.9 Gy. As can be seen, 10 patients' parotid glands had a predicted mean dose deviation exceeding a 3.9 Gy dose deviation threshold, ie, 15% of the 26 Gy prescribed mean dose for parotid glands. Among these, 3 parotid glands saw a decrease from predicted deviation to observed total dose deviation, and for 1 the observed total mean dose deviation fell under the 3.9 Gy threshold, suggesting a 90% positive predictive value (PPV) in the cohort. For the parotid glands where the predicted dose deviation did not surpass the 3.9 Gy threshold, 14 of these saw the observed final dose deviation reach above the threshold, indicating an 89.8% negative predictive value (NPV). Thus, the sensitivity of this model is only 43.5% despite a 99.2% specificity. We also investigate the two-thirds and three-fourths points of the treatment course: both of these checkpoints exhibit improved PPV (100%), NPV (92.54%), sensitivity (56.52%), and specificity (100%). However, it is worth noting that a later evaluation time point may potentially nullify the advantages gained through adaptive replanning.

To ascertain a proper threshold for predicting the need for replanning, we reorganized the parotid gland data in **Figure 3** and visualized them in **Figure 4** by sorting the parotid gland ascendingly from left to right by observed total mean dose deviation with the observed midcourse mean dose deviation. In addition to the 3.9 Gy dose deviation threshold, we also show a 1.95 Gy threshold (light blue dashed line), which is half of 3.9 Gy, serving as the observed midcourse mean dose deviation threshold. We endeavored to investigate the pattern of the corresponding midcourse dose deviation of the parotid glands, whose final deviation is above 3.9 Gy (midcourse deviation threshold at 1.95 Gy). The minimum dose deviation of this group of parotid glands at the midpoint of the treatment was −56 cGy, which indicates that after going through the first half of the treatment, the actual delivered mean dose was even lower than the prescribed mean dose. In **Figure 4**, in spite of the upward trend of the dark blue crossmarks representing different parotid glands' observed total mean dose deviation, we could not observe an upward trend in midcourse dose deviation (light blue points), regardless of the variance of the midcourse deviation increases with the trend of total dose deviation.

In the interest of identifying a specific threshold model to identify patients in need of replanning, we also investigated the correlation between predicted and actual total dose deviation. In **Figure 5A**, we plot 147 parotid glands in the 2D space with predicted total dose deviation on the *x*-axis and actual total dose deviation on the *y*-axis. The color of the sample points is proportional to the difference between the observed and predicted dose deviations.

The more red the data points are, the larger the positive dose difference that exists. The more blue the data points are, the larger the negative dose difference that exists. We leveraged a linear regression model to represent the correlation of the 2 variables and visualized it as the yellow dashed line. To yield a more intuitive illustration,

Figure 4. Correlation between observed mean dose deviation at midpoint of the treatment and at the end of the treatment. Parotid glands are sorted ascendingly from left to right by observed mean dose deviation at the end of the treatment (dark blue crossmark). The corresponding midcourse mean dose deviations (light blue points) are connected by color-coded segments to total mean dose deviation. For the parotids that saw decreases from midcourse to total observed mean dose deviation, we use light green to color the segments. For the parotids that saw increases from midcourse to total observed mean dose deviation, but the 2 are on the same side of the corresponding threshold (light blue dashed line corresponds to light blue dots, dark blue dashed line corresponds to dark blue crossmarks), we use light pink to color the segment. For the parotids for which the midcourse and total observed mean dose deviation are on the different sides of the corresponding dashed line, we use dark pink to color the segment to underscore the significance of the subject. In spite of the upward trend of the dark blue crossmarks representing different parotid glands' observed total mean dose deviation, we could not observe an upward trend in midcourse dose deviation (light blue points), regardless of the variance of the midcourse deviation increases with the trend of total dose deviation.



we also plotted a green dashed line with slope = 1 and *y*-intercept = 0. From **Figure 5A**, we observe that 116 parotid glands saw an increase from predicted total dose deviation to observed total dose deviation (points located above the green dashed line), and 72 out of 147 parotid glands had a positive predicted dose deviation and an even larger actual dose deviation. We observed that the majority of parotid glands (78.9%) received more dose in the latter half of the treatment than in the first half of the treatment. This observed pattern is consistent with our experience: many patients may experience weight loss resulting from the first half of the treatment, which can lead to a larger variation from the initial calculated dose in the latter half of the treatment.

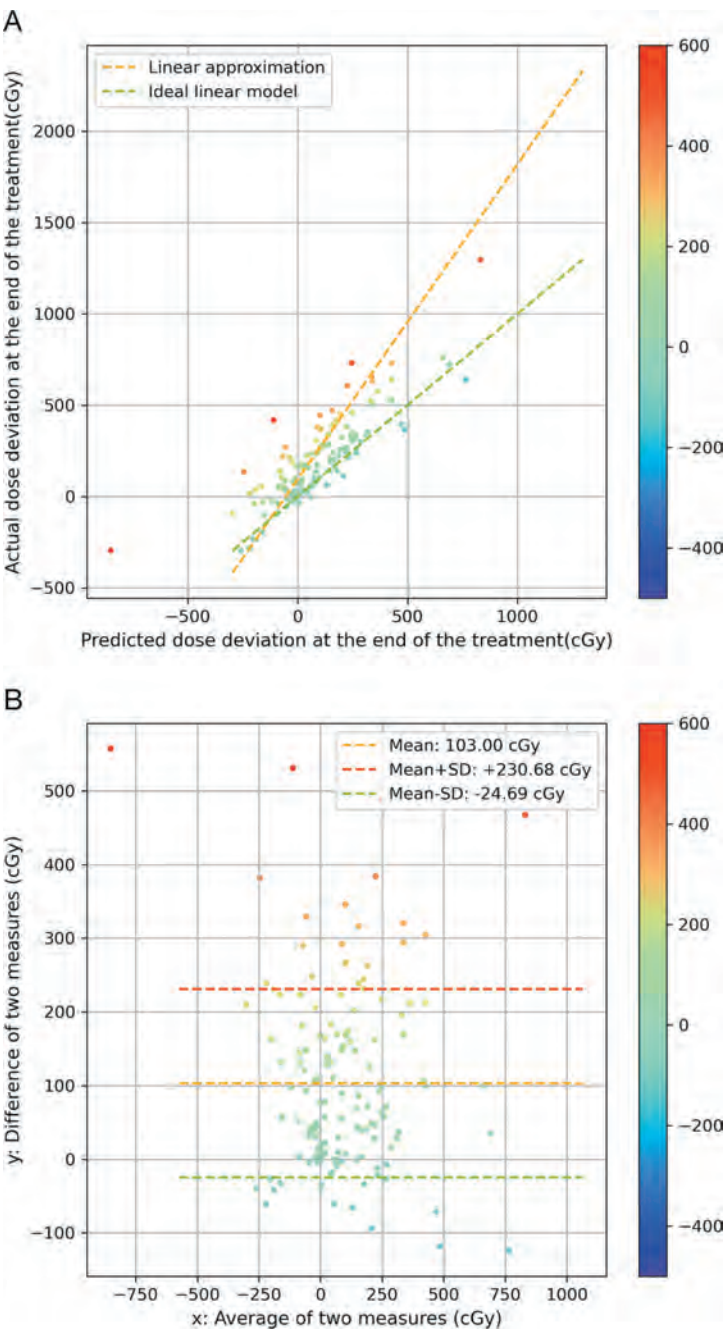
In **Figure 5B**, we present a Bland-Altman plot to analyze the agreement between the observed dose deviation and predicted dose deviation. Ideally, a reference measure should have all the sample points located on the $y = 0$ line (difference of 2 measures equals to 0). However, as shown in **Figure 5B**, most of the sample points are located above the $y = 0$ line, with the mean difference equal to 103.0 cGy and a standard deviation of 127.7 cGy. Therefore, we do not find any special pattern of the distribution with respect to the average of the 2 measures, ie, the data points are rather evenly distributed along the average of 2 measures' axes. Or, in other words, the difference between the predicted and observed total dose deviation is not strongly correlated with the predicted total dose deviation; therefore, a midcourse evaluation of the need for replanning is unable to predict overdosing of critical OARs at the end of the treatment.

The high-fidelity CTOR-derived, delivered dose data presented here make clear that a limited subset of patients may experience clinically relevant increases in delivered dose, even when these patients are treated with daily, high-resolution image guidance. Our data further confirm that, through the use of high-quality FBCT-based dose recalculation, some degree of adaptive replanning will be needed for a subset of patients and, furthermore, a midcourse evaluation of dose deviation is not necessarily effective in predicting the need for replanning for all patient populations.

Conclusions

Our use of gold standard FBCT image data allowed for characterization of the total delivered dose for each of the 74 patients with HNC studied here with accuracy comparable to the original simulation-based dose calculation and, thereby, eliminated the uncertainties of previous CBCT-based studies. The accumulated total delivered dose distributions agreed well for the vast majority of patients in this dataset. However, clinically notable deviations were observed for the summed delivered dose to the parotid glands of 10 patients, leading to NTCP increases of 11% to 44%. We further determined that a midcourse evaluation of

Figure 5. 2D distribution of parotid glands in the space of final actual dose deviation—final predicted dose deviation at the end. Points are color-coded by the residual to the ideal linear model (A). Bland-Altman plot of actual dose deviation and predicted dose deviation in parotid glands. Points are color-coded by the difference between the actual dose deviation and the predicted dose deviation.



dose deviation was not effective in predicting the need for replanning for our patient cohort.

The high-fidelity FBCT-based dose data presented here should be extremely useful for exploring novel strategies to most effectively predict the need for and timing of replanning efforts, a topic of future work for our group.

Therefore, it is important to appreciate how inherent and unavoidable setup discrepancies, combined with anatomical changes over time, can manifest as nontrivial deviations of the intended delivered dose. These nontrivial increases to parotid gland delivered dose suggest that even when rigorous, high-quality image guidance is performed, clinically concerning variations to predicted dose delivery can still occur.

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Gastric Fistula After MR-Guided Stereotactic Body Radiation Therapy for Hepatocellular Carcinoma

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Abstract

Integration of locoregional therapies such as stereotactic body radiation therapy (SBRT) is increasing in the treatment of hepatocellular carcinoma (HCC), the most common primary cancer of the liver. A 68-year-old man with hepatitis C was diagnosed with American Joint Committee on Cancer stage 2 (cT2N0M0), Child-Pugh class A, multifocal HCC. He completed adaptive MR-guided stereotactic body radiation therapy (MRgSBRT) for a total dose of 50 Gy in 5 fractions. At the 3-month follow-up, a three-phase abdominal CT showed a decrease in the size of the treated lesion and a new gastric fistula was noted. He started a proton pump inhibitor and remained under close observation. At the 6-month follow-up, imaging showed a decrease in tumor size with continued evidence of a contained fistula. Severe side effects are possible following MRgSBRT to the liver, even with the utilization of adaptive treatment, highlighting the importance of attention to high-dose isodose lines near normal tissues and adherence to dose constraints.

Keywords: hepatocellular carcinoma, MRgSBRT, fistula

Case Summary

The patient is a 68-year-old man with a history of hepatitis C, hypertension, hyperlipidemia, and an initial diagnosis of American Joint Committee on Cancer stage 2 (cT2N0M0), Child-Pugh class A, multifocal hepatocellular carcinoma (HCC). Eight years prior, he received multiple courses of chemoembolization. A surveillance follow-up CT scan recently demonstrated a solitary, active tumor in segment 2/3 abutting the stomach. Following his presentation at a multidisciplinary tumor board, he was referred for possible stereotactic body radiation therapy (SBRT). The patient reported feeling well overall, although he did endorse mild, intermittent episodes of nonradiating abdominal pain. Upon physical examination, there was no evidence of jaundice, ascites, or abdominal tenderness. His recent lab values included an international normalized ratio (INR) of 1.05, albumin of 4.2 g/dL, bilirubin of 0.8 mg/dL, and an AFP of 21.2 ng/mL. INR was measured to evaluate blood clotting and anticoagulation, and AFP was measured as a liver tumor marker.

Imaging Findings

His most recent CT scan of the abdomen demonstrated a single site of active disease within segments 2 and 3 of the liver measuring up to 7 cm with an exophytic component causing abutment of the stomach (**Figure 1**), confirming the recommendation for MRI-guided SBRT. Given the proximity of the stomach to the tumor, endoscopic evaluation was performed within 3 months of the referral for radiation consideration and no invasion of the tumor into the stomach was observed. He underwent a planning

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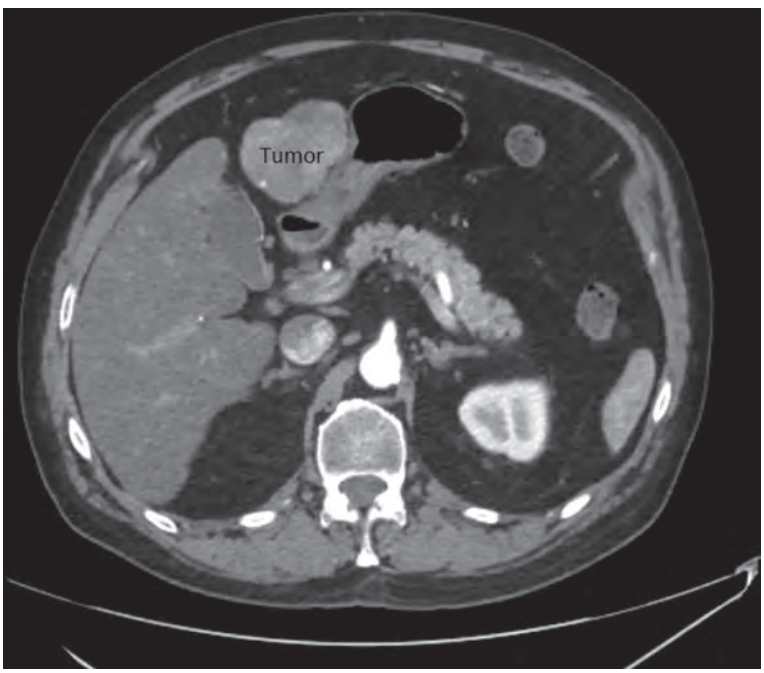
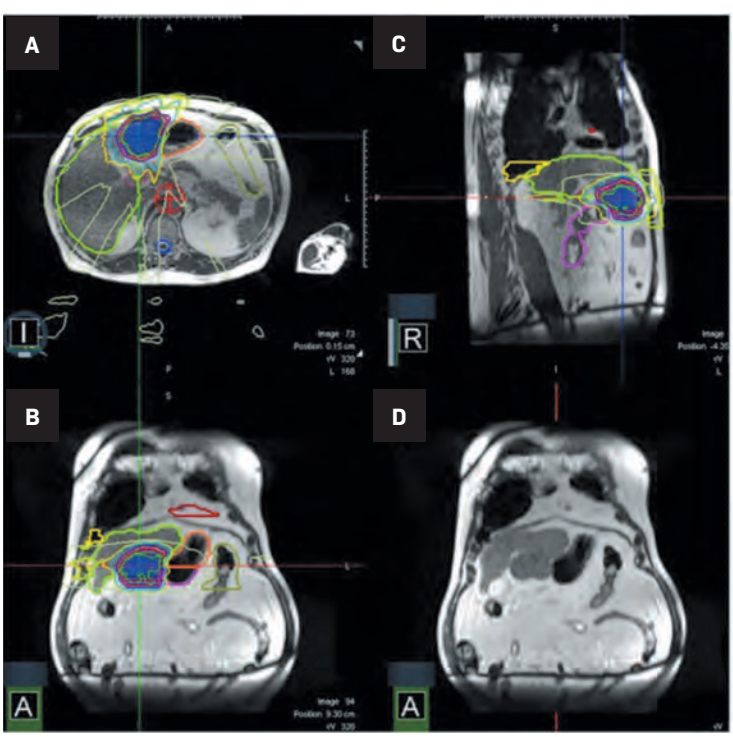
Figure 1. Patient's initial CT scan showing active disease within segments 2 and 3 of the liver measuring up to 7 cm.



CT and MRI simulation the following week. He was instructed to have nothing to eat for 3 hours prior to simulation and daily treatment. He received 50 Gy in 5 fractions with an adaptive workflow on the MRI linac (**Figure 2**). Overall time on the treatment table was roughly 1-1.5 hours, with no routine imaging post-treatment per institutional protocol. He tolerated treatment well, denying any acute side effects. All normal tissue constraints were met as per BR-001[1] with the exception of the 5 cc constraint for duodenum, which we do not commonly use; however, all constraints were met based on Radiation Therapy Oncology Group (RTOG) 1112[2] (**Table 1**).

At the 3-month follow-up, the patient endorsed intermittent episodes of nausea without vomiting and mild, intermittent

Figure 2. Isodose lines for MR-guided stereotactic body radiation therapy (MRgSBRT) treatment (A-E). (L= left, R = right, A in the bottom left corners = anterior)



E

Isodose Lines
Rx Dose = 50.00 Gy

Dose (Gy)	Rx (%)
55.00	110.00
50.00	100.00
47.50	95.0
45.00	90.0
30.00	60.0
25.00	50.0
10.00	20.0

Table 1. Dosimetric Constraints

	GOALS		ACHIEVED
	BR-001	RTOG 1112	PATIENT
Stomach	V35 < .5 cc V26.5 < 5 cc	V30 < .5 cc V25 < 5 cc	V35 at .01 cc V30 at .5 cc V25 at 2.65 cc V26.5 at 1.75 cc
Duodenum	V30 < .5 cc V18.3 < 5 cc	V30 < .5 cc	V30 at .14 cc V28 at 5 cc
Bowel	V40 < .03 cc V28.5 < 20 cc	V30 < .5 cc	V30 at .00 cc V28.5 Gy at .00 cc

Abbreviation: RTOG, Radiation Therapy Oncology Group.

episodes of nonradiating abdominal pain that had remained stable since before treatment. The patient denied any fever or chills, and there was no evidence of ascites or abdominal tenderness. Lab work revealed a decrease in AFP to 10.6 ng/mL. A triple-phase CT scan of the abdomen showed a slight decrease in size of the treated left liver mass measuring 4.6 × 5.3 cm with gas and fluid components and communication to the lumen of the stomach.

Diagnosis

The patient in this case completed adaptive MRgSBRT for 50 Gy in 5 fractions (**Figure 2**). Each of the 5 plans had luminal structures exceeding tolerance, requiring daily adaptation. Looking back at each predicted dose based on daily anatomic changes, the bowel/duodenum tolerance would have been exceeded on all days and the stomach tolerance would have been exceeded on days 2 and 4. To adapt the treatment, a 50-Gy optimization structure was created. The optimization structure was defined by the planning target volume (PTV) 50 minus planning organ at risk volume (PRV) of gastrointestinal (GI) structures (bowel, duodenum, and stomach plus 5 mm). With the adaptive workflow, we were able to meet all constraints daily and achieve reasonable coverage of the gross tumor volume (GTV) and PTV. At least 90% of the GTV received 50 Gy daily, and the area that was undercovered was the area abutting the stomach. The patient was treated with automatic beam gating and deep inspiratory breath hold for motion management.

The results of the triple-phase CT at the 3-month follow-up were consistent with gastric wall invasion and fistulization (**Figure 3**). The fistula appeared to be asymptomatic, and close observation was pursued after review with a surgical oncologist. The patient was recently placed on a proton pump inhibitor (PPI) therapy with his primary care provider and was advised to continue this medication.

At the 6-month follow-up, the patient reported feeling well, the abdominal examination was without abnormality, and the lab work revealed an alpha-fetoprotein (AFP) value of 16.1 ng/mL. A repeat triple-phase CT of the abdomen demonstrated continual decrease in size of the treated segment 2/3 left hepatic lobe mass, with an internal air-fluid level, and stable fistulization to the stomach that measured 2.1 × 3.4 cm (**Figure 3**). The soft-tissue thickening of the involved stomach wall was not significantly changed. There was an interval increase in size of a new arterial-enhancing segment 4A lesion, now measuring 2.2 × 2.6 cm, likely suggestive of disease progression.

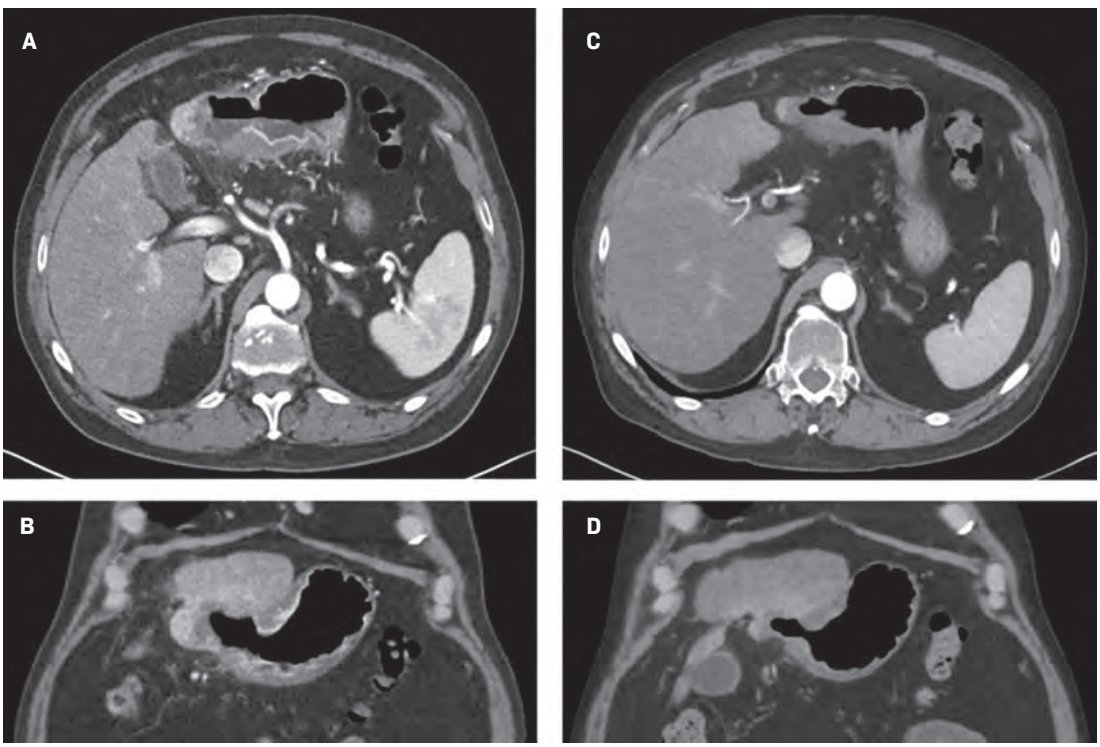
As the fistula had not changed significantly upon imaging and he remained asymptomatic, the patient was advised to continue PPI therapy and seek medical care should symptoms. He was referred to interventional radiology for consideration of percutaneous ablation for his progressive hepatic segment 4A lesion given the favorable location and size.

Discussion

Hepatocellular carcinoma is the most common primary cancer of the liver.[3] The preferred mode of treatment is transplant or resection with locoregional therapies such as ablation and external beam radiation therapy (EBRT) as bridging treatments.[3] Only 10% to 30% of patients at diagnosis are surgically eligible.[4] In nonsurgical cases, locoregional therapy is used as a primary treatment. These established local treatments include interventional radiology ablation, arterially directed therapies, and EBRT.[3,5,6]

Stereotactic body radiation therapy is a form of EBRT that delivers precise high doses of radiation to a tumor—typically in the dose range of 30-50 Gy in 3-5 fractions.[3] SBRT for HCC has potential benefits that include a decreased amount of normal

Figure 3. A 3-mo follow-up CT scan showing axial (A) and coronal views (B). A 6-mo follow-up CT scan showing axial (C) and coronal views (D).



tissue irradiation, a shorter overall treatment, and high 1-, 2-, and 3-year control rates of 87% to 93%, 74% to 89%, and 86%, respectively.[7,8] Although prospective studies have reported high rates of local control and low rates of morbidity, until recently there was no reported increase in survival.[9] In the recently reported RTOG 1112 trial, there is now a reported survival advantage of SBRT plus sorafenib (median overall survival, OS, = 15.8 mo) compared with SBRT alone (median OS = 12.3 mo).[9] With the recent evidence supporting the role of immunotherapy (IO) in HCC, there is now also interest in exploring SBRT in combination with IO, but currently, there are little data regarding outcomes.[10-13]

Due to the proximity of GI organs-at-risk (OARs), there is an increased risk for toxicity after SBRT to the liver. Late reactions and toxicities from SBRT occur 3 or more months after the completion of radiation therapy and include gastritis, ulceration, perforation, and significant GI bleeding.[14] Fistulation is a rare secondary consequence of ulceration that occurs at a rate of >5%. In a meta-analysis involving 1950 HCC patients treated with SBRT, grade 3 or higher hepatic and GI toxicities were 4.7% and 3.9%, respectively.[5] Within GI toxicity, 10.5% of patients experienced a grade 3 or higher toxicity, including grade 4 gastric ulcer perforation in 4.3% of patients.[5] Tolerance doses for structures such as the esophagus, stomach (**Table 1**), or intestine are much lower than ablative doses used for SBRT, requiring special consideration for tumors close to luminal structures.[15] Current treatments for ulcers and fistulas include PPIs, hyperbaric oxygen, and partial gastrectomy.[14]

New technologies that improve the precision of SBRT delivery, such as MRgSBRT, have allowed for a reduced risk of toxicity for abdominal SBRT.[16-18] The MR linac produces superior soft-tissue contrast and imaging while enabling daily imaging with sufficient quality that allows for daily plan adjustments according to interfraction organ motion.[17,19] The target volume and OARs are recontoured daily.[5] The use of an onboard cine-MRI during treatment allows for direct visualization of tumor motion, ensuring accuracy of radiation delivery while minimizing irradiating nondiseased tissue.[12] For tumors with respiratory motion, guided breath holds allow for maintenance of the tumor's position within the boundary for treatment and optimized target positioning.[17] Studies have shown that 66% of liver fractions have

benefited from online adaptation and that the online-adaptive planning revealed unintended OAR constraint violations that would have occurred in nonadaptive fractions at a rate of 63%.[19] MRgSBRT optimizes the dose targeting the tumor while minimizing normal tissue irradiation, thus potentially widening the therapeutic index.

Studies evaluating the extent of intrafractional and interfractional liver motion on conventional linear accelerators (linacs) before and after SBRT have reported small variation, with Case et al showing that 80% of patients had a maximum amplitude of motion < 3 mm in any direction.[20] However, in this study they did not have the capability to study motion continuously during treatment and tried to keep the treatment time < 25 minutes. There is little literature on the effects of intrafractional movement during MRI-guided radiation treatment. In a study that explored the effects of inter- and intrafraction movement, benefits from plan adaptations were noted.[21] The results showed that the intrafractional adaptation was especially useful for high-dose OAR sparing.[21] It is important to note that small variations—such as differences in respiratory phases and contouring variations—may influence high-dose OAR sparing. At our institution, we do not routinely track possible intrafractional movement of OARs throughout the course of treatment; however, we do track the tumor and that is a strength of the technology. With the upgrades that came after this patient was treated, clinicians have the ability to track intrafraction movement of multiple structures (tumor, isodose lines, and OARs).

Due to our patient's Child-Pugh class A status and the large tumor size, we opted for a plan of 50 Gy in 5 fractions to maximize local control given his only site of disease. The biologically equivalent dose of 50 Gy in 5 fractions is analogous to the 3-fraction approach used in Child-Pugh A; if the patient was Child-Pugh B, the chosen dose would be 40 Gy in 5 fractions.[22] While recognizing different lower dosage options in the RTOG 1112 trial (27.5-50 Gy), the radiosensitizer sorafenib used could allow for lower-dose sensitivities.[2] Constraints under RTOG 1112 were still met under the utilized dosing scheme for this case. The entire time to adapt and deliver the treatment exceeded 1 hour daily. Although his stomach was contoured at the beginning of treatment, there was no mechanism to ensure that his stomach volume remained constant throughout. It is possible that he had additional gastric filling during his prolonged daily treatment times, and that the change could have accounted for increased cumulative dose to this region. At our institution, we do not have the capacity to do routine post-treatment imaging. However, in cases such as this with disease immediately adjacent to normal GI mucosal structures, perhaps mid- and post-treatment imaging should be routine so that the cumulative dosimetry can be confirmed.

Conclusion

This case demonstrates that despite the adoption of technological advancements that improve SBRT, incidents of severe side effects, such as fistulation, can still occur. MRgSBRT provides an adaptive method of treatment that allows for real-time, optimized normal tissue visualization to provide highly conformal, high-dose isodose lines that strictly adhere to dose constraints. More studies are needed to determine the extent of intrafraction tumor/normal tissue movement for upper abdominal tumor sites with treatment times approaching 1 hour.

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Pennies to Policy: The Importance of Resident Financial Fluency

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Resident wellness measures tend to focus on concepts like burnout, resilience, and stress related to clinical work, and less so on other stressors like financial management during residency. Similarly, patient quality-of-life outcomes in radiation oncology trials are primarily based on radiation-related toxicities and functional outcomes, and less frequently on aspects such as financial toxicity. Financial literacy is vital to resident education as trainees develop personally and professionally and advocate for their patients.

Personal Finance

The median medical school debt is over $200K, and many residents have additional debts and low retirement savings.[1,2] Studies of residents have demonstrated increasing emotional exhaustion and burnout with increasing debt.[3] Despite high debt, financial literacy is poor among physicians. As medical students and residents, we are so focused on clinical competency that we may neglect to learn the personal finance skills that many of our nonmedical peers are proficient in. In some radiation oncology residency programs, financial education may include a lecture by a financial advisor or physician, but most residents feel unprepared to handle future financial decisions, especially in programs that do not provide any financial education.[4,5]

Professional Finance

It is easy to think the financial stressors of a resident can be solved with a future attending salary. However, radiation oncology graduates are often ill-equipped to understand the finances of independent clinical practice.[6] Though we are training in a field where technology is changing and subtle differences in coding can lead to large differences in billing, residents rarely receive training in business management. As a result, professional societies have developed some resources to demystify coding and billing, though these are targeted to early professionals and not typically to residents. Beyond the finances of an individual physician's practice, it is helpful to understand the evolving economics of radiation oncology groups. Practice consolidation is increasing as large practices are employing a greater proportion of radiation oncologists.[7] Large oncology groups are being acquired by private equity firms. This year, one of the largest community oncology networks was acquired by a private equity firm in a $2.1 billion deal.[8] Over the past two decades, 724 oncology clinics became associated with a private equity backed firm, over half of which were radiation oncology practices.[9]

Patient Finance

Medical bills are the top cause of personal bankruptcy in the United States.[10] On a more promising note, health care price transparency is

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an increasing topic of legislation.[11] As trainees, we should understand how insurance companies choose to cover expenses and how to search for resources that can assist a patient with financial concerns. Beyond radiation treatments, we provide medication prescriptions and referrals for services such as dental procedures and physical therapy that can place a financial burden on patients. We as physicians should be able to provide patients with information to access financial assistance programs, local options through the county or VA, and opportunities for discounted medications (or, if you have a social worker in your department, know how they can assist your patients).

Health Care System Finance

In a broader sense, understanding the interplay between billing, insurance payments, and governmental legislation is vital to understanding how the health care system impacts us and our patients. The ACGME requirements for radiation oncology programs state that programs must ensure resident education in administration and financial principles of medical practice and health policy.[12] Even as reimbursement models evolve, many trainees leave residency not well versed in health policy and reform. In an effort to improve exposure to health policy, resident groups within professional societies have increasingly started to integrate advocacy. Webinars on topics like payment reform and introductions to advocacy are hosted throughout the year. ACR, ACRO, and ASTRO have advocacy/government relations fellowships to provide experience in health care policy and payment reform. Multiple societies participate in their respective "Hill Day" to lobby Congress on bills, and residents can participate in these groups. Resident subcommittees focusing on advocacy are also increasing in number. This year, the ARRO Communications subcommittee has rebranded itself as "Communication and Advocacy" with the hopes of incorporating policy work into its communications efforts.

Athough there is an increasing focus on advocacy and payment reform education, residents typically seek out these resources if they have a pre-existing interest. Financial fluency as it pertains to personal wellness, professional development, patient care, and advocacy is crucial to every radiation oncology resident. Continued efforts to integrate financial education can potentially mitigate aspects of burnout during training and early career, help residents advocate for their profession and patients, and increase empathy for patients navigating a complex health care system.

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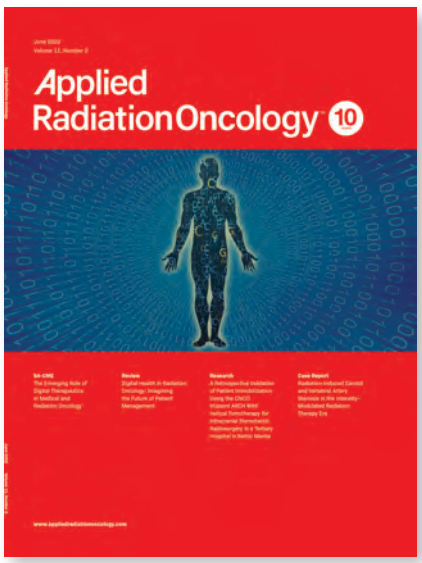

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