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Review
Peer Review in Radiation Oncology: Present and Future Directions

Review
Stereotactic Radiosurgery and Immunotherapy for Melanoma and NSCLC Brain Metastases: Practical Integration, Timing, and Toxicity

Research
Outcomes of Stereotactic Versus Conventional Radiation Therapy in Unresectable Pancreatic Cancer: A Real-World Retrospective Analysis

Radiation Oncology Case
Multiple Cranial Nerve Palsies After Reirradiation With Proton Therapy in Nasopharyngeal Carcinoma

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Advancing Radiation Oncology Through Peer Review and Continuous Learning

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Progress in radiation oncology has always depended on our willingness to evaluate, question, and refine our practice. As new technologies emerge and treatment techniques become more sophisticated, peer review remains one of the most effective mechanisms for identifying opportunities to refine treatment plans, reducing variability in care and ensuring the quality and safety of radiation therapy.

The articles in this issue of *Applied Radiation Oncology* demonstrate how thoughtful review, multidisciplinary collaboration, careful evaluation of evidence, and innovative educational approaches continue to advance our specialty.

Our featured review, *Peer Review in Radiation Oncology: Present and Future Directions*, examines one of the foundations of quality assurance in radiation oncology. The authors summarize evidence demonstrating that multidisciplinary peer review leads to clinically meaningful treatment plan modifications, particularly for complex disease sites and advanced treatment techniques. Just as importantly, they highlight the considerable variability in how peer review is implemented across institutions, emphasizing the need for more standardized frameworks that promote consistency while preserving flexibility.

The review *Stereotactic Radiosurgery and Immunotherapy for Melanoma and NSCLC Brain Metastases: Practical Integration, Timing, and Toxicity* also emphasizes the necessity of multidisciplinary collaboration and continual refinement of treatment protocols, but in the context of patients with brain metastases—particularly those with melanoma and non-small cell lung cancer. Barve points to emerging evidence that combining stereotactic radiosurgery with immunotherapy may improve outcomes, but optimal integration requires multidisciplinary decision-making that considers treatment timing, dosimetry, and patient-specific factors.

In the research article, *Outcomes of Stereotactic Versus Conventional Radiation Therapy in Unresectable Pancreatic Cancer: A Real-World Retrospective Analysis*, Tesolin and colleagues illustrate that better outcomes in the management of unresectable pancreatic cancer are linked as much to careful patient selection as to modern radiation techniques such as stereotactic body radiation therapy, MR-guided adaptive radiotherapy, and dose-escalated approaches.

This month's case report, *Multiple Cranial Nerve Palsies After Reirradiation With Proton Therapy in Nasopharyngeal Carcinoma*, illustrates the educational value of carefully documenting uncommon but clinically significant complications. Although proton therapy has expanded treatment options for recurrent disease, this report reminds us that even our most advanced technologies require ongoing scrutiny to better define dose constraints, optimize patient selection, and improve long-term survivorship care.

In Resident Voice, *Closing the Global Brachytherapy Training Gap With Virtual Reality,* Peterson explores how immersive simulation may help address persistent disparities in procedural education. By leveraging virtual reality to expand access to high-quality brachytherapy training, the International Atomic Energy Agency demonstrates how innovation can strengthen technical proficiency and broaden educational opportunities for radiation oncologists around the world.

Collectively, these articles remind us that progress in radiation oncology depends on more than technological innovation alone. It requires a willingness to examine our decisions, learn from colleagues, evaluate emerging evidence, and continually refine our practice.

On behalf of the advisory board and publisher, we sincerely appreciate your continued support of *Applied Radiation Oncology*. Enjoy your summer!

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Peer Review in Radiation Oncology: Present and Future Directions

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Abstract

Peer review is a vital process in radiation oncology that aims to enhance treatment quality, reduce errors, and standardize care through multidisciplinary evaluation of radiation treatment plans. Its implementation varies widely across institutions, with ongoing efforts to improve consistency and efficiency. This article summarizes current literature regarding the peer review process in radiation oncology. Peer review identifies change in approximately 3% to 12% of cases, particularly complex cases such as head and neck, gynecologic, and lung cancer with focus on changes in target volumes, dose, and organ-at-risk delineation. Complex treatment planning techniques such as intensity-modulated radiation therapy and proton therapy show higher rates of recommended changes that tend to decrease as departments gain experience and establish guidelines. Peer review processes differ, but often involve weekly multidisciplinary meetings to review selected cases based on complexity or treatment intent. Meeting format ranges from offline individual reviews to in-person or video conferences. Documentation practices vary widely, with inconsistencies in tracking of attendance, recommendations, and implementation of suggested changes. Effective peer review involves the treating physician and an experienced peer, but often includes support from medical physicists, dosimetrists, radiation therapists, and, occasionally, radiologists. Structured feedback varies from informal discussions to documented evaluations covering multiple aspects of treatment, with changes graded as no change, minor change, or major change; documentation of response to suggested change is inconsistent. Peer review is ideally conducted before treatment starts to allow plan modification with protected time and flexible meeting formats to enhance participation and regularity. Automation and artificial intelligence (AI) tools may streamline the review process by identifying cases needing attention, standardizing processes, and predicting dose distributions, thereby reducing clinician workload and improving accuracy. Future integration of AI tools for literature review, incident reporting, and documentation may support high-quality peer review. This underscores the need for standardized peer review frameworks in radiation oncology.

Keywords: peer review, radiation oncology, treatment plans, multidisciplinary, quality assurance, target volumes, IMRT (Intensity-Modulated Radiation Therapy), documentation, standardization, artificial intelligence (AI)

Introduction

Peer review has been a crucial component of quality improvement and harm reduction efforts in radiation oncology. Due to the complex nature of radiation treatment planning and the differences between a radiation oncologist's subjective decision-making, errors can occur, particularly regarding radiation dosing, target volumes, and normal tissue delineations. Peer review may result in the alteration of treatment plans and the identification of potentially harm-inducing errors.[1] Retrospective and prospective peer review serves as systems intended to develop and maintain high-quality and error-free treatments across physicians within a system.[2] Professional organizations, including Royal Australian and New

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Zealand College of Radiologists (RANZCR) and American Society for Radiation Oncology (ASTRO), advocate for the implementation of peer review processes to create multidisciplinary teams that work to maintain the standards of care across departments.[1,3] Despite this, significant variation exists between peer review models, and there is yet to be broadly accepted standardization.[4]

Methods

Literature was searched in the PubMed database using keywords related to radiation oncology, peer review, quality, and safety. Studies were limited to publications from 2010 to 2025. Included were prospective and retrospective cohort studies, systematic reviews, meta-analyses, guidelines, and narrative reviews. Manual citation searching was used to increase the scope of articles captured. There were no specific exclusion criteria; however, priority was placed on studies that published prospective, original research, systematic reviews/meta-analyses, and studies that were multicenter in nature. Literature was aggregated and assessed for inclusion based on recency, with newer studies being preferred, and relevance of the study's aim in assessing peer review, its process improvement, and clinical impact.

Discussion

Clinical Impact of Peer Review

Peer review identified errors that resulted in alterations to treatment plans in 3.3% to 12.2% of the time.[5-9] "Near misses" were seen and rectified in 9% of reviewed cases in some series.[10] The treatment sites most frequently associated with peer review-recommended plan changes were head and neck (1%-66%), gynecologic (6%-18%), and lung (13%-27%).[5,10-12] Changes in treatment plans that resulted from peer review centered on target volume, dose, organs at risk, and contouring, with target volume being one of the most common reasons for changes.[5,10,13] Most institutions that participated in peer review reviewed >50% of curative cases, and peer review was seen broadly to apply in some fashion to all types of radiation courses; however, palliative cases had lower rates of audit.[5,12]

The complexity of the target site and the plan was correlated with the rate of changes recommended by peer review. For example, breast plans that included regional lymph nodes had an odds ratio of 2.12 to be classified requiring changes vs breast only plans.[13] Complexity related to novel technology was attributed as a factor that resulted in increased rates of changes from peer review. For example, head and neck plans often involving advanced modalities like intensity-modulated radiation therapy, volumetric modulated arc thearpy (VMAT), and proton therapy can have higher rates of recommended changes during peer review (44.9%), compared to lung (24.5%), stereotactic body radiotherapy (SBRT) (17.4%), and other sites.[12,14] Heterogeneity in patient populations studied and peer review methods make comparison between reported outcomes difficult. It was seen that as a department overcame the hurdles with learning new treatment modalities, their rate of changes from peer review decreased.[11] Rates of change generally decreased over time after the initiation of peer review, which is thought to be from the standardization that results from frequent review, along with the education to all those involved.[12] Clear and established department guidelines may serve to reduce the variation in treatment plans and therefore reduce the needed changes from peer review, as was seen in one series.[10]

Peer Review Models and Processes

Peer review protocols differed between programs (**Table 1**). A typical process was prospective and involved a multidisciplinary team that met to examine cases (**Figure 1**). Decisions would be made during the review and plans approved, or changes recommended. Changes would be made and plans enacted or presented for a second review, depending on the nature of the proposed changes.[4,5,15,16] The selection process for cases included for peer review varies significantly among programs. Some locations attempted to audit all new patients, while others would choose cases based on the complexity, site, dosage, and modality.[1,15] Whether a patient was decided for review through random selection or because the treatment intention was curative, the decision-making behind which patients will be reviewed appears to be highly specific to the department and faculty.[4] Peer review meetings tend to occur on a weekly basis,[4] with some institutions holding sessions more frequently, and some even having impromptu meetings, if necessary, to reduce treatment delays.[1] Most of the time, meetings would be held in-person, though technology was leveraged to allow for meetings when scheduling issues came up, for example, through video-based meetings or individual review.[1,4,15]

Peer review in radiation oncology departments has been documented through structured recording systems that track case presentations, recommendations, and outcomes, though practices vary significantly across institutions. The American Society for Radiation Oncology recommends that practices create well-developed peer review strategies that include review processes for the entire practice and for individual clinical care.[17] However, documentation of peer review remains inconsistent. In a survey of German radiation oncology departments, it was found that attendance tracking and implementation of recommended changes were inconsistent.[18] On a similar note, in a Canadian provincial survey, only 36% of centers reported recording peer review outcomes on the medical record.[19]

An effective documentation system vastly improves patient outcomes in medicine. Improvements in

Table 1. Comparison of the Key Components of Peer Review Models and Their Implementation

COMPONENT	COMMON APPROACHES REPORTED	ADVANTAGES	LIMITATIONS/ VARIABILITY
Timing of review	Prospective (before treatment initiation) vs retrospective (after treatment starts)	Prospective review allows changes before planning and treatment delivery; retrospective review provides educational value	Significant institutional variation; urgent cases may require retrospective review
Case selection	All new cases; curative-intent cases; random selection; risk-stratified selection based on complexity, site, modality, or dose	Focuses resources on cases most likely to benefit from review	No standardized selection criteria across institutions
Multidisciplinary participation	Radiation oncologists, peer reviewers, medical physicists, dosimetrists, radiation therapists, trainees; occasional radiologist involvement	Diverse expertise improves detection of clinically meaningful issues	Attendance and specialty involvement vary substantially
Meeting frequency	Weekly most commonly; some institutions hold multiple sessions per week or ad hoc reviews	Regular review promotes standardization and education	Scheduling and staffing constraints
Meeting format	In-person, video conference, hybrid, asynchronous individual review	Remote participation improves flexibility and attendance	Different formats may affect interaction and consistency
Documentation systems	Electronic medical record, dedicated databases, structured audit tools, real-time documentation	Facilitates quality improvement and tracking of recommendations	Documentation practices remain inconsistent across institutions
Grading of changes	No change, minor change, major change; ABC classification systems	Allows assessment of clinical significance of recommendations	No universally accepted grading framework
Implementation tracking	Variable recording of recommendation adherence and follow-up review	Supports quality assurance and accountability	Often incompletely documented
Review duration	Approximately 2-20 min per case; most commonly 2-8 mins	Efficient review of large case volumes	Longer reviews may be required for complex cases

many aspects to the documentation system include conscious effort on the following: recording of attendance by multidisciplinary team members (physicians, medical physicists, dosimetrists, radiation therapists), documentation of case-specific recommendations and their classification (e.g., no change, minor change, major change), tracking of whether recommended changes were implemented, and use of standardized peer review audit tools (PRATs), such as those developed by the Royal Australian and New Zealand College of Radiologists.[1,3,10,18,20-22] The timing and format of documentation varies by institution. Some departments conduct prospective documentation during treatment planning conferences, while others use electronic peer review systems or collaborative methods.[1,17,23] The mean time for reviewing each plan ranges from approximately 2 to 8 minutes per case.[11,20,24] Despite recommendations for systematic documentation, surveys reveal that many institutions lack standardized approaches. A systematic review found significant variation in documentation and reporting practices internationally, with no consensus on grading systems for peer review outcomes.[4] This has led to calls for standardized frameworks to facilitate meaningful evaluation of peer review's clinical impact.[4,12]

The incorporation of video-based meeting programs allows for greater flexibility, and the involvement of multiple departments within an institution. This greater logistical freedom improves adherence to peer review sessions.[1,4] Others take a different approach, meeting for peer review sessions with the patient to allow for the incorporation of in-meeting physical examination—for example, in a head and neck oncology program.[25,26] Peer review sessions tended to be between 30 and 60 minutes at most institutions.[4,5,12] Planning sessions most commonly took less than 30 minutes, and rarely would take longer than 1 hour.[5] The time needed per case could be as low as 2.7 minutes, up to 12 to 20 minutes.[3,5,26-28] Longer time spent per patient was seen with those centers that would include physical examination and was thought to be related to the complexity of the cases.[12,26] The more time spent per patient also had a correlation with the rate of change per case, reaching as high as 22.6% to 66% of cases in those that averaged near 20 minutes per patient.[12]

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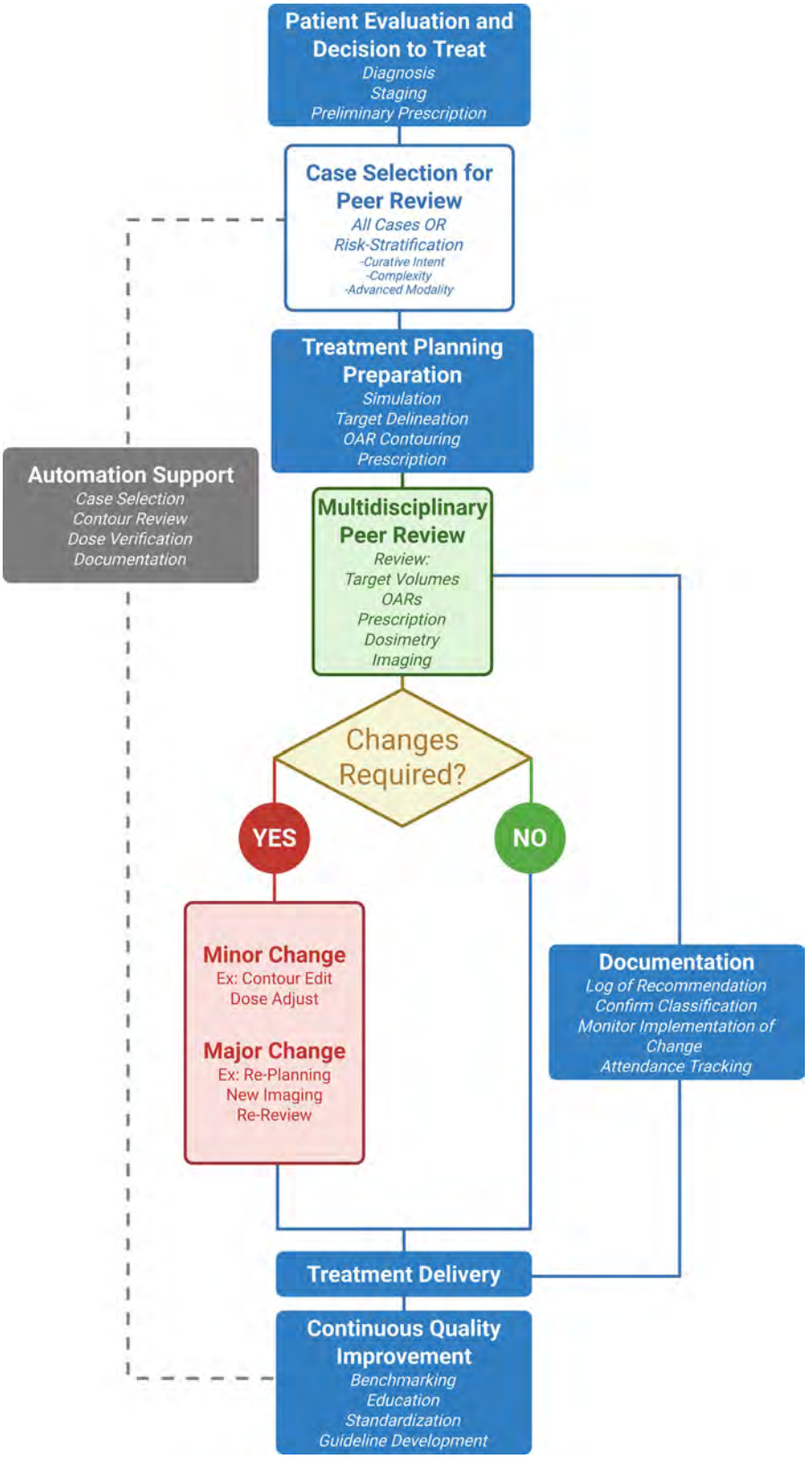
Figure 1. Peer Reveiw Process



Effective peer review, by definition, typically requires that the physician attending the case as well as a nontreating "peer" with experience in the relevant tumor site participated at minimum in each session.[4] The radiation oncologist was almost always present, as well as a reviewing physician, and teams were often multidisciplinary with attendance from the medical physicists, dosimetrist, radiation therapist, residents, and trainees.[4,5,16] The involvement of radiologists in the peer review process was not a common occurrence; however, when it was performed, there was a significant increase in the number of meaningful changes made, emphasizing the value of an interdisciplinary team.[14] Larger institutions with multiple departments are able to leverage interdepartmental peer review with faculty from different sites.[1]

The structure of the peer review proceedings was unique to institutions. Various methods have been devised, with some as simple as recommending changes as a particular case is discussed.[15] Formal case review methodologies provided a structured approach to feedback, with a systematic evaluation of various aspects of a treatment plan for each case. One institution devised a form that evaluated 8 aspects of the treatment (workup and staging, treatment intent and prescription, position/immobilization/simulation, motion assessment/management, target contours, normal tissue contours, target dosimetry, and normal tissue dosimetry).[16] Grading of changes was another area of variation among centers. Commonly, they would be graded as "no change," "minor change," and "major change."[4,5,16] Lymberiou et al. developed an ABC categorization of changes, with "A" referring to Adequate, "B" as treatment may proceed with potential changes in the future, and "C" as unsatisfactory and requiring changes before the next set of treatment.[13]

For each of the various categories of a case, the reviewing physician had a chance to approve or recommend a different course of action. The feedback that was provided during review was most often documented into the electronic medical record, in a separate secure electronic database, or the changes were made in real time through face-to-face discussion.[4,5] The response from the attending physician to the proposed changes was infrequently recorded and changes were inconsistently brought back for further peer review.[4,5]

Practical Considerations

Peer review was typically performed before treatment began. Intuitively, this allowed for changes and potential overhaul to occur freely without the burdens of re-optimizing a plan that is already in place.[4,5] When peer review occurred after the onset of treatment, changes were often met with reluctance by the attending physician due to the need to replan.[3] Particularly for technically complicated cases, peer review is best done before the medical physics or dosimetry planning steps to avoid re-planning.[4] Retrospective peer review had its benefits as an educational tool.[4] In some cases, it is a necessity to review after the treatment began if radiation was administered urgently.[15] In one study from Canada, approximately half of the surveyed programs were able to review >80% of curative treatment plans with limitations from time constraints and oncologist availability.[5] The protection of time specifically for peer review was highly successful in attaining regularity of attendance, especially when oncologist schedules were specifically planned to maintain time for the review session. Set time blocks allowed for planners and physicians to prepare appropriately.[1,12] Maintaining flexibility with the format of peer review facilitates meetings when obstacles occur. Technology and video conferencing should be leveraged to allow for members to join off-site and from other campuses.[1,4,5]

Clinical Applications of Automation

Advancements in automation should be leveraged to identify cases where peer review may have the most impact. Automated technologies may assess large numbers of patients across broad disease and treatment intent categories with an ability to flag critical issues for potential intervention. Deep learning and artificial intelligence (AI) are developing technologies that may make improvements in the quality of peer review while decreasing the clinician and team workload. For example, models have been successfully trained to rapidly predict dose distributions and aid in identifying which plans needed adjustment in the treatment of nasopharyngeal carcinoma, with applied results comparable to what was planned by the treating teams. It is important to keep in mind that AI models tend to address specific technical concerns, for example, dose distribution optimization, whereas multidisciplinary peer review engages in broader clinical decision-making.[29,30]

Algorithms can act as a safeguard against erroneous radiation prescriptions, with one trained on thoracic cancer patients achieving a lower error rate than manual peer review.[31] These models are trained on high-quality cases and end up personalized for the institution, anatomy, and the metrics that the team selects for. This allows AI to complement the process with the addition of more tangible data to the already existing multidisciplinary clinical expertise. Limitations with these models existed on complex patients and those with anomalies; however, this was thought to be because of a lack of sufficient training data, which is an area that may improve as wider incorporation leads to exposure to these rare cases.[29,31]

Administrative/Documentation Applications of Automation

Common clinical tasks can be automated, such as the review of relevant literature that informs radiation planning and scouring of the electronic health record, with nearly 95% accuracy/precision.[30] In the realm of quality improvement, the production of incident reports can be assisted with natural language processing and machine learning to aid in the classification and severity determination of incidents.[32,33] Ambient AI and other tools are being quickly adopted by institutions as a time-saving means in documentation and may find a place in the radiation oncologist's clinic.[34] The time saved from the implementation of automation in various aspects of clinical and administrative realms of practice can be employed towards high-quality peer review for manual and automated processes.

Wherever possible, aspects of the peer review process should be standardized. Protocols and local institutional guidelines should serve as a standard that aids the audit.[4] Forms should be made to ensure that all relevant aspects are addressed independently and to improve the efficiency of the review process.[4,16] Attendance, data collection, recommendation adherence, response from the attending physician, and other "process outcomes" should be tracked and documented to continually assess the efficacy of the peer review process.[5] Tools such as a color-coded automated dose volume histogram (DVH) analysis can assess DVH adherence to set department criteria.[1] The RANZCR's PRAT provides a framework to fulfill such needs.[2] Automated systems may aid in the processes of peer review documentation, for example, with the use of AI summarization and contextual enrichment to relay recommendations made during peer review sessions. With structured data gathering, automated analysis can highlight workflow steps that require intervention.

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Limitations

This study faces several limitations. The nonsystematic nature of this review inclines selection bias in terms of which papers were chosen, the potential papers that were missed in the search process, and the use of only one database to gather articles. This study is also limited in the heterogeneity of the included studies' methodologies and populations, which limits direct comparisons of results, and as such listed ranges should be interpreted with caution. Despite these limitations, we aim to provide a broad overview of the current state of peer review in radiation oncology.

Conclusion

Peer review is an essential asset to standardizing and delivering quality care in radiation oncology. It allows for changes in treatment plans that are clinically meaningful and protects against potentially harmful errors in practice. It also allows for standardization and interdisciplinary effort that leads to better care for patients. Despite efforts in peer review in the field, there persist gaps in standardization due to variability in peer review models used across institutions and its employment across the radiation oncology community. To address this gap, future standardized frameworks should incorporate several core elements: risk-stratified case selection criteria that prioritize high-risk, complex, and curative-intent cases; defaulting to prospective pre-treatment review to avoid the burden of re-planning; structured multidisciplinary participation, including radiation oncologists, medical physicists, dosimetrists, and, where feasible, radiologists and other relevant specialists; standardized documentation of case-specific recommendations, change classifications, and implementation status; and systematic tracking of process outcomes over time to enable ongoing quality assessment and benchmarking.

AI and automation hold considerable promise as adjuncts to peer review, with demonstrated applications in dose distribution prediction, prescription error detection, and administrative documentation. However, these tools remain institution-specific and require rigorous prospective validation before broad clinical adoption, and they are not a substitute for the broader clinical judgment afforded by multidisciplinary human review. There remains the pervasive need for a robust effort to develop an organized approach to peer review to maintain and improve high standards of care and avoid medical errors in the field of radiation oncology.

References

1) Duggar WN, Bhandari R, Yang CC, Vijayakumar S. Group consensus peer review in radiation oncology: commitment to quality. *Radiat Oncol*. 2018;13(1):55. doi:10.1186/s13014-018-1006-1

2) Chin S, Or M, Ong WL, et al. Radiation oncology peer review in Australia and New Zealand. *J Med Imaging Radiat Oncol*. 2022;66(2):258-266. doi:10.1111/1754-9485.13360

3) Marks LB, Adams RD, Pawlicki T, et al. Enhancing the role of case-oriented peer review to improve quality and safety in radiation oncology: executive summary. *Pract Radiat Oncol*. 2013;3(3):149-156. doi:10.1016/j.prro.2012.11.010

4) Lewis PJ, Court LE, Lievens Y, Aggarwal A. Structure and processes of existing practice in radiotherapy peer review: a systematic review of the literature. *Clin Oncol*. 2021;33(4):248-260. doi:10.1016/j.clon.2020.10.017

5) Caissie A, Rouette J, Jugpal P, et al. A pan-canadian survey of peer review practices in radiation oncology. *Pract Radiat Oncol*. 2016;6(5):342-351. doi:10.1016/j.prro.2016.01.014

6) Rubagumya F, Mushonga M, Abdihamid O, et al. Status of peer review in radiation oncology: a survey of cancer centers in Sub-Saharan Africa. *Int J Radiat Oncol Biol Phys*. 2023;116(5):984-991. doi:10.1016/j.ijrobp.2023.04.012

7) Brunskill K, Nguyen TK, Boldt RG, et al. Does peer review of radiation plans affect clinical care? A systematic review of the literature. *Int J Radiat Oncol Biol Phys*. 2017;97(1):27-34. doi:10.1016/j.ijrobp.2016.09.015

8) Boxer M, Forstner D, Kneebone A, et al. Impact of a real-time peer review audit on patient management in a radiation oncology department. *J Med Imaging Radiat Oncol*. 2009;53(4):405-411. doi:10.1111/j.1754-9485.2009.02096.x

9) Ballo MT, Chronowski GM, Schlembach PJ, et al. Prospective peer review quality assurance for outpatient radiation therapy. *Pract Radiat Oncol*. 2014;4(5):279-284. doi:10.1016/j.prro.2013.11.004

10) Mackenzie J, Graham G, Olivotto IA. Peer review of radiotherapy planning: quantifying outcomes and a proposal for prospective data collection. *Clin Oncol*. 2016;28(12):e192-e198. doi:10.1016/j.clon.2016.08.012

11) Lefresne S, Olivotto IA, Joe H, Blood PA, Olson RA. Impact of quality assurance rounds in a Canadian radiation therapy department. *Int J Radiat Oncol Biol Phys*. 2013;85(3):e117-e121. doi:10.1016/j.ijrobp.2012.10.015

12) Huo M, Gorayski P, Poulsen M, Thompson K, Pinkham MB. Evidence-based peer review for radiation therapy – updated review of the literature with a focus on tumour sub-site and treatment modality. *Clinical Oncology*. 2017;29(10):680-688. doi:10.1016/j.clon.2017.04.038

13) Lymberiou T, Galuszka S, Lee G, et al. Predictors of breast radiotherapy plan modifications: quality assurance rounds in a large cancer centre. *Radiother Oncol*. 2015;114(1):17-21. doi:10.1016/j.radonc.2014.11.042

14) Hughes RT, Razavian NB, Smith S, et al. Radiologist involvement in radiation oncology peer review: a systematic review and meta-analysis. *JAMA Netw Open*. 2024;7(12):e2452667. doi:10.1001/jamanetworkopen.2024.52667

15) Martin-Garcia E, Celada-Álvarez F, Pérez-Calatayud MJ, et al. 100% peer review in radiation oncology: is it feasible? *Clin Transl Oncol*. 2020;22(12):2341-2349. doi:10.1007/s12094-020-02394-8

16) Lo AC, Liu M, Chan E, et al. The impact of peer review of volume delineation in stereotactic body radiation therapy planning for primary lung cancer: a multicenter quality assurance study. *J Thorac Oncol*. 2014;9(4):527-533. doi:10.1097/JTO.0000000000000119

17) Beron P, Bovi J, Bresnahan B, et al. *Safety Is No Accident: A Framework for Quality Radiation Oncology Care*. 2nd ed. American Society for Radiation Oncology (ASTRO); 2019.

18) Baehr A, Guberina M, Ernst P, et al. Current practices in peer review in german radiation oncology: a nationwide survey. *Strahlenther Onkol*. 2025 Jul 24;202(5):496–507. doi:10.1007/s00066-025-02444-6

19) Brundage M, Foxcroft S, McGowan T, et al. A survey of radiation treatment planning peer-review activities in a provincial radiation oncology programme: current practice and future directions. *BMJ Open*. 2013;3(7):e003241. doi:10.1136/bmjopen-2013-003241

20) Albert AA, Duggar WN, Bhandari RP, et al. Analysis of a real time group consensus peer review process in radiation oncology: an evaluation of effectiveness and feasibility. *Radiat Oncol*. 2018;13(1):239. doi:10.1186/s13014-018-1190-z

21) Rouette J, Gutierrez E, O'Donnell J, et al. Directly improving the quality of radiation treatment through peer review: a cross-sectional analysis of cancer centers across a provincial cancer program. *Int J Radiat Oncol Biol Phys*. 2017;98(3):521-529. doi:10.1016/j.ijrobp.2016.10.017

22) Kumaar V, Gupte A, Kakade A, et al. Review of quality audit in a radiation oncology department in a tertiary care hospital– 2 year-results. *Asian Pac J Cancer Prev*. 2024;25(11):4043-4049. doi:10.31557/APJCP.2024.25.11.4043

23) Vijayakumar S, Duggar WN, Packianathan S, Morris B, Yang CC. Chasing zero harm in radiation oncology: using pre-treatment peer review. *Front Oncol*. 2019;9:302. doi:10.3389/fonc.2019.00302

24) Lawrence YR, Whiton MA, Symon Z, et al. Quality assurance peer review chart rounds in 2011: a survey of academic institutions in the United States. *Int J Radiat Oncol Biol Phys*. 2012;84(3):590-595. doi:10.1016/j.ijrobp.2012.01.029

25) Cardenas CE, Mohamed ASR, Tao R, et al. Prospective qualitative and quantitative analysis of real-time peer review quality assurance rounds incorporating direct physical examination for head and neck cancer radiation therapy. *Int J Radiat Oncol Biol Phys*. 2017;98(3):532-540. doi:10.1016/j.ijrobp.2016.11.019

26) Rosenthal DI, Asper JA, Barker Jr JL, et al. Importance of patient examination to clinical quality assurance in head and neck radiation oncology. *Head Neck*. 2006;28:967-973. doi:10.1002/hed.20446

27) Rooney KP, McAleese J, Crockett C, et al. The impact of colleague peer review on the radiotherapy treatment planning process in the radical treatment of lung cancer. *Clin Oncol*. 2015;27(9):514-518. doi:10.1016/j.clon.2015.05.010

28) Matuszak MM, Hadley SW, Feng M, et al. Enhancing safety and quality through preplanning peer review for patients undergoing stereotactic body radiation therapy. *Pract Radiat Oncol*. 2016;6(2):e39-e46. doi:10.1016/j.prro.2015.09.009

29) Zhou P, Gu H, Peng Q, et al. A deep learning-based peer review method for radiotherapy planning. *Med Phys*. 2025;52(5):3309-3324. doi:10.1002/mp.17686

30) Zhu S, Ma SJ, Farag A, et al. Artificial intelligence, machine learning and big data in radiation oncology. *Hematol Oncol Clin North Am*. 2025;39(2):453-469. doi:10.1016/j.hoc.2024.12.002

31) Li Q, Wright J, Hales R, Voong R, McNutt T. A digital physician peer to automatically detect erroneous prescriptions in radiotherapy. *NPJ Digit Med*. 2022;5(1):158. doi:10.1038/s41746-022-00703-9

32) Mathew F, Wang H, Montgomery L, Kildea J. Natural language processing and machine learning to assist radiation oncology incident learning. *J Appl Clin Med Phys*. 2021;22(11):172-184. doi:10.1002/acm2.13437

33) Syed K, Sleeman W IV, Hagan M, et al. Automatic incident triage in radiation oncology incident learning system. *Healthcare*. 2020;8(3):272. doi:10.3390/healthcare8030272

34) Bracken A, Reilly C, Feeley A, et al. Artificial Intelligence (AI) - powered documentation systems in healthcare: a systematic review. *J Med Syst*. 2025;49(1):28. doi:10.1007/s10916-025-02157-4

REVIEW

Stereotactic Radiosurgery and Immunotherapy for Melanoma and NSCLC Brain Metastases: Practical Integration, Timing, and Toxicity

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Abstract

Brain metastases remain a major cause of morbidity and mortality in patients with cancer, particularly melanoma and non-small cell lung cancer. Stereotactic radiosurgery (SRS) is a cornerstone of management for limited intracranial disease, offering high local control while minimizing the neurocognitive toxicity associated with whole-brain radiation therapy. Immune checkpoint inhibitors (ICIs) have also transformed systemic therapy for tumors with central nervous system involvement, creating an increasing clinical need to define how best to integrate these modalities. The combined use of SRS and ICIs has raised an important question regarding optimal treatment timing. Retrospective evidence suggests that concurrent or near-concurrent administration, commonly defined as treatment within approximately 2-4 weeks, may improve local control and intracranial response. Several studies also suggest a potential survival advantage compared with sequential treatment, although these findings are limited by selection bias and require prospective validation. Most contemporary analyses do not show a significant increase in radionecrosis with concurrent single-agent ICI; however, emerging data suggest that dual checkpoint blockade may increase the risk of symptomatic radionecrosis. This narrative review synthesizes the biologic rationale, clinical evidence, and toxicity considerations for combining SRS and ICIs in patients with brain metastases. We emphasize differences between single-agent and dual ICI strategies, highlight dosimetric predictors of radionecrosis such as V12 Gy, and propose a practical framework for treatment integration. Overall, concurrent SRS with single-agent ICI appears feasible and is associated with favorable intracranial outcomes in selected patients, whereas dual ICI warrants more cautious, individualized decision-making. Prospective studies are needed to define optimal sequencing, patient selection, and toxicity mitigation strategies.

Keywords: stereotactic radiosurgery, immunotherapy, brain metastases, immune checkpoint inhibitors, melanoma, non-small cell lung cancer, radionecrosis, treatment timing, V12 Gy, hypofractionation

Introduction

Brain metastases occur in up to 20%-40% of patients with advanced solid malignancies and remain a major cause of neurologic morbidity and mortality.[1] The incidence is particularly high in melanoma, non-small cell lung cancer (NSCLC), and renal cell carcinoma (RCC), reflecting tumor biology and improved systemic therapies that prolong survival.[2] Although breast cancer is also a common source, it is not emphasized here due to the evolving role of immune checkpoint inhibitors (ICIs) in this setting.[3,4] Over the past decade, management has shifted toward focal therapies such as stereotactic radiosurgery (SRS) rather than

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whole-brain radiation therapy (WBRT) in appropriately selected patients.[5]

SRS is a standard treatment for brain metastases, delivering highly conformal ablative doses with excellent local control while preserving neurocognitive function.[6] Recent randomized data suggest that, in selected patients with multiple brain metastases, SRS may provide superior cognitive outcomes compared with hippocampal avoidance WBRT.[7] Concurrently, ICIs have transformed systemic therapy for melanoma, NSCLC, and other malignancies with central nervous system involvement.[8] As a result, patients increasingly receive both SRS and ICIs during their treatment course.[9]

This convergence raises a key clinical question: how should SRS and ICIs be optimally integrated, and does treatment timing influence outcomes and toxicity? The rationale for combination is biologically compelling. Radiation enhances tumor immunogenicity through antigen release, dendritic cell activation, and T-cell priming, potentially synergizing with checkpoint blockade.[10] However, this immune activation may also increase inflammatory toxicity, including radiation necrosis (RN) and edema.[11]

Despite expanding clinical experience, optimal sequencing remains uncertain. Current evidence is largely retrospective and heterogeneous, with variable definitions of "concurrent" therapy and differences in histology and treatment regimens. Nonetheless, consistent patterns suggest improved intracranial outcomes with concurrent treatment and highlight important toxicity differences between single-agent and dual ICI strategies.[12,13]

This narrative review provides a clinically focused synthesis of the evidence on SRS-ICI integration in brain metastases, emphasizing biologic rationale, treatment timing, efficacy, and toxicity. We also propose a practical framework for clinical decision-making and highlight key areas for future research.

Methods of Literature Review

This narrative review was conducted using focused searches of PubMed, Embase, and Scopus. Search terms included combinations of "brain metastases," "stereotactic radiosurgery," "stereotactic radiation therapy," "immune checkpoint inhibitors," "PD-1," "PD-L1," "CTLA-4," "timing," "concurrent," "sequential," and "radionecrosis."

Priority was given to multicenter studies, contemporary retrospective analyses, prospective trials, and meta-analyses published between 2016 and 2026. Studies evaluating treatment timing, local control, overall survival, and RN were included, with emphasis on melanoma and NSCLC cohorts.

Biological Rationale for Combining SRS and Immunotherapy

The rationale for combining SRS with ICIs is based on radiation-induced immune modulation.[10] High-dose focal radiation promotes immunogenic cell death, enhancing antigen release, dendritic cell activation, and T-cell priming, thereby transforming the irradiated lesion into an in situ vaccine-like stimulus.[14,15]

Radiation also modulates the tumor microenvironment by increasing major histocompatibility complex expression, enhancing T-cell infiltration, and altering cytokine signaling.[16] These effects may augment ICI efficacy, which functions by relieving inhibitory signals on T cells and sustaining antitumor immune responses.[17] This biologic synergy supports combining SRS and ICIs, particularly when delivered in close temporal proximity.[18-20]

However, these same mechanisms may also increase toxicity. RN is a multifactorial process involving vascular injury, hypoxia, and immune-mediated inflammation.[21] ICIs may amplify these pathways, particularly with dual checkpoint blockade, potentially increasing the risk of treatment-related toxicity.[11]

Clinical Evidence on Treatment Timing

Definition of Concurrent Treatment

A major limitation in the literature is the lack of a standardized definition of "concurrent" treatment. Definitions vary across studies, ranging from within 1, 2, or 4 weeks to within one pharmacokinetic half-life of the ICI agent.[19]

Despite this variability, most studies adopt a practical definition of concurrent therapy as SRS delivered within approximately 2 to 4 weeks of ICI administration.[9,13] Some analyses suggest that shorter intervals, particularly within 2 weeks or one half-life, may be associated with improved intracranial response, although optimal timing remains uncertain.[19]

Evidence in Melanoma

The emergence of dual checkpoint blockade has significantly altered the management of melanoma brain metastases.[22] Prospective phase II studies have demonstrated durable intracranial activity with nivolumab plus ipilimumab in asymptomatic patients. In CheckMate 204, Tawbi et al reported an intracranial objective response rate of 57%, establishing dual checkpoint blockade as a highly active systemic therapy for untreated melanoma brain metastases.[23] Long-term follow-up demonstrated durable benefit, with 3-year intracranial progression-free survival and overall survival rates of 54.1% and 71.9%, respectively.[24] Similarly, the randomized phase II ABC trial showed superior intracranial response and long-term survival with

nivolumab plus ipilimumab compared with nivolumab alone, supporting dual checkpoint blockade as the preferred systemic approach in asymptomatic patients.[25] These findings have raised important questions regarding the optimal integration of SRS, which are being addressed in the ongoing ABC-X trial evaluating nivolumab plus ipilimumab with or without concurrent intracranial SRS.[26]

Against this backdrop of highly effective systemic therapy, multiple retrospective studies have evaluated whether the addition and timing of SRS further improve intracranial outcomes. Kotecha et al reported that timing influences efficacy more than toxicity, with concurrent ICI improving response and low RN (3%-5%),[19] while Carron et al confirmed low toxicity with anti-PD-1 therapy (adverse radiation effect 4%-5%, symptomatic <3%).[27]

Regimens incorporating CTLA-4 inhibition, particularly dual ICI, are associated with higher RN rates, although estimates vary. Minniti et al reported moderate RN (15%-25%) with concurrent nivolumab/ipilimumab.[28] In contrast, Tang et al demonstrated significantly improved local control (92% vs 64%) without excess toxicity or increased RN.[29] Fu et al similarly observed improved survival with concurrent SRS-ICI (37.1 vs 11.4 months) without increased radiation toxicity (2%-3%).[30] More recent data from Messing et al show excellent local control (90%) with low symptomatic RN (7%), while identifying prior systemic therapy as a prognostic factor.[31] Conversely, Vaios et al reported higher RN rates with dual ICI (20%-25%),[11] whereas Mandalà et al demonstrated survival benefit with moderate RN (10%).[32] Key retrospective studies are summarized in **Table 1**.

Overall, evidence is heterogeneous and predominantly retrospective yet supports close temporal integration of SRS and ICI to optimize intracranial control. ICI regimen and prior therapy exposure may influence toxicity and outcomes, warranting prospective validation.

Evidence in NSCLC

NSCLC has a growing but less mature evidence base for SRS-ICI integration compared with melanoma. Early-phase prospective studies demonstrate feasibility, safety, and encouraging intracranial control.[33-36]

Across retrospective cohorts, SRS combined with ICI has consistently been associated with improved intracranial control and, in some studies, overall survival. Foundational studies by Chen et al and Schapira et al demonstrated superior survival and intracranial control with concurrent SRS-ICI (within 2-4 wk) compared with nonconcurrent approaches.[13,37] Larger analyses, including Yomo et al, confirmed improved survival (mOS 16.9 vs 12.0 mo) and intracranial PFS without increased toxicity, findings that were also supported by Bashir et al.[38,39]

Some studies have highlighted differential response patterns. Shepard et al reported higher complete response rates with concurrent ICI (50% vs 15.6%) without a survival benefit,[40] while Singh et al demonstrated greater tumor shrinkage in larger lesions (>500 mm^3), suggesting size-dependent synergy.[41] Concurrent therapy has also been associated with improved distant intracranial control, particularly with shorter treatment intervals (≤7 d).[42,43] More recent studies by Dohm et al, Frehner et al, and Lu et al further support improved intracranial response with upfront or concurrent SRS, although overall survival benefits remain inconsistent, suggesting a potential role for selective or deferred radiation in asymptomatic patients.[44-46] Key retrospective studies are summarized in **Table 2**.

Importantly, RN and adverse radiation effects remain low (3%-10%) and are not consistently increased with ICI. Established dosimetric factors, particularly V12 Gy, appear to remain the primary drivers of radionecrosis (RN) risk in patients receiving ICIs.[47]

Evidence in RCC

RCC represents a distinct clinical scenario compared with melanoma and NSCLC. Although ICI have improved outcomes in metastatic RCC, intracranial activity remains modest, and local therapy continues to play a central role.[48,49] In the NIVOREN study, nivolumab monotherapy demonstrated limited intracranial efficacy, with an intracranial response rate of 12% and median intracranial progression-free survival of 2.7 months.[48] In contrast, CheckMate 920 reported improved outcomes with nivolumab plus ipilimumab, achieving an objective response rate of 32% and median progression-free survival of 9.0 months in patients with asymptomatic brain metastases.[49] Consequently, SRS remains a cornerstone of management for RCC brain metastases.[50,51] Emerging retrospective data suggest that concurrent SRS and ICI may improve intracranial control and survival without substantially increasing RN risk.[9,13,52] Concurrent ICI has not been associated with increased symptomatic RN, and dosimetric factors such as V12 Gy appear to remain the primary determinants of toxicity.[9,53] However, prospective data defining the optimal integration of SRS and immunotherapy in RCC remain limited.

Evidence From Pooled and Meta-Analyses

Pooled and meta-analytic evidence supports combining SRS with ICI, with stronger and more consistent benefit in melanoma than NSCLC. In melanoma, systematic reviews highlight a shift toward multimodal, patient-specific strategies integrating SRS, immunotherapy, and systemic

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Table 1. Key Retrospective Studies of Stereotactic Radiosurgery Combined With Immune Checkpoint Inhibitors in Melanoma Brain Metastases

STUDY	SAMPLE SIZE	ICI REGIMEN	TREATMENT ARMS	TIMING DEFINITION	RN DEFINITION	RN RISK	KEY EFFICACY + SURVIVAL OUTCOME	KEY TAKEAWAY
Kotecha et al[19]	150 pts / 1003 lesions	PD-1 dominant	SRS + ICI (timing cohorts)	Immediate vs concurrent vs delayed	Radiographic RN; symptomatic cases reported separately	3.2%-3.5%; 7 symptomatic cases	CR ↑ (50% vs 32%); durable response ↑ (94% vs 71%); OS ~30 mo	Timing > toxicity; immediate/ concurrent optimal; steroids detrimental
Minniti et al[28]	80 pts / 326 lesions	PD-1 vs CTLA-4	SRS + nivolumab; SRS + ipilimumab	Concurrent (~1 wk)	MRI/F-DOPA PET-defined RN; Grade 3 RN separately reported	20% (Nivo) vs 29% (Ipi); Grade 3 RN: 9% vs 11%	PFS/LC/OS favor PD-1; OS 22 vs 14.7 mo	PD-1-based SRS associated with better outcomes; higher RN with CTLA-4
Carron et al[27]	50 pts / 188 lesions	PD-1 only	SRS + anti-PD-1	Concurrent ≤3 mo	MRI defined ARE; symptomatic subset reported	4.4% of lesions (8/181); 14.6% of patients (7/48); 6 symptomatic cases (12.5%)	PFS ~13 mo; OS ~16.6 mo (1-yr ~60%)	Favorable survival with low RN; safe PD-1 + SRS
Tang et al[29]	49 pts / 158 lesions	Dual ICI	Nivo + Ipi ± SRS	Concurrent (median 8 d; within 6 wk)	Symptomatic RN only; pathologic confirmation or multidisciplinary review;	6.0% (5/84 lesions)	LC ↑ (92% vs 64%); OS similar (~72% vs 71% at 1 yr)	SRS improves LC without added toxicity; no OS benefit
Fu et al[30]	98 pts	ICI	Concurrent vs non-concurrent SRS + ICI	≤4 wk	CTCAE CNS necrosis/ARE; symptomatic status not specified	2% (concurrent) vs 3% (non-concurrent)	OS ↑ (37 vs 11 mo); PFS ↔	Concurrent ICI improves OS without ↑ RN; edema slightly ↑
Vaios et al[11]	288 pts / 1704 lesions	Dual vs single/no ICI	SRS + dual vs single vs none	Concurrent ≤4 wk	CTCAE grade ≥2 symptomatic RN only; pathologic or clinical-radiographic diagnosis	21.8% (dual ICI) vs 13.5% (single ICI); no ICI 13.7%	RN associated with worse OS	Dual ICI significantly increases RN risk
Mandalà et al[32]	453 pts	Dual ICI (Nivo + Ipi)	Dual ICI ± SRT	Concomitant ≤2 wk	MRI defined RN with clinical follow-up; symptomatic status not specified	10.3% (10.9% sequential vs 9.3% concomitant)	OS ↑ with SRT (27.3/22.2 vs 9.4 mo); no difference between concomitant vs sequential SRT	SRT improves OS regardless of timing
Messing et al[31]	68 pts / 413 lesions	Dual ICI (Nivo + Ipi)	SRS + concurrent dual ICI	≤8 wk	MRI perfusion/ permeability sequences, MR spectroscopy, symptomatic RN only	7% (5 patients)	OS 24 mo; 12-mo 64%, 24-mo 50%; LC ~ 89%	Durable control; prior ICI/targeted therapy predicts worse outcomes

Data extracted and synthesized from cited studies; table created by the authors.

ARE, adverse radiation effects; conc, concurren; CR, complete response; CTCAE, Common Terminology Criteria for Adverse Events; CTLA-4, cytotoxic T-lymphocyte-associated antigen 4; ICI, immune checkpoint inhibitor; Ipi, ipilimumab; LC, local control; Nivo, nivolumab; OS, overall survival; PD-1, programmed cell death-1; PFS, progression-free survival; pts, patients; RN, radionecrosis; seq., sequential; SRS, stereotactic radiosurgery; SRT, stereotactic radiation therapy.

Table 2. Key Retrospective Studies of Stereotactic Radiosurgery Combined With Immune Checkpoint Inhibitors in Non-Small Cell Lung Cancer Brain Metastases

STUDY	SAMPLE SIZE	ICI REGIMEN	TREATMENT ARMS	TIMING DEFINITION	RN DEFINITION	RN RISK	KEY EFFICACY + SURVIVAL OUTCOME	KEY TAKEAWAY
Yomo et al[38]	585 pts	Mixed ICIs	SRS + ICI vs SRS	Concurrent ≤3 mo	CTCAE v4.0 toxicity grading used	One grade 4 RN, 5 grade 3 RN	mOS 16.9 vs 12.0 mo; HR 0.62; IC-PFS ↑ (35% vs 26%)	Concurrent SRS-ICI associated with improved OS and IC-PFS without ↑ toxicity
Shepard et al[40]	51 pts	PD-1/PD-L1	SRS + ICI vs SRS	ICI within 3 mo	Radiographic RN; included symptomatic RN	Symptomatic RN 2.9% (1/34); no increased RN or intratumoral hemorrhage risk with concurrent ICI	No OS/PFS benefit; CR ↑ (50% vs 15.6%); faster regression	Improved radiographic response without survival benefit
Singh et al[41]	85 pts	Anti–PD-1	SRS + ICI vs SRS + chemo	Variable (subset ≤4 wk)	RN confirmed by histopathology or imaging changes	RN: 10.2% (4/39) vs 10.9% (5/46) (P = 0.7)	No OS benefit (10 vs 11.6 mo); large lesions (>500 mm^3) response ↑ (90% vs 47.8%)	Benefit limited to larger lesions; no overall survival advantage
Singh et al[42]	99 pts	PD-1/PD-L1	SRS + ICI vs SRS + chemo vs SRS + TKI	Concurrent ≤30 d	RN defined by pathology or multidisciplinary MRI review	RN in 34/136 SRS sessions (25%); no increased RN risk with ICI.	1-yr DI-PFS ↑ (67% vs 37% vs 39%); PD-L1 ≥50%: 80%	Concurrent ICI improves intracranial control, especially PD-L1-high
Frehner et al[45]	128 pts	ICI ± chemo	ICI ± chemo + upfront SRT vs ICI ± chemo	Upfront SRT vs none	CTCAE v5.0 CNS adverse events recorded; included symptomatic RN	Symptomatic RN 3.4% (2/58); no fatal CNS adverse events.	iPFS ↑ (12.6 vs 8.2 mo; HR 0.62); no OS benefit (22.8 vs 21.7 mo)	Upfront SRT improves intracranial control; deferral feasible without OS compromise
Chung et al[47]	82 pts	ICI/TKI	Reduced-dose vs standard-dose SRS	Concurrent ≤30 d	Radiographic AREs (radiation necrosis + edema) assessed	AREs: 10.8% vs 23.7% (P = 0.020)	LC similar (94.6% vs 90.3%)	Dose reduction maintains control with lower toxicity

Data extracted and synthesized from the cited studies; table created by the authors.

ARE, adverse radiation effect; CR, complete response; CTCAE, Common Terminology Criteria for Adverse Events; DI-PFS, distant intracranial progression-free survival; ICI, immune checkpoint inhibitor; IC-PFS, intracranial progression-free survival; iPFS, intracranial progression-free survival; LC, local control; OS, overall survival; PFS, progression-free survival; pts, patients; RN, radionecrosis; RN, radionecrosis; SRS, stereotactic radiosurgery; SRT, stereotactic radiation therapy; TKI, tyrosine kinase inhibitor; TKI, tyrosine kinase inhibitor.

therapy.[54] In melanoma, meta-analyses demonstrate significant survival benefit with SRS-ICI, particularly with anti-PD-1 regimens,[55] while Bayesian network analyses rank SRS + ICI as the most effective strategy for overall survival and intracranial control, albeit with increased RN risk.[56] Timing analyses further suggest that concurrent SRS-ICI (within 4 wk) improves survival and intracranial outcomes compared with nonconcurrent approaches.[12,57]

Contemporary pooled data report high local control (80%-85%) and favorable 1-year survival (65%-70%), with RN

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rates of approximately 10% to 12% in the modern immunotherapy era.[58] Importantly, large multicenter analyses indicate that RN risk is primarily driven by dosimetric factors, particularly V12 Gy, rather than treatment timing, supporting the safety of concurrent approaches when appropriate constraints are applied.[9]

In NSCLC, pooled data suggest a more nuanced interaction. Chu et al found no survival advantage with the addition of cranial radiation therapy to ICI, although concurrent treatment reduced distant brain failure.[59] In contrast, Yang et al demonstrated improved overall survival with combined radiation therapy and ICI compared with radiation therapy alone, with concurrent treatment emerging as the optimal strategy without increased toxicity.[60] Collectively in NSCLC, these findings suggest that immunotherapy is the primary driver of survival, whereas SRS primarily enhances intracranial disease control. Major pooled analyses are summarized in **Table 3**.

Comparative Considerations: Melanoma vs NSCLC

Important distinctions exist between melanoma and NSCLC in the context of SRS-ICI integration. In melanoma, evidence consistently supports a synergistic benefit, particularly with concurrent treatment.[12,55,56] In NSCLC, outcomes are more heterogeneous, with immunotherapy driving survival and radiation therapy contributing primarily to intracranial control in a context-dependent manner.[59,60] Molecular subgroups further influence treatment decisions; tumors with actionable driver mutations (e.g., EGFR, ALK) often respond well to CNS-penetrant targeted therapies,[61] and these mutations are less responsive to ICI,[62] limiting the role in SRS-ICI integration in this entity. In these cases, SRS is typically reserved for oligoprogressive or symptomatic disease.

Role of Dosimetry and Treatment Factors

RN following SRS is multifactorial and cannot be attributed to treatment timing alone. While much of the literature focuses on the temporal relationship between SRS and ICI, radiation dose-volume parameters appear to remain the primary determinants of toxicity, particularly with combined-modality therapy.

Among dosimetric parameters, the volume of normal brain receiving 12 Gy (V12 Gy) is the most robust and consistently validated predictor of RN. In a large multicenter analysis by Lehrer et al including 657 patients and over 4000 brain metastases, V12 Gy was independently associated with RN risk, not the timing of ICI administration.[9] Increasing V12 Gy correlates with stepwise toxicity, with low-risk (<12 cm^3), intermediate-risk (12-20 cm^3), and high-risk (>20 cm^3) groups demonstrating progressively higher rates.[9] These findings underscore that dosimetric optimization remains the primary determinant of RN risk, even in the era of immunotherapy.

Additional dosimetric and treatment-related factors contribute to the risk of RN. Treatment of larger lesions (typically >2 cm) requires higher integral dose and results in greater exposure of surrounding normal brain tissue.[47,63,64] In patients with multiple brain metastases, cumulative treated volume increases overall brain dose and expands the low-dose radiation bath.[65] Prior cranial irradiation, including previous SRS or WBRT, further reduces normal tissue tolerance and may further increase the risk of RN.[66]

Clinical factors, including baseline edema, corticosteroid use, and lesion location, particularly in eloquent or deep brain regions, may influence both the risk and clinical impact of RN.[67,68] These factors may interact with immunotherapy, as immune activation can amplify inflammatory responses.

Overall, these findings support a shift in clinical thinking. RN risk should not be viewed solely through treatment timing, but rather through an integrated framework incorporating dosimetry, lesion characteristics, prior treatment, and immunotherapy regimen. In particular, patients with high-risk dosimetric features (e.g., elevated V12 Gy or large target volume) combined with clinical modifiers such as dual checkpoint blockade or significant perilesional edema may warrant treatment modification strategies, including dose optimization and hypofractionation.

Fractionation and Risk Mitigation Strategies

Hypofractionated stereotactic radiation therapy is commonly employed to mitigate the risk of RN, particularly for lesions >2 cm or when V12 Gy exceeds approximately 10 cm^3,[64] or those receiving dual immune checkpoint inhibition.[9] Although prospective data remain limited, this approach is widely adopted in clinical practice. By reducing peak dose to normal brain tissue, fractionation may help offset the increased inflammatory effects associated with concurrent immunotherapy.

Radiographic Assessment and Diagnostic Challenges

Distinguishing pseudoprogression, RN, and true tumor progression after SRS in patients receiving ICIs remains a major diagnostic challenge, as all may present with enlarging contrast-enhancing lesions on MRI.[69,70] Pseudoprogression typically occurs early in the first few months (approximately 6 months), whereas RN is a delayed effect, often developing 6 to 12 months post SRS.[71-73] The combined inflammatory effects of SRS and immunotherapy further complicate interpretation. The iRANO criteria recommend confirmatory imaging within 6 months of ICI initiation.[74] Advanced imaging modalities, including perfusion MRI and amino acid PET, improve diagnostic accuracy,

Table 3. Systematic Review and Meta-Analytic Evidence on Stereotactic Radiosurgery and Immunotherapy in Melanoma and Non-Small Cell Lung Cancer Brain Metastases

STUDY	PREDOMINANT HISTOLOGY	SAMPLE SIZE	ICI REGIMEN	TREATMENT ARMS	RISK OF RADIONECROSIS	EFFICACY AND SURVIVAL OUTCOME	KEY TAKEAWAYS
Lehrer et al[12]	Mixed (melanoma dominant)	17 studies; 534 pts	CTLA-4, PD-1	Concurrent vs non-concurrent SRS + ICI	RN ~5.3%	1-yr OS: 64.6% vs 51.6%; improved LC	Early evidence supporting concurrent SRS + ICI
Badrigilan et al[57]	Predominantly melanoma	16 studies; 1356 pts	Mostly CTLA-4, some PD-1	SRS + ICI vs SRS; timing comparisons	No significant increase	Improved OS and local control	Supports concurrent strategy without clear toxicity increase
Chu et al[59]	NSCLC	46 trials; 3160 pts	PD-1, PD-L1, CTLA-4	ICI vs ICI + RT; SRS vs WBRT	Not primary endpoint	PFS HR ~0.48; OS HR ~0.64; ↓ DBF (OR 0.15)	ICI drives survival; RT improves intracranial control
Yang et al[60]	NSCLC	19 studies	PD-1/PD-L1/ CTLA-4	RT + ICI vs RT alone	No ↑ grade 3-4 toxicity	OS improved (HR ~0.77 vs RT alone)	Adding ICI to RT improves survival
Lehrer et al[12]	Mixed (melanoma, NSCLC, RCC)	657 pts; 4182 mets	PD-1, PD-L1, CTLA-4	Concurrent vs non-concurrent SRS + ICI	RN ~ 10 %; symptomatic ~6%-7%	No major OS difference by timing	RN driven by dosimetry (V12 Gy)
Williams et al[55]	Melanoma	126 studies; ~6500 pts	Anti–PD-1, CTLA-4, mixed	SRS + ICI vs SRS or ICI alone	Not consistently reported	~30%-65% reduction in mortality risk	Strong survival benefit with SRS + ICI
Li et al[56]	Melanoma	10 studies; 836 pts	ICI ± targeted therapy	SRS + ICI vs SRS alone or ICI alone	Higher RN risk with SRS + ICI vs SRS alone	OS improved vs SRS alone (HR ~0.64); intracranial PFS improved vs ICI alone (HR ~0.66)	SRS + ICI ranked best for OS and intracranial control
Grant et al[54]	Melanoma	70 studies	ICI, targeted therapy	Multimodal approaches	Low neurotoxicity	mOS ~5-16 months	Supports multimodal integration
Ahmadvand et al[58]	Mixed	16 studies; 1529 pts	PD-1/PD-L1 inhibitors	SRS + ICI	RN ~12 %; ARE ~31%	LC ~84% (12 mo); 1-yr OS ~67%	High control with measurable RN risk

Data extracted and synthesized from pooled and meta-analytic studies; table created by the authors.

ARE, adverse radiation effects; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; DBF, distant brain failure; HR, hazard ratio; ICI, immune checkpoint inhibitor; LC, local control; mOS, median overall survival; NSCLC, non-small cell lung cancer.; OR, odds ratio; OS, overall survival; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PFS, progression-free survival; pts, patients; RCC, renal cell carcinoma; RN, radionecrosis; SRS, stereotactic radiosurgery.

though uncertainty often necessitates multidisciplinary evaluation and serial imaging.[69] Amino acid PET tracers, particularly fluoroethyltyrosine PET and methionine PET, provide greater specificity than conventional MRI for distinguishing RN from tumor progression and are increasingly used in contemporary diagnostic algorithms.[69,75,76]

Comparison of reported RN rates across studies is limited by heterogeneity in diagnostic criteria and outcome definitions. Some studies report only symptomatic RN, whereas others include

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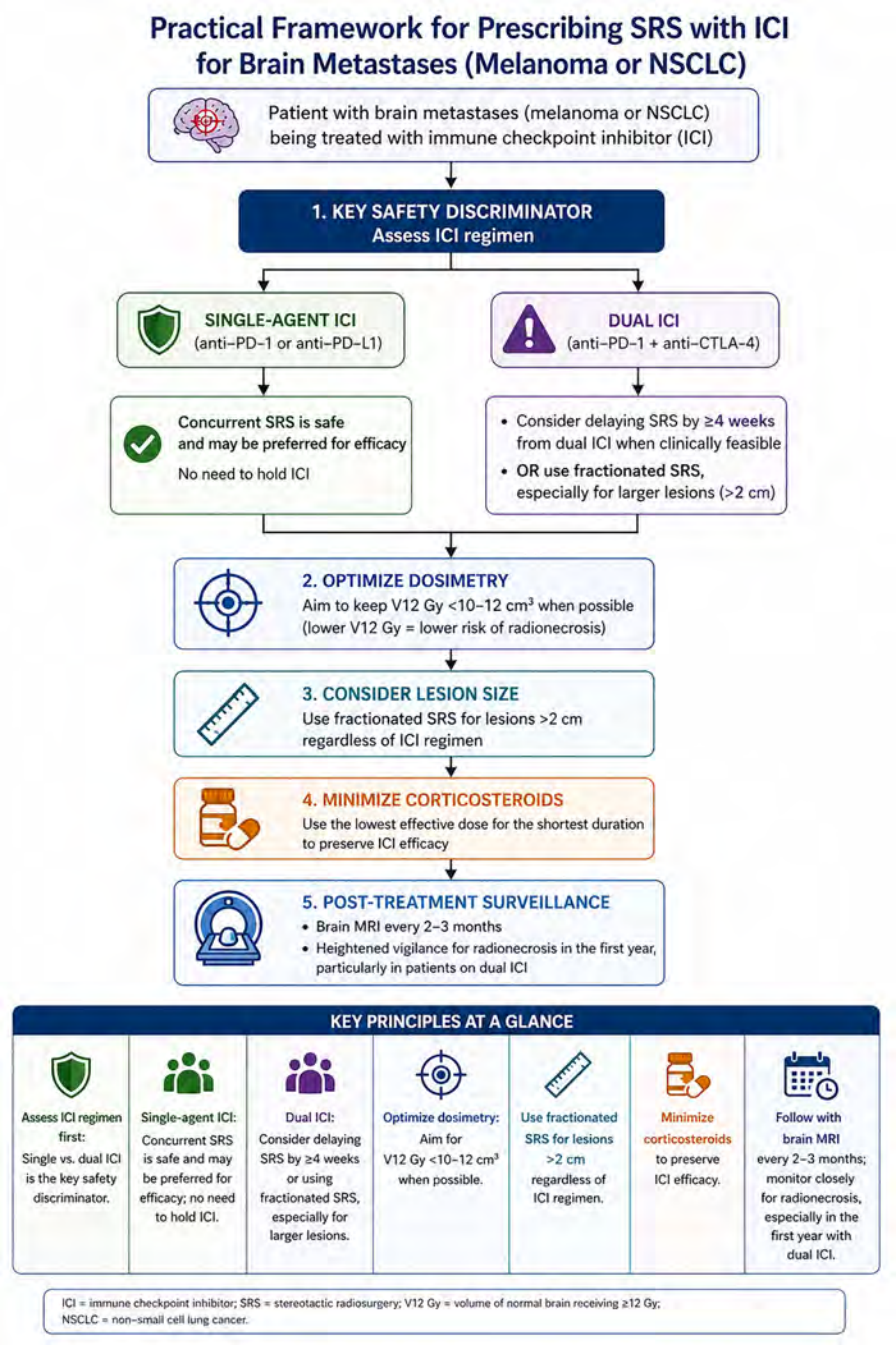
Figure 1. Practical framework for prescribing stereotactic radiosurgery (SRS) with immune checkpoint inhibitors (ICIs) for brain metastases from melanoma or non–small cell lung cancer (NSCLC). The algorithm highlights ICI regimen as the primary safety discriminator, favoring concurrent SRS with single-agent anti–PD-1/PD-L1 therapy and consideration of delayed or fractionated SRS with dual ICI therapy (anti–PD-1 plus anti–CTLA-4).



asymptomatic radiographic changes or broader adverse radiation effects, likely contributing to variability in reported RN incidence. Studies reporting only symptomatic RN generally demonstrate lower rates than those incorporating radiographic or asymptomatic RN. Therefore, RN rates should be interpreted with caution when comparing outcomes across studies.

Management of RN

Management of RN after SRS follows a stepwise, symptom-guided approach. Asymptomatic cases may be observed with serial imaging, while symptomatic patients are treated with corticosteroids using the lowest effective dose and gradual taper. Bevacizumab is effective in steroid-refractory cases, with response rates exceeding 80% and significant radiographic improvement.[77-79] Emerging evidence suggests that Boswellia serrata reduces RN-associated edema, with a retrospective series reporting radiographic improvement in approximately 60% of patients and a favorable safety profile, although prospective validation is needed.[80] Surgical resection or laser interstitial thermal therapy (LITT) is reserved for refractory or diagnostically uncertain cases, providing tissue confirmation and durable control.[81] Emerging data suggest comparable efficacy between bevacizumab and LITT.[82] Management should be individualized based on symptoms, lesion characteristics, and diagnostic certainty.

Limitations of Current Evidence

The current literature is limited by its predominantly retrospective nature, heterogeneity in study design, and variability in definitions of concurrent treatment. Confounding by indication and challenges in distinguishing RN from tumor progression further complicate interpretation.

Practical Clinical Implications

The integration of SRS with ICI in clinical practice requires a structured, risk-adapted approach that incorporates

immunotherapy regimen, dosimetric parameters, lesion characteristics, and patient-specific factors.

Concurrent SRS with single-agent ICI is generally well tolerated and may enhance local control without a substantial increase in RN risk.[19] In this context, concurrent or near concurrent SRS, typically within 2 to 4 weeks, is a reasonable and commonly adopted approach. In contrast, dual checkpoint blockade may be associated with an increased risk of symptomatic RN in some studies, although the evidence remains heterogeneous and warrants a more cautious integration strategy.[11] For these patients, delayed SRS by ≥4 weeks or the use of hypofractionated regimens should be considered, particularly for larger lesions or those with high-risk features.[11]

The volume of normal brain receiving 12 Gy (V12 Gy) has been one of the most consistently validated predictors of RN in SRS literature and remains highly relevant in patients receiving concurrent immunotherapy.[9] Efforts to minimize normal brain dose are essential, with V12 Gy thresholds serving as a practical guide for risk stratification. Hypofractionated SRS should be considered for lesions greater than 2 cm[83] or when V12 Gy constraints cannot be met, particularly in patients receiving dual ICI.

Additional factors, including baseline edema, corticosteroid use, prior cranial irradiation, and intracranial disease burden, may influence efficacy and toxicity and should inform individualized treatment planning. Minimizing corticosteroid exposure is particularly important given its potential impact on immunotherapy efficacy.[84]

Overall, optimal integration of SRS and ICI requires a composite clinical framework that prioritizes immunotherapy regimen, dosimetric risk, and lesion characteristics rather than relying on treatment timing alone. A practical decision-making framework is summarized in (**Figure 1**).

Future Directions

Future research efforts should focus on prospective trials to define optimal timing and sequencing, alongside strategies such as dose de-escalation and fractionation to reduce toxicity.[25,47] Emerging biomarkers, including neutrophil-to-lymphocyte ratio, early $CD8^+$ T-cell activation, tumor aneuploidy, and immune-inflammatory signatures, may help identify patients most likely to benefit from combined therapy and guide immunotherapy selection.[16,85] Additional areas include exploiting the abscopal effect,[86] novel immune targets, advanced imaging, and multimodality approaches.[87-89]

Conclusion

The integration of SRS and ICIs represents a major advance in the management of brain metastases. Concurrent SRS with single-agent ICI appears feasible and may enhance intracranial control without significantly increasing toxicity. In contrast, dual checkpoint blockade and higher dose volume exposure (particularly V12 Gy) define a higher-risk population for RN, necessitating more cautious, individualized strategies. Optimal integration requires consideration of not only timing, but also immunotherapy regimen, lesion characteristics, fractionation, and dosimetric parameters. Prospective studies are needed to define these relationships and guide evidence-based clinical decision-making.

References

1) Lamba N, Wen PY, Aizer AA. Epidemiology of brain metastases and leptomeningeal disease. *Neuro Oncol*. 2021;23(9):1447-1456. doi:10.1093/neuonc/noab101

2) Cagney DN, Martin AM, Catalano PJ, et al. Incidence and prognosis of patients with brain metastases at diagnosis of systemic malignancy: a population-based study. *Neuro Oncol*. 2017;19(11):1511-1521. doi:10.1093/neuonc/nox077

3) Zou Y, Wu J, Yuan Z, He X, Tang H. Targeting the neuro-immune crosstalk in breast cancer brain metastases. *J Immunother Cancer*. 2026;14(4):e014134. doi:10.1136/jitc-2025-014134

4) Schlam I, Gatti-Mays ME. Immune checkpoint inhibitors in the treatment of breast cancer brain metastases. *Oncologist*. 2022;27(7):538-547. doi:10.1093/oncolo/oyac064

5) Vogelbaum MA, Brown PD, Messersmith H, et al. Treatment for brain metastases: ASCO-SNO-ASTRO guideline. *J Clin Oncol*. 2022;40(5):492-516. doi:10.1200/JCO.21.02314

6) Cherng H-RR, Sun K, Bentzen SM, et al. Redefining neurocognitive outcomes after radiation for brain metastases: a patient-level meta-analysis of recovery following initial decline. *J Natl Cancer Inst*. 2026;118(2):269-275. doi:10.1093/jnci/djaf264

7) Aizer AA, Shin K-Y, Catalano PJ, et al. Treatment for brain metastases with stereotactic radiation vs hippocampal-avoidance whole brain radiation: a randomized clinical trial. *JAMA*. 2026;335(13):1127-1136. doi:10.1001/jama.2026.0076

8) Aquilanti E, Brastianos PK. Immune checkpoint inhibitors for brain metastases: a primer for neurosurgeons. *Neurosurgery*. 2020;87(3):E281-E288. doi:10.1093/neuros/nyaa095

9) Lehrer EJ, Kowalchuk RO, Gurewitz J, et al. Concurrent administration of immune checkpoint inhibitors and single fraction stereotactic radiosurgery in patients with non-small cell lung cancer, melanoma, and renal cell carcinoma brain metastases. *Int J Radiat Oncol Biol Phys*. 2023;116(4):858-868. doi:10.1016/j.ijrobp.2023.01.017

10) Yoo KH, Park DJ, Choi JH, et al. Optimizing the synergy between stereotactic radiosurgery and immunotherapy for brain metastases. *Front Oncol*. 2023;13:1223599. doi:10.3389/fonc.2023.1223599

11) Vaios EJ, Shenker RF, Hendrickson PG, et al. Symptomatic necrosis with dual immune-checkpoint inhibition and radiosurgery for brain metastases. *JAMA Netw Open*. 2025;8(4):e254347. doi:10.1001/jamanetworkopen.2025.4347

12) Lehrer EJ, Peterson J, Brown PD, et al. Treatment of brain metastases with stereotactic radiosurgery and immune checkpoint inhibitors: an international meta-analysis of individual patient data. *Radiother Oncol*. 2019;130:104-112. doi:10.1016/j.radonc.2018.08.025

13) Chen L, Douglass J, Kleinberg L, et al. Concurrent immune checkpoint inhibitors and stereotactic radiosurgery for brain metastases in non-small cell lung cancer, melanoma, and renal cell carcinoma. *Int J Radiat Oncol Biol Phys*. 2018;100(4):916-925. doi:10.1016/j.ijrobp.2017.11.041

14) Portella L, Scala S. Ionizing radiation effects on the tumor microenvironment. *Semin Oncol*. 2019;46(3):254-260. doi:10.1053/j.seminoncol.2019.07.003

15) Jansen CS, Pagadala MS, Cardenas MA, et al. Pre-operative stereotactic radiosurgery and peri-operative dexamethasone for resectable brain metastases: a two-arm pilot study evaluating clinical outcomes and immunological correlates. *Nat Commun*. 2024;15(1):8854. doi:10.1038/s41467-024-53034-6

16) Lynch C, Pitroda SP, Weichselbaum RR. Radiotherapy, immunity, and immune checkpoint inhibitors. *Lancet Oncol*. 2024;25(8):e352-e362. doi:10.1016/S1470-2045(24)00075-5

17) Fukumura K, Jiang P, Yeboa DN, et al. Ionizing radiation enhances prognostically significant cellular immunity programs in the brain metastasis microenvironment. *Clinical Cancer Research*. 2026;32(11):2305-2316. doi:10.1158/1078-0432.CCR-25-3525

18) Sharabi AB, Lim M, DeWeese TL, Drake CG. Radiation and checkpoint blockade immunotherapy: radiosensitisation and potential mechanisms of synergy. *Lancet Oncol*. 2015;16(13):e498-509. doi:10.1016/S1470-2045(15)00007-8

19) Kotecha R, Kim JM, Miller JA, et al. The impact of sequencing PD-1/PD-L1 inhibitors and stereotactic radiosurgery for patients with brain metastasis. *Neuro Oncol*. 2019;21(8):1060-1068. doi:10.1093/neuonc/noz046

20) Qian JM, Martin AM, Martin K, et al. Response rate and local recurrence after concurrent immune checkpoint therapy and radiotherapy for non-small cell lung cancer and melanoma brain metastases. *Cancer*. 2020;126(24):5274-5282. doi:10.1002/cncr.33196

21) Vaios EJ, Winter SF, Shih HA, et al. Novel mechanisms and future opportunities for the management of radiation necrosis in patients treated for brain metastases in the era of immunotherapy. *Cancers*. 2023;15(9):2432. doi:10.3390/cancers15092432

22) Kalaora S, Nagler A, Wargo JA, Samuels Y. Mechanisms of immune activation and regulation: lessons from melanoma. *Nat Rev Cancer*. 2022;22(4):195-207. doi:10.1038/s41568-022-00442-9

23) Tawbi HA, Forsyth PA, Algazi A, et al. Combined nivolumab and ipilimumab in melanoma metastatic to the brain. *N Engl J Med*. 2018;379(8):722-730. doi:10.1056/NEJMoa1805453

24) Tawbi HA, Forsyth PA, Hodi FS, et al. Long-term outcomes of patients with active melanoma brain metastases treated with combination nivolumab plus ipilimumab (CheckMate 204): final results of an open-label, multicentre, phase 2 study. *Lancet Oncol*. 2021;22(12):1692-1704. doi:10.1016/S1470-2045(21)00545-3

25) Long GV, Atkinson V, Lo SN, et al. Ipilimumab plus nivolumab versus nivolumab alone in patients with melanoma brain metastases (ABC): 7-year follow-up of a multicentre, open-label, randomised, phase 2 study. *Lancet Oncol*. 2025;26(3):320-330. doi:10.1016/S1470-2045(24)00735-6

26) Melanoma Institute Australia. A phase II, open-label, randomized, controlled trial of ipilimumab and nivolumab with concurrent intracranial stereotactic radiotherapy versus ipilimumab and nivolumab alone in patients with melanoma brain metastases; 2026. Accessed May 21, 2026. https://clinicaltrials.gov/study/NCT03340129

27) Carron R, Gaudy-Marqueste C, Amatore F, et al. Stereotactic radiosurgery combined with anti-PD1 for the management of melanoma brain metastases: a retrospective study of safety and efficacy. *Eur J Cancer*. 2020;135:52-61. doi:10.1016/j.ejca.2020.04.028

28) Minniti G, Anzellini D, Reverberi C, et al. Stereotactic radiosurgery combined with nivolumab or ipilimumab for patients with melanoma brain metastases: evaluation of brain control and toxicity. *J Immunother Cancer*. 2019;7(1):102. doi:10.1186/s40425-019-0588-y

29) Tang JD, Mills MN, Nakashima J, et al. Clinical outcomes of melanoma brain metastases treated with nivolumab and ipilimumab alone versus nivolumab and ipilimumab with stereotactic radiosurgery. *J Neurooncol*. 2024;166(3):431-440. doi:10.1007/s11060-023-04543-9

30) Fu AY, Bernstein K, Zhang J, et al. Outcomes of concurrent versus non-concurrent immune checkpoint inhibition with stereotactic radiosurgery for melanoma brain metastases. *J Neurooncol*. 2025;173(3):619-625. doi:10.1007/s11060-025-05026-9

31) Messing I, Linkowski L, Riina MD, et al. Outcomes after SRS and ipilimumab plus nivolumab for melanoma brain metastases following prior immune checkpoint inhibitor or targeted therapy. *Oncologist*. 2026;31(4):oyag043. doi:10.1093/oncolo/oyag043

32) Mandalà M, Amaral T, Rutkowski P, et al. Combined immunotherapy with nivolumab and ipilimumab with and without sequential or concomitant stereotactic radiotherapy in patients with melanoma brain metastasis: an international retrospective study. *Eur J Cancer*. 2025;225:115567. doi:10.1016/j.ejca.2025.115567

33) Altan M, Wang Y, Song J, et al. Nivolumab and ipilimumab with concurrent stereotactic radiosurgery for intracranial metastases from non-small cell lung cancer: analysis of the safety cohort for non-randomized, open-label, phase I/II trial. *J Immunother Cancer*. 2023;11(7):e006871. doi:10.1136/jitc-2023-006871

34) ASCO. Phase 1, 2 trial of concurrent anti-PD1 and stereotactic radiosurgery for melanoma and non-small cell lung cancer brain metastases (NCT02858869); 2026. Accessed April 22, 2026. https://www.asco.org/abstracts-presentations/196838

35) Xu Y, Chen K, Xu Y, et al. Brain radiotherapy combined with camrelizumab and platinum-doublet chemotherapy for previously untreated advanced non-small-cell lung cancer with brain metastases (C-brain): a multicentre, single-arm, phase 2 trial. *Lancet Oncol*. 2025;26(1):74-84. doi:10.1016/S1470-2045(24)00643-0

36) Li Y-S, Yu Q, Bu Q, et al. First-line camrelizumab versus placebo plus chemotherapy with or without radiotherapy for brain metastases in NSCLC: the CTONG 2003 randomized placebo-controlled trial. *J Thorac Oncol*. 2025;20(7):928-940. doi:10.1016/j.jtho.2025.02.004

37) Schapira E, Hubbeling H, Yeap BY, et al. Improved overall survival and locoregional disease control with concurrent PD-1 pathway inhibitors and stereotactic radiosurgery for lung cancer patients with brain metastases. *Int J Radiat Oncol Biol Phys*. 2018;101(3):624-629. doi:10.1016/j.ijrobp.2018.02.175

38) Yomo S, Oda K, Oguchi K. Synergistic effects of immune checkpoint inhibitors in combination with stereotactic radiosurgery for patients with lung cancer and brain metastases: a propensity score-matched analysis. *J Neurosurg*. 2023;139(6):1628-1637. doi:10.3171/2023.4.JNS2349

39) Bashir S, Wen L, Zhang P, et al. Efficacy and safety of combined immunotherapy and stereotactic radiosurgery in NSCLCBM patients and a novel prognostic nomogram: a real-world study. *Front Oncol*. 2023;13:1068592. doi:10.3389/fonc.2023.1068592

40) Shepard MJ, Xu Z, Donahue J, et al. Stereotactic radiosurgery with and without checkpoint inhibition for patients with metastatic non-small cell lung cancer to the brain: a matched cohort study. *J Neurosurg*. 2020;133(3):685-692. doi:10.3171/2019.4.JNS19822

41) Singh C, Qian JM, Yu JB, Chiang VL. Local tumor response and survival outcomes after combined stereotactic radiosurgery and immunotherapy in non-small cell lung cancer with brain metastases. *J Neurosurg*. 2020;132(2):512-517. doi:10.3171/2018.10.JNS181371

42) Singh SA, McDermott DM, Mattes MD. Impact of systemic therapy type and timing on intracranial tumor control in patients with brain metastasis from non-small-cell lung cancer treated with stereotactic radiosurgery. *World Neurosurg*. 2020;144:e813-e823. doi:10.1016/j.wneu.2020.09.082

43) Scoccianti S, Olmetto E, Pinzi V, et al. Immunotherapy in association with stereotactic radiotherapy for non-small cell lung cancer brain metastases: results from a multicentric retrospective study on behalf of AIRO. *Neuro Oncol*. 2021;23(10):1750-1764. doi:10.1093/neuonc/noab129

44) Dohm AE, Tang JD, Mills MN, et al. Clinical outcomes of non-small cell lung cancer brain metastases treated with stereotactic radiosurgery and immune checkpoint inhibitors, EGFR tyrosine kinase inhibitors, chemotherapy and immune checkpoint inhibitors, or chemotherapy alone. *J Neurosurg*. 2023;138(6):1600-1607. doi:10.3171/2022.9.JNS221896

45) Frehner L, Schär S, Hayoz S, et al. First-line immunotherapy ± chemotherapy with or without upfront stereotactic radiotherapy (SRT) in patients with non-small cell lung cancer (NSCLC) with asymptomatic brain metastases. *Lung Cancer*. 2025;210:108813. doi:10.1016/j.lungcan.2025.108813

46) Lu R, Wang Z, Tian W, et al. A retrospective study of radiotherapy combined with immunotherapy for patients with baseline brain metastases from non-small cell lung cancer. *Sci Rep*. 2025;15(1):7036. doi:10.1038/s41598-025-91863-7

47) Chung JH, Tos SM, Mantziaris G, et al. Stereotactic radiosurgery dose reduction for patients with brain metastases from non-small cell lung primary on immunotherapy or targeted therapy. *Neurosurgery*. 2026;12:10-1227. doi:10.1227/neu.0000000000003961

48) Flippot R, Dalban C, Laguerre B, et al. Safety and efficacy of nivolumab in brain metastases from renal cell carcinoma: results of the GETUG-AFU 26 NIVOREN multicenter phase II study. *JCO*. 2019;37(23):2008-2016. doi:10.1200/JCO.18.02218

49) Emamekhoo H, Olsen MR, Carthon BC, et al. Safety and efficacy of nivolumab plus ipilimumab in patients with advanced renal cell carcinoma with brain metastases: CheckMate 920. *Cancer*. 2022;128(5):966-974. doi:10.1002/cncr.34016

50) Hasanov E, Yeboa DN, Tucker MD, et al. An interdisciplinary consensus on the management of brain metastases in patients with renal cell carcinoma. *CA Cancer J Clin*. 2022;72(5):454-489. doi:10.3322/caac.21729

51) Rathmell WK, Rumble RB, Van Veldhuizen PJ, et al. Management of metastatic clear cell renal cell carcinoma: ASCO guideline. *JCO*. 2022;40(25):2957-2995. doi:10.1200/JCO.22.00868

52) Yomo S, Oda K, Oguchi K. Effectiveness of immune checkpoint inhibitors in combination with stereotactic radiosurgery for patients with brain metastases from renal cell carcinoma: inverse probability of treatment weighting using propensity scores. *J Neurosurg*. 2023;138(6):1591-1599. doi:10.3171/2022.9.JNS221215

53) Lehrer EJ, Gurewitz J, Bernstein K, et al. Radiation necrosis in renal cell carcinoma brain metastases treated with checkpoint inhibitors and radiosurgery: an international multicenter study. *Cancer*. 2022;128(7):1429-1438. doi:10.1002/cncr.34087

54) Grant K-G, Gillespie Y, Karamian A, et al. Evolving treatment paradigms for melanoma brain metastases: a systematic review of current modalities. *Clin Neurol Neurosurg*. 2025;257:109025. doi:10.1016/j.clineuro.2025.109025

55) Williams GJ, Hong AM, Thompson JF. Treatment of melanoma brain metastases with radiation and immunotherapy or targeted therapy: a systematic review with meta-analysis. *Crit Rev Oncol Hematol*. 2024;202:104462. doi:10.1016/j.critrevonc.2024.104462

56) Li C, Li K, Zhong S, et al. Which is the best treatment for melanoma brain metastases? A bayesian network meta-analysis and systematic review. *Crit Rev Oncol Hematol*. 2024;194:104227. doi:10.1016/j.critrevonc.2023.104227

57) Badrigilan S, Meola A, Chang SD, et al. Stereotactic radiosurgery with immune checkpoint inhibitors for brain metastases: a meta-analysis study. *Br J Neurosurg*. 2023;37(6):1533-1543. doi:10.1080/02688697.2021.2022098

58) Ahmadvand MH, Habibi MA, Mirjani MS, et al. The clinical outcomes of combined stereotactic radiosurgery with PD-1/PD-L1 inhibitors in patients with metastatic brain tumors: a systematic review and meta-analysis on the safety and efficacy. *Neurosurg Rev*. 2025;48(1):756. doi:10.1007/s10143-025-03909-z

59) Chu X, Niu L, Xiao G, et al. The long-term and short-term efficacy of immunotherapy in non-small cell lung cancer patients with brain metastases: a systematic review and meta-analysis. *Front Immunol*. 2022;13:875488. doi:10.3389/fimmu.2022.875488

60) Yang Y, Deng L, Yang Y, et al. Efficacy and safety of combined brain radiotherapy and immunotherapy in non-small-cell lung cancer with brain metastases: a systematic review and meta-analysis. *Clin Lung Cancer*. 2022;23(2):95-107. doi:10.1016/j.cllc.2021.06.009

61) Taslimi S, Brar K, Ellenbogen Y, et al. Comparative efficacy of systemic agents for brain metastases from non-small-cell lung cancer with an EGFR mutation/ALK rearrangement: a systematic review and network meta-analysis. *Front Oncol*. 2021;11:739765. doi:10.3389/fonc.2021.739765

62) Gainor JF, Shaw AT, Sequist LV, et al. EGFR mutations and ALK rearrangements are associated with low response rates to PD-1 pathway blockade in non-small cell lung cancer: a retrospective analysis. *Clin Cancer Res*. 2016;22(18):4585-4593. doi:10.1158/1078-0432.CCR-15-3101

63) Sneed PK, Mendez J, Vemer-van den Hoek JGM, et al. Adverse radiation effect after stereotactic radiosurgery for brain metastases: incidence, time course, and risk factors. *J Neurosurg*. 2015;123(2):373-386. doi:10.3171/2014.10.JNS141610

64) Minniti G, Scaringi C, Paolini S, et al. Single-fraction versus multifraction (3 × 9 gy) stereotactic radiosurgery for large (>2 cm) brain metastases: a comparative analysis of local control and risk of radiation-induced brain necrosis. *Int J Radiat Oncol Biol Phys*. 2016;95(4):1142-1148. doi:10.1016/j.ijrobp.2016.03.013

65) Milano MT, Grimm J, Niemierko A, et al. Single- and multifraction stereotactic radiosurgery dose/volume tolerances of the brain. *Int J Radiat Oncol Biol Phys*. 2021;110(1):68-86. doi:10.1016/j.ijrobp.2020.08.013

66) Du G, Li W, Li J, Yu J, Zhu H. Concurrent immunotherapy is associated with increased radiation necrosis risk in lung cancer patients with brain metastases treated with stereotactic radiosurgery. *Future Oncol*. 2026;22(8):953-967. doi:10.1080/14796694.2026.2642933

67) Choi S, Hong A, Wang T, et al. Risk of radiation necrosis after stereotactic radiosurgery for melanoma brain metastasis by anatomical location. *Strahlenther Onkol*. 2021;197(12):1104-1112. doi:10.1007/s00066-021-01798-x

68) Akhavan-Sigari A, Sbaih O, Hori YS, et al. Perilesional edema as a predictor of local failure in metastatic brain lesions treated with stereotactic radiosurgery: a systematic review and meta-analysis. *Int J Radiat Oncol Biol Phys*. 2026;124(5):1199-1207. doi:10.1016/j.ijrobp.2025.06.3878

69) Ivanidze J, Shih RY, Utukuri PS, et al. ACR appropriateness criteria® brain tumors. *J Am Coll Radiol*. 2025;22(5s):S108-S135. doi:10.1016/j.jacr.2025.02.036

70) Alexander BM, Brown PD, Ahluwalia MS, et al. Clinical trial design for local therapies for brain metastases: a guideline by the response assessment in neuro-oncology brain metastases working group. *Lancet Oncol*. 2018;19(1):e33-e42. doi:10.1016/S1470-2045(17)30692-7

71) Govaerts CW, Kramer MCA, Bosma I, et al. Incidence and clinical features of pseudoprogression in brain metastases after immune-checkpoint inhibitor therapy: a retrospective study. *Cancers*. 2025;17(15):2425. doi:10.3390/cancers17152425

72) Park HJ, Kim KW, Pyo J, et al. Incidence of pseudoprogression during immune checkpoint inhibitor therapy for solid tumors: a systematic review and meta-analysis. *Radiology*. 2020;297(1):87-96. doi:10.1148/radiol.2020200443

73) Chuang MT, Liu YS, Tsai YS, Chen YC, Wang CK. Differentiating radiation-induced necrosis from recurrent brain tumor using MR perfusion and spectroscopy: a meta-analysis. *PLoS One*. 2016;11(1):e0141438. doi:10.1371/journal.pone.0141438

74) Okada H, Weller M, Huang R, et al. Immunotherapy response assessment in neuro-oncology: a report of the RANO working group. *Lancet Oncol*. 2015;16(15):e534-e542. doi:10.1016/S1470-2045(15)00088-1

75) Yu J, Zheng J, Xu W, et al. Accuracy of ^{18}f-FDOPA positron emission tomography and ^{18}f-FET positron emission tomography for differentiating radiation necrosis from brain tumor recurrence. *World Neurosurg*. 2018;114:e1211-e1224. doi:10.1016/j.wneu.2018.03.179

76) Zhou C, Kou Y, Zhou W, et al. Diagnostic value of PET tracers in differentiating glioma tumor recurrence from treatment-related changes: a systematic review and meta-analysis. *AJNR Am J Neuroradiol*. 2025;46(4):758-765. doi:10.3174/ajnr.A8565

77) Vellayappan B, Lim-Fat MJ, Kotecha R, et al. A systematic review informing the management of symptomatic brain radiation necrosis after stereotactic radiosurgery and international stereotactic radiosurgery society recommendations. *Int J Radiat Oncol Biol Phys*. 2024;118(1):14-28. doi:10.1016/j.ijrobp.2023.07.015

78) Xu Y, Rong X, Hu W, et al. Bevacizumab monotherapy reduces radiation-induced brain necrosis in nasopharyngeal carcinoma patients: a randomized controlled trial. *Int J Radiat Oncol Biol Phys*. 2018;101(5):1087-1095. doi:10.1016/j.ijrobp.2018.04.068

79) Nobel H, Ofer J, Borenstein SF, et al. Long-term impact of bevacizumab for the treatment of brain radiation necrosis. *J Neurooncol*. 2025;173(2):289-296. doi:10.1007/s11060-025-04979-1

80) Upadhyay R, Elguindy ANM, Salts L, et al. Boswellia serrata for cerebral radiation necrosis after radiosurgery for brain metastases. *Int J Radiat Oncol Biol Phys*. 2025;122(5):1282-1291. doi:10.1016/j.ijrobp.2025.02.016

81) Sankey EW, Grabowski MM, Srinivasan ES, et al. Time to steroid independence after laser interstitial thermal therapy vs medical management for treatment of biopsy-proven radiation necrosis secondary to stereotactic radiosurgery for brain metastasis. *Neurosurgery*. 2022;90(6):684-690. doi:10.1227/neu.0000000000001922

82) Palmisciano P, Haider AS, Nwagwu CD, et al. Bevacizumab vs laser interstitial thermal therapy in cerebral radiation necrosis from brain metastases: a systematic review and meta-analysis. *J Neurooncol*. 2021;154(1):13-23. doi:10.1007/s11060-021-03802-x

83) Lehrer EJ, Peterson JL, Zaorsky NG, et al. Single versus multifraction stereotactic radiosurgery for large brain metastases: an international meta-analysis of 24 trials. *Int J Radiat Oncol Biol Phys*. 2019;103(3):618-630. doi:10.1016/j.ijrobp.2018.10.038

84) Jessurun CAC, Hulsbergen AFC, de Wit AE, et al. The combined use of steroids and immune checkpoint inhibitors in brain metastasis patients: a systematic review and meta-analysis. *Neuro Oncol*. 2021;23(8):1261-1272. doi:10.1093/neuonc/noab046

85) Yomo S, Oda K, Oguchi K. Pre-stereotactic radiosurgery neutrophil-to-lymphocyte ratio predicts post-stereotactic radiosurgery survival of patients with brain metastases concurrently treated with immune checkpoint inhibitors. *J Neurosurg*. 2025;142(2):454-463. doi:10.3171/2024.5.JNS24259

86) Tracz JA, Donnelly BM, Ngu S, et al. The abscopal effect: inducing immunogenicity in the treatment of brain metastases secondary to lung cancer and melanoma. *J Neurooncol*. 2023;163(1):1-14. doi:10.1007/s11060-023-04312-8

87) Levy A, Massard C, Michiels S, Deutsch E. Innovative, early-phase clinical trials of drug-radiotherapy combinations. *Lancet Oncol*. 2025;26(4):e190-e202. doi:10.1016/S1470-2045(24)00664-8

88) Bhatti NB, Young D, Lam WW, et al. Attention-guided deep learning of chemical exchange saturation transfer magnetic resonance imaging to differentiate between tumor progression and radiation necrosis in brain metastasis. *Int J Radiat Oncol Biol Phys*. 2026;125(2):630-641. doi:10.1016/j.ijrobp.2025.10.040

89) Yu Y, Luo Y, Zeng F, Liu A. Opportunities and challenges for non-small cell lung cancer brain metastases in the immunotherapy era. *Cancer Treat Rev*. 2025;140:103014. doi:10.1016/j.ctrv.2025.103014

Outcomes of Stereotactic vs Conventional Radiation Therapy in Unresectable Pancreatic Cancer: A Real-World Retrospective Analysis

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Abstract

Objectives: Unresectable pancreatic cancer (UPC) has poor outcomes, and the role of radiation therapy (RT) remains incompletely defined. This retrospective study evaluated real-world outcomes following primary tumor-directed RT in UPC and compared outcomes across different RT approaches.

Materials and Methods: We retrospectively identified 176 patients who underwent local RT for UPC between August 2007 and December 2022 at a single institution. 14 patients were excluded due to repeat RT, incomplete RT, or lack of follow-up, leaving 162 patients. Patients were stratified into cohorts by RT technique: conventionally fractionated RT (CFRT; >15 fractions) (n = 22, 14%), hypofractionated RT (HypoRT; ≤15 fractions and EQD2 <40 Gy for α/β = 3) (n = 50, 31%), and stereotactic body RT (SBRT; ≤5 fractions and EQD2 ≥40 Gy for α/β = 3) (n = 27, 17%). Patients presenting with de novo metastatic disease (n = 63) were analyzed separately irrespective of RT technique.

Results: Mean patient age was 68.9 years, and 43% were female. Median follow-up was 12.4 months. Median overall survival (OS) and local control were 16.5 and 16.6 months, in the SBRT cohort, vs 21.8 and 26.2 months, in the CFRT cohort. All CFRT patients received chemotherapy, whereas only approximately half of the SBRT and HypoRT patients received systemic therapy. Median OS was lower among patients who did not receive chemotherapy, at 7.0 months in the SBRT cohort and 4.9 months in the HypoRT cohort. Patients presenting with metastatic disease who underwent RT had a median OS of 5.4 months, which decreased to 2.3 months in those who did not receive chemotherapy.

Conclusion: Patients with good performance status who received chemotherapy appeared most likely to benefit from primary tumor-directed RT. Metastatic patients with poor performance status and inability to receive chemotherapy had limited survival and may derive less benefit from local RT. Further studies are needed to clarify the role of SBRT and optimal treatment volumes in UPC.

Keywords: unresectable pancreatic cancer, pancreatic SBRT, pancreatic radiation therapy

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Data sharing statement: Data were compiled through a retrospective review of patient charts. A database was created in a secure manner to protect the privacy of the patients. Release of anonymized data can be made possible with specific requests made to the corresponding author.

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Introduction

Pancreatic cancer is a deadly disease that ranks 3rd for cancer-related mortality in Canada, despite being only the 11th most common cancer by incidence.[1] Morbidity and mortality rates become especially abysmal when focusing on the population of patients with medically or anatomically unresectable pancreatic cancer (UPC) with reported median survival in the range of 8 to 12 months.[2] Benefit from chemotherapy in patients with UPC is consistent in multiple clinical trials, but literature defining the role of radiation therapy (RT) for patients with UPC remains sparse and controversial. Several clinical trials have investigated the effects of RT on UPC, but the results have been inconsistent and controversial. Some trials have suggested that RT may improve local control (LC) and overall survival (OS), while others have found no benefit or even harm from RT.[3-7]

In addition to the effect on patient outcomes being unclear in randomized trials, high-quality evidence for choosing the technique of RT remains limited. In Tchelebi et al.'s CRiSP meta-analysis looking at a combined 20 studies, they concluded that stereotactic body RT (SBRT) has improved OS without worse toxicity when compared to conventionally fractionated RT (CFRT).[8] There has also recently been a publication looking at CFRT vs SBRT population of patients with UPC at a single center.[9] The authors concluded SBRT improved LC and may even have benefit on OS; however, this study had many metastatic patients in their CFRT cohort and none in their SBRT cohort. A different retrospective study highlights in their recent publication on palliative RT for patients with pancreatic cancer of all stages, higher proportions of metastatic patients will negatively affect survival outcomes.[10] Knowing this, we felt it crucial to examine techniques without metastatic disease as a confounder.

We present one of the largest retrospective series in patients with UPC studying the impact of RT on OS, treatment-specific survival (TSS), freedom from progression (FFP), and LC. We strive to provide a novel approach to analyzing our patient data by separating patients with CFRT, SBRT, and HypoRT from those who are metastatic at the time of RT (de novo M1).

Materials and Methods

This was a Research Ethics Board-approved, single-institution retrospective chart review conducted at a tertiary academic center. The Mosaiq radiation oncology information system was used to identify all patients treated using a pancreatic cancer RT care plan between August 2007 and December 2022. A total of 257 consecutive RT treatment plans were identified. Patients were excluded if they had undergone pancreatic tumor resection, received re-irradiation, did not complete RT, or had non-adenocarcinoma histology, resulting in a final cohort of 176 patients with UPC who received primary tumor-directed local RT (**Figure 1**).

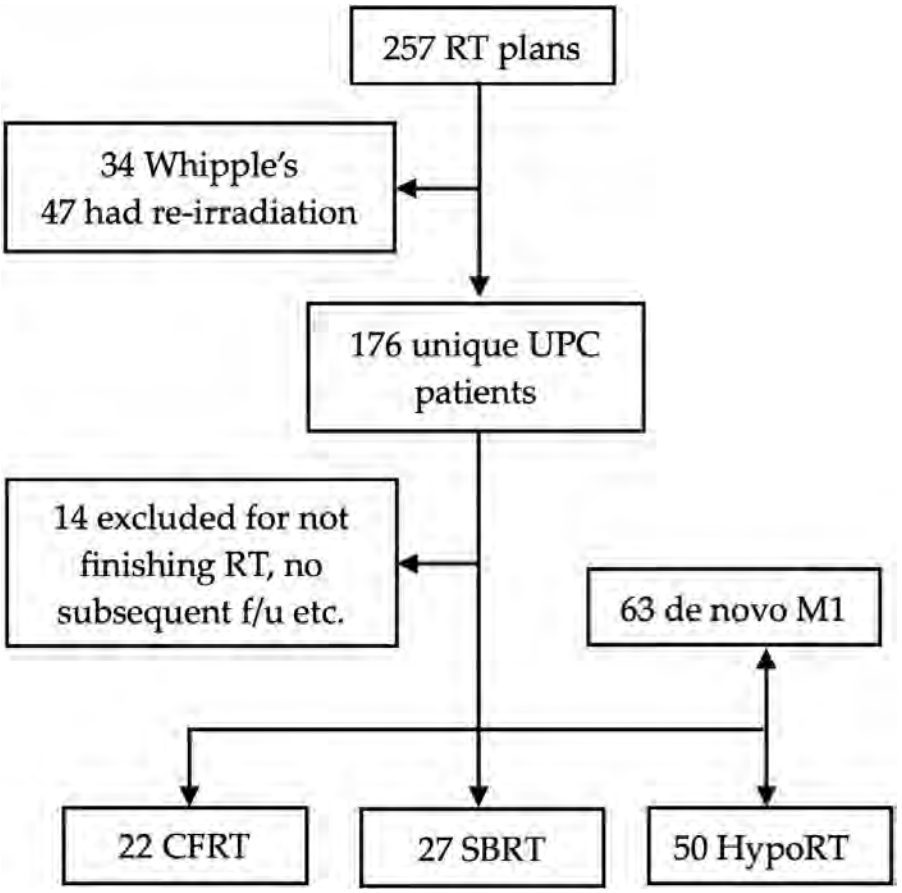
We divided the patients into 4 cohorts based on RT technique and metastatic status: CFRT, SBRT, HypoRT, and de novo M1. CFRT was defined as treatment delivered in >15 fractions. SBRT was defined as treatment delivered in ≤5 fractions with an equivalent dose in 2 Gy fractions (EQD2, $\alpha/\beta = 3$) ≥40 Gy, consistent with the Canadian Association of Radiation Oncology task force definition of SBRT as delivering doses biologically equivalent to a radical RT course.[11] HypoRT was defined as treatment delivered in ≤15 fractions with EQD2 ($\alpha/\beta = 3$) <40 Gy and therefore largely represented more palliative intent hypofractionated regimens. SBRT was delivered using linac or CyberKnife platforms with a 5 mm planning target volume (PTV) expansion from gross tumor volume (GTV), whereas CFRT typically included elective nodal coverage consistent with RTOG 0848 postoperative contouring guidelines. In some SBRT cases, PTV coverage was compromised to meet adjacent organ-at-risk constraints, particularly established gastrointestinal dose constraints described by Robert Timmerman and colleagues.

Outcomes of interest included OS, defined as time from diagnosis to death; FFP, defined as time from RT to radiographic evidence of disease progression; and LC, defined as time from RT to local progression. To better characterize outcomes following RT independent of prior chemotherapy duration, TSS was defined as the interval from initiation of RT to death or last follow-up. Time-to-event analyses were performed using the Kaplan-Meier method in R statistical software (version 4.3.1; R Core Team 2023). 95% confidence intervals (95% CIs) were calculated for all outcomes. When the upper confidence interval limit was not reached due to fewer than 50% cumulative events occurring, it was reported as not reached (NR).

Multivariable analyses were performed using Cox proportional hazards regression models with the same statistical software. Performance status was assessed using the Eastern Cooperative Oncology Group (ECOG) scale, with ECOG scores of 0 and 1 grouped together for statistical analyses.

Patients who received at least 3 cycles of chemotherapy during their disease course were identified. This included definitive chemotherapy administered either before or after RT for local disease control. The most commonly utilized systemic therapies at our institution included FOLinic acid (leucovorin), Fluorouracil (5-FU), IRINotecan, and OXaliplatin (FOLFIRINOX), as well as gemcitabine, paclitaxel, and 5-fluorouracil-based regimens.

Figure 1. Consolidated Standards of Reporting Trials diagram of the current retrospective study. A total of 176 patients were analyzed. 63 patients had metastatic disease at presentation and received local tumor-directed radiation therapy (RT). CFRT, conventionally fractionated RT; HypoRT, hypofractionated RT; M1, patients with metastatic disease at the time of diagnosis; SBRT, stereotactic body RT; UPC, unresectable pancreatic cancer.



The standard follow-up protocol included blood work and an initial CT scan approximately 3 months following RT, followed by surveillance CT imaging every 6 months thereafter unless earlier imaging was clinically indicated.

Results

A total of 162 patients with UPC were included in the final analysis, including 99 patients without metastatic disease at the time of RT (non-M1) and 63 patients with de novo metastatic disease (de novo M1). Among the non-M1 patients, 22 received CFRT, 27 received SBRT, and 50 received HypoRT.

Baseline characteristics differed between cohorts despite relatively balanced gender distributions. The CFRT cohort had the youngest mean age, the best mean performance status, and universal chemotherapy utilization, with 100% of patients receiving chemotherapy at some point during their treatment course (**Table 1**). In contrast, approximately half of the patients in the SBRT, HypoRT, and de novo M1 cohorts did not receive chemotherapy. Gemcitabine-based therapy was the most commonly utilized systemic treatment overall, although the distribution of chemotherapy regimens differed between cohorts (**Table 2**). Baseline CA 19-9 levels at the time of RT were lowest in the CFRT cohort and highest in the HypoRT and de novo M1 cohorts (**Table 1**).

The CFRT cohort demonstrated the most favorable outcomes overall in terms of OS, FFP, TSS, and LC. Outcomes in the SBRT and HypoRT cohorts were generally similar and intermediate between the CFRT and de novo M1 cohorts, while the de novo M1 cohort demonstrated the poorest outcomes overall. The median OS for the CFRT group was 21.8 months (95% CI 14.5-39.1), for the SBRT group it was 16.5 months (95% CI 7.8-43.7), and for the HypoRT group it was 10.8 months (95% CI 6.1-14.6). It was lowest for the de novo M1 group at 5.4 months (95% CI 3.6-8.8). The median LC for the CFRT group was 26.2 months (95% CI 10.6-NR), for the SBRT group it was 16.6 months (95% CI 10.7-NR), for the HypoRT group it was 16.9 months (95% CI 12.2-NR), and for the de novo M1 group it was 25.3 months (95% CI 12.2-NR) (**Figure 2**).

On multivariable Cox proportional hazards analysis, performance status (odds ratio [OR] 2.228, 95% CI 1.610-3.082, $P < 0.001$) and receipt of chemotherapy (OR 0.243, 95% CI 0.145-0.406, $P < 0.001$) were strongly associated with OS. In contrast, age, total bilirubin, CA 19-9 levels, and EQD2 were not statistically significant predictors of OS (**Table 3**).

Given the strong association between chemotherapy utilization and survival outcomes, subgroup analyses were performed for the SBRT, HypoRT, and de novo M1 cohorts stratified by receipt of chemotherapy. Median OS with and without chemotherapy was 22.7 vs 7.0 months, respectively, for SBRT patients (log-rank $P = .02$), 14.6 vs 4.9 months for HypoRT patients (log-rank $P = .02$), and 11.1 vs 2.3 months for de novo M1 patients (log-rank $P < .001$).

Median TSS with and without chemotherapy was 15.3 vs 5.1 months for SBRT patients (log-rank $P = .09$), 6.4 vs 3.6 months for HypoRT patients (log-rank $P = .02$), and 4.7 vs 1.3 months for de novo M1 patients (log-rank $P < .001$). Median FFP with and without chemotherapy was 8.5 vs 5.9 months for SBRT patients (log-rank $P = .7$), 10.5 vs 11.7 months for HypoRT patients (log-rank $P = .4$), and 12.4 months vs NR for de novo M1 patients (log-rank $P = .7$), respectively (**Table 4**).

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Table 1. Demographic and Baseline Characteristics of Patients With Unresectable Pancreatic Cancer Treated With Radiation Therapy (RT) Divided by RT Technique, Except for De Novo M1 Patients That Are Grouped Together Irrespective of RT Technique

	COHORTS (MEAN VALUE UNLESS OTHERWISE SPECIFIED)			
VARIABLES	CFRT	HYPORT	SBRT	DE NOVO M1
No. of patients	22	50	27	63
Male (%)	63.6	50.0	63.0	57.1
CA 19-9 (U/mL)	204.7	2321.8	819.4	6419.1
Median PS (ECOG)	1	2	2	3
T4 status (%)	91	74	63	84
Age (years)	65.4	70.4	71.5	67.0
Biliary stenting rate (%)	50.0	50.0	33.3	33.3
No chemotherapy (%)	0	48.0	51.9	46.0
Total dose (Gy)	36-50.4	25-40.05	21-40	8-40
Fractions (range)	18-28	1-15	3-5	1-14
BED α/β = 3 (Gy)	76.4	46.5	81.6	51.1
EQD2 α/β = 3 (Gy)	45.9	27.9	48.9	30.7

BED, biologically effective dose; CFRT, conventionally fractionated RT; de novo M1, patients with metastatic disease at the time of diagnosis; ECOG, Eastern Cooperative Oncology Group; EQD2, equivalent dose in 2 Gy fractions; HypoRT, hypofractionated RT; PS, performance status; SBRT, stereotactic body RT.

Table 2. Distribution of Systemic Therapy Regimens Administered Across Treatment Cohorts from 2007 to 2022

	COHORTS			
VARIABLES	CFRT	HYPORT	SBRT	DE NOVO M1
No. of patients	22	50	27	63
Gemcitabine (%)	50.0	32.0	25.9	23.8
FOLFOX (%)	31.8	24.0	22.2	15.9
Paclitaxel (%)	9.1	10.0	18.5	19.1
5-Fluorouracil (%)	22.7	2.0	0.0	1.6
Capecitabine (%)	22.7	0.0	7.4	3.2
Other (%)	9.1	2.0	3.7	9.5
No chemotherapy (%)	0	48.0	51.9	46.0

CFRT, conventionally fractionated RT; de novo M1, patients with metastatic disease at the time of diagnosis; HypoRT, hypofractionated RT; RT, radiation therapy; SBRT, stereotactic body RT.

Discussion

This study adds to the growing literature on RT for UPC by representing one of the larger retrospective real-world analyses of this patient population and by evaluating patients with de novo metastatic (M1) disease separately. Interestingly, the CFRT cohort demonstrated superior OS, progression-free survival, TSS, and LC compared with the SBRT cohort. However, these findings must be interpreted cautiously given important baseline differences between groups. Patients treated with CFRT were generally younger, had better performance status, more favorable biochemical parameters (including CA 19-9 and bilirubin levels), and all received chemotherapy, compared with only approximately half of the patients in the SBRT and HypoRT cohorts. In addition, unlike other cohorts, the CFRT group did not include patients with metastatic disease at the time of RT.

Multivariable Cox proportional hazards analysis demonstrated that older age was associated with a modestly increased risk of death. More importantly, poor performance status and the absence of chemotherapy were strongly associated with worse OS. Interestingly, baseline CA 19-9 and total bilirubin levels were not significant predictors of mortality in our cohort. These findings likely help explain the improved OS observed in the CFRT cohort, whose patients generally had better performance status and universal chemotherapy utilization.

Given the known importance of systemic therapy in UPC, subgroup analyses were performed based on chemotherapy utilization. Patients who received chemotherapy before or after RT demonstrated improved OS compared with those who did not receive systemic therapy. Notably, SBRT patients who also received definitive chemotherapy appeared to have OS approaching that of the CFRT cohort. These findings reinforce the critical role of chemotherapy in improving survival in UPC and suggest that patients able to tolerate multiagent chemotherapy may represent the subgroup most likely to benefit from aggressive local RT approaches. In these patients, improved LC may be clinically meaningful given the impact of local progression on symptoms and quality of life.

LC also appeared lower in the SBRT cohort receiving chemotherapy compared with the CFRT cohort. This may in part relate to differences in treatment volumes, as SBRT generally targets only the gross disease without elective nodal coverage, whereas CFRT typically encompasses regional nodal drainage areas using larger treatment volumes. A small phase II study comparing focal SBRT (33 Gy in 5 fractions to the tumor and involved vasculature) with a larger elective

Figure 2. Kaplan-Meier estimates of (A) overall survival (OS), (B) freedom from progression (FFP), (C) time to systemic therapy (TTS), and (D) local control (LC) between the various radiation therapy (RT) techniques and the de novo M1 cohort. CFRT, conventionally fractionated RT; HypoRT, hypofractionated RT; de novo M1, patients with metastatic disease at the time of diagnosis; SBRT, stereotactic body RT.

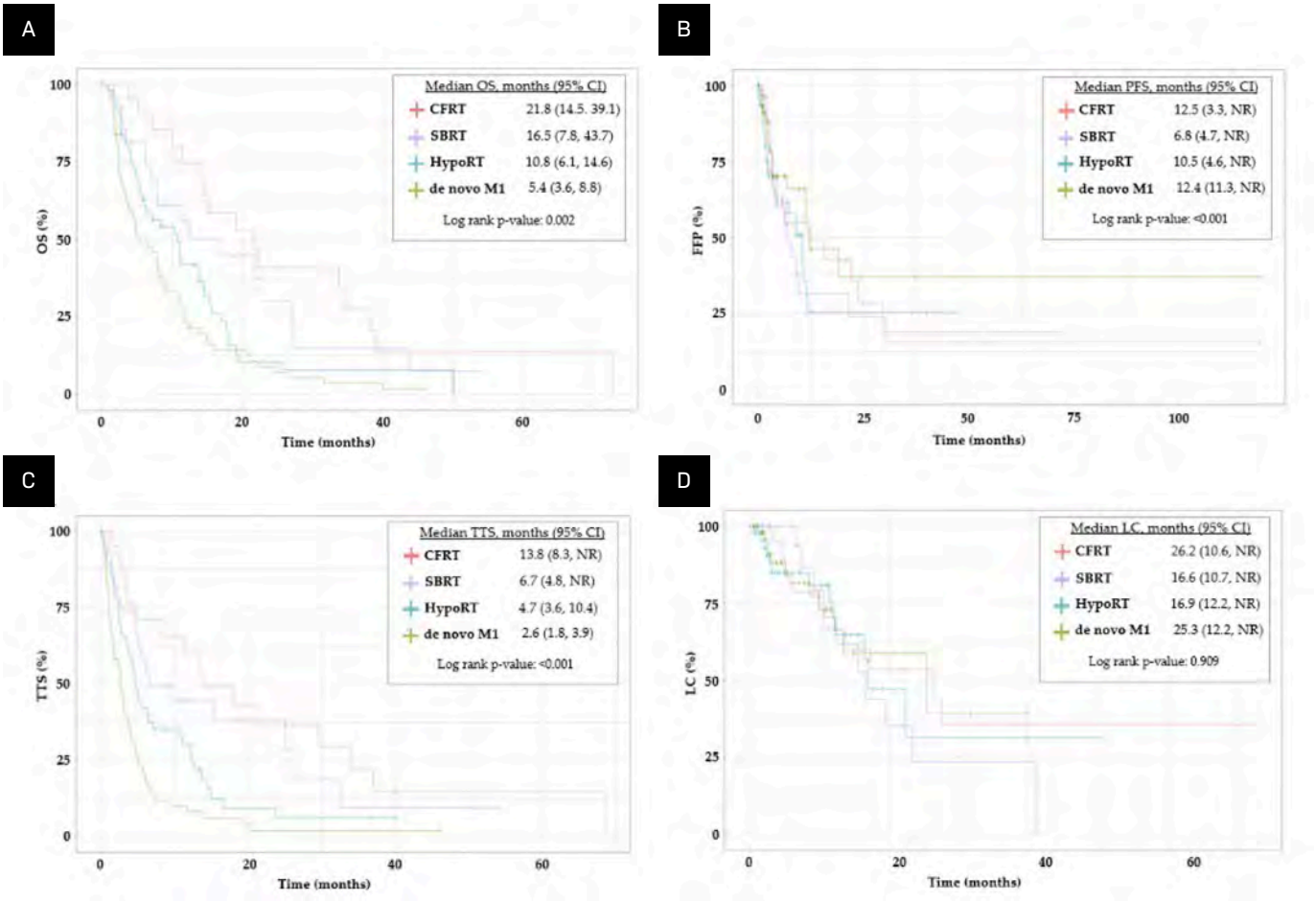

Table 3. Multivariable Cox Proportional Hazards Regression Analysis of Variables Associated With Overall Survival

VARIABLES	HAZARDS RATIO (95% CI)	*P* VALUE
Age at diagnosis	1.028 (0.153-6.916)	.02
Total bilirubin	1.001 (0.995-1.006)	.81
CA 19-9	1.000 (1.000-1.000)	.04
ECOG performance status	2.228 (1.610-3.082)	<.001
EQD2	0.982 (0.964-0.999)	.04
Chemotherapy	0.243 (0.145-0.406)	<.001

ECOG, Eastern Cooperative Oncology Group; EQD2, equivalent dose in 2 Gy fractions.

treatment volume that additionally encompassed the pancreatic head/body, adjacent vasculature, superior mesenteric artery origin, and celiac artery origin demonstrated improved 1-year progression-free survival (60% vs 25%), suggesting that elective nodal coverage may reduce local-regional failures without excessive toxicity.[12]

Conversely, Fogaroli et al. demonstrated a relatively low local failure rate of 23.3% using involved-field CFRT, arguing that reduced elective treatment volumes may be feasible in selected patients and could potentially decrease toxicity.[13] As such, the optimal treatment volumes for both SBRT and CFRT remain controversial and incompletely defined.

Importantly, the SBRT data in this study were collected prior to the implementation of MR-Linac-based adaptive RT and contemporary dose-escalation strategies at our institution. These newer approaches are increasingly associated with improved LC and potentially superior clinical outcomes, and therefore the present SBRT results may not fully reflect modern practice.

Another important observation from our study relates to patients presenting with de novo metastatic (M1) disease and

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Table 4. Differences in Outcomes Between SBRT, HypoRT, and De Novo M1 Cohorts, Adjusting for Addition of Definitive Chemotherapy to RT

VARIABLES (MONTHS)	CHEMOTHERAPY	COHORTS (MEDIAN MONTHS)					
		SBRT	*P* VALUE	HYPORT	*P* VALUE	DE NOVO M1	*P* VALUE
OS	Yes	22.7	.02	14.6	.02	11.1	<.001
	No	7.0		4.9		2.3	
TSS	Yes	15.3	.09	6.4	.02	4.7	<.001
	No	5.1		3.6		1.3	
FFP	Yes	8.5	.70	10.5	.40	12.4	.70
	No	5.9		11.7		NR	

de novo M1, patients with metastatic disease at the time of diagnosis; FFP, freedom from progression; HypoRT, hypofractionated RT; NR, not reached; OS, overall survival; RT, radiation therapy; SBRT, stereotactic body RT; TSS, treatment-specific survival.

those treated with lower-dose HypoRT regimens. The de novo M1 cohort likely reflects a real-world clinical scenario in which selected patients with metastatic disease and preserved performance status undergo primary tumor-directed RT for symptom palliation and improved local disease control despite the presence of systemic disease. As expected, these patients demonstrated poorer outcomes across all endpoints compared with the CFRT and SBRT cohorts, raising questions regarding the degree of benefit provided by local RT in certain subsets of patients. Survival outcomes appeared to be strongly influenced by receipt of chemotherapy, likely reflecting the importance of underlying performance status and systemic disease burden. For example, de novo M1 patients who received chemotherapy had a median OS of 11.1 months compared with only 2.3 months in those who did not receive chemotherapy (log-rank $P < .001$).

These findings suggest that metastatic patients who are not candidates for systemic therapy may not live long enough to derive meaningful benefit from primary tumor-directed RT and may be better managed with best supportive care measures alone. Conversely, metastatic patients with good performance status who are able to receive chemotherapy may still benefit from local RT despite presenting with metastatic disease. Additionally, patients without metastatic disease but with poor performance status appeared to derive symptomatic and clinical benefit from lower-dose HypoRT approaches, supporting a potential role for palliative RT in carefully selected patients.

Our study is limited by its retrospective design. The sample size for each treatment cohort was relatively small, particularly for subgroup analyses. In addition, patients were treated over a prolonged period (2007-2022), during which there were substantial changes in systemic therapy regimens, imaging quality, supportive care, and RT techniques. In particular, SBRT was implemented only in more recent years, which may introduce temporal treatment bias and influence outcomes over time.

Routine follow-up imaging was also not consistently performed in metastatic or poor performance status patients, particularly in de novo M1 patients who were not candidates for chemotherapy due to poor functional status and limited expected survival. As a result, local failure rates may be underreported in this subgroup. This likely contributes to the apparently higher LC observed in de novo M1 patients compared with the SBRT cohort, although this difference was not statistically significant. Importantly, this subgroup may also reflect a more "real-world" population of patients receiving palliative RT outside the setting of clinical trials. Finally, none of the patients in this study were treated using newer technologies such as proton therapy or adaptive MR-guided RT, which may allow for improved target coverage, dose escalation, and reduced toxicity compared with conventional treatment platforms.[14,15]

Conclusions

RT for UPC using CFRT was associated with encouraging OS and LC outcomes in this retrospective cohort. While outcomes appeared favorable compared with historical SBRT series, this study was not designed as a comparative analysis and should be considered hypothesis-generating only. Differences in outcomes may reflect important baseline imbalances and patient selection factors, including younger age, better performance status, higher rates of chemotherapy receipt (100% vs approximately 50%), more favorable biochemical parameters (including CA 19-9 and bilirubin at the time of RT), and the absence of metastatic (M1) disease at the time of RT in the CFRT cohort. These findings suggest that carefully selected patients with UPC may derive meaningful benefit from aggressive local therapy, warranting further prospective evaluation of modern CFRT approaches, particularly in the MR-Linac and dose-escalation era.

Furthermore, patients with de novo metastatic (M1) disease who are not candidates for systemic therapy appeared to have limited survival, suggesting that primary tumor-directed RT alone may provide minimal clinical benefit in this setting.

References

1) Brenner DR, Poirier A, Woods RR, et al. Projected estimates of cancer in Canada in 2022. *Can Med Assoc J*. 2022;194(17):E601-E607. doi:10.1503/cmaj.212097

2) Golden DW, Novak CJ, Minsky BD, Liauw SL. Radiation dose ≥54 gy and CA 19-9 response are associated with improved survival for unresectable, non-metastatic pancreatic cancer treated with chemoradiation. *Radiat Oncol*. 2012;7(1):156. doi:10.1186/1748-717X-7-156

3) Katz MHG, Shi Q, Meyers J, et al. Efficacy of preoperative mFOLFIRINOX vs mFOLFIRINOX plus hypofractionated radiotherapy for borderline resectable adenocarcinoma of the pancreas: the A021501 phase 2 randomized clinical trial. *JAMA Oncol*. 2022;8(9):1263-1270. doi:10.1001/jamaoncol.2022.2319

4) Hammel P, Huguet F, van Laethem J-L, et al. Effect of chemoradiotherapy vs chemotherapy on survival in patients with locally advanced pancreatic cancer controlled after 4 months of gemcitabine with or without erlotinib: the LAP07 randomized clinical trial. *JAMA*. 2016;315(17):1844-1853. doi:10.1001/jama.2016.4324

5) Chauffert B, Mornex F, Bonnetain F, et al. Phase III trial comparing intensive induction chemoradiotherapy (60 gy, infusional 5-FU and intermittent cisplatin) followed by maintenance gemcitabine with gemcitabine alone for locally advanced unresectable pancreatic cancer. Definitive results of the 2000-01 FFCD/SFRO study. *Ann Oncol*. 2008;19(9):1592-1599. doi:10.1093/annonc/mdn281

6) Loehrer PJ Sr, Feng Y, Cardenes H, et al. Gemcitabine alone versus gemcitabine plus radiotherapy in patients with locally advanced pancreatic cancer: an eastern cooperative oncology group trial. *J Clin Oncol*. 2011;29(31):4105-4112. doi:10.1200/JCO.2011.34.8904

7) Fietkau R, Ghadimi M, Grützmann R, et al. Randomized phase III trial of induction chemotherapy followed by chemoradiotherapy or chemotherapy alone for nonresectable locally advanced pancreatic cancer: first results of the CONKO-007 trial. *JCO*. 2022;40(16_suppl):4008-4008. doi:10.1200/JCO.2022.40.16_suppl.4008

8) Tchelebi LT, Lehrer EJ, Trifiletti DM, et al. Conventionally fractionated radiation therapy versus stereotactic body radiation therapy for locally advanced pancreatic cancer (CRiSP): an international systematic review and meta-analysis. *Cancer*. 2020;126(10):2120-2131. doi:10.1002/cncr.32756

9) Kamel R, Dennis K, Doody J, Pantarotto J. Ablative vs. non-ablative radiotherapy in palliating locally advanced pancreatic cancer: a single institution experience and a systematic review of the literature. *Cancers*. 2023;15(11):3016. doi:10.3390/cancers15113016

10) Liu AKN, Lefresne S. Palliative radiotherapy in pancreatic cancer: a retrospective study of 100 cases and regional patterns of practice. *Ann Palliat Med*. 2023;12(5):891-899. doi:10.21037/apm-22-1417

11) Sahgal A, Roberge D, Schellenberg D, et al. The canadian association of radiation oncology scope of practice guidelines for lung, liver and spine stereotactic body radiotherapy. *Clin Oncol*. 2012;24(9):629-639. doi:10.1016/j.clon.2012.04.006

12) Kharofa J, Mierzwa M, Olowokure O, et al. Pattern of marginal local failure in a phase II trial of neoadjuvant chemotherapy and stereotactic body radiation therapy for resectable and borderline resectable pancreas cancer. *Am J Clin Oncol*. 2019;42(3):247-252. doi:10.1097/COC.0000000000000518

13) Fogaroli RC, Castro DG, Silva ML, et al. Involved-field radiation therapy for patients with unresectable pancreatic adenocarcinomas: failure pattern analysis. *Cureus*. 2023;15(11):e48106. doi:10.7759/cureus.48106

14) Parikh PJ, Lee P, Low DA, et al. A multi-institutional phase 2 trial of ablative 5-fraction stereotactic magnetic resonance-guided on-table adaptive radiation therapy for borderline resectable and locally advanced pancreatic cancer. *Int J Radiat Oncol Biol Phys*. 2023;117(4):799-808. doi:10.1016/j.ijrobp.2023.05.023

15) Eckstein J, Choi JI, Lozano A, et al. Proton therapy for unresectable and medically inoperable locally advanced pancreatic cancer: results from a multi-institutional prospective registry. *Adv Radiat Oncol*. 2023;8(5):101250. doi:10.1016/j.adro.2023.101250

Multiple Cranial Nerve Palsies After Reirradiation With Proton Therapy in Nasopharyngeal Carcinoma: A Case Report

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Abstract

Nasopharyngeal carcinoma (NPC) is a rare form of cancer that has a strong association with the Epstein-Barr virus. There is little consensus on treatment for recurrent NPC, and depending on the extent of the disease, options include surgery, reirradiation, or enrollment in a clinical trial. Reirradiation, although a common and accepted treatment for recurrent NPC, carries a risk of significant late toxicity. Here, we describe the case of a young patient who experienced multiple cranial neuropathies after reirradiation for NPC recurrent to an intraparotid lymph node. The patient, while disease-free, continues to have symptoms related to these neuropathies, with significant atrophy of the left side of the tongue, dysphonia, and a winged scapula, and the focus of care is now on improving his overall quality of life. Further research is needed to explore the effects of systemic therapies on cranial nerves, as well as strategies to reduce the risk of damage to these structures.

Keywords: Nasopharyngeal carcinoma, cranial nerve palsy, proton therapy, case report, intensity-modulated radiation therapy, radiation therapy, Epstein-Barr virus

Case Summary

A 19-year-old patient with T2 N2 M0, stage III, nasopharyngeal carcinoma (NPC) and no significant medical history presented with progressive, left-ear pain presumed to be the result of an ear infection. He completed a course of antibiotics, but his symptoms did not improve, and he started to have associated epistaxis and nasal fullness, and developed a left neck mass. Physical examination revealed no signs of a tumor in the left external auditory canal. He had vague, palpable adenopathy in the left side of his neck, with no adenopathy in the posterior triangle.

Imaging Findings

Pretreatment imaging (PET/CT and MRI) revealed a 3.1 × 2.6 cm mass in the left fossa of Rosenmuller, as well as bilateral cervical lymphadenopathy, left greater than right, involving level 2 and retropharyngeal nodes bilaterally, as well as level 3 on the left.

Diagnoses and Treatment

Biopsy revealed non-keratinizing squamous cell carcinoma, Epstein-Barr encoding region in situ hybridization (EBER-ISH) positive. The patient tolerated his initial chemoradiotherapy to 70 Gy in 33 fractions using proton therapy with concurrent cisplatin (100 mg/m^2) every 3 weeks (**Figure 1**). Initial side

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Availability of data and materials: All the data and materials will be available upon request to the corresponding author.
Author contributions: CH treated and managed the patient, and CH edited the manuscript. CB wrote the manuscript. All authors have read and approved the manuscript for publication.

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Figure 1. Dose color wash showing the patient's initial treatment that includes treatment to the primary tumor and bilateral neck lymph node levels.

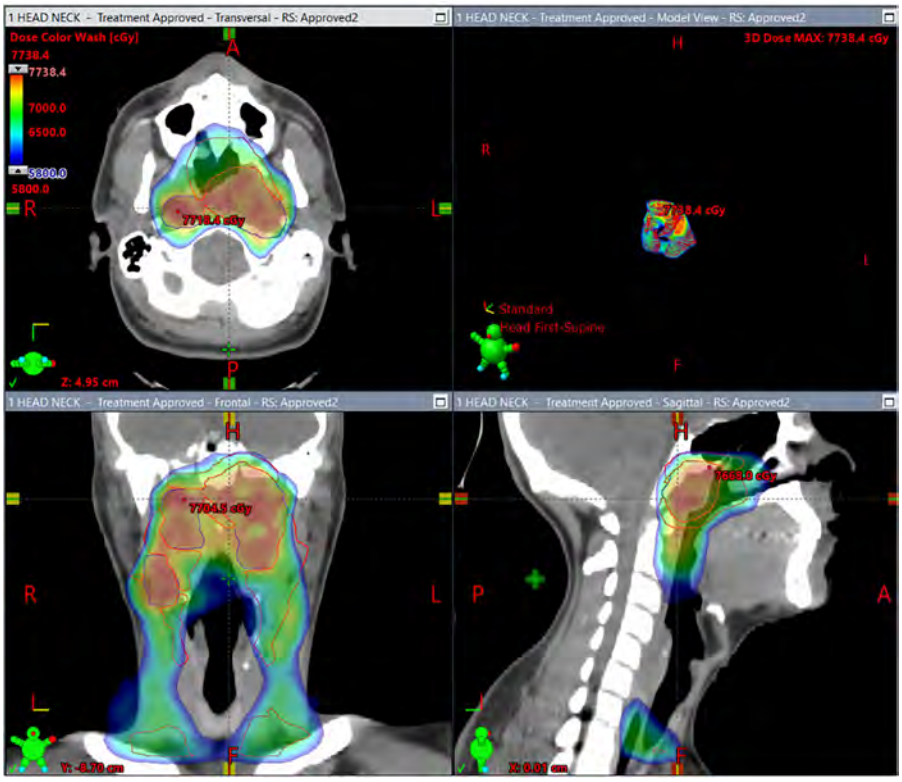
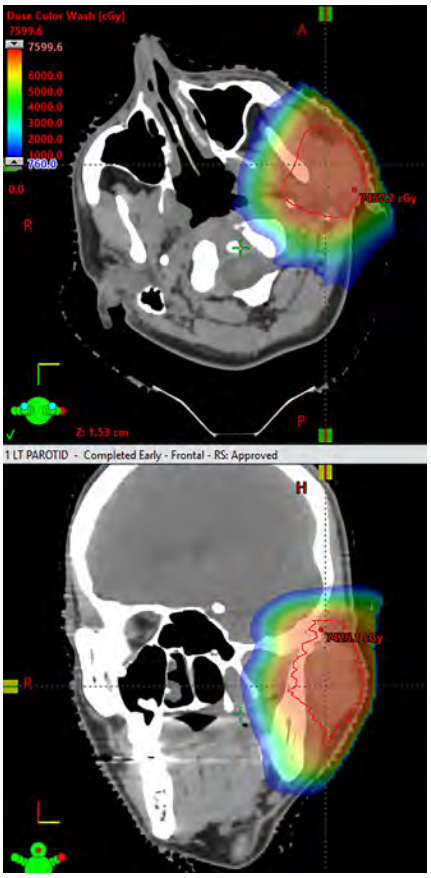


Figure 2. Dose wash of the proton radiation plan of the patient's left parotid recurrence.

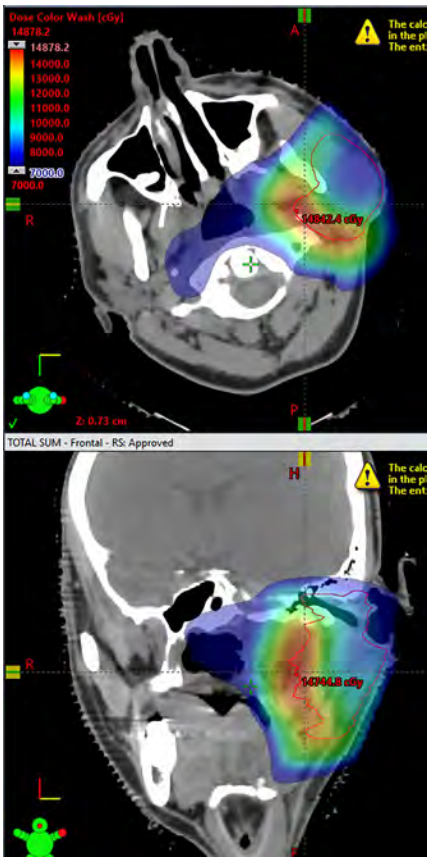


effects included faint erythema of the skin of the neck bilaterally and grade 2 mucositis of his soft palate. The patient developed progressive dysgeusia and odynophagia during treatment, and his weight decreased overall by 9 kg (20 lbs). He had a G-tube placed, which stabilized his weight. He completed treatment with good recovery and an isolated episode of parotitis 3 weeks post-completion.

The patient presented 27 months later for mild dysphonia and left-ear discharge. MRI revealed a 2.5 cm mass in the left parotid gland, and fine needle aspiration confirmed recurrent non-keratinizing NPC that was CK5/6+, p40+, and Epstein-Barr virus-positive (EBV+). PET imaging showed a new hypermetabolic 3.9 × 3.4 cm lesion in the left deep parotid space with a standardized uptake value (SUV) of 14.0. Additionally, there was mild FDG uptake in a left cervical level 2 node measuring 0.7 × 0.6 cm with an SUV of 2.9. The case was discussed at tumor board, with a recommendation for salvage reirradiation. He was reirradiated with 70 Gy in 35 fractions using proton therapy (**Figures 2, 3**). After reirradiation, there was excellent clinical response, evidenced by decreased swelling on palpation with occasional production of exudate in his left external auditory canal.

He began to experience hoarseness 3 months following the final dose of radiation. Laryngoscopy showed left vocal cord immobility with incomplete closure on phonation, deemed to be secondary to left cranial nerve X palsy. A month later, he presented with numbness of the left side of his tongue (left cranial nerve V3 palsy) and altered tongue mobility (L cranial nerve XII palsy), which was making it difficult to swallow. Following placement of a G-tube, the patient was referred to otolaryngology for vocal cord augmentation by injection medialization of the left vocal cord. A speech-language pathologist assisted with the patient's care and recommended exercises to bolster oral/pharyngeal strength, swallow reflex, and voice control, with hopes to eventually wean from the G-tube. Then, 4 months later, he continued to have ongoing dysphonia and dysphagia, along with a new onset of palsies of nerves V3, VII, and XI, trismus, decreased sensation along the mandibular division of the trigeminal nerve, weakness of the left cervical division of the facial nerve, and atrophy of the left sternocleidomastoid and the left hemitongue. Radiation imaging confirmed radiation scarring of the left parapharyngeal and carotid spaces. MRI of his head and neck

Figure 3. Dose wash of the proton therapy plan sum.



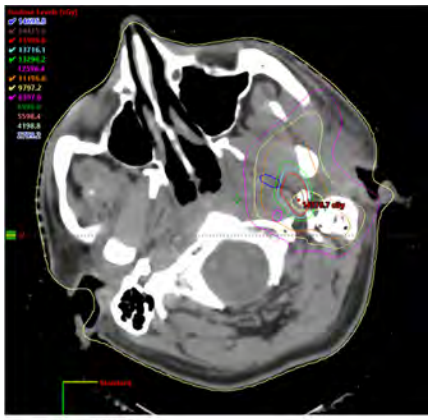
showed a loss of fat signal within the left parapharyngeal and left carotid fat space consistent with post-radiation scarring and a possible explanation of his left vocal-cord palsy. He continued to experience dysphonia and underwent left medialization thyroplasty of his left vocal cord. His voice improved, but with some weakness and reduced volume.

Discussion

Location vs Dose

The most common area of recurrence in NPC is locally (within the nasopharynx) or in cervical lymph nodes. In a retrospective study of 1852 patients, Xu et al. found that only 9 patients (4.9%) who were initially treated with intensity-modulated radiotherapy (IMRT) experienced intraparotid recurrence.[1] Xiao et al. similarly found that the

Figure 4. Paths of cranial nerves V3, VII, and XII through the high-dose region.



recurrence of NPC to the parotid gland was 6.9%.[2] It is suspected that spread can occur through the lateral retropharyngeal lymph nodes and level 2 neck cervical lymph nodes through extracapsular spread. Our patient had left-sided positive nodes at levels 2B and 3 at initial diagnosis. During treatment planning, we did not include his left parotid. So, it is possible that parotid-sparing IMRT missed subclinical disease, even though the left parotid mean dose on this patient's initial plan was 30 Gy (exceeding the goal constraint of <26 Gy mean dose). Perhaps an even higher dose was warranted, given the extent of this patient's lymphadenopathy.

The patient's cranial nerve palsies likely occurred due to high total doses of radiation to the skull base region and deep neck. Patients can be considered for reirradiation if they have a small volume of disease, but even the most "ideal" cases carry a risk of late toxicity.[3] Dosing guidelines for reirradiation of the nasopharyngeal and head-and-neck regions do not account for cranial nerves and follow the recommendations applied to vital neurologic structures (brainstem, spinal cord, optic nerves).[4,5] Given the proximity of recurrence to the carotid artery, we kept the dose below 125 Gy.

Proton vs Photon Therapy

Proton therapy has been shown to decrease radiation dose to at-risk organs.[6] In a study of nonmetastatic NPC patients, Li et al. observed fewer acute and late side effects in participants who received proton therapy compared with photon therapy.[7] In the reirradiation setting, Dionisi et al. evaluated 17 patients with recurrent NPC treated with protons and showed only one acute grade 1 and one late grade 2 cranial nerve palsy.[8] In a larger, single-institution study, Lee et al. evaluated 242 patients with head and neck squamous cell carcinoma treated with protons in the reirradiation setting. Of those cases, 24 patients were diagnosed with cancer of the nasopharynx, nasal cavity, or sinuses. Although rates of 1 year overall survival (OS, 66.6%) and 2-year locoregional control (63.0%) were favorable, a considerable number of patients had grade 3, 4, and 5 late toxic effects.[9] One explanation is that these patients are living longer, giving time for late effects to be realized.

Hyperfractionation vs Standard Fractionation

You et al. explored the role of hyperfractionation vs standard fractionation in recurrent NPC patients using IMRT in a multicenter, open-labeled, phase 3 trial. The hyperfractionation group received 65 Gy in 54 fractions with a minimum of 6 hours between fractions. The standard fractionation group received 60 Gy in 27 fractions. Hyperfractionation improved 3-year OS at 74.6% vs 55%, while decreasing grade 3 or worse radiation-induced toxicities.[10] This new study makes a compelling case for the use of hyperfractionation in recurrent NPC.

The cumulative dose to the area of overlap in our patient reached 140 Gy (**Figure 4**). This has proved successful from a local control standpoint, but the patient is now dealing with the late effects of having received 2 rounds

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of radiation, with the area of overlap existing primarily in the deep neck.

A recent, retrospective study found that radiation-induced hypoglossal nerve palsy occurs in 8.7% of nasopharyngeal cancer patients, with higher risks linked to high radiation doses and advanced T-stage.[11] A D1cc constraint of <74 Gy could help limit this risk.[12,13] A pre-IMRT review from a single institution reported a 14% rate of cranial nerve palsy after head and neck radiation, with a median onset of 7.7 years.[14] While most studies show lower incidence rates, our patient continues to experience cranial nerve palsy, and full recovery seems unlikely given the extent of treatment. This underscores the importance of multidisciplinary survivorship care and highlights the complexity of balancing long-term disease control with its impact on quality of life.

Conclusion

NPC is a rare form of malignancy that remains treatable during primary presentation but becomes difficult to treat with recurrence. Here, we present a case of NPC in a 19-year-old patient, who, after receiving concurrent cisplatin and radiation therapy, developed recurrence in the left parotid gland. Salvage reirradiation was delivered using proton therapy. Afterward, the patient developed significant cranial nerve palsies. This case emphasizes the amount of attention that must be paid to fractionation scheme and dosage and also the fact that, even despite our meticulousness, late toxicities can and do occur. By optimizing the treatment plan and thoroughly assessing risks and benefits in conjunction with the patient, the treating radiation oncologist can best balance the chances of cure vs the risk of late side effects and optimize the patient's quality of life.

References

1) Xu Y, Zhang M, Yue Q, et al. Analysis of rare periparotid recurrence after parotid gland-sparing intensity-modulated radiotherapy for nasopharyngeal carcinoma. *Cancer/Radiothérapie*. 2016;20(5):377-383. doi:10.1016/j.canrad.2016.05.012

2) Xiao X-T, Wu Y-S, Chen Y-P, et al. Patterns and prognosis of regional recurrence in nasopharyngeal carcinoma after intensity-modulated radiotherapy. *Cancer Med*. 2023;12(2):1399-1408. doi:10.1002/cam4.5020

3) Simone CB 2nd, Plastaras JP, Jabbour SK, et al. Proton reirradiation: expert recommendations for reducing toxicities and offering new chances of cure in patients with challenging recurrence malignancies. *Semin Radiat Oncol*. 2020;30(3):253-261. doi:10.1016/j.semradonc.2020.02.007

4) Ward MC, Koyfman SA, Bakst RL, et al. Retreatment of recurrent or second primary head and neck cancer after prior radiation: executive summary of the american radium society appropriate use criteria. *Int J Radiat Oncol Biol Phys*. 2022;113(4):759-786. doi:10.1016/j.ijrobp.2022.03.034

5) Ng WT, Soong YL, Ahn YC, et al. International recommendations on reirradiation by intensity modulated radiation therapy for locally recurrent nasopharyngeal carcinoma. *Int J Radiat Oncol Biol Phys*. 2021;110(3):682-695. doi:10.1016/j.ijrobp.2021.01.041

6) Lewis GD, Holliday EB, Kocak-Uzel E, et al. Intensity-modulated proton therapy for nasopharyngeal carcinoma: decreased radiation dose to normal structures and encouraging clinical outcomes. *Head Neck*. 2016;38(suppl 1):E1886-E1895. doi:10.1002/hed.24341

7) Li X, Kitpanit S, Lee A, et al. Toxicity profiles and survival outcomes among patients with nonmetastatic nasopharyngeal carcinoma treated with intensity-modulated proton therapy vs intensity-modulated radiation therapy. *JAMA Netw Open*. 2021;4(6):e2113205. doi:10.1001/jamanetworkopen.2021.13205

8) Dionisi F, Croci S, Giacomelli I, et al. Clinical results of proton therapy reirradiation for recurrent nasopharyngeal carcinoma. *Acta Oncol*. 2019;58(9):1238-1245. doi:10.1080/0284186X.2019.1622772

9) Lee A, Woods R, Mahfouz A, et al. Evaluation of proton therapy reirradiation for patients with recurrent head and neck squamous cell carcinoma. *JAMA Netw Open*. 2023;6(1):e2250607. doi:10.1001/jamanetworkopen.2022.50607

10) You R, Liu Y-P, Xie Y-L, et al. Hyperfractionation compared with standard fractionation in intensity-modulated radiotherapy for patients with locally advanced recurrent nasopharyngeal carcinoma: a multicentre, randomised, open-label, phase 3 trial. *Lancet*. 2023;401(10380):917-927. doi:10.1016/S0140-6736(23)00269-6

11) Au KH, Ngan RKC, Ng AWY, et al. Treatment outcomes of nasopharyngeal carcinoma in modern era after intensity modulated radiotherapy (IMRT) in hong kong: a report of 3328 patients (HKNPCSG 1301 study). *Oral Oncol*. 2018;77:16-21. doi:10.1016/j.oraloncology.2017.12.004

12) Janssen S, Glanzmann C, Yousefi B, et al. Radiation-induced lower cranial nerve palsy in patients with head and neck carcinoma. *Mol Clin Oncol*. 2015;3(4):811-816. doi:10.3892/mco.2015.558

13) Aggarwal P, Goepfert RP, Garden AS, et al. Risk and clinical risk factors associated with late lower cranial neuropathy in long-term oropharyngeal squamous cell carcinoma survivors. *JAMA Otolaryngol Head Neck Surg*. 2021;147(5):469-478. doi:10.1001/jamaoto.2020.5269

14) Dong Y, Ridge JA, Ebersole B, et al. Incidence and outcomes of radiation-induced late cranial neuropathy in 10-year survivors of head and neck cancer. *Oral Oncol*. 2019;95:59-64. doi:10.1016/j.oraloncology.2019.05.014

Closing the Global Brachytherapy Training Gap With Virtual Reality

John Peterson, MD

Brachytherapy is among the most consequential procedures residents learn to perform during their training. It is also one of the most technically complex. Mastery demands hands-on repetition, close mentorship, and sufficient case volume. All 3 can be difficult to guarantee, whether you train in a high-resource setting with declining referrals or in a low- or middle-income country where only a handful of clinicians may serve millions of patients.

The stakes are not abstract. Cervical cancer remains a leading cause of cancer death in women worldwide, and outcomes are sensitive to brachytherapy quality. The 2024 Lancet Oncology Commission on Radiotherapy and Theranostics was unambiguous: gaps in access to high-quality brachytherapy are significant, preventable contributors to avoidable mortality.[1] Building new infrastructure matters, but without parallel investment in education, we risk scaling capacity without scaling competence.

The International Atomic Energy Agency (IAEA) is working to close this gap. Its Rays of Hope: Cancer Care for All initiative, launched in 2022, coordinates with Rays of Hope Anchor Centres—established regional hubs for oncology training, research, mentorship, and quality assurance—to expand capacity outward.[2] The IAEA's Nucleus initiative uses scalable digital tools, including virtual reality (VR), to facilitate workforce development.[3]

With the global radiation therapy workforce needing to grow by more than 60% by 2050 and brachytherapy training a recognized bottleneck, the case for technology-assisted education is compelling. In 2025, the IAEA equipped all Rays of Hope Anchor Centres with VR headsets loaded with a harmonized gynecological radiation therapy training curriculum developed by a global team of experts.[3]

For those of us in residency, including well-resourced programs, tools like these provide highly valuable learning opportunities, especially as brachytherapy volumes decline. Integrating VR-based introductory modules into residency curricula could potentially standardize foundational learning and build procedural confidence before trainees ever enter the suite.

The evidence base for simulation in procedural training is well established across other specialties — brachytherapy should be no different. Although a standardized VR module will not capture the full spectrum of complexities encountered by a brachytherapist, such as managing a patient in distress or navigating a difficult consent conversation, it can allow trainees to rehearse the technique in a risk-free environment and arrive to real-world procedures feeling more confident and prepared.

Brachytherapy is an essential component of radiation oncology care, and the increasing demand for brachytherapy expertise makes expanding access to high-quality training a global priority. VR can play an important role in bridging existing skill gaps by simulating the procedural experience that might not otherwise be possible.

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Ultimately, the goal is a future where a patient in Karachi receives the same quality of brachytherapy as one in Kansas City. Although that reality is still in the distance, residency is exactly the right time to start building the path there using the tools that are available.

References

1) Abdel-Wahab M, Giammarile F, Carrara M, et al. Radiotherapy and theranostics: a lancet oncology commission. *Lancet Oncol*. 2024;25(11):e545-e580. doi:10.1016/S1470-2045(24)00407-8

2) International Atomic Energy Agency. Rays of hope anchor centres. Accessed April 1, 2025. https://www.iaea.org/services/rays-of-hope/anchor-centres

3) International Atomic Energy Agency. Virtual reality boosts gynaecological radiotherapy training at rays of hope anchor centres; 2025. Accessed April 1, 2025. https://www.iaea.org/newscenter/news/virtual-reality-boosts-gynaecological-radiotherapy-training-at-rays-of-hope-anchor-centres