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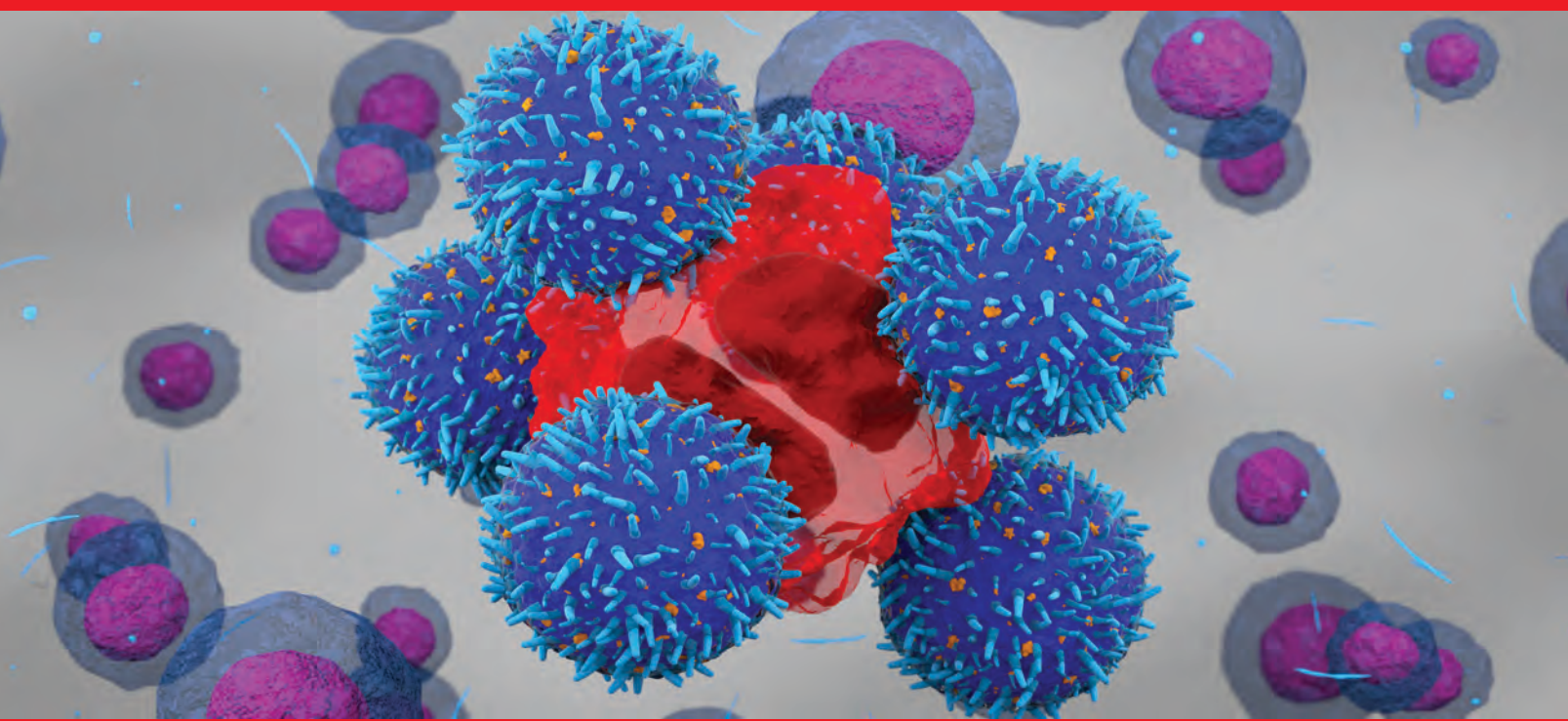

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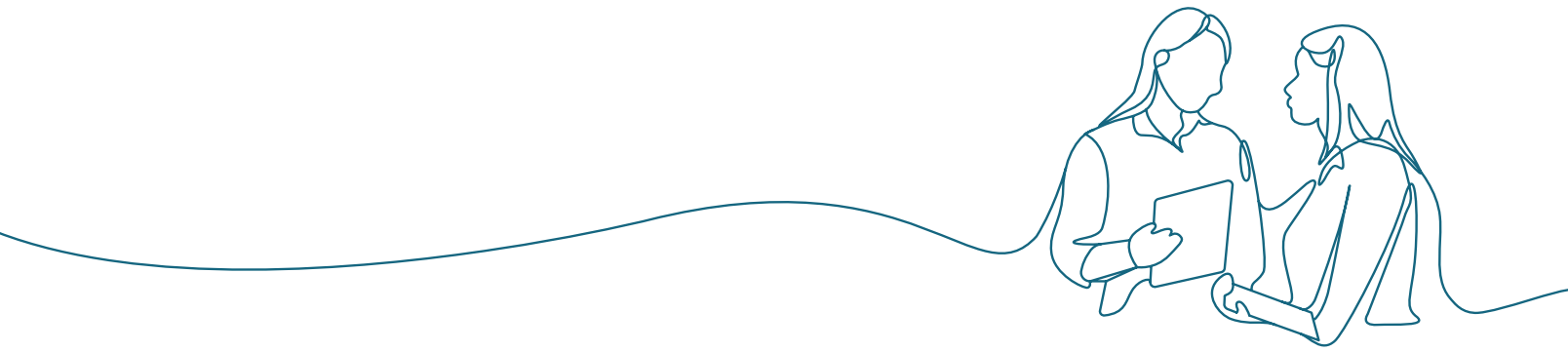

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Celebrating Service and a New (Green) Leaf

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

John J. Suh, MD, FASTRO, FACR

Happy autumn! We hope the shift in seasons and recent annual ASTRO meeting have motivated you to adopt some new techniques or approaches in patient care, research, education, or leadership. It's an exciting time of year brimming with change.

We have a few changes of our own to share, namely that *ARO* is going green in 2025, transitioning to all-digital issues. In addition to offering PDFs of all journal articles, appliedradiationoncology.com will host a complete edition of each issue that can be digitally paged through, as we have done for many years. This move underscores our commitment to sustainability while continuing to provide the high-quality content our readers expect.

We also want to acknowledge and thank Farzan Siddiqui, MD, PhD, for his exceptional service and dedication to *ARO* for more than 10 years. Dr Siddiqui is rotating off our editorial advisory board as he assumes new leadership roles at ASTRO and Henry Ford Hospital. His contributions to both clinical practice and the development of our journal have been invaluable, and we celebrate his unwavering commitment to advancing the field of radiation oncology.

Change also underscores the theme of this issue's Resident Voice column, *Help Us Swim*, which reflects on the intense demands of residency. This compelling editorial advocates for structured assessments and entrustable professional activities that would better equip future radiation oncologists. The goal: transforming an overwhelming residency experience into one that fosters deeper mastery and confidence.

We are also proud to feature *Anal Squamous Cell Carcinoma (ASCC): From Standard Treatment to Personalized Therapy*. This CME-approved article examines both the current standard-of-care and innovative, future approaches to managing ASCC including therapy de-escalation strategies and the exciting potential of integrating liquid biopsies and molecular biomarkers. This shift toward a personalized, biomarker-driven approach shows great promise in ASCC treatment.

Next, we present *Viral-Mediated Hepatocellular Carcinomas (HCCs): A Review on Mechanisms and Implications for Therapy,* a thorough examination of the pathogenesis of HCC. The article discusses the encouraging clinical outcomes seen with immunotherapy and radiation therapy for advanced HCC and explores the synergistic effects of immune checkpoint inhibitors combined with radiation.

Our issue also features a research article comparing 2 hypofractionation protocols for prostate cancer treatment. *CHHiP vs PROFIT for Localized Prostate Cancer: A Retrospective Dosimetric Comparison of Organs at Risk* discusses that while the CHHiP protocol involves more complex contouring and planning, it ultimately reduces toxicity in patients receiving moderately hypofractionated radiation therapy. These findings provide important data for radiation oncologists seeking to minimize side effects in prostate cancer treatment.

Another excellent article is *Extracapsular Prostate Brachytherapy Using Iodine-125 for Intermediate and Selected High-Risk Prostate Cancer: Technical Notes*. The authors describe an advanced brachytherapy technique that improves precision in prostate cancer treatment by combining ultrasound and fluoroscopy to optimize seed placement.

We feature several interesting case reports as well. *Exploring the Rarity: A Case Report of Adenosquamous Carcinoma of the Nasal Cavity* presents one of the few reported cases of this aggressive cancer, offering a detailed look at its histology and clinical management. Additionally, *A Rare Case of Skull Base Phosphaturic Mesenchymal Tumor* discusses a rare tumor associated with tumor-induced osteomalacia, highlighting diagnostic challenges and treatment strategies. Finally, *A Rare Case of Mycosis Fungoides of the Scalp Treated With Electron-Beam Radiation Therapy* reports on a case of cutaneous T-cell lymphoma, which is difficult to diagnose due to its similarities with more common skin conditions.

We hope this issue provides valuable insights and stimulates further exploration in our ever-changing field, one that makes a difference in the lives of many patients. Thank you, as always, for your continued support!

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Anal Cancer Review: From Standard Treatment to Personalized Therapy

Description

Anal squamous cell carcinoma (ASCC) is a rare but increasingly prevalent disease, predominantly driven by human papillomavirus infection, with decreasing prevalence among individuals of vaccination-eligible age. This review examines the current standard of care for managing ASCC and explores how advancements in molecular biomarkers are paving the way for personalized treatment strategies. The authors also discuss the potential of immunotherapy as an adjunct to standard-of-care management in all stages of disease.

Learning Objectives

Upon completing this activity:

1. Clinicians will understand the role of emerging biomarkers and treatment options in the management of ASCC.
2. Clinicians will learn how to adopt a personalized approach to ASCC treatment by integrating disease stage and tumor biology into clinical decision-making.
3. Clinicians will learn how to apply current guidelines on the use of biomarkers in the treatment of ASCC.

Authors

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Target Audience

1. Radiation oncologists.
2. Related oncology professionals.

Commercial Support

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Anal Squamous Cell Carcinoma: From Standard Treatment to Personalized Therapy

Mustafa M. Basree, DO, MS;[1]* Ryan Hutten, MD;[1] Quaovi Sodji, MD, PhD;[1,2] Michael F. Bassetti, MD, PhD;[1] Jacob A. Miller, MD[3]

Abstract

Anal squamous cell carcinoma (ASCC) is a rare but increasingly prevalent disease, predominantly driven by human papillomavirus infection, with decreasing prevalence among individuals of vaccination-eligible age. In this review, we discuss both the current standard of care and future approaches for managing ASCC. There is interest in de-escalating therapy to minimize treatment-related morbidity, with studies such as DECREASE and PLATO currently ongoing. The integration of liquid biopsies as well as molecular biomarkers into clinical practice offers an exciting new frontier for personalized ASCC treatment. The future of anal cancer management lies in a personalized, biomarker-driven approach, which holds promise to transform clinical decision-making and enhance both the quantity and quality of life for patients with ASCC.

Keywords: anal cancer, anal squamous cell carcinoma, chemoradiation, virally mediated cancers, HPV-related anal cancer

Introduction

Anal squamous cell carcinoma (ASCC) is a relatively rare disease, accounting for roughly 0.5%[1] of all new cancer diagnoses in the United States (US). There is an annual percentage increase in new cases per year from 2.2 to 2.5 cases per 100,000 since the 1970s across racial categories.[1] Women are more likely to develop invasive carcinoma of the anus compared with men, with 7180 vs 3360 cases in the US in 2024, respectively.[2,3] Mortality estimates in 2024 are 2190 deaths, roughly equal between male and female patients.[2] The median age at diagnosis is 64 years, with a 1.65% annual increase in cases among patients aged 65 and older over the past decade and a 3.12% annual decrease in cases among patients younger than 50.[1]

A cross-sectional study of the US Cancer Statistics database showed that human papillomavirus (HPV) vaccination significantly reduced the incidence of ASCC among roughly 8000 vaccine-eligible patients aged 20-44 years.[3] The authors reported a 24% risk reduction (Relative Risk [RR], 0.76; 95% CI, 0.71-0.83) for in situ cases and 15% (RR, 0.85; 95% CI, 0.81-0.88) for invasive cases from 2009 to 2018 compared with 2001 to 2008.[3] Interestingly, rates of both in situ and invasive cases continue to rise in older, nonvaccination-eligible patients in the same period, highlighting the potential for prevention and early detection.[4] Despite the impact of

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HPV vaccination on the incidence of ASCC, vaccination rates remain low in the US, with only 38.6% of children aged 9-17 years having received at least 1 dose of the vaccine in 2022.[5]

This review will discuss the current standard of care for the management of ASCC and explore how advancements in molecular biomarkers are paving the way for personalized treatment strategies. Additionally, a summary of ongoing clinical trials in the context of those biomarkers will also be provided.

Risk Factors and Screening Considerations

Factors associated with ASCC include HPV infection (predominately genotypes 16 and 18), human immunodeficiency virus (HIV) positivity, sexually transmitted infections, immunosuppression, and tobacco use.[4,6] HPV status and p16 overexpression correlate with survival and recurrence outcomes.[7,8] In HPV-positive tumors, the dysfunction of p53 due to the HPV-E6 protein can sensitize tumors to chemoradiation (CRT). In non-HPV mediated anal cancers (10%-15% of cases), p53 suppression is often unrecoverable due to gene mutations,[7] lowering CRT effectiveness.[9,10] Non-HPV-16 genotypes are potentially more common among patients with HIV.[11]

Individuals with a history of HPV-mediated gynecologic cancers are at high risk for ASCC. The International Anal Neoplasia Society's (IANS) consensus guidelines recommend that women with a history of vulvar cancer or high-grade intraepithelial lesion (HSIL) to start screening for anal cancer within 1 year of diagnosis.[12] Screening for patients over 45 years old with a history of cervical or vaginal cancers or HSIL is determined on a case-by-case basis. A list of screening and diagnostic procedures is further reviewed in IANS consensus guidelines.[12] Furthermore, patients with a new diagnosis of anal intraepithelial lesion or ASCC are recommended to undergo screening for synchronous gynecologic malignancies or HSIL (cervical, vulvar, and/or vaginal) with a gynecologic examination including biopsy of suspicious lesions.[13] A Swedish population-based study of more than 3.7 million women showed an association between history of grade 3 cervical intraepithelial lesions (CIN) and the risk of developing anogenital cancers.[14] The risk of anal cancer was zero in the first year after a CIN diagnosis but increased yearly, with an incidence rate ratio of 4.98 after 10 years compared to women without a CIN diagnosis.[14] Therefore, physicians should remain vigilant in screening for anal cancer in patients with a prior history of gynecologic cancers.

Pretreatment evaluation involves a complete history, physical examination, digital rectal examination (DRE), inguinal nodal evaluation and, if applicable, a gynecologic examination. Staging involves CT scans of the chest, abdomen, and pelvis; pelvic MRI aids in anatomy delineation, treatment planning, and evaluating suspicious findings.[4,13] F-18 fluorodeoxyglucose positron emission tomography/CT (FDG-PET/CT) is recommended for nodal staging and metabolic activity of suspicious features on CT and/or MRI.[13]

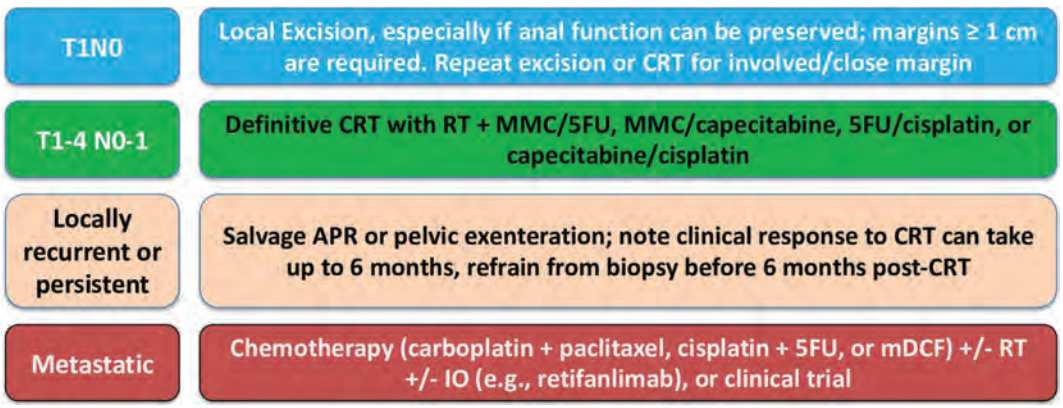
Standard-of-Care Management

Organ preservation is the standard of care for patients with nonmetastatic ASCC (**Figure 1**). For localized tumors less than or equal to 2 cm (T1 per American Joint Committee on Cancer 8th edn), local excision with at least a 1 cm margin may be considered if anal function can be preserved.[4,13] Local excision should generally be reserved for patients with an anal margin or peri-anal tumors with no or minimal involvement of anal sphincter complex. Involved or close margins warrant repeat excision, although this is often challenging. For cases in which excision is not feasible, definitive CRT with 5-fluorouracil (5FU) and either mitomycin C (MMC) or platinum is preferred.

Patients with locoregional disease (T1-4 N0-1 M0) are generally recommended definitive MMC/5FU-based CRT. Radiation alone[15-17] as well as MMC omission are associated[18] with inferior disease control (with better toxicity profiles) compared with CRT. Although MMC remains standard, replacement with cisplatin may achieve similar disease control and decreased hematological toxicity.[19] Capecitabine may be substituted for 5FU.[20-22] There is no role for induction[23,24] or maintenance[19] chemotherapy in nonmetastatic disease. Radiation doses are institution- and country-specific and range from 50 to 60 Gy to the primary tumor, 30.6 to 45 Gy to elective nodes, and 50 to 54 Gy to involved nodes.[4,13,19,24,25] Intensity-modulated radiation therapy (IMRT) is associated with lower toxicity profiles and fewer treatment breaks compared with 3D conformal radiation therapy.[22,25-27] Proton radiation therapy has not been shown to improve disease control,[28] toxicity profile[29] despite favorable dosimetry, or patient-reported outcomes compared with photon-based radiation therapy.[30]

Clinical response can continue up to 6 months post-CRT, even if a complete clinical response (cCR) is not observed by 3 months.[31] Biopsy before 6 months post-CRT is not recommended. The primary method

Figure 1. Clinical management



Abbreviations: 5FU, 5-fluorouracil; APR, abdominal peritoneal resection; CRT, chemoradiation; IO, immunotherapy; mDCF, modified docetaxel (40 mg/m^2), cisplatin (40 mg/m^2), and 5FU (1200 mg/m^2/day for 2 days), every 2 weeks intravenously; MMC, mitomycin C; RT, radiation therapy

of assessing treatment response is DRE and anoscopy, typically 26 weeks after CRT in line with the ACT-II study.[6] Post-treatment radiographic evaluation with pelvic MRI and/or FDG-PET/CT may also be utilized, although that is not routine. Surveillance for patients with cCR includes DRE and inguinal nodal examination every 3 to 6 months for 5 years, and anoscopy every 6 to 12 months for 3 years.[32] In patients with stage II-III disease, imaging of the chest, abdomen, and pelvis is completed annually for 3 years.[32] Approximately 80% of recurrences occur in the first 2 years post-CRT.[33] Up to a third of patients with persistent or recurrent disease will ultimately require salvage abdominal peritoneal resection or even pelvic exenteration depending on extent of disease.[4,13]

Patients with metastatic disease at diagnosis are recommended chemotherapy as first line with carboplatin + paclitaxel, cisplatin + 5 FU, or modified docetaxel + cisplatin + 5FU (mDCF).[4,13,32,34] The addition of checkpoint inhibition with chemotherapy as first-line treatment is institution dependent. While broadly speaking immunotherapy (IO) has been reserved as second-line treatment here, early readout from the PODIUM-303/InterAACT 2 study shows a modest PFS benefit (9.30 vs 7.39 months; $P = 0.0006$) with no difference in OS, although data is maturing.[35] Ongoing trials across the care continuum are summarized below. Five-year overall survival (OS) is 72% for all patients (76% for women; 64% for men), 86% and 39% for patients with localized and distant disease, respectively, with a trend for better outcomes among women.[1] Five-year overall and disease-free survival for those who underwent salvage surgery after CRT are lower, at approximately 40% to 50%.[4]

There does not appear to be a difference in OS between HIV-positive and HIV-negative ASCC patients.[36,37] One series reported higher local failures among HIV-positive patients, which are likely due to toxicity-related treatment breaks.[38] Importantly, low CD4 count (< 350 cells in one study[39] and < 200 in others[40,41]) and high viral load (> 700 copies/mL[39]) correlated with increased grade 3 or higher toxicity, treatment interruptions, and hospitalizations. Wexler and colleagues reported that patients with low CD4 count and high viral load had significantly worse 5-year overall- and cancer-specific survival.[39] Collectively, those studies underscore the importance of treating HIV in this patient population. Additionally, a review of 13 population-based HIV and cancer registries throughout the US with 24,486 patients (10.9% with HIV and 9.3% with AIDS) showed that HIV was associated with increased all-cause mortality (1.53, 95% CI, 1.42-1.64) and with increased anal cancer-specific mortality among female patients (1.52, 95% CI, 1.18-1.97).[42] The National Comprehensive Cancer Network provides a good review of the management of people living with HIV undergoing cancer treatment.[43]

Tailored Treatment Strategies

Reducing long-term toxicity without compromising cancer control is the focus of ongoing trials. The PersonaLising RadioTherapy dOse for Anal Cancer (PLATO; ISRCTN88455282) integrates ACT-3, ACT-4, and ACT-5 to tailor management using biology and margin data (**Table 1**).[44] For example, ACT-3 is a de-escalation phase 2 protocol that is evaluating observation in T1N0 patients with negative margins (no tumor on ink) post local excision while those

Table 1. Summary of Ongoing Clinical Trials in Anal Squamous Cell Carcinoma

TRIAL	PHASE	STUDY POPULATION	SAMPLE SIZE	STUDY ARMS	TARGET/ BIOMARKER	PRIMARY ENDPOINT
DECREASE (NCT04166318)	II, R	T1-2N0, M0	252	Standard vs lower-dose CRT	Clinical stage	2-year disease control; 1-year change in fecal incontinence Quality of life
PLATO[44] (ISRCTN88455282)						
ACT3	II, NR	T1N0 who underwent local excision	252	Observation or lower-dose CRT if close margin ≤1 mm)	Clinical stage	3-year locoregional failure
ACT4	II, R	T1-2 (< 4 cm) N0		Standard vs lower-dose CRT		
ACT5	Pilot/II/III, R	T3-4N0-3 or T2N1-3, M0		Standard vs higher-dose CRT		
CoRInTH[45] (NCT04046133)	Ib/II, NR	T3-4N+, M0	50	Pembrolizumab + CRT	PD-1/PD-L1	Safety and tolerability, up to 1 year
INTERACT-ION[46] (NCT04719988)	II, NR	T1-3N1 or T4N0, M0	55	Induction ezabenlimab + mDCF followed by consolidation ezabenlimab + mDCF + involved nodal radiation (if clinical response > 30%) or consolidation standard CRT (if < 30% response)	PD-1	10-month clinical complete response
TIRANUS[47] (NCT05661188)	II, NR	T1-4N0-1, M0	45	Atezolizumab + tiragolumab in combination with CRT	PD-L1/ TIGIT	26-week clinical complete response
ECOG-ACRIN EA2165[48] (NCT03233711)	III, R	T3-4N0 or T2-4N1, M0	344	CRT followed by nivolumab vs observation	PD-1	5-year DFS
NCI[49] (NCT04929028)	II, NR	T3-4N0 or T2-4N1 (high-risk), T1-2N0 (low-risk), M0, HIV+	53	Low-risk = reduced intensity CRT followed by observation High-risk = CRT followed by nivolumab	Clinical stage; HIV+	5-year incidence of grade 3-4 adverse events
SPARTANA[50] (NCT04894370)	II, NR	Metastatic	34	Immune stimulatory XRT (8 Gy to target lesions), followed by mDCF + spartalizumab, with consolidation multimodal treatment for residual disease (ablative treatment) Maintenance spartalizumab	PD-1	1-year PFS
ECOG-ACRIN EA2176[51] (NCT04444921)	III, R	Inoperable, recurrent, or metastatic	205	Carboplatin-paclitaxel followed by observation vs nivolumab	PD-1	2-year PFS
POD1UM-303/ InterAACT 2[52] (NCT04472429)	III, R	Inoperable, recurrent, or metastatic	308	Carboplatin-paclitaxel followed by observation vs retifanlimab	PD-1	4.5-year PFS

Abbreviations: ACT, UK anal cancer trial; CRT, chemoradiation; DCF, docetaxel (75 mg/m^2), cisplatin (75 mg/m^2), and 5-fluorouracil (750 mg/m^2/day for 5 days), every 3 weeks intravenously; DECREASE, De-Intensified ChemoRadiation for Early-Stage Anal Squamous Cell Carcinoma; DFS, disease-free survival; HIV, human immunodeficiency virus; mDCF, docetaxel (40 mg/m^2), cisplatin (40 mg/m^2), and 5-fluorouracil (1200 mg/m^2/day for 2 days), every 2 weeks intravenously; NCI, National Cancer Institute; NR, nonrandomized design; PD-1, programmed cell death-1; PD-L1, programmed cell death lignad-1; PFS, progression-free survival; PLATO, personalizing radiation therapy dose in anal cancer; R, randomized design; TIGIT, T cell immunoglobulin and ITIM domain.

with a close margin (≤ 1 mm) receive dose-reduced CRT (41.4 Gy/23 fractions).[44] Similarly, the ACT-4 study is evaluating dose-reduced CRT for patients with small tumors (T1-2N0 ≤4 cm). Early data show comparable 6-month cCR between dose-reduced (41.4 Gy/23 fractions) and standard (50.4 Gy/28 fractions) CRT, with lower toxicity in the dose-reduced arm.[53] These results support the feasibility of safely de-intensifying treatment in carefully selected patients. The ongoing DECREASE phase II trial[54] (ECOG-ACRIN 2182; NCT04166318) is evaluating de-escalated treatment for node-negative disease. T1N0 patients receive 36 Gy to the primary tumor and 32 Gy to elective nodes in 20 fractions, while T2N0 patients receive 41.4 Gy to the primary tumor and 34.5 Gy to elective nodes in 23 fractions. The standard arm delivers 50.4 Gy to the primary tumor and 42 Gy to elective nodes in 28 fractions. In addition, patients in the experimental arm receive a lower MMC dose (10 mg/m^2 vs 12 mg/m^2) and 1 less cycle of 5FU compared with the standard arm.

Conversely, treatment intensification is being explored for patients with more advanced disease, who are at higher risk of treatment failure. Secondary analysis of RTOG 9811 demonstrated poor 5-year disease-free survival (DFS) in patients with T3-4N+ disease ranging from 43% to 27%,[55] highlighting the need for more aggressive treatment. Within the PLATO framework, the ACT-5 trial intensifies radiation dose for high-risk patients (T3-4N0 or T2-4N+) up to 61.6 Gy in an effort to improve control. Moreover, a recent phase 3 study in Russia also evaluated adding paclitaxel to CRT in 144 ASCC patients (~72% N+; ~78% stage III).[56] The study was terminated prematurely in 2019 due to loss of access to mitomycin C. Within this limitation, paclitaxel appears to significantly improve 3-year DFS (87.1% vs 64.4%, $P = .001$) and OS (95.5% vs 80.0%, $P < .001$), with increased grade 3 to 4 toxicities (56.9% vs 26.4%, $P < .0001$), compared with CRT with doublet chemotherapy. This provides a signal for possible benefit of intensifying chemotherapy in this group of patients. Lastly, immunotherapy is being investigated in conjunction with chemotherapy for this higher risk population, which is reviewed later in this article.

While strides have been made in organ preservation and overall disease outcomes with CRT for patients with anal cancer, challenges remain in balancing long-term toxicity and treatment morbidity. There is a need to tailor these treatments to an individual patient's anatomic stage (as in DECREASE and PLATO) and also their molecular signatures, which provides a richer overview of each tumor's biology.

Emerging Biomarkers

Understanding the molecular interplay between HPV pathogenesis and genomic alterations is crucial for optimizing treatment outcomes and personalizing therapy. Patients with HPV-positive disease have better outcomes partly due to inherent HPV oncogenesis. PIK3CA mutations and PTEN loss are present in 30% and 14% of HPV-positive cases, respectively,[7] which was also observed in an exploratory whole-exome sequencing (WES) analysis of RTOG 9811 patients ($n = 62$).[57] In contrast, patients with HPV-independent disease are more likely to harbor higher p53 and CDKN2A mutation burdens, at 67% and 56%, respectively.[7] In 2010, Lampejo and colleagues reviewed multiple biomarkers and reported a potential prognostic value for p21, Bcl-2, NF-kB, and cyclin A.[58]

Exploratory analysis of RTOG 9811 noted additional mutations such as *FBXW7*, which were prevalent in 15% of the cohort and associated with worse disease-free survival (hazard ratio [HR] 2.47 [1.02-5.96], $P = .045$) and a signal for inferior OS (HR 2.61 [0.97-7.04], $P = .058$).[57] Aldersley and colleagues performed WES on 72 patients with anal cancer ($n = 56$ primary; $n = 31$ recurrent).[11] HPV integration was noted in 38% of cases and was more common in stages III-IV, at a rate of 2.69 integrations per sample compared with 0.91 integrations per sample for stages I-II ($P = .008$).[11] They were numerically more common in recurrent and metastatic disease than in primary disease (1.88 vs 1.10; $P = .092$). The integration events were often associated with copy number variations and amplifications of genes such as *PI3KCA*, *MYC*, and *CCND1*.[11] Interestingly, amplification of *TERT* and deletions of *ATR*, *FANCD2*, and *FHIT* were reliably more common in recurrent/metastatic vs primary tumors, with corresponding enrichment of DNA damage response gene in recurrent tumors.[11] The authors posit that enrichment of those genes in the context of recurrent deletions may contribute to tumor recurrence post CRT. It is conceivable that HPV integrants across human cancers take advantage of host genomic aberrations, increasing instability, and ultimately leading to tumorigenesis early on and treatment resistance later.[59,60] Since viral integration and genomic instability may worsen as infected cells progress to malignancy,[11,59,60] this provides a rationale for the prevention and aggressive treatment of premalignant lesions such as HSIL. The Anal Cancer-HSIL Outcomes Research (ANCHOR) study was a multi-institutional phase III study that sought to determine whether treating anal

HSIL reduces the risk of progression to anal cancer among HIV-positive patients compared with active surveillance.[61] Treatment included excision, ablation, or administration of topical agents. Active surveillance included high-resolution anoscopy at least every 6 months and an annual biopsy. In a cohort of roughly 4500 patients with a median follow-up of 25.8 months, risk of progression to invasive disease was reduced by 57% (95% CI, 6-80; $P = .03$) among those who received treatment.[61]

Liquid biopsies, including circulating tumor cells and circulating tumor DNA (ctDNA), have emerged as an adjunct in identifying genomic alterations and monitoring treatment response across various cancers, including gastrointestinal cancer. In the noncomparative phase II study SCARCE C17-02 PRODIGE 60, combining IO with chemotherapy, patients with complete molecular response (cMR) as measured by HPV ctDNA pre- and post-treatment had better 1-year progression-free survival (PFS) (60.4% vs 15.4%) and OS (90.7% vs 64.2%) compared with those without cMR, respectively.[62] Moreover, Epitopes-HPV02 was a phase II single-arm study (NCT02402842) of patients with unresectable locally advanced/recurrent or metastatic ASCC where HPV ctDNA was evaluated as a predictive biomarker.[63] Positive HPV ctDNA at baseline did not correlate with PFS, although patients with a baseline ctDNA level < 2940 copies/mL had better PFS (HR, 2.1; 95% CI, 1.0-4.2; $P = .04$).[63] Like the SCARCE C17-02 study, cMR was associated with better 1-year OS (87% vs 50%) with an odds ratio of 7 (95% CI, 1.5-28.5; $P = .02$).[63] This is an exciting area of care in anal cancer; the use of blood biomarkers to guide clinical decision-making is under study in other virally[64] and nonvirally[65-68] mediated cancers. While prospective studies are underway evaluating its role in guiding management,[69,70] data show that HPV ctDNA in anal cancer may indeed be an important prognosticator.

Furthermore, tumor-infiltrating lymphocytes (TILs) have been suggested to correlate with outcomes in patients with HPV-mediated disease, supporting a role for the way the adaptive immune system behaves in virally mediated cancers.[9,71] Patients with high TILs had significantly longer disease-free intervals compared with patients with absent/low TILs (92% vs 63 %; log-rank $P = .006$),[71] in line with other HPV-mediated cancers.[72-76]

The identification and integration of these biomarkers into clinical practice have expanded our understanding of ASCC, offering new avenues for targeted therapies. Immunotherapy has gained significant interest recently as a promising treatment for ASCC as it revolutionized the field of oncology with its success across many different cancers.

The Promise of Immunotherapy

HPV inherently furnishes an immunosuppressive and evasive environment through multiple mechanisms, one of which is upregulation of programmed death ligand-1 (PD-L1).[77-79] While this provided a rationale to try different IO agents, outcomes in ASCC have been suboptimal.[80] Results of the randomized noncomparative phase II study SCARCE C17-02 PRODIGE 60 were recently published.[62] In nonbiomarker selected, chemo-naïve, patients with locally advanced or metastatic ASCC, the addition of atezolizumab to mDCF vs mDCF alone did not meet the primary endpoint of 1-year PFS (45% vs 43%). The combination of mDCF + IO was associated with higher grades 3-4 (61% vs 42%) and serious adverse events (25% vs 12%).[62] Interestingly, in patients with a PD-L1 combined positive score (CPS) of ≥ 5% ($n = 10$), 1-year PFS with atezolizumab + mDCF was 70% (95% CI, 47-100) compared with 39% (24-62) in the CPS-negative group ($n = 28$). This is in line with other studies showing IO responders are more likely to have higher PD-1/PD-L1 levels,[81-83] albeit low response overall.

The INTERACT-ION is another phase II study from the French group that is studying the role of induction ezabenlimab, an anti-PD-1 antibody, in combination with mDCF as an induction regimen before CRT in treatment-naïve patients with locally advanced, stage III (T4N0 or TxN+), ASCC, with promising early results.[46] Moreover, dual checkpoint inhibition is of interest in ASCC as it has been shown to be more efficacious in activating the immune system.[84-87] T cell immunoglobulin and ITIM domain (TIGIT) is an immune checkpoint receptor constitutively expressed on Tregs and is critical in mediating immunosuppression.[88] TIRANUS out of Spain is a single-arm phase II study (NCT05201612) that is studying the co-inhibition of PD-L1/TIGIT with atezolizumab and tiragolumab in combination with CRT for nonmetastatic patients with ASCC.[47]

Several trials of IO are underway across the continuum of ASCC care. For instance, pembrolizumab is currently part of the single-arm phase Ib/II CoRInTH trial (NCT04046133) combining the PD-1 agent with CRT in locally advanced stage III-IV ASCC.[45] The National Cancer Institute (NCI) has 2 phase II studies with nivolumab following definitive CRT. The first study is in high-risk stage II-IIIB patients (EA2165; NCT03233711)[48] with primary endpoint of PFS. The second study is a risk-adapted trial (NCT04929028) of either nivolumab (high-risk, T3-4N0M0 or T2-4N1M0) or observation

(low-risk, T1-2N0M0 or tumors <4 cm) following CRT in HIV-positive patients.[49] In more advanced disease, SPARTANA (NCT04894370) is a unique phase IIA study in metastatic ASCC that leverages radiation synergistic priming of the immune response (single-fraction 8 Gy to a target lesion) before starting spartalizumab (PD-1 inhibitor) and mDCF.[50] This regimen is then followed by consolidative ablative treatment to residual disease and maintenance spartalizumab, with the primary end point of PFS. Nivolumab (EA2176; NCT04444921)[51] and retifanlimab (PODIUM-303/InterAACT 2; NCT04472429)[52] are also being investigated in a phase III randomized fashion in combination with carboplatin/paclitaxel in metastatic and locally advanced/metastatic disease, respectively. As noted above, early data from the PODIUM-303/InterAACT 2 study show a signal of efficacy in terms of PFS but not OS at this time, with data continuing to mature. A summary of ongoing clinical trials is provided in **Table 1**.

While studies are ongoing, IO holds great potential as an adjunct to standard-of-care management in all stages of the disease. However, nonbiomarker-driven IO studies may prove futile, underscoring the importance of personalizing therapy.

Conclusion

The future of anal cancer management has the potential to provide personalized treatment and follow-up, moving away from a one-size-fits-all approach. This hope is derived from advancements in molecular and genomic profiling. The integration of emerging biomarkers such as HPV DNA and PD-L1 expression, along with disease staging, into clinical practice allows for tailored treatment strategies. This can improve patient outcomes and reduce treatment-related morbidity. As our understanding of the molecular underpinnings of ASCC deepens, this approach has the potential to transform care and improve both the quantity and quality of life for patients with ASCC.

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Viral-Mediated Hepatocellular Carcinoma: A Review on Mechanisms and Implications for Therapy

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Abstract

Hepatocellular carcinoma (HCC) is one of the most common cancers in the United States. Chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infections are major risk factors of HCC. This review article discusses the pathogenesis behind HBV- and HCV-induced HCC, examining the ways these viruses contribute to the development of liver cancer. Furthermore, we aim to explore the therapeutic implications of viral-mediated HCC, with an interest in preventing chronic infections and subsequent HCC development. By understanding the underlying pathogenesis and therapeutic targets, we aim to contribute to improved outcomes for hepatitis-related liver cancer.

Keywords: hepatitis, hepatocellular carcinoma, radiation

Introduction

Hepatocellular carcinoma (HCC) poses a significant global health challenge, accounting for about 90% of liver cancer cases and projected to affect over 1 million individuals annually by 2025.[1] HCC is the sixth most common cancer diagnosis and the fourth most common cause of cancer-related death worldwide.[1,2] It has a poor prognosis as well, as patients have a 5-year survival of 18%.[3] The risk factors of HCC include hepatitis B virus (HBV), hepatitis C virus (HCV), non-alcoholic steatohepatitis, chronic alcohol use, aflatoxins, liver flukes, and inherited metabolic disorders, including hemochromatosis and α1-antitrypsin deficiency.[1,2,4] HBV infection contributes to around 60% of HCC cases in Asia and Africa and 20% of cases in the West. Likewise, chronic HCV infection is seen among HCC patients in North America, Europe, and Japan.[1,5] Viral-mediated HCC poses a unique challenge as patients who have viral-mediated disease tend to have worse outcomes than patients with a nonviral etiology.

Treatment for viral-mediated HCC depends on the stage of the disease. The Barcelona Clinic Liver Cancer (BCLC) guidelines are commonly referenced and personalized to patients. For early stage HCC (BCLC-0 and BCLC-A), curative options include ablation, surgical resection, or liver transplantation (LT).[6] In intermediate stages (BCLC-B), treatments such as transarterial chemoembolization (TACE) or LT are considered to manage tumor burden. For advanced HCC, particularly in patients with viral-mediated disease, systemic therapies — primarily immunotherapy — are the mainstay.[6] These therapies aim to address the unique challenges posed by viral infections,

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including higher recurrence rates and an immunosuppressive tumor microenvironment.

Current treatment paradigms have limitations, such as the high recurrence rates after curative treatments, resistance to systemic therapies, and the immunosuppressive tumor microenvironment. These challenges drive interest in exploring combination strategies like radiation therapy (RT) with immune checkpoint inhibitors (ICIs), which could potentially overcome resistance mechanisms, enhance antigen presentation, and improve systemic responses by altering the tumor microenvironment in viral-mediated HCC.

Pathogenesis of HBV- and HCV-Induced HCC

HBV is a double-stranded DNA virus implicated in the onset of HCC. By integrating its DNA into the host's genome, HBV disrupts normal cellular function and leads to chromosomal instability, a precursor to cancer development.[3,6] The HBV X protein (HBx), central to this process, initiates a cascade of cellular events that promote oncogenesis. It activates key signaling pathways such as MAPK and PI3K/Akt, which leads to inflammation and cellular proliferation, while also suppressing the tumor-suppressive actions of proteins like p53 by sequestering them away from the nucleus.[3,6] This leads to uncontrolled cell growth and genomic instability.[6] Furthermore, HBx alters the epigenetic landscape, affecting gene expression patterns linked to cancer progression and silencing tumor suppression.[3]

While HBV-induced HCC is most prevalent in patients with cirrhosis, accounting for around 80% of all HBV-related HCC, HBV can induce HCC without the presence of cirrhosis, partly due to mutations in its genome.[3] Notably, mutations in the TERT, ARID2, and ARID1A genes are implicated in increasing cancer risk.[3] Besides these genomic alterations, HBV's interaction with the host's immune system plays a critical role in its oncogenic process. The inhibitory effect of HBV on innate and adaptive immune cells causes evasion of host defenses and creates an environment conducive to tumor development.[3] Emerging research points to the involvement of additional mechanisms in HBV's pathogenicity. The virus influences processes like exosome release and metabolic regulation, which can accelerate the progression from liver inflammation to HCC. For instance, the virus's influence on the body's metabolic pathways could lead to the creation of a tumor-friendly microenvironment. Lastly, the release of exosomes loaded with viral particles or oncogenic proteins can facilitate cell-to-cell communication that promotes cancer progression.[3,7] These intricate and interconnected pathways underscore the complexity of HBV's role in hepatocarcinogenesis and highlight the virus's ability to hijack multiple cellular processes to facilitate the development of HCC.

HCV is a small, enveloped virus with a single-stranded RNA genome that significantly increases the risk of HCC. Chronic HCV infection increases oxidative stress in hepatocytes, leading to DNA damage and mutations that can progress to cancerous changes.[8] Cirrhosis-induced carcinogenesis is one of the major contributors of HCV-induced HCC, and this can occur even with HCV clearance.[1] The annual incidence rate of HCC in cirrhotic patients is 1% to 7%. HCV infection often results in chronic liver inflammation, driven by continuous immune cell activation and cytokine production, leading to fibrosis and eventually cirrhosis.[8] HCV's core proteins influence cell cycle and apoptosis pathways, contributing to malignant transformation of hepatocytes. Furthermore, HCV is associated with downregulation of tumor-suppressor genes such as TP53, TP73, and RB1, leading to uncontrolled cellular proliferation.[8-10] This virus also disrupts normal metabolic processes, including glucose and lipid metabolism, which contributes to conditions like steatosis, which are risk factors for HCC.[8] Finally, HCV can impair the immune system's ability to detect and destroy infected cells by interfering with immune checkpoint pathways.[8] Chronic HCV infection can evolve over decades from mild liver inflammation to severe conditions such as cirrhosis and finally HCC, especially when combined with other risk factors like alcohol use or co-infection with other viruses. Given the complexity of HCV-induced hepatocarcinogenesis, consistent monitoring and treatment are required to decrease the burden of HCC in patients with HCV infection.

Prevention of Chronic Viral Infection-Induced HCC

HBV-related HCC has had a reduced incidence rate due to preventive measures such as HBV vaccination and antiviral therapies.[1] It is estimated that the initiation of neonatal HBV vaccination in the 1980s in East Asian countries has reduced the incidence of HBV infection by 70% to 80%. For example, after 30 years of universal neonatal vaccination, the HCC rates decreased by 80%.[4] Nucleoside/nucleotide analogs (NUCs) are the first-line antiviral treatments for patients with chronic HBV due to high efficacy in viral suppression, high barrier to viral resistance, and favorable safety profile. It is reported that HCC prevention is mostly seen in patients with complete

viral suppression.[11-13] Additionally, NUCs prevent HBV reactivation in immunocompromised patients.[12] Meanwhile, pegylated-interferon has shown sustained virological response (SVR) in about 20% of patients with short duration of treatment, but it has lower efficacy and safety compared with NUCs.[11-14] The antiviral treatment does not cure chronic hepatitis B infection; however, their main goals are to provide viral suppression, progression of liver disease, and even reverse cirrhosis.[14] Some clinical trials have shown that direct acting antivirals (DAA) based interferon-free therapy has SVR rates of above 90%.[15] Furthermore, DAA therapy has contributed to a decreased incidence rate of HCV-induced HCC, with data suggesting a 76% risk reduction of HCC in patients who achieved SVR with DAA therapy compared with those who did not achieve SVR.[1,16] However, the risk of HCC remains high in patients with HCV cirrhosis despite achieving SVR, emphasizing the importance of continued surveillance with imaging and alpha fetoprotein (AFP) testing.[15]

Immunotherapy

Given the multiple mechanisms contributing to chronic viral infection-induced tumorigenesis, such as alternation of immune pathways and invasion of the immune system, the use of targeted immunotherapy in advanced HCC has been a promising research area. In viral-mediated HCC, chronic infections with HBV or HCV cause persistent inflammation and immune evasion, which not only promotes the progression of liver disease but also contributes to the establishment of an immunosuppressive tumor microenvironment. This immune invasion is crucial for the survival and proliferation of HCC cells, particularly in the context of viral infections. The PD-1 pathway, involving the PD-1 receptor on T cells and the PD-L1 ligand on cancer cells, is a key target for many ICIs. By blocking the PD-1 receptor or the PD-L1 ligand, these therapies help prevent cancer cells from evading immune detection, enabling T cells to recognize and attack them.[17] Additionally, the CTLA-4 checkpoint protein, which further impairs T cell function, is another critical target for ICI therapy.[18]

A phase 3 trial compared combination of tremelimumab (an anti-CTLA-4 antibody) and durvalumab (an anti-PD-L1 antibody) with durvalumab alone and sorafenib in patients with unresectable HCC. The trial demonstrated that combination immunotherapy significantly improved overall survival (OS) compared with sorafenib (hazard ratio [HR], 0.78; 95% confidence interval [CI], 0.65-0.92; $P = .0035$), while durvalumab alone was found to be noninferior to sorafenib (HR, 0.86; 96% CI, 0.73-1.03). The incidence of grade 3/4 treatment-related adverse events was 25.8% for the combination, 12.9% for durvalumab, and 36.9% for sorafenib.[19]

Interestingly on subgroup analysis, HBV cirrhosis drove a strong survival benefit (HR, 0.64; 95% CI, 0.48-0.86). Similarly, the IMBRAVE-150 study evaluated the combination of atezolizumab (an anti-PD-L1 antibody) and bevacizumab (a VEGF inhibitor) compared with sorafenib alone in patients with unresectable HCC. The 12-month OS rates were 67.2% in combination arm compared with 54.6% for sorafenib alone. Median progression-free survival (PFS) was also significantly longer at 6.8 months for the combination group vs 4.3 months for sorafenib (HR, 0.59; 95% CI, 0.47-0.76; $P < .001$).[20] These ICIs work in synergy as inhibiting PD-L1 activated T-effector cells and VEGF inhibition allows T cells to enter the tumor microenvironment to prevent cancer growth.[20] Similar to durvalumab and tremelimumab on subgroup analysis, patients with HBV had improved OS with immunotherapy (HR, 0.47; 0.33-0.67), while nonviral and hepatitis C etiology did not. Similarly, tremelimumab treats HCC by blocking the CTLA-4 checkpoint on T cells, which enhances T cell activation and proliferation. This improves the immune system's ability to recognize and attack cancer cells.[21] Meanwhile, adoptive cell immunotherapy (ACI) requires specific tumor antigens and is hindered by the tumor microenvironment, and sorafenib targets specific kinases that do not boost the immune response. ICIs overcome these limitations, providing a more comprehensive and durable treatment for viral HCC compared with ACI and sorafenib.[22,23]

Radiation Therapy

Currently, the BCLC staging does not include RT as part of the treatment paradigm for HCC. However, RT is increasingly recognized as a viable locoregional treatment for inoperable HCC, now included in the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines).[24] Technological improvements in RT, including the use of stereotactic body radiation therapy (SBRT), have enabled more precise targeting of tumors, minimizing damage to healthy liver tissue and improving treatment outcomes.[17] RT can turn cancer cells into a personalized vaccine by causing them to release tumor-specific antigens, antigen-presenting cells, and primes T cells that activate the immune system. During radiation, reactive oxygen species are generated, which modify proteins and DNA, increasing

antigenicity and making the cancer cells more recognizable.[18] This triggers the cGAS-STING pathway, leading to type I interferon production and enhanced T cell priming by antigen-presenting cells.[25] Additionally, radiation upregulates immune markers like major histocompatibility complex (MHC) class I and FAS on tumor cells, attracting immune cells into the tumor microenvironment and facilitating a robust anticancer response throughout the body.[26,27] Clinical use of SBRT for patients with HCC who are not eligible for other curative therapy has shown promising data with high local control (LC) rates of 68% to 95% 2-3 years following treatment.[17] The use of partial liver RT to a median dose of 40-66 Gy using standard fractionation regimen has shown response rates ranging from 57% to 92%.[17] Even with these promising data, it is important to remember that RT can reactivate hepatitis, and retrospective data on HBV show that patients on antivirals undergoing radiation treatment have lower rates of HBV reactivation compared with patients who are not on antiviral treatment (7.5% vs 33.3%, $P < .001$).[28]

A promising synergistic systemic therapy for use with radiation is chimeric antigen receptor T cell therapy (CAR-T). CAR-T works by taking T cells from a patient and then they are modified to express receptors that can target specific antigens and proteins. Studies with CAR-T therapy and T cell receptor T cells targeting HBV antigens are promising, and the specificity of the tumor-specific antigens it targets can be used synergistically with RT.[28] The use of such adoptive cell therapy is a new and emerging field that could improve the efficacy of RT in viral-mediated HCC. While no studies are available focusing on the combination of RT and adoptive cell therapies for viral HCC, it is an unexplored field with a promising future.

A recent randomized phase 3 trial, RTOG 1112, compared clinic outcomes of SBRT followed by sorafenib with sorafenib alone in patients with new or recurrent HCC, unsuitable for surgery, ablation or TACE. Out of all 193 patients, 41% had hepatitis C and 19% had hepatitis B or B/C. It was found that SBRT with sorafenib improved OS (15.8 months vs 12.3 months) and PFS (9.2 months vs 5.5 months) compared with sorafenib alone. There was no difference in adverse effects in both groups.[29] Whether subgroup analysis will predict a greater benefit among patients with viral-induced cirrhosis remains to be evaluated, pending the final publication of these data.

In a study from the Asian Liver Radiation Therapy Study Group, a retrospective evaluation was conducted on the efficacy of SBRT in treating HCV infection-induced HCC compared with other etiologies. Patients with HCV-related HCC had superior 2-year LC of 88% compared with 78% for other patients. This pattern persisted across different schedules and tumor sizes. HCV etiology was associated with approximately 50% relative risk reduction and 10% to 20% absolute risk reduction for local recurrence post SBRT.[30] This association is particularly notable as it is the first report to demonstrate such a link, suggesting that HCV status could be a critical factor in tailoring SBRT for patients with HCC. RT has been shown to be an effective alternative for inoperable patients with HCC, with many studies showing favorable outcomes. RT should be a part of multidisciplinary team recommendation for patients with HCC based on the clinical presentation.

Synergistic Effect of Radiation Therapy and Immune Checkpoint Inhibitors

RT causes tumor cells to release tumor-associated antigens that help stimulate tumor-specific immune responses, leading to the recognition and death of tumor cells. Additionally, radiation can lead to the destruction of tumor stroma and tumor microenvironment, allowing evasion by immune cells.[28,31] ICIs further boost this response by blocking immune evasion mechanisms, leading to increased antitumor activity. The combination of RT with ICIs such as ipilimumab, which blocks CTLA-4, has gained significant attention for enhancing T cell activation and improving the ratio of CD8+ T cells to Treg cells.[32] This boosts the in situ vaccination effect of RT, where the tumor itself becomes a source of antigens that "vaccinates" the immune system to attack cancer cells throughout the body.[25] This strategy has shown promising results in both mouse models and human studies, leading to Food and Drug Administration approval for treating metastatic melanoma. Additionally, hypofractionated RT can increase PD-L1 expression in tumors, contributing to RT resistance, which suggests that combining PD-1/PD-L1 blockade with RT could help overcome tumor immunosuppression.[33] Anti-PD-1/PD-L1 monoclonal antibodies have already shown positive outcomes in treating cancers such as non-small cell lung cancer (NSCLC), melanoma, and kidney cancer.[34]

The combination of RT and ICIs has demonstrated promising outcomes in various cancers, including colorectal, breast, melanoma, and lung cancers. Preclinical studies in mouse models of colorectal, breast, and melanoma tumors showed that administering

Table 1. Comparison of Adverse Effects in Studies of ICI + RT, RT Monotherapy, and ICI Monotherapy

STUDY	TREATMENT ARMS	ADVERSE EVENTS
NCT03857815[40]	SBRT + sintilimab	Grade 3: 12% Grade 4 or 5: 0
NCT03203304[41]	SBRT + nivolumab vs SBRT + nivolumab + ipilimumab	SBRT + nivolumab Any grade: 83.3% Grade 3: 50% Grade 4 or 5: 0 SBRT + nivolumab + ipilimumab Any grade: 100% Grade 3: 71.4% Grade 4 or 5: 0
NCT04611165[42]	EBRT + nivolumab	Grade 3 or 4 adverse event: 12% Grade 3 or 4 severe adverse event: 4%
NCT02576509[43] (CheckMate 459)	Nivolumab vs sorafenib	Nivolumab Grade 3: 18% Grade 4: 4% Grade 5: < 1% Sorafenib Grade 3: 47% Grade 4: 2% Grade 5: < 1%
NCT03298451[19] (HIMALAYA)	Tremelimumab + durvalumab (STRIDE) vs durvalumab (D) vs sorafenib (S)	STRIDE Grade 3 or 4: 25.8% Grade 5: 2.3% D group Grade 3 or 4: 12.9% Grade 5: 0 S group Grade 3 or 4: 36.9% Grade 5: 0.8%
UMIM000013011[44] (The STRSPH study)	SBRT	Grade 3 or higher: 11.4% Grade 5: 0

Abbreviations: ICI, immune checkpoint inhibitor; RT, radiation therapy; SBRT, stereotactic body radiation therapy; EBRT, electron-beam radiation therapy.

anti-PD-L1 concurrently with RT led to better long-term tumor control compared with delayed administration.[35-37] This combination has shown potential in HCC, suggesting that it could offer better outcomes for this cancer.[21,38,39] Multiple studies are exploring the synergistic effects of combined immunotherapy and RT in HCC. One retrospective case series of 5 patients with unresectable HCC evaluated clinical response when treated with SBRT and checkpoint inhibitors. Out of the 5 patients, 3/5 had hepatitis B infection and 4/5 had BCLC stage C. All patients responded to this combination therapy, with 2 complete and 3 partial responses. The 1-year LC and OS were 100%.[28] Similarly, a phase 2 study evaluated the efficacy and safety of combining SBRT with sintilimab (a PD-1 antibody) in patients with recurrent or oligometastatic HCC. The study involved 25 patients, and the combination treatment resulted in a confirmed overall response rate (ORR) of 96%, with 17 complete responses and 7 partial responses. The 12-month and 24-month PFS rates were 68% and 45.3%, respectively.[40] The adverse effects with a combination of ICI and RT, ICI alone and RT alone as seen in some studies are summarized in **Table 1**.

HBV and HCV drive HCC by promoting genetic mutations, altering the immune response, and creating a tumor-friendly microenvironment. Immunotherapy, particularly PD-1/PD-L1 and CTLA-4 inhibitors, can help counteract immune evasion mechanisms exploited by these viral infections.[17,18] When combined with RT, which enhances antigen release and alters the tumor microenvironment, there is potential to overcome the immunosuppressive effects caused by viral hepatitis.[32] By boosting the immune system's ability to recognize and attack cancer cells, this combination strategy may offer a more effective approach for treating HCC driven by chronic hepatitis infection.

There is no consensus regarding the timing of ICIs and radiation. Concurrent administration of anti-PD-L1 with RT appears to yield better long-term tumor control compared with delayed ICI initiation, while preclinical models also indicate that anti-CTLA-4 is

Table 2. Ongoing Trials on Radiation and Immunotherapy for Patient Outcomes

STUDY NAME	TREATMENT ARMS	DOSE	ENDPOINTS
NCT06313190[45]	SBRT alone vs SBRT + sintilimab.	SBRT: 30-54 Gy in 3 fractions over 1 week Sintilimab: 200 mg every 3 weeks for up to 6 cycles, with the first dose within 1 week after the completion of SBRT.	Primary: PFS; secondary: OS, LC, AEs
NCT06261125[46]	SBRT followed by adebrelimab + lenvatinib in 2 cohorts. Arm A includes patients without prior PD-1/PD-L1 therapy. Arm B includes those with progression after prior PD-1/PD-L1 therapy.	SBRT using VMAT: 33-48 Gy in 6 fractions over 2 weeks. Adebrelimab: 1200 mg every 3 weeks for up to 35 cycles after the completion of SBRT. Lenvatinib: 12 mg/day for bodyweight ≥ 60 kg or 8 mg/day for bodyweight < 60 kg, orally once daily after the completion of SBRT.	Primary: PFS; secondary: OS, ORR, DCR, DOR, AEs
NCT05917431[47]	SBRT + tislelizumab + regorafenib.	SBRT: 8 Gy × 3-5 fractions. Tislelizumab: dose of 200 mg every 21 days. Regorafenib: dose of 120 mg for the first 21 days of a 28-day cycle. Systemic therapy will start concurrently and last 2 years, or until disease progression, intolerable side effects or death.	Primary: PFS; secondary: OS, recurrence pattern

Abbreviations: SBRT, stereotactic body radiation therapy; PFS, progression-free survival; OS, overall survival; LC, local control; AEs, adverse events; VMAT, volumetric arc therapy; DCR, disease control rate; DOR, duration of response.

most effective when administered a few days before RT, likely due to its role in depleting regulatory T cells.[24,43] Further studies on this can help guide upcoming treatment paradigms. There are ongoing clinical trials testing outcomes in patients treated with radiation and immunotherapy (**Table 2**). The addition of local therapy to immunotherapy and its impact on national practice guidelines remain to be determined by ongoing trials as well as the implication and synergism with specific subset of HCC such as viral-mediated disease.[24] Follow-up surveillance should be as per NCCN Guidelines with serial AFP evaluation and imaging response.

Conclusion

HCC remains a critical health concern with an intricate web of etiological factors such as HBV and HCC, and lifestyle choices contributing to its pathogenesis. Emerging treatments, particularly SBRT and ICIs, offer significant potential. Notably, research has shown that HCV-related HCC responds more favorably to SBRT compared with non-HCV etiologies, highlighting the potential for etiology-specific treatment customization. As research progresses, the integration of novel systemic therapies, advancements in radiation technology, and the development of predictive biomarkers will be pivotal in enhancing the management of HCC.

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CHHiP vs PROFIT for Localized Prostate Cancer: A Retrospective Dosimetric Comparison of Organs at Risk

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ABSTRACT

Objectives Moderate hypofractionation for localized prostate cancer has become a standard of care in many radiation therapy centers worldwide. Several fractionation and planning protocols exist, with CHHiP and PROFIT (60 Gy in 20 fractions) being 2 of the most commonly used. We retrospectively compared the doses received by organs at risk (OARs) using these 2 protocols.

Materials and Methods We retrospectively reviewed the charts of 25 randomly selected de-identified patients treated with intensity-modulated radiation therapy (IMRT) for prostate cancer in a single tertiary care center. For each patient, we generated 2 sets of contours for target volumes and OARs in accordance with both CHHiP and PROFIT protocols. A total of 50 IMRT plans, using Prowess Panther software version 5.10, were generated and achieved the respective planning targets and normal tissue constraints. The related-samples Wilcoxon signed-rank test was used to compare the mean dose, V60, V50, and V40 of each of the bladder, rectum, and penile bulb.

Results Patients had a mean age of 73 years, average prostate-specific antigen level of 9.8 ng/mL, mostly a Gleason score of 7, and a clinical stage that ranged from T1c to T2c. In the CHHiP plans, the rectum averaged a significantly lower V60 (0.5% vs 4.5%, $P < .001$) and V50 (13.1% vs 15.7%, $P = .026$) than with PROFIT. Similarly, the bladder in CHHiP averaged a significantly lower V60 (1.9% vs 7.7%, $P < .001$) and V50 (13.2% vs 15.5%, $P = .035$). The penile bulb received a lower mean dose (21.9 Gy vs 30.5 Gy, $P < .001$), V50 (5.6% vs 14.4%, $P = .037$), and V40 (11.4% vs 35.2%, $P < .001$) on average in the CHHiP plans as well.

Conclusion In our dosimetric comparison, CHHiP spared the OARs to a greater degree than PROFIT. While contouring and planning using the CHHiP protocol are usually more demanding, we expect that greater sparing of OARs will minimize clinical toxicity in patients with prostate cancer receiving moderately hypofractionated radiation therapy.

Keywords: dosimetry, target volume, prostate cancer, hypofractionation, radiation regimen, toxicity

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Introduction

Prostate cancer is the second most common cancer in men, with more than 1.4 million estimated new cases in the year 2020 alone.[1] Radiation therapy is a standard treatment option for patients with localized disease in all risk categories, and it can be used as monotherapy or in combination with systemic therapies.[2] The response of cells to radiation is depicted in a linear-quadratic model incorporating a tissue-specific α/β ratio, which informs how sensitive the tissue is to fractionation. Prostate cancer has a low α/β value, suggesting that delivering higher radiation doses per fraction (ie, hypofractionation) may provide a therapeutic advantage.[3] Several randomized trials, including CHHiP and PROFIT, compared hypo-fractionated radiation regimens (>2 Gy per fraction) with standard fractionation (1.8-2 Gy per fraction), showing noninferiority in clinical outcomes and acceptable toxicity profiles.[4-8] These favorable results have made moderate hypofractionation (2.4-3.4 Gy per fraction) the preferred approach at many institutions worldwide in the treatment of low- and intermediate-risk prostate cancer[9] as it allows the reduction of treatment time by half.

Two commonly used radiation regimens are those applied in CHHiP and PROFIT, both employing 60 Gy in 20 fractions. While the dose and fractionation are similar in the 2 regimens, there are large differences in the target and normal tissues delineation between them. Notably, the PROFIT protocol prescribes the total dose to a single target volume with volumetric expansions, whereas CHHiP prescribes 3 different doses to 3 target volumes using a simultaneous integrated boost technique, in such a way that the prostate receives 60 Gy in both protocols.[6,8]

While both protocols had acceptable toxicity compared with standard fractionated radiation therapy,[6,8] they have not been tested head-to-head to compare their toxicity profiles. Therefore, aside from single institutional preferences, it is unknown whether one protocol can offer an advantage in decreasing normal tissue toxicity over the other. In an attempt to fill this knowledge gap, we retrospectively compared the doses received by organs at risk (OARs) using these 2 protocols in a homogeneous patient population treated at our institution from January 2017 to January 2020.

Materials and Methods

Patient Selection and Simulation

We retrospectively reviewed the charts of 25 randomly selected patients treated with intensity-modulated radiation therapy (IMRT) for prostate cancer in a single tertiary care center between January 2017 and January 2020. Only adult patients who received definitive radiation therapy at our institution for localized prostate cancer were included. Patients who underwent radical prostatectomy or who had metastatic disease were excluded. The study was approved by our institutional review board.

As per institutional practice, all patients were originally planned and treated with the CHHiP protocol. Each of these patients had a planning CT simulation with a full bladder and an empty rectum.

Contouring and Treatment Planning

For each patient, we generated 2 sets of contours for target volumes and OARs in accordance with both CHHiP and PROFIT protocols. The CHHiP protocol stratifies patients into either low- or moderate-/high-risk groups based on the T stage and the risk of seminal vesicle invasion (SVI) as per the Roach formula: PSA + (10 × [Gleason score - 6]).[10] If a patient has a T stage of T2c or T3a or an SVI risk > 15%, then he is deemed to be at moderate/high risk for SVI. The PROFIT protocol also stratifies patients based on the risk of SVI, but it uses the Partin tables instead, with the cutoff being 15% as well.[11,12]

The CHHiP protocol requires the contouring of 3 different target volumes planned to different doses using simultaneous integrated boost technique, whereas the PROFIT protocol requires only a single target volume. **Table 1** compares both regimens in terms of target delineation.

The protocols also differ in contouring of the OARs, especially the bladder and the rectum. CHHiP contours them as solid organs, while PROFIT only contours the bladder and rectal walls. The penile bulb is contoured in the CHHiP protocol but not in PROFIT. **Table 2** compares both regimens in terms of OAR delineation.

Using Panther software (Prowess Inc.) version 5.10, IMRT plans were generated (total 50 plans). Assessment and approval of the plans followed the guidelines of the 2 protocols, relying on their respective planning targets and normal tissue constraints, as summarized in **Table 2**.

Plan Comparison

In treatment planning and approval, the CHHiP protocol contours the whole bladder and rectum, whereas the PROFIT protocol only considers the bladder and rectal walls as elaborated above. For the purpose of comparing the doses received by the OARs, namely the bladder, rectum, and penile bulb, whole organ contours were considered. Using Panther software version 5.10, we extracted the mean doses to the OARs as well as the percentage of each volume receiving at least 40 Gy, 50 Gy,

Table 1. Comparison of CHHiP and PROFIT Protocols in Terms of Target Delineation

	CHHIP	PROFIT
Patient risk stratification	Yes	Yes
Estimation of SVI risk	Roach formula	Partin table
Number of target volumes	3	1
	Clinical target volumes	
	CTV1	**CTV**
	If low risk of SVI: prostate gland + base of SV + 5 mm If moderate/high risk of SVI: prostate gland + SV + 5 mm	If risk of SVI < 15%: prostate gland only If risk of SVI > 15%: prostate gland + proximal 1 cm of SV
	PTV1 = CTV1 + 5 mm	PTV = CTV + 10 mm (7 mm posteriorly)
	48.0 Gy	60.0 Gy
	CTV2	
	If low risk of SVI: prostate gland + 5 mm If moderate/high risk of SVI: prostate gland ± base of SV* + 5 mm	
	PTV2 = CTV2 + 5 mm (0 mm posteriorly, or 5 mm if rectum is moderate-large in size)	
	57.6 Gy	
	CTV3	
	Prostate gland only	
	PTV3 = CTV3 + 5 mm (0 mm posteriorly)	
	60.0 Gy	

Abbreviations: CTV, clinical target volume; PTV, planning target volume; SVI, seminal vesicle invasion.

**Include the base of the seminal vesicles in CTV2 if seminal vesicle invasion is evident on MRI (ie, if the tumor has a clinical stage of T3b).*

or 60 Gy (V40, V50, and V60, respectively). Even though the femoral heads and necks were contoured, dose volume data were not extracted for this OAR as their location is not in the vicinity of the prostate and the comparison was deemed not to be relevant herein.

Statistical Analysis

For the statistical analysis, we used IBM SPSS Statistics for Windows, version 28 (IBM Corp.). Given that we have 25 patients only, we relied on nonparametric tests for comparison, namely the related-samples Wilcoxon signed-rank test, with the significance level being 0.05.

Results

Patient Characteristics

A total of 25 patient charts were reviewed, and a total of 50 patient plans were generated. Patients had a mean age of 73 years (range, 54-79 years), an average prostate-specific antigen (PSA) level of 9.8 ng/mL (range, 2-25 ng/mL), mostly a Gleason score of 7 (range, 6-7), and a clinical stage that ranged from T1c to T2c, with most patients having a stage of either T2a or T2c. As per the CHHiP protocol, the majority of patients were labeled as having a high risk of SVI (80%). On the other hand, as per the PROFIT protocol, only 16% were considered to have a high risk of SVI. **Table 3** summarizes the patient characteristics and their respective risk of SVI in either CHHiP or PROFIT. The exact risk percentages of SVI can be found in the supplementary information found in the online version of this article (Table S1).

Target Coverage

All plans followed the respective protocols in terms of target coverage and satisfied the prescription aims, which are depicted in **Table 2**. We did not compare target coverage between either protocol as our objective involves OAR sparing only.

Doses to Organs at Risk

In the CHHiP protocol, the bladder and the rectum were less exposed to higher radiation doses, manifesting as lower V60 and V50 on average than in the PROFIT protocol. The differences were statistically significant (*P* value < .05). The mean dose and V40 were similar.

As for the penile bulb, the mean dose was significantly less with CHHiP than with PROFIT (21.9 vs 30.5 Gy, respectively, *P* value < .001). V50 and V40 were also significantly lower with CHHiP (5.6% vs 14.4% and 11.4% vs 35.2%, respectively, *P* value < .05) than with PROFIT.

On subgroup analysis of patients categorized as high or low risk for SVI, bladder V60, rectum V60, as well as penile bulb mean and V40

Table 2. Comparison of CHHiP and PROFIT Protocols in Terms of Organs at Risk (OAR) Delineation, Prescription Aims, and Normal Tissue Dose Constraints[13]

OAR	CHHIP	PROFIT
OAR delineation		
Bladder	Solid organ, from base to dome	Bladder wall (3 mm ring), for 18 mm below and above the contoured CTV
Rectum	Solid organ, from anus to recto-sigmoid junction	Rectal wall (3 mm ring), for 18 mm below and above the contoured CTV
Penile bulb	Contoured	Not contoured
Femoral head and neck	Contoured	Contoured
Prescription aims and dose constraints		
CTV		D99 ≥ 60 Gy
PTV	D99 ≥ 57 Gy	D99 ≥ 57 Gy
	D1cc ≤ 63 Gy	D1cc ≤ 63 Gy
Bladder	V60 ≤ 5% V48 ≤ 25% V40 ≤ 50%	V46 ≤ 30% V37 ≤ 50%
Rectum	V57 ≤ 15% V40 ≤ 60%	V46 ≤ 30% V37 ≤ 50%
Penile bulb*	V40 ≤ 50%	Not applicable
Femoral head	V40 ≤ 50%	V43 ≤ 5%

Abbreviations: CTV, clinical target volume; PTV, planning target volume.

**The values for the penile bulb are nonmandatory constraints as per CHHiP and are for clinician guidance only.*

remained significantly lower with CHHiP (Tables S3-6).

Table 4 summarizes the average and median values of the mean dose, V60, V50, and V40 for each of the OARs in both CHHiP and PROFIT, and a breakdown of all patient doses can be found in the supplementary material (Table S2). **Figure 1** illustrates the isodose lines covering the OARs, particularly the penile bulb, for one of the patients (patient #14).

Discussion

In this retrospective dosimetric study comparing doses to OARs, we demonstrated that CHHiP treatment protocol delivers less dose to the bladder, rectum, and penile bulb. The results of this study favor the use of CHHiP protocol over the PROFIT protocol when treating patients with localized, low- to intermediate-risk prostate cancer with moderate hypofractionated external beam radiation therapy.

The radiobiological rationale for using hypofractionation in the treatment of prostate cancer is the low α/β value, which indicates that higher doses per fraction can have a therapeutic advantage while minimizing long-term adverse effects on the surrounding normal tissues.[3] Safely decreasing the number of fractions also has logistic and socioeconomic advantages to patients and radiation centers. There have been several trials comparing different dose fractionations to the standard regimens, which use 1.8-2 Gy per fraction. Among these trials are CHHiP and PROFIT.

CHHiP is the largest of these randomized trials that enrolled more than 3000 patients across Europe and New Zealand, and it demonstrated noninferiority of the hypofractionated 60 Gy arm compared with the standard fractionated 74 Gy arm in terms of biochemical and clinical failure-free survival at 5 years (> 90%)[6] and at 8 years (>80%).[14] The hypofractionated regimen had an acceptable toxicity profile as per the Radiation Therapy Oncology Group (RTOG) scale: the cumulative incidence of grade ≥ 2 bladder and bowel toxicity at 5 years was estimated at 11.7% and 11.9%, respectively.[6]

PROFIT was also a randomized trial comparing standard and hypofractionated radiation therapy, by enrolling more than 1200 patients from Canada, Australia, and France. It showed a 5-year biochemical/clinical failure disease-free survival of 85% in both arms with no difference in overall RTOG grade ≥ 3 bladder and bowel toxicity. Although gastrointestinal (GI) adverse events grade ≥ 2 were higher in the hypofractionated arm in the acute setting (first 14 weeks), this was reversed in the long term (6 months onward), with late GI toxicity in the hypofractionated arm being lower than in the standard arm (7.4% vs 11%, *P* value = .006).[8]

We decided to compare the CHHiP and PROFIT regimens due to identical dose and fractionation in the 2 studies as well as their popularity. PROFIT is more user friendly for both the radiation oncologist and the dosimetrist because there is a single target volume that is treated

Table 3. Characteristics of the Patients and Their Respective Risk of Seminal Vesicle Invasion (SVI) as per CHHiP and PROFIT

	AGE (YEARS)	PSA (NG/ML)	GLEASON SCORE	CLINICAL STAGE	CHHIP SVI RISK	PROFIT SVI RISK
1	66	10.5	7 (4 + 3)	T1c	High	High
2	75	8.5	7 (4 + 3)	T2a	High	Low
3	68	13.0	7 (3 + 4)	T2a	High	Low
4	54	7.2	6 (3 + 3)	T1c	Low	Low
5	76	15.0	7 (3 + 4)	T2a	High	Low
6	78	15.0	7 (4 + 3)	T2c	High	High
7	79	11.0	6 (3 + 3)	T2a	Low	Low
8	74	12.0	6 (3 + 3)	T2b	Low	Low
9	78	14.7	7 (3 + 4)	T2b	High	Low
10	70	25.0	7 (4 + 3)	T1c	High	High
11	72	6.2	7 (4 + 3)	T1c	High	Low
12	70	6.7	7 (4 + 3)	T2a	High	Low
13	77	8.0	6 (3 + 3)	T2a	Low	Low
14	78	21.0	7 (4 + 3)	T2c	High	High
15	73	6.2	7 (3 + 4)	T2c	High	Low
16	74	10.8	6 (3 + 3)	T2c	High	Low
17	76	11.6	6 (3 + 3)	T2c	High	Low
18	79	6.5	7 (3 + 4)	T2a	High	Low
19	78	5.2	7 (3 + 4)	T2a	High	Low
20	75	5.3	7 (4 + 3)	T2c	High	Low
21	76	9.8	7 (4 + 3)	T2a	High	Low
22	78	4.3	7 (3 + 4)	T2c	High	Low
23	78	3.8	7 (4 + 3)	T2b	Low	Low
24	73	2.0	7 (4 + 3)	T2c	High	Low
25	56	5.7	7 (4 + 3)	T2c	High	Low

Abbreviation: PSA, prostate-specific antigen.

CHHiP uses the Roach formula, whereas PROFIT uses the Partin tables.

to a dose of 60 Gy in 20 fractions contrary to the CHHiP protocol where 3 different target volumes exist, requiring a simultaneous integrated boost technique. It may be argued that a comparison between CHHiP and PROFIT cannot be done due to the differential dose distribution in either regimen (ie, CHHiP delivers 60 Gy to PTV1, 57.6 Gy to PTV2, and 48 Gy to PTV3, whereas PROFIT delivers the entire 60 Gy to a single PTV). Both protocols were compared in phase 3 randomized trials to standard fractionation and were shown to be equivalent in terms of oncological outcomes. The question of which shall be preferred in terms of radiation toxicity cannot be answered unless they are compared head-to-head without delineation and dose prescription modifications. To the best of our knowledge, our dosimetric study is the first to compare the two.

Despite moderate hypofractionation becoming standard of care for localized prostate cancer, significant variety exists in target volume definitions in the literature. The American College of Radiology Appropriateness Criteria mentions 2 CTVs in case the risk of seminal vesicle involvement is high (ie, >15%). The first CTV involves both prostate and seminal vesicles, while the second covers the prostate only.[15] The French Genito-urinary Group (GETUG) recommendations mention a single CTV, which may include the first centimeter of the seminal vesicles if the tumor is deemed to be high-intermediate risk for SVI.[16] Given the different guidelines and recommendations among treatment groups, our comparison is relevant to the current practice of radiation oncology in prostate cancer.

When CHHiP and PROFIT were initiated, image-guided radiation therapy (IGRT) was not yet widespread. When image guidance became more available, the CHHiP trialists started a substudy, where patients either received no IGRT, or IGRT with the original margins, or IGRT with reduced margins: 6 mm/6 mm/3 mm and posteriorly 6 mm/3 mm/0 mm.[17] The reduced margins significantly spared the bladder and rectum to a greater degree, as illustrated in lower dose volume and surface percentages (P value < .0001). Even though radiation oncologists are now inclined to reduce the margins, significant variability still exists in clinical practice. For example, GETUG recommends a margin of 7-10 mm (5-7 mm posteriorly),[16] whereas physicians at the Memorial Sloan Kettering Cancer Center suggest margins to be reduced as much as 5 mm (3 mm posteriorly) in a recently published treatment planning guide.[18] Similarly, the moderately hypofractionated plans in the PACE-B trial used 5-9 mm margins (3-7 mm posteriorly),[19]

Table 4. Comparison of the CHHiP and PROFIT Protocols in Terms of Average and Median Values of the Mean Doses to the Bladder, Rectum, and Penile Bulb and in Terms of the Volume Receiving 40 Gy, 50 Gy, and 60 Gy (V40, V50, and V60)

		CHHIP		PROFIT		*P* VALUE
		MEAN (± SD)	MEDIAN	MEAN (± SD)	MEDIAN	
Bladder	Mean (Gy)	22.7 ± 7.2	22.9	21.2 ± 10.1	19.6	0.110
	V60 (%)	1.9 ± 2.0	1.1	7.7 ± 5.7	6.2	**<0.001***
	V50 (%)	13.2 ± 7.5	11.6	15.5 ± 10.1	12.9	**0.035***
	V40 (%)	21.2 ± 10.4	18.8	21.8 ± 13.4	18.1	0.753
Rectum	Mean (Gy)	27.8 ± 4.5	27.2	26.0 ± 6.6	25.3	0.201
	V60 (%)	0.5 ± 0.9	0.1	4.5 ± 3.2	3.8	<0.001*
	V50 (%)	13.1 ± 5.6	12.3	15.7 ± 6.1	15.2	0.037*
	V40 (%)	26.4 ± 8.3	25.1	25.3 ± 10.0	22.1	0.667
Penile bulb	Mean (Gy)	21.9 ± 10.8	20.0	30.5 ± 12.4	27.9	<0.001*
	V60 (%)	<0.1	<0.1	1.3 ± 5.9	<0.1	0.180
	V50 (%)	5.6 ± 20.5	<0.1	14.4 ± 24.1	<0.1	0.037*
	V40 (%)	11.4 ± 24.4	<0.1	35.2 ± 31.4	30.3	<0.001*

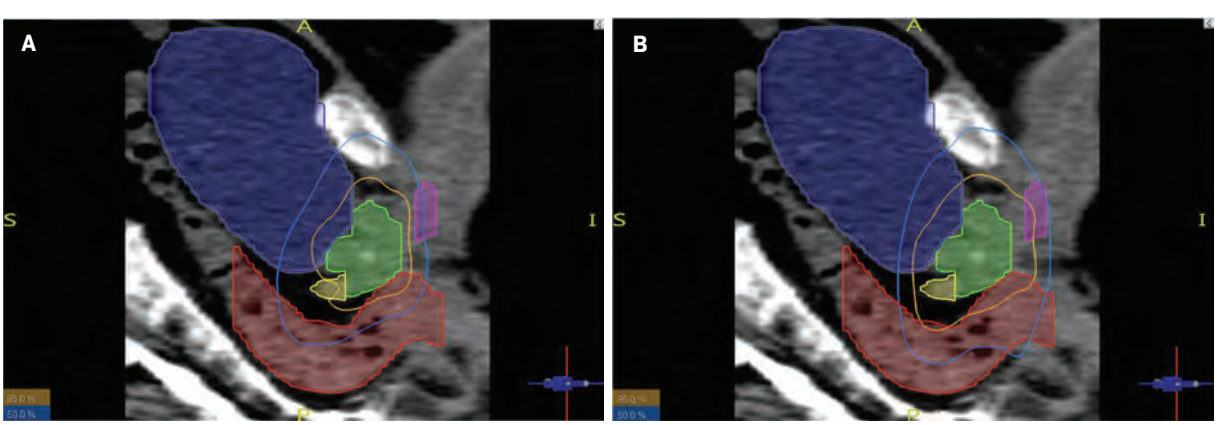
** P values < 0.05 were considered statistically significant as per the related-samples Wilcoxon signed-rank test.*

while those in POP-RT had them at 7 mm (5 mm posteriorly).[20] Some protocols require the insertion of fiducial markers, which may not be available in all centers, or the availability of daily cone beam CT imaging, which may be problematic in busy radiation therapy centers with limited resources. As such, in our comparison, we decided to rely on the PTV margins as originally described in the trial protocols.

Our study illustrated that the CHHiP treatment protocol delivered less dose to the bladder, rectum, and penile bulb compared with the PROFIT protocol. While the 2 regimens have not been compared head-to-head in terms of toxicity, we expect this dosimetric benefit to translate into clinical benefit as per dose-toxicity relationships.

In terms of GI toxicity, several reports have correlated the dose received by the rectum in prostate radiation therapy to the incidence of late rectal bleeding. The quantitative analysis of normal tissue effects in the clinic (QUANTEC) review suggested dose constraints in order to decrease the risk of late rectal toxicity of grade ≥ 2 and of grade ≥ 3 to less than 15% and 10%, respectively.[21] Accordingly, it was recommended that the rectal volumes receiving 75 Gy, 70 Gy, 65 Gy, 60 Gy, and 50 Gy not

Figure 1. Prostate gland (green), seminal vesicles (yellow), penile bulb (pink), bladder (blue), and rectum (red) in relation to the 95% and 50% isodose lines in CHHiP (A) and PROFIT (B) plans for the same patient (patient #14)



exceed 15%, 20%, 25%, 35%, and 50%, respectively. In its recommendations, the QUANTEC review relied on studies where three-dimensional conformal radiation therapy was applied and where radiation was given in standard fractionation. More recently, Wilkins et al presented a dose-volume study that is more applicable to prostate cancer care nowadays.[22] Relying on the CHHiP trial, they were the first to derive anorectal dose constraints for hypofractionated IMRT: the volumes receiving 60 Gy, 50 Gy, 40 Gy, 30 Gy, and 20 Gy should be kept below 0.01%, 22%, 38%, 57%, and 85%, respectively. The constraints on the higher doses (40-60 Gy), much tighter than those of QUANTEC, were particularly significant in minimizing rectal bleeding.[22] In our comparison, both CHHiP and PROFIT plans met the tighter V50 and V40 constraints suggested by Wilkins et al, but neither satisfied that of V60. That said, V60 in the CHHiP plans was on average 0.5%, which was 9 times less than the average V60 in PROFIT (4.5%). We infer that the CHHiP protocol potentially decreases GI toxicity as opposed to PROFIT, even with the original margins used. We also acknowledge that the plans can be further optimized by using IGRT and reducing the margins, so that all constraints by Wilkins et al may be met and that GI toxicity may be minimized.

Urinary toxicity is also a significant consideration for the quality of life of patients after radiation therapy for prostate cancer, with long-term symptoms including hematuria, dysuria, and increased frequency. However, the QUANTEC review reported that there were no comprehensive data to extract generalizable dose constraints for the bladder.[23] With that, it recommended the reliance on the constraints as per the conventional fractionation arm in the noninferiority RTOG 0415 trial, which limited the bladder volume receiving 80 Gy, 75 Gy, 70 Gy, and 65 Gy from exceeding 15%, 25%, 35%, and 50%, respectively.[7] Interestingly, for that same trial, a later dose-toxicity analysis found no correlation between the dose received by the bladder and the incidence of genitourinary (GU) toxicity in patients assigned to the hypofractionated arm.[24] In our comparison, both CHHiP and PROFIT plans satisfy V48 and V40, but only CHHiP satisfies V60 (1.9% vs 7.7% in PROFIT). While more evidence is surely required to better understand dose and GU toxicity relationships, it is prudent to reduce the dose to the bladder if possible, providing one more reason to favor CHHiP.

The penile bulb is considered a surrogate for neurovascular structures necessary for erectile function, and doses to the penile bulb have been implicated in sexual toxicity. In 2010, the QUANTEC review based on standard fractionated regimens suggested 50 Gy as a threshold mean dose to the penile bulb so as not to increase the risk of impotence post radiation therapy.[25] More recently, studies based on hypofractionated regimens have recommended stricter thresholds. In the CHHiP IGRT substudy, researchers found a correlation between the mean and maximum dose to the penile bulb and the incidence of erectile dysfunction.[26] With a Royal Marsden Hospital (RMH) grade 2 erectile potency at 2 years as an endpoint, the derived mean dose constraint was 22 Gy, delivered in 3 Gy per fraction, in such a way that the odds of an RMH grade 2 erectile potency were 2.6 times higher in patients whose plans met the constraint than in those whose plans did not. Similar cutoff values have been suggested by a dose-response study from the HYPO-RT-PC trial[27] and by another smaller trial from the University of Alabama at Birmingham,[28] both of which delivered hypofractionated radiation therapy. In our study, CHHiP plans, which averaged a mean dose of 21.9 Gy, performed significantly better in respecting the stricter threshold (ie, 22 Gy) than the PROFIT plans, which averaged 30.5 Gy. Given the impact of erectile dysfunction on patients' quality of life, our results once again favor CHHiP.

This study provides the first head-to-head dosimetric comparison between these 2 popular treatment protocols. However, it has several limitations. The IMRT plans generated were step and shoot IMRT and not volumetric-modulated arc therapy. The study was conducted retrospectively in a single tertiary care center on a homogeneous patient population and did not have long-term clinical follow-up to assess for toxicity profiles. It is important to note that these differences in doses delivered to the OARs may not directly correlate to clinical toxicity, especially when the constraints are met. Also, our study is limited to patients with localized low-intermediate-risk disease, and conclusions cannot be extrapolated to other patient populations or to other dose fractionations. Our conclusions may also not apply in case different PTV margins are defined. In other words, our results apply within the scope of the comparison herein, and further studies are needed to corroborate our findings: CHHiP offers superior sparing of the bladder, rectum, and penile bulb compared with PROFIT.

Conclusion

This dosimetric analysis shows that treatment planning with the CHHiP protocol yields lower doses to the bladder, rectum, and penile bulb compared with the PROFIT protocol. These results favor the use of CHHiP as it may decrease the risk of radiation toxicity. Our results need

to be validated in a larger cohort of prospectively treated patients.

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Extracapsular Prostate Brachytherapy Using Iodine-125 for Intermediate and Selected High-Risk Prostate Cancer: Technical Notes

Barry W. Goy, MD*

Abstract

Introduction: Our aim is to describe extracapsular prostate brachytherapy (ECPB) techniques using low-dose-rate (LDR) for patients with intermediate-risk prostate cancer (IRPC) and selected high-risk prostate cancer (HRPC).

Materials and Methods: Using stranded iodine-125 seeds, dose can be extended to the capsule and seminal vesicles (SVs). Intraoperative use of fluoroscopy with a cystogram can increase the extracapsular dose at the base and proximal SV compared with using ultrasound alone, with a seed source at the tip of each needle to push the dose cephalad. Visualization of the prostate base can be improved with a urinary catheter, with additional seeds placed posterior to the catheter balloon, along with additional stranded sources placed into the SV. For apical disease, a needle tip can be placed at the apex of the prostate under ultrasound guidance, and a fluoroscopic image can be referenced during the case, to ensure seed placement below the prostate apex. A peripheral loading technique is applied so that there is at least 3 mm coverage beyond the prostate radially, while additional seeds are inserted into areas of gross disease.

Results: Our prior published experience of IRPC and selected HRPC showed excellent freedom from biochemical failure with 10-year follow-up. Our ECPB approach requires the use of more seeds ($P < .0001$), compared with a standard prostate brachytherapy approach, while requiring the use of fluoroscopy in addition to ultrasound.

Conclusion: LDR prostate brachytherapy using iodine-125 alone with extracapsular techniques is a reasonable treatment option for IRPC and selected HRPC, but unfortunately is becoming a lost art.

Keywords: prostate cancer, low-dose-rate brachytherapy, monotherapy

Introduction

Low-dose-rate (LDR) prostate brachytherapy using iodine-125 delivers the radiation with a half-life of 60 days, thus named LDR, but gives the highest numerical dose of radiation to the prostate of 14,400 cGy, delivering ablative doses to the prostate. Modern techniques of LDR were developed in 1985 and applied mostly to low-risk prostate cancer, while used as a boost for intermediate-risk prostate cancer (IRPC) and high-risk prostate cancer (HRPC).[1-3]

Studies have shown that dose escalation using external radiation leads to improved oncological outcomes for IRPC and HRPC, so why shouldn't brachytherapy alone be used in this setting?[4,5] Can brachytherapy adequately dose the capsule, without supplemental external

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beam radiation therapy (S-EBRT)? Randomized trials have not shown a clear benefit with the addition of S-EBRT.[6,7] Our aim is to describe extracapsular prostate brachytherapy (ECPB) techniques so that it can used as monotherapy for patients with unfavorable IRPC and selected HRPC.

Materials and Methods

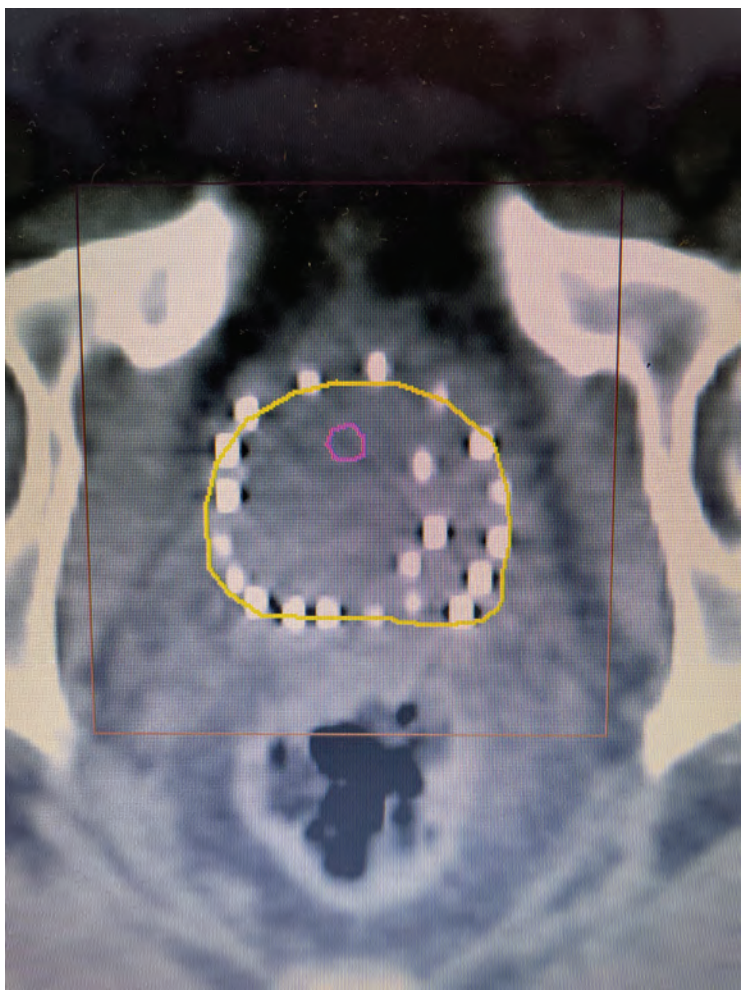
Origins

Techniques of modern LDR prostate brachytherapy started in 1985 using transperineal needle placement under ultrasound guidance and a stepper-stabilizer apparatus, which began using loose iodine-125 and palladium-103 seeds.[8] Because of migration of individual loose seeds placed beyond the capsule, it was felt that LDR brachytherapy might not adequately cover capsular disease, and thus its use was limited to low-risk prostate cancer, or as a boost for those with IRPC and HRPC. With advances in computer planning, it was later felt that capsular coverage could still be obtained by a peripheral loading technique (**Figure 1**), although seed migration could occur, and post-procedure CT dosimetry was required to document dosimetric parameters of the implant.[9,10] In the past, stranded seeds would jam in the needle, but later reliable stranded seeds became available, and we prefer the braided strand, which has a rougher external texture as opposed to a sleeve strand that feels smooth.

Dosimetric Goals

Our preplanning goal is to achieve a minimum prostate V100 of > 95%, prostate D90 of > 115%, urethral V150 close to 0, and rectal V100 of < 1.5 cc. Our planning target volume (PTV) margin is 3 mm beyond the prostate, but less posteriorly near the rectum, depending on the anatomy and tumor location.

Figure 1. CT image of peripheral loaded seeds, with extra at left tumor location.

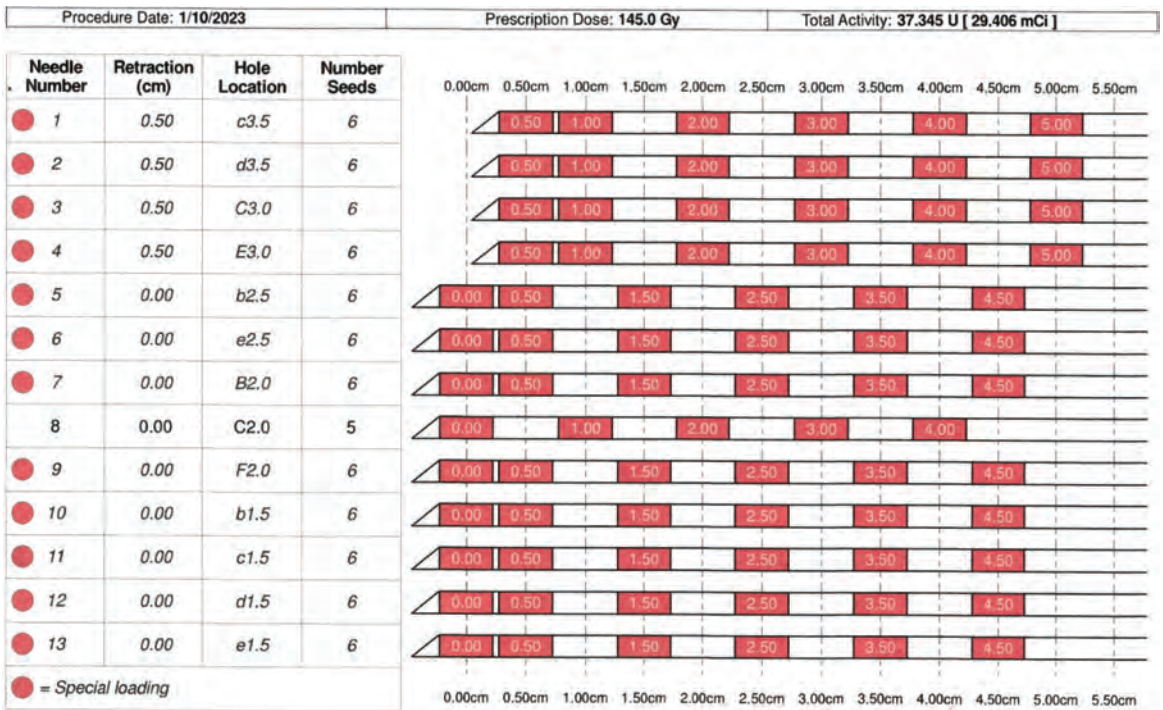


Preplanning

Preplanning studies should include cross-sectional imaging to calculate prostate size and assess pubic arch interference. Measurement of post-void residual should be performed, along with a uroflow study, and assessment of the patient's American Urological Association (AUA) urinary score.[11]

Our preference is to perform preplanning ultrasound, so that strands can be customized to the patient's anatomy and tumor location, during which a urethral catheter is placed with a 10 mL balloon in the bladder, which helps visualize the urethra, and the prostate base as it extends posterior to the catheter balloon. In most cases, the urethra is in the middle of the prostate, although it tends to course anteriorly at the base. However, in a minority of patients, the urethra is deviated to the side, so urethral mapping may help reduce future urinary toxicity. The zero plane should be the most cephalad portion of the prostate and proximal seminal vesicles (SVs), which in most cases should have the catheter balloon visualized anteriorly. Five-mm images are loaded onto the Variseed 8.0.1 fusion program using 0.4 milliCuries per seed. Two slices are added below the apex of the prostate to achieve an

Figure 2. Zero plane showing anterior needle placement 5 mm caudal to posterior needles due to the anterior location of the bladder.



adequate PTV margin. However, at the anterior prostate base, additional sources cannot be placed due to the location of the bladder. Thus, when preplanning, each needle should have a source at the needle tip to obtain adequate coverage at the prostate base and proximal SV (**Figure 2**). The plan may show an absence of seeds at the zero plane anteriorly since this is the location of the catheter balloon. The anterior needle tips ending at the prostate/bladder junction are normally ~5 mm caudal to the posterior needle tips as the prostate/bladder junction is not a vertical line. Additional sources can be placed in areas where the tumor is known to be present based on digital rectal exam, imaging, and/or location of core biopsies to perform simultaneous integrated boost (**Figure 1**). Seeds are alternated with spacers, although back-to-back seeds can be placed in areas away from the rectum and urethra. Advances in software make preplanning user-friendly, and should only take about 20 minutes. Delegating this task to a physicist/dosimetrist is not ideal as they may not understand the anatomy as well, nor have knowledge of tumor location, and may not be aware of prior areas of suboptimal coverage or excess dose to the urethral and rectum on prior post plans.

Operating Room Implant

Patients are placed in high lithotomy, and the legs may be extended to avoid pubic arch interference. In addition to the patient's bowel prep, after the patient is anesthetized, a pool suction is placed into the rectum, to suction out any residual stool, liquid, or gas, which can markedly interfere with the ultrasound image of the prostate. Also, the transducer cover should be aspirated for any air bubbles using a blunt catheter tip syringe. Prior to inserting the urethral catheter, viscous lidocaine is inserted into the penile urethra for additional lubrication, and the catheter is inserted all the way until it reaches the balloon port, with evidence of urine returning, to minimize the risk of the balloon being inflated inside the prostate. Once the catheter is inserted into the bladder, 10 mL of iodinated contrast is used to inflate the catheter balloon, after which the bladder is emptied with a large catheter tip syringe, and an additional 30 mL of iodinated contrast is placed into the bladder for a cystogram, which can be viewed during the entire case using fluoroscopy (**Figure 3**).

Many physicians implant using ultrasound alone, with fluoroscopy used only to align the angle of the probe parallel to the symphysis pubis, and to document final placement at the end of the implant, which is the standard prostate brachytherapy (SPB) approach (**Figure 4**).[8] During the implantation of each needle,

Figure 3. Extracapsular prostate brachytherapy using a cystogram showing extracapsular placement of seeds at the prostate/bladder junction.

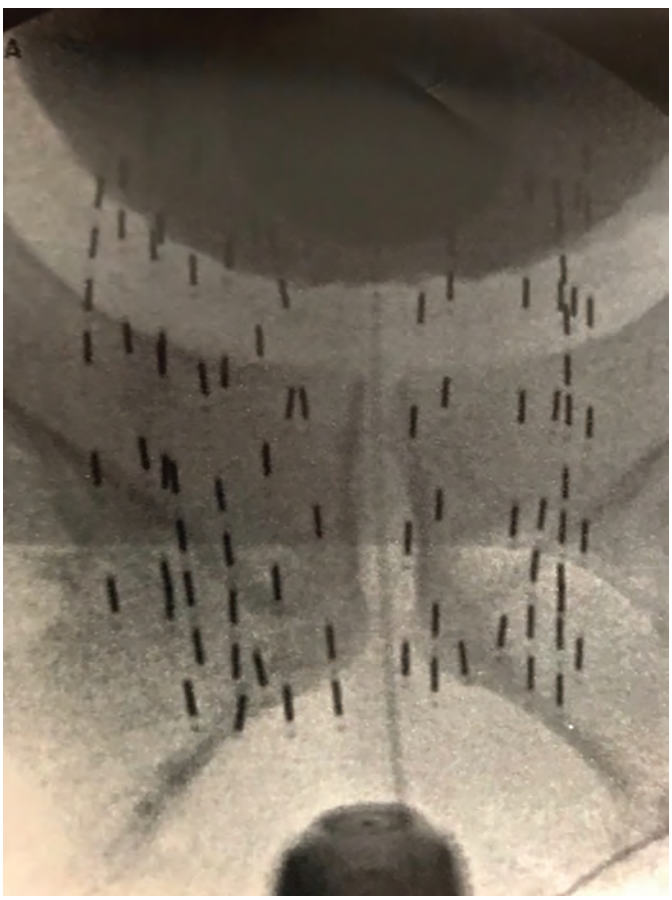
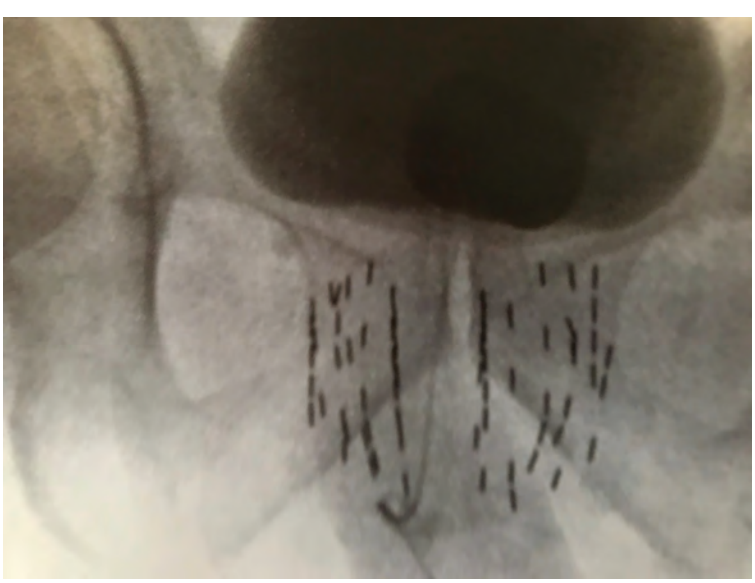


Figure 4. Prostate-only implant or standard prostate brachytherapy (SPB) using ultrasonography alone to place seeds.



fluoroscopy can provide additional anatomic information during the implant, in addition to ultrasound. I do not prioritize aligning the probe parallel to the symphysis, but rather to the urethra at the base and apex of the prostate. Both the contrast in the catheter balloon and the bladder help visualize the prostate/bladder junction using fluoroscopy, in addition to the ultrasound (**Figure 3**). When using ultrasound alone, the most cephalad portion of the seeds may still be 5-10 mm below the bladder base (**Figure 4**). Thus, using fluoroscopy with a cystogram allows further advancement of seeds, covering extracapsular disease at the base and proximal SV, which illustrates our ECPB approach (**Figure 3**), compared with SPB (**Figure 4**). When placing the first two anterior needles, which are periurethral (5 mm from midline), localize the most cephalad extent of needle tip placement using ultrasound, pushing each needle to the prostate/bladder junction anteriorly. Then perform fluoroscopy, and for many cases, there is additional needle advancement that can be performed toward the prostate/bladder junction, based on the cystogram. When the tip reaches the prostate/bladder junction, one normally feels a rebound of the needle going caudal. Carefully advance the needle tip going as far cephalad as possible, without puncturing the bladder/catheter balloon. This should be repeated for all the needles. If you feel a sudden release of pressure, you've gone too far and likely punctured the bladder and/or catheter balloon. When loading the seeds, the physicist/dosimetrist may suggest retracting the anterior needles, assuming the prostate/bladder base junction to be a straight vertical line; but it's not. In most patients, the prostate/bladder junction anterior needle tips are

Figure 5. Needle tip marking the bottom of the prostate apex.

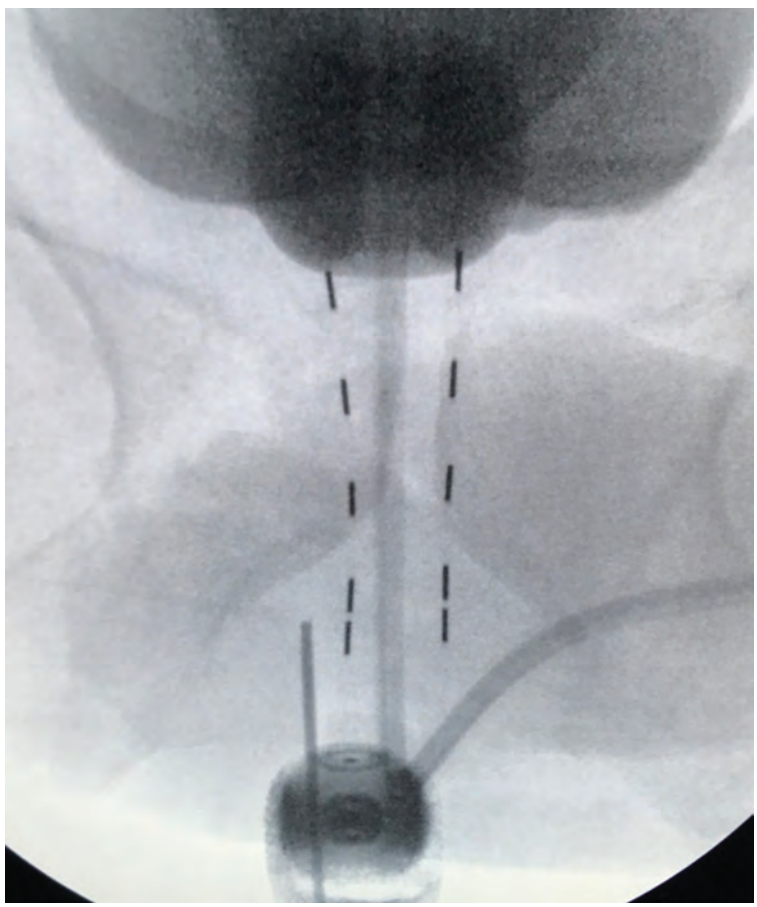
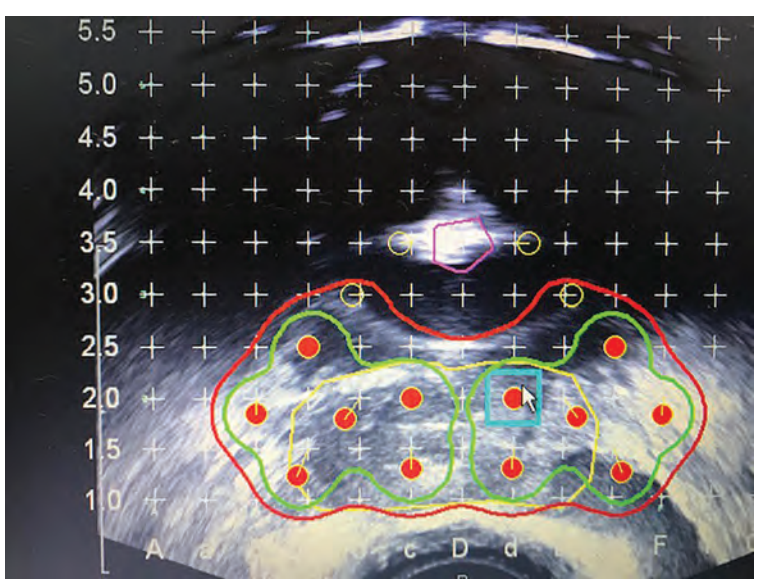


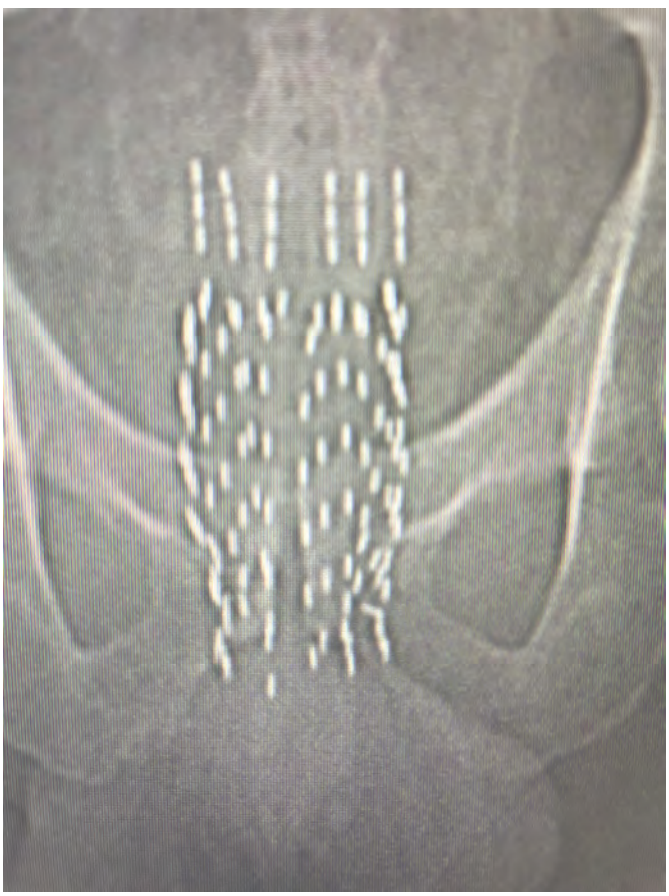
Figure 6. Additional loose seeds placed posterior to the catheter balloon in rows 2 and 2.5 to fill in isodose at the central prostate base. Red = 100% (14,400 cGy), green = 150% (21,600 cGy), and yellow = proximal seminal vesicle clinical target volume.



slightly caudal to the posterior needle tips, and normally the anterior needles are already retracted ~5 mm distally, so that they do not puncture the bladder. Thus, initial retraction of the stepper is not required for these anterior needles (**Figure 2**). After placement of the two most anterior rows of seeds, place an empty needle through the perineum and place the needle tip at the bottom of the prostate apex based on ultrasound, and then save this image onto the fluoroscopy unit. This image can serve as a reference to the bottom of the apex throughout the case as one can see where the needle tip is in relation to the two anterior rows of seeds. If you did your preplan correctly, the caudal extent of the anterior strands should be just below the needle tip (**Figure 5**). Since these two rows of strands are fixed, they can serve as a reference to the saved fluoroscopy image with the empty needle tip at the apex of the prostate. Continue implanting from anterior to posterior, and when placing needles at the proximal SV, one may also feel a rebound of the needle going caudal. Carefully advance ~5-10 mm, so that one is as far cephalad without puncturing the bladder, in which the posterior needles usually are placed more cephalad than the anterior needles. However, in implanting each needle, confirm that the needles that were meant to go below the prostate apex, in obtaining PTV coverage on your preplan, are still below the needle tip that marked the prostate apex on your saved fluoroscopy image.

During the placement of each needle, one may use a needle adjustment device, otherwise known as a "diddler," which looks like a crochet needle with a reverse function. While a helpful device, one must be careful not to overbend as the needle may break, resulting in a retained needle inside the patient.

Figure 7. Prostate fluoroscopy image with seminal vesicles implanted.



Also, be mindful of the spacing of strands relative to one another and the prostate movement that may be happening, as you may need to readjust the stepper-stabilizer unit. Additional loose seeds may be placed posterior to the catheter balloon to fill in the central isodose at the base of the prostate and proximal SV (**Figure 6**).

Postplanning

We typically schedule postplanning CT about 1 week after the implant as some patients require catheter removal and to assess whether the seeds are covering the base and apex of the prostate adequately. We use the Variseed 8.0.1 fusion program to fuse our preplanning ultrasound onto the CT postplan, although the fusion may need editing since the ultrasound images are affected by the presence of the probe. If the physician considers the postplan suboptimal, additional seeds can be placed later. It is important that the physician be involved in delineating the prostate on the CT postplan as this process gives the physician feedback about areas of suboptimal coverage, as well as areas of excessive dose near the urethra and rectum. Assigning CT postplanning contouring to the physicist/dosimetrist may give different dosimetric outcomes since their perception of prostate anatomy may be different from the physician's.

Implanting the Mid-Distal Seminal Vesicle

Depending on the size and shape of SV on cross-sectional imaging, one may use 3 parallel needles per vesicle using a seed at the most proximal extent, followed by a spacer, and then 2-4 additional back-to-back seeds, so that each needle will have 3-5 seeds per needle. The purpose of the proximal seed spacer is to reduce the potential rectal hot spot that may occur near the prostate base/proximal SV due to the contribution of radiation from the prostate sources, which can be seen on the preplan. The zero plane would be the location of the most proximal source, above which would be a spacer and back-to-back seeds in the strand (**Figure 7**). If one is concerned about rectal dose, a rectal spacer may be placed after placement of all the seeds. Prior to implanting the SVs, deflate the contrast out of the catheter balloon so that one can visualize the placement of the SV strands under fluoroscopy.

Results

Our experience using predominantly monotherapy LDR brachytherapy alone for IRPC and HRPC prostate has yielded encouraging 10-year freedom from biochemical failure (FFBF) results with acceptable complications.[12-14] This ECPB with peripheral loading may not require S-EBRT, but does require more seed sources; whereas if one implants with SPB, one can see a significantly lower number of seeds required per unit size of the prostate ($P < .0001$; **Figures 8 and 9**).[15] When one compares ECPB (**Figure 3**) vs SPB (**Figure 4**) in which fluoroscopy is not used to place extracapsular seeds beyond the base, there is an absence of seed coverage

Figure 8. Number of seeds needed per unit prostate size using peripheral loading and fluoroscopy with extracapsular prostate brachytherapy (ECPB) approach.

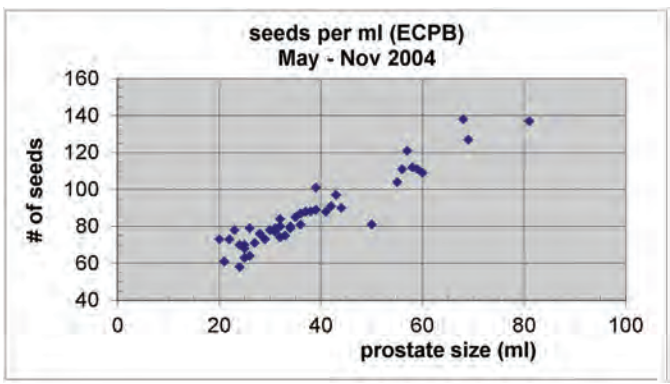
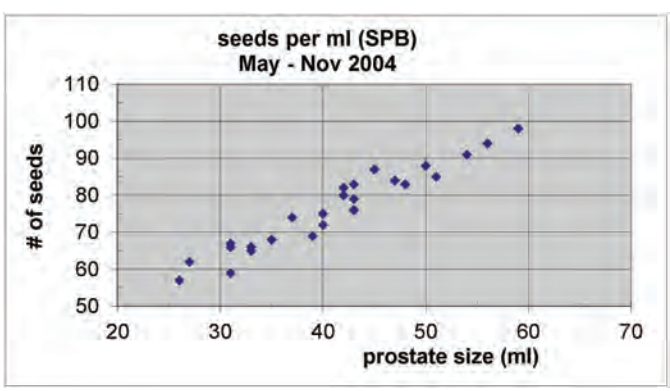


Figure 9. Number of seeds needed per unit prostate size using standard prostate brachytherapy (SPB).



between the bladder and prostate base for SPB.

Discussion

Current Status

According to the National Comprehensive Cancer Network guidelines in 2015, the role of LDR brachytherapy should be limited to patients with low-risk disease but later allowed favorable IRPC.[16] Our 10-year results using mostly monotherapy LDR for unfavorable IRPC and HRPC have shown impressive FFBF results, which may be partly due to ECPB techniques in implanting the prostate and surrounding capsule, while providing ablative doses to the prostate, with a median PSA nadir value of < 0.1.[12,14,17] A SPB approach may be more suited as a boost for patients with unfavorable IRPC and HRPC (**Figure 4**).

Despite these encouraging results, we do not recommend implanting those with gross SV invasion, nor those with a significant risk of long-term urinary retention. These include patients with a large median lobe, prostate size > 70 cc, AUA urinary score > 15, and/or peak urinary flow of ≤ 5 mL/s.[13] It is worth noting that our 10-year LDR brachytherapy results mostly implanted the prostate and proximal SV using ECPB (**Figure 3**).[12,14]

Important Principles

An important key to a good implant procedure is visualization. Many of the tips listed above emphasize knowing where the base and apex of the prostate are located during the implant, so that higher doses can be extended beyond the capsule. The priority should be implanting the prostate, not the prostate template grid. Be mindful of needle/seed spacing and prostate movement when using the techniques listed above.

Future Direction

With the advent of prostate-specific membrane antigen positron emission tomography (PSMA-PET) scans, we have noticed cases of isolated SV recurrence after brachytherapy alone. With the availability of reliable stand products, the SVs can be implanted with the goal of reducing one's risk of isolated SV recurrence (**Figure 7**). While our 10-year results of IRPC and selected HRPC only implanted the proximal SV, this more extensive SV implant described in **Figure 7** is a newer approach for which we do not have long-term outcomes. Our goal is to see if future risk of isolated SV failures for unfavorable IRPC and HRPC can be reduced, although we still do not routinely recommend brachytherapy alone for those with initial SV involvement on MRI or PSMA-PET. With the increasing use of MRI and PSMA-PET, one can better select unfavorable IRPC and HRPC who may not have initial SV invasion.

Due to low reimbursements and higher complexity of the LDR brachytherapy procedure, we have seen a substantial decline in the number of centers offering standard LDR for prostate cancer, as well as a reduction in graduating physicians being trained in standard LDR

prostate brachytherapy.[18-20] It is our hope with this publication that physicians may have more tools to perform ECPB using iodine-125 as LDR prostate brachytherapy is becoming a lost art, and few institutions have published successful 10-year results using brachytherapy alone for unfavorable intermediate and high-risk prostate cancer, which require extracapsular techniques.[7,12,14]

Conclusions

LDR prostate brachytherapy using iodine-125 alone with extracapsular techniques is a reasonable treatment option for IRPC and selected HRPC.

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Exploring the Rarity: A Case of Adenosquamous Carcinoma of the Nasal Cavity With Literature Review

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Abstract

Adenosquamous carcinoma (ADSC) is a rare tumor of the head and neck region, a phenomenon initially delineated by Gerughty and colleagues in 1968. To our knowledge, only 16 cases have been reported with primary ADSC of the nasal cavity (excluding the paranasal sinuses). ADSC is recognized for its aggressive nature and deep tissue infiltration, possessing distinct histomorphology compared with conventional head and neck squamous cell carcinomas (HNSCC) and mucoepidermoid cancers. However, some authors suggest comparable outcomes to conventional HNSCC. Herein, we describe a case report of this uncommon disease and its comprehensive management, along with a brief review of the literature.

Keywords: adenosquamous carcinoma, nasal cavity, head and neck squamous cell carcinoma, radiation therapy

Case Summary

A 38-year-old man with no relevant past medical or surgical history and no family history of cancer presented to the ear, nose and throat (ENT) clinic with complaints of painful swelling over his nasal bridge, nasal congestion, and intermittent nose bleeding on blowing for 8 to 12 months. This was not relieved by over-the-counter medications, antibiotics, and nasal sprays. He denied any nasal trauma or intranasal drug use. He reported occasional alcohol use but no smoking. He also used oral marijuana. Physical examination showed approximately 2 cm of soft swelling along the left nasal dorsum at the junction of the nasal facial groove, with a similar area of raised soft fluctuant swelling along the right nasal dorsum located more cephalad, with tenderness to palpation. Office nasal endoscopy showed that bilateral inferior turbinates had significant edema with perforation at the anterior nasal septum. The scope could not be negotiated further to the back of the nose.

Computed tomography (CT) of the sinuses revealed nasal mucosal thickening, a 15-mm anterior nasal septal defect, and bilateral subcutaneous cystic nodules overlying the right nasal ridge superiorly and left nasal ridge inferiorly measuring up to 10 mm in diameter. No underlying bony erosive changes were seen. Differential diagnoses included granulomatosis with polyangiitis, sarcoidosis, tuberculosis, and non-Hodgkin lymphoma. MRI of the face and neck showed a large enhancing mass in the nasal cartilaginous septum with mildly prominent bilateral neck nodes as described in **Figure 1**. A chest CT was also obtained, which was negative for metastatic disease.

Initial biopsy was reported as squamous cell carcinoma (SCC), invasive and in situ with colonization

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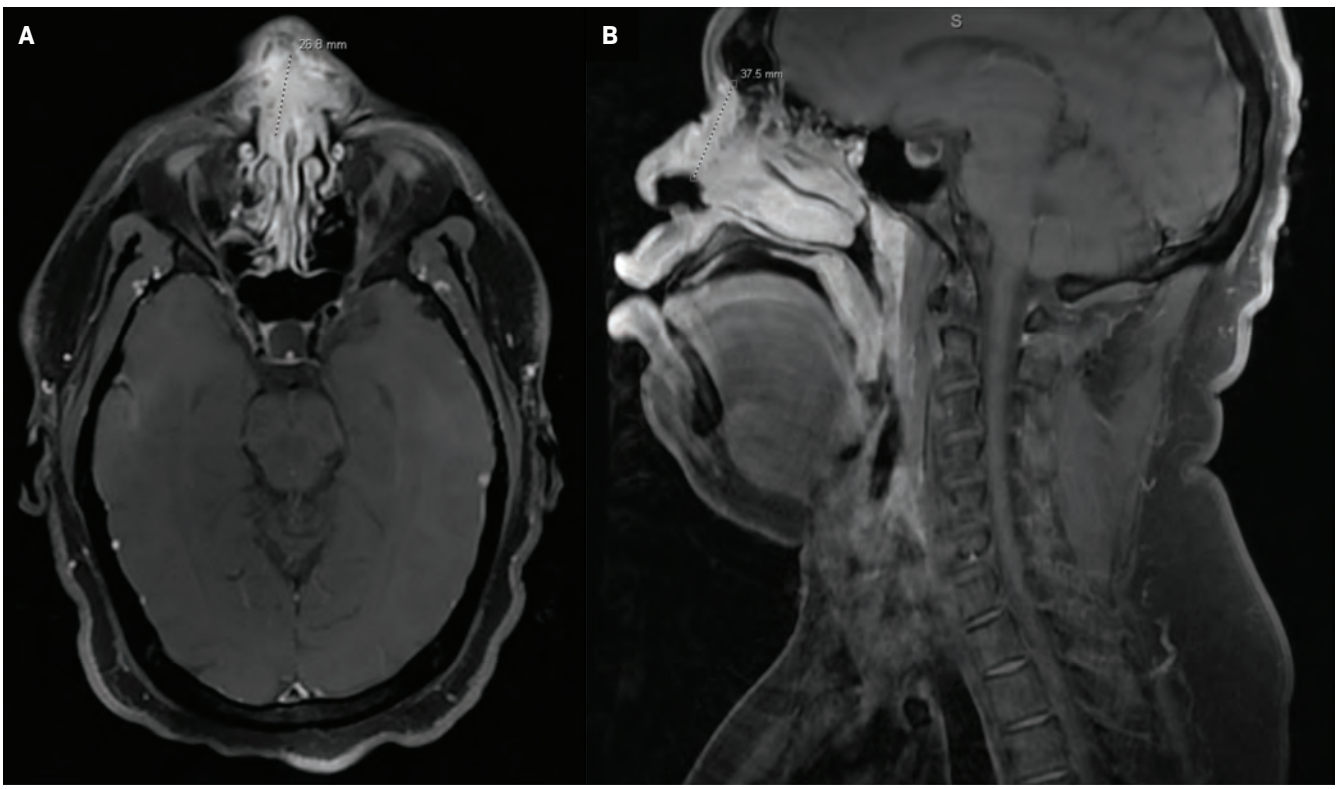
Figure 1. Axial (A) and sagittal (B) T1 postcontrast MRI of the face and neck demonstrates the large enhancing mass in the nasal cartilaginous septum superiorly with involvement of the nasal soft tissues bilaterally eroding the nasal bones, superior extension at the midline along the nasal bridge, and dorsal extension into the nasal cavity on the right greater than the left in close proximity to the middle and inferior turbinates and perforating the nasal septum, ventrally consistent with known squamous cell carcinoma. This measures 3.8 cm in maximum dimension.



of ducts of minor salivary glands. The patient was presented in the multidisciplinary head and neck tumor board. The cancer was staged as cT4a cN0 cM0 SCC (stage IVA) of the nasal cavity. The patient underwent surgery with total rhinectomy, total septectomy, bilateral inferior turbinate resection, left middle turbinate resection, and medial canthoplasty (bilateral) with Crawford stent placement. **Figure 2** shows the patient's image after the extensive surgery.

Final surgical pathology showed 3.9-cm moderately differentiated adenosquamous carcinoma (ADSC) of the nasal septum (midline) with extension to the inferior soft-tissue margin and right inferior nasal bone margin (positive margins). Lymphovascular invasion and perineural invasion were not identified. The patient again underwent resection of positive oncological margins; however, the pathology report showed no evidence of residual neoplasm. He was staged as pathological stage IVA, pT4a pN0 cM0, of the nasal cavity. Pathology details are shown in **Figure 3A-B**. P40 and CK5/6 were positive in both squamous components and in situ components. CK7 was positive in the in situ and adenocarcinoma component. P16 was strongly and diffusely positive with positive human papillomavirus (HPV) high-risk RNA in situ hybridization (ISH).

The patient received adjuvant radiation therapy (RT) to the resection bed and bilateral neck (levels I and II) to 60 Gy in 30 fractions over 6 weeks using 6 MV photons with the intensity-modulated radiation therapy (IMRT) technique (**Figures 4, 5**). The patient was simulated in the supine position with arms by his side. A 9-point head and neck face mask was used for immobilization with a customized headrest. A tongue depressor was used. Postoperative dressing/bandage was left in place to act as a bolus. IV contrast was used during the simulation CT scan. Then, 3-mm cuts were obtained and preoperative MRI images were fused for volume delineation. The patient developed Radiation Therapy Oncology Group (RTOG) acute grade 1 mucositis, nasal pain managed with narcotics, and grade 2 acute eye toxicity with dryness and redness requiring steroid eyedrops. Follow-up clinical examination

Figure 2. Clinical patient image after surgery.

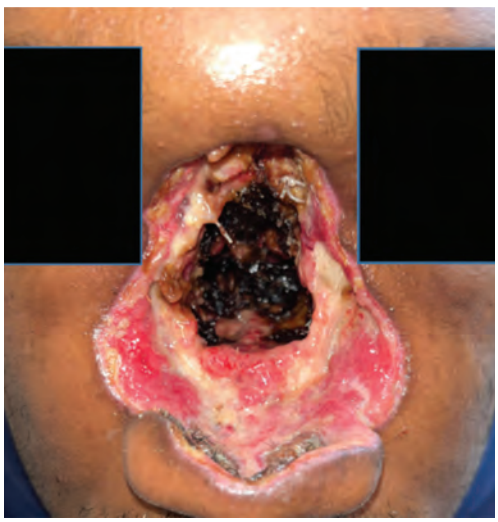
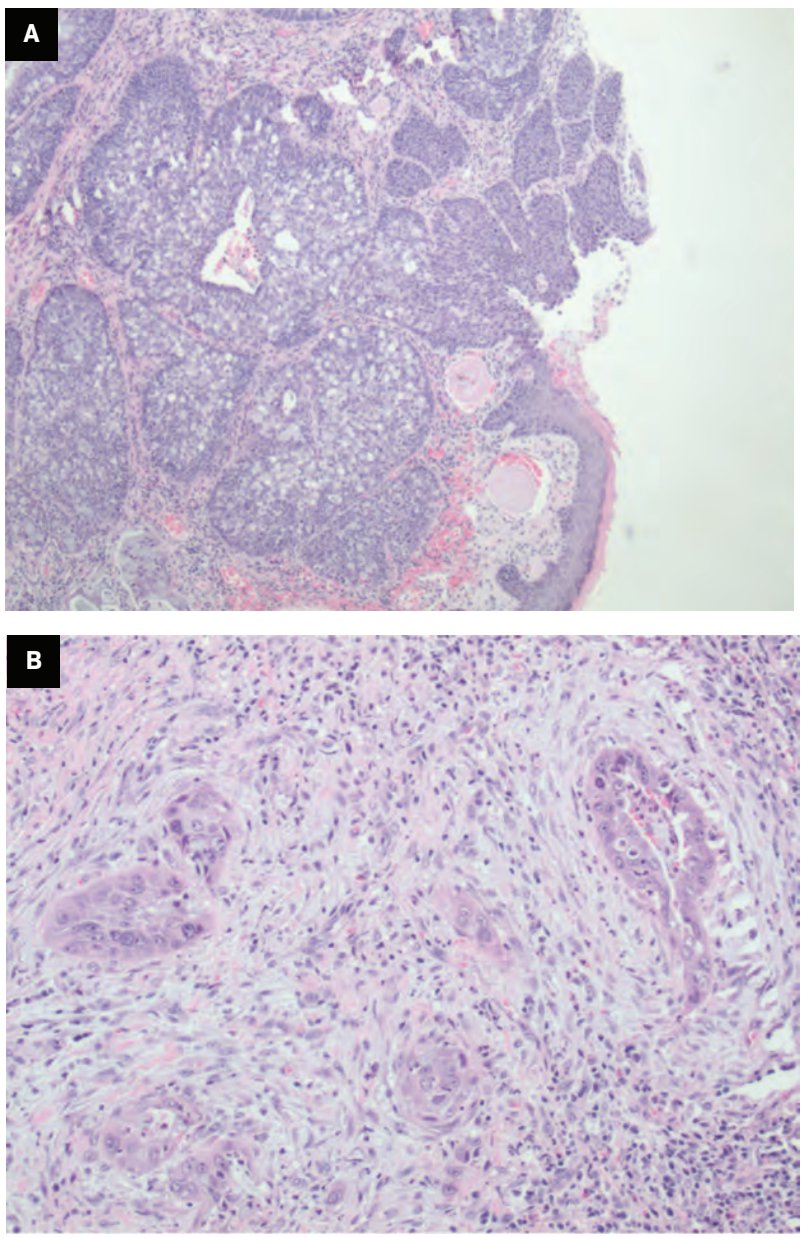


Figure 3. Histopathology images of the resected tumor. In situ carcinoma (A) can be seen in the overlying epithelium, with the invasive component underneath both neoplastic squamous cells and glandular cells containing intracellular mucin. Squamous and glandular infiltration (B).



and imaging (**Figure 6**) showed no new or progressive soft-tissue thickening in the nasal cavity with no suspicious cervical lymphadenopathy. He is doing well 18 months out of his radiation treatment and is planning to undergo a delayed reconstruction with ENT/plastic surgery.

Discussion

The 5th edition of the WHO Classification of Head-and-Neck Tumors (2022) divides SCC into the following subtypes: verrucous carcinoma, basaloid, papillary, spindle cell, ADSC, and lymphoepithelial carcinoma.[1] In ADSC, the SCC component manifests superficially, appearing either as carcinoma in situ or invasive SCC, while the glandular component tends to reside in a deeper region of the tumor. It is imperative to differentiate ADSC from mucoepidermoid cancer (MEC), which generally carries a more favorable prognosis.[1] Molecular analysis provides valuable insights, with the presence of MAML2 translocation being characteristic of MEC and effectively ruling out ADSC.[2]

The majority of patients with nasal ADSC initially exhibit either no symptoms or experience nonspecific sinonasal symptoms, which may resemble benign conditions. Common symptoms include pain, nasal obstruction/congestion, nasal bleeding/discharge, headaches, and reduced sense of smell. Patients with locally advanced disease may present with facial asymmetry/swelling, visible intranasal disease, cranial neuropathy, and vision loss. The diagnostic approach involves a detailed history and physical

Figure 4. Intensity-modulated radiation therapy (IMRT) plan showing different isodose levels.

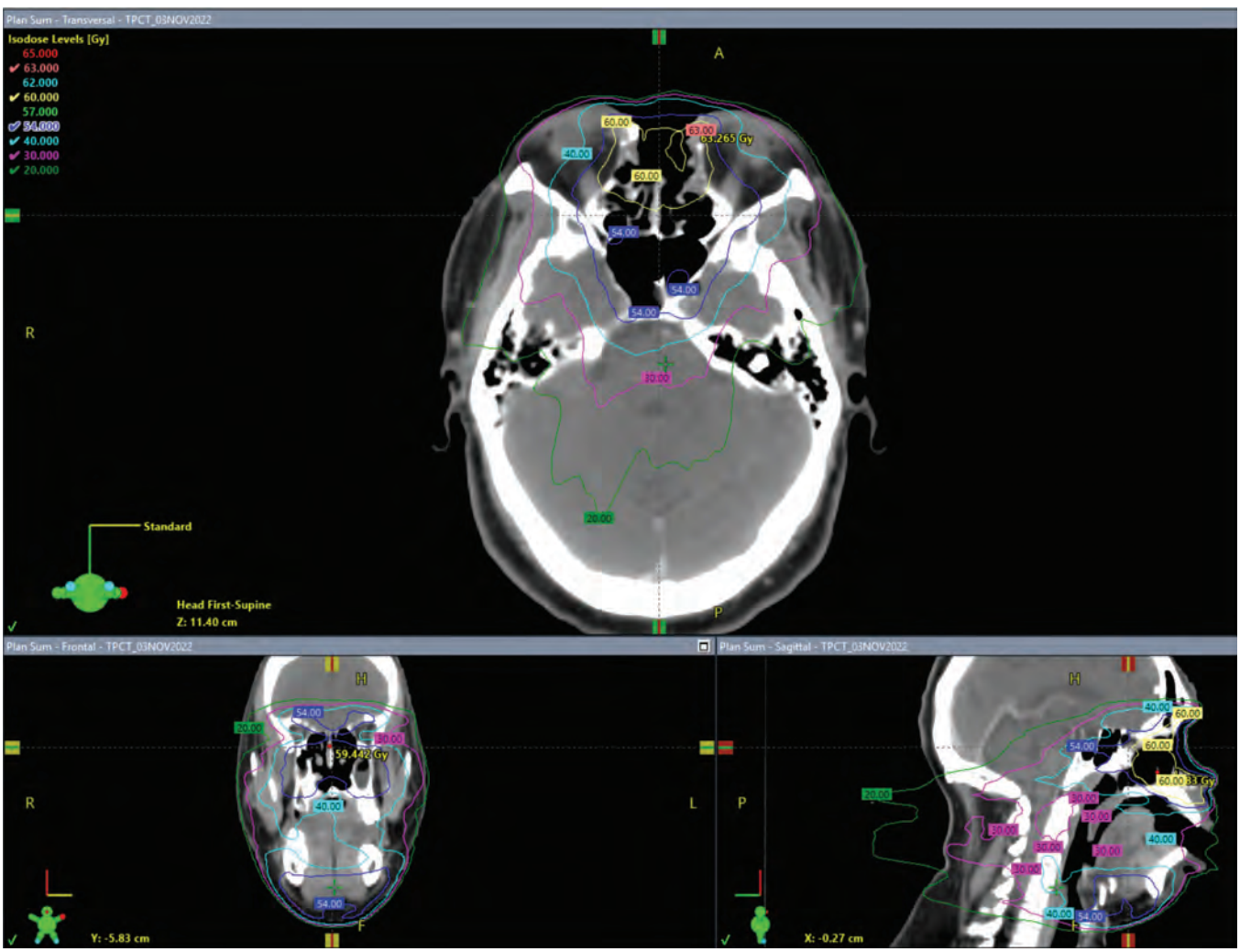


Figure 5. Cumulative dose-volume histogram for the intensity-modulated radiation therapy (IMRT) plan.

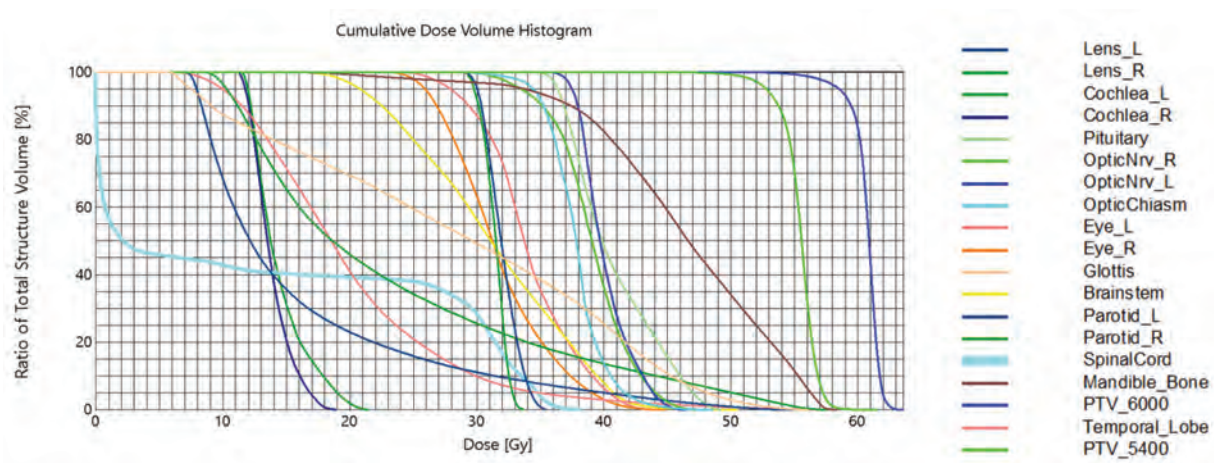
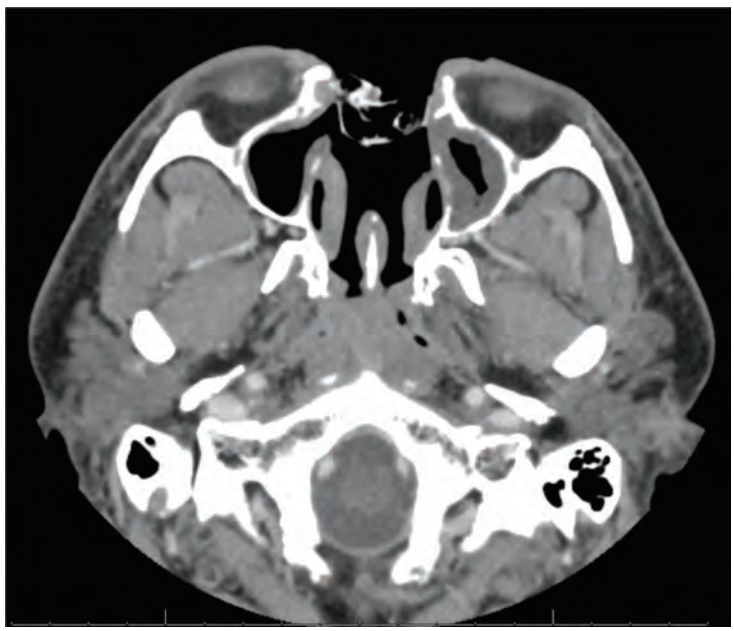


Figure 6. CT scan with contrast 1 year post radiation therapy. Postsurgical changes compatible with near-total rhinectomy, nasal septal resection, and middle and inferior turbinate resection are seen. Packing material is within the surgical defect. There is no new or enlarging enhancing soft tissue suggesting any recurrence.



examination, specifically focusing on cranial nerves and signs of local invasion. Nasal endoscopy is conducted for direct tumor visualization. Laboratory investigations typically include a complete blood count and a basic metabolic panel. Imaging studies such as CT of the sinuses/face and neck and MRI are performed to assess the extent of the disease and differentiate it from benign causes. CT provides insights into bone invasion while MRI offers information on soft-tissue involvement, nerves, skull base, and brain, aiding in the differentiation of fluid from solid tumors. These tumors are isointense on T1 precontrast, whereas with gadolinium they have diffuse moderate hyperintense signals that differentiate them from inflamed mucosa, which displays more intense peripheral enhancement. The short tau inversion recovery sequence aids in detecting lymph nodes and identifying bone marrow edema/involvement. Diffusion-weighted MRI is a crucial tool for differentiating primary tumors from surrounding edema. The integration of apparent diffusion coefficient mapping also allows MRI to distinguish between benign/inflammatory lesions and malignant tumors.[3] Endoscopic biopsy is the preferred method to obtain tissue unless the tumor protrudes through the nasal or oral cavity. Chest CT and/or positron emission tomography/CT (PET/CT) is employed for metastatic disease staging. A dental consultation is done as needed.

There is a lack of randomized trials to establish optimal treatment protocols for such a rare and heterogeneous disease. A recent single-institution retrospective review analyzed 29 patients with ADSC of all subsites of head and neck (in which 5 patients had nasal cavity). The treatment approach primarily involved surgery for the majority (n = 23, 79.3%), with 19 patients (82.6%) undergoing adjuvant radiation therapy (RT) to a median dose of 60 Gy, 7 of whom received concurrent chemotherapy. Also, 6 patients received definitive RT, with a median dose of 70 Gy, of which 2 underwent concurrent chemotherapy. The 3-year progression-free survival (PFS) and overall survival (OS) rates were 54.2% and 72.9%, respectively. Among participants who underwent primary surgery, the 3-year PFS and OS rates were 45.6% and 69.6%, whereas those treated with definitive RT exhibited notably higher rates of 83.3% for both PFS and OS. Furthermore, the 3-year PFS was observed at 50% in HPV-negative patients, contrasting with a more favorable outcome of 75% in HPV-positive patients. The authors concluded that locoregional recurrence emerged as the primary mode of treatment failure in 34.5% of patients.[4] Kass et al showed that the median survival times for ADSC and head and neck squamous cell carcinomas (HNSCC) were 4 and 6 years, respectively. The study included 42 patients, with 7 being nasal cavity/paranasal sinuses (PNS) combined.[2] **Table 1** summarizes the current literature for nasal ADSC.

Surgery remains the cornerstone of treatment, aiming for gross total resection of the affected bone and soft tissue, whether through open or endoscopic approaches. Endoscopic techniques, increasingly favored, are associated with lower surgical complications and reduced morbidity compared with traditional open surgery, with advantages of no facial incision, avoidance of craniotomy, shorter hospital stays, and faster recovery times. Regarding neck management, cervical lymph node metastases are generally uncommon in sinonasal cancers. However, neck management should be considered for patients with documented cervical lymph node involvement or locally advanced

Table 1. Review of the Literature for Adenosquamous Carcinoma of the Nasal Cavity

YEAR	ARTICLE	AUTHORS	DESIGN	TOTAL PATIENTS	PATIENTS WITH NC/PNS ADSC	OUTCOMES STUDIED	FINDINGS
1968	Adenosquamous carcinoma of the nasal, oral and laryngeal cavities[5]	Gerughty et al	Case series	10	2, NC	Histopathological features, survival	ADSCs are extremely malignant and aggressive, 80% of patients had histopathologically proven metastases.
1989	A clinico-pathological study of adenocarcinomas of the nasal cavity and paranasal sinuses[6]	Ogawa	Case series	19	3, NC/ PNS	Histological oncogenesis	Proteins of the apical membrane surface and squamous metaplasias might be the cause of developing SCC vs ADC in the NC & PNS.
1994	Adenosquamous carcinoma of the inferior turbinate: a case report[7]	Minic et al	Case report	1	1, NC	Clinico pathological features	The differential diagnosis of ADSC includes SCC & mucoepidermoid carcinoma.
2003	Adenosquamous carcinoma of the head and neck: criteria for diagnosis in a study of 12 cases[8]	Alos et al	Case series	12	2, NC	Clinicopathological data, IHC features	ADSCs have presence of severe dysplasia or carcinoma in situ. Alongside mucin stains, the detection of positive immunoreactivity for CEA, CK7, and CAM5.2 aids in delineating the glandular component.
2008	Adenosquamous carcinoma of the nasal cavity[9]	Shinhar et al	Case report	1	1, NC	Clinicopathological, radiological features	Physical exam, endoscopy, & imaging are important for staging.
2011	Adenosquamous carcinoma of the head and neck: relationship to human papillomavirus and review of the literature[10]	Masand et al	Retro spective review	18	2, NC 1, PNS	Clinicopathological data, HPV status by ISH and IHC	A minority of ADSC cases harbor HPV, & HPV-related oropharyngeal cases appeared to do clinically well. The remaining cohort of patients with ADSC did poorly.

Table 1. continued

YEAR	ARTICLE	AUTHORS	DESIGN	TOTAL PATIENTS	PATIENTS WITH NC/PNS ADSC	OUTCOMES STUDIED	FINDINGS
2013	Adenosquamous carcinoma of the head and neck: report of 20 cases and review of the literature[11]	Schick et al	Case series	20	2, NC 2, PNS	Clinical profile and prognostic factors, survival	Locoregionally advanced ADSCs have a poor prognosis. Early stage ADSC managed with combined modality tx (surgery and/or RT ± chemotherapy) may have prolonged DFS.
2015	Adenosquamous carcinoma of the head and neck: molecular analysis using CRTC-MAML FISH and survival comparison with paired conventional squamous cell carcinoma[2]	Kass et al	Case-control retrospective study	42	7, NC/ PNS	Molecular FISH, testing, survival	No OS difference for ADSC compared with conventional HNSCC. ADSCs were negative for the CRTC1-MAML2 translocation distinguishing them from mucoepidermoid carcinoma.
2016	Adenosquamous carcinoma of the head and neck: a case–control study with conventional squamous cell carcinoma[12]	Mehrad et al	Case- control study	23	2, NC/ PNS	Histopathology, survival	ADSCs have slightly more aggressive behavior than conventional HNSCC, even after controlling for p16 status.
2021	Outcomes of patients with adenosquamous carcinoma of the head and neck after definitive treatment (abstract)[4]	Buchberger et al	Retrospective review	29	5, NC	Survival	ADSCs have 34.5% recurrence rate, with locoregional recurrence being the primary pattern of failure.
2023	Adenosquamous carcinoma of the nasal septum: a rare variant[13]	Hassan et al	Case report	1	1, NC	Clinicopathological, radiological features	ADSC is a rare variant of SCC.

Abbreviations: ADC, apparent diffusion coefficient; ADSC, adenosquamous carcinoma; DFS, disease-free survival; FISH, fluorescence in situ hybridization; HNSCC, head and neck squamous cell carcinomas; HPV, human papillomavirus; IHC, immunohistochemistry; ISH, in situ hybridization; PNS, paranasal sinuses; NC, nasal cavity; OS, overall survival; RT, radiation therapy; SCC, squamous cell carcinoma.

disease (T3/T4), involving either RT or neck dissection. The chemotherapy recommendations can be extrapolated from treatments for other HNSCCs. Cisplatin-based chemotherapy, given concurrently with RT, is recommended for unresectable disease or postoperatively in patients with positive margins and extracapsular spread. Adjuvant RT, typically initiated within 6 weeks post surgery, can be considered for completely resected disease or incompletely resected with positive margins.[14-16]

In conclusion, ADSC occurring in the nasal region represents an exceptionally rare tumor. Recognized for its local aggressiveness and elevated rates of locoregional recurrence, early detection, coupled with accurate staging and comprehensive treatment involving surgery and RT, presents the most promising avenue for achieving good long-term outcomes.

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A Rare Case of Skull Base Phosphaturic Mesenchymal Tumor

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Abstract

Phosphaturic mesenchymal tumor (PMT) is a rare type of tumor that presents as a paraneoplastic syndrome causing tumor-induced osteomalacia. So far, close to 500 cases have been reported in the literature, making it a rare entity in clinical practice. The most common sites of PMT involvement are extremities. Here, we report a rare case of PMT involving the skull base.

Keywords: phosphaturic mesenchymal tumor (PMT), tumor-induced osteomalacia (TIO), paraneoplastic syndrome

Case Summary

A 55-year-old woman presented with a history of multiple bone fractures, headache, double vision, left-ear impaired hearing, and impaired urinary control. In 2018, she sustained a left hip fracture, in 2019 a right hip fracture, in 2020 a right ulnar fracture following a fall, and in 2021 a left ulnar fracture. The patient was evaluated by an orthopedic surgeon initially and later by an endocrinologist. Imaging with PET/CT and MRI in January 2022 showed features suggestive of a large lytic lesion involving the skull base. PET/CT revealed an intensely avid lytic lesion with an enhancing soft-tissue component involving the left petrous temporal bone extending into the squamous temporal, occipital bone, sphenoid bone, arch of atlas and clivus. MRI showed extensive hypointense and heterogeneously hyperintense lesions at the left petrous temporal bone, mastoid and part of the occipital bone, with extensive destruction of the bone, which was replaced by soft-tissue component lesions and cystic areas. There was extensive destruction of bone at the skull base involving the clivus and basi-sphenoid.

Biopsy (January 2022) and immunohistochemistry (IHC) findings (S100 positive, DOG1 noncontributory, and Ki67 1%-2%) were suggestive of a phosphaturic mesenchymal tumor. Serum FGF-23 (fibroblast growth factor) levels were 2088 pg/mL (biological reference range, 23.2-95.4 pg/mL), and serum phosphorus levels were 1.6 mg/dL (biological reference range, 2.5-4.5 mg/dL).

The case was discussed in our tumor board meeting with the decision to consider surgical debulking followed by radiation therapy as R0 resection (surgical resection with negative margins) was considered not feasible in view of extensive skull base involvement. The patient refused to undergo surgery after discussing potential benefits and complexities of the procedure with the neurosurgeon, and instead opted for external-beam radiation therapy.

Treatment Details

CT simulation was performed on a 16-slice PET/CT simulator. The patient was immobilized in the treatment position using a thermoplastic mask. CT images were acquired in 1.25-mm slice thickness from the vertex of the skull to the mid-chest. PET/CT image fusion was performed and target volumes and organs at risk

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were contoured on the planning CT scan (**Figure 1**). The planning target volume (PTV) included the gross tumor volume with a uniform 0.5-cm margin for setup errors. Treatment planning was performed using the Varian Eclipse treatment planning system. Prescription dose was 54 Gy in 30 fractions, 1.8 Gy per fraction to the PTV (**Figure 2**). Treatment was delivered with the Varian TrueBeam linear accelerator using 6 MV photons with the Varian RapidArc technique. The patient tolerated the treatment well. Acute radiation side effects such as nausea, headache, and skin hyperpigmentation were managed conservatively with symptomatic medications such as oral ondansetron and paracetamol. Follow-up at 6 months revealed no symptom progression and mild improvement regarding headaches. The patient experienced no bone fractures after the treatment.

Imaging Findings

A gallium 68 dotatate PET/CT (**Figure 3**) performed in January 2022 revealed an intensely avid lytic lesion with an enhancing soft-tissue component involving the left petrous temporal bone extending into the squamous temporal, occipital bone, sphenoid bone, arch of atlas, and clivus, with a standardized uptake value (SUV) max of 10. Anteriorly, it was involving the longus coli muscles, extending into the nasopharynx and sphenoid sinus. Inferiorly, it was abutting the posterior margin of the left parotid gland. Superomedially, it was extending up to the cavernous sinus, encasing the left petrous internal carotid artery and compressing the left internal jugular vein. It was causing a mass effect on the left cerebellar hemisphere, brainstem, and fourth ventricle. Multiple bony fractures were noticed in the skeleton. No distant metastasis was detected.

MRI of the brain (**Figure 4**) performed in January 2022 showed extensive T1 iso- to hypointense and T2 heterogeneously hyperintense lesions at the left petrous temporal bone, mastoid, part of the occipital bone with extensive destruction of the bone, and replaced with soft-tissue component lesions and cystic areas. There was extensive destruction of the bone at the skull base involving the clivus and basi-sphenoid. The lesion was extending through the floor of the pituitary fossa into the sella. There was destruction of the clinoid process on both sides and greater wing of the sphenoid on the left side. Inferior extension of the lesion was causing bony destruction of the left occipital condyle and left half of the anterior arch of C1 vertebra. A postcontrast study showed extensive and homogeneous enhancement of the lesion, measuring approximately 6.6 × 5.5 × 3.4 cm. The left internal auditory canal and VII/VIII cranial nerves were not visualized separately. MR spectroscopy revealed a high possibility of a malignant lesion with elevated choline and an altered choline/N-acetylaspartate ratio.

Diagnosis

The patient was diagnosed with PMT, which often tends to be small and can be located anywhere in the body, mimicking many other common tumors of the bone and soft tissue. Differential diagnosis includes chondromyxoid fibroma, chondroblastoma, aneurysmal bone cyst, glomus jugulare, chordoma, vestibular schwannoma, and osteosarcoma.

Discussion

PMT is a rare entity that usually presents with a clinical picture of tumor-induced osteomalacia (TIO).[1-3] To date, fewer than 500 cases have been reported in the literature.[4] Osteomalacia is a metabolic disorder in which there is insufficient mineralization of the mature bone. The most common cause of osteomalacia is vitamin D deficiency. Other rare causes include inborn errors of metabolism and chronic kidney disease. TIO is a type of paraneoplastic syndrome that can be seen in osteoblastoma, osteosarcoma, hemangiopericytoma, and plasmacytoma.[4]

TIO was first reported by McCance in a 15-year-old teenager who presented with weakness and gait disturbance, along with hypophosphatemia.[4] The term phosphaturic mesenchymal tumor was coined by Wiedner and Santa Cruz in 1987.[5] PMT was included in the WHO 2013 classification of tumors for bone and soft tissue.[6]

The pathophysiology of TIO involves excessive production of FGF-23 by the tumor cells, which is a type of phosphate-regulating substance in the body.[4] FGF-23 reduces phosphate reabsorption in the proximal renal tubules, leading to excessive renal excretion of phosphates. FGF-23 also increases bone resorption of calcium and phosphate, and decreases intestinal absorption of calcium and phosphate, decreasing bone mineralization.[4]

PMT is characteristically a benign tumor.[5,6] However, local recurrences and malignant behavior in the form of lung metastasis have also been reported in the literature.[5,7] Hence, patients need to be followed up with appropriate imaging of the chest, serum phosphates, and FGF-23 levels to detect any recurrence.[3,6,8,9]

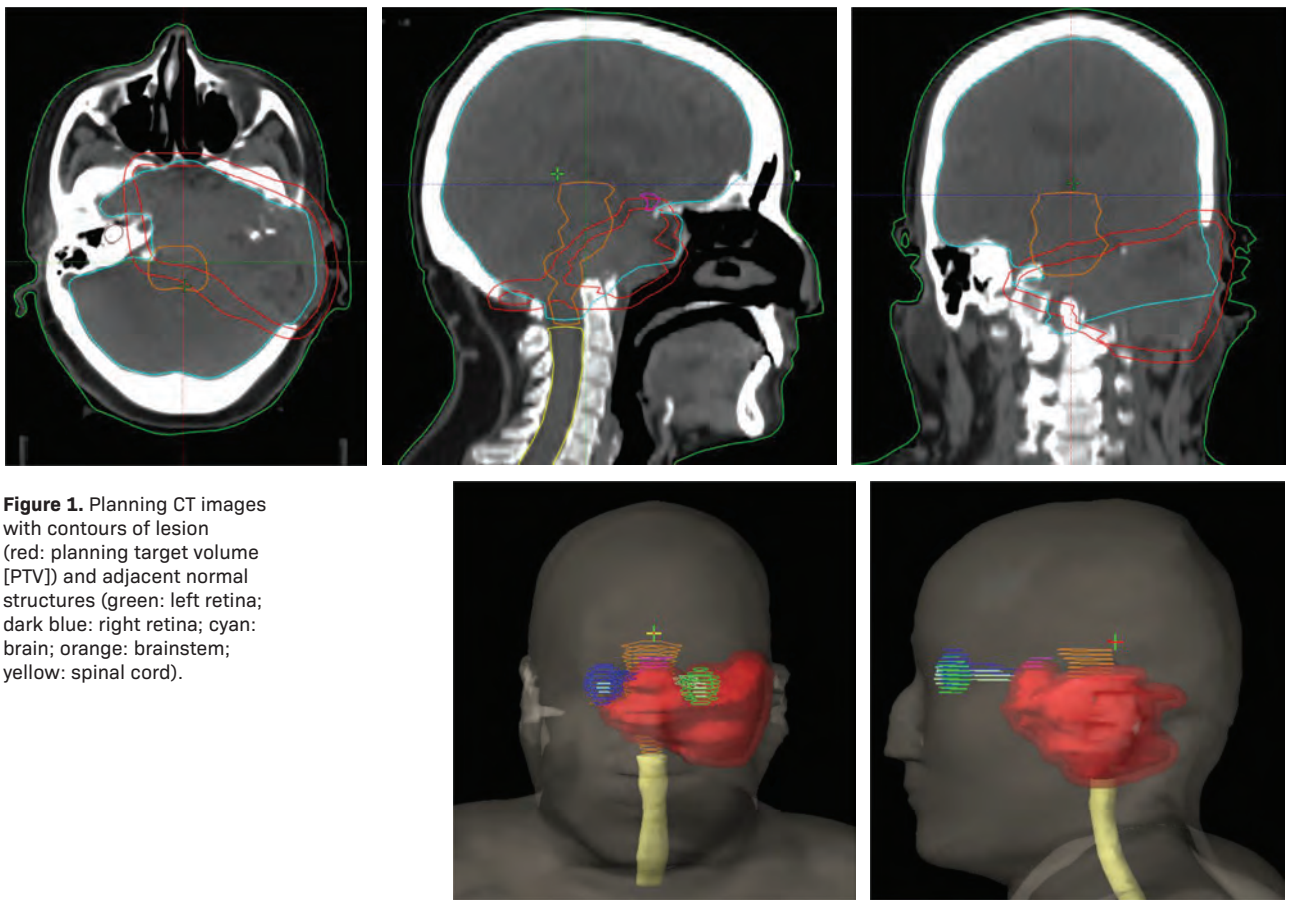


Figure 1. Planning CT images with contours of lesion (red: planning target volume [PTV]) and adjacent normal structures (green: left retina; dark blue: right retina; cyan: brain; orange: brainstem; yellow: spinal cord).

Figure 2. Treatment plan showing radiation dose distribution (green color) in color wash and planning target volume (PTV) (red contour).

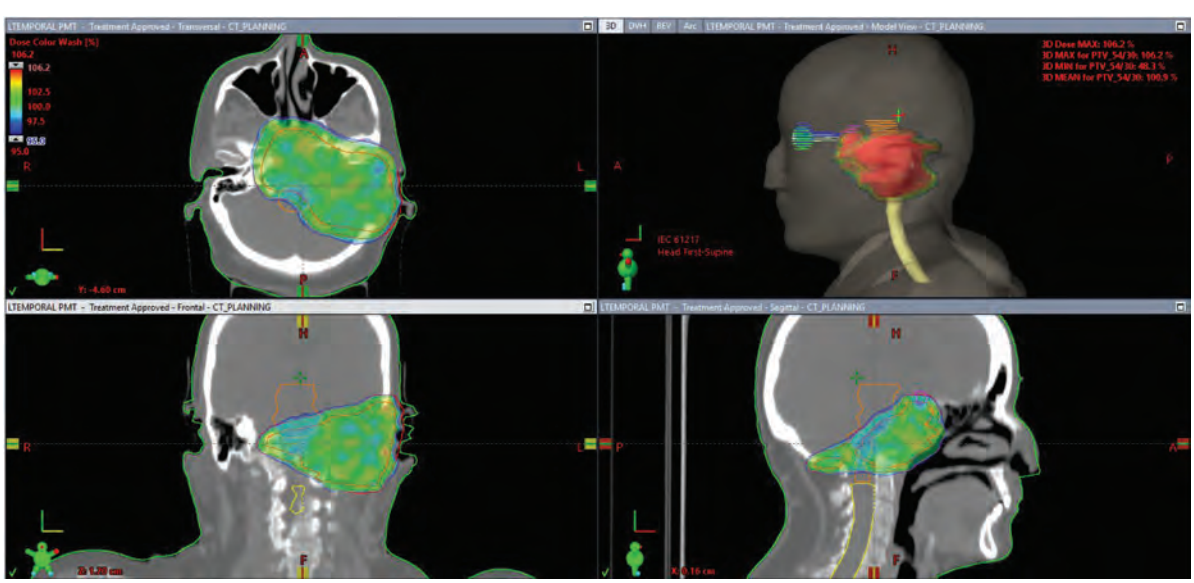
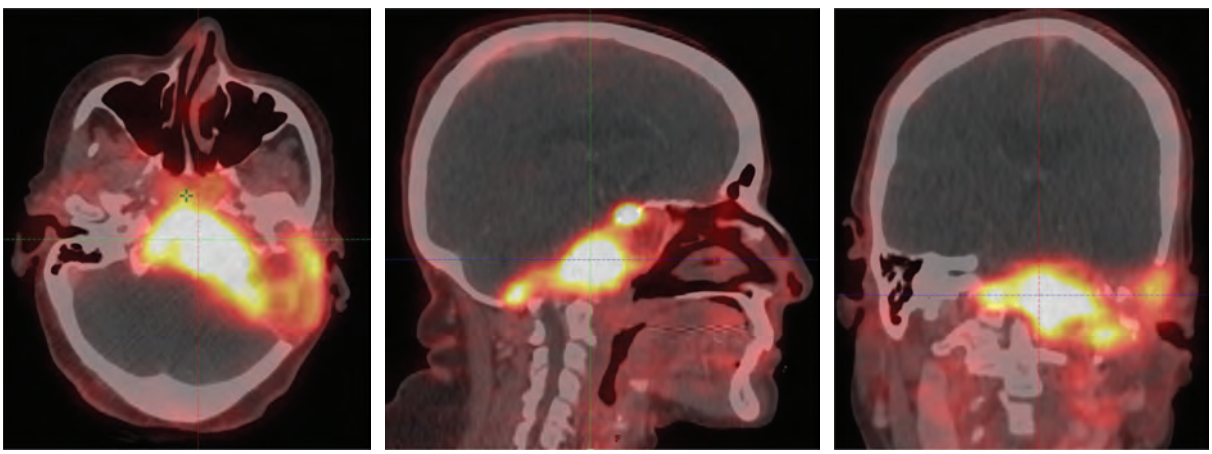


Figure 3. Gallium 68 dotatate PET/CT images showing a tracer avid lytic lesion at the skull base.



PMT commonly affects the extremities of middle-aged patients and can originate from the bone or soft tissue. It often tends to be small and can be located anywhere in the body, mimicking many other common tumors of the bone and soft tissue.[10]

The diagnosis is often delayed due to vague symptomatology and low degree of suspicion of PMT.[8] Patients usually present with recurrent fractures, bone pains, muscle pains, and generalized weakness.[9] Biochemical findings include hypophosphatemia, hyperphosphaturia, and elevated levels of FGF-23.[4]

Imaging modalities for diagnosis may include CT, MRI, FDG PET/CT, dotatate PET/CT, and a Tc-99m sestamibi scan. Radiographic features of PMTs have been described recently in detail.[11] On CT scans, bone lesions are typically osteolytic, show a narrow zone of transition, and contain internal matrix.[12] On MRI, they are usually T1 isointense, T2 hyperintense, and solidly enhancing, with areas of dark T2 signal.[12]

Histologically, there are 4 types of PMTs: osteoblastoma-like variant, nonossifying fibroma-like variant, ossifying fibroma-like variant, and mixed connective tissue variant.[1,6] The most common type is the mixed connective tissue variant.[4] Morphological differential diagnosis includes chondromyxoid fibroma, chondroblastoma, aneurysmal bone cyst, glomus jugulare, chordoma, vestibular schwannoma, and osteosarcoma.[4] Histological findings of benign cartilage-forming lesion in correlation with IHC, typical clinical presentation of recurrent fractures, and biochemical profile showing hypophosphatemia with elevated levels of FGF-23 confirm the diagnosis of PMT and differentiate it from other differentials.

Treatment options include surgery for resectable lesions. Complete surgical resection with negative surgical margins of at least 10 mm is the mainstay treatment.[4] Radiation therapy is used for surgically or medically inoperable patients, incompletely resected tumors, or positive margins after resection.[4] Although the detailed mechanism of the effectiveness of radiation therapy for PMT is unclear, the obstruction and fibrosis of the tumor vessels could occur, thus inhibiting growth, similar to the mechanism observed in other hormone- or cytokine-producing tumors.[13,14] It is important to use a high-precision radiation therapy technique such as intensity-modulated radiation therapy or volumetric-modulated arc therapy for critical sites such as the skull base or the head and neck region to spare the adjacent normal anatomical structures. Data regarding radiation therapy doses for PMT are very limited. As discussed in the case report by Shah et al, 54 Gy in 30 fractions was used in the postoperative adjuvant setting.[15] Another case report by Uramoto et al mentioned the use of 66 Gy in 33 fractions after marginal resection of PMT of the tongue.[16] In addition to local control, radiation therapy was found effective in improving oncogenic osteomalacia.[17] Radiofrequency ablation (RFA) can be used for small bony lesions.[4] Concomitant medical management includes phosphorus and calcitriol supplementation.[3,6]

Conclusion

PMT is a rare histological type of mesenchymal tumor involving the bone and soft tissue. In most cases, it is benign, but a few cases of malignant PMTs have also been reported. PMT is one of the most common causes of TIO. Clinical presentation of recurrent fractures,

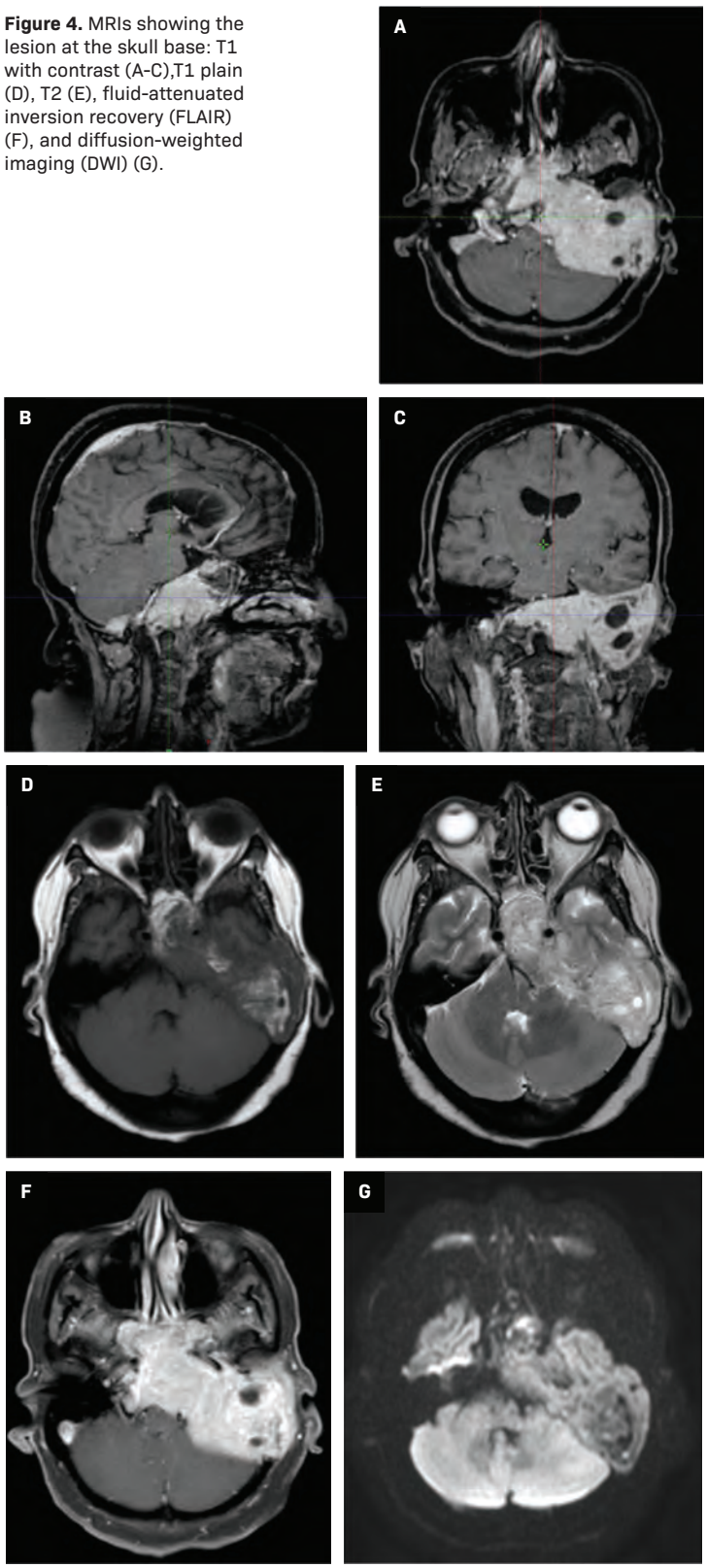


Figure 4. MRIs showing the lesion at the skull base: T1 with contrast (A-C),T1 plain (D), T2 (E), fluid-attenuated inversion recovery (FLAIR) (F), and diffusion-weighted imaging (DWI) (G).

osteomalacia with biochemical findings of hypophosphatemia, and elevated levels of FGF-23 suggest a possible diagnosis of PMT. Surgery with negative margins is the mainstay treatment for operable lesions. Other nonsurgical treatment options for inoperable or incompletely resected tumors include radiation therapy and RFA. Here, we report a case of PMT of the skull base that was considered inoperable and was treated with definitive radiation therapy.

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A Rare Case of Mycosis Fungoides of the Scalp Treated With Electron-Beam Radiation Therapy

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Abstract

Mycosis fungoides (MF) is the most common cutaneous T-cell lymphoma comprising 44% of cutaneous lymphomas and accounting for less than 1% of non-Hodgkin lymphomas. It is clinically characterized by a focal or diffuse cutaneous patch, plaque, and tumor nodules, and is difficult to diagnose in the early stages because the symptoms and skin biopsy findings are similar to those of other skin conditions such as psoriasis, eczema, and lichenoid dermatoses. Here, we present a case about a patient who presented with a focal nodular skin lesion over the scalp.

Keywords: mycosis fungoides, cutaneous lymphoma, electron-beam radiation therapy (EBRT), total skin electron therapy (TSET), case report

Case Summary

A 70-year-old man presented with a cutaneous swelling of 3-month duration over the left side of the scalp. The swelling gradually progressed in size, and no other significant issues were present. The patient was evaluated initially by a dermatologist. Local examination revealed a 3 × 2.5-cm plaque-like keratotic lesion over the scalp on the left side (**Figure 1A**), and the lesion was mobile, nontender, nonpulsatile, and not fixed to the underlying skull bone. No palpable cervical or other regional lymph nodes were found, and no other similar skin lesions elsewhere on the body could be visualized.

Laboratory Investigations

Peripheral blood smear showed a normocytic normochromic blood picture with an adequate number of platelets, and white blood cell count was within the normal limits. Mantoux and VDRL (venereal disease research laboratory) tests were negative. Liver function and renal function tests were within the normal limits.

Scalp Lesion Biopsy and Immunohistochemistry

Scalp lesion biopsy and immunohistochemistry (IHC) were CD3 positive in atypical cells, CD4 positive in atypical cells, CD20 negative, CD30 negative, CD8 positive in occasional background cells, and Ki67 8% to 10%. The final impression of morphology and immunohistochemistry correlation was suggestive of folliculotropic mycosis fungoides (MF), plaque stage.

The patient was finally diagnosed with MF, stage 1A (T1N0M0B0), according to the modified TNMB (tumor-node-metastasis-bone marrow) classification, originally adopted by the Mycosis Fungoides Cooperative Study Group. As the skin lesion was localized to a single site, we decided to treat it with radiation therapy. Electron-beam radiation therapy is the modality of choice to treat superficial skin malignant lesions as the tissue-penetrating capacity of electron beam is less compared with photons. Hence, by using electrons, it is possible to treat superficial target volumes without exposing the deep normal tissues to radiation.

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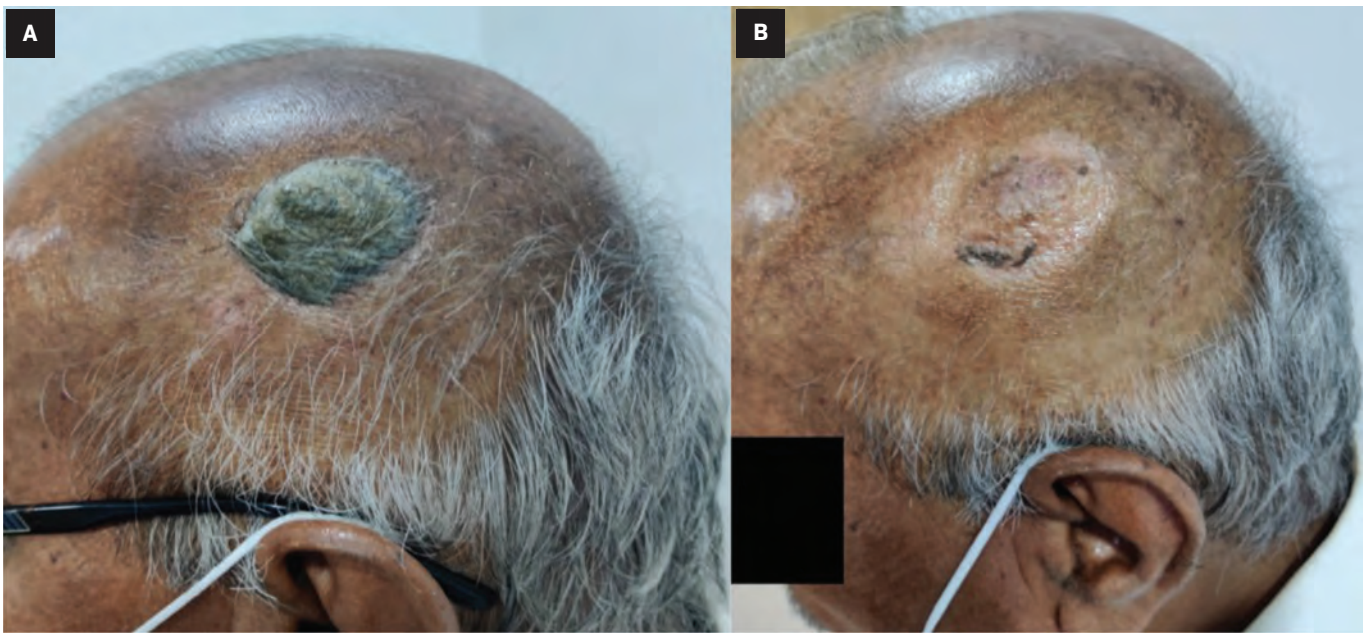
Figure 1. Clinical photographs of pretreatment (A) and post-treatment (B) showing complete response.



Electron-Beam Treatment Planning Process

Simulation using computed tomography (CT) was performed with the patient immobilized in the supine treatment position using a thermoplastic mask. Target volume was contoured (on the planning CT images), which included the gross scalp lesion visible on clinical examination (**Figure 1A**), planning CT scan, and positron emission tomography/CT (PET/CT) (**Figure 2**). A 2-cm uniform circumferential clinical target volume (CTV) margin was given to include the possible microscopic extension of the disease in the adjacent surrounding tissue. A 5-mm planning target volume (PTV) margin was given from the CTV to create the final target volume. Treatment planning was done on the Varian Eclipse treatment planning system using a 6-MeV nonisocentric electron beam and a gantry angle of 90° and collimator angle of 0°, with a 5-mm wet cotton bolus covering the PTV. The patient received 30 Gy in 15 fractions, 2 Gy per fraction, 5 days a week over 3 weeks. **Figure 3** shows the radiation dose coverage of the target volume. Here, 99% of the gross tumor volume (GTV) and CTV received 95% of the prescribed dose. Also, 94% of the PTV received 85% of the prescribed dose (**Figure 4**). The patient tolerated the treatment well without any significant side effects. At the end of the treatment, the patient had grade 2 skin reactions (grading based on RTOG [Radiation Therapy Oncology Group] acute radiation morbidity) that subsided over 2 weeks.

Clinical response assessment was done 3 months after treatment. Clinical examination revealed complete disappearance of the scalp lesion (**Figure 1B**).

Diagnosis

The diagnosis was folliculotropic MF, plaque stage. Differential diagnosis included psoriasis, eczema, and lichenoid dermatoses.

Imaging Findings

Whole-body PET/CT (**Figure 2**) showed a cutaneous lesion on the left parietal scalp measuring 25 × 7-mm, with a mild 18-fluorodeoxyglucose (FDG) standardized uptake value (SUV)max of 3.5. No other skin lesions were seen, and there was no evidence of any significant lymph nodal or other organ involvement.

Discussion

The cutaneous lymphomas comprise a heterogeneous group of malignancies of both T and B lymphocytes that localize to the skin. The Dutch and Austrian cutaneous lymphoma registries report that more than 70% of all cutaneous lymphomas are of T-cell origin and 22% are of B-cell

Figure 2. Pretreatment positron emission tomography/computed tomography (PET/CT) showing the left scalp lesion (yellow arrow).

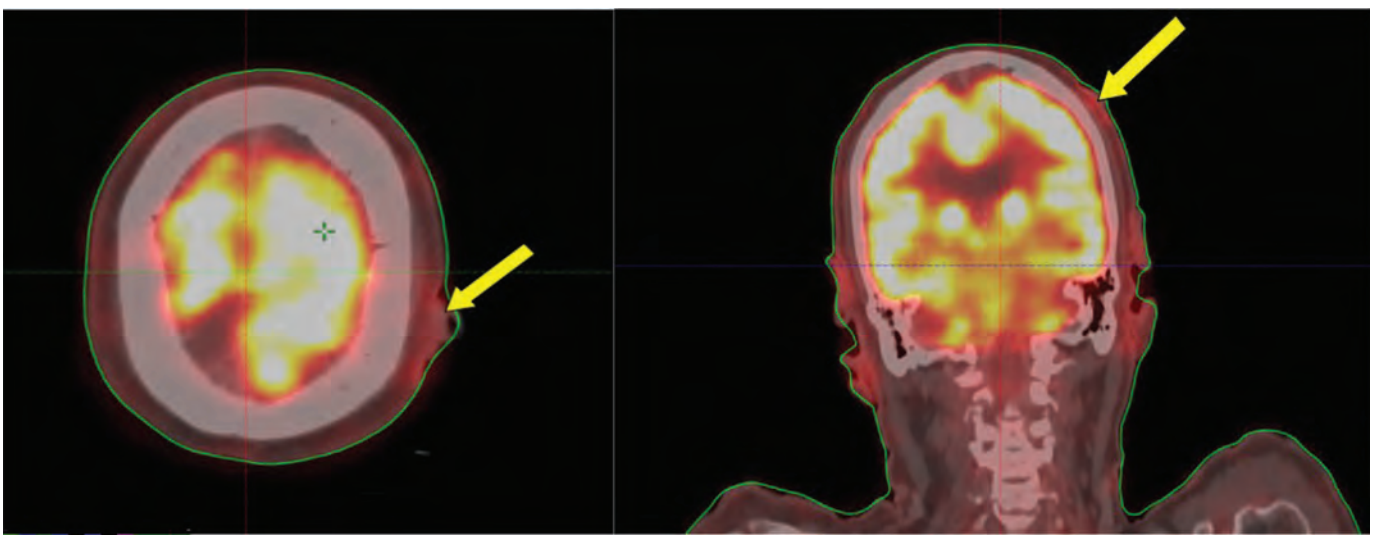
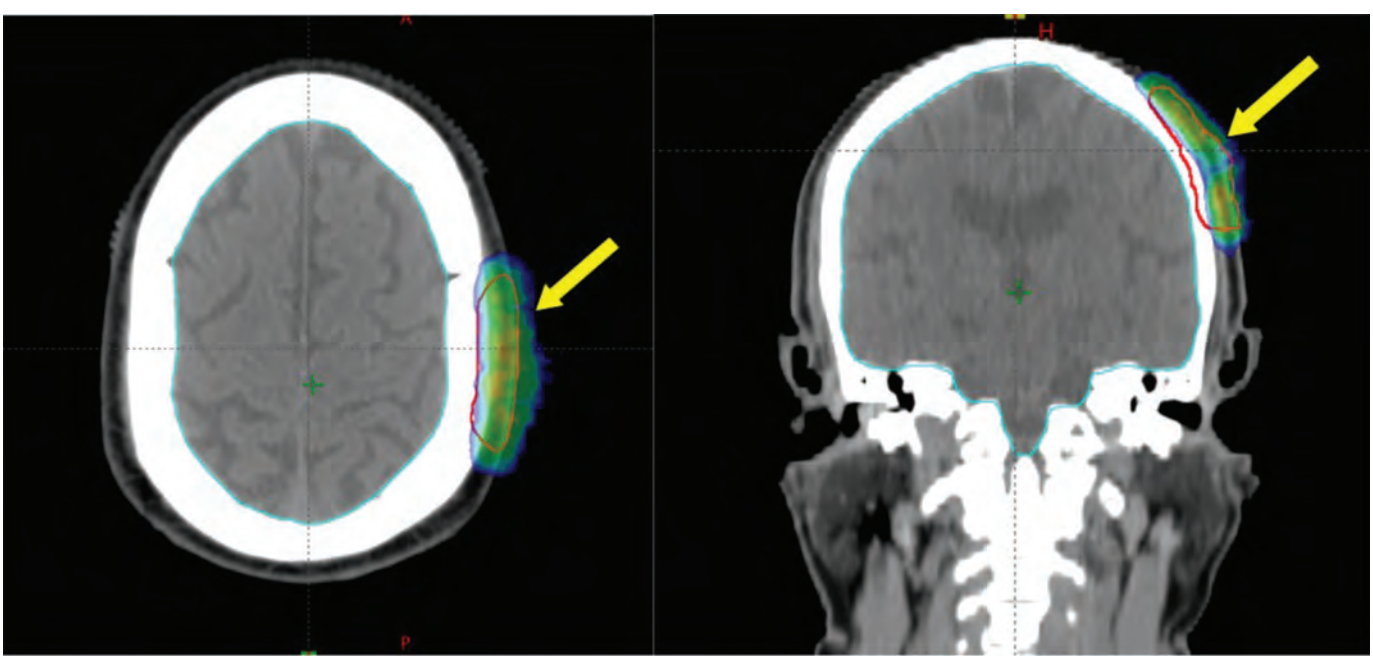


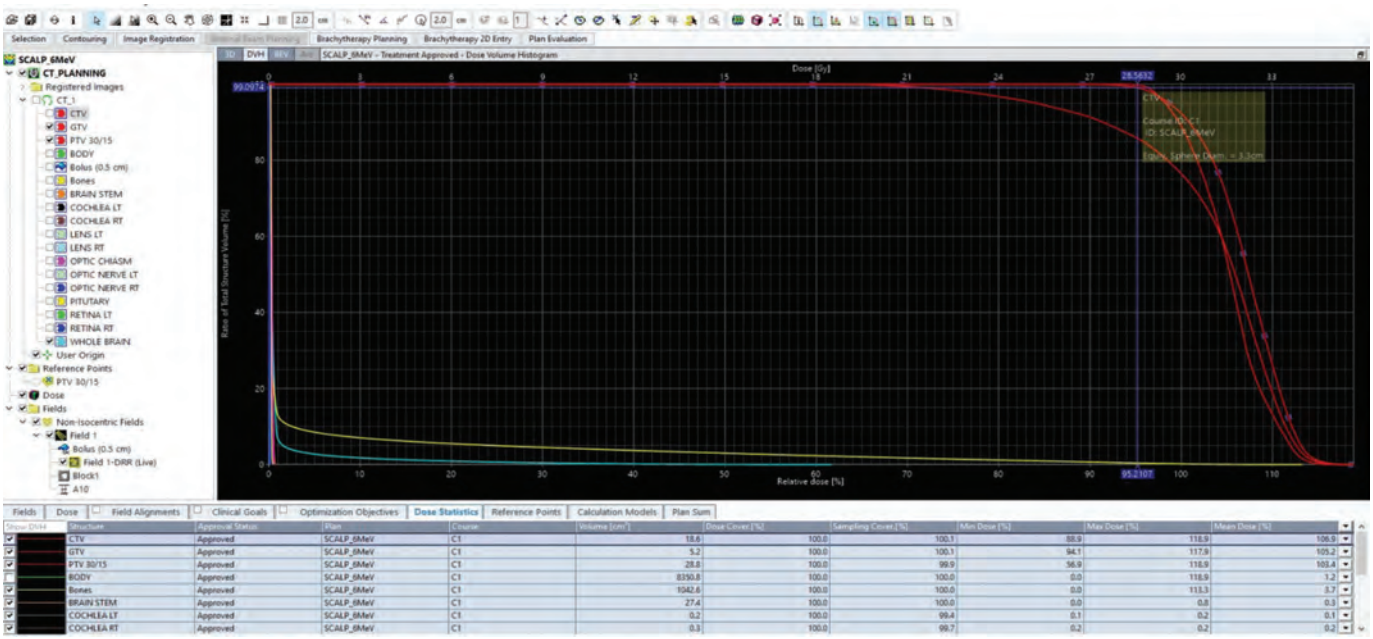
Figure 3. Electron-beam treatment plan showing dose coverage (green and blue color wash) of the left parietal scalp lesion. The planning target volume (PTV) is contoured in red.



origin.[1,2] Mycosis fungoides was first reported by Alibert in 1806 as an epidermotropic lymphoma with an indolent evolution characterized by cutaneous lesion in the form of patches, plaques, or skin tumors.[3] Both incidence and mortality data demonstrate greater frequency of MF among men than women. The risk also increases with advancing age, and the median age at diagnosis is 55 years.[4]

One hypothesis regarding the etiology of MF is that it may represent a clonal evolution from chronic antigenic stimulation. Associations with exposure to occupational chemicals or pesticides have also been proposed but not definitely demonstrated in epidemiological studies.[5,6] The association between human T-cell leukemia virus type 1 (HTVL-1) and adult T-cell leukemia/lymphoma is not reflected in the epidemiology of MF, but there are reports of detection of HTVL-1-like viral

Figure 4. Dose-volume histogram showing dose coverage details of the treatment plan.



particles and antibodies to HTVL-1 tax protein in patients with MF.[7]

The diagnosis of MF is based on clinical and histopathology criteria. The skin manifestations can be in the form of patches, plaques, erythroderma, cutaneous tumors, or ulcers. Early diagnosis can be difficult and may require multiple biopsies obtained from different lesions over time.[8] Most commonly, patients present with multifocal involvement of the skin, but localized skin involvement is also common. Extracutaneous involvement may be seen in advanced stages with the involvement of lymph nodes, bone marrow, or, less commonly, other organs. A multidisciplinary team approach involving a hemato-oncologist, dermatologist, radiation oncologist, and pathologist is often optimal for deciding the best management plan. The goals of therapy should be individualized based on the extent of disease.

For diseases confined to the skin lesions with no nodal or other organ involvement, skin-directed therapies such as local radiation, phototherapy, topical corticosteroids, topical retinoids, or topical chemotherapy agents like nitrogen mustard are used and have an excellent chance of cure or long-term control.[9] Skin-directed therapies exert their primary effects on the skin by inducing apoptosis of tumor cells and modulation of the immune micro-environment in the skin.

Diffuse involvement of the skin with multiple skin lesions all over the body is usually treated with total skin electron therapy,[10-13] whereas patients presenting with a solitary focal skin lesion can be treated with focal electron-beam therapy (as presented in this case). Patients with involvement of nodes, bone marrow, or other organs require treatment with systemic chemotherapy.[14,15] The use of supportive care measures to minimize the risk of skin infections and treat pruritus is an important part of disease and symptom control.

Alemtuzumab, a humanized monoclonal antibody that targets the CD52 antigen, has been shown to be active in relapsed or refractory T-cell lymphomas.[16]

Conclusion

Mycosis fungoides is the most common cutaneous T-cell lymphoma, and is usually not fatal. Most patients with MF exhibit an indolent clinical course with slow progression of the lesions. Most commonly, patients present with multifocal involvement of the skin; localized skin involvement is rarely seen. Localized MF can be safely treated with electron-beam therapy for better local control with minimal treatment-related toxicity.

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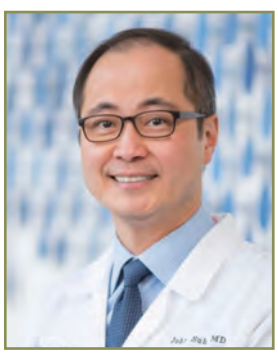

John Suh, MD, FASTRO, FACR

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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.

Help Us Swim

Stephanie O. Dudzinski, MD, PhD

Dr. Dudzinski is a PGY4 radiation oncology resident physician at The University of Texas MD Anderson Cancer Center.

Radiation oncology has often endearingly been called "the best-kept secret in medicine," but this common statement may actually be a disservice to our field. While medical students complete rotations focused on inpatient medicine or surgical specialties, their exposure to radiation oncology is often nonexistent or minimal unless they are interested in the field. However, even colleagues who believe they grasp the main aspects of a radiation oncologist's job often lack insight into key components required to treat a patient with radiation.

During medical school, we were all warned about the "fire hose" that was about to be turned on with an abundance of new medical knowledge taught during our didactic years. By separating the didactic education from clinical rotations, most trainees master the content and feel confident with inpatient care by the end of their intern year. While medical school often focuses on one topic or organ system at a time, our radiation oncology residency training requires us to learn a significant amount of anatomy, medical and surgical oncology, pathology, toxicity management, and so on for the clinical service that we are rotating on while simultaneously learning the didactic curriculum, radiation biology, and radiation physics. Additionally, new technologies have further increased the number of tasks required of a resident, such as contours needed for intensity-modulated radiation treatment compared with the 2D/3D treatment era and the even more extreme example of treatment plan daily adaptions.

Most residency specialties have clear proficiency goals for residents during each year of training. Given the apprenticeship model used in radiation oncology, an attending's service is covered by one resident, whose goal is to complete all service tasks and "run the service" by the end of their PGY5 year. As a PGY2 tries to learn and manage all the tasks, this can feel like being thrown into a deep ocean without a flotation device in a manner that is more overwhelming than the firehose of medical school. Additionally, in discussing daily tasks with residents across various institutions, there seems to be significant variation in how residents spend their time on attending CT simulation scans or weekly see visits, contouring, reviewing plans, adapting daily treatments, studying, etc.

Physician training followed an apprenticeship model through the 19th century, and this "worked" before medical knowledge and treatment methods expanded, resulting in formalized medical school training. Similarly, the rapid explosion of technology, clinical trials, systemic therapies, and new radiation treatment indications (oligometastases, osteoarthritis, etc.) further necessitates the need to standardize education beyond case numbers through competency-based training with entrustable professional activity (EPA) assessments. The Radiation Oncology Education Collaborative Group is actively working on creating EPAs to direct resident task prioritization.[1] Creating guidelines that emphasize which tasks should be mastered in each residency year will hopefully transform the PGY2 transition into a sensation of being thrown into a shallow pool instead of a deep ocean, as well as normalize resident training to increase proficiency in all aspects of future radiation oncologists' careers.

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