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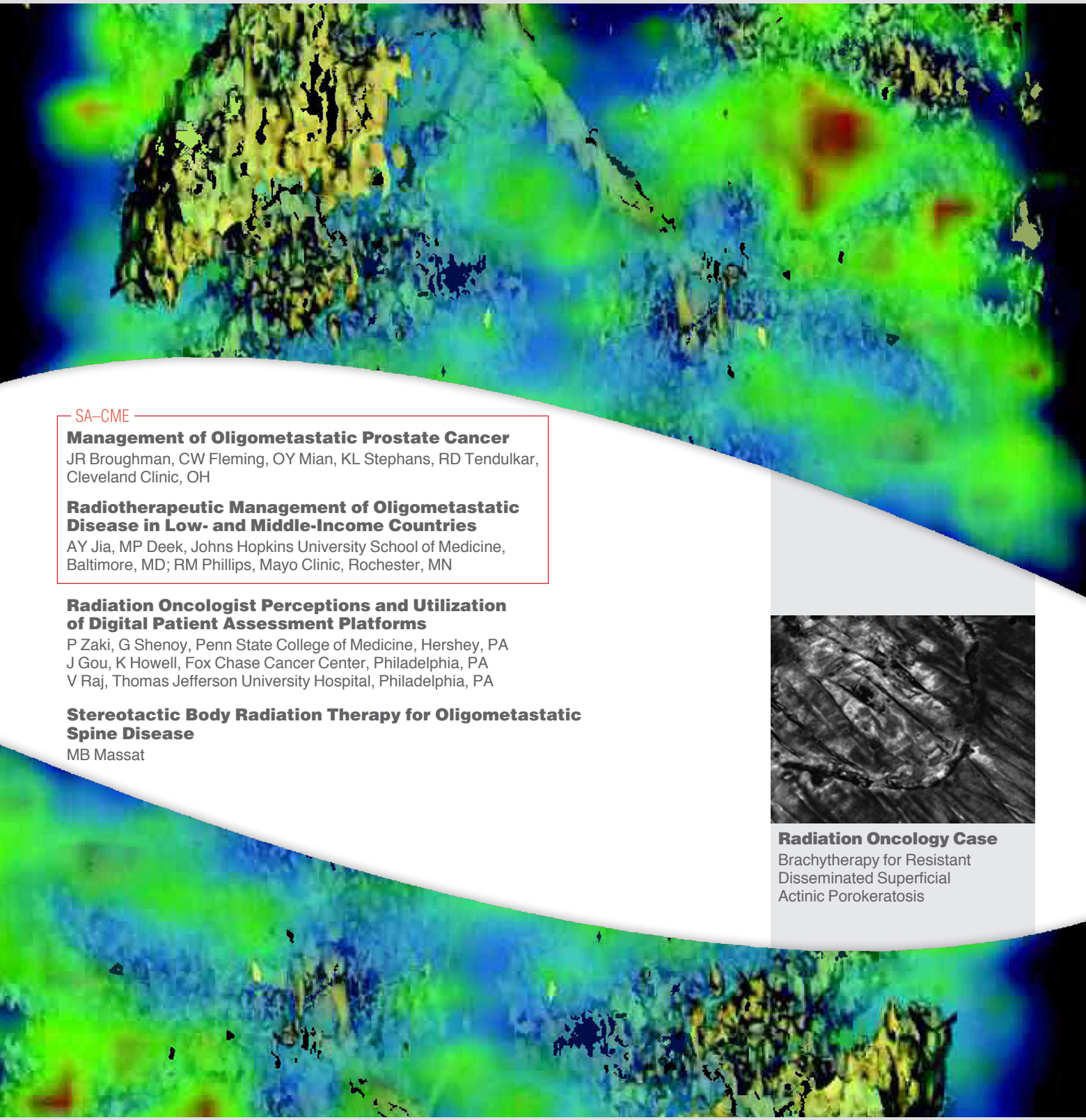
RADIATION ONCOLOGY™



SA–CME

Management of Oligometastatic Prostate Cancer
JR Broughman, CW Fleming, OY Mian, KL Stephans, RD Tendulkar, Cleveland Clinic, OH

Radiotherapeutic Management of Oligometastatic Disease in Low- and Middle-Income Countries
AY Jia, MP Deek, Johns Hopkins University School of Medicine, Baltimore, MD; RM Phillips, Mayo Clinic, Rochester, MN

Radiation Oncologist Perceptions and Utilization of Digital Patient Assessment Platforms
P Zaki, G Shenoy, Penn State College of Medicine, Hershey, PA
J Gou, K Howell, Fox Chase Cancer Center, Philadelphia, PA
V Raj, Thomas Jefferson University Hospital, Philadelphia, PA

Stereotactic Body Radiation Therapy for Oligometastatic Spine Disease
MB Massat

Radiation Oncology Case
Brachytherapy for Resistant Disseminated Superficial Actinic Porokeratosis

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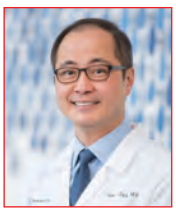

APPLIED RADIATION ONCOLOGY™

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FOCUS: OLIGOMETASTATIC DISEASE

SA-CME CREDITS

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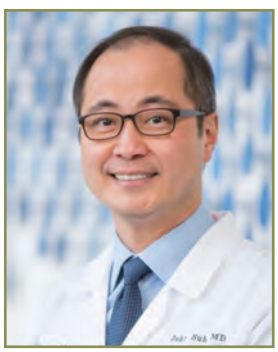
DEPARTMENTS

EDITORIAL

Advancing Treatment for Oligometastatic Disease



John Suh, MD, FASTRO, FACR
Editor-in-Chief

Welcome to the September issue of *ARO*, which focuses on the rapidly evolving field of oligometastatic disease (OMD). While no universally accepted definition of OMD exists, more trials, data and classification efforts are helping to bridge gaps and shift this disease state from deadly to chronic.

Because of its relatively slow disease course and early detection inroads for metastatic disease, prostate cancer has become a front runner for the oligometastatic paradigm. The SA-CME-accredited review article, *Management of Oligometastatic Prostate Cancer,* provides an excellent update on local and systemic multimodality treatment approaches, literature highlights, ongoing trials, and key areas of future study for this patient population.

We are also pleased to present *Radiotherapeutic Management of Oligometastatic Disease in Low- and Middle-Income Countries (LMICs): A Current State of Affairs and Perspectives on Future Implementation.* This informative review, which also offers SA-CME credit, examines barriers and benefits to expanding radiation treatment to patients with OMD in LMICs based on recent clinical trials including SABR-COMET, ORIOLE, and others. The authors further discuss technological advances to improve access to radiation therapy in these developing countries, which face extensive challenges and a disproportionate burden of cancer deaths—a theme that will be discussed in depth at the annual ASTRO meeting held virtually October 25-28.

Additionally, this month's Technology Trends article discusses stereotactic body radiation therapy (SBRT) for treating oligometastatic spine disease, and explores patient selection, systemic vs local control, optimal dose, multidisciplinary efforts and related issues.

Beyond the OMD theme, we are excited to offer the insightful research article, *Radiation Oncologists Perceptions and Utilization of Digital Patient Assessment Platforms*. This well-designed study offers timely findings regarding increased patient expectations in today's digital age and the impact that online physician reviews can have.

We are also excited to feature the most case reports to date in one issue on a wide range of topics, a third SA-CME-accredited article on radioresistance and therapeutic implications, and a Resident Voice editorial on the new ARRO Equity and Inclusion Subcommittee. This editorial stresses the critical importance yet discouraging lack of diversity in radiation oncology, despite its proven contributions to innovation, creativity and better patient care. Our December issue will continue this essential dialogue on racial disparities, featuring review articles on health care inequalities relating to lung and colorectal cancer management.

Please enjoy our September edition, and thank you for your continued support throughout this exceptionally challenging year where unity, perseverance, and hope are cornerstones to progress.

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

RESIDENT VOICE

Filling a Void: The Creation of the ARRO Equity and Inclusion Subcommittee

Karen E. Tye, MD, MS; Vonetta M. Williams, MD, PhD; Idalid "Ivy" Franco, MD, MPH; Shekinah N. C. Elmore, MD, MPH; Oluwadamilola Oladeru, MD, MA; Amanda Rivera, MD; Onyinye D. Balogun, MD, Ankit Agarwal, MD, MBA; Austin J. Sim, MD, JD

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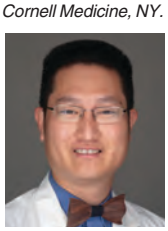

Dr. Sim is a PGY4 resident physician, H. Lee Moffitt Cancer Center, Tampa FL.

The killings of George Floyd, Breonna Taylor, and Ahmaud Arbery have again magnified the lethality of institutional anti-Black racism. Medicine is not exempt. Black physicians have been systematically and disproportionately excluded from radiation oncology (RO).[1] Physicians from backgrounds under-represented in medicine (UIM) are also subject to the deleterious effects of structural racism.[2] Although the number of RO residents doubled from 1974 to 2016, the number of Black residents decreased from 5.9% to 3.2% over the same period. Diversity is essential for innovation, creativity and improved patient care.[3] Moreover, the full and equitable inclusion of UIM physicians in RO and all fields is a moral imperative.

The Association of Residents in Radiation Oncology (ARRO) was founded in 1982 to advocate for all RO residents. Membership in ARRO has been correlated with increased membership in the American Society for Radiation Oncology (ASTRO), as it enables trainees to connect beyond their own programs.[4] The ARRO Equity and Inclusion Subcommittee (EISC) was formed to create a space for support and mentorship for excluded trainees within RO. Eschewing old models pressuring UIM physicians to spearhead initiatives, we welcome all trainees with a desire to create meaningful change.

The ARRO EISC's goals are threefold: 1) to create a shared space for UIM trainees to mitigate isolation in training from being "the rarest of the rare;" 2) to elevate UIM voices on issues of diversity, equity, inclusion, and social justice within RO; and 3) to assess and report workforce trends to generate impactful solutions. Building upon the success of our first journal club, which drew over 130 attendees, we intend in future events to center equity using intersectional frameworks that include race, class, gender identity, sexual orientation, and ability. We intend to build on previous work, including the LEADS recommendations to reduce anti-Black racism in RO.[5] Our next step is to survey attitudes and practices related to diversity, equity, and inclusion among program directors and residents. We are committed to the long-term work of making our shared world of RO more anti-racist, equitable, and inclusive for all. We invite anyone interested in these efforts to join us.

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SA–CME Information

MANAGEMENT OF OLIGOMETASTATIC PROSTATE CANCER

Description

Recent data suggest that aggressive treatment of the primary tumor or metastasis-directed therapy may confer a survival advantage in carefully selected patients with metastatic prostate cancer. This review outlines treatment approaches, while highlighting existing literature, ongoing trials, and important areas for future study.

Learning Objectives

After completing this activity, participants will be able to:

1. Understand current evidence supporting the use of systemic and local therapies in the treatment of oligometastatic prostate cancer.
2. Employ systemic and local therapies in their practice to improve outcomes for patients with oligometastatic prostate cancer.

Authors

James R. Broughman, MD, *is a PGY4 chief resident,* ***Christopher W. Fleming, MD,*** *is PGY5 resident, and* ***Kevin L. Stephans, MD, Omar Y. Mian, MD, PhD,*** *and* ***Rahul D. Tendulkar, MD,*** *are associate staff, all in the Department of Radiation Oncology, Taussig Cancer Institute, Cleveland Clinic, OH.*

RADIOTHERAPEUTIC MANAGEMENT OF OLIGOMETASTATIC DISEASE IN LOW- AND MIDDLE-INCOME COUNTRIES: A CURRENT STATE OF AFFAIRS AND PERSPECTIVES ON FUTURE IMPLEMENTATION

Description

This review provides a perspective regarding barriers to expansion of radiation treatments in low- and middle-income countries (LMICs). The authors review the benefit of expanding radiation treatment to patients with oligometastatic disease based on several recent clinical trials including SABR-COMET, ORIOLE. The authors discuss limitations and barriers to receiving radiation treatment in less developed countries including the sparsity of treatment machines, personnel expertise, and distribution of resources in urban vs rural environments. They further discuss technological advances that may help to develop and increase access to radiation therapy in LMICs.

Learning Objectives

After completing this activity, participants will be able to:

1. Understand how oligometastatic disease may be classified and the justification for treatment with local consolidation.
2. Learn the magnitude and causes of the high cancer mortality seen in low- and middle-income countries.
3. Enhance global collaboration toward progress against cancer in low- and middle-income countries by understanding specific, addressable barriers to the implementation of modern cancer care paradigms.

Authors

Angela Y. Jia, MD, PhD, *and* ***Matthew P. Deek, MD,*** *are residents in the Department of Radiation Oncology and Molecular Radiation Sciences, Johns Hopkins University School of Medicine, Baltimore, MD.* ***Ryan M. Phillips, MD, PhD,*** *is a senior associate consultant in the Department of Radiation Oncology, Mayo Clinic, Rochester, MN.*

TRANSCRIPTIONAL MECHANISMS OF RADIORESISTANCE AND THERAPEUTIC IMPLICATIONS

Description

While numerous mechanisms impact sensitivity to radiation, the authors examine the transcriptional alterations and gene expression programs that allow neoplastic cells to withstand radiation. They review the recurring mechanisms co-opted by cancer cells in radiation resistance: upregulation of DNA repair, suppression of apoptotic programs, hypoxia, immune evasion and exhaustion, cellular plasticity, as well as aberrant intracellular signaling. They also explore the therapeutic implications of these preclinical findings.

Learning Objectives

After completing this activity, participants will be able to:

1. Define the transcriptional alterations and gene expression programs that influence radioresistance in cancer cells.
2. Acknowledge the importance of transcriptional changes that occur during treatment of tumors with radiotherapy.
3. Put into practice the use of therapeutic agents that target upregulated pathways to improve radiotherapy outcomes.

Authors

Daniel Y. Kim, BS,* *is a research technologist, Molecular Pathology Unit and Center for Cancer Research, Massachusetts General Hospital, Charlestown, MA.* ***Jimmy A. Guo, BA,**** *is a medical student, School of Medicine, University of California San Francisco (UCSF); Broad Institute of MIT and Harvard, Cambridge, Massachusetts; and Koch Institute for Integrative Cancer Research, MIT, Cambridge.* ***Daniel Zhao, BA,*** *is a medical student, New York Medical College, Valhalla, NY.* ***Errol J. Philip, PhD,*** *is a medical student, UCSF.* ***Yun R. Li, MD, PhD,*** *is a resident physician, Department of Radiation Oncology and Helen Diller Family Comprehensive Cancer Center, UCSF. *These authors contributed equally to this work.*

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SA-CME (see page 5)

Management of Oligometastatic Prostate Cancer

James R. Broughman, MD; Christopher W. Fleming, MD; Omar Y. Mian, MD, PhD; Kevin L. Stephans, MD; Rahul D. Tendulkar, MD

Metastatic prostate cancer has long been considered incurable and managed with systemic therapies alone. However, there is increasing evidence of an "oligometastatic" state where patients with low-volume metastatic disease may achieve sustained disease-free intervals as well as potentially improved overall survival (OS) with combinations of systemic and local therapy. The concept of oligometastatic disease was first described by Hellman and Weichselbaum who hypothesized that there may be an intermediate state between locally confined disease and fulminant metastatic disease.[1] Accordingly, recent data suggests that aggressive treatment of the primary tumor or metastasis-directed therapy (MDT) may confer a survival advantage in carefully selected patients with metastatic prostate cancer.[2-4]

Among the 190,000 new cases of prostate cancer diagnosed each year in the US, about 20% present with primary metastatic disease.[5,6] Prostate-specific antigen (PSA) screening and imaging advances have led to a relative increase in the detection of cases with early metastatic disease. Even after detection of distant metastases (DM), metastatic prostate cancer is relatively indolent and marked by a long disease course.[7] Due to its long natural history, prostate cancer has been at the forefront of efforts investigating aggressive treatment in oligometastatic disease. In this review we aim to outline treatment approaches for these patients, while highlighting existing literature, ongoing trials, and important areas for future study.

Defining the Oligometastatic State

Although the definition of oligometastatic disease varies considerably in the literature, most definitions limit the maximum number of metastatic sites to between 3 to 5.[8] Furthermore, a major challenge in synthesizing the available literature is the wide array of clinical scenarios represented. In the landmark paper by Hellman and Weicheslbaum, the authors described two scenarios that both fell under the umbrella of oligometastatic disease, but likely have different clinical courses. The first are "tumors early in the chain of progression with metastases limited in number and location" and "another group of patients with oligometastases who had widespread metastases that were mostly eradicated by systemic agents, the chemotherapy having failed to destroy those remaining because of the number of tumor cells, the presence of drug-resistant cells, or the tumor foci being located in some pharmacologically privileged site." Consequently, more granularity is needed when describing oligometastatic disease. One such effort is the European Society for Radiotherapy and Oncology and European Organization for Research and Treatment of Cancer (ESTRO/EORTC) consensus recommendations for characterization and classification of oligometastatic disease, which identified 9 distinct states of oligometastatic disease.[9] Standardized definitions of oligometastatic disease will lead to a more uniform understanding of study results and allow for cross-study comparisons.

Role of Prostate-directed Therapy

Many have hypothesized that treatment of the primary tumor in the set-

Dr. Broughman *is a PGY4 chief resident,* ***Dr. Fleming*** *is a PGY5 resident, and* ***Dr. Stephans, Dr. Mian,*** *and* ***Dr. Tendulkar*** *are associate staff, all in the Department of Radiation Oncology, Taussig Cancer Institute, Cleveland Clinic, OH.* *Disclosure: Dr. Tendulkar has received honoraria from Varian for educational talks. No other authors have conflicts of interest to disclose. None of the authors received outside funding for the production of this original manuscript and no part of this article has been previously published elsewhere.*

SA-CME (see page 5)

ting of metastatic disease could lead to improved clinical outcomes due to cytoreduction, reduced seeding of new metastases, and stimulation of an anti-tumor immune response. Indeed, some prospective studies across various disease sites have reported improved outcomes with treatment of the primary tumor,[10-12] although this remains controversial.[13,14] Within the realm of prostate cancer, there is increasing prospective data to support prostate-directed radiation therapy (RT) in carefully selected patients with metastatic disease. The HORRAD and Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy (STAMPEDE) trials have established a survival benefit to prostate-directed RT in patients with low-volume metastatic disease. HORRAD was a phase III randomized trial investigating the addition of prostate-directed RT to lifelong androgen deprivation therapy (ADT) in men with newly diagnosed prostate cancer with bone metastases.[15] Patients received 70 Gray (Gy) in 35 daily fractions or 57.76 Gy in 19 fractions 3 times per week to the prostate. There was no difference in OS for the entire cohort; however, an unplanned subgroup analysis suggested a potential benefit in patients with 4 or fewer bone lesions, although this did not reach significance (HR 0.68, 95% CI 0.42-1.10). STAMPEDE is a multi-arm, phase III randomized trial that investigated the role of delivering RT to the prostate in men with newly diagnosed metastatic prostate cancer receiving lifelong ADT.[3] Patients could receive either 36 Gy in 6 weekly fractions, or 55 Gy in 20 daily fractions. Radiation fields did not include pelvic nodes or any metastatic sites. Prostate-directed RT was well tolerated with only 5% experiencing acute grade 3-4 radiation toxicity (4% GU and 1% GU). While no OS benefit was seen in the entire population, a pre-specified subgroup analysis of patients with low-volume disease showed a statistically significant improvement in 3-year OS from 73% to 81%. High-volume disease was defined as 4 or more bone metastases with 1 or more outside the vertebral bodies or pelvis, or visceral metastases; all other patients were considered to have low-volume disease. The Systemic Treatment Options for Prostate Cancer (STOPCAP) meta-analysis of the 2 preceding trials reclassified STAMPEDE patients into low- or high-volume using the HORRAD definition of 4 or fewer bone lesions, and found a statistically significant survival benefit in low-volume patients, with RT improving the 3-year survival rate from 70% to 77%.[16]

Taken together, these studies support prostate-directed RT for patients with limited metastatic disease. Additional ongoing trials such as Patients With Metastatic Hormone-naïve Prostate Cancer (PEACE-1), Impact of Radical Prostatectomy as Primary Treatment in Patients With Prostate Cancer With Limited Bone Metastases (G-RAMMP), Testing Radical prostatectomy in men with prostate cancer and oligoMetastases to the bone (TRoMbone), STAMPEDE arm M, and SWOG 1802 will further clarify the role of prostate-directed therapy, including surgery, in the era of modern systemic therapy for metastatic prostate cancer.[17-21]

Role of Metastasis-directed Therapy

An important limitation of defining oligometastatic disease by the number of lesions is reliance on imaging techniques that are neither perfectly sensitive nor specific. Emerging imaging techniques have allowed for more accurate characterization of disease burden. The most promising of these is prostate-specific membrane antigen (PSMA) positron emission tomography – computed tomography (PET-CT), which has demonstrated superior performance compared to conventional imaging and other contemporary radiotracers.[22,23] Unfortunately, PSMA PET-CT is not approved by the Food and Drug Administration and, therefore, is unavailable in the US. A readily available alternative is ^{18}F-fluciclovine (Axumin) PET-CT, which is commercially available in the US and demonstrates superior sensitivity and specificity compared to conventional imaging modalities.[24] These imaging improvements have led to detection of metastases in some patients who would have previously been classified as having localized disease, and polymetastases in some who would have been classified as having oligometastatic disease. Additionally, advanced imaging allows for accurate characterization and subsequent treatment of the full extent of oligometastatic disease.

The importance of pretreatment imaging on the efficacy of MDT was shown by the randomized phase II Observation in Oligometastatic Prostate Cancer (ORIOLE) study.[25] Fifty-four men with recurrent, hormone-sensitive prostate cancer with 3 or fewer lesions were randomized to stereotactic body radiation therapy (SBRT) to all metastatic lesions or observation. Salvage RT to the prostate bed or pelvis was permitted, and patients were allowed to receive ADT or other systemic therapy during initial management or salvage treatment, but not within 6 months of enrollment. SBRT patients received 19.5 to 48.0 Gy in 3 to 5 fractions. Those randomized to MDT underwent a PSMA scan prior to MDT; however, the treating radiation oncologists were blinded to the results of PSMA and selected targets were based only on CT, MRI, or bone scan. PSMA scans were then compared to treatment plans, and patients were categorized as having had total (n = 19) or subtotal (n = 16) consolidation of PSMA-avid lesions. The proportion

SA-CME (see page 5)

of men with disease progression at 6 months was 10% in the SBRT arm vs 61% in the observation arm ($P=0.005$). Within the SBRT group, patients who had undergone total consolidation had significantly reduced rates of new metastases at 6 months compared with those who had undergone subtotal consolidation (16% vs 63%, $P = 0.006$). There were no grade 3 or higher adverse events, and no significant differences in quality of life (QOL) between the two groups. Median distant metastasis-free survival was 29 months in men with no untreated lesions and 6 months in men with any untreated lesions. These results highlight the importance of optimal pretreatment imaging in maximizing the efficacy of MDT.

Traditionally, management of metastatic prostate cancer has consisted of lifelong ADT alone. However, long-term ADT and its hypogonadal sequelae negatively impact QOL with side effects including hot flashes, fatigue, weight gain, mood changes, and sexual dysfunction. Advances in radiation planning have made it possible to deliver ablative doses of radiation to sites of metastatic disease with minimal toxicity while delaying initiation of ADT. The role of MDT in delaying systemic therapy was demonstrated in the phase II STOMP trial, which randomized patients with biochemically recurrent prostate cancer with 1 to 3 lesions (nodal or metastatic) on choline PET-CT to observation vs MDT (surgery or SBRT) to all detected lesions, with the primary endpoint of ADT-free survival.[26] Patients undergoing SBRT received 30 Gy in 3 fractions. ADT was given for progression of symptoms, progression to more than 3 metastases, or progression of known lesions. Asymptomatic progression in 3 or fewer new lesions could be treated with further MDT. Tolerance of MDT was excellent with no grade 2 or higher toxicity reported. The time to both PSA progression and initiation of ADT was longer in the MDT arm, with an increase in median ADT-free survival from 13 to 21 months. PSA doubling times ≤ 3 months were predictive of a larger magnitude of benefit from MDT. Five-year ADT-free survival increased 8% to 34% with MDT, showing that some patients may delay systemic therapy for a prolonged period. Additionally, 76% of the MDT group remained castration sensitive at 5 years, as opposed to 53% in the surveillance group.[27] Longer follow-up is required to determine the effect of MDT and delayed onset of metastatic castrate-resistant prostate cancer on survival.

Despite attempts to delay systemic therapy using MDT, ADT remains the standard-of-care treatment for patients with metastatic prostate cancer, and delivery of consolidative MDT with concurrent ADT may represent a viable form of treatment intensification. Results of the phase II Stereotactic Ablative Radiotherapy Versus Standard of Care Palliative Treatment in Patients With Oligometastatic Cancers (SABR-COMET) trial support the use of concurrent MDT and systemic therapy. Patients with 1-5 metastatic lesions and a controlled primary tumor were randomized to receive standard-of-care treatment with or without SBRT to all oligometastatic sites. Sixteen patients with prostate cancer were included (16% of the study population). Importantly, standard-of-care systemic therapy was recommended as indicated, and choice of systemic agent was left to the discretion of the treating medical oncologist. Nearly 60% of patients in both arms received systemic therapy after MDT. Patients in the MDT arm had improved median progression-free survival from 5.4 to 11.6 months ($P = 0.001$), as well as improved OS from 28 to 50 months ($P = 0.006$) with no significant change in QOL.[28] The results of SABR-COMET illustrate the potential survival benefits of integrating MDT into standard-of-care systemic therapy.

Role of Systemic Therapy

Although ADT remains the backbone of treatment for metastatic prostate cancer, the optimal duration of systemic therapy in the oligometastatic setting is unknown. Patients with widespread metastatic disease generally receive lifelong ADT. Conversely, patients with high-risk localized disease treated with RT are recommended to receive up to 3 years of long-term ADT.[29,30] Presumably, just as oligometastatic tumor burden lies between these two states, so too does optimal ADT duration.

The optimal choice of systemic therapy is also unknown, but likely includes the addition of a second agent to ADT. The Enzalutamide in First Line Androgen Deprivation Therapy for Metastatic Prostate Cancer (ENZAMET) and TITAN trials found a survival benefit with the use of enzalutamide and apalutamide, respectively, for metastatic patients with either high- or low-volume metastatic disease.[31,32] The STAMPEDE arm randomizing patients to ADT with or without abiraterone enrolled half nonmetastatic patients; an OS benefit was seen with the addition of abiraterone for all patients, including those with nonmetastatic and low-volume metastatic disease.[33] Data for docetaxel in limited volume disease has been mixed, with the STAMPEDE investigators finding benefit for both high- and low-volume patients,[34] whereas the Androgen Ablation Therapy With or Without Chemotherapy in Treating Patients With Metastatic Prostate Cancer (CHAARTED) trial found a benefit for only those with high-volume disease.[35]

Accordingly, for optimal disease control, data suggests that systemic therapy and MDT, as well as treatment of the prostate, should be incorporated into the treatment of oligometastatic patients. However, the optimal ADT duration and sequencing of systemic and local therapy remains unknown.

SA-CME (see page 5)

Treatment of Isolated Nodal Recurrences

Isolated pelvic nodal disease represents a unique scenario within the array of oligometastatic disease states, in that regionally metastatic disease signifies an early intermediate point on the spectrum between locally confined and diffusely metastatic disease. A Surveillance, Epidemiology, and End Results (SEER)-Medicare analysis of nearly 4,000 patients with metastatic prostate cancer demonstrated a median OS of 43 months, 24 months, 16 months, and 14 months for those with nodal metastases, bone metastases, visceral metastases, and bone plus visceral metastases, respectively.[36] As such, the potential for durable disease control with curative-intent salvage therapies is higher in this cohort than in other types of oligometastatic patients, and aggressive definitive therapy such as ADT and whole-pelvis RT with an additional boost to gross disease should be considered. SBRT can be considered; however, at least one pattern of failure analysis found that 68% of relapses after nodal SBRT occurred in other regional nodal regions.[37] Therapeutic lymphadenectomy is a reasonable alternative to RT. A recent systematic review of 27 series reporting outcomes after lymph-node dissection for recurrent prostate cancer found complete biochemical response in a mean of 44% of cases, showing the potential for nodal-confined disease.[38] The ideal extent of lymph-node dissection is unknown, but more extensive dissection has been associated with improved PSA response.[39] The ongoing Salvage Treatment of Oligorecurrent Nodal Prostate Cancer Metastases (STORM) trial seeks to provide insight into optimal management for these patients; men with oligorecurrent prostate cancer isolated to the pelvic lymph nodes will receive 6 months of ADT along with MDT, and are subsequently randomized to pelvic RT or not.[3]

Conclusion

There is increasing evidence of an oligometastatic state, an intermediate between localized and polymetastatic disease, in which patients may experience prolonged survival with multimodality combinations of local and systemic therapy. Prostate cancer has become a flagship for the oligometastatic paradigm due to a relatively indolent disease course and early detection of metastatic disease using PSA screening and advanced imaging. Because oligometastatic prostate cancer encompasses a vast array of disease biology and clinical trajectories, the optimal management of oligometastatic disease remains unclear. Systemic therapy remains the cornerstone of treatment for patients with metastatic disease, but several studies demonstrate benefits to the integration of local therapy to the prostate and metastatic sites. Further study is needed to identify genomic and clinicopathologic classifiers to better select patients most likely to benefit from MDT.

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SA-CME (see page 5)

Radiotherapeutic Management of Oligometastatic Disease in Low- and Middle-Income Countries: The Current State of Affairs and Perspectives on Future Implementation

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In 2018, there were an estimated 18.1 million new cancer cases and 9.6 million cancer deaths based on data from 185 countries.[1] Radiation therapy (RT) is required in 45% to 55% of all new cancer diagnoses[2] and 5-year overall survival (OS) benefits from RT can reach as high as 16% in head and neck and 18% in cervix populations.[3] Historically, curative-intent therapy was applied only to locally confined primary disease, but with improvements in detection, systemic therapies, surgical techniques, and conformal radiation, we can now identify and intervene upon oligometastatic disease (OMD) with the goal of changing patterns of recurrence, delaying progression, and improving quality of life as well as survival. Drs. Hellman and Weichselbaum[4] were early proponents of this counterpoint to an all-or-nothing dichotomous theory of cancer spread, wherein early metastases, limited in number and location, may still be curable through local intervention.

Definition and Management of OMD

There is no single universally accepted definition of OMD, but current clinical practice and trial designs most commonly use a numerical threshold of 3 to 5 lesions. While exciting work is ongoing, there have been, to date, no prospectively validated OMD-specific biomarkers.[5] The European Society for Radiotherapy and Oncology (ESTRO) and European Organization for Research and Treatment of Cancer (EORTC) recently outlined nomenclature to categorize states of OMD as a reflection of metastatic capacity.[6] In this classification, they proposed 5 characteristics of metastatic progression (history of polymetastatic disease, prior OMD, interval between diagnosis of primary cancer and diagnosis of OMD, prior active systemic therapy, and any OMD progression by imaging) and define 9 distinct states of OMD. This paradigm allows tailoring treatment aims to the OMD state, which can be dynamic, with the overall goal of preventing or delaying polymetastatic progression.

The principles of treating OMD include primary tumor control, local consolidation of all metastatic sites, and minimizing treatment duration of metastasis-directed therapy (MTD) to allow cure for a minority of cases or a quick initiation of or return to systemic therapy for most.[7] Recent randomized data support MTD using stereotactic ablative radiation (SABR), which allows the precise delivery of high doses of radiation under image guidance. The SABR-COMET trial reported that, when added to standard systemic therapy, MTD with SABR in patients with a controlled primary cancer of any histology and up to 5 metastatic lesions was associated with a median survival of 41 months compared to 28 months in the standard palliative therapy arm.[8] Secondary analyses have also shown SABR to be cost-effective and not associated with greater decline in quality of life compared to standard of care.[9,10] Two phase II oligometastatic non-small cell lung cancer (NSCLC)

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SA-CME (see page 5)

trials demonstrated significant progression-free survival benefit following upfront systemic therapy with the use of local consolidative SABR to sites of metastatic disease consisting of 3 to 5 lesions; the absolute PFS benefit ranged from 6.2 months[11] to 9.8 months.[12] Furthermore, the Gomez trial[12] showed an absolute median OS benefit of 24.2 months associated with SABR and also highlighted the importance of the window of treatment, suggesting that early local consolidative therapy (LCT) was favorable to LCT at time of progression. The Surveillance or Metastasis-directed Therapy for Oligometastatic Prostate Cancer Recurrence (STOMP) trial demonstrated that for prostate cancer with up to 3 metastatic lesions the use of MDT (primarily SABR) significantly prolonged median androgen-deprivation therapy (ADT) free survival from 12 months (surveillance) to 21 months (LCT) with no grade 2 or higher toxicity.[13] Similarly, in the Observation vs Stereotactic Ablative Radiation for Oligometastatic Prostate Cancer (ORIOLE) trial,[14] SABR resulted in significantly reduced risk of progressive disease in men with oligorecurrent prostate cancer and 1 to 3 metastases detectable by conventional imaging, with a median PFS not reached (median follow-up: 18.8 months) in the SABR arm compared to 5.8 months with observation alone. These trials demonstrate that SABR can improve PFS, OS, and may in some cases permit a safe delay in initiating systemic therapy.

Classification and Cancer Burden in Low- and Middle-Income Countries

Currently, three-quarters of global cancer deaths are in low- and middle-income countries (LMICs)[15] and the combination of reduced death from infectious etiologies and longer life expectancies are contributing to increased cancer incidence in these countries. World Bank classifies LMICs based on gross national income (GNI) per capita. Specifically, low-income economies are defined as < $1,025, lower middle-income economies are between $1,026 and $3,995, and upper middle-income economies are between $3,996 and $12,375.[16] While incidence of cancer types is influenced by societal, economic, and lifestyle factors, the ratio of mortality to incidence is consistently elevated across all cancer types in LMICs. For instance, Asia accounts for 48.4% of total cancer cases and 57.3% of cancer deaths, and Africa accounts for 5.8% of cases and 7.3% of deaths. Despite elevated incidence of prostate cancer in high-income countries (primarily in Australia, Northern and Western Europe, and North America), the highest mortality rates are in Sub-Saharan Africa and the Caribbean. Furthermore, mortality is likely underestimated in LMICs, where most cancer registries are hospital- rather than population-based and frequently offer insufficient coverage. In 2010, only 7.5%, 6.5%, and 1% of the total population of South America, Asia, and Africa, respectively, were covered by high-quality cancer registration.[17]

Impediments to Radiation Therapy in LMICs

The Directory of Radiotherapy Centers (DIRAC) of the International Atomic Energy Agency (IAEA) is a continuous central registry and quantification of international RT capacity. Member states self-report data on teletherapy machines, sources and devices used in brachytherapy, dosimetry equipment, patient dose calculation, and quality assurance. Of the 138 countries classified as LMICs, 119 are part of the IAEA and 90 have radiation capability.[16] The number of RT machines per million people decreases from 7.7 in high-income countries to 1.5 in upper middle, 0.43 in lower middle, and 0.05 in low-income countries.[18] This is much lower than the 4 per 1 million recommended by the IAEA and only approximately 20% of LMICs have a current organization to consistently offer RT.[19,20] One of the greatest impediments to implementing RT in general is a lack of infrastructure: There is a direct correlation between gross domestic product and access to RT.[21] Equipment costs can be several million dollars[22] and LMICs often rely on donated linear accelerators, which can be more than 20 years old. In 2019, 29 of the 54 African countries listed by World Bank have photon- and electron-beam teletherapy machines and only 6 (Kenya, Tunisia, Algeria, Morocco, South Africa, and Egypt) have more than 10 machines.[18] It is no surprise that machine deficit correlates with decreased life expectancy,[21,23,24] as the contribution of RT to cancer survival is around 40%, compared to a 49% contribution from surgery and an 11% contribution from systemic therapy.[25] Additional costly infrastructure considerations include appropriate radiation shielding of treatment vaults and reliable water and power supplies. Even greater expense is tied to SABR use for oligometastatic disease due to the time-intensive nature of planning and delivery as well as more stringent engineering tolerances.

Personnel limitations also complicate availability of high-quality RT. The ESTRO - Quantification of Radiation Therapy Infrastructure and Staffing Needs (ESTRO-QUARTS) estimates RT units and staffing requirements. Based on ESTRO-QUARTS and DIRAC, Datta et al[26] estimated the percentage of additional infrastructure and personnel required in 2020 based on 2014 inventory in LMICs as follows: medical physicists (+292.3%), RT technologists (+270.3%), teletherapy units (+221.6%), and radiation oncologists (+102.9%). While the demand of these professions has risen in LMICs, the supply has not proportionally increased. For example, Lebanon has 11 radiation oncologists for a population of 5 million people.[27] Additionally, these limited staff are usually in centralized urban areas in contrast to the high percentage

SA-CME (see page 5)

of rural inhabitants in LMICs. This disconnect results in patients traveling great distances for treatment, often finding limited temporary housing.[28] There are several explanations for the lack of personnel support in LMICs. Foremost are financial reasons: Annual salaries of professionals in the field are 5 times higher in developed countries, prompting considerable relocation of qualified personnel to higher income countries where the profession is better supported.[22] Second, training often necessitates travel abroad with no guarantee that trainees will return to practice in their home country. Finally, the engineering support for RT units is commonly provided by the manufacturer and availability is severely limited in LMICs where low overall supply does not make it economical for companies to provide greater levels of support.

MDT Integration in LMICs

While curative-intent treatment of OMD has shown great promise, implementing such a paradigm in LMICs requires careful consideration of resource availability and allocation. In a resource-limited setting, cost-effectiveness is paramount. The argument for developing MDT capacities in LMIC begs several key questions: (1) To what degree is any treatment of metastatic cancer a feasible economic priority? (2) Is the population of patients eligible for treatment sufficient to justify the infrastructure required? (3) Is SABR inclusion into OMD management paradigms expected to add value over traditional systemic therapies? The first answer will be highly specific to the financial, cultural, and medical landscape of each nation and is beyond the scope of this discussion. Discussion regarding the second and third questions are as follows:

Understanding the eligible patient population requires knowledge of disease staging as well as ability to pay for care. As discussed above, many patients in LMICs are not covered by high-quality national cancer registries.[17] Without nation-level or, at minimum, robust hospital-level data expected to provide a representative sampling of the population, analysts and researchers can only extrapolate from nations where such data exists. While registries are critical to understanding population-level trends and needs, the other side of this coin with respect to OMD is the ability of patients to be adequately imaged. WHO recommends at least one imaging department (x-ray and ultrasound) per 50,000 people.[29] Most countries in Africa report < 1 CT unit per 1 million people, as compared to Denmark with 24 CT units per 1 million inhabitants.[30] Organizations such as RAD-AID are working to address this radiology gap through education (development of a US medical school clerkship curriculum in public health and radiology) and acquisition of technology through donation or lower-cost older machines, and lower-cost technology such as cellular phones.[31,32]

When the incidence of OMD and, in turn, the resources required to implement a modern management strategy can be satisfactorily estimated, the ability of patients to pay for sophisticated cancer care must then be assessed. Even in highly developed nations, cancer care can be prohibitively expensive to individuals and cost-sharing mechanisms are critically important. Limited public health care coverage options in LMICs result in proliferation of private, fee-for-service options causing high out-of-pocket expenses and further widening of health inequity. Universal health care coverage is essential to ensure risk pooling and protect from the destabilizing financial consequences of poor health. Mexico established a national health insurance program, Seguro Popular, in 2003 that introduced the concept of nonpersonal health-related public goods (immunization, primary prevention, early detection, epidemiological surveillance) and personal health services. Nonpersonal health services were financed through the Ministry of Health via general taxation. In contrast, personal health services were funded through prepaid contributions based on capacity to pay in addition to general taxation.[33] Mexico's implementation of universal health coverage serves as a model for other LMICs.

With adequate detection capabilities, registry management, and identification of payers, we must ask if OMD is a cost-effective component of cancer care. Currently data is limited to adequately comment on SBRT cost effectiveness in treating OMD compared with systemic therapy. It has been described, however, that the average monthly cost of targeted agents is between $12,000 for oral kinase inhibitors to $150,000 for monoclonal antibodies[34] and on average launch prices increase by approximately 10% (or $8,500) per year.[35] Furthermore, the lower expected revenues from LMICs may not justify the initial investment that companies undertake to overcome regulatory barriers.[34] In one Canadian study, SBRT was more cost-effective (expected cost per net quality-adjusted life years) than video-assisted thoracic surgery or systemic therapy in treating pulmonary metastases from melanoma or non-EGFR mutant lung adenocarcinoma.[36] An analysis of the SABR-COMET trial found that the addition of MDT was cost-effective compared with standard-of-care management alone for patients with 1 to 5 oligometastatic lesions.[9] While radiation has been shown to be a cost-effective cancer treatment – curative intent and palliation – compared with other cancer interventions in Australia,[37] it is unclear whether this translates to LMICs.

Lessons From Existing Efforts, Potential Future Directions

Fostering the development of RT capabilities in any LMIC will no doubt require addressing specific local considerations and no template will provide a single best approach. With that said, valuable lessons can be learned from

SA-CME (see page 5)

the published experience in Botswana, classified as lower income, including the necessity of obtaining government support and establishment of quality cancer registries for diagnosis, care, and evaluating patient outcome. While the private sector identified the oncology market and constructed the radiation bunker to house a donated linear accelerator,[28] the public sector was instrumental in the delivery of radiation through financial compensation of personnel, infrastructure support, and coordination with neighboring South Africa (from whom Botswana initially obtained its electrical power).

Another valuable example is the development of RT capabilities in the Dominican Republic (DR). DR is an upper-middle income country where most physicians are trained abroad. A radiation oncology residency program was established in 2010; however, there is no formal training program for radiation therapists, dosimetrists, or medical physicists. While radiation was established in 1945, 76% of the existing machines were installed from 2010 onward. For DR, three key events led to the increase in RT units: In 2004, IAEA analysis of DR noted a severe deficiency in radiation capability with only three centers housing four machines.[38] In 2007, a publicly financed health insurance scheme was established. In 2009, the Ministry of Public Health recognized cancer and noncommunicable diseases as a priority, which allowed cancer care to be covered under the public health insurance. Now with 12 radiation centers housing 21 machines, DR contains the highest number of RT centers in the Caribbean. They have both a public sector and private sector offering radiation, and 95% of patients have health insurance.[38] Despite these successes, however, challenges remain in DR with respect to treatment of OMD. While SBRT technology is available, it is used infrequently due to limitations of availability and lower reimbursement rates. Also, most patients in DR still present with advanced stage disease. This is thought to be attributable to limited patient education, cultural taboos regarding cancer, and reliance on natural remedies. This highlights the importance of community engagement in the coordinated effort to manage cancer.

Technological advancements might also someday help to develop and increase access to RT in LMICs. Mobile linear accelerators are now feasible[39] and may help bring RT to underserved parts of high-income countries as well as patients in LMICs. While likely not a permanent solution, it might act as an impetus to support the growing expansion of RT in underserved parts of the world, especially if combined with hypofractionation or ultrafractionation approaches, which significantly decrease the number of treatments for an RT course.

A noteworthy disadvantage of current SBRT approaches in resource-limited settings such as LMICs is the increased treatment times required, meaning fewer patients can be treated each day. One solution may be to extend practice hours, which has been shown to be feasible in Zambia.[40] However, Yahya et al[23] found the extended working hours model was able to fulfill RT needs in high- and upper-middle income countries in Southeast Asia but not in LMICs. The natural alternative to increased working hours would be some combination of decreased treatment duration and/or decreased total treatments per patient. FLASH RT, in which ultrahigh dose rate radiation is delivered in milliseconds, appears to be less toxic to healthy tissues and may broaden the applicability of single-fraction regimens.[41,42] This is beneficial in situations where patients travel long distances, often from other countries, to receive treatment and will reduce time burden for the patient. Additionally, compressing treatment into one session allows for high efficiency use of the linear accelerator.[43]

As discussed, a major limitation to RT delivery in LMICs is lack of personnel, often driven by emigration to seek training. The increasingly interconnected global environment offers the opportunity for remote collaboration in the RT process. Remote planning[44-45] and quality assurance are feasible[46] and may help increase access to radiation. A commitment to greater remote collaboration might someday permit remote training to reduce the need for physicians, physicists, and dosimetrists from LMICs to emigrate to obtain the necessary knowledge to practice. These types of efforts can and should be coordinated with international agencies such as IAEA and professional societies in radiation oncology to facilitate increased access to radiation around the globe.

Conclusions

Without adequate cancer registries, it is difficult to estimate at what cancer stage patients from LMICs typically present. The high mortality-to-incidence ratio is likely a combination of presenting at a more advanced stage, due to lack of screening and access to health care, and lack of treatment options. Implementing RT and MDT in LMICs has many barriers; however, with technological advances, some of these may be overcome. With scarce resources available to many LMICs, it may be difficult to adequately treat patients presenting with metastatic disease. However, an approach to OMD that includes RT-based MDT would likely benefit patients in LMICs, providing a possibility of cure in a patient subset and survival improvements in others, all with a low risk of serious toxicity. Continued efforts to integrate MDT in LMICs are needed.

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SA-CME (see page 5)

Transcriptional Mechanisms of Radioresistance and Therapeutic Implications

Daniel Y. Kim, BS*; Jimmy A. Guo, BA*; Daniel Zhao, BA; Errol J. Philip, PhD; Yun R. Li, MD, PhD

Radiation therapy can be a powerful localized cancer treatment modality, but its efficacy is limited for some tumors due to the survival of resistant subclones. While numerous mechanisms impact sensitivity to radiation, here we examine the transcriptional alterations and gene expression programs that allow neoplastic cells to withstand radiation. Specifically, we review the recurring mechanisms co-opted by cancer cells in radiation resistance: upregulation of DNA repair, suppression of apoptotic programs, hypoxia, immune evasion and exhaustion, cellular plasticity, as well as aberrant intracellular signaling (**Figure 1, Table 1**). Finally, we explore the therapeutic implications of these preclinical findings.

Enhanced DNA Repair

It is well-established that a principal mechanism through which radiation therapy achieves therapeutic efficacy is the generation of DNA double-stranded breaks, leading to the activation of apoptotic and cell death programs.[1,2] As such, a common mechanism of resistance to radiation therapy is through the upregulation of pathways that enable cell survival and continued proliferation in spite of radiation-induced DNA damage, insights that have been derived from numerous in vitro and preclinical studies.[1-4] When PC-3 and LNCaP prostate cancer cell lines were irradiated, for instance, upregulation of genes associated with DNA repair, such as BRCA1, RAD51, and FANCG, was observed in the more radioresistant PC-3 cell line, while downregulation of the same genes was observed in the more radiosensitive LNCaP line.[3] As further validation, when inhibitors of the DNA repair enzyme, poly ADP-ribose polymerase inhibitors (PARP), were added to PC-3 cells followed by irradiation, viability was significantly reduced relative to cells receiving only radiation,[3] suggesting that increased DNA repair activity contributes to radioresistance in cancer cells and that blocking this capacity may improve radiosensitivity. Likewise, cancers associated with human papillomavirus (HPV) have been shown to be more radiosensitive than HPV-negative cancers. Although the precise mechanism of HPV-induced radiosensitivity is unclear, the HPV 16 E7 oncoprotein suppresses nonhomologous end-joining,[4-6] a commonly used DNA repair process. HPV-positive cancers, therefore, present a more favorable prognosis and improved clinical outcomes following radiation therapy. Interestingly, this suggests that a subset of cancer patients might naturally respond well to radiation by virtue of the origin of their oncogenic lesions.[4-6]

Similar mechanisms and observations have been broadly reported in several studies for various cancer types.[3,7,8] Transcriptome profiling of U251 MG glioma cells after gamma ray treatment, for instance, showed enrichment of 1656 genes, many of which are implicated in DNA repair and replication programs.[7] The mechanisms through which tumor cells enhance their DNA repair capacity are diverse and related to cellular plasticity, ranging from reverting to stem-like states or undergoing epithelial-mesenchymal transition

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SA-CME (see page 5)

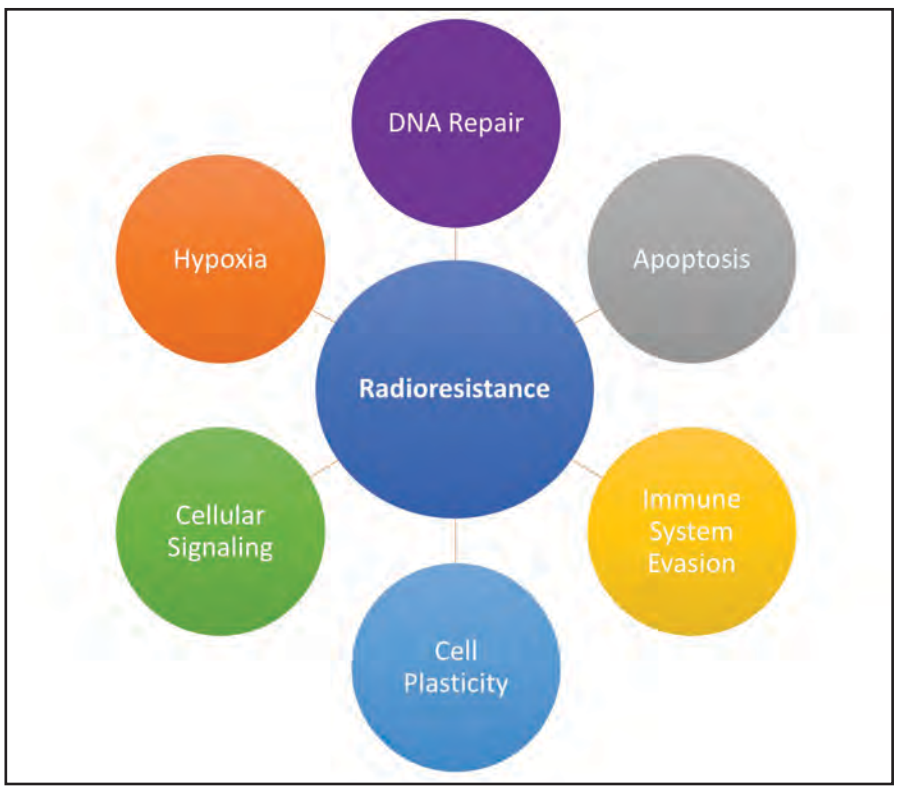

FIGURE 1. *Diagram of crucial biological processes that lead to radioresistance.*

Table 1. Mechanisms of Action that Enable Radioresistance

Biological Process	Mechanism of Action
DNA Repair	⬆ DNA repair genes
	⬆ MMR, NER, HR, NHEJ, MMEJ
Apoptosis	⬆ Anti-apoptotic genes
	⬇ Pro-apoptotic genes
Hypoxia	⬆ Hypoxia induction genes
	⬆ eg. HIF-1α
Immune System	⬆ Immune system evasion genes
	⬆ eg. TIM-3
Cell Plasticity	⬆ Epithelial-to-mesenchymal transition genes
	⬆ eg. ZEB1
Cellular Signaling	⬆ Notch signaling
	⬆ Nagnog signaling
	⬆ P13K/Akt/mTOR pathway

Key: MMR = mismatch repair, NER = nucleotide excision repair, HR = homologous recombination, NEJH = nonhomologous end joining, MMEJ = microhomology-mediated end joining

(EMT), in which a polarized epithelial cell undergoes cell state changes to assume a more mesenchymal-like phenotype. Such changes can confer greater repair efficiency,[8,9] increase the expression of noncoding RNAs,[10] and increase nucleotide deamination events.[11] Furthermore, the types of DNA lesions generated from irradiation are varied and can be repaired by a number of pathways, such as mismatch repair (MMR), nucleotide excision repair (NER), homologous recombination (HR), nonhomologous end joining (NHEJ), and microhomology-mediated end joining (MMEJ).[12] Interestingly, these routes of DNA damage protection are not mutually exclusive from subsequent themes presented in this review, indicating overlap and interplay between multiple modes of radioresistance (**Table 2**).

Clinical Implications of Enhanced DNA Repair

PARP inhibitors are small molecules that inhibit the function of poly ADP ribose polymerases, which are usually involved in DNA repair of single-strand breaks and base excision repair, thereby conferring preferential cell death to cancer cells that attempt to divide rapidly.[13] Several PARP inhibitors such as niraparib and olaparib that impair DNA repair capacity have been tested in or entered into clinical trials alongside radiation therapy treatment of brain metastases, ovarian cancer, breast cancer, rectal cancer, or glioblastoma, among others.[14,15] Preliminary studies have not shown notable or unexpected toxicity profiles, but there also has not been convincing and consistent proof of synergy between RT and PARP inhibition.[16,17] It is possible, however, that a patient subset with specific genetic alterations may exhibit enhanced sensitivity to PARP inhibition. Niraparib in a phase III trial of ovarian cancer was used after platinum-based chemotherapy and was

SA-CME (see page 5)

Table 2. Clinical Agents and Trials Targeting Mechanisms of Radioresistance

Biological Process	Mechanism of Action	Clinical Trial
DNA Repair	Decrease NHEI-based repair and DNA damage checkpoints	DNA-dependent protein kinase inhibitors with radiotherapy or immunotherapy for advanced solid tumors (NCT02516813, NCT03724890, NCT03770689)
	Inhibit mTOR signaling and DNA-dependent protein kinase	CC-115, a DNA-PK inhibitor, in combination with RT and temozolomide for glioblastoma (NCT02977780)
Apoptosis	Suppress inhibitors of apoptosis proteins (IAP)	SMAC mimetic LCL161 alone or with cyclophosphamide in patients with relapsed or refractory multiple myeloma (NCT01955434)
Hypoxia	Increase radiosensitivity using hypoxic-selective cytoxins	Tirapazamine in conjunction with chemotherapy or radiotherapy in patients with non-small cell lung cancer (NCT00033410)
Immune System	Activate immune system through CTLA-4 targeting	Ipilimumab and stereotactic body radiation therapy (SBRT) in advanced solid tumors (NCT02239900)
	Inhibit PD-1 activity	Nivolumab in patients wtih advanced or recurrent malignancies (NCT00730639)
Cell Plasticity	Inhibit STAT3 (EMT-involved transcription factor)	BBI608 in adult patients with advanced malignancies (NCT01775423, NCT02352558)
Cellular Signaling	Inhibit γ-secretase and Notch signaling pathway	R04929097 in previously treated metastatic pancreas cancer (NCT01232829) and in young patients with relapsed or refractory tumors (NCT01088763)

effective in BRCA-mutated patients, those with HR deficiencies, and even in some patients without canonical mutations.[18] The success of PARP inhibition may, therefore, be enhanced by an initial screen for hallmark DNA repair mutations that confer exceptional sensitivity, although this requires further investigation. It would be beneficial to understand which mutations augment response to combined PARP inhibition and cytotoxic agents, and how to screen for them with affordable and clinically scalable assays.

Similarly, early phase clinical trials of DNA-dependent protein kinase (DNA-PK) inhibitors (M3814) that suppress NHEJ-based repair and DNA damage checkpoints in combination with radiation therapy +/- immunotherapy are being applied to advanced solid tumors (NCT02516813, NCT03724890, NCT03770689). CC-115, another DNA-PK inhibitor that additionally inhibits mTOR signaling, is being used in combination with RT and temozolomide for glioblastoma (NCT02977780). Early reports from such trials have shown some toxicity to non-neoplastic tissues, manifesting in dysphagia, prolonged mucosal inflammation/stomatitis, and skin injury.[19-21]

Interestingly, there may be synergies of DNA repair inhibition with RT that extend beyond suppression of radioresistance. As DNA repair proteins help preserve genome stability, inhibiting repair pathways may enhance total tumor mutation burden. This may in turn increase potential neoantigens and the probability of immune recognition of the neoplastic cells.[22] Indeed, clinical trials are already combining anti-PD-L1 with DNA repair inhibitors (NCT02484404, NCT02264678, NCT02617277). **Table 2** provides an overview of clinical trials associated with use of agents interfering with DNA repair as well as other mechanisms described in this review.

Anti-apoptosis

Upregulation of genes suppressing apoptotic programs has been observed after irradiation in an in vitro setting. Interestingly, there appears to be a time dependency to the activation of these genetic programs; immediately following γ-irradiation of the U-251 MG glioma line, pro-apoptotic genes such as TP5313 and BBC3 had increased expression, likely as a natural stress response to the DNA lesions induced by the radiation. However, when cells surviving the radiation were profiled at a subsequent time point, upregulation of anti-apoptotic genes PTGS2 and NOTCH1 was observed instead, suggesting an association between apoptotic suppression and radioresistance.[23] Other studies point to similar findings, albeit different genes, such as BNIP3

SA-CME (see page 5)

and SOD2 in a U87 glioblastoma line.[24] In the same study, when RNA-seq was performed on U87 post-irradiation, p53-dependent-apoptotic genes were found to be downregulated; this was further substantiated in a separate study by downregulation of related gene TP73, which is known to be involved in induction of apoptosis in response to DNA damage.[23] The modulation of radioresistance through apoptosis management, therefore, appears to be bidirectional, as both downregulation of apoptosis and upregulation of anti-apoptosis are viable mechanisms. These principles are validated in the context of HPV-positive cancers, where greater radiosensitivity can, in part, be attributable to the ability of HPV protein E6 to upregulate genes involved in the TP53 pathway. The result is that apoptotic programs are more readily induced in the presence of irradiation.[25]

Regulation of apoptosis in response to RT also appears to be intertwined with other cellular phenotypes and programs. Specifically, miRNAs such as miR-210, which have a role in suppressing apoptosis,[26] also promote DSB repair and stabilize HIF-1-α,[27,28] a transcription factor subunit central to the hypoxia response. IL-6, a cytokine usually involved in inflammation but aberrantly overexpressed in the tumor microenvironment (TME), drives oncogenesis by triggering activation of antioxidant and prosurvival pathways.[29] Hijacking cancer stem cell states in prostate cancer also reduces apoptosis.[30] Regardless of the exact transcriptional alteration used, evading apoptosis remains a central theme in cancer cell survival after irradiation.

Clinical Implications of Anti-Apoptosis

Several small molecules have been developed to target a family of proteins called the inhibitors of apoptosis proteins (IAPs), which are involved in anti-apoptotic programs used by neoplastic cells. These efforts were, in part, spurred by the discovery of a mitochondrial protein and endogenous IAP ligand called Smac, or DIABLO, which frees up caspases to activate cell death.[31] Indeed, several Smac mimetic inhibitors are currently in clinical trials, including LCL161, birinapant, Debio 1143, and ASTX660. In general, IAP inhibitors have tolerable safety profiles up to a certain dosage, although cytokine release syndrome has been reported as a major adverse event. Overall, when these agents are used without radiation, clinical efficacy has been modest and trials have been terminated for lack of clinical benefit.[31] Debio 1143, in particular, is being investigated with cisplatin and radiation treatment in squamous cell carcinoma of the head and neck following favorable safety profiles in early phase clinical trials.[31] Inhibitors of other anti-apoptotic gene products are also being explored; gossypol (AT-101), a small molecule inhibitor of Bcl-2 and Bcl-xL, is being investigated with temozolomide with or without radiation in glioblastoma (NCT00390403). The clinical benefit of these agents alongside RT remains to be seen, however.

Hypoxia

Solid tumors are generally poorly oxygenated, and neoplastic cells have adapted ways to thrive in these hypoxic environments. In fact, prior studies have demonstrated that hypoxia is associated with poorer prognosis in many cancer types including cervical carcinoma, head and neck cancer, and some sarcomas.[32] Many studies support the association between oxygen levels and DNA damage through mechanisms such as the generation of free radicals by ionizing radiation.[33] In conditions of oxygen scarcity, the production of free radicals is reduced, contributing to radioresistance. Transcriptionally, this phenomenon may be attributed to the upregulation or increased reliance on the HIF-1 transcription factor axis, which has been shown to influence the expression levels of more than 800 downstream genes in the adaptation to hypoxic conditions.[34] In an in vitro experiment performed on HeLa cells and the cervical cancer cell line, C33A, exposure to RT upregulated the expression of HIF-1α, and sensitivity to and apoptosis following radiation was increased upon knockdown of HIF-1α.[35]

The gene modules regulated by the HIF-1 transcription factor are varied and numerous. Some of these include pathways involved in promoting tumor survival and growth, including metabolic reprogramming, escaping hypoxia through increased invasion and migratory abilities, and enabling access to oxygen through angiogenesis and neovascularization.[35-41]

Clinical Implications of Hypoxia

A long history of strategies to counter hypoxia-induced radioresistance have been explored, and include hypoxia-selective cytoxins and oxygen mimetic radiosensitizers.[42] In fact, more than 10000 patients in many clinical trials have received oxygen-related modifications for radiosensitization and, as a whole, targeting hypoxia improved RT efficacy and also led to overall survival benefits across multiple cancer types.[42] Use of hypoxia-related RT sensitizers, however, does not benefit all patients equally and may require stratification. Tirapazamine, a prominent hypoxic-selective cytotoxin, yielded mixed results in phase I trials when used with RT; some patients reported significant outcomes, while others had poor or no tumor response.[43] In addition, multiple phase III randomized trials have demonstrated efficacy and safety of sanazole (AK 2123), a nitrotriazole hypoxic cell sensitizer, in cervical and oropharyngeal cancers,[44,45] with evidence of radiosensitization and greater local tumor control.[44,45] Targeting hypoxia-related pathways to overcome radioresistance has shown clinical promise in investigative studies but its

SA-CME (see page 5)

clinical adoption remains limited[42] and could further benefit from identifying patients likely to respond (such as those with highly hypoxic tumors). Although beyond the scope of this review, several resources exist for quantifying tumor hypoxia, including oxygen electrodes and hypoxia gene signatures, and could assist these patient stratification efforts.

Immune System Evasion

In addition to causing direct cytotoxicity, RT can modulate the immune system. This includes mechanisms that improve the immunogenicity of tumor-specific antigens,[46] enabling greater T-cell infiltration in regions generally poorly penetrated by activated immune cells.[46] In addition, RT has been shown to increase tumor MHC antigen presentation and stimulate T cell secretion of interferon gamma (IFNγ), intensifying tumor-targeted T cell killing.[47] Interestingly, upregulation of PD1/PD-L1 on immune and tumor cells has also been observed following RT, suggesting that immune checkpoint blockade (ICB) may have synergy with RT.

However, these positive impacts of RT on the immune response may be countered by other negative effects. For example, immune cells exposed to radiation can undergo transcriptomic changes that result in a "cold" immunological niche, even when ICB of certain axes are used. In head and neck squamous cell carcinoma (HNSCC), combined RT and PD-1/PD-L1 inhibitors led to increased mRNA abundance of TIM-3, an orthogonal co-inhibitory cancer immune checkpoint receptor expressed on T cells.[48] Previous studies have shown that upregulation of TIM-3 is an important mediator of CD8 T cell exhaustion and dysfunction,[49] allowing tumor progression via immune system evasion. Evidence has also suggested that RT immunogenicity is at least partially dose- and fractionation-dependent. Single fractions >15 Gy in mice were less immunostimulatory than those < 15 Gy and resulted in greater proportions of regulatory T cells (Tregs). Furthermore, dividing single fractions into multiple fractions reduced tumor burden.[50]

Clinical Implications of RT and Immunotherapy

Optimizing synergy between RT and immune checkpoint blockade has the potential to yield significant clinical benefits, but to date most pilots of RT and ICB have been carried out in a small number of patients. In a phase I trial of 9 participants for advanced melanoma, a cancer type in which checkpoint blockade has been significantly explored, patients receiving both RT and ipilimumab and/or nivolumab presented stable disease or response within all irradiated metastases on first assessment.[51] These results have not been generalizable across all cancer types, however, as combination RT and pembrolizumab in a phase I trial failed to halt progression of metastatic renal cell carcinoma and resulted in a relatively low number of tumor infiltrating lymphocytes.[52] Several phase III randomized studies are ongoing, including an ipilimumab trial targeting CTLA-4 being administered with radiation (NCT02239900) in patients with any cancer type bearing metastatic or primary lesions in the liver or lungs. Promising cases have begun to emerge, including a patient with anaplastic thyroid cancer (median survival 2 months) with 5 metastatic lesions who experienced regression of all lesions following irradiation of only 1. Other trials are also underway for PD-1 inhibitors and conventional wide-field or stereotactic body radiation therapy (SBRT) for non-small cell lung cancer (NSCLC) (NCT02444741), PD-1 inhibitors plus chemoradiation for small cell lung cancer (NCT02402920), and SBRT plus immunotherapy for brain metastases.

Further investigation of optimal scheduling of RT and ICB is also warranted. A retrospective examination of studies has indicated that a wide range of schedules has been used, including regimens in which RT has come before and even 1 year after ICB. However, the results from this retrospective study have not been conclusive and may be limited by multiple confounders; as such, it remains challenging to assess optimal scheduling based on existing clinical data.[50] Hence, despite promising preclinical evidence and early phase I studies, more data on the timing of administration and dose/fractionation is needed to determine the best regimen for synergizing radiation and ICB. As more patients receive RT plus immunotherapy, it will be important to identify risk factors as well as understand and identify target mechanisms of resistance.

Cell Plasticity

EMT can manifest in greater invasiveness, migratory capacity, metastatic potential, and even resistance to chemoradiation in the case of cancer.[53,54] Indeed, neoplastic cells often undergo partial EMT and co-opt mechanisms of trans- or dedifferentiation to enable tumor progression and resistance to cytotoxic therapies.[55,56] Numerous environmental stimuli such as cytokines and hypoxic conditions can initiate EMT and, in response, intracellular signaling cascades engage crucial transcription factors (ZEB1, ZEB2, among many others) and generate significant downstream transcriptional changes.[56] In a radioresistant subpopulation of breast cancer cells, for instance, upregulation of ZEB1 was observed to promote radioresistance both in vitro and in vivo.[57] The pathways that cell plasticity-related transcription factors activate are varied and often involve other mechanisms of resistance. ZEB1 in particular has been suggested to interact with USP7, a deubiquitylase that stabilizes CHK1, a critical effector kinase in the DNA damage response (DDR) pathway.[57]

SA-CME (see page 5)

Targeted perturbations of EMT have validated the importance of this phenotype in treatment resistance and suggest potential avenues for radiosensitization as well. For example, in PCa, a prostate cancer cell line, reconstitution of miR-875-5p counteracted EMT and decreased DNA damage repair. In the same study, the authors showed that direct siRNA knockdown of EMT transcription factors led to greater cell killing by radiation.[9] A preponderance of evidence for the role of EMT in malignant cancer behavior has prompted development of strategies to inhibit this process.

Clinical Implications of Cell Plasticity

While inhibitors of EMT are not specifically thought of as radiosensitizers in a clinical context, many strategies to inhibit this process are moving into the clinic and may have complementary benefits to RT.[58] These range from interfering with upstream ligands/receptors to inhibit TME signals that induce EMT, intracellular signaling that activates EMT, the transitioned state itself, and phenotypes induced as a result of EMT.[59] These pharmacological inhibitors span a range of targets from receptors to enzymes to transporter proteins and have been or are being tested in numerous cancer types.[59] The EMT-involved transcription factor STAT3, for example, has been a target of a small molecule inhibitor (BBI608) being piloted in clinical trials;[58] a phase I study is examining dose escalation of BBI608 to patients with relapsed, refractory hematologic malignancies (NCT02352558). Another phase I/II clinical trial has been conducted to determine whether BBI608 and chemotherapy will enhance outcomes in advanced hepatocellular carcinoma (NCT02279719). Moving forward, however, if EMT inhibitors are to be explored alongside RT, investigation on a cancer type basis will likely be needed, as prior studies have shown that upregulation of EMT phenotypes postradiation is not generalizable to other types of cancer.[54]

Dysregulated Intracellular Signaling

Aberrant intracellular signaling is a hallmark of tumorigenesis, and many of these pathways have been implicated in resistance to RT. Among these are Notch, Nanog, RhoB, Wnt, and PI3K/Akt/mTOR signaling.[30,60] Notch signaling is a highly conserved pathway that transmits information through a transmembrane receptor by cleaving an intracellular domain upon binding of a ligand. Its activation has been shown to promote neoplastic self-renewal and repress differentiation and has been observed in many cancer types such as leukemia, breast cancer, and glioma.[61-65] Indeed, in vitro administration of the gamma-secretase Notch pathway inhibitor and direct knockdown of Notch1 and Notch2 to glioma stem cells sensitized them to radiation.[61] Similarly, in mouse models of NSCLC, high Notch signaling was associated with radioresistance.[66] Nanog signaling has been implicated in radioresistance through enhanced DSB repair in breast cancer, RhoB GTPase expression with radioresistance in colorectal cancer, WNT2B protein level changes with radiosensitivity of nasopharyngeal carcinoma cells,[67] and overexpression of Wnt transcription factor TCF4 with colorectal cancer radioresistance.[68] The PI3K/Akt/mTOR pathway has a prominent role role in cell growth and proliferation and its aberrant regulation is well-associated with hallmark cancer phenotypes.[30] Across various cell lines from lung and prostate cancer, upregulation of PI3K/Akt/mTOR has been associated with increased resistance to RT.[70,71] Indeed, mutations upstream of the PI3K/Akt/mTOR pathway, such as those in KRAS, have led to poor prognoses and radioresistance, as they can result in cancer stem-cell-like subpopulations with high invasiveness and tumor-initiating properties.[72] Although K-Ras has been difficult to drug, targeting its downstream signaling pathways has played and may continue to play a role in sensitizing these cancers to RT.[73]

Clinical Implications of Dysregulated Intracellular Signaling

Targeting signaling pathways and associated pathway proteins has become a viable option to increase radiosensitivity in cancer cells. With regard to Notch signaling, γ-secretase inhibitors (GSIs) that prevent generation of the oncogenic intracellular domain are undergoing clinical trials.[74] In one clinical trial, 21 patients with newly diagnosed glioblastoma or anaplastic astrocytoma received RO4929097, a γ-secretase inhibitor, in addition to temozolomide and RT.[75] Based on initial results, administration of RO4929097 to temozolomide and RT was well tolerated with evidence of target modulation,[75] as measured through neuroimaging and gene expression.

PI3K/AKT/mTOR inhibitors have shown promising preliminary activity in solid tumor in vivo models[76,77] and are being investigated clinically as well. A phase I study is currently examining buparlisib with RT and temozolomide in glioblastoma multiforme (NCT01473901), and another is exploring buparlisib with thoracic RT on advanced NSCLC.[78] Interestingly in the latter study, two-thirds of evaluable patients showed a response to therapy and reduction of tumor hypoxia, indicating that suppression of PI3K/AKT/mTOR may additionally improve radiosensitization by affecting other mechanisms of radioresistance.

Conclusion

Radioresistance is a multifactorial issue with roots in DNA repair, apoptosis, cell plasticity, hypoxia, immune system evasion, and cell signaling pathways. By better understanding the underlying transcriptional mechanisms of the aforementioned factors within

SA-CME (see page 5)

their specific cancer-type contexts, various strategies can be developed and introduced into the clinic to enhance RT efficacy. Importantly, however, examination of these various pathways reveals significant redundancy in these transcription programs. The ability of cellular plasticity to mediate radioresistance, for instance, is at least enhanced by its altered capacity for DNA repair. Therefore, identifying and inhibiting core pathways crucial to radioresistance, as opposed to those that are redundantly involved, will be necessary to maximize clinical impact and reduce the rate of relapse. As it stands, many clinical studies of radiosensitizers that target resistance pathways have demonstrated significant promise but remain in early phases and await further verdict from trial results.

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Radiation Oncologist Perceptions and Utilization of Digital Patient Assessment Platforms

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Abstract

Background: Patient engagement is increasing in the presence of digital patient assessment platforms, or physician rating websites. Despite this rapid growth, data remains insufficient regarding how these evaluations impact radiation oncologists.

Objectives: The purpose of this study was to assess radiation oncologists worldwide on their awareness and noted effects of digital patient assessment platforms.

Methods: An electronic survey was delivered to 6,199 members of the American Society of Radiation Oncology. Subjects were radiation oncologists practicing throughout the world. The survey consisted of 14 questions focused on demographics, practice details, patient volume, institutional utilization of patient reviews, and perceptions of radiation oncologists on health care reviews provided by patients.

Results: There were 447 responses from practicing radiation oncologists in total, 321 (72%) of which are in the US. Most respondents (228; 51%) either agreed or strongly agreed that patients consider online reviews when deciding which physician to visit. Of all respondents, 188 (42%) reported that their institution checks their online feedback, whereas 157 (36%) and 99 (22%) respectively reported not knowing, or to their knowledge their institution does not check their online feedback. Respondents who saw more than the average number of consults per week were significantly more likely to receive negative feedback ($P = 0.005$). Forty-five percent of respondents agreed or strongly agreed that online virtual assessment tools contribute to physician burnout. Respondents (100; 22%) who received inappropriate or misdirected feedback were significantly more likely to report that virtual reviews contribute to burnout ($P = 0.001$).

Conclusions: Radiation oncologists need to be aware that self-reported patient assessments are a data point in the quality of a physician and health care establishment. To best ensure appropriate feedback of a physician's capabilities as a doctor, leadership and employee alignment for patient experience are now more important than ever.

In modern health care, patients' engagement with health care selection and evaluation is growing. Patients' expectations are being shaped by the customized and convenient experiences they have grown accustomed to in other industries. As a result, they are demanding greater capabilities including more engaging digital experiences.[1,2] This increase in digital patient engagement is evident in the presence of digital public physician rating platforms, or physician rating websites, alongside the more conventional institutional feedback surveys and third-party survey vendors approved by the Centers for Medicare & Medicaid (CMS). Although patient experience does not always correlate with quality care, patient experience measures can address attributes of care that improve quality. Eliciting the patient's

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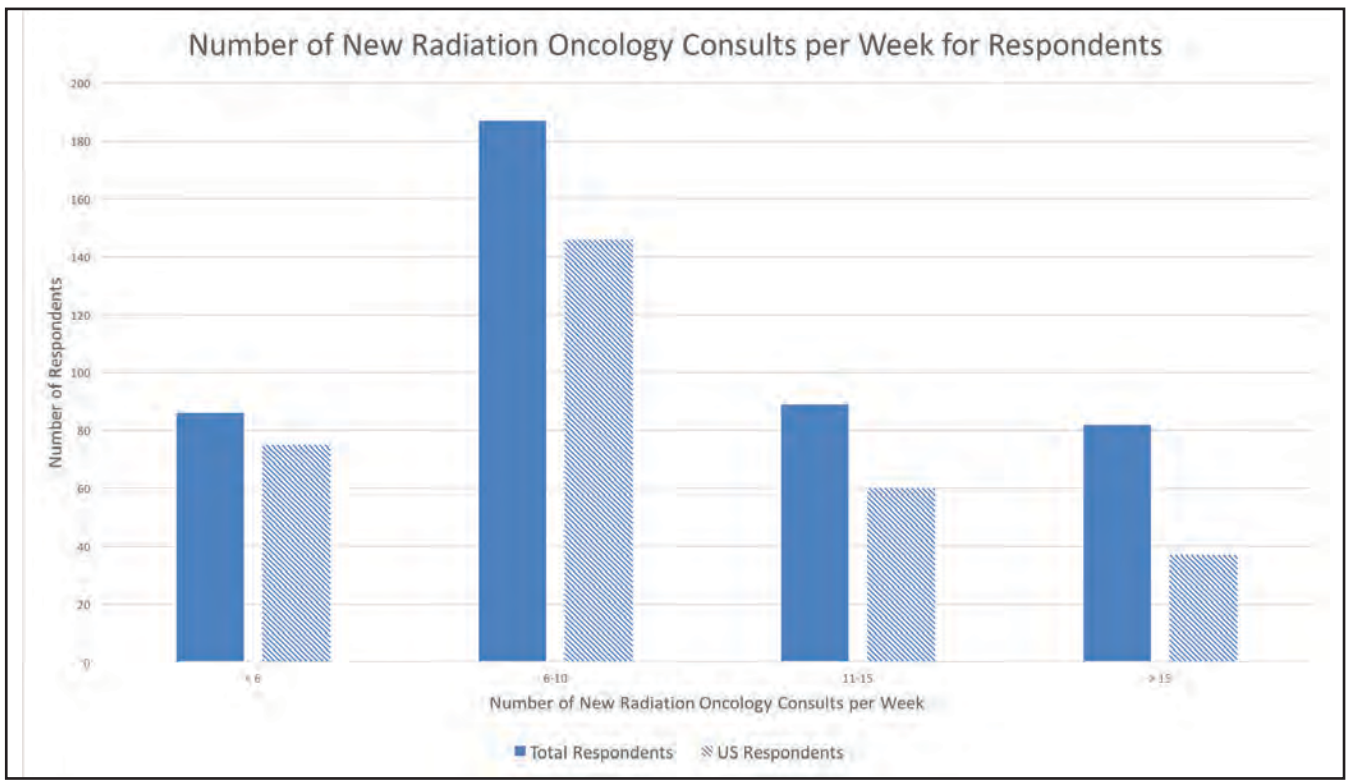

FIGURE 1. *The average number of consults per week was 9.9 ± 5.0 for all respondents, 8.9 ± 4.6 for US respondents, and 12.3 ± 5.0 for non-US respondents. The mode was 6-10 and median was 8 consults per week.*

perspective is considered essential in appropriate shared decision-making, understanding safety and confidentiality information, and understanding how care impacts a patient's life.[3]

Digital physician rating platforms in the form of various sites allow patients to evaluate their physicians in a public forum with the option for free text responses. In particular, the presence of physician rating websites has grown considerably with increasing numbers of practicing physicians in the US searchable on at least one site.[4] In a survey conducted by Deloitte, 23% of respondents in 2018 (compared to 16% to 18% in 2015) had looked up a report card for a physician in the past year, and 53% intended to in the future.[2,4] In searching for care, 20% of polled patients listed "high user reviews from other patients" as one of their most important factors.[2] In a 2015 study by Mayo Clinic, 28% of patients strongly agreed that a positive review would cause them to seek care from that physician, and 27% indicated that a negative review would cause them to avoid care from that physician.[4] This suggests that a sizeable fraction of the population places considerable weight on physician reviews.

Despite the rapid growth of digital platform services for patients to rate physicians and hospitals, insufficient data has been gathered about how these evaluations are collected, impact health care providers, and are interpreted. In some cases, negative online reviews have been associated with nonphysician variables.[5] In addition, physicians with negative online feedback compared with those without negative online feedback had similar scores on CMS-approved surveys.[5] Naturally, physicians may be concerned about their online reputation, which may be affected by nonquality metrics.[6,7]

As physicians in different specialties may serve different patient populations, it is important to stratify perception of these surveys by specialty. In fact, one study found overall patient satisfaction scores varied by specialty, with radiation oncology scoring the highest amongst medical specialties.[8] In this report, radiation oncologists in the US and abroad were surveyed about their perception of patient feedback surveys. This study aims to provide insights into how radiation oncologists use and view patient evaluations.

Methods

An electronic survey was delivered to 6,199 members of the American Society for Radiation Oncology (ASTRO) using a list compiled by ASTRO leaders. While membership includes radiation oncologists, physicists, radiation therapists, dosimetrists, and nurses, inclusion criteria for survey subjects were radiation oncologists currently practicing throughout the world. There were no exclusion criteria. The survey was developed by the authors and consisted of 14 questions focused on perceptions of radiation oncologists on patient health care

Table 1. Responses Compared Between US and Non-US Respondents

	US Respondents	Non-US Respondents	Total Respondents	*P* value
	321	126	447	
Gender				0.91
Male	226 (70%)	88 (70%)	314 (70%)	
Female	93 (29%)	38 (30%)	131 (29%)	
Non-conformal	2 (0.4%)	0 (0%)	2 (0.4%)	
Age (years)	55.4 (±10.9)	51.7 (±9.2)	54.3 (±10.6)	0.003
Number of Consults per Week	8.9 (±4.6)	12.3 (±5.0)	9.9 (±5.0)	<0.001
Practice Type				<0.001
Private	186 (58%)	50 (40%)	236 (53%)	
Academic	70 (22%)	44 (35%)	114 (26%)	
Academic Satellite	39 (12%)	9 (7%)	48 (11%)	
Government	8 (3%)	16 (13%)	24 (5%)	
Other	7 (5%)	17 (6%)	24 (5%)	
Institution Promotes CMS Survey				<0.001
Yes	208 (65%)	33 (26%)	241 (54%)	
Institution Promotes Additional Feedback				0.019
Yes	198 (62%)	75 (60%)	273 (61%)	
Institution Checks Feedback				<0.001
Yes	149 (46%)	39 (31%)	188 (42%)	
Review Own Feedback				0.011
Yes	170 (53%)	50 (40%)	220 (49%)	
Received Negative Feedback				0.83
Yes	114 (36%)	43 (34%)	157 (35%)	
Did Not Anticipate Negative Feedback				0.007
Yes	91 (28%)	24 (19%)	115 (26%)	
Challenged a Review				0.66
Yes	20 (6%)	6 (5%)	26 (6%)	
Patients Use Online Reviews				0.45
Strongly Agree	36 (11%)	10 (8%)	46 (10%)	
Agree	136 (42%)	46 (37%)	182 (41%)	
Neither Agree nor Disagree	106 (33%)	47 (37%)	153 (34%)	
Disagree	31 (10%)	17 (14%)	48 (11%)	
Strongly Disagree	10 (3%)	5 (4%)	15 (3%)	
Numerical Mean	3.5 (±0.9)	3.3 (±0.9)	3.4 (±0.9)	0.059
Reviews Contribute to Burnout				0.38
Strongly Agree	37 (12%)	9 (7%)	46 (10%)	
Agree	106 (33%)	48 (38%)	154 (35%)	
Neither Agree nor Disagree	146 (46%)	54 (43%)	200 (45%)	
Disagree	27 (8%)	12 (10%)	39 (9%)	
Strongly Disagree	3 (1%)	3 (2%)	6 (1%)	
Numerical Mean	3.5 (±0.8)	3.4 (±0.8)	3.4 (±0.8)	0.58

reviews. Demographic questions collected information on age, gender, practice location, practice type, and patient volume. Five-point Likert scales were used to assess radiation oncologists' opinions on patient utilization of online reviews when deciding which doctor to visit and contribution of virtual reviews on physician burnout. Additional questions were designed to assess institutional use of patient-filled assessments and physician opinions of reviews. All responses to the survey questions were analyzed. Descriptive statistics were used to summarize the results. Data were analyzed in R Statistics (version 3.6.1). Fisher's exact test was analyzed to compare proportions and Wilcoxon rank sum test was used for continuous values. A generalized linear model with a suitable link function was implemented when

Table 2. Potentially Inapplicable Causes of Negative Feedback Via Public Portal and Examples of Comments Provided by Respondents

Potentially inapplicable negative feedback	Examples of comments by respondents
Misdirected (eg, facilities, colleagues, parking, waiting to be seen, appointment time, etc.)	"It was upsetting that this feedback was delivered to me as though I could fix it." "Not sure if the patient who left it ever saw me."
Confounding issues (medical or social) for patient	"Yes, on one occasion, that was stimulated by an apparent psychiatric problem, and was unsubstantiated when it went to a full review. But, in the meantime it was damaging to me, potentially to my department, and was damaging to my reputation and professional success."
Nonpatient	"Mine was placed by [a] friend of a [relation] whose [family member] I supposedly treated."

multiple explanatory variables were involved. Statistical significance of alpha level was determined using a priori criteria $P < 0.05$. This study (18-8011) was approved by an institutional review board.

Results

Characteristic Data of Respondents

There were 447 respondents, 321 (72%) of whom were practicing in the US. The majority 314 (70%) identified as male, 131 (29%) identified as females and 2 (1%) identified as other gender. The mean age was 54 years, ranging from 35 to 86 years. Of all respondents, 126 (28%) were practicing outside of the US, 87 (20%) were from the Northeast, 83 (19%) were from the Midwest, 78 (17%) were from the South, and 73 (16%) were from the West. **Figure 1** shows the estimated weekly volume of radiation oncology consults dichotomized into all respondents and US respondents. **Table 1** compares demographic information of US respondents and non-US respondents.

Types of Health Care Reviews

Of all respondents, 200 (45%) reported that their institution promotes the Press Ganey vendor survey, 111 (25%) reported not knowing whether their institution promotes a CMS-approved health care survey, 94 (21%) reported that their institution does not promote a CMS-approved health care survey, and 41 (9%) reported that their institution promotes a CMS-approved health care survey other than that by Press Ganey. **Table 1** compares answers of US respondents and non-US respondents.

Regardless of CMS-approved survey usage, 342 (77%) of respondents reported that their institution encourages patient feedback. Other types of promoted patient feedback beyond the CMS-approved surveys consisted of paper forms (205; 46%), online rating or digital platform sites (98; 22%), and a supported social media page (39; 9%). The remaining respondents either reported that their institution did not solicit additional patient feedback (92; 21%) or were not aware of additional options for soliciting patient feedback (89; 20%). Those practicing in the US were significantly ($P = 0.02$) more likely to report that their institution encouraged additional patient feedback vs those practicing outside the US (**Table 1**).

Of all respondents, 188 (42%) reported that their institution checks their online feedback, 157 (36%) reported not knowing, and 99 (22%) reported that, to their knowledge, their institution did not check their online feedback. Online feedback checking by institutions in the US was more common than that by institutions outside the US (46% vs 31% respectively, $p < 0.001$). There was no significant association between institutions checking online feedback and practice type ($P = 0.07$).

Awareness of Respondents

Of all respondents, 225 (51%) reported not reviewing their online feedback, 76 (17%) reported checking monthly, 59 (13%) reported checking yearly, 50 (11%) reported checking less than once a year, 24 (5%) reported checking weekly, and 11 (3%) reported checking daily. Respondents who reported checking their feedback (220) were in the following settings: 60% at private practices 18% in academic, 12% in academic satellite, 5% in government, and 5% in other practices. For respondents who reported not checking their feedback (225), the distribution was 45.3% private, 33.3% academic, 9.3% academic satellite, 6.0% government, and 6.0% other ($P = 0.002$). Respondents who check their feedback (220) were more likely to be working at an institution that promotes a CMS-approved survey (62%) than working at institutions that do not promote (18%) or not knowing if their institutions promote (20%) CMS-approved surveys ($P = 0.02$).

Most respondents either agree (182; 41%) or strongly agree (46; 10%) that patients consider online reviews when deciding which physician to visit. The remaining neither agree nor disagree (153; 35%), disagree (48; 11%), or strongly disagree (15; 3%). When the categorical answers were replaced with a numerical scale 1 to 5 with 1 being strongly disagree and 5 being strongly agree, the mean response for those practicing at institutions that check online feedback was 3.7 ± 0.9, and the mean for those practicing at institutions that do not check online feedback was 3.2 ± 1.0 ($P < 0.001$).

Negative Feedback in Health Care Reviews

Sixty-five percent (290) of respondents did not receive negative online feedback. Of the 157 respondents who received negative feedback via public portal, 54 (34%) answered that they were concerned the feedback was confounded by the patient's other active medical or social issues, 52 (33%) anticipated the feedback, 25 (16%) believe the feedback was incorrectly directed, and 26 (17%) believe the feedback was placed by a nonpatient. See **Table 2** for additional comments.

The majority (131; 83%) of respondents who received negative feedback did not challenge an online review by a patient. The respondents who challenged an online review (26; 17%) were significantly more likely to review their own feedback ($P = 0.04$) and more likely to have received negative feedback ($P < 0.001$). A generalized linear model with a logistic link was performed and found that respondents who saw more than the average number of consults per week were significantly more likely to receive negative feedback ($P = 0.005$). Age, gender, and region of practice were not found to be significant factors.

Effect of Reviews on Respondents

Most respondents (200; 45%) answered that they neither agree nor disagree that virtual health care reviews contribute to burnout. More respondents answered that they agree (154; 35%) and strongly agree (46; 10%) vs disagree (39; 9%) or strongly disagree (6; 1%) that virtual health care reviews contribute to burnout. When the categorical answers were replaced with a 1 to 5 scale with 1 being strongly disagree and 5 strongly agree, the mean overall response was 3.5 ± 0.8. The mean response for those who did not anticipate negative feedback was 3.6 ± 0.8, and the mean response for those who anticipated negative feedback was 3.2 ± 0.9 ($P = 0.008$). Respondents (100; 22%) who received inappropriate or misdirected feedback were significantly more likely to report that virtual reviews contribute to burnout ($P = 0.001$). Reviewing one's own feedback ($P = 0.46$), frequency of reviewing one's own feedback ($P = 0.25$), and receiving negative feedback ($P = 0.25$) were not found to be significantly correlated with the belief that virtual health care reviews contribute to burnout.

Discussion

The results reported here provide insights into the types of health care reviews used in evaluating radiation oncologists as well as how physicians view these reviews. Most respondents either agreed or strongly agreed that patients consider online reviews when deciding which physician to visit. Of all respondents, more reported that their institution checks their online feedback than those who reported not knowing, or to their knowledge, their institution did not check their online feedback. US health care organizations and radiation oncologists were more likely to check patient feedback compared to non-US organizations and radiation oncologists. In general, radiation oncologists who saw more than the average number of consults per week were more likely to receive negative feedback. More radiation oncologists agreed than disagreed that virtual assessment sites contribute to physician burnout. Additionally, respondents who received inappropriate or misdirected feedback were significantly more likely to report that virtual reviews contribute to burnout.

Surprisingly, 25% of surveyed radiation oncologists were not sure whether their institution promoted a CMS-approved health survey – a finding that may be explained by physicians being unaware which surveys are mandated or simply due to physicians not being involved in reviewing patient feedback. Since 28% of respondents reported practicing outside of the US, it is reasonable that 21% of respondents reported that their institution did not promote a CMS-approved health survey. Notably, both physicians in the US and abroad received similar rates of negative feedback (36% and 34% respectively, $P = 0.83$). US health care organizations were more likely to check patient feedback compared to non-US organizations (46% vs 31% respectively, $P < 0.001$). US radiation oncologists were also more likely to review their feedback compared to their counterparts abroad (53% vs 40%, respectively, $P = 0.01$), which may be due to cultural differences. The US, for instance, may practice a form of medicine that places more value on patient feedback.[9-11]

How physicians interpret patient evaluation feedback needs to be further investigated. As demands on physicians' time continues to grow, shorter appointments and less face-to-face time with increasingly complex patients may contribute to negative patient reviews. In fact, a generalized linear model of the data in this survey suggests that radiation oncologists who saw more than the average number of consults per week were more likely to receive negative feedback ($P = 0.005$). Whether negative patient feedback contributes to physician burnout is a crucial question that needs to be answered since burnout has been associated with worse patient outcomes.[12] When queried whether negative reviews contribute to burnout, the majority of physicians in the U.S. and abroad gave neutral answers of neither agreeing nor disagreeing. However, responses trended toward negative reviews contributing to burnout with more physicians either agreeing or strongly agreeing that negative reviews contribute to burnout than those disagreeing or strongly disagreeing. Additionally, respondents who received inappropriate or misdirected feedback were significantly more likely to report that virtual reviews contribute to burnout ($P = 0.001$).

While CMS-approved surveys were constructed to limit bias and validate a true patient experience, digital patient assessment platforms are less regulated and their accessibility is greater than conventional patient assessment tools. Some physicians reported that negative reviews attributed to them were due to factors beyond their control (**Table 2**) such as patients being upset with support staff, wait times, and hospital facilities rather than the physician interaction. In fact, staff engagement, such as communication and responsiveness, appointment ease, and discharge information are strongly associated with perceived good clinical quality and drivers of patient experience.[3,13] In addition, physicians in our survey reported receiving negative feedback by relatives or acquaintances of patients who did not directly receive care from the physician. Misdirected negative reviews can hurt physician morale and hinder the quality improvement process.[14]

Improving the patient experience can likely address attributes of care that promote quality, suggesting that improvements in patient experience scores might be associated with increased clinical quality. However, misdirected or misappropriated ratings remind us that patient expectations do not always correlate with relevant clinical quality indicators.[13] Subjectivity is inherent in health care as patient-reported experience measures are inherently subjective. Factors as diverse as demographic characteristics, social status, health, and personality can influence the patient experience.[15] Although respondent randomization in CMS-approved surveys accounts for these factors, digital health care rating platforms give no indications of controls. Certain facets of care – such as a radiation oncologist's skill and judgement in setting fields on a plan, staff teamwork, and compliance to standards of care – cannot be entirely observed by patients and, thus, cannot be accurately reflected by patient experience metrics. These aspects, however, are intrinsic to good outcomes.

Conclusion

In summary, radiation oncologists need to be aware that self-reported patient assessments are a data point in quality of a physician and health care establishment. Digital rating platforms are less structured than CMS-approved surveys, but are more easily accessible and increasingly utilized. More radiation oncologists agreed than disagreed that virtual assessment sites contribute to physician burnout, and receiving inappropriate or misdirected negative reviews may contribute. Physicians who see more than the average number of consults per week may be more likely to receive negative feedback. To best ensure appropriate feedback of a physician's capabilities as a doctor, leadership and employee alignment for enhancing the patient experience are now more important than ever.

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Stereotactic Body Radiation Therapy for Oligometastatic Spine Disease

Mary Beth Massat

Oligometastatic disease (OMD) is an intermediate stage of cancer between an isolated tumor and widespread metastatic disease, where cancer cells from the primary tumor travel through the body/bloodstream to form a small number of clinically detectable metastatic lesions – typically less than 5 – elsewhere in the body. It is a disease state in which therapy may enable long-term disease management, much like with diabetes and heart disease, and unlike prior paradigms where metastatic disease was incurable, treatment may be potentially curative.[1]

From Fatal to Chronic

"Our overall goal is to make stage 4 cancer well-controlled, so it becomes more of a chronic illness than a deadly disease," says Yoshiya (Josh) Yamada, MD, co-chief of Multidisciplinary Spine Tumor Service at Memorial Sloan Kettering Cancer Center (MSKCC). "In oligometastatic disease, stage 4 is very controllable with a good prognosis for patients. Many of us in oncology are very excited to see this vision we had 5 years ago now becoming a reality."

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OMD is believed to be a precursor to more aggressive stage 4 disease, says Dr. Yamada, and stereotactic body radiation therapy (SBRT) is a cornerstone for treating oligometastatic patients. "If you believe the oligometastatic disease paradigm, then early intervention should make a difference," she says.

Kristin Janson Redmond, MD, MPH, an associate professor of Radiation Oncology and Molecular Radiation Sciences at Johns Hopkins Medicine who leads the institution's spinal radiosurgery program, frequently uses SBRT for spine oligometastases. "We hypothesize that SBRT may provide a unique opportunity for durable, long-term local control in patients with oligometastases," says Dr. Redmond. "If we truly control those few sites, we may be able to prevent other metastases from arising and, thereby, actually improve their overall survival compared to patients with widely metastatic disease where the goal of local therapy is palliation."

The perception is that if cancer spread is minimal, the patient may live longer and potentially be cured, says Mitchell C. C. Liu, MDCM, FRCPC, clinical associate professor at the University of British Columbia, Disease Site Leader of Lung Cancer, and a leader in SBRT in radiation oncology at the British Columbia Cancer, Vancouver Center. "This can be difficult for some oncologists to accept, as most of us learned in medical school that cancer is incurable once it has spread. So, oligometastatic disease is changing what we were taught."

Patient Selection

Careful patient selection and the ability to provide local control and durable pain relief for patients with spine metastases are crucial elements to optimizing treatment. For patients to benefit from SBRT for spine oligometastases, they should have presumed better survival as well as good prognostic features, specifically young age, patient fitness, slow-growing cancers, and minimal disease burden.[2]

"Specifically for spine SBRT, radioresistant pathology such as renal cell, melanoma, sarcoma and colorectal seem to benefit better with higher dose per fraction, with SBRT likely to give a more durable local control compared to conventional palliative radiotherapy," he says.

Some patients may also need surgery before SBRT for spine OMD, notes Dr. Redmond. "If a patient has a

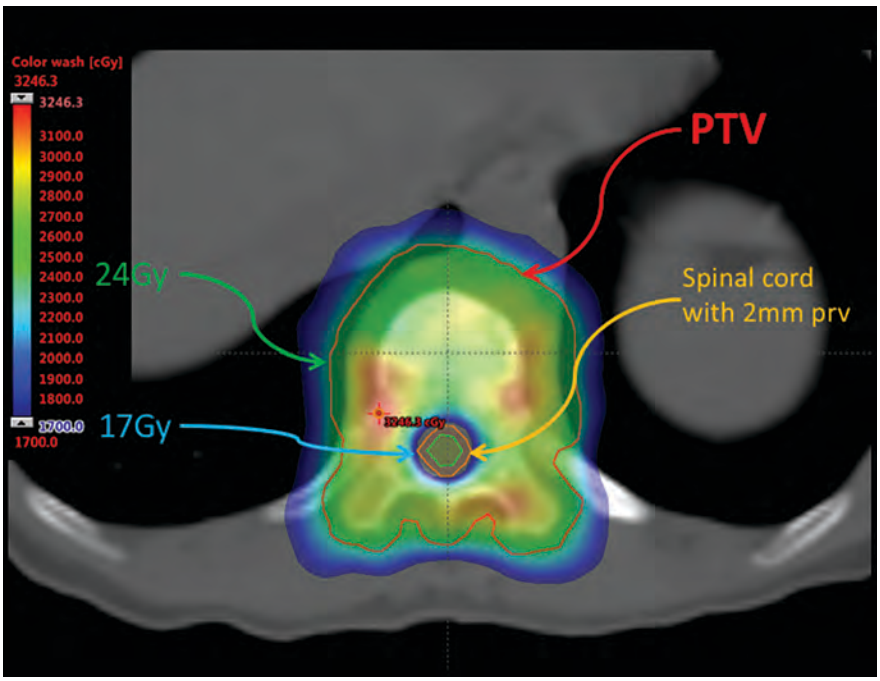

FIGURE 1. *A patient with oligometastatic lung cancer with a T11-spine lesion being treated with spine SBRT. The dose was 24 Gy/2 fractions and the dose to the spinal cord (planning organ at risk volume of 2 mm) was kept below 17 Gy/2 fractions. Image courtesy of Dr. Mitchell C. C. Liu and British Columbia Cancer, Vancouver Center.*

lot of epidural disease, we will need to underdose the gross disease adjacent to the spinal cord in order to keep the treatment plan safe. These patients may benefit from surgery (first) to downgrade their epidural disease and optimize their outcome."

Local and Systemic Treatment

The use of systemic therapy is patient- and disease-specific. One approach is to use SBRT for local control and then employ systemic therapies if the patient develops disease in other sites.

If a patient is truly oligometastatic, that individual will not likely need systemic therapy after irradiating the known disease, adds Dr. Liu. However, identifying all metastatic disease in a patient can prove challenging. "We don't have a way of knowing if [OMD is present] because our technology limits how well we can detect all the metastatic lesions or cells in a patient's body," he says. Emerging technologies may help, such as circulating tumor DNA, which is a biomarker of a biological molecule found in the bloodstream that flags disease.

Another approach is to use certain systemic agents to help improve local control of the SBRT treatment or use SBRT to improve effectiveness of systemic therapy. "SBRT may enhance immunogenicity of a tumor, making it more likely that the immune system can attack it," says Dr. Yamada.

Dose and Fractionation

There is no broad consensus on the optimal dose fractionation when using SBRT for spine oligometastases. Dr. Liu believes it will be extremely difficult to determine the ideal treatment regimen without a large phase 3 study. Consequently, each institution must prescribe the best treatment for individual patients that aligns with the institution's or oncologist's experience and comfort level.

"Ten years ago, we started with 35 Gy and 5 fractions because we were not that experienced with SBRT and we perceived that more fraction numbers appeared to be safer," Dr. Liu explains. "Now we are moving to 24 Gy/2 fractions and some of our oncologists are more comfortable with this prescription." (**Figure 1**)

Dr. Liu says in the range of 20 Gy/1 is also appropriate; however, preliminary results from RTOG 0631 showed that 16 Gy/1 did not improve pain control compared with conventional palliative radiation. Thus, a higher dose than 16 Gy is likely necessary,[3] he says. Final results on whether 16 Gy may provide better local control are eagerly awaited.

Dr. Redmond typically uses 24 Gy/2 in her practice. If she cannot meet the core constraints in 2 fractions, she uses 27 Gy/3. Control rates with SBRT for spine metastases in her practice are around 90 percent, she notes, adding that data comparing outcomes using different prescription doses is lacking, and interpreting existing data is complex. For example, a treatment plan prescribing to the 50 or 60 percent isodose line would be substantially "hotter" than the same prescription delivered to the 80 or 90 percent isodose line.

"The reason I use 2 fractions is the increasing body of literature of the risk of fracture in the spine induced by the radiation," Dr. Redmond says. "By reducing the dose per fraction, we believe we can decrease that fracture risk, although it is highly variable across practices."

That "ground truth" of whether more fractionated regimens are as effective as single-fraction treatments is unknown without a head-to-head study, she adds.

At MSKCC, Dr. Yamada uses 24 Gy/1 in his practice. "We are a little more aggressive than other centers. Our experience and data suggest that the highest dose level – 24 Gy, 1 fraction – is really an ablative dose with local failure around 2.3 percent at 4 years."

In a study by Tseng et al, the use of 24 Gy/2 resulted in a cumulative local failure rate of 17 percent.[4] Yet, higher

single doses are not for everyone, he says. A single high dose may be unsafe in patients with large tumors, where the risk of exposing the esophagus is high. If the tumor is in the spinal canal, a high dose may enter the spinal cord, leading to additional complications. Patients who were previously irradiated are also not offered 24 Gy/1 at MSKCC, although Dr. Yamada says the institution is actively recruiting patients to further study this protocol.

Patient Response

The biggest predictor of survival for patients with spine oligometastases is whether the disease is truly oligometastatic. "Overall survival is dictated by the big picture," says Dr. Redmond. "Sometimes a few months after treatment the patient will develop other sites of disease. It also depends on the systemic options that patients have and whether or not they can be salvaged if more sites of the disease arise."

More high-quality randomized trials are needed to compare different treatments, prescriptions, and techniques, she adds, to help oncologists optimize local control and minimize toxicity.

Some metastatic pathologies, such as breast, prostate and renal cancers, have been shown to have favorable outcomes when treated with SBRT,[5] Dr. Liu says. He also cites a recent study by Milano et al that reported women with breast-bone-only oligometastases treated with SBRT had an 83 percent overall survival rate at 5 years and a 75 percent survival rate at 10 years. All 12 patients with bone-only oligometastases treated had no local recurrence at 2-, 5- and 10-year follow-up, and 67 percent had no widespread metastases at 5- and 10-year follow-up.[6]

Dr. Liu hopes the results of the Canadian Cancer Trials Group SC24[7] comparing 24 Gy/2 vs palliative radiation therapy will be presented soon. He would also like to see more investigation on the use of systemic therapy, including the best time to deliver it in conjunction with spine SBRT.

"Is it better to use systemic therapies before SBRT and, if so, when is the best timing for SBRT? Is it for persistent residual disease or at the first sign of recurrence?" Dr. Liu poses. "In the setting where surgery is required, what is the role of preoperative SBRT instead of the more conventional post-op SBRT, where it can be more challenging to contour the targets and organs at risk due to artifacts. And, if pre-op SBRT is doable, what is the optimal dose and timing?"

Dr. Yamada says the safest way to re-irradiate with high doses that provide durable tumor control is with SBRT. "SBRT is a biologically different treatment," she states. "In our data, patients who received salvage SBRT after prior radiation treatment on tumors that required surgical intervention had outcomes just as good as the patients who never had radiation before SBRT. I think SBRT is really becoming a preferred treatment approach for patients who have been previously irradiated, and that is especially true for all metastatic patients."

Team Approach

A key component in treating spine metastases is multidisciplinary care, Dr. Yamada adds. A team of radiation oncologists, orthopedic surgeons, neurosurgeons, physiatrists, radiologists and interventionalists all work together at MSKCC to develop a comprehensive plan that individualizes each patient's treatment plan.

"It is absolutely a key component of our program that we are able to function in a multidisciplinary environment," she stresses. "I think without that, SBRT probably would not have flourished at our institution, and I imagine that's the same in many other centers."

Yet, SBRT may not be an option for all patients, Dr. Redmond cautions. "Ultimately, when looking at the patient's best interest, if they don't have access to high-quality SBRT, they are actually better off having conventional radiation that is done well," she says. "If you are doing a very precise therapy like SBRT incorrectly, you could miss the target or overdose the spinal cord."

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Wernicke's Encephalopathy Secondary to Severe Malnutrition After Definitive Chemoradiation for Oropharyngeal Squamous Cell Carcinoma

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CASE SUMMARY

A 59-year-old female former smoker, never-drinker, diagnosed with cT1N1 p16+ squamous cell carcinoma of the right tonsil (stage I) received definitive chemoradiation at a community cancer center. Her treatment course was complicated by dehydration, weight loss (28%), dysphagia, oral mucositis and candidiasis. The patient was not evaluated by a dietitian, and neither received nutrition supplements nor was recommended for a percutaneous endoscopic gastrostomy (PEG) tube during her treatment course. She completed a total dose of 66 Gy in 33 fractions to the right tonsil/ipsilateral involved neck utilizing an intensity-modulated radiation therapy (IMRT) step-blocking technique with concurrent platinum-based chemotherapy. Six weeks after treatment, she presented to a local emergency department with altered mental status, lethargy and failure to thrive. Due to lack of symptom improvement, she transferred her care to our institution. Physical examination was consistent with acute encephalopathy, nystagmus, diplopia, asterixis, ataxia and clonus.

IMAGE FINDINGS

Brain MRI fluid-attenuated inversion recovery (FLAIR) sequence showed hyperintensity of the hypothalamus, margins of the third ventricle, and tectal plate (**Figures 1 A-C**). Other findings included enhancement of the inferior tectal plate involving the inferior colliculus. Follow-up MRI 1 year later showed resolution of previous findings (**Figures 1 D-F**).

DIAGNOSIS

The patient presented with a painless enlarged right level II mass. Excisional biopsy of the lymph node was positive for metastatic poorly differentiated squamous cell carcinoma p16+. Right tonsil biopsy demonstrated p16+ nonkeratinizing squamous cell carcinoma. A staging pretreatment positron emission tomography/computed tomography (PET/CT) scan was obtained.

The workup to evaluate the etiology for encephalopathy included brain MRI; lumbar puncture with cell count, protein, cytology, autoimmune/paraneoplastic/encephalitis panel; GQ1b antibodies; HIV test; thiamine and B12 levels. Thiamine levels were noted to be significantly low. The rest of her workup was negative. She was started empirically on IV antibiotics and high-dose thiamine. Her neurologic symptoms started to improve the following day and the patient was diagnosed with nonalcoholic Wernicke's encephalopathy (WE). Of note, the patient did not have a known genetic or underlying predisposition to develop this condition.

DISCUSSION

The triad of altered mental status, ophthalmoplegia, and ataxia was described by Carl Wernicke in 1881, and in the 1930s thiamine (vitamin B1) deficiency in the context of alcoholism

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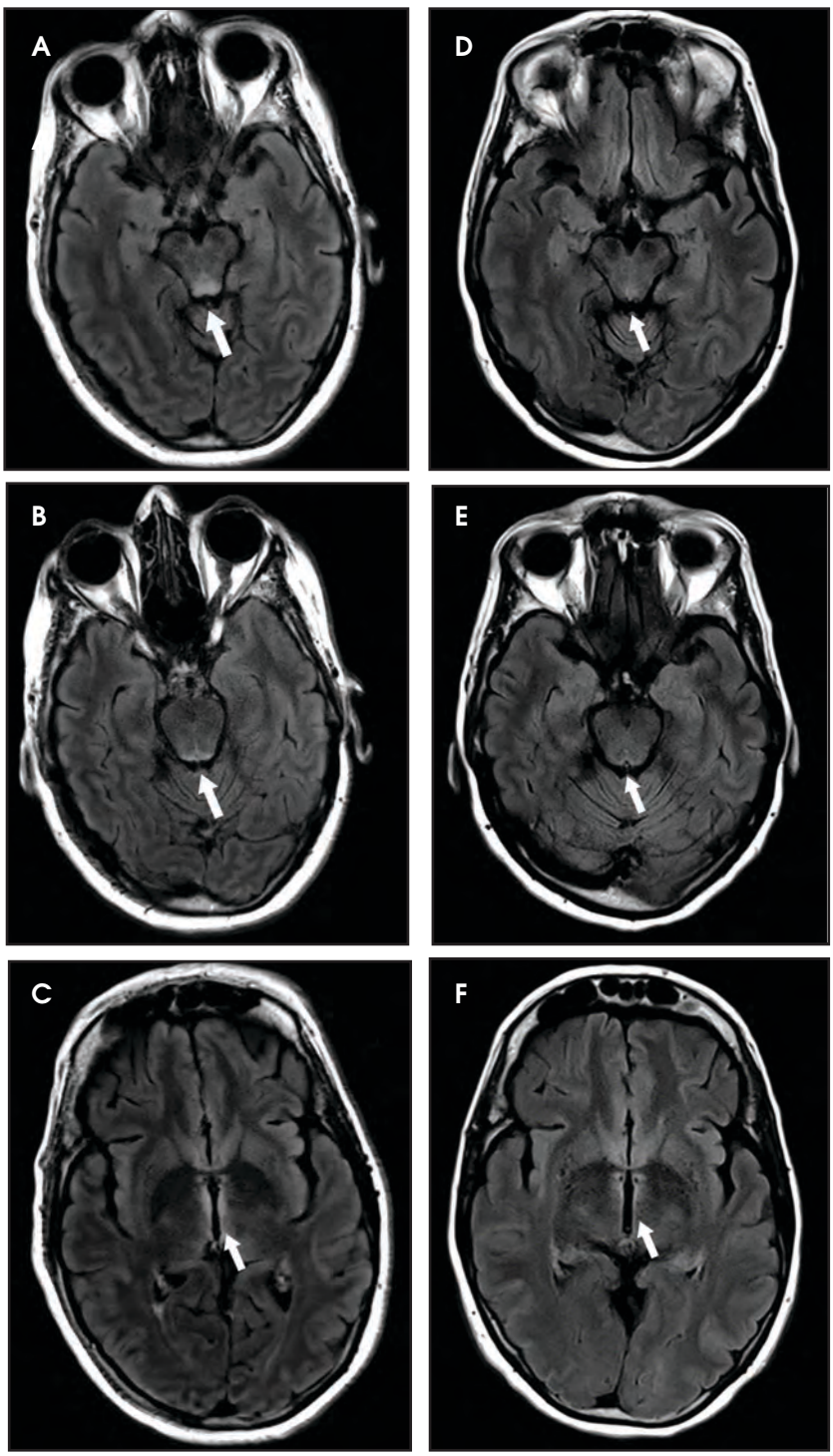

FIGURE 1. *Brain MRI FLAIR sequence at presentation and at 12-month follow-up shows a sequence done at patient presentation (**A**, **B**, **C**) and 1 year after initiating empiric thiamine therapy (**D, E, F**). Enhancement of the inferior tectal plate involving the inferior colliculus was noted at presentation **(A, B)**, but resolved in follow-up scans **(D, E)**. Hyperintensity of the hypothalamus and margins of the third ventricle was seen at presentation **(C)** and resolved in follow-up scans **(F)**. FLAIR = fluid-attenuated inversion recovery.*

was ascribed to be the culprit. Since then, we have come to learn and understand that malnourishment in the setting of alcoholism is not the only cause of WE. Any condition that leads to severe malnourishment/vitamin B1 deficiency, such as infection, chronic diseases, and cancer can cause WE. Patients with cancer of the head and neck are especially vulnerable to malnutrition due to treatment side effects, such as mucositis, dysphagia, poor oral intake, and weight loss.

Case reports of WE in nonalcoholic patients with cancer of the head and neck are rare, with only a few cases reported in the literature.[1,2] In a *Lancet* systematic review of 129 cases of cancer patients with WE, only one-third of patients presented with the classic triad of symptoms, and only 7 cases (5%) were head and neck cancers. Twenty-eight patients received radiation therapy as part of their treatment, and only 6 (21%) of the patients who developed WE in this group received head and neck radiation, with a median time of 3 weeks since their last fraction.[3] Our patient started to exhibit her first neurologic symptoms approximately 6 weeks after treatment completion.

Clinicians often have difficulties and delays in diagnosing cancer-related WE, possibly due to variability in clinical presentation, different diagnostic criteria, and lack of clinical suspicion, with up to 17% of patients diagnosed postmortem in a case series study.[3] Prompt recognition of the entity and early treatment are key, since only about a third of the patients will be able to achieve a complete full clinical recovery.[3] Therefore, empiric treatment with high doses of thiamine are recommended when clinical suspicion is high. One year after diagnosis and treatment, our patient has not fully recovered from her neurologic symptoms, with persistent ataxia and memory impairment despite having normal thiamine levels and an unremarkable brain MRI. Currently, she has no evidence of disease from her primary head and neck malignancy.

It is important to recognize that head and neck cancer treatment-related toxicities could lead to poor oral intake, dehydration, weight loss, malnutrition and a negative impact on

the outcomes and quality of life of these patients.[4] For example, different series of patients treated for locally advanced head and neck cancer have reported rates of PEG tube placement as high as 50% to 70%.[5] Therefore, preventive measurements, close monitoring and early symptom management such as the use of serial intravenous hydration, implementation of a feeding tube, and professional nutritional counseling are recommended and required during treatment.[6]

Also well known is the importance of multidisciplinary care in head and neck cancer patients.[7] Furthermore, it has been reported that these patients when treated at high-volume radiation centers (ie, those that treat the top one-third of their region's total patient volume), centers with high clinical trial accrual (≥ 42 patients per center), and by high-volume head and neck radiation oncologists will have better oncologic outcomes and lower treatment-related toxicities.[8-10]

CONCLUSIONS

Nonalcoholic WE or thiamine-related encephalopathy is an acute neurologic complication. Cancer patients, particularly those with head and neck cancers who have completed definitive chemoradiation, can be at risk due to severe malnutrition associated with acute treatment-related toxicities. It is important that oncologists are familiar with the potential causes, symptoms, diagnostic criteria and management of this serious condition. This case underscores the critical role of multidisciplinary care at a high-volume institution in managing head and neck cancer patients.

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RADIATION ONCOLOGY CASE

Radiation-induced Syringomatous Carcinoma: A Case Report

Sarah O'Neill, BSc; Sondos Zayed, MD; Belal Ahmad, MD

CASE SUMMARY

A 51-year-old patient presented to her family physician with a 14-year history of a tender, "pimple-like" lesion on her left nostril (see **Figure 1** for timeline). Biopsy of the area confirmed squamous cell carcinoma (SCC), stage 1.[1] Computed tomography (CT) of the face and neck reported a small soft-tissue mass along the left nose extending to (but not crossing) midline and no nodal involvement. Treatment involved 61 Gy in 25 daily fractions using the parallel-opposed pair (POP) technique with 4 MV. The radiation field covered the left nose with superior margin falling off the nose, onto the upper lip, and including the left nasolabial fold and septum.

Eight years later, the patient presented again with a lesion in the left nostril. Pathology and external consultation confirmed syringomatous carcinoma due to the infiltrative growth pattern of a dermal tumor. Treatment included re-excision of positive margins, partial rhinectomy, and forehead flap for nasal reconstruction. Fourteen years after the diagnosis of syringomatous carcinoma, the patient presented for surgery to improve cosmesis and relieve breathing obstruction. Biopsy of the left nose revealed recurrent syringomatous carcinoma that extended deeply up to but not invading the level of the cartilage. The patient was not considered a good candidate for further radiation therapy primarily due to previous radiation and the relatively indolent nature of her disease. A subtotal rhinectomy was therefore recommended.

DIAGNOSIS

Radiation-induced syringomatous carcinoma of the left nose. Differential diagnosis included fibroblastic/desmoplastic trichoepithelioma, basal cell carcinoma, syringoma, and syringomatous carcinoma.

DISCUSSION

Syringomatous carcinoma (SC) is a rare, slow-growing, heterogenous tumor of sweat gland origin.[2] Rarely metastatic, the most common sites include the head and neck regions, particularly the scalp.[3] Histologically, the absence of keratinizing cysts and squamous differentiation (ie, islands with parakeratotic keratinization) distinguish SC from other sclerosing adnexal tumors such as microcystic adnexal carcinoma (MAC) and squamoid eccrine ductal carcinoma (SEDC), respectively.[3] Historically, the literature did not consistently distinguish between SC and MAC. Providing an accurate estimate of incidence for SC is therefore challenging. More generally, skin adnexal carcinomas have an incidence rate of 5.1 per 1 million person-years.[4]

Due to the rare nature of SC, its pathogenesis is not yet well understood. Development of a closely related neoplasm, MAC, however, has been linked to patients who previously received radiation treatment.[5-7] Exposure to radiation, whether therapeutic or otherwise, causes changes in the DNA of normal tissues, which can lead to tumorigenesis.[8] The site of previous radiation is at highest risk of radiation-induced secondary malignancy due to the high therapeutic radiation doses administered.[9] Secondary radiation-induced malignancies can occur decades after the initial radiation treatment.[9] The documented link between previous radiation and developing MAC suggests that mutagenesis caused by radiation treatment for this patient's squamous cell carcinoma likely contributed to the development of syringomatous carcinoma.

In the reported case, the patient had no other comorbidities. Her risk factors included a 50-pack-year smoking history (she quit in 1972), and minimal alcohol consumption. Her family history was significant for a brother who died from an unknown type of cancer at the age of 65, and a sister who died from a brain tumor at the age of 42.

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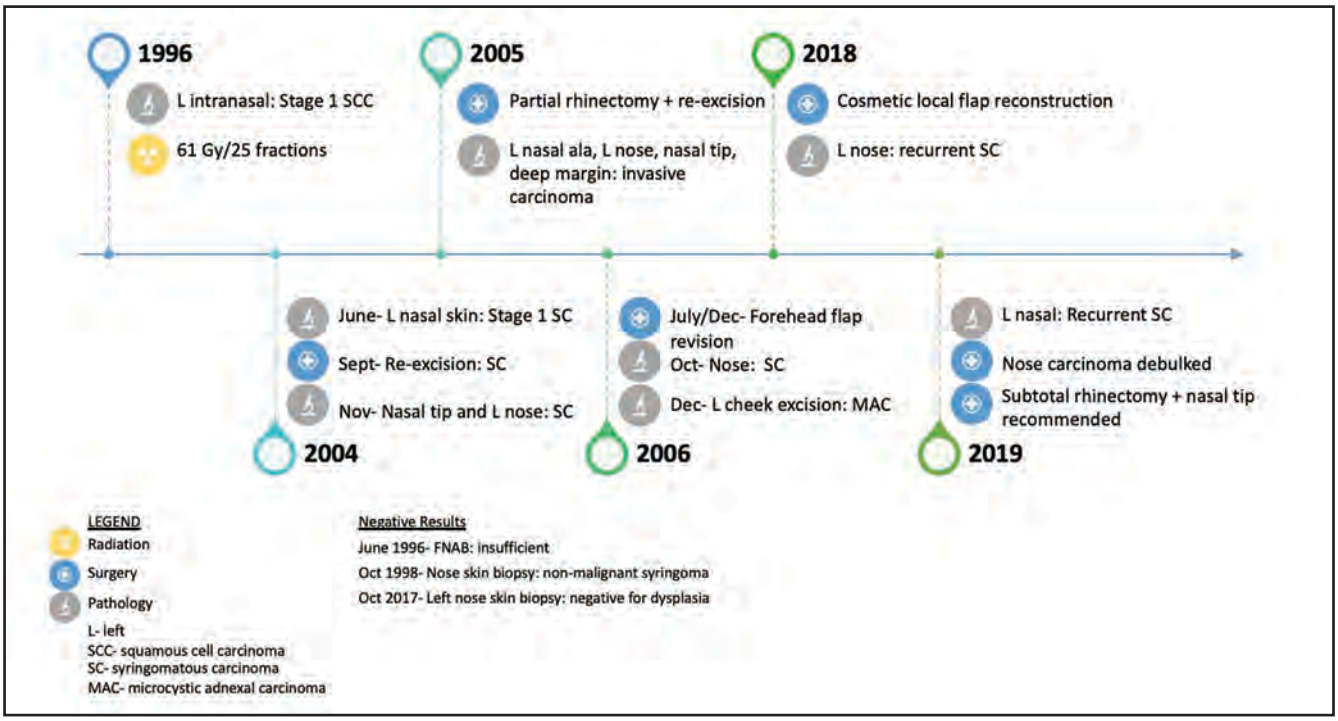

FIGURE 1. *Chronological timeline of patient case including anatomical location, pathology, and treatment modalities.*

In addition to the patient's ineligibility for further radiation, syringomatous carcinomas are thought to be resistant to radiation due to their slow-growing nature. Wide surgical excision was performed in this case, as it is the first-line treatment. It has been reported in the literature, however, that Mohs micrographic surgery allows for a lower rate of recurrence.[10] Micrographic surgery involves removing layers of tissue in stages and examining them microscopically for cancerous cells. The process is repeated until no cancerous cells remain, resulting in up to 99% cure rates for skin malignancies that have not been previously treated.[11] Mohs micrographic surgery is also considered the first-line treatment for skin malignancies previously treated with radiation, and should be considered in future cases.[11]

CONCLUSION

Although radiation-induced MAC has been reported, there are no previous reports of radiation-induced syringomatous carcinoma. This report presents a unique case of likely radiation-induced syringomatous carcinoma in a patient previously treated with radiation for a left intranasal squamous cell carcinoma. It highlights the difficult balance between radiation therapy as an effective oncologic treatment and as a risk factor for the development of secondary malignancies. It is additionally challenging to treat radiation-induced malignancies, as radiation therapy is generally no longer an effective treatment option. In delicate locations such as the head and neck, advanced surgical techniques such as Mohs micrographic surgery may be required to treat cutaneous radiation-induced malignancies.

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RADIATION ONCOLOGY CASE

External-Beam Radiation Therapy for Treatment of Sialorrhea in Amyotrophic Lateral Sclerosis: A Case Report and Review of the Literature

Timothy D. Smile, MD; Kristine Bauer-Nilsen, MD; Chirag S. Shah, MD

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease of upper and lower motor neurons resulting in weakness, debility and eventually death.[1] In progressive ALS, upper motor neuron dysfunction can lead to bulbar palsy, a syndrome characterized by dysfunction of the muscles controlling speech, mastication and swallowing.[2] Up to 80% of patients with ALS will develop bulbar palsy, which can result in malnutrition, dehydration, and aspiration.[3] Patients suffering from bulbar palsy often experience sialorrhea, or the unintentional loss of saliva from the mouth, not secondary to increased saliva production, but rather due to an inability to swallow secretions.[4] This can have a significantly negative impact on quality of life in patients whose other complications are otherwise well-managed. If conservative interventions like speech therapy, postural changes, repetitive swallowing, or biofeedback fail, medical therapy can be considered with anticholinergic medications including atropine, glycopyrrolate, amitriptyline, hycosyamine, and transdermal scopolamine.[2] For refractory symptoms, more invasive local therapies can be utilized including botulinum toxin injections,[5-7] external-beam radiation therapy (RT),[8,15] and surgery.[16-19]

CASE SUMMARY

The patient was a 55-year-old woman with history of ALS diagnosed 8 years ago with initial presenting symptoms of dyspnea and sleep apnea. She developed respiratory failure requiring placement of a diaphragmatic pacemaker system shortly after diagnosis. She subsequently developed bulbar palsy symptoms 3 years ago requiring PEG-tube placement, and progressive respiratory failure requiring tracheostomy with ventilator use. Around this time, she also developed sialorrhea from copious secretions that resulted in 2 episodes of aspiration pneumonia requiring hospital admission and antibiotics. After sialorrhea symptoms were refractory to medical therapy with amitriptyline, she underwent Botox injection of the bilateral parotid and submandibular glands with relief of symptoms for 10 months. When symptoms recurred, she underwent a second Botox injection, which was effective for roughly 6 months before symptoms recurred. In the interim, her ALS progressed to the point of locked-in-syndrome with quadriplegia and loss of motor function to the lower half of her face.

With sialorrhea symptoms continuing to be bothersome and requiring frequent suctioning, the patient was referred to radiation oncology for consideration of palliative RT. After a discussion of the literature surrounding RT for ALS-related sialorrhea, the recommendation was for RT to the bilateral parotid and submandibular glands with 20 Gy in 4 fractions of 5 Gy per fraction delivered twice weekly. After considering treatment for several months with persistent sialorrhea, she returned to clinic and was consented for planning and treatment.

Computed tomography (CT) simulation was performed in the supine position with arms at sides (**Figure 1A, B**). A 3-point Aquaplast mask was utilized

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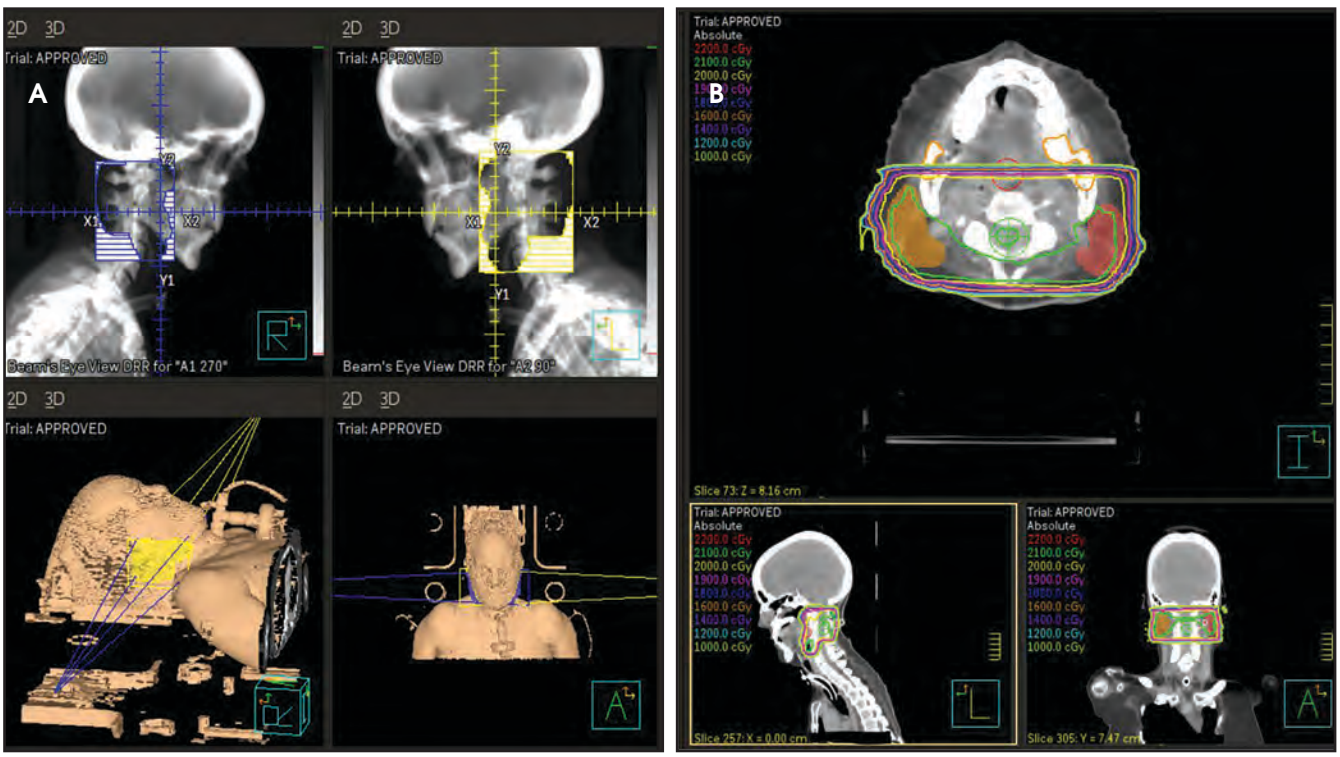

FIGURE 1. *Photon-beam radiation to the salivary glands. A). Digitally reconstructed radiographs and 3-dimensional (3D) reconstructed images depicting opposed lateral fields. B). Axial, sagittal and coronal computed tomography (CT) images showing dosimetry and treatment fields.*

for motion management that would also accommodate her tracheostomy ventilator adapter. The parotid and submandibular glands were contoured bilaterally, and treatment was planned using opposed lateral technique with 6 MV photon beams prescribed to a calculation point at the 96.5% isodose line. The 4 fractions were delivered on Monday and Wednesday over 2 consecutive weeks. She tolerated treatment well, with a subjective decrease in the amount of secretions and increased thickness of saliva by the final fraction requiring less suctioning per her caregivers. The only acute adverse effects noted were mild jaw and chin discomfort after the first fraction related to the mask and trace erythema of the bilateral neck after the final fraction.

DISCUSSION

Sialorrhea due to progressive ALS is associated with decreased quality of life and increased risk of developing life-threatening aspiration pneumonia; it can also require significant intervention from caregivers with frequent suctioning.[20]

Radiation Therapy Outcomes

Table 1 presents a summary of studies evaluating the use of RT for sialorrhea associated with ALS. While prospective data for RT is limited for this population, Assouline et al published the largest prospective series for evaluating 50 patients with ALS-related sialorrhea treated with either 10 Gy in 2 fractions delivered on days 1 and 3, or with 20 Gy in 4 fractions delivered on days 1, 3, 8, and 10.[12] Efficacy outcomes were measured using the prospectively validated 9-point Sialorrhea Scoring Scale.[21] The authors report favorable results at the end of RT including improvement in all patients treated, of whom 92% experienced complete response (CR) and 8% had partial response (PR). Durable response was also seen with 71% CR and 26% PR at 6 months after RT. Both dose and fractionation schemes produced excellent responses, but the 20 Gy group had more CR and PR than the 10 Gy cohort ($P = 0.02$), and 8 of the 9 patients who underwent repeat RT for recurrent symptoms came from the 10 Gy arm. The dose and fractionation schedule used on the case report patient above was chosen using this study because of the prospective design and favorable outcomes. A retrospective case series examining photon RT with 15 Gy delivered in 3 fractions to unilateral parotid gland showed subjective improvement in symptoms for all 10 ALS patients included.[15] The authors report 5 of the 10 patients were able to discontinue their anticholinergic medications, and 2 others were able to decrease their doses. This study suggests photon RT with 20 Gy in 4 fractions twice weekly is an effective and safe treatment for palliating ALS-related sialorrhea.

Table 1. Radiation Therapy for ALS-related Sialorrhea

Study	Patients, No.	Dose, Gy	Dose per Fraction, Gy	Target Volume	Follow-up Time	Response Rate	Toxicity
Borg et al *(Int J Radiat Oncol Biol Phys.* 1998)[22]	19 15	6-20 24-44	0.83-6 2-4	NR	Median 12 months (range 6-324)	82%	grade 1 dermatitis (24%) grade 1 mucositis (3%)
Andersen et al (*J Neurol Sci.* 2001)[8]	13 5	7 7.5	7 7.5	Bilateral parotids, posterior submandibulars	24 hours and 4 months	89% at both timepoints	grade 2 xerostomia (6%) grade 1 jaw pain (NR%)
Harriman et al (*J Otolaryngol.* 2001)[14]	9	8 12.5	8 6.25	Bilateral SMG and SLG, tail of PG	2 months	67% and 100%	NR
Stalpers et al (*Neurology* 2002)[23]	19	12	6	Bilateral PG	2 to 3 weeks	74%	grade 1 xerostomia (24%) grade 1 jaw pain (35%)
Neppelberg et al (*Eu J Neurol.* 2007)[9]	14	7.5	7.5	Bilateral SMG, majority of bilateral PG	3 months	21% reduction	None
Postma et al (*Mov Dis.* 2007)[24]	28	12	6	Bilateral PG, part of bilateral SMG	1 and 6 months	80%	grade 1 taste loss (42%) grade 1 xerostomia (39%) grade 1 mucosal irritation (18%)
Guy et al (*J Pall Med.* 2011)[10]	16	20-48 4-16	4-4.36 4-7	Bilateral SMG, 2/3 of bilateral PG	1 and 6 months	100% and 67%, respectively 67% and 44% respectively	grade 1 xerostomia (25%)
Kasarskis et al (*J Neurol Sci.* 2011)[15]	10	15	5	Single PG	6-8 weeks	78%	None
Bourry et al (*Cancer/ Radiotherapie* 2013)[11]	13 8	3-48 (photons) 20 (electrons)	3-8 4	Bilateral PG & SMG (n = 18) Bilateral SMG & unilateral PG (n = 1) Bilateral PG (n = 2)	Median 10.4 months	50% (photons) 87.5% (electrons)	grade 1 oral pain (10%) grade 1 xerostomia (5%) grade 1 edema (5%)
Assouline et al (*Int J Radiat Oncol Biol. Phys* 2014)[12]	30 20	10 20	5 5	Bilateral SMG, 2/3 of bilateral PG	6 months	96%	acute grade 1-2 taste loss, xerostomia, thick saliva, or dysphagia (34%)

Key: PG = parotid gland, SMG = submandibular gland, SLG = sublingual gland, NR: not reported

RT can be delivered with either photon or electron beams with some evidence that the treatment modality may impact efficacy. In a retrospective series by Borg et al, 82% of patients experienced satisfactory improvement in their symptoms.[22] The authors reported improved response rates associated with utilization of electron-beam energy > 7 MeV when compared with orthovoltage photon beams (76% vs. 38% maintained response, $P < 0.05$), and with radiation fields encompassing both parotid and submandibular glands (74% vs. 33% maintained response, $P < 0.01$). Another study from the Netherlands by Stalpers et al delivered 12 Gy in 2 fractions to the bilateral parotid glands in 19 patients with sialorrhea, of whom 14 were treated with 250 kV photons and 5 were treated with 8 to 14 MeV electrons.[23] The authors report satisfactory response to RT in 14 patients (74%) including complete response in 11 and partial response in 3 patients. However, the authors did not report a significant difference between treatment modalities. Both these studies used subjective relief of excessive salivation as the primary outcome. Two retrospective series from France compared photons to electrons for treatment of ALS-related sialorrhea.[10,11] Guy et al compared efficacy and safety outcomes for photon and electron RT protocols for ALS-related sialorrhea treatment using 4-point Likert symptom improvement scores.[10] Of all patients, 80% experienced improvement in symptoms at 1 month after RT, and 43% at 6 months. While both treatment modalities were equally efficacious 1 month after treatment, the authors report significantly more durable control of symptoms at 6 months in the group receiving electron RT compared to photons ($P = 0.02$). Bourry et al reviewed outcomes for ALS-related sialorrhea RT with 5.5-6 MV photons or 6-15 MeV electrons in 13 and 8 patients, respectively.[11] The authors evaluated symptom improvement outcomes using the ALS Functional Rating Scale, reporting an overall response rate of 65% at a mean follow-up time of 7 months. The authors observed improved outcomes with electrons over photons (87.5% vs 50%, $P = 0.09$) and with total dose ≥ 16 Gy compared to < 16 Gy (78.6% vs 33%, $P = 0.07$), although neither finding was statistically significant given the small number of patients. Together, these retrospective data suggest electron therapy is associated with improved outcomes, but that clinicians are afforded discretion regarding treatment modality chosen for RT.

Dose, Fractionation, and Target Volumes

With regard to dose and fractionation, Harriman et al examined efficacy of single-fraction vs multifraction RT for the treatment of ALS-related sialorrhea in 9 patients using a subjective questionnaire about salivary flow.[14] The authors report 8 Gy in a single fraction was similarly efficacious compared with 12.5 Gy in 2 fractions, although they report long-term follow-up was limited by the shortened life expectancy in advanced ALS patients. Single-fraction RT with 12 Gy to the bilateral parotid glands was also delivered to 28 patients with sialorrhea related to Parkinsonism in a retrospective study by Postma et al.[24] The authors reported efficacy in 80% of patients at 1-year follow-up when measured using the Unified Parkinson's Disease Rating Scale questionnaire. The data, along with that by Assouline et al, suggest that longer courses can be considered for those patients with longer life-expectance; for patients with shorter life expectancy, single- or 2-fraction regimens should be considered.

While there is limited comparative data on RT for ALS-related sialorrhea, RT with 7.5 Gy in a single fraction was compared to botulinum toxin injection for ALS-related sialorrhea in a study from Norway by Neppelberg et al.[9] The primary outcome was quantitative salivary flow measurement in mL/minute. While numbers were small in this trial, RT was significantly associated with improvement in salivary flow while botulinum toxin injection was not.

Target volumes generally include bilateral parotid and submandibular glands, either completely or partially covered by prescription isodose lines. The prospective trial by Assouline et al included bilateral submandibular glands and two-thirds of the bilateral parotid glands. All other retrospective series included bilateral parotid and/or submandibular glands except for one series in which authors report treatment was limited to a single parotid gland.[15]

Toxicity

Palliative RT for sialorrhea in ALS patients is associated with mild acute toxicity that usually is self-limited. The studies included in this review did not report any grade 3 or higher acute or late toxicities. While late toxicities were uncommon among patients treated with RT to the salivary glands, several studies reported persistent xerostomia. Borg et al reported a 13% rate of mild late toxicity, most of which was xerostomia with one case of temporomandibular joint fibrosis.[22] The authors suggest late xerostomia may be ameliorated by sparing a small volume of the superior parotid gland in the treatment volume when planning RT. Andersen et al reported one case of persistent xerostomia with no other late toxicities, and several cases of acute post-RT discomfort that were relieved by administration of a lemon slice on the tongue and gentle parotid gland massage.[8] Radiation doses of 8, 12.5 and 15 Gy delivered in 1, 2 and 3 fractions, respectively, were reported to have no acute or late toxicities in multiple series.[14,15] In the largest series that examined 20 Gy delivered in 4 fractions, the authors report no grade 3 or 4 toxicities, and no

treatment-related deaths. The rate of grade 1-2 acute toxicity was 34% and was limited to transitory taste modification, mild pain, xerostomia, salivary thickening, and swallowing difficulty. While some patients were lost to follow-up, the rates of toxicity at 1, 3 and 6 months were 8%, 15% and 5%, respectively.

CONCLUSION

RT is an effective and well-tolerated treatment option for ALS patients with bulbar palsy symptoms resulting in sialorrhea. The treatment can be delivered without significant complexity in patients with significant debility related to progressive disease, and has been shown to have low rates of significant toxicity. RT can also be considered for sialorrhea associated with other conditions, particularly Parkinson's disease.[25]

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Brachytherapy for Resistant Disseminated Superficial Actinic Porokeratosis

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CASE SUMMARY

A 61-year-old Caucasian woman with a past medical history of hidradenitis suppurativa and Hashimoto's thyroiditis presented with a 15-year history of disseminated superficial actinic porokeratosis (DSAP) on her bilateral legs and forearms. Previous treatments for her DSAP have included photodynamic therapy (PDT), cryotherapy, and imiquimod with no improvement. Physical examination revealed diffuse subcentimeter to centimeter papules on her bilateral legs and forearms **(Figure 1A).** Because of failure with previous treatments, high-dose-rate iridium-192 brachytherapy (HDR-BT) was delivered to a small lesion on the left leg with plans to perform wider spread treatment if this course was successful. This lesion was chosen due to its small size, accessibility to the applicator, and because any changes in the lesion could be readily observed and verified. In addition, this DSAP lesion was adjacent to a lentigo, which would allow for quick identification at subsequent treatment sessions and follow-ups. A total of 20 Gy in 4 fractions of 5 Gy each was delivered (1 fraction per week) using a 3.0 cm Leipzig applicator with a Varisource Afterloader (Varian). The dose was prescribed at surface (0 mm depth). No side effects were noted other than mild hyperpigmentation, which arose in the treated area 1 to 2 weeks after the start of treatment **(Figure 1B).** At 4 months post-treatment, there was resolution of the DSAP papule (**Figure 1B**). At 10 months post-treatment, there was persistent faint hyperpigmentation in the treated area with no clinical reoccurrence of the DSAP lesion.

IMAGING FINDINGS

An untreated area on the same leg revealed atrophic papules with a circumferential hyperkeratotic rim under dermoscopy **(Figure 2A)**, while dermoscopy of the treated area showed no remaining hyperkeratosis **(Figure 2B).** Reflectance confocal microscopy (RCM) of the untreated site revealed mild inflammation, well-defined focal parakeratosis in the epidermis (cornoid lamellation), focal atypia of keratinocytes, and several dilated blood vessels in the dermis (**Figure 2C**), while the treated site had absent cornoid lamellation, with only dendritic cells at the

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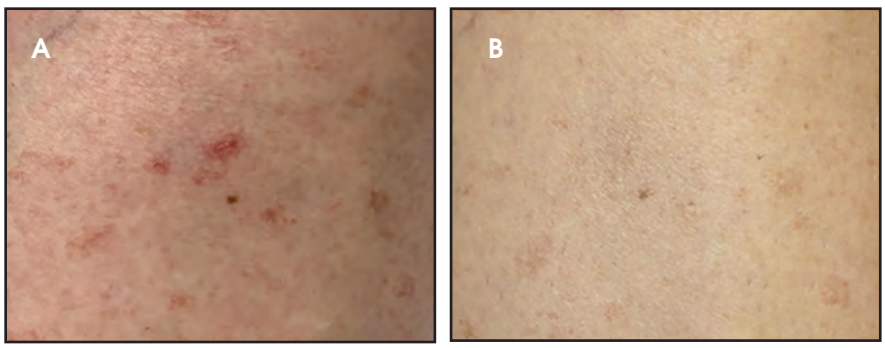

FIGURE 1. *Clinical examination of disseminated superficial actinic porokeratosis (DSAP). DSAP on the left leg before 4 weeks of brachytherapy treatment (A) and 4 months post-treatment (B).*

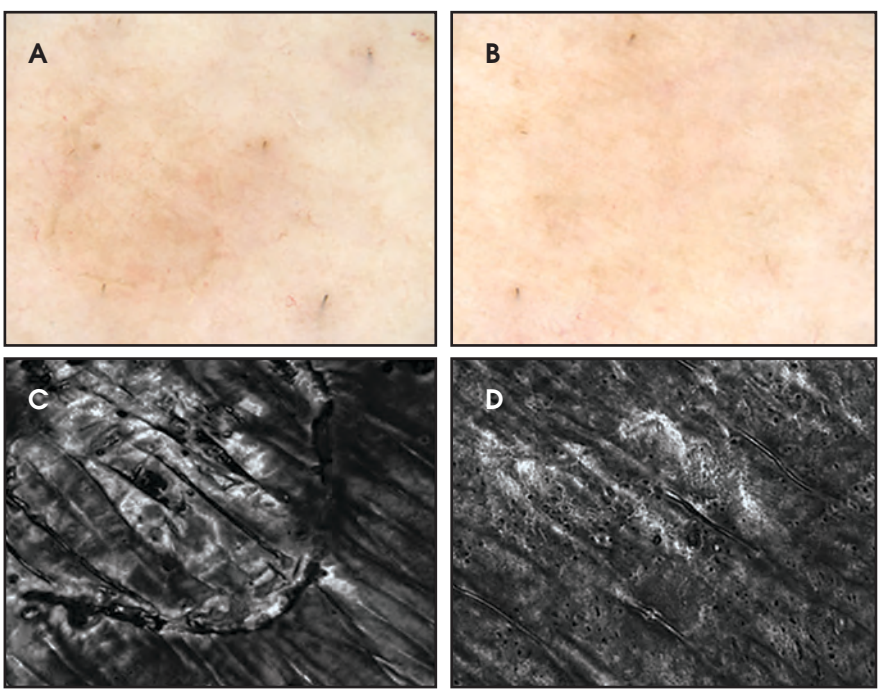

FIGURE 2. *Dermoscopic and reflectance confocal microscopy (RCM) imaging of DSAP. DSAP of the left leg showing a dermoscopic view of a well-defined atrophic lesion with surrounding hyperkeratosis in an untreated area (A), and a dermoscopic view with no remaining hyperkeratosis after 4 weeks of brachytherapy (B), RCM of focal atypia of keratinocytes surrounded by cornoid lamellation on an untreated area (C), and RCM showing resolution of cornoid lamellation and mild spongiosis in the treated area (D).*

dermal-epidermal junction, and mild spongiosis present **(Figure 2D).**

DIAGNOSIS

Physical examination as well as dermoscopic and RCM findings were consistent with a diagnosis of DSAP.

DISCUSSION

Porokeratosis describes six chronic progressive conditions of disordered keratinization that lead to pruritus, cosmetic distress and, occasionally, malignant transformation.[1] Porokeratotic lesions begin as red to brown papules with raised borders that may coalesce to form plaques. DSAP is one of the six variants of porokeratosis, including linear porokeratosis, porokeratosis of Mibelli, punctate porokeratosis, porokeratosis palmaris et plantaris disseminata, and nonactinic disseminated superficial porokeratosis.[2] DSAP lesions are distinguished by their late onset and prevalence in sun-exposed areas while sparing the palms and soles.[1] Most commonly, DSAP occurs in fair-skinned women between 30 and 50 years old, and risk factors include genetics, immunosuppression, and sun exposure.[1] The incidence and prevalence of DSAP is unknown; however, in the US, it is classified as an orphan disease.[3] There is a 7.5% to 10% risk of malignant transformation to squamous cell carcinoma (SCC) or basal cell carcinoma (BCC).[2]

The histology of DSAP is characterized by parakeratotic cells arranged around a circumferential ridge called a cornoid lamella.[1] The cornoid lamella distinguishes DSAP from other cutaneous lesions found on sun-exposed sites such as actinic keratosis (AK) and SCC.[1] Conventional histology requires biopsy of the lateral border of a DSAP papule, while RCM provides a precise and noninvasive view of different skin layers in vivo. Under RCM, DSAP papules have demarcated hyper-refractile borders in the corneal layer, cellular and nuclear atypia at the spinous and granulosa layers, and dilated blood vessels and lymphatic infiltrates at the upper dermis.[4]

While the aesthetic appearance and therapeutic resistance of this condition has a significant psychosocial and economic burden, there remains no standard or effective treatments for DSAP. Only variable improvement has been shown with imiquimod, 5-fluorouracil PDT, vitamin D, retinoids, and lasers.[1] Due to recent advancements in safety, superficial radiation therapy (RT) is gaining popularity for the treatment of unresectable skin tumors and benign dermatoses.[5] While earlier reports document the development of porokeratosis in cancer patients treated with RT, it remains unclear whether the development resulted from impaired immunity or DNA-damaging cotreatments.[6] Grenz rays (GR), a low-energy form

of x-ray therapy, has been used to successfully treat DSAP, but the use of GR remains controversial due to a 1989 study warning of the risk of secondary skin cancer development following this treatment.[7] However, this report has been disputed as an overestimate of this risk due to conflations of GR with other forms of superficial radiation and superficial x-ray therapy.[8,9] Long-term follow-up (15 years) of 14,140 patients who received GR therapy for benign conditions reported only 58 cases of malignant skin tumors, each diagnosed more than 5 years after GR therapy had first been administrated. Of that group, 19 patients had malignant melanomas and 39 patients had other malignant skin tumors.[10] Only 8 of those with malignant tumors had received GR at the site of their secondary malignancy and 6 of those 8 had exposures to other known carcinogens.[10]

HDR-BT is another form of superficial radiation therapy that involves the application of radionuclides in or near a tumor. Treatment diameter reduction and added shielding to HDR-BT have allowed for the safer delivery of superficial radiation to the skin especially in benign conditions such as keloids.[11] Previous studies have examined safety outcomes 10 years after HDR-BT treatment in 520 patients treated SCC, BCC, melanoma, paraneoplastic skin manifestations, and keloids.[12] Of these patients, 91% obtained complete remission with no severe late reactions.[12] A similar study of 200 patients who received HDR-BT for SCC and BCC concluded that HDR-BT provided good to excellent cosmesis (88%), low recurrence (2%), and no significant acute or long-term skin toxicities after 25 to 121 months.[5] Thus, similar to GR, HDR-BT offers limited penetration and does not carry a significant risk for secondary skin malignancies. However, HDR-BT may cause long-term side effects such as mild hypo- or hyperpigmentation, hair loss, fibrosis and telangiectasias in the treated area. Other limitations of the use of HDR-BT for the treatment of DSAP may include cost, amount of body surface area involved, age, a patients' other medical history, and risk of secondary malignancy.[13]

CONCLUSION

This case demonstrates that HDR-BT can be an effective treatment for resistant DSAP to a selective area. Dermoscopy of the treated area showed no remaining hyperkeratosis, and RCM demonstrated absence of the cornoid lamellation, characteristic of DSAP. Due to the significant cosmetic distress and lower malignant transformation of this condition, HDR-BT may be a reasonable therapy in patients who have failed conservative treatments. However, further large-scale studies are needed to determine the long-term safety, efficacy, and practicality of HDR-BT use in DSAP.

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RADIATION ONCOLOGY CASE

Radiation Recall Dermatitis with Docetaxel and Cyclophosphamide in a Case of Early Stage Breast Cancer Considered High Risk by Molecular Profiling

John Paul F. Abrina, MD; Kathleen H. Baldivia, MD

CASE SUMMARY

The patient was a 55-year-old woman with an unremarkable history, presenting with a screen-detected mass on the left breast. Biopsy revealed grade II invasive ductal carcinoma, ER/PR-positive, HER2/neu-negative, and a Ki-67 of 5%.

Lumpectomy and sentinel lymph node biopsy yielded a 0.5 cm tumor and 2 uninvolved lymph nodes. Chemotherapy was not considered outright due to perceived low-risk clinical features; specimens were instead sent out for gene profiling to guide systemic therapy. Whole-breast radiation therapy to 42.6 Gy (16 fractions) was initiated 4 weeks after surgery (**Figure 1**). Only grade 1 radiation dermatitis (NCI-CTCAE v. 4.03)[1] was observed.

Results from gene profiling (MammaPrint, Agendia, Inc.) arrived later, revealing high-risk luminal B disease, indicating a benefit from chemotherapy. Docetaxel (75 mg/m^2) and cyclophosphamide (600 mg/m^2) were given 4 weeks after completing radiation therapy. On the second day of chemotherapy, the patient developed linear, erythematous, pruritic, nonpainful plaques on the left breast, corresponding to the previously irradiated area (**Figure 2**).

DIAGNOSIS AND TREATMENT

The reaction, atypical of a chemotherapeutic side effect, was ascribed to radiation recall dermatitis. The symptoms were managed with oral cetirizine and betamethasone cream and it subsided to dry desquamation within 2 weeks (**Figure 3**).

Pulsed steroids were given with subsequent cycles of chemotherapy using the same agents and no recurrences of the reaction were observed. The patient completed 4 cycles of treatment.

DISCUSSION

Radiation recall dermatitis (RRD) is an acute inflammatory reaction occurring in previously irradiated sites, triggered by a variety of chemotherapeutic agents, including conventional medications such as anthrayclines, taxanes, and antimetabolites.[2-4] More contemporary agents[5] have also elicited this reaction.

A review by Burris and Hurtig documented RRD involving other drug classes.[2] Notably, several of the implicated agents are drugs commonly used in the treatment of breast cancer.[1,5]

Data regarding the frequency of this phenomenon has been limited and most information has been documented through case reports. Rates from 1.8% to 15.1% have been reported.[2] In an observational study by Kodym et al, 8.8% of 91 patients who received sequential palliative radiation therapy and chemotherapy developed a reaction.[6]

D'Angio first described RRD with actinomycin in 1959[7] but the heterogeneity of the cases reported has precluded a definitive characterization of the reaction and it remains a poorly understood

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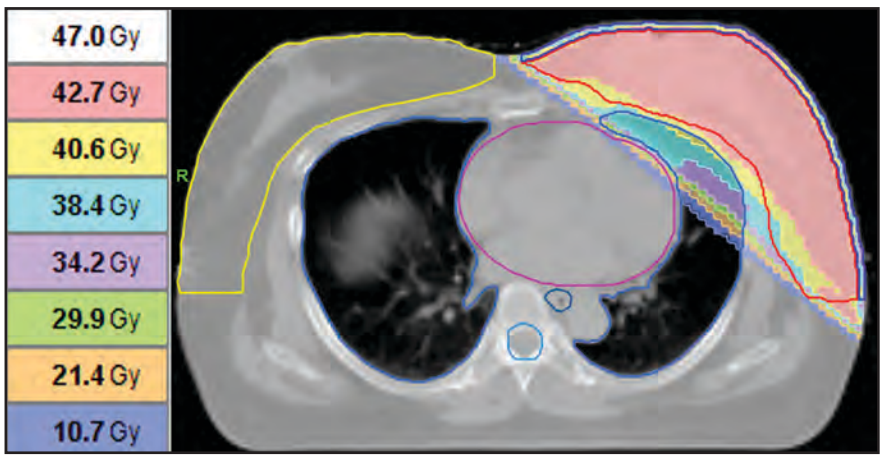

FIGURE 1. *A representative image from the patient's treatment plan showing an average dose of 41.05 Gy received by the skin within the planning target volume (PTV).*

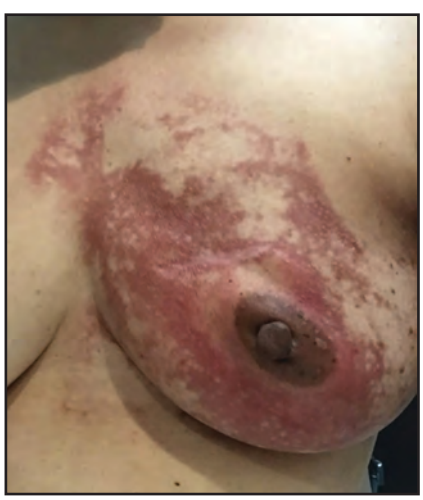

FIGURE 2. *Progression with confluence of lesions overlying the breast, with development of dryness and scaling.*

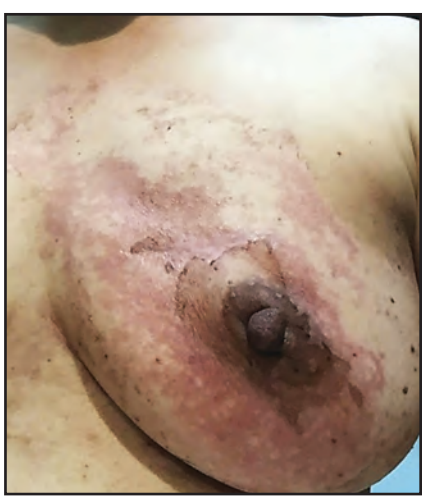

FIGURE 3. *Skin lesions 2 weeks after the first cycle of chemotherapy. Symptoms were controlled with oral cetirizine for pruritus and betamethasone cream for inflammation. Dry desquamation with residual erythema and hyperpigmentation are evident.*

phenomenon. Its occurrence is difficult to predict with incidences occurring months to years after radiation therapy. The drugs implicated differ from one person to another. The pathophysiology is also unclear, with several theories describing vascular damage, stem cell inadequacy, epithelial stem cell sensitivity, and drug hypersensitivity as possible etiologies. There is no clear threshold dose and it can develop at doses from 10 Gy to 61.2 Gy.[1,8]

Although RRD can occur over a wide range of time intervals between treatments, some evidence points to a shorter duration as a risk factor. In the American Society of Breast Surgeons Mammosite breast brachytherapy trial, accelerated partial breast irradiation (APBI) was given prior to chemotherapy. Adjuvant doxorubicin was given to 75% of patients and RRD was identified in 15 out of 131 (11.4%) patients. The time interval between completion of brachytherapy to the start of chemotherapy was a significant factor to its development, with an 18% occurrence in those who received chemotherapy < 3 weeks after APBI in contrast to 7.4% for an interval > 3 weeks ($p = 0.09$).[9]

A more complex interplay between total dose and time interval may exist, as shown by the development of RRD in a field treated to 38 Gy 7 days prior to etoposide administration but not in another site treated to 45 Gy 8 months before. The severity of the skin reaction during radiation therapy has not been correlated with the risk of developing RRD.[8]

The route of administration also affects the natural history of RRD. Agents given intravenously elicit the reaction rapidly while oral agents are protracted in development. The resolution of lesions seems to follow a similar pattern: Reactions from intravenous drugs have been observed to disappear more promptly than reactions from oral drugs.[2]

RRD may be approached in several ways and most cases are managed symptomatically. Observation is sufficient if there is only a mild, tolerable reaction. Steroids, NSAIDS, and anti-histamines can be used to reduce inflammation. In severe cases, the implicated drugs should be withheld as lesions rarely heal with continuation of medications.

A drug re-challenge is a viable option. Among factors to consider are patient-physician preference and the extent of RRD. Some may choose to lower the dose while others attempt premedication to prevent the inflammatory response. Alternative chemotherapy regimens may also be explored.[2,8]

The high prevalence of breast cancer combined with changing treatment paradigms predicts for a potential increased risk of RRD. Most of our information comes from well-described case reports and series; however, the rarity of the condition, the inability to predict which patient groups develop the reaction, the lack of a database, and the heterogeneity among cases have precluded a definitive characterization of this risk.

We have demonstrated that symptom control, re-challenge with the RRD-triggering drug, and premedication can be employed successfully. In

this situation, we highlight the increasing use of molecular profiling to guide chemotherapy utilization in patients who otherwise have a clinically low risk of recurrence. Chemotherapy might not be part of initial management plans due to the time-lag from the arrival of results. The usual sequence of giving radiation therapy after chemotherapy is reversed and this potentially increases the risk of RRD.

CONCLUSION

Although current figures indicate that RRD is rare, the symptoms are easily identifiable and the reaction can be effectively controlled. Risk factors have been identified but these are not uniform across all patients with RRD. One of the most critical elements we need is how to identify those at greatest risk of developing it. A database may be useful to characterize this reaction. This crucial body of data can help clinicians predict, identify, and treat RRD, especially in the setting of increased utilization of adjuvant treatment.

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