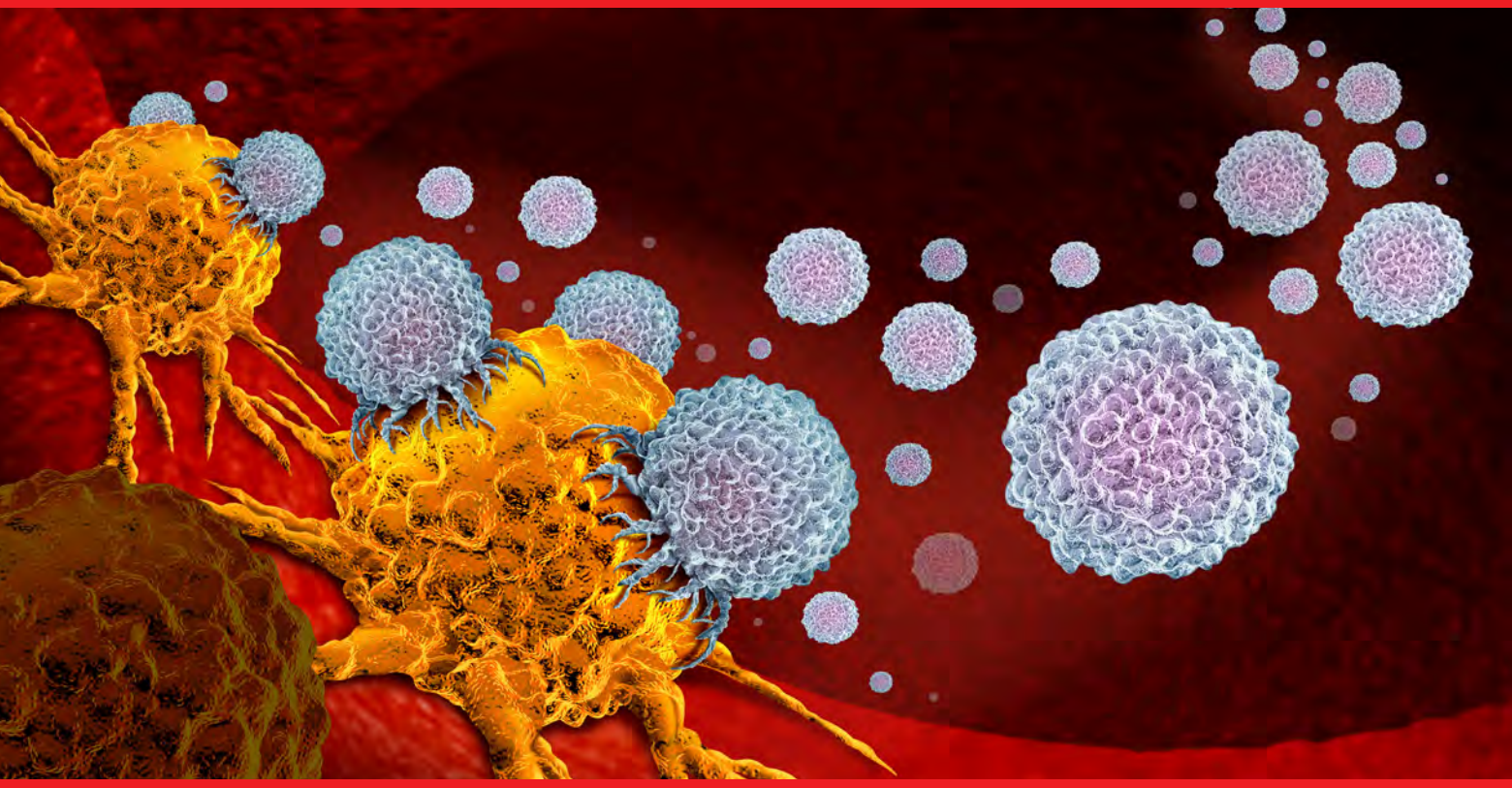
March 2025
Volume 14, Number 1

# Applied Radiation Oncology™



**CME**
Clinical Evidence of Combining Radiopharmaceutical Therapy with Immune Checkpoint Inhibitors

**Review**
Combination of External Beam Radiation Therapy and Immune Checkpoint Inhibitors in Cancer Treatment: Mechanisms, Limitations, and Clinical Applications

**Research**
RefleXion X1 Treatment Planning Feasibility Study for Cranio-Spinal Irradiation

**Case Report**
Robotic-assisted Seminal Vesicle Excision vs Brachytherapy for Isolated Seminal Vesicle Recurrence

www.appliedradiationoncology.com

# Applied Radiation Oncology™

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





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


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


*Applied Radiation Oncology* Print ISSN: 3065-4467, Online ISSN: 2334-5446, USPS 25688 is published quarterly by Anderson Publishing, LTD at 180 Glenside Avenue, Scotch Plains, NJ 07076. Readers can renew or subscribe at appliedradiationoncology.com/subscribe.

Applied Radiation Oncology™

March 2025, Vol 14, No 1

FOCUS: RADIOIMMUNOTHERAPY

REVIEW | CME

6 **Clinical Evidence of Combining Radiopharmaceutical Therapy With Immune Checkpoint Inhibitors**

Malick Bio Idrissou, PhD; Anusha Muralidhar, PhD; Reinier Hernandez, PhD; Quaovi H. Sodji, MD, PhD;

Radiopharmaceutical therapy (RPT) and immune checkpoint inhibitors (ICIs) are groundbreaking treatments for metastatic cancers. RPT delivers targeted radiation to both primary and metastatic tumors, altering the tumor microenvironment (TME) and potentially modulating the immune system's response to cancer. This review examines the clinical trials combining RPT with ICIs, emphasizing their potential to improve outcomes in metastatic cancer while addressing challenges such as toxicity, immunosuppressive TME, and logistical barriers, offering hope for reshaping cancer treatment.

REVIEW

17 **Combination of External Beam Radiation Therapy and Immune Checkpoint Inhibitors in Cancer Treatment: Mechanisms, Limitations, and Clinical Applications**

Anusha Muralidhar, PhD; Malick Bio Idrissou, PhD; Quaovi H. Sodji, MD, PhD

External Beam Radiation Therapy (EBRT) is a key cancer treatment that targets localized and metastatic tumors, while immunotherapy, particularly immune checkpoint inhibitors (ICIs), uses the immune system to fight cancer. However, ICIs face challenges like treatment resistance. EBRT can enhance the efficacy of ICIs by inducing immunogenic cell death, potentially overcoming resistance and improving outcomes. The reviewers discuss the rationale for combining EBRT with ICIs and highlight selected clinical trials while recognizing the need for further research to optimize outcomes and efficacy.

RESEARCH

26 **RefleXion X1 Treatment Planning Feasibility Study for Craniospinal Irradiation (CSI)**

Tracy Ngo, CMD; Daniel Pham, PhD, CMD; Ignacio Omar Romero, PhD; Eric Simiele, PhD; Bin Han, PhD; Murat Surucu, PhD; Iris Gibbs, MD; Susan Hiniker, MD; Nataliya Kovalchuk, PhD

Medulloblastoma is the most common malignant central nervous system (CNS) tumor in children. The standard treatment includes surgical resection, craniospinal irradiation (CSI), and chemotherapy, but traditional CSI techniques, such as 3D conformal radiation therapy (3DCRT) and Volumetric Modulated Arc Therapy (VMAT) have limitations in terms of dose conformity and homogeneity. This study evaluated the feasibility of using the RefleXion X1 clinical biology-guided radiation therapy (BgRT) system for treating pediatric medulloblastoma patients with complex craniospinal targets. Although based on a limited dataset, the study demonstrates the feasibility of CSI treatment planning with the RefleXion X1 system.

EDITORIAL

4 Revisiting Radioimmunotherapy

John H. Suh, MD, FASTRO, FACR

RADIATION ONCOLOGY CASES

33 Robotic-Assisted Seminal Vesicle Excision vs Brachytherapy for Isolated Seminal Vesicle Recurrence: 2 Case Reports

Barry W. Goy, MD; David S. Finley, MD

36 Volumetric Changes in Cervical Schwannoma in Response to Adjuvant Stereotactic Body Radiation Therapy: A Case Report

Neil D. Almeida, MD; Tyler V. Schrand, BS; Julia Rupp, BS; Rohil Shekher, MD; Venkatesh Madhugiri, MD; Victor Goulenko, MD; Michael T. Milano, MD, PhD; Elad I. Levy, MD, MBA; Dheerendra Prasad, MD, MCh

41 Radiation Therapy for the Management of Refractory Giant Condyloma Acuminata: A Case Report

Prinska Ghimire Wagle, MBBS; Samuel To, BA; William C. Chen, MD

RESIDENT VOICE EDITORIAL

46 Artificial Intelligence in Radiation Oncology Training: Integrating Clinical Skills and Automation

Kishan Patel, MD

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

# Revisiting Radioimmunotherapy

John H. Suh, MD, FASTRO, FACR

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

Six years ago, *Applied Radiation Oncology* dedicated its March issue to the topic of radioimmunotherapy (RIT), exploring the safety and efficacy of combination immunotherapy and radiation therapy, and its potential to invoke the abscopal response. At that time, RIT was generating excitement for its effectiveness in treating hematological malignancies.

Today, RIT has moved from being a niche treatment for specific hematologic cancers to an emerging therapeutic option for solid tumors, metastatic cancers, and even non-cancer diseases. The field is on the brink of a new era with advanced precision medicine, personalized treatment strategies, and combination therapies that harness the power of RIT in novel ways. We revisit the topic of RIT with two review articles.

The first, *Clinical Evidence of Combining Radiopharmaceutical Therapy* (RPT) *with Immune Checkpoint Inhibitors* (ICIs), highlights clinical trials in which this therapeutic combination is improving outcomes in cancer treatment with reduced toxicities and enhanced immune response. The second article, *Combination of External Beam Radiation Therapy (ERBT) and Immune Checkpoint Inhibitors in Cancer Treatment: Mechanisms, Limitations, and Clinical Applications*, explores how RPT with ICIs enhances treatment effectiveness by overcoming treatment resistance and promoting immunogenic cell death.

This month's research article, *RefleXion X1 Treatment Planning Feasibility Study for Cranio-Spinal Irradiation (CSI)*, highlights the success of a clinical biology-guided radiation therapy (BgRT) system in treating pediatric medulloblastoma patients. The study compares treatment planning using the BgRT system with multi-isocenter linac-based VMAT.

In clinical case studies, we examine a patient with a cervical spine schwannoma who experiences transient swelling following stereotactic body radiotherapy (SBRT) in *Volumetric Changes in Cervical Schwannoma in Response to Adjuvant Stereotactic Body Radiation Therapy*. In *Robotic-assisted Seminal Vesicle Excision vs Brachytherapy for Isolated Seminal Vesicle* and *Recurrence* and *Radiation Therapy for the Management of Refractory Giant Condyloma Acuminata*, the authors demonstrate the effectiveness of common therapeutic approaches in managing these cases.

Finally, the Resident Voice column, A*rtificial Intelligence in Radiation Oncology Training: Integrating Clinical Skills and Automation*, weighs the opportunities that AI presents in clinical training programs against its potential to contribute to a loss of fundamental skills.

Looking ahead, our issue for June will explore the impact of heavy particle treatment on the field, particularly in the application of intractable cancers. Until then, please remember to pause and admire the renewal and wonder that spring brings every year. Thank you, as always, for supporting this journal!

Published: March 1, 2025. https://doi.org/10.37549/ARO-D-25-00011

# Clinical Evidence of Combining Radiopharmaceutical Therapy With Immune Checkpoint Inhibitors

## Introduction

Radiopharmaceutical therapy (RPT) and immune checkpoint inhibitors (ICIs) represent transformative approaches to treating metastatic cancers. This review article discusses how RPT delivers targeted radiation to primary and metastatic tumors and the therapeutic advantages of combining RPT with ICIs while focusing on outcomes and challenges such as toxicity, immunosuppressive tumor microenvironment, and logistical barriers.

## Learning Objectives

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

1. Distinguish the physical properties of $\alpha$, $\beta$, and Auger-emitting radioisotopes to guide informed selection of radionuclides for RPT based on therapeutic goals and tumor characteristics.
2. Evaluate clinical trial data on RPT-ICI combinations and integrate evidence-based insights into patient selection, dosing strategies, and treatment sequencing for optimized therapeutic outcomes.

## Authors

Malick Bio Idrissou, PhD;[1]
Anusha Muralidhar;[2]
Reinier Hernandez;[1,3,4]
Quaovi H. Sodji[4,5,6*]

Affiliations: [1]Department of Medical Physics, University of Wisconsin-Madison, Madison, WI; [2]Department of Cancer Biology, University of Wisconsin-Madison, Madison, WI ; [3]Department of Radiology, University of Wisconsin-Madison, Madison, WI; [4]Carbone Cancer Center, University of Wisconsin-Madison, Madison, WI; [5]Department of Human Oncology, University of Wisconsin-Madison, Madison, WI; [6]William S. Middleton Memorial Veterans Hospital, Madison, WI.

## Target Audience

- Radiologists
- Related imaging professionals

## Commercial Support

None

## Accreditation/Designation Statement

This activity has been planned and implemented in accordance with the accreditation requirements and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint providership of the Institute for Advanced Medical Education (IAME) and Anderson Publishing. IAME is accredited by the ACCME to provide continuing medical education for physicians. IAME designates this activity for a maximum of 1 *AMA PRA Category 1 Credit™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

## Instructions

1. Review this article in its entirety.
2. Visit appliedradiology.org/SAM2.
3. Login or create an account.
4. Complete the post test and review the discussion and references.
5. Complete the evaluation.
6. Print your certificate.

**Estimated Time for Completion**
1 hour

**Date of Release and Review**
4/1/2025

**Expiration Date**
3/31/2026

## Disclosures

The authors disclose no relationships with ineligible companies.

IAME has assessed conflicts of interest with its faculty, authors, editors, and any individuals who were in a position to control the content of this CME activity. Any relevant financial relationships were mitigated with an independent peer review of this activity, and no conflicts or commercial bias were detected. IAME's planners, content reviewers, and editorial staff disclose no relationships with ineligible entities.

DETAILS ON PAGE 5

# Clinical Evidence of Combining Radiopharmaceutical Therapy With Immune Checkpoint Inhibitors

Malick Bio Idrissou, PhD;[1†] Anusha Muralidhar, PhD;[2†] Reinier Hernandez, PhD;[1,3,4] Quaovi H. Sodji, MD, PhD[4,5,6*]

## Abstract

Radiopharmaceutical therapy (RPT) and immune checkpoint inhibitors (ICIs) represent transformative approaches in treating metastatic cancers. RPT uniquely delivers targeted radiation to primary and metastatic tumors, modulating the tumor microenvironment (TME) to enhance antitumor immunity. The therapeutic advantages of combining RPT with ICI have been shown preclinically. Clinical trials are now emerging, offering insights into the potential therapeutic synergy between RPT and ICI. This review highlights clinical trials of RPT combined with ICI, emphasizing their ability to improve metastatic cancer outcomes while addressing challenges such as toxicity, immunosuppressive TME, and logistical barriers, and underscores their promise to redefine cancer care.

**Keywords:** metastatic cancer, radiopharmaceutical therapy, β-particle emitters, α-particle emitters, immune checkpoint inhibitors

## Introduction

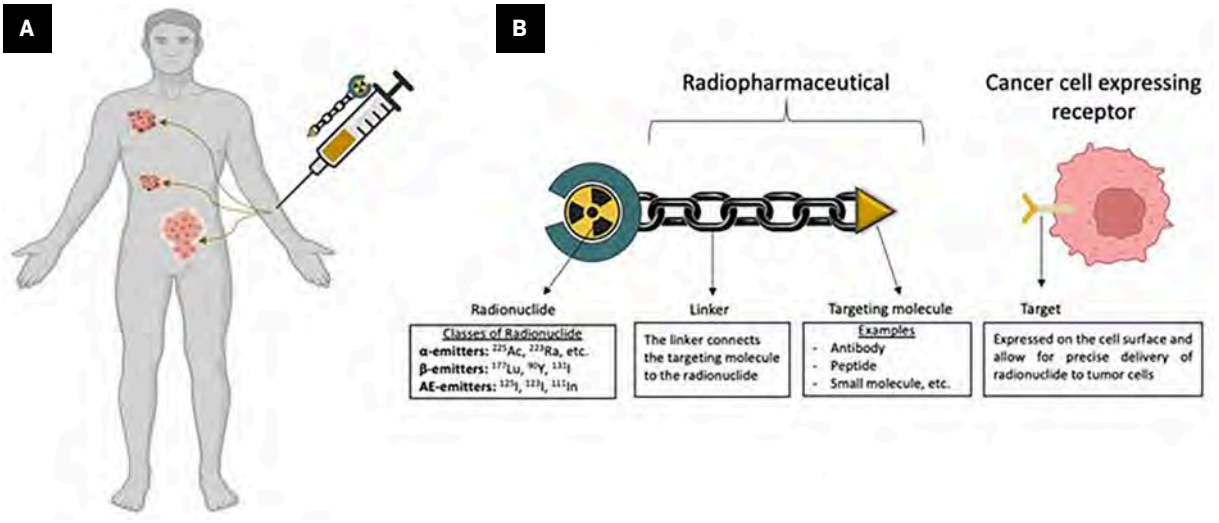
Metastatic disease accounts for approximately 90% of cancer-related deaths.[1-6] Unfortunately, effective therapeutic strategies remain limited despite tremendous advances in cancer research.[7] Radiopharmaceutical therapy (RPT) represents a groundbreaking approach to treating metastatic disease by delivering targeted radiation to tumors throughout the body.[8,9] Leveraging pharmaceuticals that selectively bind to cancer cells or accumulate through physiological mechanisms, RPT provides a precise and effective treatment modality. Remarkably, RPT has demonstrated significant therapeutic efficacy with minimal toxicity in several cancer types.[8] As the role of RPT in metastatic disease management is on the rise, its combination with immune checkpoint inhibitors (ICIs) holds the potential to enhance clinical responses beyond that achievable by either monotherapy alone.

For over a century, radiation therapy, including external beam radiation therapy (EBRT) and RPT, has shown dual benefits: tumor eradication and immune activation.[10] Radiation triggers cancer cells to release damage-associated molecular patterns

**Affiliations:** [1]Department of Medical Physics, University of Wisconsin-Madison, Madison, WI. [2]Department of Cancer Biology, University of Wisconsin-Madison, Madison, WI. [3]Department of Radiology, University of Wisconsin-Madison, Madison, WI. [4]Carbone Cancer Center, University of Wisconsin-Madison, Madison, WI. [5]Department of Human Oncology, University of Wisconsin-Madison, Madison, WI. [6]William S. Middleton Memorial Veterans Hospital, Madison, WI. †Malick Bio Idrissou and Anusha Muralidhar contributed equally to this work
**Corresponding author:** *Quaovi H. Sodji, MD, PhD, 600 Highland Ave, Madison, WI 53792. (qsodji@humonc.wisc.edu)
**Author contributions:** All authors contributed to the writing, reviewing and editing of the manuscript. No artificial intelligence-assisted technology was used in the preparation of this article.
**Disclosures:** RH: consulting fees from MonoPar Inc and Archeus technologies Inc.; Chief Technology Officer for Archeus Technologies Inc and received stocks from Archeus. All other authors have no conflicts of interest to disclose. None of the authors received outside funding for the production of this original manuscript and no part of this article has been previously published elsewhere.
**Funding:** NIH K08 CA285941 (QHS).

Published: March 1, 2025. https://doi.org/10.37549/ARO-D-24-00039

**Figure 1.** Radiopharmaceutical therapy delivers systemic radiation to tumor. (A) A radiolabeled, tumor-specific compound known as a "radiopharmaceutical" is administered intravenously, resulting in selective accumulation of radionuclide in the tumor microenvironment. (B) Pharmacophoric model of radiopharmaceutical agent. A targeting molecule is conjugated to a therapeutic radionuclide via a linker and chelator, forming a radiopharmaceutical that ensures precise delivery of radiation to tumor cells.




(DAMPs), activating the cGAS-STING pathway, which induces type I interferons and the release of cytokines that recruit immune cells.[11,12] The growing promise of RPT in treating metastatic cancer, coupled with emerging insights into the immunogenic effects of radiation, has spurred preclinical and clinical studies exploring the combination of RPT and immunotherapy, such as ICIs. This review explores clinical trials investigating the combination of RPT with ICI, highlighting key clinical findings, potential challenges, and future directions in this emerging field.

## Radiopharmaceutical Therapy

RPT has emerged as a promising systemic therapy, enabling radiation delivery to both local and metastatic lesions while sparing healthy tissues (**Figure 1A**).[8,13] Unlike EBRT, which delivers radiation to all tissues in the radiation field, including malignant and adjacent normal tissues, RPT uses tumor-targeting biomolecules (eg, antibodies, peptides, or small molecules) linked to a radionuclide to form a "radiopharmaceutical" that preferentially targets cancer cells (**Figure 1**). The radiopharmaceutical binds selectively to receptors overexpressed on tumor cells, thus delivering radiation to the tumor while minimizing damage to surrounding tissues.[14] This molecularly targeted approach makes RPT particularly effective for treating metastatic and microscopic tumors,[8,15-17] where EBRT's utility is often limited. The efficacy of RPT depends on the targeting molecule's properties, the radionuclide's physical characteristics, and tumor characteristics such as receptor expression, size, and tumor type. Additional factors, such as the administrated activity, tumor uptake, and pharmacokinetics, also impact the treatment outcome.[18] Therefore, carefully considering these factors is crucial for RPT's clinical efficacy and safety. The approvals of several radiopharmaceuticals, such as [$^{223}$Ra]Ra-dichloride (Xofigo) and [$^{177}$Lu]Lu-PSMA-167 (Pluvicto) for metastatic castration-resistant prostate cancer (mCRPC) and [$^{177}$Lu]Lu-DOTATATE (Lutathera) for gastroenteropancreatic neuroendocrine tumors (GEP-NETs), have sparked a new excitement in the field.[19-21] RPT faces challenges like suboptimal targeting, radioresistance, and limited immune stimulation, hindering tumor eradication.[22-24] Combining RPT with systemic therapies like ICIs may overcome these limitations and improve outcomes.

### Targeting Molecules

In RPT, antibodies, peptides, or small molecules are designed to bind selectively to tumor-specific receptors or antigens, ensuring precise delivery of radiation to cancer cells while sparing healthy tissues.[25]

#### *Antibodies*

Their high specificity and potentially strong binding affinity make antibodies ideal for targeting tumor-associated antigens and delivering radiation to cancer cells.[26,27] Effective antibodies target antigens that are highly expressed on tumors but minimally expressed or absent in healthy tissue.

However, antibody size can limit tumor microenvironment (TME) penetration[28] and prolong circulation,[29] increasing off-target toxicities. Smaller monoclonal antibody (mAb) fragments like single-chain variable fragments partially retain target binding capacity while improving TME penetration. The US Food and Drug Administration/European Medical Agency (FDA/EMA)-approved examples of antibody-based radiopharmaceuticals include Zevalin ([$^{90}$Y]Y-ibritumomab tiuxetan)[30] and Bexxar ([$^{131}$I]I-tositumomab),[31] which target the CD20 protein on the surface of B-cells expressed by non-Hodgkin lymphoma.

### *Peptides*

Peptides are versatile for RPT owing to rapid TME penetration, high uptake, and quick clearance from nontarget tissues, offering optimized pharmacokinetics. Their relatively higher stability enables chemical modifications and radiolabeling, making them versatile agents in nuclear medicine. A notable example of a peptide-based FDA/EMA-approved radiopharmaceutical is Lutathera ([$^{177}$Lu]Lu-DOTA-TATE), indicated for the treatment of somatostatin receptor 2-positive gastroenteropancreatic neuroendocrine tumors.[32,33]

### *Small Molecules*

Small molecule-based radioligands offer advantages as radiopharmaceuticals due to their efficient TME penetration and rapid clearance from systemic circulation, reducing off-target effects and toxicity. Although less specific than antibodies or peptides, small molecules effectively target cancer-associated antigens, such as the prostate-specific membrane antigen (PSMA) in prostate cancer. A notable example is the FDA-approved [$^{177}$Lu]Lu-PSMA-167 (Pluvicto) for mCRPC,[34] showcasing radioligand therapy's potential in precision oncology.

Each targeting molecule in RPT offers a unique balance of strengths and limitations, with selection guided by tumor traits, precision, clearance, and off-target risks. This enables personalized and effective cancer therapy.

## Radionuclides

A wide range of radionuclides is available for RPT, and selecting the appropriate one is crucial, as it directly influences treatment safety and efficacy. This choice is guided by factors such as physical half-life, availability, cost, radiochemical methods, and radiation properties, including energy level, type (α, β, or Auger electrons), linear energy transfer (LET), and penetration range (**Figure 2** and **Table 1**).

### *Physical Half-Life*

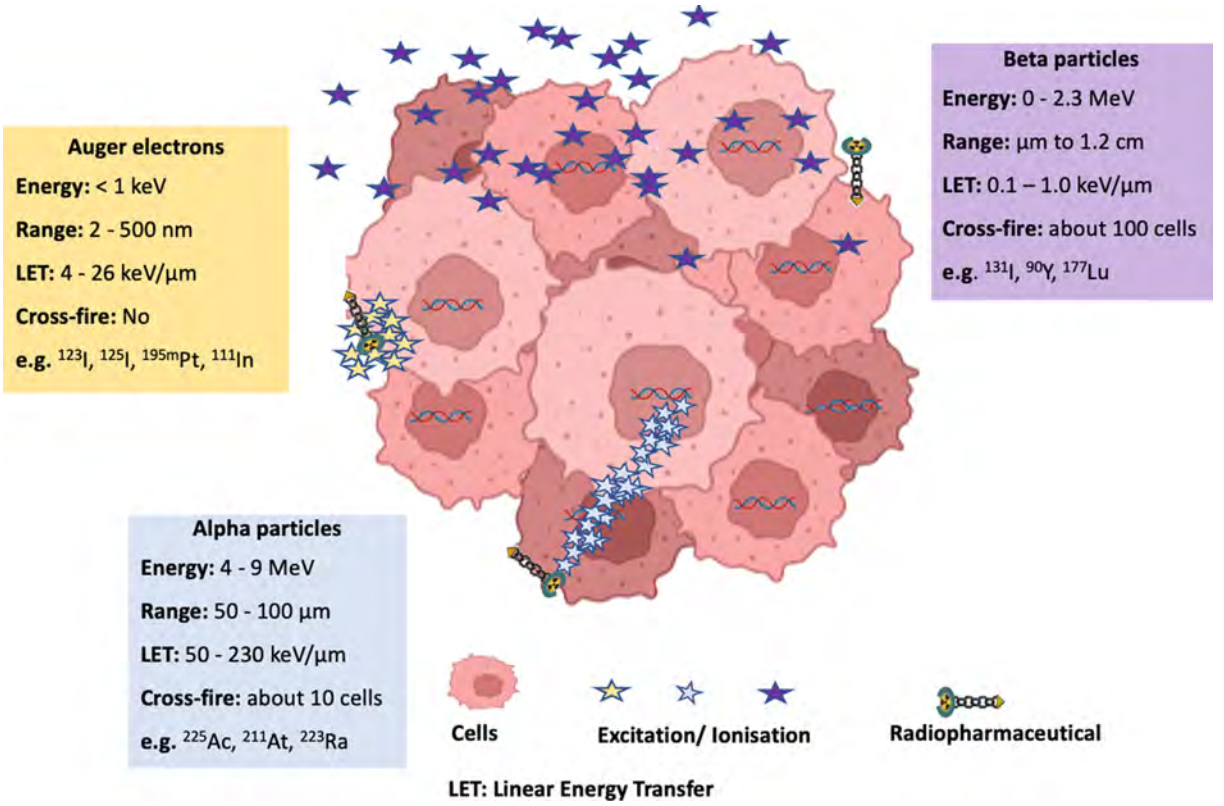
The time needed for half of an RPT's radioactive atoms to decay is critical. The half-life must be amenable to the radiolabelling process, the distribution logistics of the agent, and the targeting molecule's pharmacokinetics. While radionuclides with a short half-life, measured in hours, are preferred for imaging application, RPTs featuring short $T_{1/2}$ radionuclides may lead to a significant decay before the radiopharmaceutical reaches the TME, thus reducing treatment efficacy. Conversely, a long half-life can increase radiation exposure to healthy tissue, thus increasing treatment-related side effects. Ideally, RPT radionuclides should have a half-life of 1 to 7 days for optimal balance.[35]

### *Linear Energy Transfer*

The linear energy deposited by ionizing radiation per unit distance in tissue (keV/μm) significantly influences its biological effect. High LET of radiation (eg, α-particles, 50-230 keV/μm) induces dense clusters of double-strand DNA breaks (DSBs), causing irreparable DNA damage and high cytotoxicity. Intermediate LET radiation (eg, Auger electrons, 4-26 keV/μm) generates localized single-strand DNA breaks (SSBs) and DSBs, with cytotoxicity dependent on nuclear proximity due to limited penetration. Low LET radiation (eg, β-particles, 0.2 keV/μm) primarily induces SSBs and indirect damage via free radicals, which are often repairable, though clustered SSBs may result in DSBs.[36,37] Radionuclides used in RPT are classified into 3 main categories based on their radiation type: β-particle emitters, α-particle emitters, and Auger/conversion electrons emitters.

- β-particle emitters such as lutetium-177 ($^{177}$Lu), yttrium-90 ($^{90}$Y), and iodine-131 ($^{131}$I), with a low LET (~0.2 keV/μm) and tissue penetration up to 12 mm, have been widely used in RPT. Owing to their deeper penetration range (several millimeters), low-LET $\beta^-$-emitters can effectively treat heterogeneous (target expression) tumors,[38,39] resulting in more effective tumor coverage,[40,41] but may have lower lethal damage efficiency per unit dose.
- α-particle emitters such as radium-223 ($^{223}$Ra) and actinium-225 ($^{225}$Ac) deliver potent therapy with high LET (50-230 keV/μm) and a short tissue range (50-100 μm); thus, they are ideal for treating micrometastases.[39,40,42] Their high LET causes dense clusters of DSBs, which are difficult to repair,[39] making them highly cytotoxic.[43]
- Auger/conversion electron emitters such as iodine-123 ($^{123}$I), iodine-125 ($^{125}$I),

**Figure 2.** Characteristics of various radionuclides used for radiopharmaceutical therapy.




and indium-111 ($^{111}$In) have a very short tissue range (< 1 µm), making them effective near critical cell structures like nuclear DNA, and a medium-to-high LET (4-26 keV/µm) inducing a mix of SSBs and DSBs.[16,39,42]

Many β-particle and Auger emitters also emit γ rays, enabling their dual use for therapy and imaging.[44] For example, γ emissions from $^{177}$Lu allow real-time visualization of radiopharmaceutical distribution, ensuring accurate targeting and dose optimization.[45,46]

Overall, radionuclide selection for RPT depends on properties like half-life, LET, radiation type, and tissue penetration. β-emitters appear to be better suited for larger tumors, while α-emitters target micrometastases with high cytotoxicity, and Auger emitters provide precise, localized radiation (< 1 µm) near critical structures like nuclear DNA.

## Immunomodulatory Effects of RPT and Rationale for Combining RPT With ICI

The efficacy of RPT extends beyond direct cytotoxicity as it induces significant pro-inflammatory immune responses.[47,48] Ionizing radiation enhances tumor immunogenicity, modulates the TME, and promotes innate and adaptive immunity.[47,48] Irradiated tumor cells release DAMPs[49] and express immunomodulatory molecules, recruiting antigen-presenting cells to activate T cells and drive systemic antitumor immunity.[50] Potluri et al showed that [$^{90}$Y]Y-NM600 modified the TME by increasing CD8+ T cell infiltration and PD-L1 expression on myeloid cells.[51] In a murine study, Hernandez et al observed a reduction in immunosuppressive regulatory T cells and a notable increase in activated CD8+ T cells in EL4 murine tumors treated with [$^{90}$Y]Y-NM600 compared with controls.[52] Furthermore, upon rechallenging [$^{90}$Y]Y-NM600-treated complete responders with EL4 cells, none developed tumors,[52] suggesting the induction of a tumor-specific memory in RPT-treated mice. Emerging preclinical data suggest that targeted α-particle therapy (TAT) can also induce immunostimulatory effect.[53] Lejeune et al further demonstrated that TAT triggers transcriptional and

**Table 1. Radionuclides Used in Radiopharmaceutical Therapy and Their Physical Properties**

| PARTICLE EMITTED | ENERGY | RANGE IN TISSUE | LET (keV/μm) | KEY DNA DAMAGE CHARACTERISTICS | EXAMPLE OF RADIONUCLIDES |
|---|---|---|---|---|---|
| β-particles | 0-2.3 MeV | μm to1.2 cm | 0.1-1.0 | Most single-strand breaks and some double-strand breaks but is easily repairable. (lower lethal damage efficiency) | $^{131}$I, $^{90}$Y, $^{177}$Lu |
| α-particles | 5-9 MeV | 50-100 μm | 50-230 | Mostly clustered double-strand breaks, making them complex and difficult to repair. (higher lethal damage efficiency) | $^{225}$Ac, $^{211}$At, $^{223}$Ra |
| Auger and conversion electrons | <1 keV | <1 μm | 4-26 | Mix of clustered double-strand breaks and single-strand breaks (lethality dependent on nuclear DNA proximity) | $^{123}$I, $^{125}$I, $^{195m}$Pt, $^{111}$In |

*Abbreviation: LET, linear energy transfer.*

molecular signatures consistent with immunogenic cell death in preclinical syngeneic tumor models.[54] Despite the reported immunomodulatory effects of RPT, its efficacy as a monotherapy often lacks durability, underscoring the compelling rationale for combining RPT with immunotherapy.[55] Foundational studies have shown the synergism between RPT and immunotherapy, such as improved survival with [$^{90}$Y]-anti-CEA (carcinoembryonic antigen) antibodies in combination with a CEA/TRICOM (TRICOM: 3 T-cell costimulatory molecules B7-1, ICAM-1, and LFA-3) vaccine in colon cancer models.[56] This combination represents a promising strategy for achieving durable tumor control; thus, it may pave the way for enhancing patient outcomes through synergistic treatment strategies.

## Clinical Trials Combining RPT With ICI

Building on preclinical evidence, several clinical trials have been initiated to evaluate the safety and efficacy of RPT-ICI combinations across cancers. Key outcomes are discussed here, underscoring the potential of these combination therapies to advance clinical treatment paradigms. **Table 2** concisely summarizes these clinical trials, categorized by disease type for clarity.

### Prostate Cancer

A phase Ib study (NCT02814669) investigated the combination of [$^{223}$Ra]$RaCl_2$ with atezolizumab in mCRPC patients with bone, lymph node, or visceral metastases. This combination resulted in greater toxicity than either agent alone and failed to show clinical benefit.[57] Among the grade 3/4 adverse events, 34.1% were attributed to atezolizumab, while 27.3% were associated with [$^{223}$Ra]$RaCl_2$.

A randomized phase II study (NCT03093428) evaluated [$^{223}$Ra]$RaCl_2$ with pembrolizumab in patients with mCRPC. A recent report showed a median progression-free survival (PFS) of 6.1 months for [$^{223}$Ra]$RaCl_2$ + pembrolizumab versus 5.7 months for [$^{223}$Ra]$RaCl_2$ alone and a median overall survival (OS) of 16.9 months versus 16.0 months, respectively.[58] While the combination was well tolerated with no unexpected toxicity, it did not demonstrate improved efficacy.

PRINCE (NCT03658447), a phase I clinical trial, evaluated the safety and efficacy of [$^{177}$Lu]Lu-PSMA-617 in combination with pembrolizumab in patients with mCRPC. The prostate-specific antigen response rate (PSA-RR) was 76% compared with 46% with [$^{177}$Lu]Lu-PSMA-617 alone. The median radiographic PFS, PSA-PFS, and OS were 11.2 months, 8.2 months, and 17.8 months, respectively.[59] No additional safety concerns were identified with the addition of pembrolizumab, confirming the favorable safety profile of this combination.

### Lung Cancer

Advanced lung cancer has also been the focus of clinical trials exploring the combination of RPT with immunotherapy. A phase I/II trial (NCT03325816) investigating nivolumab with Lutathera in patients with extensive-stage small cell

**Table 2. Selected Clinical Trials Evaluating Radiopharmaceutical Therapy Combined With Immune Checkpoint Blockade in Cancer**

| DISEASE | TRIAL | PHASE | DISEASE STATUS | TARGET | RPT | ICI | COMBINATION SEQUENCE | TRIAL STATUS/ RESULT | REFERENCE |
|---|---|---|---|---|---|---|---|---|---|
| Prostate cancer | NCT02814669 | Ib | mCRPC | Bone metastases | [$^{223}$Ra]Ra: 55 kBq/kg (IV) every 28 days, 6 administrations | Atezolizumab: 840 mg (IV) every 14 days | Concurrent or staggered | Combination: greater toxicity | 57 |
| | NCT03093428 | II | mCRPC | Bone metastases | [$^{223}$Ra]Ra: every 4 weeks at a predetermined dose (IV) | Pembrolizumab: every 3 weeks at a predetermined dose (IV) | Concurrent | No improved efficacy | 58 |
| | NCT03658447 (PRINCE) | I | mCRPC | PSMA | [$^{177}$Lu]Lu-PSMA-617: 8.5 GBq (IV), every 6 weeks, up to 6 cycles | Pembrolizumab: 200 mg every 3 weeks (IV) | Concurrent | PSA-RR: 76%<br>No safety concerns<br>rPFS: 11.2 months<br>PSA-PFS: 8.2 months<br>OS: 17.8 months | 59 |
| Lung cancer | NCT03325816 | I/II | Extensive stage SCLC | SSTR | [$^{177}$Lu]Lu -DOTA0-Tyr3-Octreotate: 3.7 or 7.4 GBq (IV), every 8 weeks, 4 cycles | Nivolumab: 240 mg every 2 weeks (IV) | Concurrent | Combination well tolerated<br>PR: 1 out 7 patients | 60 |
| | NCT03996473 | I | Metastatic NSCLC | Bone metastases | [$^{223}$Ra]Ra: 55 kBq/kg (IV), every 6 weeks, up to 6 cycles | Pembrolizumab: 200 mg every 3 weeks (IV) up to 35 doses | Concurrent | Study closed | |
| Renal cancer (ccRCC) | NCT05663710 | Ib/II | Advanced ccRCC | CAIX | [$^{177}$Lu]Lu-girentuximab: 1.48 GBq/m$^2$ (IV), every 12 weeks, up to 3 cycles | Nivolumab (dose not available) Cabozantinib: given orally | Concurrent | Ongoing | 61 |
| | NCT05239533 (STARLITE 2) | II | Advanced ccRCC | CAIX | [$^{177}$Lu]Lu-girentuximab: 1.8 or 2.4 GBq/m$^2$ (IV), every 12-14 weeks, up to 3 cycles | Nivolumab: 200 mg every 2 weeks | Concurrent | Ongoing | 62 |

**Table 2. Continued**

| DISEASE | TRIAL | PHASE | DISEASE STATUS | TARGET | RPT | ICI | COMBINATION SEQUENCE | TRIAL STATUS/ RESULT | REFERENCE |
|---|---|---|---|---|---|---|---|---|---|
| Merkel cell cancer | NCT05583708 | II | Metastatic | SSTR | [$^{177}$Lu]Lu-DOTATATE: 7.4 GBq (IV), every 2 months, up to 4 doses | Pembrolizumab: 400 mg every 6 weeks (IV) | Concurrent | Temporarily suspended | |
| | NCT04261855 (GoTHAM) | Ib/II | Metastatic | SSTR | [$^{177}$Lu]Lu -DOTATATE: 2 administrations separated by 8-10 weeks | Avelumab: 10 mg/kg every 2 weeks for 24 months (IV) | Concurrent | Ongoing | |
| Thyroid cancer | NCT03215095 | I | Recurrent/ metastatic | rhTSH | [$^{131}$I]I : 100 mCi | Durvalumab: 1500 mg IV every 4 weeks | Concurrent | Active, not recruiting | |
| Refractory neuroblastoma | NCT02914405 (MiNivAN) | I | Relapsed or refractory High risk | Norepinephrine transporter | [$^{131}$I]I-meta-iodobenzylguanidine | Nivolumab: 3 mg/kg Dinutuximab (anti-GD2 monoclonal antibody): 50 or 100 mg/m$^2$ | Concurrent | Recruiting | |
| NETs with liver metastases | NCT03457948 | II | Metastatic | SSTR | [$^{177}$Lu]Lu-DOTA0-Tyr3-Octreotate | Pembrolizumab | Concurrent | Recruiting | |

*Abbreviations: CAIX, carbonic anhydrase IX; ccRCC, clear cell renal cell carcinoma; ICI, immune checkpoint inhibitor; IV, intravenous injection; mCRPC, metastatic castration-resistant prostate cancer; NET, neuroendocrine tumor; NSCLC, non-small cell lung cancer; OS, overall survival; PR, partial response; PSA-PFS, prostate-specific antigen progression-free survival; PSA-RR, PSA response rate (≥50% decrease in PSA level); PSMA: prostate-specific membrane antigen; rhTSH, recombinant human thyroid stimulating hormone; rPFS, radiographic progression-free survival; RPT, radiopharmaceutical therapy; SCLC, small cell lung cancer; SSTR, somatostatin receptor.*

lung cancer (SCLC) demonstrated a tolerable toxicity profile. Lutathera, a β-emitting [$^{177}$Lu]Lu-labeled somatostatin analog approved for GEP-NETs,[63] targets somatostatin receptor-expressing cells. The combination therapy was well tolerated. Furthermore, 1 out of 7 patients achieved a partial response (PR), while 2 with pulmonary atypical carcinoid maintained stable disease (SD) for 6 months. Notably, the patient with PR exhibited the highest tumor uptake of $^{68}$Ga-DOTATATE on PET/CT, underscoring the potential of this approach.[60]

A phase I study (NCT03996473) sought to evaluate the safety and efficacy of combining [$^{223}$Ra]$RaCl_2$ with pembrolizumab in metastatic non-SCLC. The trial included patients who were either treatment-naïve for advanced disease or had progressed after prior PD-1/PD-L1 checkpoint blockade. The primary objectives were assessing tumor shrinkage, duration, and treatment safety. However, the study was closed early due to insufficient accrual.

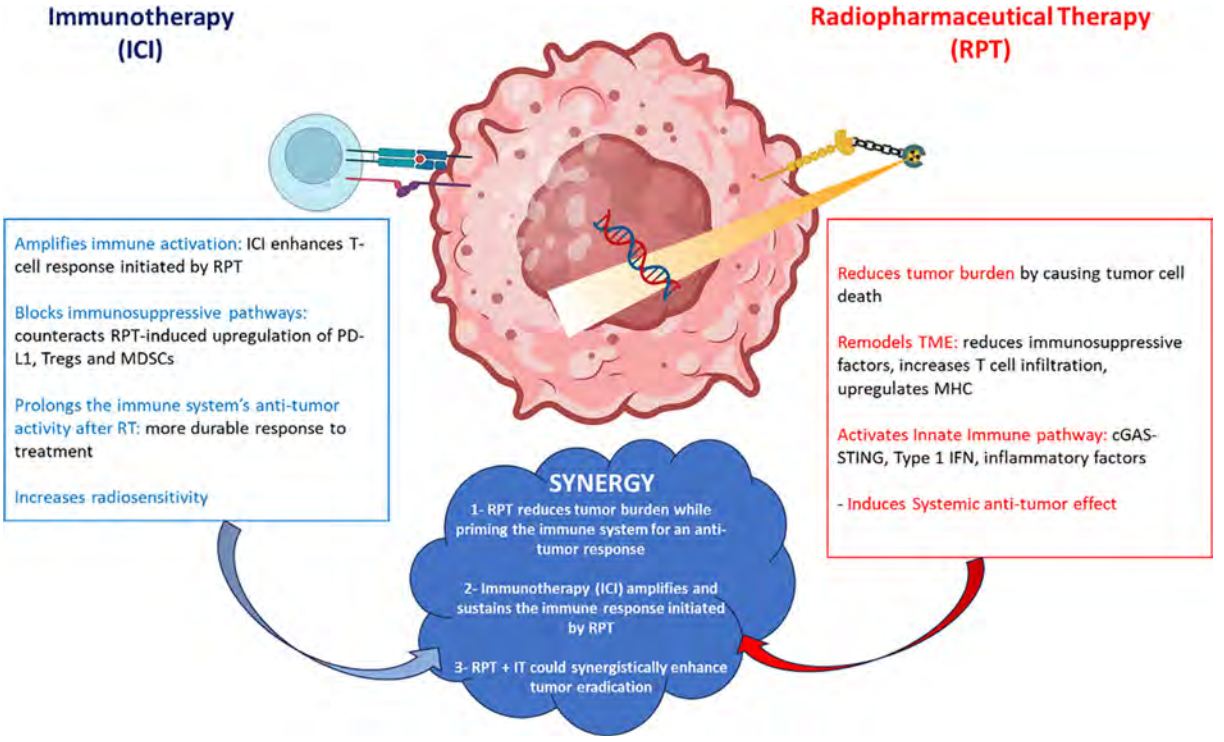
## Renal Cancer

Clear cell renal cell carcinoma (ccRCC) is characterized by carbonic anhydrase IX expression resulting from von Hippel-Lindau loss, representing a compelling target for RPT-based therapies. The integration of RPT with immunotherapy in advanced ccRCC is gaining momentum, with 2 phase II clinical trials currently underway (NCT05239533; NCT05663710). These trials aim to evaluate the safety and efficacy of combining [$^{177}$Lu]Lu-girentuximab with nivolumab as a novel treatment strategy for advanced ccRCC.[61,62]

## Merkel Cell Carcinoma

Two case reports underscore the significant therapeutic potential of combining RPT with ICI in metastatic Merkel cell carcinoma (MCC). These cases involved patients who had progressed on first-line avelumab or second-line therapies combining ipilimumab, nivolumab, and EBRT.[64,65] While up to half of patients with MCC either may not respond to or may develop resistance

**Figure 3.** Potential synergistic interactions between radiopharmaceutical therapy and immune checkpoint inhibitors (ICIs).




*Abbreviations: MCH, melanin-concentrating hormone; MDSCs, myeloid-derived suppressor cells; TME, tumor microenvironment.*

to ICIs,[65] the frequent expression of somatostatin receptors in MCC makes it a suitable target for [$^{177}$Lu]Lu-DOTATATE. In one case, a patient with extensive MCC metastases treated with [$^{177}$Lu]Lu-DOTATATE and anti-PD-L1 therapy demonstrated a rapid response, achieving a near-complete response within 1 month.[64] Another patient receiving [$^{177}$Lu]Lu-DOTATOC, along with ipilimumab and nivolumab, achieved and sustained a PR for 5 months.[65] Clinical trials (NCT05583708; NCT04261855) have been initiated to evaluate [$^{177}$Lu]Lu-DOTATATE combined with nivolumab or pembrolizumab in patients with metastatic MCC.

Other ongoing clinical trials are exploring RPT with ICI, including radioiodine ($^{131}$I) with durvalumab (NCT03215095) for thyroid cancer, $^{131}$I-MIBG with nivolumab and dinutuximab (anti-GD2 monoclonal antibody) for refractory neuroblastoma (NCT02914405), and $^{177}$Lu-DOTA0-Tyr3-Octreotate with pembrolizumab (NCT03457948) for NETs with liver metastases.

## Challenges and Future Perspectives

Combining RPT with immunotherapy is a promising therapeutic option for metastatic cancers. With its targeted radiation delivery and ability to modulate the TME, RPT can complement the systemic antitumor effects of immunotherapy. Preclinical studies highlight the potential of RPT and ICI combination,[47-54] but robust clinical evidence remains limited. Nevertheless, few studies have shown promising results, including case reports with [$^{177}$Lu]Lu-DOTATATE or [$^{177}$Lu]Lu-DOTATOC plus ICI in MCC metastases,[64,65] and the phase I PRINCE trial with [$^{177}$Lu]Lu-PSMA-617 in combination with ICI in mCRPC.[59] Beyond these studies, we are awaiting results from ongoing clinical trials (**Table 2**). Nevertheless, challenges persist, including increased toxicities[57] with immune-related events and radiation-induced toxicities. The immunosuppressive TME, influenced by regulatory T cells and immune checkpoint expression, may further dampen treatment efficacy. Variability in patient responses, driven by tumor heterogeneity, highlights the need for predictive biomarkers for optimal patient selection. Economic and logistical barriers also hinder implementation.[66-70] The production and administration of RPT require specialized

infrastructure and expertise, while its high costs necessitate cost-benefit analyses for integration into clinical practice. Future research should optimize trial designs for sequencing, dosing, and timing of RPT-ICI combinations. Advances in imaging, dosimetry, and collaboration among specialists, along with efforts to reduce costs and improve access, are key to transforming metastatic cancer treatment. Moreover, most trials do not clearly differentiate whether observed toxicities stem from immune-related effects or radiation exposure. Gaining a deeper understanding of the predominant mechanism, whether immune-mediated or radiation-induced, is essential for optimizing toxicity management and improving the safety profile of these combinations.

## Conclusion

The combination of RPT and immunotherapy offers a transformative approach to metastatic cancer, overcoming current treatment limitations. As shown in **Figure 3**, RPT synergizes with immunotherapy, including ICIs, by reducing tumor burden, releasing neo-antigens, enhancing MHC-I expression, and modifying the TME, while immunotherapy amplifies and sustains these effects, countering immune evasion and optimizing tumor control, especially in "cold" tumors. Despite challenges such as toxicity and logistical barriers, advances in radiopharmaceutical design, immune modulation, and personalized biomarkers driven by interdisciplinary collaboration could redefine cancer care for advanced, treatment-resistant, and metastatic malignancies.

## References

1) Seyfried TN, Huysentruyt LC. On the origin of cancer metastasis. *Crit Rev Oncog*. 2013;18(1-2):43-73. doi:10.1615/critrevoncog.v18.i1-2.40

2) Spano D, Heck C, De Antonellis P, Christofori G, Zollo M. Molecular networks that regulate cancer metastasis. *Semin Cancer Biol*. 2012;22(3):234-249. doi:10.1016/j.semcancer.2012.03.006

3) Ganesh K, Massagué J. Targeting metastatic cancer. *Nat Med*. 2021;27(1):34-44. doi:10.1038/s41591-020-01195-4

4) Coleman RE. Clinical features of metastatic bone disease and risk of skeletal morbidity. *Clin Cancer Res*. 2006;12(20 pt 2):6243s-6249s. doi:10.1158/1078-0432.CCR-06-0931

5) van Roij J, Brom L, Youssef-El Soud M, van de Poll-Franse L, Raijmakers NJH. Social consequences of advanced cancer in patients and their informal caregivers: a qualitative study. *Support Care Cancer*. 2019;27(4):1187-1195. doi:10.1007/s00520-018-4437-1

6) Costa L, Badia X, Chow E, Lipton A, Wardley A. Impact of skeletal complications on patients' quality of life, mobility, and functional independence. *Support Care Cancer*. 2008;16(8):879-889. doi:10.1007/s00520-008-0418-0

7) Lambert AW, Pattabiraman DR, Weinberg RA. Emerging biological principles of metastasis. *Cell*. 2017;168(4):670-691. doi:10.1016/j.cell.2016.11.037

8) Sgouros G, Bodei L, McDevitt MR, Nedrow JR. Radiopharmaceutical therapy in cancer: clinical advances and challenges. *Nat Rev Drug Discov*. 2020;19(9):589-608. doi:10.1038/s41573-020-0073-9

9) Salih S, Alkatheeri A, Alomaim W, Elliyanti A. Radiopharmaceutical treatments for cancer therapy, radionuclides characteristics, applications, and challenges. *Molecules*. 2022;27(16):5231. doi:10.3390/molecules27165231

10) Murphy JB, Hussey RG, Nakahara W, Sturm E. Studies on X-ray effects: Vi. Effect of the cellular reaction induced by X-rays on cancer grafts. *J Exp Med*. 1921;33(3):299-313. doi:10.1084/jem.33.3.299

11) Storozynsky Q, Hitt MM. The impact of radiation-induced DNA damage on cgas-STING-mediated immune responses to cancer. *Int J Mol Sci*. 2020;21(22):8877. doi:10.3390/ijms21228877

12) Constanzo J, Faget J, Ursino C, Badie C, Pouget JP. Radiation-induced immunity and toxicities: the versatility of the cgas-STING pathway. *Front Immunol*. 2021;12:680503. doi:10.3389/fimmu.2021.680503

13) Dumortier J, Decullier E, Hilleret M-N. Adjuvant intraarterial lipiodol or $^{131}$I-lipiodol after curative treatment of hepatocellular carcinoma: a prospective randomized trial. *J Nucl Med*. 2014;55(6):877-883. doi:10.2967/jnumed.113.131367

14) Shea AG, Idrissou MB, Torres AI, et al. Immunological effects of radiopharmaceutical therapy. *Front Nucl Med*. 2024;4:1331364. doi:10.3389/fnume.2024.1331364

15) Brady D, O'Sullivan JM, Prise KM. What is the role of the bystander response in radionuclide therapies? *Front Oncol*. 2013;3:215. doi:10.3389/fonc.2013.00215

16) Idrissou MB, Pichard A, Tee B, et al. Targeted radionuclide therapy using auger electron emitters: the quest for the right vector and the right radionuclide. *Pharmaceutics*. 2021;13(7):980. doi:10.3390/pharmaceutics13070980

17) Gudkov SV, Shilyagina NY, Vodeneev VA, Zvyagin AV. Targeted radionuclide therapy of human tumors. *Int J Mol Sci*. 2015;17(1):33. doi:10.3390/ijms17010033

18) Capello A, Krenning E, Bernard B, et al. $^{111}$In-labelled somatostatin analogues in a rat tumour model: somatostatin receptor status and effects of peptide receptor radionuclide therapy. *Eur J Nucl Med Mol Imaging*. 2005;32(11):1288-1295. doi:10.1007/s00259-005-1877-x

19) Poeppel TD, Handkiewicz-Junak D, Andreeff M, et al. EANM guideline for radionuclide therapy with radium-223 of metastatic castration-resistant prostate cancer. *Eur J Nucl Med Mol Imaging*. 2018;45(5):824-845. doi:10.1007/s00259-017-3900-4

20) Hennrich U, Eder M. [$^{177}$Lu]LU-PSMA-617 (pluvictotm™): the first FDA-approved radiotherapeutical for treatment of prostate cancer. *Pharmaceuticals*. 2022;15(10):1292. doi:10.3390/ph15101292

21) Hennrich U, Kopka K. Lutathera®: the first FDA- and EMA-approved radiopharmaceutical for peptide receptor radionuclide therapy. *Pharmaceuticals*. 2019;12(3):114. doi:10.3390/ph12030114

22) Wu Y, Song Y, Wang R, Wang T. Molecular mechanisms of tumor resistance to radiotherapy. *Mol Cancer*. 2023;22(1):96. doi:10.1186/s12943-023-01801-2

23) Gao Z, Zhao Q, Xu Y, Wang L. Improving the efficacy of combined radiotherapy and immunotherapy: focusing on the effects of radiosensitivity. *Radiat Oncol*. 2023;18(1):89. doi:10.1186/s13014-023-02278-5

24) Bellavia MC, Patel RB, Anderson CJ. Combined targeted radiopharmaceutical therapy and immune checkpoint blockade: from preclinical advances to the clinic. *J Nucl Med*. 2022;63(11):1636-1641. doi:10.2967/jnumed.122.264373

25) Zhang T, Lei H, Chen X, et al. Carrier systems of radiopharmaceuticals and the application in cancer therapy. *Cell Death Discov*. 2024;10(1):16. doi:10.1038/s41420-023-01778-3

26) Zhao Z, Ukidve A, Kim J, Mitragotri S. Targeting strategies for tissue-specific drug delivery. *Cell*. 2020;181(1):151-167. doi:10.1016/j.cell.2020.02.001

27) Almagro JC, Kodangattil S. Novel approaches in discovery and design of antibody-based therapeutics. *Novel Approaches and Strategies for Biologics, Vaccines and Cancer Therapies*. Elsevier; 2015:147-170. doi:10.1016/B978-0-12-416603-5.00007-9

28) Cruz E, Kayser V. Monoclonal antibody therapy of solid tumors: clinical limitations and novel strategies to enhance treatment efficacy. *Biologics*. 2019;13:33-51. doi:10.2147/BTT.S166310

29) Beckman RA, Weiner LM, Davis HM. Antibody constructs in cancer therapy: protein engineering strategies to improve exposure in solid tumors. *Cancer*. 2007;109(2):170-179. doi:10.1002/cncr.22402

30) Grillo-López AJ. Zevalin: the first radioimmunotherapy approved for the treatment of lymphoma. *Expert Rev Anticancer Ther*. 2002;2(5):485-493. doi:10.1586/14737140.2.5.485

31) Friedberg JW, Fisher RI. Iodine-131 tositumomab (Bexxar®): radioimmunoconjugate therapy for indolent and transformed B-cell non-hodgkin's lymphoma. *Expert Rev Anticancer Ther*. 2004;4(1):18-26. doi:10.1586/14737140.4.1.18

32) Research C for DE. FDA approves lutetium Lu 177 dotatate for treatment of GEP-NETS. *FDA*. 2024. Accessed October 30, 2024. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-lutetium-lu-177-dotatate-treatment-gep-nets

33) Lutathera. European Medicines Agency (EMA). 2018. Accessed October 30, 2024. https://www.ema.europa.eu/en/medicines/human/EPAR/lutathera

34) Fallah J, Agrawal S, Gittleman H, et al. FDA approval summary: lutetium lu 177 vipivotide tetraxetan for patients with metastatic castration-resistant prostate cancer. *Clin Cancer Res*. 2023;29(9):1651-1657. doi:10.1158/1078-0432.CCR-22-2875

35) Qaim SM. Therapeutic radionuclides and nuclear data. *Radiochim Acta*. 2001;89(4-5):297-304. doi:10.1524/ract.2001.89.4-5.297

36) Howell RW, Rao DV, Hou DY, Narra VR, Sastry KSR. The question of relative biological effectiveness and quality factor for auger emitters incorporated into proliferating mammalian cells. *Radiat Res*. 1991;128(3):282)-282-292:. doi:10.2307/3578051

37) Rao D, Howell R, Narra V, Govelitz G, Sastry K. IN-vivo radiotoxicity of DNA-incorporated 125I compared with that of densely ionising alpha-particles. *Lancet*. 1989;334(8664):650-653. doi:10.1016/S0140-6736(89)90896-9

38) Marcu L, Bezak E, Allen BJ. Global comparison of targeted alpha vs targeted beta therapy for cancer: in vitro, in vivo and clinical trials. *Crit Rev Oncol Hematol*. 2018;123:7-20. doi:10.1016/j.critrevonc.2018.01.001

39) Pouget J-P, Navarro-Teulon I, Bardiès M, et al. Clinical radioimmunotherapy—the role of radiobiology. *Nat Rev Clin Oncol*. 2011;8(12):720-734. doi:10.1038/nrclinonc.2011.160

40) Dekempeneer Y, Keyaerts M, Krasniqi A, et al. Targeted alpha therapy using short-lived alpha-particles and the promise of nanobodies as targeting vehicle. *Expert Opin Biol Ther*. 2016;16(8):1035-1047. doi:10.1080/14712598.2016.1185412

41) Czerwińska M, Bilewicz A, Kruszewski M, Wegierek-Ciuk A, Lankoff A. Targeted radionuclide therapy of prostate cancer-from basic research to clinical perspectives. *Molecules*. 2020;25(7):1743. doi:10.3390/molecules25071743

42) Poty S, Francesconi LC, McDevitt MR, Morris MJ, Lewis JS. α-emitters for radiotherapy: from basic radiochemistry to clinical studies-part 1. *J Nucl Med*. 2018;59(6):878-884. doi:10.2967/jnumed.116.186338

43) Sgouros G, Roeske JC, McDevitt MR, et al. MIRD pamphlet no. 22 (abridged): radiobiology and dosimetry of alpha-particle emitters for targeted radionuclide therapy. *J Nucl Med*. 2010;51(2):311-328. doi:10.2967/jnumed.108.058651

44) Stokke C, Kvassheim M, Blakkisrud J. Radionuclides for targeted therapy: physical properties. *Molecules*. 2022;27(17):5429. doi:10.3390/molecules27175429

45) Othman MFB, Mitry NR, Lewington VJ, Blower PJ, Terry SYA. Re-assessing gallium-67 as a therapeutic radionuclide. *Nucl Med Biol*. 2017;46:12-18. doi:10.1016/j.nucmedbio.2016.10.008

46) Pirovano G, Jannetti SA, Carter LM, et al. Targeted brain tumor radiotherapy using an auger emitter. *Clin Cancer Res*. 2020;26(12):2871-2881. doi:10.1158/1078-0432.CCR-19-2440

47) Gaipl US, Multhoff G, Scheithauer H, et al. Kill and spread the word: stimulation of antitumor immune responses in the context of radiotherapy. *Immunotherapy*. 2014;6(5):597-610. doi:10.2217/imt.14.38

48) Filatenkov A, Baker J, Mueller AMS, et al. Ablative tumor radiation can change the tumor immune cell microenvironment to induce durable complete remissions. *Clin Cancer Res*. 2015;21(16):3727-3739. doi:10.1158/1078-0432.CCR-14-2824

49) Bianchi ME. DAMPs, PAMPs and alarmins: all we need to know about danger. *J Leukoc Biol*. 2007;81(1):1-5. doi:10.1189/jlb.0306164

50) Takeshima T, Chamoto K, Wakita D, et al. Local radiation therapy inhibits tumor growth through the generation of tumor-specific CTL: its potentiation by combination with th1 cell therapy. *Cancer Res*. 2010;70(7):2697-2706. doi:10.1158/0008-5472.CAN-09-2982

51) Potluri HK, Ferreira CA, Grudzinski J, et al. Antitumor efficacy of 90Y-NM600 targeted radionuclide therapy and PD-1 blockade is limited by regulatory T cells in murine prostate tumors. *J Immunother Cancer*. 2022;10(8):e005060. doi:10.1136/jitc-2022-005060

52) Hernandez R, Walker KL, Grudzinski JJ, et al. 90Y-NM600 targeted radionuclide therapy induces immunologic memory in syngeneic models of T-cell non-hodgkin's lymphoma. *Commun Biol*. 2019;2(1):79. doi:10.1038/s42003-019-0327-4

53) Perrin J, Capitao M, Allard M, et al. Targeted alpha particle therapy remodels the tumor microenvironment and improves efficacy of immunotherapy. *Int J Radiat Oncol*. 2022;112(3):790-801. doi:10.1016/j.ijrobp.2021.10.013

54) Lejeune P, Cruciani V, Berg-Larsen A, et al. Immunostimulatory effects of targeted thorium-227 conjugates as single agent and in combination with anti-PD-L1 therapy. *J Immunother Cancer*. 2021;9(10):e002387. doi:10.1136/jitc-2021-002387

55) Zukotynski K, Jadvar H, Capala J, Fahey F. Targeted radionuclide therapy: practical applications and future prospects: supplementary issue: biomarkers and their essential role in the development of personalised therapies. *Biomark Cancer*. 2016;8s2:S31804. doi:10.4137/BIC.S31804

56) Chakraborty M, Gelbard A, Carrasquillo JA, et al. Use of radiolabeled monoclonal antibody to enhance vaccine-mediated antitumor effects. *Cancer Immunol Immunother*. 2008;57(8):1173-1183. doi:10.1007/s00262-008-0449-x

57) Fong L, Morris MJ, Sartor O, et al. A phase Ib study of atezolizumab with radium-223 dichloride in men with metastatic castration-resistant prostate cancer. *Clin Cancer Res*. 2021;27(17):4746-4756. doi:10.1158/1078-0432.CCR-21-0063

58) Choudhury AD, Kwak L, Cheung A, et al. Randomized phase II study evaluating the addition of pembrolizumab to radium-223 in metastatic castration-resistant prostate cancer. *Cancer Immunol Res*. 2024;12(6):704-718. doi:10.1158/2326-6066.CIR-22-0306

59) Sandhu S, Joshua AM, Emmett L, et al. PRINCE: phase I trial of $^{177}$lu-PSMA-617 in combination with pembrolizumab in patients with Metastatic Castration-Resistant Prostate Cancer (mcrpc). *JCO*. 2022;40(16_suppl):5017-5017. doi:10.1200/JCO.2022.40.16_suppl.5017

60) Kim C, Liu SV, Subramaniam DS, et al. Phase I study of the 177Lu-DOTA0-Tyr3-Octreotate (lutathera) in combination with nivolumab in patients with neuroendocrine tumors of the lung. *J Immunother Cancer*. 2020;8(2):e000980. doi:10.1136/jitc-2020-000980

61) Feldman DR, Motzer RJ, Knezevic A, et al. STARLITE 2: phase 2 study of nivolumab plus $^{177}$ lutetium-labeled anti-carbonic anhydrase IX (CAIX) monoclonal antibody girentuximab ( $^{177}$ lu-girentuximab) in patients (pts) with advanced clear cell renal cell carcinoma (ccrcc). *JCO*. 2022;40(16_suppl):TPS4603. doi:10.1200/JCO.2022.40.16_suppl.TPS4603

62) Jonasch E, Hasanov E, Flynt L, et al. Phase 1b/2 study of combination $^{177}$ lu girentuximab plus cabozantinib and nivolumab in treatment naive patients with advanced clear cell RCC. *JCO*. 2024;42(16_suppl):TPS4610. doi:10.1200/JCO.2024.42.16_suppl.TPS4610

63) Strosberg JR, Wolin EM, Chasen B, et al. NETTER-1 phase III: progression-free survival, radiographic response, and preliminary overall survival results in patients with midgut neuroendocrine tumors treated with 177-LU-dotatate. *JCO*. 2016;34(4_suppl):194-194. doi:10.1200/jco.2016.34.4_suppl.194

64) Kasi PM, Sharma A, Jain MK. Expanding the indication for novel theranostic 177Lu-dotatate peptide receptor radionuclide therapy: proof-of-concept of PRRT in merkel cell cancer. *Case Rep Oncol*. 2019;12(1):98-103. doi:10.1159/000496335

65) Ferdinandus J, Fendler WP, Luecker-ath K, et al. Response to combined peptide receptor radionuclide therapy and checkpoint immunotherapy with ipilimumab plus nivolumab in metastatic merkel cell carcinoma. *J Nucl Med*. 2022;63(3):396-398. doi:10.2967/jnumed.121.262344

66) Decroisette C, Monnet I, Berard H, et al. Epidemiology and treatment costs of bone metastases from lung cancer: A french prospective, observational, multicenter study (GFPC 0601). *J Thorac Oncol*. 2011;6(3):576-582. doi:10.1097/JTO.0b013e318206a1e3

67) Félix J, Andreozzi V, Soares M, et al. Hospital resource utilization and treatment cost of skeletal-related events in patients with metastatic breast or prostate cancer: estimation for the portuguese national health system. *Value Health*. 2011;14(4):499-505. doi:10.1016/j.jval.2010.11.014

68) Hoefeler H, Duran I, Hechmati G, et al. Health resource utilization associated with skeletal-related events in patients with bone metastases: results from a multinational retrospective - prospective observational study - a cohort from 4 european countries. *J Bone Oncol*. 2014;3(2):40-48. doi:10.1016/j.jbo.2014.04.001

69) Lüftner D, Lorusso V, Duran I, et al. Health resource utilization associated with skeletal-related events in patients with advanced breast cancer: results from a prospective, multinational observational study. *Springerplus*. 2014;3(1):328. doi:10.1186/2193-1801-3-328

70) Pockett RD, Castellano D, McEwan P, et al. The hospital burden of disease associated with bone metastases and skeletal-related events in patients with breast cancer, lung cancer, or prostate cancer in spain. *Eur J Cancer Care*. 2010;19(6):755-760. doi:10.1111/j.1365-2354.2009.01135.x

# Combination of External Beam Radiation Therapy and Immune Checkpoint Inhibitors in Cancer Treatment: Mechanisms, Limitations, and Clinical Applications

Anusha Muralidhar, PhD;[1†] Malick Bio Idrissou, PhD;[2†] Quaovi H. Sodji, MD, PhD[3,4,5*]

## Abstract

External beam radiation therapy (EBRT) has long been integral in cancer treatment, effectively targeting localized and metastatic tumors. Immunotherapy, especially immune checkpoint inhibitors (ICIs), leverages the immune system to eliminate cancer cells but faces challenges such as treatment resistance. EBRT may provide an approach to overcoming resistance to ICI therapy, thus enhancing ICIs' efficacy and broadening their clinical scope. EBRT, by inducing immunogenic cell death, primes the immune system and can potentiate ICIs. This combination strategy has shown promise in preclinical studies, highlighting the potential of EBRT to overcome the limitations of ICI monotherapy and vice versa. Clinical trials have demonstrated the safety and feasibility of this combination, with evidence suggesting improved tumor control and patient outcomes. Nevertheless, numerous challenges remain. This review explores the mechanisms, challenges, and clinical trials evaluating the combination of EBRT and ICIs, underscoring the need for optimized approaches to maximize clinical efficacy, while minimizing toxicities.

**Keywords:** combination therapy, external beam radiation therapy, immunotherapy, immune checkpoint inhibitors

## Introduction

Radiation therapy (RT) is a pillar in cancer therapy, predominantly delivered in the clinical setting by linear accelerators as external beam radiation therapy (EBRT) to eradicate cancer cells or provide symptom relief.[1] By inducing DNA damage in cancer cells, RT disrupts their ability to divide and proliferate, ultimately leading to cell death.[2] Over the years, RT has evolved significantly with advances in both technology and methodology, enhancing its precision while minimizing damage to surrounding healthy tissues.[3]

The integration of advanced imaging and computer technologies has profoundly transformed RT planning and delivery, significantly enhancing treatment safety and patient outcomes.[4]

Intensity-modulated radiation therapy, image-guided radiation therapy, and stereotactic body radiation therapy (SBRT) represent

**Affiliations:** [1]Department of Cancer Biology, University of Wisconsin-Madison, Madison, WI. [2]Department of Medical Physics, University of Wisconsin-Madison, Madison, WI. [3]Department of Human Oncology, University of Wisconsin-Madison, Madison, WI. [4]Carbone Cancer Center, University of Wisconsin-Madison, Madison, WI. [5]William S. Middleton Memorial Veterans Hospital, Madison, WI. †Anusha Muralidhar and Malick Bio Idrissou contributed equally to this work
**Corresponding author:** *Quaovi H. Sodji, MD, PhD, 600 Highland Ave, Madison, WI 53792. (qsodji@humonc.wisc.edu)
**Author contributions:** All authors contributed to the writing, reviewing and editing of the manuscript. No artificial intelligence-assisted technology was used in the preparation of this manuscript.
**Disclosure:** The authors have no conflicts of interest to disclose. None of the authors received outside funding for the production of this original manuscript and no part of this article has been previously published elsewhere.
**Funding:** QHS is supported by the NIH grant K08 CA285941.

Published: March 1, 2025. https://doi.org/10.37549/ARO-D-24-00038

major technological advances that have made EBRT an effective and indispensable tool in modern oncology.[5,6]

Exploring the role of RT in enhancing the effectiveness of immune checkpoint blockade (ICB) therapy has gained attention as a promising strategy in advancing cancer treatment. In recent years, immunotherapy has gained considerable clinical attention, with ICB emerging as a transformative strategy in cancer therapy.[7] ICB therapy with immune checkpoint inhibitors (ICIs) targets immune checkpoints, such as CTLA-4 and PD-1/PD-L1, which tumors exploit to suppress T-cell activity.[8,9] By suppressing the inhibition signal from these immune checkpoints, ICB boosts the immune system, leading to durable tumor regression and improved survival outcomes in cancers, including melanoma, non-small cell lung cancer, and renal cell carcinoma.[10]

## Resistance to ICB Therapy

Patients receiving ICIs as monotherapy can develop primary resistance, and thus never respond to ICIs, or acquire resistance and subsequently develop disease progression after an initial response. While there are numerous mechanisms underlying the resistance to ICB, they are broadly dichotomized into tumor-intrinsic or tumor-extrinsic factors. Tumor-intrinsic mechanisms include the loss of neoantigens, especially in low-tumor mutational burden disease, aberrations in cell signaling and metabolic pathways, loss of major histocompatibility complex (MHC) I expression resulting in decreased antigen presentation, and epigenetic gene silencing through DNA demethylation and histone deacetylation. Tumor-extrinsic mechanisms encompass factors such as a decrease in immune cell infiltration in the tumor microenvironment (TME), compensatory upregulation of other immune checkpoint molecules, epithelial-mesenchymal transition, and aberration in angiogenesis. For further reading, Alsaafeen et al provide a comprehensive discussion of the mechanisms of resistance to ICB.[11]

## Radiation to Enhance the Efficacy of ICB

Aside from directly eliminating cancer cells, EBRT also possesses immunomodulatory effects. A key mechanism of such immunomodulation is the activation of type I interferon (IFN1) response through the cyclic GMP-AMP (cGAMP) synthase and stimulator of interferon genes (cGAS-STING) pathway.[12-15] This results in the production of IFNβ, which promotes the activation of dendritic cells and tumor antigen-presenting cells, leading to T-cell activation and an antitumor immune response.[15,16] In preclinical models, EBRT-induced IFN1 responses have been shown to convert immunologically "cold" tumors, lacking immune cell infiltration into the TME, into immunologically "hot" tumors.[17,18] This shift subsequently boosts the immune response that can be further potentiated by cytokines secreted by irradiated tumor cells.[15,19] Additionally, post-RT immune modulation activates CD8+ T cells, increasing the number of stem-like CD8+ T cells, which become terminally differentiated effector cells responsible for tumor destruction. Tumor-draining lymph nodes (LNs) serve as reservoirs for these stem-like CD8+ T cells, facilitating their expansion and migration to the tumor. Interestingly, targeting both the LN and tumor with RT reduces the abscopal effect and decreases the number of tumor-specific and stem-like CD8+ T cells, highlighting the important role of LNs in mediating the abscopal response.[20] RT also induces the release of exosomes from tumor cells capable of stimulating dendritic cell maturation and promoting natural killer (NK) cell infiltration into the TME. This immune activation significantly delays tumor growth, with NK cells producing IFNγ as a key mediator of such antitumor response. The subsequent depletion of NK cells abolishes this effect, underscoring their pivotal role in the immune response.[21] As such, the aforementioned immunostimulatory effects of EBRT can be exploited to enhance suboptimal clinical efficacy of ICIs.

## Combining EBRT With ICIs in Cancer Treatment: Rationale and Preclinical Data

The combination of EBRT and ICIs represents a promising frontier in cancer treatment, with the capacity to enhance patient outcomes through synergistic mechanisms. This dual approach leverages radiation's ability to enhance tumor immunogenicity by triggering the release of tumor antigens and damage-associated molecular patterns, such as calreticulin and high mobility group box 1 (HMGB1).[22] These effects can create an "in situ vaccine," effectively priming immune cells to recognize and attack the tumor, thereby enhancing the overall immune response.[23] EBRT also increases the expression of tumor-associated antigens and MHC molecules, further making tumors more susceptible to immune recognition

and eradication.[24] Radiation also induces the expression by the tumor of neoantigens, stimulating the expansion of CD8+ T cells, potentially contributing to an abscopal response.[25] This combination approach has also been found to increase the infiltration of cytotoxic T lymphocytes into the TME and the release of proinflammatory cytokines, potentiating the immune response.[26-29] **Figure 1** summarizes the potential synergistic interactions between radiation delivered by EBRT and ICIs.

Several preclinical studies have explored the potential of combining EBRT with ICIs. Verbrugge et al demonstrated that concurrent radiation and PD-1 blockade enhanced the curative effects of radiation in a murine breast cancer model.[30] Sharabi and colleagues showed that SBRT, given 1 day prior to PD-1 blockade, enhanced the antitumor immune response and led to the formation of memory T cells through cross-presentation of tumor antigens.[31] Furthermore, Friedman et al showed that response to SBRT can be augmented by concurrent treatment with anti-PD-1.[32]

Despite the promising results of combining RT with ICB, determining the optimal approach for this combination remains an area of active research. Key factors such as radiation dose, fractionation schemes, and treatment sequencing continue to be explored to maximize the therapeutic benefits.[33]

## Clinical Trials Investigating the Combination of EBRT and ICIs

Combining EBRT with ICIs has emerged as a promising approach to enhance antitumor immune responses and improve patient outcomes across multiple cancer types as shown in **Table 1**. Herein, we focus our discussion mostly on phase III trials.

### Non-Small Cell Lung Cancer (NSCLC)

The PACIFIC trial remains the cornerstone study for combining immunotherapy with EBRT in NSCLC.[48] This phase III trial showed that compared with placebo, durvalumab, administered sequentially 1 to 42 days after chemoradiotherapy (CRT) significantly improved progression-free survival (PFS) (median: 16.9 vs 5.6 mo) and overall survival (OS) (median: 47.5 vs 29.1 mo) in patients with unresectable stage III NSCLC.[34] Thus, it cemented the role of durvalumab in the management of unresectable stage III NSCLC.

Considering the success of the PACIFIC trial, the PACIFIC 2 phase III trial evaluated the concurrent administration of durvalumab vs placebo with CRT followed by consolidation with durvalumab or placebo in patients with unresectable stage III NSCLC.[49] Unfortunately, no statistically significant improvement in the PFS (HR, .85; 95% CI: .65-1.12; $P$ = .247) or OS (HR, 1.03; 95% CI: .78-1.39; $P$ = .823) was noted.[35] The observed difference between the outcomes of the PACIFIC and PACIFIC 2 trials highlights the crucial role of the sequencing of the combination and suggests that with standard fractionation, sequential combination of durvalumab with CRT in patients with unresectable stage III NSCLC may be superior to a concurrent administration.

With respect to ablative radiation dose regimen, in the metastatic setting the PEMBRO-RT phase II trial reported a doubling of the objective response rate (ORR) with pembrolizumab administered after SBRT (24 Gy in 3 fractions), 36% compared with 18% with pembrolizumab alone. Although trends toward improvement of the median PFS (6.6 vs 1.6 mo) and median OS (15.9 vs 7.6 mo) were noted with pembrolizumab plus SBRT, these were not statistically significant due to the small sample size of the study cohort.[36] In early stage disease, a randomized phase II trial (I-SABR) by Chang et al demonstrated a significant improvement of the 4-year event-free survival with the combination of stereotactic-ablative radiation therapy (SABR) and 4 cycles of nivolumab (77%) compared with SABR alone (53%).[37]

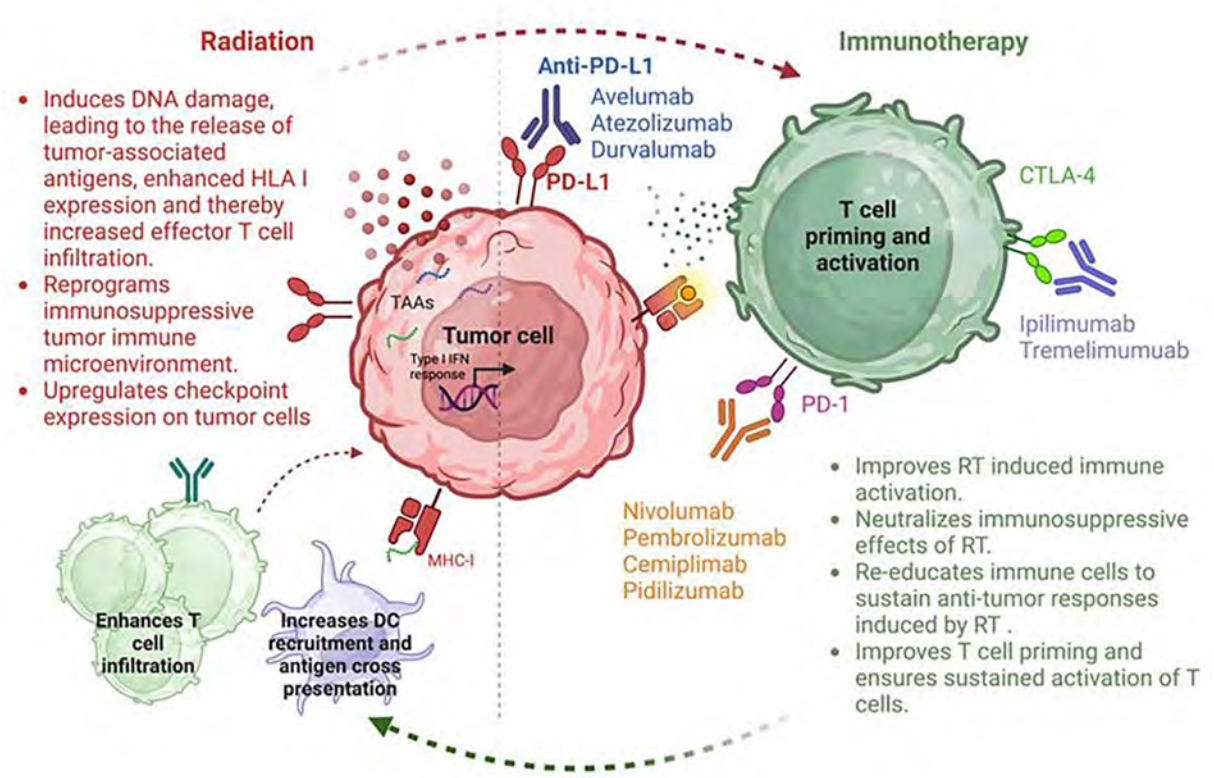
### Small Cell Lung Cancer (SCLC)

The STIMULI phase II trial evaluated the consolidation immunotherapy with ipilimumab and nivolumab compared with observation after CRT in limited-stage (LS) SCLC. No improvement in the PFS was noted, and high toxicity rates dampened the efficacy of this therapeutic combination.[38] The ADRIATIC phase III trial randomized patients with LS SCLC to receive after CRT durvalumab alone, durvalumab plus tremelimumab, or placebo. Interim results revealed that adjuvant durvalumab led to a significant improvement of OS compared with placebo (median OS: 55.9 mo, 95% CI: 37.3-not reached; vs 33.4 mo, 95% CI: 25.5-39.9; HR: .73, 98% CI: .54-.98; $P$ = .01). Although the rates of grade 3 or 4 toxicities were similar in patients receiving durvalumab or placebo, 24.4% and 24.2%, respectively, treatment stoppage was higher in the durvalumab arm (16.4%) compared with the placebo group (10.6%).[39]

### Head and Neck Squamous Cell Carcinoma (HNSCC)

Multiple phase III trials have evaluated the effects of various combination sequences of ICIs with EBRT on locally advanced (LA) HNSCC. JAVELIN Head &

**Figure 1.** Synergistic effects between radiation therapy (RT) and immunotherapy (IT) in improving tumor control. Red arrows highlight the mechanisms by which RT enhances the immune response facilitated by IT, while green arrows depict how IT strengthens the therapeutic outcomes of RT.




Neck 100 evaluated avelumab in combination with CRT (70 Gy/35 fractions with high-dose cisplatin) in LA-HNSCC compared with CRT alone. Patients in the experimental group were administered a loading dose of avelumab, followed by a concurrent administration with CRT and a maintenance dose. No difference in PFS and OS was noted between CRT alone and CRT in combination with avelumab.[40]

The IMvoke010 trial evaluated adjuvant atezolizumab vs placebo in patients with LA-HNSCC who underwent multimodal definitive treatment, including surgery or CRT. Interim analysis revealed no improvement in event-free survival and OS with adjuvant atezolizumab.[41] Nevertheless, we are still awaiting the results of the ECOG ACRIN EA3161, which is evaluating adjuvant nivolumab after CRT in patients with LA intermediate-risk HPV-positive oropharyngeal carcinoma.[42] In the metastatic setting, McBride et al evaluated during a phase II randomized trial the ORR of nivolumab plus SBRT (27 Gy in 3 fractions) compared with SBRT alone. The addition of nivolumab to SBRT did not improve the ORR or led to an abscopal effect.[50] For a more comprehensive review of clinical trials investigating the combination of ICIs with EBRT, the readers are referred to existing publication.[51]

## Esophageal Cancers

The phase II/III trial ECOG-ACRIN Cancer Research Group (EA2174) is currently evaluating perioperative nivolumab and ipilimumab in patients with locoregional esophageal and gastroesophageal junction adenocarcinoma. Surgical candidates are administered CRT with or without nivolumab. Following surgical resection, disease-free patients receive nivolumab alone or in combination with ipilimumab.[43]

KEYNOTE-975 is a phase II trial evaluating the safety and efficacy of pembrolizumab in combination with definitive CRT in patients with unresectable esophageal carcinoma.[44] The results from these trials will shed light on the potential role of ICIs in the management of resectable and unresectable esophageal cancers.

## Genitourinary Cancers

In prostate cancer, a phase III trial by Kwon et al assessed

**Table 1. Selected Clinical Trials Evaluating Radiation Therapy Combined With Immune Checkpoint Blockade in Cancer**

| CANCER TYPE | TRIAL IDENTIFIER | PHASE | DISEASE STAGE | RT TYPE | RT DOSE/ FRACTIONATION | COMBINATION IMMUNOTHERAPY | IMMUNOTHERAPY DOSE | TIMING | TRIAL STATUS/ RESULT | REFERENCE |
|---|---|---|---|---|---|---|---|---|---|---|
| NSCLC | NCT02434081 (PACIFIC trial) | III | Stage III NSCLC | EBRT | 60-66 Gy in 30-33 fractions | Durvalumab | 10 mg/kg every 2 wk | Sequential | Completed; improved PFS and OS | 34 |
| | NCT02788404 (PACIFIC 2 trial) | III | Stage III NSCLC | EBRT | 60-66 Gy in 30-33 fractions | Durvalumab | 1500 mg every 4 wk | Concurrent | Completed; no improvement in PFS and OS | 35 |
| | NCT02492568 (Pembro-RT) | II | Metastatic NSCLC | SBRT | 27 Gy in 3 fractions | Pembrolizumab | 200 mg/kg every 3 wk | Sequential | Completed; trend toward improved PFS and OS | 36 |
| | NCT03110978 | II | Early stage NSCLC | SABR | 50 Gy in 4 fractions or 70 Gy in 10 fractions | Nivolumab | 480 mg every 4 wk | Concurrent | Completed; significantly improved 4-y event-free survival | 37 |
| SCLC | NCT02046733 (STIMULI trial) | II | Limited-stage SCLC | EBRT | Recommended: 45 Gy twice daily<br>Allowed: 56 Gy once daily | Nivolumab + ipilimumab | Nivolumab (1 mg/kg) + ipilimumab (3 mg/kg) every 3 wk→ nivolumab (240 mg) every 2 wk | Sequential | Completed; no improvement in PFS | 38 |
| | NCT03703297 (ADRIATIC trial) | III | Limited-stage SCLC | EBRT | 60-66 Gy once daily or 45 Gy twice daily | Durvalumab alone or in combination with tremelimumab | Durvalumab alone (1500 mg) every 4 wk or<br>durvalumab (1500 mg)+ tremelimumab (75 mg) every 4 wk | Sequential | Ongoing; interim results: improvement of OS with durvalumab | 39 |
| Head and neck cancer | NCT02952586 (JAVELIN Head & Neck 100) | III | Locally advanced HNSCC | EBRT | 70 Gy in 35 fractions | Avelumab | 10 mg/kg every 2 wk | Sequential | Completed; no PFS and OS improvement | 40 |
| | NCT03452137 (IMvoke010 trial) | III | High-risk locally advanced HNSCC | EBRT | Definitive treatment (surgery or CRT) | Atezolizumab | 1200 mg every 3 wk | Sequential | Terminated; no event-free survival (EFS) or OS improvement | 41 |

**Table 1. continued**

| CANCER TYPE | TRIAL IDENTIFIER | PHASE | DISEASE STAGE | RT TYPE | RT DOSE/ FRACTIONATION | COMBINATION IMMUNOTHERAPY | IMMUNOTHERAPY DOSE | TIMING | TRIAL STATUS/ RESULT | REFERENCE |
|---|---|---|---|---|---|---|---|---|---|---|
| NCT03811015(ECOG ACRIN EA3161) | II/III | Locally advanced Human papilloma virus (HPV) + oropharyngeal carcinoma | EBRT | 70 Gy in 35 fractions | Nivolumab | Every 4 wk | Sequential | Ongoing | 42 | |
| Gastrointestinal (GI) cancers | NCT03604991 (ECOG-ACRIN EA2174) | II/III | Locoregional esophageal and gastroesophageal junction (GEJ) adenocarcinoma | EBRT | 41.4-50.4 Gy in 1.8 Gy /fraction | Nivolumab + ipilimumab | ---- | Perioperative | Ongoing | 43 |
| | NCT04210115 (KEYNOTE-975) | III | Unresectable esophageal carcinoma | EBRT | 50 or 60 Gy | Pembrolizumab | 200 mg every 3 wk (8 cycles) → 400 mg every 6 wk (5 cycles) | Concurrent→ adjuvant | Ongoing | 44 |
| Genitourinary (GU) cancers | NCT00861614 | III | Metastatic castration-resistant prostate cancer | EBRT | 8 Gy in one fraction | Ipilimumab | 10 mg/kg | Sequential | Completed; no statistically significant OS but survival benefit for patients with favorable prognostic factors (no visceral mets or anemia) | 45 |
| | NCT04241185 (KEYNOTE-992) | III | Muscle-invasive bladder | EBRT | 64 Gy in 2 Gy/ fraction or 55 Gy in 2.75 Gy/ fraction | Pembrolizumab | 400 mg every 6 wk | Concurrent→ adjuvant | Ongoing | 46 |
| Cervical cancers | NCT04221945 (ENGOT-cx11/GOG-3047/ KEYNOTE-A18) | III | High-risk locally advanced cervical cancer | EBRT ±bracytherapy | Median total cervix dose 76 Gy (median total $EQD_{2Gy}$: 87 Gy) | Pembrolizumab | 200 mg every 3 wk + CRT → 400 mg every 6 wk (15 cycles) | Concurrent → adjuvant | Improvement of PFS | 47 |

*Abbreviations: CRT, chemoradiotherapy; EBRT, external beam radiation therapy; EFS, event-free survival; HNSCC, head and neck squamous cell carcinoma; HPV, human papillomavirus; GEJ, gastroesophageal junction; GEJ, gastroesophageal junction; GI, gastrointestinal; GU, genitourinary; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival; RT, radiation therapy; SABR, stereotactic ablative body radiation therapy; SCLC, small cell lung cancer; SBRT, stereotactic body radiation therapy.*

ipilimumab following palliative radiation of 8 Gy in one fraction to a bone metastasis in patients with metastatic castration-resistant prostate cancer. While the OS benefit was not statistically significant, subgroup analyses highlighted a survival advantage in patients with favorable prognostic factors such as the absence of visceral metastases, normal to slight elevation in alkaline phosphatase and without anemia.[45] This study emphasized the importance of patient selection. For muscle-invasive bladder cancer, the phase III trial KEYNOTE-992 is currently ongoing and randomizes patients seeking bladder preservation to concurrent and adjuvant pembrolizumab plus CRT vs placebo plus CRT.[46]

### Cervical Cancer

ENGOT-cx11/GOG-3047/KEYNOTE-A18 is a phase III trial that evaluated concurrent and adjuvant pembrolizumab plus CRT vs placebo plus CRT in patients with high-risk LA cervical cancer. After a median follow-up of 17.9 months, the addition of pembrolizumab to CRT yielded a significant PFS improvement.[47]

### Other Cancers

In a phase II trial, a single fraction of 8 Gy in combination with pembrolizumab showed early response in relapsed multiple myeloma, with 32% of patients experiencing clinical benefit at 3 months. An abscopal response was reported in 20% of all patients, including 3 out of the 7 patients previously treated with CAR T-cell therapy.[52] Multiple phase III trials have evaluated the combination of CRT with temozolomide plus nivolumab in glioblastoma with methylated or unmethylated methylguanine-DNA methyltransferase. However, no improvement in survival was observed.[53,54]

## Limitations and Challenges of Combination Therapy

Combining EBRT with ICIs presents substantial therapeutic potential but also creates significant limitations and challenges. One major hurdle is the immunosuppressive effects of RT. These effects include the activation of regulatory T cells, recruitment of tumor-associated macrophages, and release of immunosuppressive cytokines such as TGF-ß, which collectively reduce the infiltration and activity of cytotoxic T cells within the TME.[55] These mechanisms can undermine the clinical efficacy of ICIs. Determining optimal dosing and sequencing strategies is another significant challenge. High radiation doses can potentially be immunosuppressive, while suboptimal doses may fail to induce sufficient tumor cell death or antigen release necessary to prime the immune system.[56] The timing of radiation relative to ICIs is also critical. While administering ICIs after radiation can leverage radiation-induced immune activation, the concurrent administration may abrogate the immune system activation and increase the risk of systemic toxicities, including overlapping immune-related adverse events.[57] Emerging data also suggest that elective nodal irradiation targeting tumor-draining LNs may interfere with the potential synergism that may ensue from the combination of EBRT with ICIs.[58,59] Thus, lymphatic sparing radiation may be an effective strategy to enhance the synergism between EBRT and ICIs.

## Conclusion

The combination of EBRT and immunotherapy has shown considerable potential in improving treatment outcomes across various cancer types. This approach results in enhanced clinical outcomes, including prolonged OS and PFS. However, various challenges persist. Optimizing the radiation dose, field, combination sequence, and timing will be critical for maximizing the potential of EBRT and ICI combinations. Nevertheless, results from current phase III trials are likely to clarify the synergistic relationship between EBRT and ICIs.

## References

1) Jaffray DA, Gospodarowicz MK. Radiation therapy for cancer. In: Gelband H, Jha P, Sankaranarayanan R, Horton S, eds. *Cancer: Disease Control Priorities*. 3rd ed. Vol. 3. The International Bank for Reconstruction and Development / The World Bank. 2015. http://www.ncbi.nlm.nih.gov/books/NBK343621/

2) Jackson SP, Bartek J. The DNA-damage response in human biology and disease. *Nature*. 2009;461(7267):1071-1078. doi:10.1038/nature08467

3) Bernier J, Hall EJ, Giaccia A. Radiation oncology: a century of achievements. *Nat Rev Cancer*. 2004;4(9):737-747. doi:10.1038/nrc1451

4) Pereira GC, Traughber M, Muzic RF. The role of imaging in radiation therapy planning: past, present, and future. *Biomed Res Int*. 2014;2014(1):231090):231090:. doi:10.1155/2014/231090

5) Koka K, Verma A, Dwarakanath BS, Papineni RVL. Technological advancements in External Beam Radiation Therapy (EBRT): an indispensable tool for cancer treatment. *Cancer Manag Res*. 2022;14:1421-1429. doi:10.2147/CMAR.S351744

6) Alongi F, Arcangeli S, Filippi AR, Ricardi U, Scorsetti M. Review and uses of stereotactic body radiation therapy for oligometastases. *Oncologist*. 2012;17(8):1100):1100-1107:. doi:10.1634/theoncologist.2012-0092

7) Robert C. A decade of immune-checkpoint inhibitors in cancer therapy. *Nat Commun*. 2020;11(1):3801. doi:10.1038/s41467-020-17670-y

8) Topalian SL, Drake CG, Pardoll DM. Immune checkpoint blockade: a common denominator approach to cancer therapy. *Cancer Cell*. 2015;27(4):450-461. doi:10.1016/j.ccell.2015.03.001

9) Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. *Nat Rev Cancer*. 2012;12(4):252-264. doi:10.1038/nrc3239

10) Huang Q, Zheng Y, Gao Z, et al. Comparative efficacy and safety of PD-1/PD-L1 inhibitors for patients with solid tumors: a systematic review and bayesian network meta-analysis. *J Cancer*. 2021;12(4):1133-1143. doi:10.7150/jca.49325

11) Alsaafeen BH, Ali BR, Elkord E. Resistance mechanisms to immune checkpoint inhibitors: updated insights. *Mol Cancer*. 2025;24(1):20. doi:10.1186/s12943-024-02212-7

12) Gan Y, Li X, Han S, et al. The cGAS/STING pathway: a novel target for cancer therapy. *Front Immunol*. 2021;12:795401. doi:10.3389/fimmu.2021.795401

13) Zhang F, Manna S, Pop LM, et al. Type I interferon response in radiation-induced anti-tumor immunity. *Semin Radiat Oncol*. 2020;30(2):129-138. doi:10.1016/j.semradonc.2019.12.009

14) Deng L, Liang H, Xu M, et al. STING-dependent cytosolic DNA sensing promotes radiation-induced type I interferon-dependent antitumor immunity in immunogenic tumors. *Immunity*. 2014;41(5):843-852. doi:10.1016/j.immuni.2014.10.019

15) Burnette BC, Liang H, Lee Y, et al. The efficacy of radiotherapy relies upon induction of type I interferon-dependent innate and adaptive immunity. *Cancer Res*. 2011;71(7):2488-2496. doi:10.1158/0008-5472.CAN-10-2820

16) Woo S-R, Fuertes MB, Corrales L, et al. STING-dependent cytosolic DNA sensing mediates innate immune recognition of immunogenic tumors. *Immunity*. 2014;41(5):830-842. doi:10.1016/j.immuni.2014.10.017

17) Manda K, Glasow A, Paape D, Hildebrandt G. Effects of ionizing radiation on the immune system with special emphasis on the interaction of dendritic and T cells. *Front Oncol*. 2012;2:102. doi:10.3389/fonc.2012.00102

18) Jagodinsky JC, Jin WJ, Bates AM, et al. Temporal analysis of type 1 interferon activation in tumor cells following external beam radiotherapy or targeted radionuclide therapy. *Theranostics*. 2021;11(13):6120-6137. doi:10.7150/thno.54881

19) Du M, Chen ZJ. DNA-induced liquid phase condensation of cgas activates innate immune signaling. *Science*. 2018;361(6403):704-709. doi:10.1126/science.aat1022

20) Buchwald ZS, Nasti TH, Lee J, et al. Tumor-draining lymph node is important for a robust abscopal effect stimulated by radiotherapy. *J Immunother Cancer*. 2020;8(2):e000867. doi:10.1136/jitc-2020-000867

21) Jella KK, Nasti TH, Li Z, et al. Exosome-containing preparations from postirradiated mouse melanoma cells delay melanoma growth in vivo by a natural killer cell-dependent mechanism. *Int J Radiat Oncol Biol Phys*. 2020;108(1):104-114. doi:10.1016/j.ijrobp.2020.06.016

22) Apetoh L, Ghiringhelli F, Tesniere A, et al. Toll-like receptor 4-dependent contribution of the immune system to anticancer chemotherapy and radiotherapy. *Nat Med*. 2007;13(9):1050-1059. doi:10.1038/nm1622

23) Chen DS, Mellman I. Oncology meets immunology: the cancer-immunity cycle. *Immunity*. 2013;39(1):1-10. doi:10.1016/j.immuni.2013.07.012

24) Reits EA, Hodge JW, Herberts CA, et al. Radiation modulates the peptide repertoire, enhances MHC class I expression, and induces successful antitumor immunotherapy. *J Exp Med*. 2006;203(5):1259-1271. doi:10.1084/jem.20052494

25) Formenti SC, Rudqvist N-P, Golden E, et al. Radiotherapy induces responses of lung cancer to CTLA-4 blockade. *Nat Med*. 2018;24(12):1845-1851. doi:10.1038/s41591-018-0232-2

26) Garnett CT, Palena C, Chakraborty M, et al. Sublethal irradiation of human tumor cells modulates phenotype resulting in enhanced killing by cytotoxic T lymphocytes. *Cancer Res*. 2004;64(21):7985-7994. doi:10.1158/0008-5472.CAN-04-1525

27) Kwilas AR, Donahue RN, Bernstein MB, Hodge JW. In the field: exploiting the untapped potential of immunogenic modulation by radiation in combination with immunotherapy for the treatment of cancer. *Front Oncol*. 2012;2:104. doi:10.3389/fonc.2012.00104

28) Liu S, Ren J, Ten Dijke P. Targeting TGFβ signal transduction for cancer therapy. *Signal Transduct Target Ther*. 2021;6(1):8. doi:10.1038/s41392-020-00436-9

29) Lhuillier C, Rudqvist NP, Elemento O, Formenti SC, Demaria S. Radiation therapy and anti-tumor immunity: exposing immunogenic mutations to the immune system. *Genome Med*. 2019;11(1):40. doi:10.1186/s13073-019-0653-7

30) Verbrugge I, Hagekyriakou J, Sharp LL, et al. Radiotherapy increases the permissiveness of established mammary tumors to rejection by immunomodulatory antibodies. *Cancer Res*. 2012;72(13):3163-3174. doi:10.1158/0008-5472.CAN-12-0210

31) Sharabi AB, Nirschl CJ, Kochel CM, et al. Stereotactic radiation therapy augments antigen-specific PD-1-mediated antitumor immune responses via cross-presentation of tumor antigen. *Cancer Immunol Res*. 2015;3(4):345-355. doi:10.1158/2326-6066.CIR-14-0196

32) Friedman D, Baird JR, Young KH, et al. Programmed cell death-1 blockade enhances response to stereotactic radiation in an orthotopic murine model of hepatocellular carcinoma. *Hepatol Res*. 2017;47(7):702-714. doi:10.1111/hepr.12789

33) Wang Y, Deng W, Li N, et al. Combining immunotherapy and radiotherapy for cancer treatment: current challenges and future directions. *Front Pharmacol*. 2018;9:185. doi:10.3389/fphar.2018.00185

34) Spigel DR, Faivre-Finn C, Gray JE, et al. Five-year survival outcomes from the PACIFIC trial: durvalumab after chemoradiotherapy in stage III non-small-cell lung cancer. *J Clin Oncol*. 2022;40(12):1301-1311. doi:10.1200/JCO.21.01308

35) Bradley JD, Sugawara S, Lee KHH, et al. LBA1 durvalumab in combination with chemoradiotherapy for patients with unresectable stage III NSCLC: final results from PACIFIC-2. *ESMO Open*. 2024;9:102986. doi:10.1016/j.esmoop.2024.102986

36) Theelen WSME, Peulen HMU, Lalezari F, et al. Effect of pembrolizumab after stereotactic body radiotherapy vs pembrolizumab alone on tumor response in patients with advanced non-small cell lung cancer: results of the PEMBRO-RT phase 2 randomized clinical trial. *JAMA Oncol*. 2019;5(9):1276-1282. doi:10.1001/jamaoncol.2019.1478

37) Chang JY, Lin SH, Dong W, et al. Stereotactic ablative radiotherapy with or without immunotherapy for early-stage or isolated lung parenchymal recurrent node-negative non-small-cell lung cancer: an open-label, randomised, phase 2 trial. *Lancet*. 2023;402(10405):871-881. doi:10.1016/S0140-6736(23)01384-3

38) Peters S, Pujol J-L, Dafni U, et al. Consolidation nivolumab and ipilimumab versus observation in limited-disease small-cell lung cancer after chemo-radiotherapy - results from the randomised phase II ETOP/IFCT 4-12 STIMULI trial. *Ann Oncol*. 2022;33(1):67-79. doi:10.1016/j.annonc.2021.09.011

39) Cheng Y, Spigel DR, Cho BC, et al. Durvalumab after chemoradiotherapy in limited-stage small-cell lung cancer. *N Engl J Med*. 2024;391(14):1313-1327. doi:10.1056/NEJMoa2404873

40) Lee NY, Ferris RL, Psyrri A, et al. Avelumab plus standard-of-care chemoradiotherapy versus chemoradiotherapy alone in patients with locally advanced squamous cell carcinoma of the head and neck: a randomised, double-blind, placebo-controlled, multicentre, phase 3 trial. *Lancet Oncol*. 2021;22(4):450-462. doi:10.1016/S1470-2045(20)30737-3

41) Wong DJ, Fayette J, Teixeira M, et al. Abstract CT009: imvoke010: a phase III, double-blind randomized trial of atezolizumab (atezo) after definitive local therapy vs placebo in patients (pts) with high-risk locally advanced (LA) squamous cell carcinoma of the head and neck (SCCHN). *Cancer Res*. 2024;84(7_supplement):CT009. doi:10.1158/1538-7445.AM2024-CT009

42) Saba NF, Li S, Hussain ZA, et al. Locally advanced high-risk HPV related oropharyngeal squamous cell carcinoma (OPSCC); have we forgotten it is a different disease? *Cancers Head Neck*. 2018;3:8. doi:10.1186/s41199-018-0035-7

43) Eads JR, Weitz M, Gibson MK, et al. A phase II/III study of perioperative nivolumab and ipilimumab in patients (pts) with locoregional esophageal (E) and gastroesophageal junction (GEJ) adenocarcinoma: A trial of the ECOG-ACRIN cancer research group (EA2174). *JCO*. 2020;38(15_suppl):TPS4651. doi:10.1200/JCO.2020.38.15_suppl.TPS4651

44) Shah MA, Bennouna J, Doi T, et al. KEYNOTE-975 study design: a phase III study of definitive chemoradiotherapy plus pembrolizumab in patients with esophageal carcinoma. *Future Oncol*. 2021;17(10):1143-1153. doi:10.2217/fon-2020-0969

45) Kwon ED, Drake CG, Scher HI, et al. Ipilimumab versus placebo after radiotherapy in patients with metastatic castration-resistant prostate cancer that had progressed after docetaxel chemotherapy (CA184-043): a multicentre, randomised, double-blind, phase 3 trial. *Lancet Oncol*. 2014;15(7):700-712. doi:10.1016/S1470-2045(14)70189-5

46) Gupta S, Fujii Y, Van Der Heijden MS, et al. Phase 3 KEYNOTE-992 study of pembrolizumab plus chemoradiotherapy versus placebo plus chemoradiotherapy in patients with muscle-invasive bladder cancer (MIBC). *JCO*. 2024;42(4_suppl):TPS720. doi:10.1200/JCO.2024.42.4_suppl.TPS720

47) Lorusso D, Xiang Y, Hasegawa K, et al. Pembrolizumab or placebo with chemoradiotherapy followed by pembrolizumab or placebo for newly diagnosed, high-risk, locally advanced cervical cancer (ENGOT-cx11/GOG-3047/KEYNOTE-A18): a randomised, double-blind, phase 3 clinical trial. *Lancet*. 2024;403(10434):1341-1350. doi:10.1016/S0140-6736(24)00317-9

48) Antonia SJ, Villegas A, Daniel D, et al. Durvalumab after chemoradiotherapy in stage III non-small-cell lung cancer. *N Engl J Med*. 2017;377(20):1919-1929. doi:10.1056/NEJMoa1709937

49) Bradley JD, Nishio M, Okamoto I, et al. PACIFIC-2: phase 3 study of concurrent durvalumab and platinum-based chemoradiotherapy in patients with unresectable, stage III NSCLC. *JCO*. 2019;37(15_suppl):TPS8573. doi:10.1200/JCO.2019.37.15_suppl.TPS8573

50) McBride S, Sherman E, Tsai CJ, et al. Randomized phase II trial of nivolumab with stereotactic body radiotherapy versus nivolumab alone in metastatic head and neck squamous cell carcinoma. *J Clin Oncol*. 2021;39(1):30-37. doi:10.1200/JCO.20.00290

51) Sodji QH, Nambiar DK, Le QT. Translational and clinical approach to combining immunotherapy with radiotherapy in the treatment of head and neck cancer. In: Chan ATC, Ma BBY, eds. *Immunotherapy for Head and Neck Cancer*. Springer Nature Switzerland. 2023:83-99. doi:10.1007/13905_2022_31

52) Khan MK, Nasti TH, Qian JY, et al. Pembrolizumab and low-dose, single-fraction radiotherapy for patients with relapsed or refractory multiple myeloma: a prospective, single-centre, single-group, open-label, phase 2 pilot trial in the USA. *Lancet Haematol*. 2024;11(7):e510-e520. doi:10.1016/S2352-3026(24)00105-4

53) Lim M, Weller M, Idbaih A, et al. Phase III trial of chemoradiotherapy with temozolomide plus nivolumab or placebo for newly diagnosed glioblastoma with methylated MGMT promoter. *Neuro Oncol*. 2022;24(11):1935-1949. doi:10.1093/neuonc/noac116

54) Omuro A, Brandes AA, Carpentier AF, et al. Radiotherapy combined with nivolumab or temozolomide for newly diagnosed glioblastoma with unmethylated MGMT promoter: an international randomized phase III trial. *Neuro Oncol*. 2023;25(1):123-134. doi:10.1093/neuonc/noac099

55) Formenti SC, Demaria S. Systemic effects of local radiotherapy. *Lancet Oncol*. 2009;10(7):718-726. doi:10.1016/S1470-2045(09)70082-8

56) Lumniczky K, Impens N, Armengol G, et al. Low dose ionizing radiation effects on the immune system. *Environ Int*. 2021;149:106212. doi:10.1016/j.envint.2020.106212

57) Aliru ML, Schoenhals JE, Venkatesulu BP, et al. Radiation therapy and immunotherapy: what is the optimal timing or sequencing? *Immunotherapy*. 2018;10(4):299):299-316:. doi:10.2217/imt-2017-0082

58) Marciscano AE, Ghasemzadeh A, Nirschl TR, et al. Elective nodal irradiation attenuates the combinatorial efficacy of stereotactic radiation therapy and immunotherapy. *Clin Cancer Res*. 2018;24(20):5058-5071. doi:10.1158/1078-0432.CCR-17-3427

59) Darragh LB, Gadwa J, Pham TT, et al. Elective nodal irradiation mitigates local and systemic immunity generated by combination radiation and immunotherapy in head and neck tumors. *Nat Commun*. 2022;13(1):7015. doi:10.1038/s41467-022-34676-w

# RefleXion X1 Treatment Planning Feasibility Study for Craniospinal Irradiation (CSI)

Tracy Ngo, CMD;[1] Daniel Pham, PhD, CMD;[2] Ignacio Omar Romero, PhD;[2] Eric Simiele, PhD;[2,3] Bin Han, PhD;[2] Murat Surucu, PhD;[2] Iris Gibbs, MD;[2] Susan Hiniker, MD;[2] Nataliya Kovalchuk, PhD[2]*

## Abstract

**Objective:** The first clinical biology-guided radiation therapy system, RefleXion X1, was commissioned for clinical use at our institution. This study evaluates the X1 treatment planning feasibility of complex craniospinal targets for pediatric medulloblastoma patients and compares plan quality to multi-isocenter linac-based Volumetric Modulated Arc Therapy (VMAT) plans.

**Methods:** Five pediatric patients treated with multi-isocenter VMAT craniospinal irradiation (CSI) were selected for this retrospective study. All planning target volumes (PTVs) had a craniocaudal length < 50 cm and received 36 Gy in 20 fractions. The target volumes and organs-at-risk (OARs) used for VMAT plans were utilized to generate plans using RefleXion X1. PTV D2%, OARs $D_{mean}$ and $D_{max}$, and treatment times were collected for analysis. A paired-sample *t*-test was performed to detect significance at $P < 0.05$.

**Results:** All 5 X1 CSI plans were successfully generated and deemed clinically acceptable for treatment. PTV D2% was found to be greater for X1 compared with VMAT plans ($P = .08$). For the X1 plans, the $D_{mean}$ to the bowel, cochleas, heart, kidneys, lungs, and oral cavity was not found to be statistically significant ($P > .05$) compared with VMAT plans. The average treatment beam-on time for X1 plans was 16.7 minutes vs 3.6 minutes for VMAT plans ($P < .01$). However, the RefleXion X1 platform enables one isocenter treatment and 90-cm-long kilovoltage CT scan, which has the potential to reduce the setup/imaging time, and thus the total treatment time compared with multi-isocenter linac-based VMAT, where the total treatment time of up to 43.5 minutes was observed.

**Conclusion:** Apart from a greater maximum dose to PTV, X1 plans showed comparable dosimetry to multi-isocenter VMAT plans. Although the average beam-on time with X1 was longer, there is a potential for a more streamlined setup and IGRT using a single isocenter plan.

**Keywords:** Cranio-spinal irradiation, VMAT CSI, RefleXion X1, pediatric CSI, treatment planning

## Introduction

Medulloblastoma is the most common childhood malignant central nervous system tumor.[1] Peak incidence occurs at age 7, with slightly greater incidence in males.[1,2] A large proportion of patients with medulloblastoma have craniospinal fluid spread at diagnosis. The standard of care for medulloblastomas involves surgical resection, craniospinal irradiation (CSI) with post fossa or surgical cavity bed boost to 54 Gy and chemotherapy.[3] For average-risk patients, the 5-year

**Affiliations:** [1]The University of Texas MD Anderson Cancer Center, School of Health Professions, Houston, TX. [2]Department of Radiation Oncology, Stanford University, Stanford, CA. [3]Department of Radiation Oncology, University of Alabama at Birmingham, Birmingham, AL.
**Corresponding author:** *Nataliya Kovalchuk, PhD, Radiation Oncology Department, Stanford University School of Medicine, 875 Blake Wilbur Dr CC G209, Stanford, CA 94305. (natkoval@stanford.edu)
**Disclosure:** The authors have no conflicts of interest to disclose. None of the authors received outside funding for the production of this original manuscript and no part of this article has been previously published elsewhere.

Published: March 1, 2025. https://doi.org/10.37549/ARO-D-24-00032

survival rate is higher than 80%, while high-risk patients have a 5-year survival rate lower than 50%.[2,4]

Craniospinal irradiation presents challenges because of its large target volume, which extends beyond the 40 cm × 40 cm field size limitation of a commonly used C-arm linear accelerator collimator opening.[5,6] The use of multiple plan isocenters overcomes this limitation by dividing the target volume into 3 fields: the whole brain, the upper spine, and the lower spine. Craniospinal irradiation is commonly performed using the 3D conformal radiation therapy technique, which is prone to errors owing to the complexity of the planning and the treatment delivery setup.[7-12] This technique results in dose inhomogeneity and nonconformity, which yields significant dose to the anterior of the spine target volume. Three-dimensional CSI also requires feathering the junctions, resulting in multiple plan pairs, gap calculation, and couch rotations, making planning and treatment complex, cumbersome, and time consuming.

Overall, Volumetric Modulated Arc Therapy (VMAT) CSI creates plans with superior dose conformality, superior dose homogeneity, greater normal tissue sparing, lower sensitivity to positioning errors, and shorter treatment time compared with 3D CSI.[13-17] While VMAT can produce clinically favorable plans even with setup errors of up to 3 mm, accurate patient alignment with minimal setup remains important. A multicenter study conducted by Gram et al[11] showed that daily image guidance with 6-DoF couch corrections was found optimal in significantly reducing positioning errors and uncertainties for patients with pediatric CSI.

While daily image guidance and 6-degrees-of-freedom couch corrections can assist in optimizing patient setup, the inherent risks for positioning errors and uncertainties cannot be eliminated for VMAT CSI owing to the use of multiple isocenters and field matching. Helical-delivery radiation treatment techniques such as Tomotherapy can reduce these risks associated with multicenter CSI treatments by using a ring-based gantry to deliver a single-field CSI treatment as the patient moves into the treatment ring.[18-20] A study by Lee et al[19] reported Tomotherapy CSI to have acceptable inter- and intra-fractional errors, and setup verification based on the measurements and evaluations of treatment setup for 83 patients. In addition, Tomotherapy CSI techniques have been demonstrated to produce highly conformal and homogeneous treatment plans compared with 3D CSI.[21-23]

RefleXion (RefleXion Medical Inc) is a novel PET/CT treatment modality that similarly utilizes a ring-based gantry for axial step-and-shoot Intensity-Modulated Radiation Therapy (IMRT) delivery. The first clinical installation of RefleXion X1 was recently conducted at our institution.[24,25] The RefleXion X1 design provides potential advantages to CSI treatments using a single isocenter that can potentially decrease the complexity of planning, image guidance, and delivery, reducing the risk of shift and localization errors. This study aims to test the feasibility of treatment planning of X1 CSI and compare the plan quality and beam-on time to the current standard of care at our institution—VMAT CSI planned in Eclipse and delivered using Trilogy or TrueBeam linear accelerator (Varian Medical Systems).

## Methods

### Patient Selection and Simulation

Of 81 patients previously treated with VMAT CSI at Stanford University from 2012 to 2022, only 5 had a planning target volume (PTV) length of less than 50 cm in the craniocaudal direction (current RefleXion X1 TPS limitation). These 5 patients were included in this retrospective treatment planning feasibility study. Patients were simulated using a Siemens CT scanner (slice thickness 2 mm) in the head-first-supine position with arms by side, immobilized in a 5-point head and neck mask and AccuForm cushion (CIVCO) in the neutral neck position. All patients were treated under anesthesia.

### VMAT CSI Planning

VMAT CSI plans were generated on Eclipse v15.6 (Varian Medical Systems) using 6 MV energy beams, a photon optimization algorithm, an analytical anisotropic algorithm dose calculation, and a calculation grid of 2.5 mm. Two full arcs were used to treat the brain and a single arc was used to treat the spine, with an overlap of at least 2 cm between the brain and spine fields. Brain and spine isocenters were placed such that there was only a longitudinal shift between them. Auto-feathering was enabled during optimization to create smooth dose gradients in the overlapping areas between fields. The spine arcs used avoidance sectors to limit the dose entering through the arms. VMAT CSI plans were normalized at 95% PTV coverage by the prescription dose of 36 Gy.

### RefleXion X1 Linear Accelerator

RefleXion X1 is the first biology-guided radiation therapy system consisting of a 6 MV flattening-filter-free (FFF) linear accelerator

mounted on the 85 cm gantry ring rotating at 60 rpm and delivering the treatment using one isocenter in axial fashion advancing the couch every 2.1 mm. Modulation is achieved using 64 binary, pneumatically driven, multi-leaf fast-transitioning collimators (MLC). Two sets of jaws, positioned above and below the MLCs, are used to set the maximum field extent in the patient superior-inferior direction: either 1 cm or 2 cm at isocenter. The X1 is also equipped with fan-beam kilovoltage CT of near-diagnostic image quality, megavoltage portal, and PET imaging subsystem.

### RefleXion X1 Planning

CT scans and structure sets used for VMAT CSI plan generation were imported to RefleXion X1 TPS for planning. The PTV_CSI target ranged between 48.1 and 49.3 cm and was the same for VMAT and X1 planning. All cases were planned on the RefleXion X1 v1.0.46 TPS using step-and-shoot IMRT technique with 6 MV FFF energy, 2 cm jaws, accelerated proximal gradient-based on FISTA and Collapsed Cone Convolution superposition dose calculation algorithm, and a calculation grid of 2.1 mm. The plan isocenter was placed in the middle of the target. As plan dose normalization was not available in RefleXion X1 v1.0.46, each plan was optimized to allow for 95% of the PTV to receive the prescription dose (36 Gy in 20 fractions).

### Plan Evaluation

Plans created in Eclipse and RefleXion X1 for each patient were evaluated for dose heterogeneity using dose to 2% of the PTV (D2%), conformity index, homogeneity index, and mean dose to critical structures.

### Plan Comparison

A paired sample *t*-test was performed to evaluate the dosimetric quantities between the Eclipse and the RefleXion X1 plans for each patient, with statistical significance defined at $P < 0.05$.

### Beam-on Time and Treatment Time Analysis

Beam-on times for Eclipse and RefleXion X1 TPS were collected and compared. The RefleXion X1 system dose rate used for the beam-on time study was 850 MU/min. Total time from imaging to end of treatment session was recorded using Aria offline review for Eclipse VMAT plans for every fifth fraction for each patient. Institutional guidelines for VMAT CSI treatment include imaging all isocenters separately using kV/kV orthogonal pairs and shifting and adjusting positioning to obtain an accurate match for each isocenter position. Cone beam CT is used for the first fraction and every fifth fraction or when alignment is problematic. After the imaging and adjustments, each isocenter position is confirmed with planar MV port added to the arc to confirm the accuracy of the shifts.

## Results

RefleXion X1 plans were successfully created for all 5 patients with pediatric medulloblastoma. **Figure 1** illustrates a comparison between axial and sagittal dose distributions between an Eclipse VMAT plan and a RefleXion X1 plan.

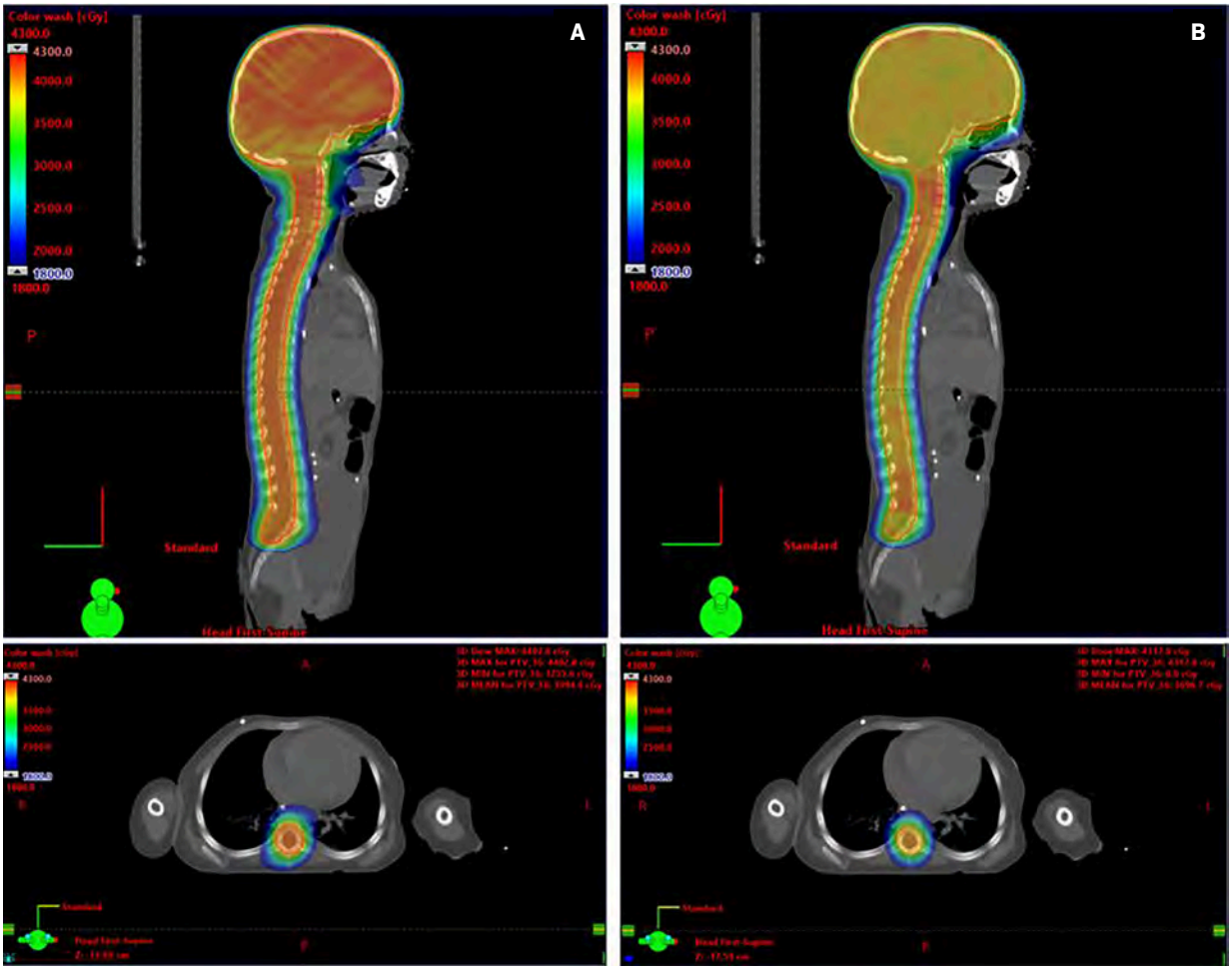
**Table 1** displays the summary of the average dosimetric indices and parameters achieved for VMAT and X1 plans. The dose to 2% of PTV (PTV D2%) was reported as 39.2 Gy for VMAT plans and 41.3 Gy for X1 plans. This difference was not found to be statistically significant ($P = .08$). The organs-at-risk (OAR) doses for the RefleXion X1 and Eclipse VMAT plans were comparable. However, all of the mean OAR doses were higher with the X1 even though the differences were not found to be statistically significant. Statistical significance was detected only for the difference in $D_{mean}$ to the bowel bag, with RefleXion X1 plans reporting a lower average $D_{mean}$ compared with Eclipse VMAT of 1.4 Gy ($P = .04$).

The average beam-on time for Eclipse VMAT and RefleXion X1 plans were 3.6 minutes and 16.7 minutes, respectively ($P < .01$). The average total treatment time from imaging to completion of treatment for Eclipse VMAT was 29.2 minutes (range 16.3-43.5 min). No average total treatment time was acquired for RefleXion X1 because no treatment was delivered using this technology.

## Discussion

To our knowledge, this is the first treatment planning study of CSI using the RefleXion X1 system. We have previously reported on treatment planning comparison between RefleXion X1 and Eclipse VMAT for 42 patients across 6 cancer sites.[26] In this study, we tested the feasibility of CSI using RefleXion X1. We have successfully generated clinically acceptable RefleXion CSI plans for 5 pediatric medulloblastoma patients with target length less than 50 cm. Dosimetric indices were comparable between the RefleXion X1 and Eclipse VMAT modalities, except for statistically significantly improved bowel sparing with RefleXion X1.

**Figure 1.** Comparison of sagittal (top) and axial (bottom) dose distributions between (A) Eclipse VMAT craniospinal irradiation (CSI) plan and (B) RefleXion X1 CSI plan. Colorwash dose threshold of 1800 cGy indicates 50% of prescription dose.




Owing to the 2 cm field size and long PTV CSI targets, the average beam-on time was approximately 4.5 times greater using RefleXion X1 compared with Eclipse VMAT. For VMAT CSI delivery using 2-isocenter plans and implemented on a Varian C-arm linear accelerator, treatment times for the first fraction from start of imaging to completion of treatment ranged widely, from 16.3 to 43.5 minutes (mean, 29.2 min), signifying challenges in separately imaging and aligning each isocenter. RefleXion X1 can overcome this challenge by imaging a long extent of the patient, localizing, and delivering the whole treatment using one isocenter in axial mode and moving the couch in the craniocaudal direction with 2.1 mm increments. This may reduce beam matching and shifting errors that could arise from multi-isocenter delivery. In addition, X1 was recently upgraded to enable a 1000 MU/min dose rate from the initial dose rate of 850 MU/min improving the beam-on time.

While no studies currently compare RefleXion CSI and VMAT CSI, literature discussing the delivery of treatment using Tomotherapy with 2.5 cm jaws in helical fashion may be useful as a comparison due to its similarity to X1. A study in 2019 by Sun et al[27] comparing VMAT, IMRT, and Tomotherapy plans found that the Tomotherapy plans offered superior PTV homogeneity, conformity, and brainstem, optic chiasm, and optic nerve sparing compared with those of VMAT plans. IMRT was superior to VMAT and Tomotherapy in terms of OAR sparing in the mid-body region (esophagus and heart). Results of this study by Sun et al differed from the results of the current RefleXion X1 study, which found difference in $D_{mean}$ to the bowel bag as the only statistically significant dosimetric parameter. However, just as the average

**Table 1. Dosimetric and Time Parameters for RefleXion X1 and Eclipse VMAT Craniospinal Irradiation Plans**

| | | | REFLEXION X1 | | | | | | | ECLIPSE VMAT | | | | | | | DIFFERENCE | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| STRUCTURE | PARAMETER | CONSTRAINT | 1 | 2 | 3 | 4 | 5 | AVERAGE | SD | 1 | 2 | 3 | 4 | 5 | AVERAGE | SD | DIFFERENCE | *P* VALUE |
| PTV_CSI | D95% (Gy) | >36 | 36.3 | 35.9 | 35.6 | 36.1 | 36.9 | 36.2 | 0.5 | 36 | 36 | 36 | 36 | 36.1 | 36 | 0 | 0.2 | .53 |
| PTV_CSI | D2% (Gy) | <40.3 | 39.9 | 40.3 | 39.7 | 39.6 | 44.2 | 40.7 | 1.9 | 39.1 | 39.5 | 42.3 | 38.8 | 38.9 | 39.2 | 1.5 | 1.5 | .46 |
| PTV_CSI | CI | 1.00 | 1.01 | 0.99 | 0.89 | 0.96 | 1.12 | 0.99 | 0.1 | 0.97 | 0.97 | 1.05 | 0.93 | 0.96 | 0.98 | 0 | 0 | .74 |
| PTV_CSI | HI | 0 | 0.16 | 0.14 | 0.23 | 0.31 | 1.04 | 0.38 | 0.38 | 0.11 | 0.12 | 0.25 | 0.17 | 0.1 | 0.15 | 0.06 | 0.23 | .28 |
| BrainStem | $D_{max}$ (Gy) | <40.3 | 40.6 | 41.3 | 39.1 | 39.9 | 43.4 | 40.9 | 1.6 | 38.3 | 39.3 | 42.1 | 39.1 | 38.5 | 39.5 | 1.5 | 1.4 | .34 |
| BowelBag | $D_{mean}$ (Gy) | <10.0 | 7.5 | 11.4 | 7.4 | 12.1 | 13.5 | 10.4 | 2.8 | 8.3 | 13.4 | 9 | 12.1 | 16 | 11.7 | 3.2 | -1.4 | **.04** |
| Cochleas | $D_{mean}$ (Gy) | <39.6 | 38 | 37.7 | 37 | 38.3 | 41.7 | 38.5 | 1.8 | 37.9 | 38.4 | 40.2 | 37.4 | 38.1 | 38.4 | 1.1 | 0.1 | .93 |
| Esophagus | $D_{mean}$ (Gy) | <30.0 | 29.4 | 25.1 | 20.2 | 29.7 | 37 | 28.3 | 6.2 | 27.2 | 25.2 | 22.5 | 27.3 | 29.1 | 26.3 | 2.5 | 2 | .3 |
| Globes | $D_{max}$ (Gy) | <39.6 | 38.6 | 42.7 | 36.9 | 39.2 | 41.1 | 39.7 | 2.3 | 38.6 | 38.5 | 38.1 | 35 | 38.9 | 37.8 | 1.6 | 1.9 | .16 |
| Heart | $D_{mean}$ (Gy) | <12 | 11.5 | 12 | 7.6 | 13.6 | 17.6 | 12.5 | 3.6 | 10.8 | 10.6 | 9.9 | 12.9 | 13.8 | 11.6 | 1.7 | 0.9 | .43 |
| Kidneys | $D_{mean}$ (Gy) | <18 | 18.8 | 19.8 | 9.9 | 17.4 | 25.3 | 18.2 | 5.5 | 19.3 | 12.2 | 9.9 | 16.1 | 20.4 | 15.6 | 4.5 | 2.7 | .16 |
| Larynx | $D_{mean}$ (Gy) | <25 | 23.9 | 24.6 | 16.2 | 27.4 | 25.3 | 23.5 | 4.3 | 20.2 | 21.9 | 21.6 | 25.8 | 21.9 | 22.3 | 2.1 | 1.2 | .52 |
| Lungs | $D_{mean}$ (Gy) | <18 | 14 | 15.7 | 9 | 14.6 | 15 | 13.7 | 2.7 | 14 | 13.1 | 9.2 | 14.5 | 15.8 | 13.3 | 2.5 | 0.4 | .58 |
| OpticChiasm | $D_{max}$ (Gy) | <39.6 | 39.5 | 39.5 | 38.2 | 38.9 | 41 | 39.4 | 1 | 37.9 | 37.9 | 41 | 38.1 | 37.5 | 38.5 | 1.4 | 0.9 | .42 |
| OpticNerves | $D_{max}$ (Gy) | <39.6 | 38.2 | 40.6 | 37.8 | 39 | 40.4 | 39.2 | 1.3 | 38.6 | 38.4 | 40 | 38.1 | 38.5 | 38.7 | 0.7 | 0.5 | .57 |
| OralCavity | $D_{mean}$ (Gy) | <20 | 15.8 | 18.9 | 10.9 | 15.9 | 18.4 | 16 | 3.2 | 13.1 | 14.6 | 15 | 16 | 16.1 | 15 | 1.2 | 1 | .52 |
| Parotids | $D_{mean}$ (Gy) | <26 | 25.3 | 31.3 | 22.4 | 24.5 | 27.3 | 26.1 | 3.4 | 19.7 | 30 | 23.6 | 22.8 | 20.1 | 23.2 | 4.1 | 2.9 | .13 |
| Pituitary | $D_{max}$ (Gy) | <39.6 | 39.6 | 39.3 | 37.7 | 38.2 | 40.9 | 39.1 | 1.3 | 37 | 38.7 | 40 | 37.6 | 37.6 | 38.2 | 1.2 | 1 | .38 |
| SpinalCord | $D_{max}$ (Gy) | <40.3 | 42.5 | 41.6 | 42.2 | 40 | 45.4 | 42.3 | 2 | 40.4 | 41.9 | 42.3 | 39.7 | 40.4 | 40.9 | 1.1 | 1.4 | .23 |
| Submandibulars | $D_{mean}$ (Gy) | <20 | 19 | 20.9 | 13.7 | 20.6 | 20.4 | 18.9 | 3 | 17.8 | 18 | 19.1 | 20.3 | 17.9 | 18.6 | 1.1 | 0.3 | .85 |
| Thyroid | $D_{mean}$ (Gy) | <25 | 24.2 | 23.7 | 16.6 | 24.4 | 28.6 | 23.5 | 4.3 | 19.9 | 20.1 | 18.4 | 23.8 | 23.8 | 21.2 | 2.5 | 2.3 | .14 |
| Beam-on | Time (min) | | 16.9 | 17.5 | 15.6 | 16.8 | 16.8 | 16.7 | 0.7 | 3.6 | 3.6 | 3.6 | 3.6 | 3.6 | 3.6 | 0 | 13.1 | <**.01** |
| Total treatment | Time (min) | | | | | | | | | 43.5 | 22.3 | 41.6 | 16.3 | 22.4 | 29.2 | 12.4 | | |

*Difference is an absolute difference between RefleXion X1 and Eclipse VMAT. Statistically significant P value <.05 is shown in bold font.*

beam-on time for RFX plans was estimated to be longer than the average beam-on time for VMAT plans in our study, Tomotherapy delivery time was found to be longer than that of VMAT by Sun et al. The long treatment time increases the potential for significant intrafraction motion. In future studies, the impact of intrafraction motion management on treatment time for RefleXion CSI will need to be evaluated.

Another study by Herdian et al[28] found that differences in oral cavity $D_{mean}$, kidneys $D_{mean}$, and mean D2% to the spinal PTV were statistically significant between IMRT and Tomotherapy plans. Differences in oral cavity $D_{mean}$, kidneys $D_{mean}$, mean D2% to the cranial PTV, and mean D2% to the spinal PTV were also statistically significant between 3D-CRT plans and HT plans. Additionally, Tomotherapy plans resulted in longer mean beam-on times than both IMRT and 3D-CRT.[28]

One limitation of this study is the small sample size ($n$ = 5) due to the maximum target length threshold of 50 cm. The vendor is planning in its next clinical release to upgrade the system with the capability to treat targets greater than 50 cm. This will permit us to expand patient selection, include larger target sizes, and collect and further analyze treatment delivery times. In the system's current version, treatment would require an additional plan to cover the entire target. Future studies will have to explore the issue of field matching in these situations. Another limitation is that this study focuses only on comparing the VMAT and RefleXion X1 plans. It would be interesting to include Tomotherapy plans in the testing cohort. This work shows the feasibility of CSI planning using RefleXion X1, potentially paving the way to use RefleXion X1 for CSI treatment. This could simplify Image-Guided Radiation Therapy (IGRT) workflow and streamline treatment, an especially important benefit for patients with pediatric CSI being treated under anesthesia.

## Conclusion

Based on our limited data set, we were able to demonstrate the feasibility of CSI treatment planning for RefleXion X1. The successfully generated RefleXion plans resulted in dosimetric indices comparable to Eclipse VMAT plans as no statistically significant differences were detected in the PTV near-maximum dose or average $D_{mean}$ to critical structures except in the bowel bag. Despite its longer average beam-on time than VMAT plans, RefleXion X1 utilizes a moving couch to allow for single-isocenter technique by encompassing the entire volume in one scan. This has the potential to reduce translational and dosimetric matching errors associated with multi-isocenter setups using C-arm linear accelerators.

## References

1) Dressler EV, Dolecek TA, Liu M, Villano JL. Demographics, patterns of care, and survival in pediatric medulloblastoma. *J Neurooncol*. 2017;132(3):497-506. doi:10.1007/s11060-017-2400-5

2) Taylor MD, Northcott PA, Korshunov A, et al. Molecular subgroups of medulloblastoma: the current consensus. *Acta Neuropathol*. 2012;123(4):465-472. doi:10.1007/s00401-011-0922-z

3) Warren KE, Vezina G, Poussaint TY, et al. Response assessment in medulloblastoma and leptomeningeal seeding tumors: recommendations from the response assessment in pediatric neuro-oncology committee. *Neuro Oncol*. 2018;20(1):13-23. doi:10.1093/neuonc/nox087

4) Ramaswamy V, Remke M, Bouffet E, et al. Risk stratification of childhood medulloblastoma in the molecular era: the current consensus. *Acta Neuropathol*. 2016;131(6):821-831. doi:10.1007/s00401-016-1569-6

5) McNeill KA. Epidemiology of brain tumors. *Neurol Clin*. 2016;34(4):981-998. doi:10.1016/j.ncl.2016.06.014

6) Hansen EK, Roach M. *Handbook of Evidence-Based Radiation Oncology*. 2nd ed. Springer; 2010.

7) Parker WA, Freeman CR. A simple technique for craniospinal radiotherapy in the supine position. *Radiother Oncol*. 2006;78(2):217-222. doi:10.1016/j.radonc.2005.11.009

8) Kiltie AE, Povall JM, Taylor RE. The need for the moving junction in craniospinal irradiation. *Br J Radiol*. 2000;73(870):650-654. doi:10.1259/bjr.73.870.10911789

9) Cao F, Ramaseshan R, Corns R, et al. A three-isocenter jagged-junction IMRT approach for craniospinal irradiation without beam edge matching for field junctions. *Int J Radiat Oncol Biol Phys*. 2012;84(3):648-654. doi:10.1016/j.ijrobp.2012.01.010

10) Wang Z, Jiang W, Feng Y, et al. A simple approach of three-isocenter IMRT planning for craniospinal irradiation. *Radiat Oncol*. 2013;8:217. doi:10.1186/1748-717X-8-217

11) Gram D, Haraldsson A, Brodin NP, et al. Residual positioning errors and uncertainties for pediatric craniospinal irradiation and the impact of image guidance. *Radiat Oncol*. 2020;15(1):149. doi:10.1186/s13014-020-01588-2

12) Sugie C, Shibamoto Y, Ayakawa S, et al. Craniospinal irradiation using helical tomotherapy: evaluation of acute toxicity and dose distribution. *Technol Cancer Res Treat*. 2011;10(2):187-195. doi:10.7785/tcrt.2012.500194

13) Chen J, Chen C, Atwood TF, et al. Volumetric modulated arc therapy planning method for supine craniospinal irradiation. *J Radiat Oncol*. 2012;1(3):291-297. doi:10.1007/s13566-012-0028-9

14) Cao F, Harrop S, Cooper N, et al. The dose junction issue associated with photon beams for large volume radiation therapy and the sensitivity to set-up error. *J Med Phy Appl Sci*. 2017;2(2):8.

15) Zhou Y, Ai Y, Han C, et al. Impact of setup errors on multi-isocenter volumetric modulated arc therapy for craniospinal irradiation. *J Appl Clin Med Phys*. 2020;21(11):115-123. doi:10.1002/acm2.13044

16) Fogliata A, Bergström S, Cafaro I, et al. Cranio-spinal irradiation with volumetric modulated arc therapy: a multi-institutional treatment experience. *Radiother Oncol*. 2011;99(1):79-85. doi:10.1016/j.radonc.2011.01.023

17) Lee YK, Brooks CJ, Bedford JL, Warrington AP, Saran FH. Development and evaluation of multiple isocentric volumetric modulated arc therapy technique for craniospinal axis radiotherapy planning. *Int J Radiat Oncol Biol Phys*. 2012;82(2):1006-1012. doi:10.1016/j.ijrobp.2010.12.033

18) Schiopu SRI, Habl G, Häfner M, et al. Craniospinal irradiation using helical tomotherapy for central nervous system tumors. *J Radiat Res*. 2017;58(2):238-246. doi:10.1093/jrr/rrw095

19) Lee J, Kim E, Kim N, et al. Practical aspects of the application of helical tomotherapy for craniospinal irradiation. *Sci Rep*. 2021;11(1):6120. doi:10.1038/s41598-021-85574-y

20) Bandurska-Luque A, Piotrowski T, Skrobała A, et al. Prospective study on dosimetric comparison of helical tomotherapy and 3DCRT for craniospinal irradiation—a single institution experience. *Rep Pract Oncol Radiother*. 2015;20(2):145-152. doi:10.1016/j.rpor.2014.12.002

21) Mallick S, Benson R. *Helical Tomotherapy*. Springer eBooks; 2019:69-71. doi:10.1007/978-981-15-0073-2_10

22) Seravalli E, Bosman M, Lassen-Ramshad Y, et al. Dosimetric comparison of five different techniques for craniospinal irradiation across 15 european centers: analysis on behalf of the SIOP-E-BTG (radiotherapy working group). *Acta Oncol*. 2018;57(9):1240-1249. doi:10.1080/0284186X.2018.1465588

23) Sharma DS, Gupta T, Jalali R, et al. High-precision radiotherapy for craniospinal irradiation: evaluation of three-dimensional conformal radiotherapy, intensity-modulated radiation therapy and helical tomotherapy. *Br J Radiol*. 2009;82(984):1000-1009. doi:10.1259/bjr/13776022

24) Han B, Kovalchuk N, Capaldi DP, et al. First beam commissioning report of a novel medical linear accelerator designed for biologically guided radiotherapy. *Int J Radiat Oncol Biol Phys*. 2021;111(3):e512. doi:10.1016/j.ijrobp.2021.07.1404

25) Simiele E, Capaldi D, Breitkreutz D, et al. Treatment planning system commissioning of the first clinical biology-guided radiotherapy machine. *J Appl Clin Med Phys*. 2022;23(8):e13638. doi:10.1002/acm2.13638

26) Pham D, Simiele E, Breitkreutz D, et al. IMRT and SBRT treatment planning study for the first clinical biology-guided radiotherapy system. *Technol Cancer Res Treat*. 2022;21:15330338221100231. doi:10.1177/15330338221100231

27) Sun Y, Liu G, Chen W, et al. Dosimetric comparisons of craniospinal axis irradiation using helical tomotherapy, volume-modulated arc therapy and intensity-modulated radiotherapy for medulloblastoma. *Transl Cancer Res*. 2019;8(1):2019):191-202:. doi:10.21037/tcr.2019.01.30

28) Herdian F, Lestari A, Jayalie VF, et al. Analysis of dosimetric parameter on craniospinal irradiation with Helical Tomotherapy (HT), 3D Conformal RadioTherapy (3DCRT), and Intensity Modulated RadioTherapy (IMRT). *Oncol Radiother*. 2020;14(4):1-6.

# Robotic-Assisted Seminal Vesicle Excision vs Brachytherapy for Isolated Seminal Vesicle Recurrence: 2 Case Reports

Barry W. Goy, MD;[1]* David S. Finley, MD[2]


## Abstract

The most common treatment for isolated seminal vesicle recurrence (ISVR) has been androgen deprivation therapy (ADT). Prior to the introduction of prostate-specific membrane antigen PET (PSMA-PET), detecting ISVR was imprecise, with most patients treated with ADT in the setting of biochemical failure. However, with the advent of high-sensitivity and -specificity PSMA-PET, identifying patients with ISVR is now possible, and local therapy may potentially offer cure with acceptable morbidity. We present 2 cases of ISVR treated with robotic-assisted seminal vesicle excision (RASVE) vs low-dose-rate (LDR) salvage brachytherapy, both of which rendered the patients disease free with undetectable prostate-specific antigen with short-term follow-up. RASVE and LDR salvage brachytherapy are reasonable treatment options for ISVR, with curative intent.


**Keywords:** brachytherapy, robotic-assisted seminal vesicle excision, isolated seminal vesicle recurrence, prostate cancer

## Case Summary

Case 1 was a 62-year-old patient with a T1c Gleason score (GS) of 4+3, initial PSA 12.1, +5/12 cores. The patient underwent low-dose-rate (LDR) brachytherapy in 2014 using 114 loose iodine-125 seeds, 0.414 milliCuries per seed, to a minimum peripheral dose (MPD) of 14,400 cGy. He developed biochemical failure in 2017, with a prostate-specific antigen (PSA) score of 3.9. MRI and prostate biopsies were negative. The PSA continued to rise to 8.8 in 2018, and Axumin-PET demonstrated uptake in multiple subcentimeter periaortic lymph nodes, with a maximum standardized uptake value (SUV) of 4.5. In 2019, the patient was started on leuprolide and administered nodal radiation to 4000/200 cGy, but his PSA rose to 2.3 with a testosterone level of 60 in 2024.

Case 2 was a 68-year-old patient with cT2a, GS 6, and iPSA 16.0 who underwent brachytherapy in 2016 using 93 loose iodine-125 seeds to an MPD of 14,400 cGy. He developed biochemical failure with a PSA of 4.8 in 2024, and prostate biopsies were negative.

## Diagnosis and Treatment

For case 1, PSMA-PET had an SUV of 15 at the left seminal vesicle (SV) (**Figure 1**) in 2024, when his PSA was 2.3 with a testosterone level near castrate. Uronav (Invivo Corp) MRI fusion biopsy showed GS 4+3 in 5 cores with 70% involvement of the left SV, but prostate biopsies were negative. The patient subsequently underwent robotic-assisted seminal vesicle excision (RASVE) with extended pelvic lymph node dissection, in which bilateral SV and the adjacent prostate base were resected en bloc. Pathology demonstrated GS 3+4 involving bilateral SV with extension into peri-SV soft tissue, with

**Affiliations:** [1]Department of Radiation Oncology, Kaiser Permanente, Los Angeles Medical Center, Los Angeles, CA. [2]Department of Urology, Kaiser Permanente, Los Angeles Medical Center, Los Angeles, CA.
**Corresponding author:** *Barry W. Goy, MD, 4950 Sunset Blvd, Los Angeles, CA 90027. (barry.w.goy@kp.org)
**Disclosure:** The interpretation and reporting of these data are the sole responsibility of the authors. Dr. Goy had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. The views expressed in the submitted article are the authors' own and are not an official position of the Southern California Kaiser Permanente Medical Group. Generative AI was not used to write this article.
**Informed Consent:** The patients involved in our paper provided informed written consent to publish their case information.

Published: March 1, 2025. https://doi.org/10.37549/ARO-D-25-00001

**Figure 1.** Prostate-specific nembrane antigen PET for case 1 showing abnormal uptake left seminal vesicle.

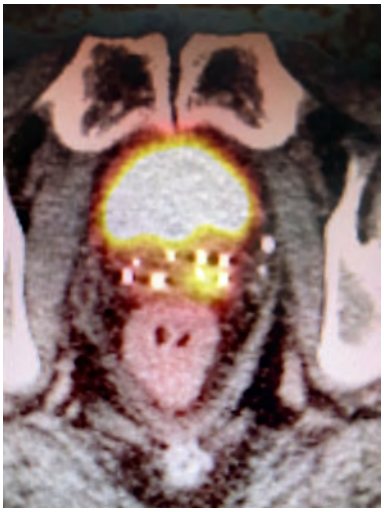
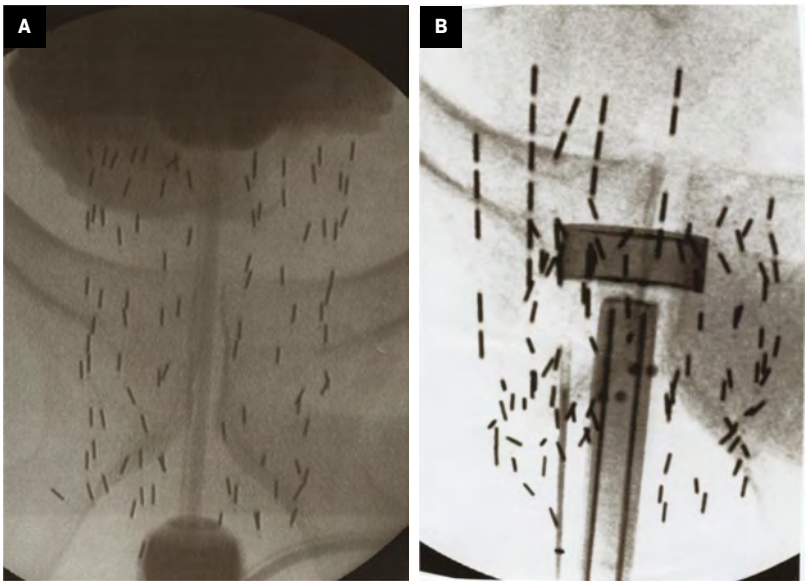


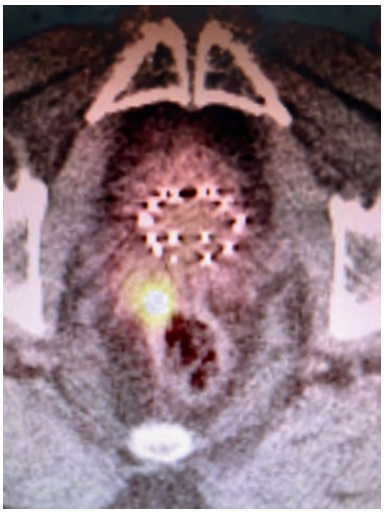
**Figure 2.** Brachytherapy implant for case 2 for definitive treatment in 2016 on the left (A), while on the right (B) showing brachytherapy implant of seminal vesicles in 2024 in addition to patient's seeds from 2016.




negative deep margins and negative nodes (0/13). The patient's PSA was undetectable 4 months post-surgery with no side effects or complications. In retrospect, we felt that his prior Axumin-PET, which showed positive nodal disease, likely represented a false-positive scan, as PSMA-PET is now considered more accurate.

For case 2, the patient's initial MRI in 2016 showed diffusion restriction and enhancement of an anterior midline lesion at mid-gland, an adjacent anterior lesion just left of the midline anterior lesion as well as a third lesion at the posterior right apex, but the SVs were normal. After brachytherapy in 2016 (**Figure 2**a), he developed biochemical failure in 2022 with a PSA of 4.8, but his sextant prostate biopsies were negative. PSMA-PET in 2024 showed recurrence in the right medial SV (SUV 16.7, **Figure 3**). This patient then underwent salvage brachytherapy with rectal spacer placement (Spacer OAR, Boston Scientific) as this was salvage treatment with previous radiation. We used 3 strands on the right SV, 2 of which had 5 seeds, while the third strand contained 6 seeds in the middle of the abnormal PSMA uptake. Also, 2 strands using 4 seeds each were placed in the left SV, for a total of 24 seeds with an activity of 0.382 milliCuries per seed using stranded iodine-125 (**Figure 2**b). Our prescription was 14,400 cGy to the entire right SV and proximal-mid-left SV. Interestingly, **Figure 2B** demonstrates a significant decrease in the size of the prostate over 8 years compared with **Figure 2A**, while **Figure 2B** contains 24 additional seeds to the SV. Androgen deprivation therapy (ADT) was not used for this patient, whose PSA 12 months post-implant was <0.1 without any complications from his salvage brachytherapy/SV implant.

**Figure 3.** Prostate-specific membrane antigen PET for case 2 showing abnormal uptake right seminal vesicle.



## Discussion

Historically, SV failure has portended systemic disease, and patients were usually treated with ADT, owing to suboptimal assessment of isolated seminal vesicle recurrence (ISVR). With the advent of PSMA-PET, finding patients with a locally recurrent, curable disease is now possible. Robotic-assisted salvage prostatectomy has been performed on patients developing local recurrence after external radiation and/or brachytherapy, although

this is done less commonly due to its high complication rate. For special cases of ISVR, RASVE may be used, with cure rates comparable to salvage prostatectomy but with the added benefit of lower morbidity.

The largest series of RASVE reported on 17 patients, with a positive margin rate of 41% and a 3-year failure-free survival of 53%.[1] In this series, 71% had bilateral SV involvement pathologically. Pretreatment biopsies showed only 35% with bilateral disease, while MRI demonstrated 12% with bilateral disease, and PSMA-PET showed 6% with bilateral disease. Thus, during any treatment of ISVR, we recommend treating both SVs, as was the situation in case 1 pathologically, where preclinical assessment only demonstrated unilateral disease. The treatment of ISVR using salvage brachytherapy has been described in only a few case reports of patients treated with SV recurrence with or without prostate recurrence.[2,3] With the advent of reliable stranded seeds, implantation in the SV is now possible, whereas previously, loose seeds would not stick to the SV owing to its spongy consistency.

Our institutional treatment preference for ISVR is RASVE as it offers pathologic staging with nodal assessment, and its side effects seem acceptable for either approach. One may hypothesize that salvage brachytherapy can be performed as a first salvage and, if unsuccessful, followed by RASVE as a backup treatment. However, this approach could increase complications as excessive radiation to the uretero-vesicle junction may lead to devascularization after RASVE if extracapsular techniques of brachytherapy are used initially.[4]

Our recommendation is to offer salvage brachytherapy to patients considered medically inoperable or to those who decline RASVE. Owing to the small number of patients with ISVR treated with RASVE or salvage brachytherapy, however, applying both these techniques to other institutions may be challenging as they may not be offered at most institutions, and most patients historically have been treated with ADT on an indefinite basis.

Our sample size is small, with only a short-term follow-up. However, in our experience, when patients reach a PSA of <0.1 after brachytherapy alone without ADT, the long-term cure rates are extremely high in the setting of de novo disease (unpublished data). There has been a significant decline in the number of institutions offering standard LDR brachytherapy,[5-7] and even fewer offer more advanced extracapsular prostate brachytherapy, which can be used to treat unfavorable intermediate- and high-risk prostate cancer with brachytherapy alone.[4,8-10] We have implanted the SV and the prostate with the goal of reducing future risk of ISVR.[4] Thus, we describe here a case where LDR salvage brachytherapy can be used to treat ISVR. Nevertheless, finding physicians technically able to perform the procedure is challenging as even standard LDR brachytherapy for prostate cancer may become obsolete due to low reimbursements.

## Conclusion

RASVE and LDR salvage brachytherapy are reasonable treatment options for ISVR, with possible curative results, sparing some patients from long-term ADT.

## References

1) Langley S, Eden C, Perry M, et al. Robot-assisted salvage seminal vesicle excision for isolated recurrence after low-dose-rate prostate brachytherapy. *BJU Int*. 2022;129(6):731-736. doi:10.1111/bju.15586

2) Hori S, Tanaka N, Asakawa I, et al. Salvage brachytherapy for seminal vesicle recurrence after initial brachytherapy for prostate cancer: a case report. *BMC Res Notes*. 2014;7:760. doi:10.1186/1756-0500-7-760

3) Sasaki H, Kido M, Miki K, et al. Salvage partial brachytherapy for prostate cancer recurrence after primary brachytherapy. *Int J Urol*. 2014;21(6):572-577. doi:10.1111/iju.12373

4) Goy BW. Extracapsular prostate brachytherapy using iodine-125 for intermediate and selected high-risk prostate cancer: technical notes. *Appl Radiat Oncol*. 2024;13(3):32-39. doi:10.37549/ARO-D-24-00018

5) Schad M, Kowalchuk R, Beriwal S, Showalter TN. How might financial pressures have impacted brachytherapy? A proposed narrative to explain the declines in cervical and prostate brachytherapy utilization. *Brachytherapy*. 2019;18(6):780-786. doi:10.1016/j.brachy.2019.07.001

6) Petereit DG, Frank SJ, Viswanathan AN, et al. Brachytherapy: where has it gone? *J Clin Oncol*. 2015;33(9):980-982. doi:10.1200/JCO.2014.59.8128

7) Yashar C. Stormy "fourcast" for brachytherapy. *Int J Radiat Oncol Biol Phys*. 2015;93(4):733-736. doi:10.1016/j.ijrobp.2015.06.022

8) Goy BW, Burchette R, Soper MS, Chang T, Cosmatos HA. Ten-year treatment outcomes of radical prostatectomy vs external beam radiation therapy vs brachytherapy for 1503 patients with intermediate-risk prostate cancer. *Urology*. 2020;136:180-189. doi:10.1016/j.urology.2019.09.040

9) Goy BW, Baecker AS. Unfavorable intermediate- and high-risk prostate cancer treated with predominantly brachytherapy alone with long-term follow-up. *Appl Radiat Oncol*. 2023;12(4):20-28. doi:10.37549/ARO-D-23-00023

10) Merrick GS, Wallner KE, Galbreath RW, Butler WM, Adamovich E. Is supplemental external beam radiation therapy essential to maximize brachytherapy outcomes in patients with unfavorable intermediate-risk disease?*Brachytherapy*. 2016;15(1):79-84. doi:10.1016/j.brachy.2015.09.011

# Volumetric Changes in a Cervical Schwannoma in Response to Adjuvant Stereotactic Body Radiation Therapy: A Case Report

Neil D. Almeida, MD;[1†] Tyler V. Schrand, BS;[1,2†] Julia Rupp, BS;[3] Rohil Shekher, MD;[1] Venkatesh Madhugiri, MD;[1] Victor Goulenko, MD;[1] Michael T. Milano, MD, PhD;[4] Elad I. Levy, MD, MBA;[3,5] Dheerendra Prasad, MD, MCh[1,3,6*]

## Abstract

Stereotactic radiosurgery (SRS) and stereotactic body radiation therapy (SBRT) are the commonly employed treatment modalities for intra- and extracranial schwannomas. Transient swelling is common following SRS for vestibular schwannomas. We highlight the volumetric change following adjuvant SBRT of a schwannoma of the cervical spine. The patient initially presented with pain and numbness in the left arm, which led to diagnosis of a benign schwannoma in the cervical spine region. She then underwent subtotal surgical resection, followed by SBRT of the residual tumor. The volume of the schwannoma was measured on subsequent neuroimaging to ascertain the post-SBRT treatment response. To our knowledge, this is the first published report of transient swelling of a cervical schwannoma.

**Keywords:** stereotactic body radiation therapy, schwannoma, spinal tumor, cervical spine, tumor response

## Case Summary

Schwannomas are rare tumors that arise from Schwann cells, which function to myelinate the peripheral nervous system. Within this benign entity, cervical schwannomas account for just 0.1% of all diagnoses.[1] The preferred treatment for cervical schwannomas entails total tumor resection; however, obtaining clear margins may not be feasible in some patients owing to the proximity of nearby critical structures.[2-4] Adjuvant radiation therapy is considered for positive margins or gross residual disease.[5]

Stereotactic body radiation therapy (SBRT) delivers a highly conformal tumoricidal dose while minimizing radiation exposure to the surrounding tissues.[6] The steep dose fall-off achieved by SBRT is paramount in cases where the tumor is close to critical structures or vasculature, as is common in cervical schwannomas. The post-stereotactic radiosurgery (SRS) response of vestibular schwannomas (historically termed acoustic neuromas) is well documented in the literature, as cranial nerve VIII is the most common site of schwannoma development.[7] These tumors tend to expand after SRS, which can be misinterpreted as tumor progression.[8-12] Regardless of actual or pseudoprogression, volume expansion following SRS poses a threat to critical structures. Indeed, tumor expansion may cause temporary or permanent hearing loss, gait imbalance, facial twitching, palsy or sensory changes from impingement of inflammation of cranial nerves V and VII; hydrocephalus from the 4th ventricle obstruction; or brainstem injury.[13] By extrapolation, when irradiating extracranial schwannomas with

**Affiliations:** [1]Department of Radiation Medicine, Roswell Park Comprehensive Cancer Center, Buffalo, NY. [2]Department of Biochemistry and Molecular Biology, Tulane University School of Medicine, New Orleans, LA. [3]Jacobs School of Medicine and Biomedical Sciences, State University of New York at Buffalo, Buffalo, NY. [4]Department of Radiation Oncology, University of Rochester Medical Center, Rochester, NY. [5]Department of Neurosurgery,, State University of New York at Buffalo, Buffalo, NY. [6]Department of Neurosurgery, Roswell Park Comprehensive Cancer Center, Buffalo, NY. †Neil D. Almeida and Tyler V. Schrand contributed equally to this work
**Corresponding author:** *Dheerendra Prasad, MD, MCh, Department of Neurosurgery, Roswell Park Comprehensive Cancer Center, 665 Elm St, Buffalo, NY 14203. (D.Prasad@roswellpark.org)
**Disclosure:** The authors have no conflicts of interest to disclose. None of the authors received outside funding for the production of this original manuscript and no part of this article has been previously published elsewhere. The patient has provided informed consent for the publication of this case report.

Published: March 1, 2025. https://doi.org/10.37549/ARO-D-25-00005

SBRT, radiation oncologists must be cognizant of the potential volumetric changes post-SBRT treatment. However, a paucity of literature describes post-SBRT changes in cervical schwannomas. We describe here for the first time, to the best of our knowledge, volumetric changes in a cervical schwannoma following adjuvant SBRT.

## Presentation

The patient was a 60-year-old female non-smoker with a history of left breast mastectomy for stage 3A breast cancer 11 years earlier and left shoulder replacement 7 years earlier. She initially presented with pain involving the left shoulder and arm and described the pain as a sharp intermittent sensation with no exacerbating factors. The pain was initially attributed to a combination of left shoulder replacement and lymphedema in the left arm following breast cancer treatment. However, the pain persisted, and the patient underwent a contrast-enhanced cervical MRI, which revealed a nerve sheath tumor in the C6-C7 region, extending extracanalicular and into the canal with some spinal cord compression (**Figure 1**). She underwent a left partial C6 and C7 schwannoma resection with hemilaminectomy and posterior C4-T2 fusion for postlaminectomy kyphosis. Surgical intervention resulted in moderate pain relief. Pathology showed a myxoid peripheral nerve sheath tumor, with S100 protein diffusely positive and MIB-1 estimated to be 3%. A surveillance MRI ~7 months postsurgery revealed a residual tumor with a volume of 9.47 $cm^3$ in the anterior region near the brachial plexus (**Figure 2**). The patient was followed by neurosurgery and referred to radiation oncology 11 months postresection.

**Figure 1.** Contrast- and noncontrast-enhanced MRI of the cervical spine demonstrating preoperative cervical schwannoma (top) and postoperative surgical cavity (bottom). (A) Preoperative sagittal T2, (B) preoperative sagittal T1 sequence with contrast, (C) postoperative sagittal T2, and (D) postoperative sagittal T1 sequence with contrast.

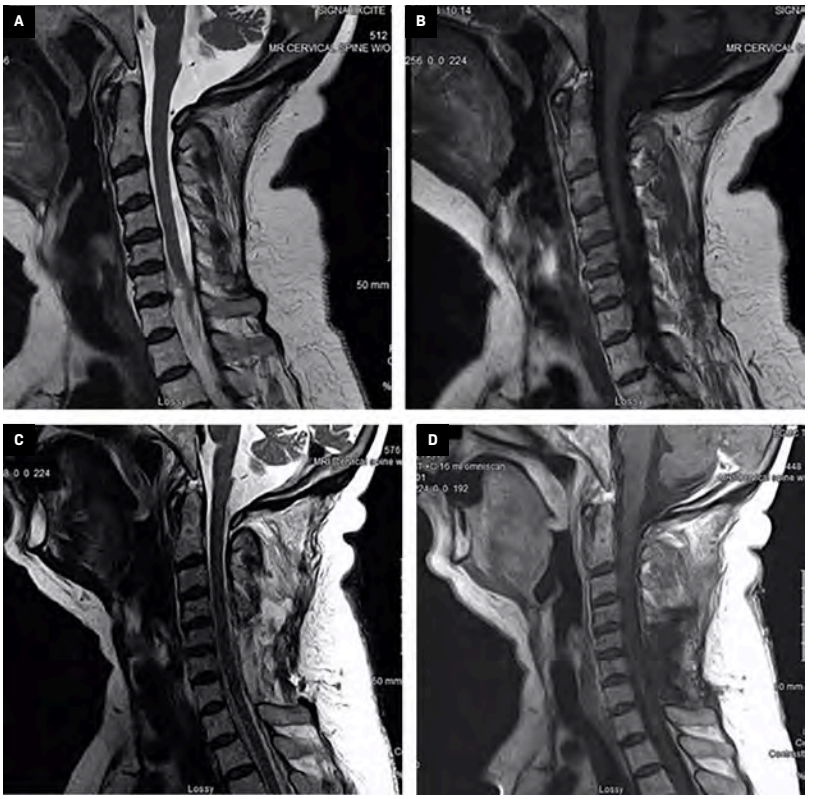
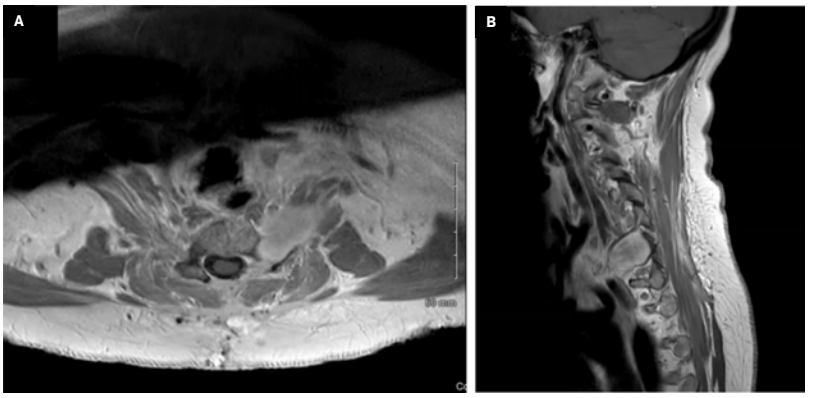



**Figure 2.** Contrast-enhanced MRI of the cervical spine demonstrating a postoperative residual tumor in the anterior region adjacent to the brachial plexus. (A) Axial T1 sequence with contrast; (B) sagittal T1 sequence with contrast.



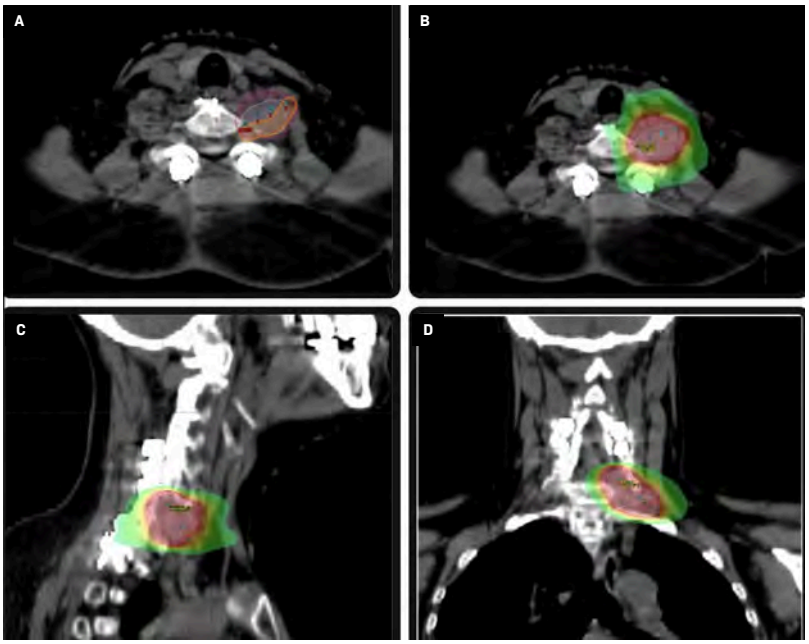

Eleven months following resection, the patient underwent SBRT with a dose of 2100 cGy in 3 fractions delivered every other day over a 5-day period. The patient was simulated and treated with an aquaplast mask on an Accufix board indexed to the table for immobilization. The gross tumor volume (GTV) was contoured

using the planning CT scan and fused volumetric MR images. The planning target volume (PTV) was defined as a 5 mm circumferential expansion of the GTV. A volumetric modulated arc therapy plan was generated with 3 coplanar 6 MV flattening filter-free beams. The plan was normalized such that the prescription dose covered 95% of the PTV. The maximum PTV dose was 2363.5 cGy(**Figure 3**). The patient was treated on a Varian TrueBeam linear accelerator. Serial MRI was utilized to monitor tumor response to SBRT. Volumetric changes were calculated retrospectively from MRI by importing the MRI into the treatment planning system to contour the post-SBRT residual tumor and compute volumes.

Three months following SBRT, MRI revealed that the tumor initially shrank to 8.16 $cm^3$. However, this regression in size was short-lived, and a scan 5 months later (8 months post-SBRT) demonstrated that the mass had grown to 15.8 $cm^3$. Three months later (11 months post-SBRT), the tumor had shrunk to 9.94 $cm^3$. Fourteen months after SBRT, the patient complained of increasing numbness in her left hand, but an MRI scan at that time revealed that the tumor had continued to shrink steadily. She described numbness in the left middle finger with occasional involvement of the 1st and 2nd digits but reported no upper extremity weakness or other neurologic symptoms. The tumor continued to shrink, stabilizing to a final volume of 8.85 $cm^3$ > 5 years after SBRT. The patient reported persistent tingling and numbness along the left middle finger at the latest follow-up.

In total, tumor volume was obtained via cervical MRI 8 times—the first of which followed surgical resection just before radiation therapy. Tumor volumes at various periods are shown in **Table 1** and **Figure 4**. The patient was last seen in a follow-up 5 years after completing SBRT.

**Figure 3.** Axial CT images (A) illustrating gross tumor volume 2100 (cyan), planning target volume (PTV) 2100 (magenta), and brachial plexus contour (orange). Stereotactic body radiation therapy axial (B), sagittal (C), and coronal planes (D) illustraing dose color wash (PTV 2100 shown in magenta).




## Discussion

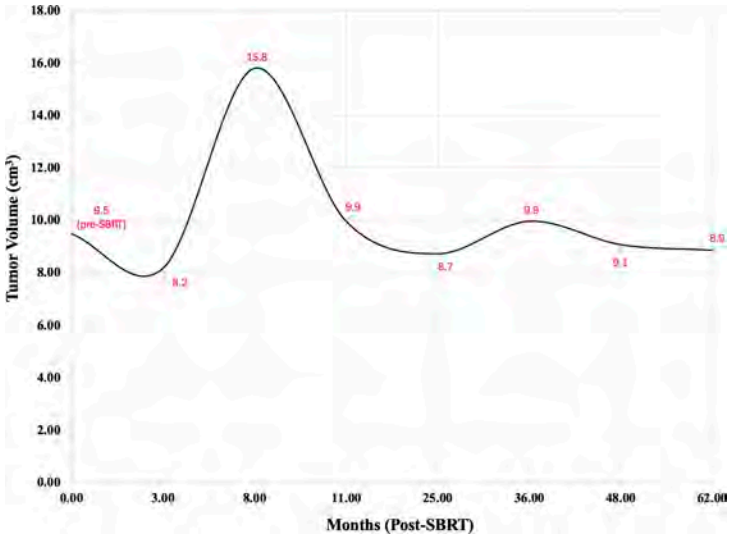
As schwannomas are extremely rare in the cervical spine,[1] the majority of data describe vestibular schwannoma treatment. SRS is often employed nonoperatively to achieve local control of vestibular schwannomas[14]; the high doses and steep dose falloffs offer local control rates of up to 90% while minimizing damage to the surrounding structures.[15] Tumor expansion peaks approximately 6-12 months after SRS and can generally be attributed to pseudo-progression; this postradiotherapeutic tumor change is not indicative of treatment failure.[9] Our case highlights the utility of SBRT to target the residual lesion adjacent to the brachial plexus. Using adjuvant stereotactic radiation therapy for vestibular schwannomas, Dhayalan et al reported a local control rate of 77.3%.[16] In the spine, adjuvant SBRT has been shown to achieve successful local control of S1 nerve root melanotic schwannomas[5] and benign thoracic spine schwannomas.[17] However, the effect of adjuvant SBRT on benign schwannomas in the cervical region is not well documented.

This is the first report on volumetric changes of a cervical schwannoma following adjuvant SBRT. The tumor swelled approximately two-thirds of its pre-SBRT size ~8 months following treatment. After this initial expansion, the size steadily decreased and was slightly smaller than its pre-SBRT size 48 months after treatment.

**Table 1. MRI-Determined Tumor Volume ($cm^3$) Before and After Stereotactic Body Radiation Therapy (SBRT) Treatment on 9/2019**

| MRI DATE | TUMOR VOLUME ($CM^3$) |
|---|---|
| Pre-SBRT | 9.5 |
| 3 months post-SBRT | 8.2 |
| 8 months post-SBRT | 15.8 |
| 11 months post-SBRT | 9.9 |
| 25 months post-SBRT | 8.7 |
| 3 years post-SBRT | 9.9 |
| 4 years post-SBRT | 9.1 |
| >5 years post-SBRT | 8.9 |

**Figure 4.** Graphical depiction of tumor volume over time. SBRT, stereotactic body radiation therapy.




In contrast to cervical schwannomas, characteristic volumetric changes following SRS are well documented for vestibular schwannomas. Meijer et al reported that 11 of 45 (24%) treated tumors initially increased in volume and eventually decreased to below pretreatment volume.[18] The mean increase in volume was reported to be 25% after a mean follow-up time of 15 months. The tumors then shrank eventually to a volume lower than the pretreatment volume at an average of 34 months. Mohammed et al described 7 of 18 (39%) vestibular schwannomas that demonstrated pseudoprogression and then shrank below their pre-SRS volume.[11] They reported a mean tumor volume increase of 35% and an average time to regression of 24 months.[11] In contrast, the tumor in our case demonstrated a 67% increase in volume, which is markedly higher than the averages reported by these studies.

The patient was noted on the last follow-up to have persistent left middle finger numbness and tingling. We postulate that these symptoms could likely be the result of a late brachial plexopathy or neuropathy from the nerve root. Upon review, the dose to the brachial plexus was 2337.3 cGy (max dose per Dose Volume Histogram), which met the constraint of D0.03cc < 26 Gy, but the partial volume of 8.50 cc exceeded D3cc < 22 Gy, per the BR002 trial.[19] Prior studies have demonstrated that brachial plexus volume exposure may be more critical than the maximum dose in terms of symptomatic motor or sensory deficits of the upper extremity.

## Conclusion

Unlike the high number of studies regarding vestibular schwannomas, there is a significant dearth of data regarding the post-SBRT expansion of schwannomas in other areas, with little to no reports of volume expansion or percent changes in volume. To better understand the risks of complications following SBRT, the dynamics of tumor volumes of schwannomas in all locations should be investigated in greater depth. The result of such investigations would allow radiation oncologists and patients to make more educated decisions regarding the use of radiation therapy.

## References

1) Airlangga PA, Prijambodo B, Hidayat AR, Benedicta S. Schwannoma of the upper cervical spine—a case report. *Chin J Traumatol.* 2019;22(6):368-372. doi:10.1016/j.cjtee.2019.07.005

2) Batra UB, Usha G, Gogia AR. Anesthetic management of schwannoma of the base of the tongue. *J Anaesthesiol Clin Pharmacol.* 2011;27(2):241-243. doi:10.4103/0970-9185.81830

3) de Bree R, Westerveld GJ, Smeele LE. Submandibular approach for excision of a large schwannoma in the base of the tongue. *Eur Arch Otorhinolaryngol.* 2000;257(5):283-286. doi:10.1007/s004050050241

4) Sitenga JL, Aird GA, Nguyen A, Vaudreuil A, Huerter C. Clinical features and surgical treatment of schwannoma affecting the base of the tongue: a systematic review. *Int Arch Otorhinolaryngol.* 2017;21(4):408-413. doi:10.1055/s-0037-1598609

5) Hall JC, Chang SD, Wilson TJ, et al. Post-operative stereotactic radiosurgery of malignant melanotic schwannoma. *Cureus.* 2022;14(3):e22849. doi:10.7759/cureus.22849

6) Mintz A, Heron DE. CyberKnife® robotic stereotactic radiosurgery and stereotactic body radiation therapy. *Technol Cancer Res Treat*. 2010;9(6):539-540. doi:10.1177/153303461000900601

7) Cioffi G, Yeboa DN, Kelly M, et al. Epidemiology of vestibular schwannoma in the United States, 2004-2016. *Neurooncol Adv*. 2020;2(1):vdaa135. doi:10.1093/noajnl/vdaa135

8) Fouard O, Daisne JF, Wanet M, Regnier M, Gustin T. Long-term volumetric analysis of vestibular schwannomas following stereotactic radiotherapy: practical implications for follow-up. *Clin Transl Radiat Oncol*. 2022;33:1-6. doi:10.1016/j.ctro.2021.12.003

9) Hayhurst C, Zadeh G. Tumor pseudoprogression following radiosurgery for vestibular schwannoma. *Neuro Oncol*. 2012;14(1):87-92. doi:10.1093/neuonc/nor171

10) Malone J, Tiberi D, Sinclair J, Gaviolli E, Malone S. Delayed pseudoprogression of a vestibular schwannoma postradiosurgery. *Radiol Case Rep*. 2020;15(6):749-752. doi:10.1016/j.radcr.2020.03.001

11) MohammedFF, SchwartzML, Lightstone A, A, Beachey DJ,DJ, Tsao MN. Pseudoprogression of vestibular schwannomas after fractionated stereotactic radiation therapy. *J Radiat Oncol*. 2(1):15-20. doi:10.1007/s13566-012-0084-1

12) Rueß D, Schütz B, Celik E, et al. Pseudoprogression of vestibular schwannoma after stereotactic radiosurgery with cyberknife®: proposal for new response criteria. *Cancers*. 2023;15(5):1496. doi:10.3390/cancers15051496

13) Kim Y-H, Kim DG, Han JH, et al. Hearing outcomes after stereotactic radiosurgery for unilateral intracanalicular vestibular schwannomas: implication of transient volume expansion. *Int J Radiat Oncol Biol Phys*. 2013;85(1):61-67. doi:10.1016/j.ijrobp.2012.03.036

14) Persson O, Bartek J Jr, Shalom NB, et al. Stereotactic radiosurgery vs. fractionated radiotherapy for tumor control in vestibular schwannoma patients: a systematic review. *Acta Neurochir*. 2017;159(6):1013-1021. doi:10.1007/s00701-017-3164-6

15) Soltys SG, Milano MT, Xue J, et al. Stereotactic radiosurgery for vestibular schwannomas: tumor control probability analyses and recommended reporting standards. *Int J Radiat Oncol Biol Phys*. 2021;110(1):100-111. doi:10.1016/j.ijrobp.2020.11.019

16) Dhayalan D, Perry A, Graffeo CS, et al. Salvage radiosurgery following subtotal resection of vestibular schwannomas: does timing influence tumor control? *J Neurosurg*. 2023;138(2):420-429. doi:10.3171/2022.5.JNS22249

17) Niazi TN, Bowers CA, Schmidt MH. Role of adjuvant radiosurgery after thoracoscopic microsurgical resection of a spinal schwannoma. *Case Rep Neurol Med*. 2012;2012(1):345830. doi:10.1155/2012/345830

18) Meijer OWM, Weijmans EJ, Knol DL, et al. Tumor-volume changes after radiosurgery for vestibular schwannoma: implications for follow-up MR imaging protocol. *AJNR Am J Neuroradiol*. 2008;29(5):906-910. doi:10.3174/ajnr.A0969

19) Chmura SJ, Winter KA, Woodward WA, et al. NRG-BR002: a phase IIR/III trial of standard of care systemic therapy with or without Stereotactic Body Radiotherapy (SBRT) and/or Surgical Resection (SR) for newly oligometastatic breast cancer (NCT02364557). *JCO*. 2022;40(16_suppl):1007-1007. doi:10.1200/JCO.2022.40.16_suppl.1007

# Radiation Therapy for the Management of Refractory Giant Condyloma Acuminata: A Case Report

Prinska Ghimire Wagle, MBBS;[1] Samuel To, BA;[2] William C Chen, MD[1]*


## Abstract

Giant condyloma acuminata (GCA), also known as Buschke-Löwenstein tumor, is a rare human papillomavirus-related lesion that can affect the anorectal region and is characterized by aggressive local growth and a high recurrence rate. This case report details a 46-year-old immunocompetent man with refractory anorectal GCA that recurred despite multiple surgical interventions, including abdominoperineal resection (APR). Due to the extensive and refractory nature of the recurrent disease following APR, definitive radiation therapy was offered. Intensity-modulated radiation therapy to 50 Gy in 25 fractions resulted in rapid disease regression, symptom relief, and a complete clinical and metabolic response. This case highlights the efficacy of radiation therapy in managing challenging GCA cases.


**Keywords:** giant condyloma acuminata, radiation therapy, Buschke-Löwenstein tumor, fistulas, HPV, intensity-modulated radiation therapy (IMRT), FDG PET, PET/CT, condyloma

## Case Summary

A 43-year-old HIV-negative, immunocompetent man initially presented to the anal neoplasia clinic with a several-month history of growing, friable pink lesions in the anal area. These lesions extended from the perianal skin to the anal verge and were associated with significant anal pain. He underwent local excision and hyfrecation of extensive condylomas. Pathology of 2 excised lesions showed low-grade squamous intraepithelial lesions, positive for low-risk human papillomavirus (HPV) by in situ hybridization. Unfortunately, he developed rapid local recurrence within 1 month of this initial surgery. Despite subsequent repeat excision/fulguration procedures (6 in total) over a 3-year period, followed by an abdominoperineal resection (APR) with rectus myocutaneous flap reconstruction, the condylomas continued to recur aggressively.

## Diagnosis

Repeated histopathology of the excised lesions, including the extensively sampled APR specimen, revealed well-differentiated squamous epithelium with orderly maturation, marked acanthosis with hyperkeratosis, associated with low-risk HPV positivity, high-risk HPV negativity, and without any high-grade dysplasia. An institutional next-generation sequencing (NGS) panel identified an activating hotspot mutation in the *TERT* gene promoter, inactivating frameshifts in *KMT2B* and *KMT2D*, and an inactivating nonsense mutation in *NOTCH3*. Few large-scale chromosomal alterations were noted, including a gain of distal 7q and loss of interstitial

**Affiliations:** [1]Department of Radiation Oncology, University of California San Francisco, San Francisco, CA. [2]Department of Radiation Oncology, Keck School of Medicine, University of Southern California, Los Angeles, CA.
**Corresponding author:** *William C Chen, MD, Department of Radiation Oncology, University of California, San Francisco, CA. (william.chen@ucsf.edu)
**Disclosure/informed consent:** The authors have no conflicts of interest to disclose. None of the authors received outside funding for the production of this original manuscript and no part of this article has been previously published elsewhere. The patient has provided informed consent for the publication of this case report.

Published: March 1, 2025. https://doi.org/10.37549/ARO-D-24-00029

7q. Overall, the lack of large-scale copy number changes and absence of *TP53* or *CDKN2A* alterations, along with the benign histology with low-risk HPV positivity and high-risk HPV negativity throughout an extensively sampled tumor, were most consistent with giant condyloma acuminatum without clear evidence of malignant transformation.

## Imaging Findings

His post-APR course was complicated by wound-healing issues, persistent drainage, and the development of intra-abdominal abscesses and suspected fistulas connecting the bladder, rectal stump, and perineal wound. Recurrent condylomas appeared at the perineal incision site within 6 months, extending to the anterior aspect of the perineum and scrotum. Further surgery was felt not to be feasible, and the patient was referred for multidisciplinary discussion with radiation oncology and medical oncology. An F-18 fluorodeoxyglucose (FDG) PET/CT was obtained, which showed extensive abnormal enhancement and marked hypermetabolism in the pelvis (**Figure 1A**), including abnormal hypermetabolic tissue along multiple fistulous and percutaneous drain tracts. The bladder was abnormally thickened, though a cystoscopy and Foley catheter placement under anesthesia by urology did not identify clear involvement of the bladder. At this time, both definitive chemoradiation or radiation alone were felt to be reasonable options, and the risks and benefits of both were presented to the patient, who expressed a strong desire to avoid chemotherapy. Given the lack of evidence of malignant transformation in his extensively sampled APR specimen, radiation alone was offered.

The patient received 50 Gy in 25 fractions to a high-risk volume and 45 Gy in 25 fractions to a larger pelvic field via a volumetric modulated arc therapy plan encompassing all areas of FDG avidity (**Figure 1B**). The high-risk volume receiving 50 Gy was delineated based on FDG PET avid areas and regions of abnormal contrast enhancement on CT. A 2-3 cm customized expansion was used to delineate a clinical target volume (CTV) respecting anatomic boundaries. The CTV was also expanded to include the pelvis, with a superior border of L5/S1, encompassing the entire prior surgical field and all potential fistulous tracts, and received 45 Gy. Treatment was well tolerated with grade 2 radiation dermatitis and mild fatigue. Rapid regression of his condylomas was noted during the treatment course (**Figure 2**), along with a significant decrease in drain output and an improvement in pain levels. By the end of treatment, the condylomas had completely regressed, leaving behind a large perineal cavity. An FDG PET/CT obtained 7 weeks post-radiation showed a complete metabolic response (**Figure 1C**, **Figure 1D**). At 7 months post-radiation, he remains recurrence free and is presently undergoing hyperbaric oxygen therapy to assist healing of his fistulas and perineal cavity.

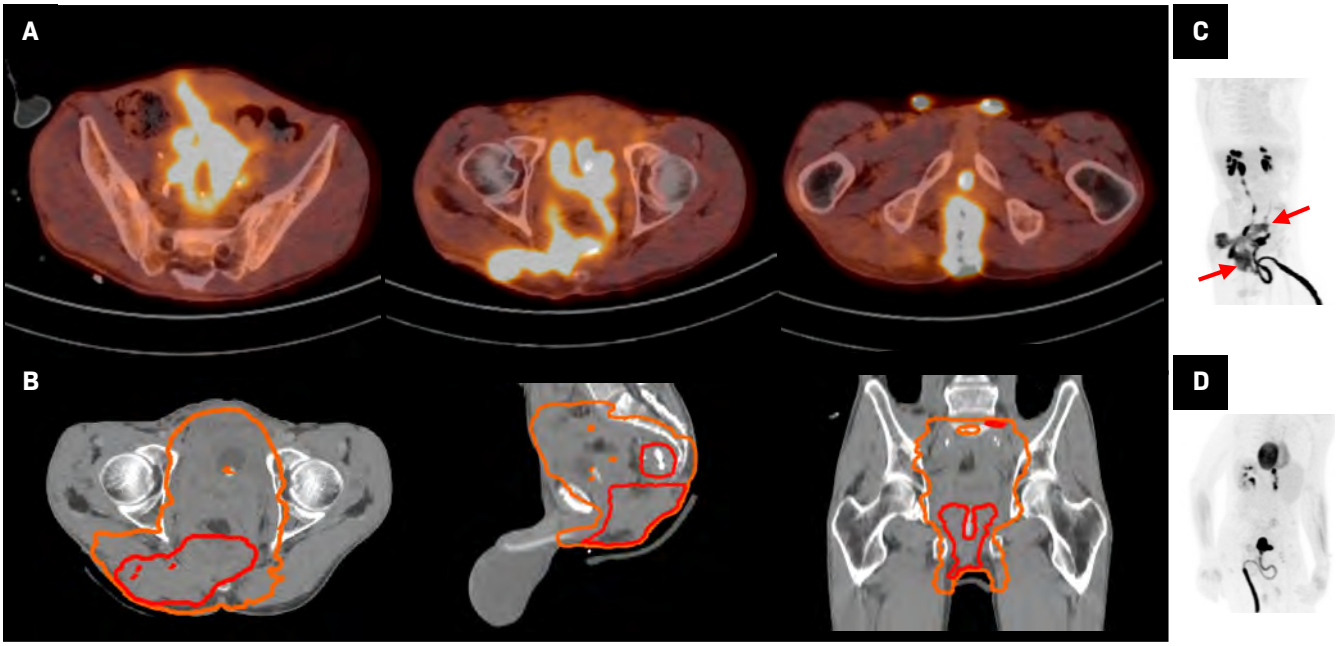
## Discussion

Giant condyloma acuminata (GCA), also known as Buschke-Löwenstein tumor, is a rare and aggressive form of condyloma acuminata, characterized by benign histology, which belies its persistent and locally destructive growth, high risk of recurrence, and potential for malignant transformation.[1,2] Although associated with low-risk HPV (HPV-6 and HPV-11) and characterized by benign histological appearance, GCA can exhibit clinical behavior akin to malignant tumors, including aggressive tissue infiltration and destruction, a high rate of recurrence, and a mortality rate of up to 20%-30% in historical series.[3,4]

Genomic characteristics of GCA have rarely been reported, and the biological underpinnings of its pathogenesis are poorly understood.[1] Among the alterations found via NGS in this case, *KMT2B* and *KMT2D* are mutations that affect histone methyltransferases, which may contribute to epigenetic dysregulation and have been reported in many cancer types, notably in squamous cell carcinomas of the lung, esophagus, anus, and head and neck.[5] An activating *TERT* promoter hotspot mutation was also seen; activating *TERT* promoter mutations have been identified frequently in many cancer types and in pre-cancerous settings.[6] The NGS also revealed few large-scale chromosomal losses or gains, which are much more commonly seen in anal squamous cell carcinomas.[7]

Traditionally, GCA is managed through locoregional therapies, including topical therapies, wide local excision, or APR. A literature review of 42 cases of surgically managed GCA found that up to 56% of these tumors were associated with histologically confirmed malignancy, underlining the high malignant risk of these tumors.[3] Moreover, GCA

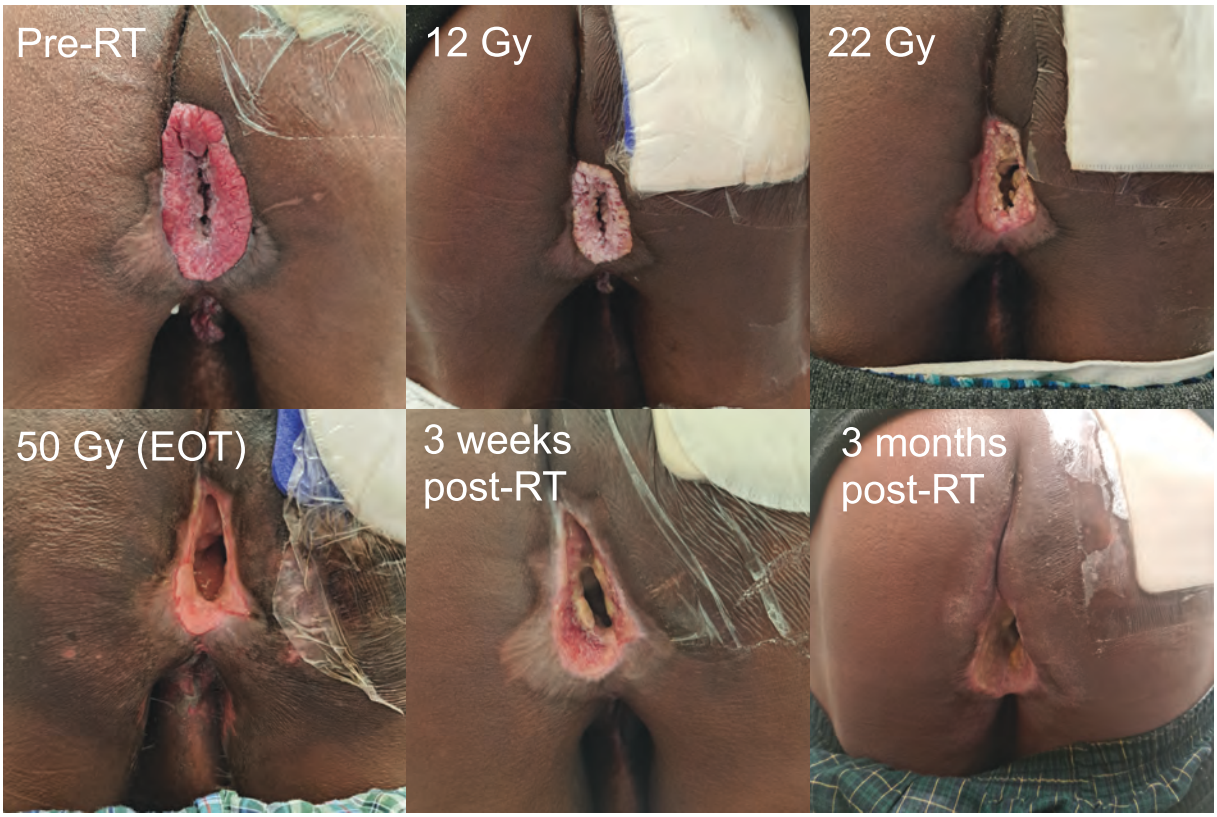
**Figure 1.** Pre- and post-radiation F-18 fluorodeoxyglucose (FDG) PET/CT fusion images. Pre-radiation FDG PET/CT (A) showing extensive abnormal hypermetabolism in the pelvis, including extensions anteriorly and posterolaterally along fistulous tracts. Axial, sagittal, and coronal views of radiation treatment plan (B), with high-risk volume (50 Gy) outlined in red and pelvic field (45 Gy) outlined in orange. Pre-radiation attenuation-corrected PET (C) showing disease extending posteriorly and anteriorly as indicated by red arrows. Post-radiation attenuation-corrected PET (D) obtained 7 weeks after treatment showing complete metabolic response.




were frequently associated with deep infiltration of surrounding structures and formation of fistulas filled with condylomas. Our case highlights the utility of FDG PET in delineating the full extent of involvement with GCA as condylomatous involvement of the deep pelvis and fistulous tracts had not been suspected, but was evident on the pre-radiation therapy FDG PET. Indeed, intense FDG avidity within condyloma acuminata has previously been described in case reports, but the use of FDG PET for GCA has not, to our knowledge, been reported on before.[8-10]

Reports of definitive radiation therapy for GCA remain rare, but the existing examples suggest that radiation therapy is a viable treatment option for managing refractory GCA and condyloma acuminata. Moodley and Govender reported on 54 HIV-positive patients with unresectable vulvar GCA treated with 30 Gy in 10 fractions, resulting in a 30% complete response and 61% partial response rate.[11] Partial responders received further local therapies, and 52 of 54 (96%) of patients were recurrence free at 5 years. Dhadda et al reported complete regression of extensive genital warts incidentally within a postoperative vulvar radiation field treated with 40 Gy in 15 fractions.[12] Sobrado et al reported complete response to 45 Gy in 25 fractions of a large recurrent perianal GCA with fistulous involvement, with the patient remaining disease free through 20 months of follow-up.[13] Kim et al describe a case of a giant perianal condyloma recurrent after APR, successfully treated with 45 Gy in 15 fractions with apparent complete clinical response at 6 weeks post-radiation therapy.[14] Sivapalan et al reported complete clinical response to 50.4 Gy in 28 fractions of a perianal GCA with deep pelvic infiltration extending into the mesorectal and periprostatic space, with the patient remaining disease free at 6 months of follow-up.[15] They also provided a literature review of 8 cases of GCA associated with histologically confirmed malignancy and 3 cases of GCA without histologic confirmation of malignancy, treated with definitive chemoradiation. Of these 11 cases, 3 developed recurrences, an outcome similar to that of anal squamous cell carcinoma. These data and the present case suggest that radiation therapy may be an effective therapy for GCA in cases where traditional treatments are inadequate, providing effective local control and potential disease regression, particularly in cases with clearly benign histology of condyloma acuminata. The effectiveness of radiation therapy in the definitive setting also lends support to its

**Figure 2.** Image series of the patient's response to treatment. Images taken at various time points, including before beginning treatment, during treatment, and after the completion of treatment.




efficacy in the neoadjuvant setting, which may be particularly important in maximizing the opportunities for avoidance of permanent colostomy. Multidisciplinary discussion is essential to improve outcomes of patients with this rare and often complex condition.

Key takeaways from the present case include the utility of FDG PET in delineating the true extent of pelvic involvement of GCA, and the unexpectedly extensive imaging findings identified during workup of this case underlines the potential of GCA to infiltrate insidiously within the pelvis, particularly along surgical and fistulous tracts. Additionally, the GCA in the present case was extensively sampled and examined by pathology over time, including with an NGS panel, without evidence of malignant transformation, which provided equipoise regarding treatment with definitive radiation therapy or chemoradiotherapy and patient-centered decision-making.

## Conclusion

This case illustrates the usefulness of radiation therapy in the management of GCA. A multidisciplinary approach is essential for optimizing management strategies and improving patient outcomes in this complex condition.

## References

1) Purzycka-Bohdan D, Nowicki RJ, Herms F, et al. The pathogenesis of giant condyloma acuminatum (buschke-lowenstein tumor): an overview. *Int J Mol Sci*. 2022;23(9):4547. doi: 10.3390/ijms23094547

2) Trombetta LJ, Place RJ. Giant condyloma acuminatum of the anorectum: trends in epidemiology and management: report of a case and review of the literature. *Dis Colon Rectum*. 2001;44(12):1878-1886. doi:10.1007/BF02234473

3) Wiedemann A, Diekmann WP, Holtmann G, Kracht H. Report of a case with giant condyloma (buschke-Löwenstein tumor) localized in the bladder. *J Urol*. 1995;153(4):1222-1224.

4) Chu QD, Vezeridis MP, Libbey NP, Wanebo HJ. Giant condyloma acuminatum (buschke-lowenstein tumor) of the anorectal and perianal regions: analysis of 42 cases. *Dis Colon Rectum*. 1994;37(9):950-957. doi:10.1007/BF02052606

5) Rao RC, Dou Y. Hijacked in cancer: the KMT2 (MLL) family of methyltransferases. *Nat Rev Cancer*. 2015;15(6):334-346. doi:10.1038/nrc3929

6) Bell RJA, Rube HT, Xavier-Magalhães A, et al. Understanding TERT promoter mutations: a common path to immortality. *Mol Cancer Res*. 2016;14(4):315-323. doi:10.1158/1541-7786.MCR-16-0003

7) Aldersley J, Lorenz DR, Mouw KW, D'Andrea AD, Gabuzda D. Genomic landscape of primary and recurrent anal squamous cell carcinomas in relation to HPV integration, copy-number variation, and DNA damage response genes. *Mol Cancer Res*. 2021;19(8):1308-1321. doi:10.1158/1541-7786.MCR-20-0884

8) Wada T, Kubota K, Minamimoto R, et al. FDG uptake by a condylomata acuminata in an HIV-infected patient mimicked urine contamination. *Clin Nucl Med*. 2012;37(4):420-421. doi:10.1097/RLU.0b013e318238f48e

9) Kim BS. The 18F-FDG PET/CT finding of a condyloma acuminata mimicking primary anorectal carcinoma in an HIV-infected patient. *Clin Nucl Med*. 2013;38(10):e402-3. doi:10.1097/RLU.0b013e318266cea2

10) Kishimoto T, Mabuchi S, Kato H, Kimura T. Condyloma acuminata induces focal intense FDG uptake mimicking vaginal stump recurrence from uterine cervical cancer: a case report. *Eur J Gynaecol Oncol*. 2013;34(1):99-100.

11) Moodley M, Govender P. External beam radiotherapy for large genital warts: does it work. *Eur J Gynaecol Oncol*. 2019;40(2):275-277. doi:10.12892/ejgo4413.2019

12) Dhadda AS, Anand A, Boynton C, Chan S. External beam radiotherapy for extensive genital condyloma acuminate: a role in selected patients? *Clinical Oncology*. 2008;20(1):91-92. doi:10.1016/j.clon.2007.08.016

13) Sobrado CW, Mester M, Nadalin W, et al. Radiation-induced total regression of a highly recurrent giant perianal condyloma: report of case. *Dis Colon Rectum*. 2000;43(2):257-260. doi:10.1007/BF02236991

14) Kim HC, Schlenker JD, Post AB, et al. The conundrum of the giant condyloma: is it carcinoma? *J Surg Case Rep*. 2024;2024(10):rjae668. doi:10.1093/jscr/rjae668

15) Sivapalan S, Loving BA, Ramanathan S, Schukow CP, Robertson JM. Radiation therapy in the management of extensive giant condyloma acuminata with rectal involvement: a case report. *Cureus*. 2024;16(3):e56882. doi:10.7759/cureus.56882

# Artificial Intelligence in Radiation Oncology Training: Integrating Clinical Skills and Automation

Kishan Patel, MD

Dr Patel is a PGY2, radiation oncology resident physician at McGaw Medical Center,Northwestern University.

Artificial Intelligence (AI) is transforming radiation oncology, automating it, and assisting in decision making. This integration poses challenges and opportunities for residents, and the future of radiation oncology will significantly depend on how well these technologies are absorbed into their training. AI can enhance efficiency and optimize patient care but can also raise concerns about skill retention and the evolving role of radiation oncologists. The future of radiation oncology will largely depend on how well residents incorporate AI into their training while maintaining core clinical competencies.

One well-developed application of AI is in auto-segmenting organs at risk and tumor volumes. Historically, contouring was painstakingly labor-intensive, requiring high precision and artistry. Today, AI algorithms carry out this function in a fraction of the time and with accuracy levels commensurate with truly competent radiation oncologists.[1] This allows residents to concentrate on other aspects of patient care, like treatment planning. However, it begs the question of how much practice of manual contouring should be expected of the residents if AI can do it effectively.

Manual contouring remains a fundamental skill for understanding anatomical relationships and ensuring accurate radiation dose delivery. While AI-assisted tools can standardize contours and reduce interobserver variability, over-reliance on automation may erode residents' proficiency in this critical area. AI-generated contours still require validation, and potential errors can have significant clinical consequences. Therefore, training programs must balance the use of AI with the development of strong manual contouring skills to maintain clinical competence.

Machine-learning predictive analytics also improve patient care in several realms, including segmentation. AI may analyze outcomes based on predictive modeling, arriving at toxicity-risk estimates for different radiation dose levels. Examples include the use of machine-learning models to predict acute radiation dermatitis in patients with breast cancer.[2] Another example consists of the RAD-AI trial investigating the use of AI to determine dose recommendations during stereotactic body radiation therapy for lung cancer patients.[3] This phase II trial aims to assess the effectiveness and safety of AI-driven dose planning, potentially leading to more tailored and effective treatment strategies. Such advancements underscore the importance of residents understanding AI applications to effectively interpret and integrate these tools into clinical practice. Though these tools can aid with treatment personalization, residents should rely on their

**Disclosure:** The author has no conflicts of interest to disclose. No outside funding was received for the production of this original manuscript and no part of this article has been previously published elsewhere. ChatGPT version 3.5 was used for grammatical and stylistic edits after the manuscript was written.
**Corresponding author:** Kishan Patel, MD, McGaw Medical Center, Northwestern University, 600 N Kingsbury Street, Unit 502, Chicago, IL 60654. (kipatel11.12.95@gmail.com)

Published: March 1, 2025. https://doi.org/10.37549/ARO-D-25-00008

sound clinical judgment when interpreting outputs.

Despite these advancements, AI cannot replace the clinical judgment and expertise that radiation oncologists bring to patient care. AI models rely on training data, which may not always reflect the diversity of real-world clinical scenarios. Additionally, AI cannot contextualize unique patient circumstances, such as comorbidities, social determinants of health, and patient preferences, that play a crucial role in treatment decision-making. Radiation oncologists provide the critical thinking, adaptability, and ethical reasoning that AI cannot replicate. Residents must learn to interpret AI-generated recommendations within the broader clinical picture by understanding model limitations and biases.

While AI is helpful and makes things efficient, residents must maintain the power of clinical skills. Integrating AI into training for future radiation oncologists will help establish a practical relationship between technology and sound judgment in patient care. The future of equitable cancer care will depend on striking the right balance between technological innovation and human expertise, ensuring that AI serves as a tool to enhance—not replace—the art and science of radiation oncology.

## References

1) Baroudi H, Brock KK, Cao W, et al. Automated contouring and planning in radiation therapy: what is "clinically acceptable"? *Diagnostics (Basel)*. 2023;13(4):667. doi:10.3390/diagnostics13040667

2) Bhinder B, Gilvary C, Madhukar NS, Elemento O. Artificial intelligence in cancer research and precision medicine. *Cancer Discov*. 2021;11(4):900-915. doi:10.1158/2159-8290.CD-21-0090

3) National Cancer Institute. Stereotactic body radiation therapy planning with artificial intelligence in treating patients with lung cancer (RAD-AI). Accessed February 21, 2025. https://www.cancer.gov/research/participate/clinical-trials-search/v?id=NCI-2023-01822

AppliedRadiationOncology

www.appliedradiationoncology.com