September 2022
Volume 11, Number 3

Applied RadiationOncology™

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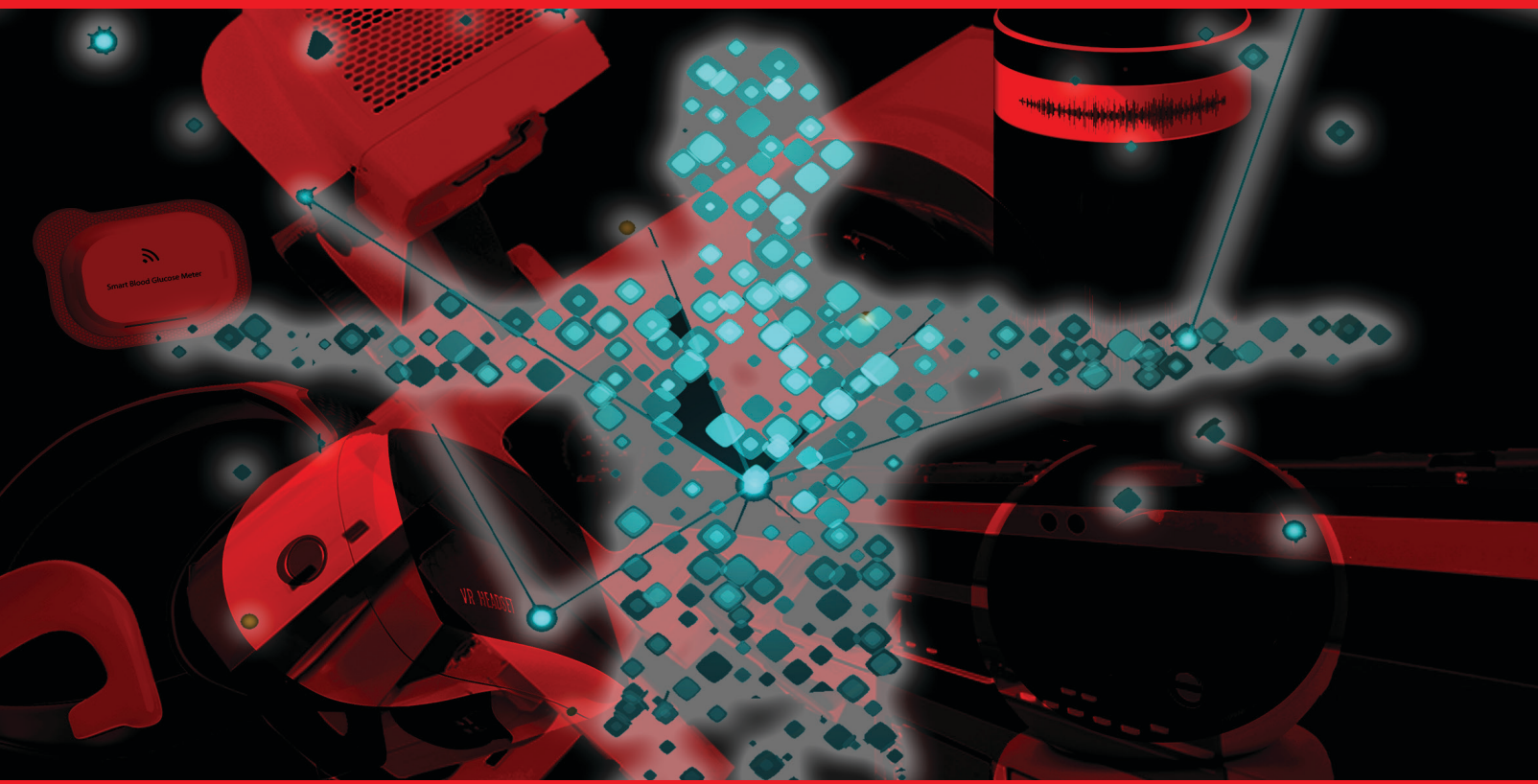

SA-CME
Practical Applications of the Internet of Things in Radiation Oncology

Review
The Evidence and Rationale for a Coronary Brachytherapy Dose-Response

Research
Radiation Therapy Techniques in the Management of Locally Advanced, High-Grade, Soft-Tissue Sarcoma

Case Report
Aggressive Multimodality Therapy for Treatment of a Locally Advanced Radiation-Related Chest Wall Sarcoma

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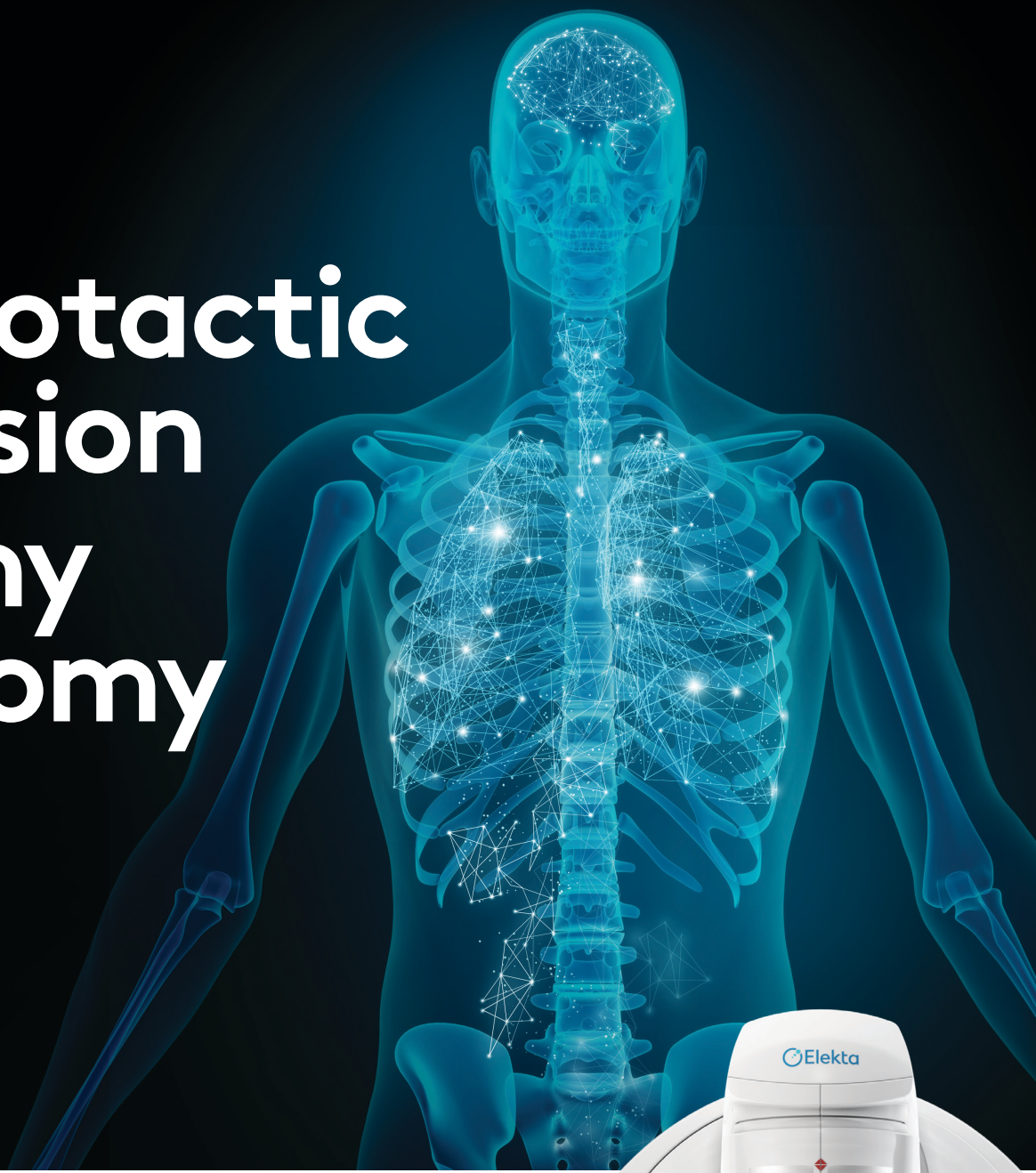

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ESSN: 2334-5446 (online)

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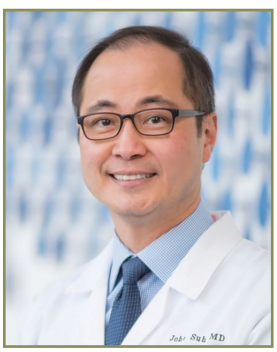

John Suh, MD, FASTRO, FACR

Dear Colleagues:

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

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

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

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

Sincerely,

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

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

Applied Radiation Oncology™

September 2022, Vol 11, No 3

FOCUS: SARCOMA

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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.

Education Updates and Spotlight on Sarcoma

John Suh, MD, FASTRO, FACR

Each year, autumn arrives with its traditional promises of cooler weather, striking foliage, and all things pumpkin. Marking the start of the academic year, it's also replete with exciting educational opportunities, including a few of our own. In our previous issue, we introduced 4 new medical student committees for *Applied Radiation Oncology*: First Pass Peer Review Committee, Podcast and Webinar Committee, Future Content Committee, and the Social Media Committee. Please join us in welcoming these bright new members and co-chairs for the 2022-2023 academic year (see p. 45 for details) and be sure to stay tuned to their contributions to *ARO*.

In the Issue

We are also pleased to present our issue theme of sarcoma and the role that radiation therapy plays in treating this uncommon cancer. The research article, *Radiation Therapy Techniques in the Management of Locally Advanced, High-Grade, Soft-Tissue Sarcoma (STS),* presents a relevant study investigating prognostic factors associated with local recurrence and wound complications. Among findings, the authors discuss how high-grade STS (greater or equal to 5 cm) may benefit from increased radial CTV margins in the absence of a fascial boundary. They also discuss important considerations regarding bolus techniques and wound complications.

Two case reports on sarcoma are featured as well. *Shingles After a Single Fraction of Radiation for Ewing Sarcoma* describes the first reported case of varicella-zoster virus reactivation after 1 fraction of radiation. The authors posit that a common mechanism, which may be distinct from immunosuppression, may exist whereby radiation therapy lowers the threshold for reactivation of latent alphaherpesviruses. The second case, *Aggressive Multimodality Therapy for Treatment of a Locally Advanced Radiation-Related Chest Wall Sarcoma,* is a novel case showing successful treatment using neoadjuvant thermochemoradiation, surgical resection, and complex reconstruction with a titanium mesh implant and multisite flap closure.

In addition, the issue features the SA-CME-accredited review, *Practical Applications of the Internet of Things in Radiation Oncology*. This timely article explores the applications – and major challenges – of IoT in radiation oncology, including the integration of electronic health records and nonhealth care data with therapeutic augmented reality, wearable technologies, smart voice assistants, digital medications, artificial intelligence, robots, continuous Bluetooth-enabled monitors, and smart cameras. We hope you enjoy this review and its promising outlook on how IoT applications can augment the quality and efficiency of cancer care, bringing several practical applications to radiation oncology.

A second review article, *The Evidence and Rationale for a Coronary Brachytherapy Dose-Response,* offers a compelling and comprehensive look at how and why increasing the prescription dose or prescription depth could improve effectiveness of intravascular brachytherapy. While IVB has been shown to reduce restenosis by half, recurrence rates of 40% at 3 years call for

Webinars and SA-CMEs

Additional educational offerings include our webinars and SA-CME activities, which are both complimentary, housed at www.appliedradiationoncology.com. Attending webinars live is ideal given the real-time Q&A session, but archived webinars afford the bonus of round-the-clock convenience. Our most recent topics include:

- Clinical Applications of FLASH Radiation Therapy
- Using Decision Theory for Re-irradiation of Head & Neck Cancer
- Radiation-Induced Carotid & Vertebral Artery Stenosis in the Intensity-Modulated Radiation Therapy Era
- The Emerging Role of Digital Therapeutics in Clinical Oncology Practice
- Formalized Mentorship in Radiation Oncology in the COVID Era
- Radiation Recall After the COVID-19 Vaccine
- MR-Guided Radiotherapy: Patient Selection and New Opportunities
- The Benefits and Future of Proton FLASH
- Technological Basis for Clinical Trials in FLASH Radiation Therapy
- Managing Anxiety & Minimizing Sedation in Pediatric Radiation Oncology

Recent SA-CME courses include:

- The Emerging Role of Digital Therapeutics in Medical, Surgical and Radiation Oncology
- A Proposed Way Forward From the Prior Authorization Crisis in Radiation Oncology
- Stereotactic Body Radiation Therapy (SBRT) vs Stereotactic Ablative Radiation Therapy (SABR): Does Terminology Differentiate Treatment Intent in Metastatic Cancer?
- Actualizing Risk-Adapted Thoracic Stereotactic Body Radiation Therapy With MR Guidance
- Integrating MR-Guided Radiation Therapy Into Clinical Practice: Clinical Advantages and Practical Limitations
- MR-Guided Radiation Therapy for Oligometastatic Malignancies
- FLASH Radiation Therapy: Review of the Literature and Considerations for Future Research and Proton Therapy FLASH Trials
- Technological Basis for Clinical Trials in FLASH Radiation Therapy: A Review
- Managing Anxiety and Minimizing Sedation Requirements in the Pediatric Radiation Oncology Population
- Applications of Artificial Intelligence in Head and Neck Radiation Therapy

improvement. The authors examine how better methods to individualize dose delivery to a patient's vessel walls seem a viable way to improve IVB effectiveness.

Rounding out the issue is the Resident Voice editorial, *Environmentally Sustainable Radiation Oncology: Can We Turn the Tides?* Discussing the newly formed Climate Health, Equity, and Sustainability Taskforce (CHEST) – created by the Association of Residents in Radiation Oncology's Global Health Subcommittee – the column underscores the critical need for advocacy and commitment to sustainable practices in our field and beyond. We applaud these important efforts and urge your support to help decarbonize energy sources, reduce waste, recycle more often, promote climate health equity, and enact additional measures toward a greener future.

Connecting at ASTRO

In closing, fall also plays host to the annual ASTRO conference – the ultimate occasion to gather, learn, teach, share, and connect. I hope to see you in San Antonio to harvest all these opportunities and more. Thank you for your continued support over the years, and happy autumn!

Practical Applications of the Internet of Things in Radiation Oncology

Description

As health care systems transform from traditional care delivery models to digital health models, IoT will enable integration of electronic health records and nonhealth care data with therapeutic augmented reality, wearable technologies, smart voice assistants, digital medicines, robots with artificial intelligence capabilities, continuous and Bluetooth-enabled monitors, and smart cameras. This review discusses the digital transformation of health care systems, IoT technology in cancer care, its practical applications in radiation oncology, and ongoing opportunities and challenges.

Learning Objectives

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

- define the internet of things (IoT) and describe its promise in health care,
- understand the various applications of IoT in radiation oncology, and
- describe the challenges of IoT adoption in radiation oncology.

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Target Audience

- Radiation Oncologists
- Related Oncology Professionals

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Estimated time for completion:
1 hour

Date of release and review:
September 1, 2022

Expiration date:
August 31, 2024

Disclosures

Dr. Thaker reports food and beverage payments from Merck Sharp & Dohme Corporation, Myovant Sciences, Inc., Amgen, Inc., Incyte Corporation, Merck Sharp & Dohme Corporation, and GlaxoSmithKline, LLC. Dr. De reports honoraria from Sermo, Inc. Dr. Shah reports consulting relationships with Impedimed, PreludeDX, Videra Surgical, and Evicore, and grants from VisionRT, Varian, and PreludeDX. Dr. Royce reports employment at Flatiron Health, Inc., an independent subsidiary of the Roche Group, and reports stock ownership in Roche and Agilix Health. Dr. Beriwal reports a consulting relationship with Elsevier and is on the XOFT data and safety monitoring board.

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Practical Applications of the Internet of Things in Radiation Oncology

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Abstract

As the global population ages, there will be an ever-increasing demand on health care systems worldwide for managing chronic conditions, including cancer care. A shift to automated health care solutions will be necessary to improve quality of care while also reducing resource burden to practitioners. Health care systems are amidst a digital transformation from traditional brick-and-mortar care delivery models to those that include virtual care, telehealth, and remote treatment delivery.

The internet of things (IoT) is a system of wireless, interconnected digital devices that can collect, send, and store data over a network without requiring human intervention, and it holds promise of improving the quality of health care while streamlining and enhancing health care delivery. This is especially relevant in technologically oriented medical fields such as radiation oncology. Various applications of IoT have been described in cancer care with immediate relevance to radiation oncology, including the integration of electronic health records (EHR) and nonhealth care data with therapeutic augmented reality, wearable technologies, smart voice assistants, digital medications, artificial intelligence (AI), robots, continuous Bluetooth-enabled monitors, and smart cameras. IoT holds promise of improving primary care through disease prevention and population health initiatives, and improving secondary and tertiary care including cancer care through integration of IoT data to create more coordinated, improved, and proactive care.

However, several challenges to IoT adoption in radiation oncology exist, including the need for more robust policy measures, enhancements in usability and cost effectiveness of IoT devices, improvements in cybersecurity and privacy, transparency of data governance, standardization of protocols to enhance interoperability, and finally, more favorable reimbursement.

Keywords: Internet of Things, IoT, IoMT, therapeutic augmented reality, wearable technologies, smart voice assistants, digital medications, artificial intelligence, robots, smart cameras

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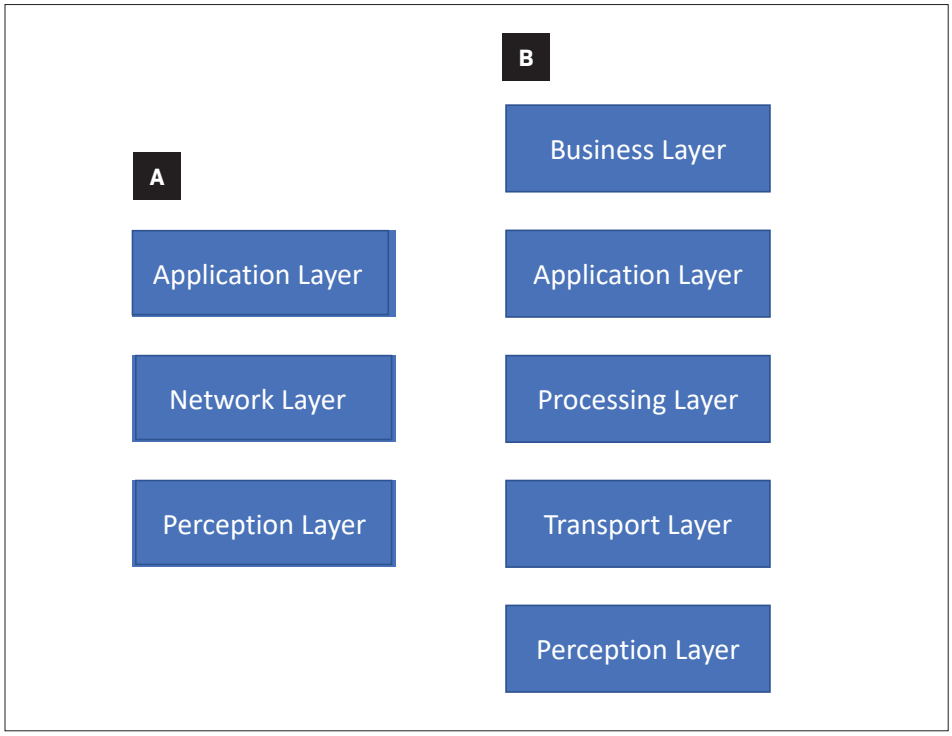
Disclosure: Dr. Thaker reports food and beverage payments from Merck Sharp & Dohme Corporation, Myovant Sciences, Inc., Amgen, Inc., Incyte Corporation, Merck Sharp & Dohme Corporation, and GlaxoSmithKline, LLC. Dr. De reports honoraria from Sermo, Inc. Dr. Shah reports consulting relationships with Impedimed, PreludeDX, Videra Surgical, and Evicore, and grants from VisionRT, Varian, and PreludeDX. Dr. Royce reports employment at Flatiron Health, Inc., an independent subsidiary of the Roche Group, and reports stock ownership in Roche and Agilix Health. Dr. Beriwal reports a consulting relationship with Elsevier and is on the XOFT data and safety monitoring board. The authors have no other 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.

Figure 1. There are 3- and 5-layer IoT architectures that describe the main ideas of IoT. The 3-layer architecture includes the perception layer, which is the physical layer; the network layer, which is responsible for connecting to other smart things; and the application layer, which is responsible for delivering application-specific services to the user. Research purposes require a more nuanced framework using a 5-layer architecture. The 5-layer architecture adds a transport layer, which transfers the sensor data to and from the perception layer to the processing layer; the processing layer, which stores, analyzes, and processes huge amounts of data that come from the transport layer; and the business layer, which manages applications, business models, and user data/privacy.



The pace of population aging is much faster today than in the past; by 2030, 1 in 6 people worldwide will be aged 60 years or older, and between 2015 and 2050, the proportion of the world's population over 60 years will nearly double from 12% to 22%.[1] As the population ages, there will be an ever-increasing global demand on health care systems for managing chronic conditions, including hypertension, diabetes, obesity, infectious diseases, hematologic disorders, and cancer.[2]

The cost of cancer care in the US is substantial and rising. The total cost in 2015 was $183 billion and is projected to increase 34% to $246 billion by 2030.[3] This expected increase is attributable not only to population growth and increasing life expectancy, but also to suboptimal care coordination, inappropriate or duplicative services, inefficiencies that require outpatient/inpatient follow-up rather than home monitoring, and the high cost of novel therapies.[4] This will create major challenges to delivering quality care within our health care system that is safe, timely, effective, efficient, equitable, and patient-centered.[5] These demands will ultimately require improved population health management techniques and opportunities for enhancing value-based care delivery. The 2020 response to the COVID-19 pandemic has also highlighted the need to transition to technology-based remote health care delivery options.[6,7]

A shift to automated health care solutions in the information age will be necessary to improve quality of cancer care while also reducing resource burden to practitioners.[8] This is particularly important in cancer care where there is a growing emphasis on technologically oriented care delivery such as radiation oncology. IoT includes a world where interconnected internet-enabled devices or "things" can collect and share data (machine-to-machine) without human intervention. In 2020, more than 21 billion devices are estimated to be connected to the internet, and health care IoT (or internet of medical things [IoMT]) could collect health-related data from individuals to improve care delivery and reduce provider burden.[9,10] In this review, we provide an overview of the digital transformation of health care systems, IoT technology in cancer care, its practical applications in radiation oncology, and ongoing opportunities and challenges.

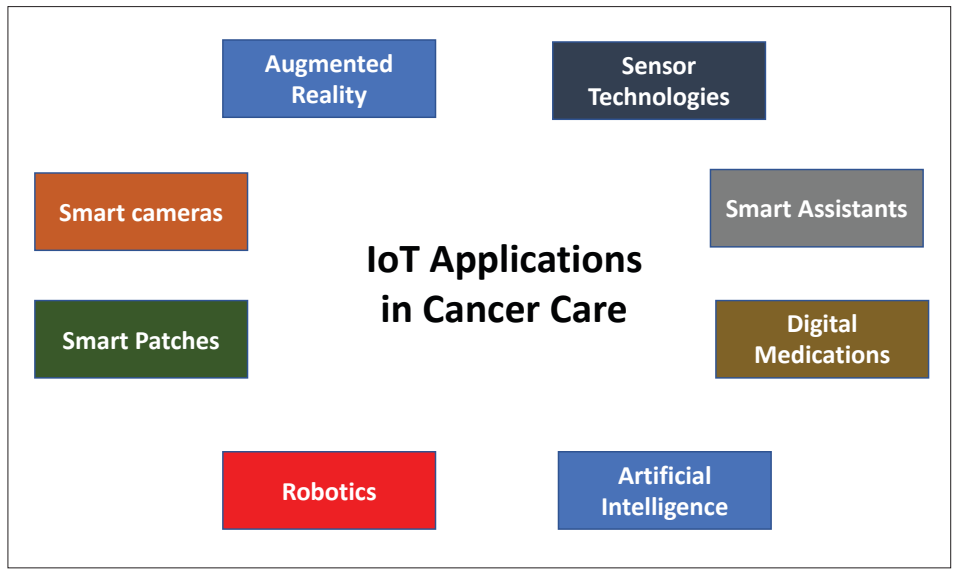
The Internet of Things

Digital Transformation of Health Care Systems

Many health care systems are amidst a digital transformation as they move from traditional brick-and-mortar care delivery models to models that include virtual care, telehealth, and remote treatment delivery.[11] The COVID-19 pandemic (in 2020 to the present) has especially emphasized the need for a technology-enabled health care system that can facilitate digital transformation.[6,7] Health care systems view digital transformation as a way to become more consumer-friendly, but will need to focus on interim milestones to justify value; acquire the talent, data, and key performance indicators needed to overcome digital transformation challenges; and cultivate executive champions.[12] However, in a recent survey, only 7 percent of health care and pharmaceutical companies said they had "gone digital," compared with 15 percent of companies in other industries.[13]

In response to technological evolutions, IoT technology holds promise to support health care systems to deliver higher quality care and to improve population health initiatives. From a health care perspective, IoT can be considered as any device that can collect health-related data from computing devices, mobile phones, smart bands and wearables, digital medications, implantable surgical devices, or other portable devices that may communicate through channels such as radiofrequency identification that can measure health data and connect to the internet.[10] IoMT has been described in health care, with immediate applications to cancer care and radiation oncology, including mobile health, ambient assisted living, wearable devices, smartphones, eHealth, community-based health care and other uses.[14] These applications can be leveraged in nearly all health care settings, from primary care to tertiary care.

Figure 2. Internet of Things (IoT) applications in cancer care explored in this review include augmented reality, sensor technology, smart patches, smart cameras, smart voice assistants, digital medications, and artificial intelligence and robotics.



IoT and Healthcare Architecture

There are 3- and 5-layer IoT architectures that have previously been described and that can be applied to IoT in health care.[15-17] Architectures are the way that the components – such as devices, network structure, and cloud technology – are organized. The most basic architecture includes the perception layer, the network layer, and the application layer[15,18] (**Figure 1A**), which we will cover briefly here:

Perception layer. The perception layer is the physical layer that is the foundation of IoT. This layer has sensors for sensing and gathering information about the environment. It senses some physical parameters, identifies other smart objects in the environment, and provides geographic location recognition. This includes radiofrequency identification (RFID), infrared sensors, cameras, GPS, medical sensors, and smart device sensors that can allow for real-time monitoring and network transmission (eg, an implanted, continuous blood glucose level sensor as detailed below). There are numerous examples of IoT devices in health care but limited data on quality and safety.[9] Some examples include therapeutic augmented reality, wearable technologies, smart voice assistants, digital medicines, robots, continuous monitors, Bluetooth-enabled monitors, and smart cameras, all of which are discussed in detail below.

Network layer. The network layer is responsible for connecting to other smart things, network devices, and servers. This includes wireless and wired networks that communicate, store, process and transmit sensor data either locally or in a centralized way. Most IoT devices use high frequencies with short-range communication technologies. High-frequency 4G cellular networks have improved potential for communications, and 5G networks are expected to provide a reliable connection for numerous devices simultaneously.[19] Centralized cloud-based computing is becoming more popular as it improves flexibility, scalability and access. However, centralization could lead to slower transmission times between central data centers and IoT devices as well as accumulation of unnecessary data. Conversely, the edge cloud allows IoT sensors and network gateways to process and analyze data in a decentralized fashion, reducing the amount of data required to be communicated and managed at a centralized location.[20] As an example, blockchain uses decentralized data storage that can be regulated by patients and may improve mobile health applications, monitoring devices, sharing and storing of electronic medical records, clinical trial data, and insurance information storage.[21]

Application layer. The application layer is responsible for delivering application-specific services to the user, such as smart homes, smart cities, and smart health.[15] Some examples include therapeutic augmented reality, wearable technologies, smart voice assistants, digital medicines, robots, continuous monitors (eg, an application that records and reads out blood glucose levels from a continuous, implanted sensor), Bluetooth-enabled monitors, and smart cameras (**Figure 2**), which have immediate applications

Table 1. Application Layer Examples

DEVICE	BRIEF DESCRIPTION AND SAMPLE APPLICATIONS (SEE TEXT FOR DETAILS)
Therapeutic augmented reality	Includes augmented reality, mixed reality, and virtual reality that can visualize data collected from sensors. Applications have included a broad range of diseases in both the inpatient and outpatient settings. For cancer care, applications include oncologic surgery, brachytherapy, patient education, and practitioner training.
Sensor technologies (including smart monitors and wearable tech)	Devices worn by a user that connect to sensors, apps (such as a smart phone), or web portals through wireless connections. Applications include glucose monitors, insulin pens, Fitbits and smartwatches, fall detectors, electrocardiograms, and blood pressure monitors. Such smart monitors are being deployed on linear accelerators for continuous analytic data monitoring (including feedback for equipment maintenance and fault prevention).
Smart patches	Superficial patches on the skin that can track vital signs including heart rate, respiratory rate, and temperature, as well as sleep/wake cycle and step counts. May be used for transdermal diagnosis/assessment and therapeutic delivery.
Smart cameras	Cameras (such as smartphones or standalone technology that includes camera and smart technology infrastructure) that capture and analyze images or changes in the environment. Applications include assessing skin lesions, wounds, or conditions; monitoring ocular pathology; enhancing privacy through masking technology; enhancing patient/resident safety through fall monitoring and prevention; and enhancing efficiency of patient check-in and monitoring processes. These cameras can aid a radiation oncologist's assessment of skin lesions and radiation toxicity.
Smart voice assistants	Installed in a private setting (such as home or car) and provide AI-supported conversation agents, including Amazon's Alexa, Google Assistant, and Apple's Siri. Applications have included appointment scheduling, chatbots, web browser searches, answering health care questions, phone calls. Conversation agents may help educate cancer patients about treatments, provide feedback on pain management options, refill medications, locate practitioners, assist in documentation through ambient clinical intelligence, and other applications.
Digital medications	Ingestible sensors made from magnesium, copper, and silicon that communicate with an external body sensor such as a patch, mobile app, or website. Can be used to monitor medication adherence and absorption, and prompt patients to take medications. Potential use for patients on oral chemotherapeutics. Bluetooth inhalers, which are devices that use a Bluetooth sensor paired to a mobile app that provides analytics and patient/practitioner feedback, may be a digital medicine and have analytic sensor technology.
Artificial intelligence (AI) and robotics	AI-powered robots that can interact with humans. Applications include medication management and assisting rehabilitation in the home setting, patient navigation, abnormality detection, and collection of patient data in hospital setting. Could assist with oncologic surgeries, brachytherapy, chemotherapeutic and other systemic therapy delivery, and patient education at point of care.

in radiation oncology. **Table 1** lists a brief description of each application, although many others exist.

Research purposes require a more nuanced framework using a 5-layer architecture. The 5-layer architecture adds a transport layer, which transfers the sensor data to and from the perception layer to the processing layer; the processing layer, which stores, analyzes, and processes huge amounts of data that come from the transport layer; and the business layer, which manages applications, business models, and user data/privacy (**Figure 1B**).

IoT Applications in Cancer Care

Augmented Reality

Therapeutic augmented reality (or extended reality) includes augmented reality (AR), mixed reality (MR), and virtual reality (VR) that can visualize data collected from sensors that are part of the IoT. This technology combines high-quality stereoscopic computer displays such as with goggles to display an immersive 3D environment, with 6 degrees-of-freedom spatial tracking to capture the movements of the user and controllers, and interact with virtual or augmented surroundings.[22] Examples have included a broad range of inpatient and outpatient applications to learn about anatomy, anesthesia, central vein catheterization,[23] mental health and anxiety disorders,[24] stroke,[25] pain management,[26, 27] and obesity.[28] Augmented reality may aid oncologic surgeries,[29-31] education for patients undergoing radiation therapy,[32,33] immersive virtual reality to reduce patient anxiety and psychological symptoms,[26,34] practitioner training,[35,36] and brachytherapy.[37]

Within radiation oncology, AR can provide 3D and 360-degree views to simulate the entire process of radiation therapy, from clinics to simulation rooms and treatment rooms.[38] AR will also provide 360-degree views of the treatment room to correct positioning in real-time.[39,40] A projector-based display has already been used to simulate controlling a linac for training and education.[41] Physicians, dosimetrists, physicists and even patients can explore spatial relationships of dosimetric distribution. For example, a patient with a meningioma may be considering stereotactic radiation therapy and may want to utilize AR to understand the concepts of how the brain and adjacent critical organs at risk may be exposed to radiation due to its proximity to the primary target.

Sensor Technology

Sensor technologies are devices placed on equipment or worn by a user that connect to sensors, apps (such as on a smartphone), or web portals, through wireless connections. Although only 21% of adults and fewer elderly people own wearable devices, the majority of US adults own a smartphone, allowing smartphone technology to rapidly scale IoT-based interventions.[42] Applications include continuous glucose monitors, smart insulin pens, loneliness detectors, sleep trackers, smartwatches and Fitbits, fall detectors, wireless electrocardiogram monitors, wearable blood pressure monitors, and others.[43-45] Bluetooth inhalers are a related technology that use a Bluetooth sensor paired to a mobile app that provides analytics and patient/practitioner feedback.[46]

Commonly, wearable devices have been used to assess physical activity levels, as these levels before, during, and after cancer treatment have been established as robust predictors of clinical outcomes as well as quality of life.[42,47,48] Interestingly, lower levels of activity during chemoradiation (head and neck, lung, and gastrointestinal cancer) as measured with Garmin devices were associated with greater hospitalization risk, lower likelihood of completing treatment without delays, and shorter survival.[49,50] Similarly, daily step count for abdominal cancer patients on postoperative day 7 was inversely correlated with the postoperative complication index.[51] Published prospective studies incorporating mobile sensor data with clinical outcomes have focused mostly on patient-reported outcomes, toxicity and symptom burden,[51-54]quality of life,[55] hospitalizations or readmissions,[49,50,56,57] or postoperative events.[58]

Smart monitors are also being deployed on linear accelerators. Such technology allows for continuous background analytic data monitoring that provides feedback for equipment maintenance, proactive service and fault prevention for field service technicians.[59] This application has already helped technicians identify early trends in equipment malfunction – such as couch faults or slow multileaf collimator motors – and order and install replacement parts before machine downtime. IoT offers an opportunity to maximize machine uptime and provide personalized, continuous remote support for radiation oncology clinics. Analytics can also be applied to the continuously monitored historical logs and configuration files using machine-learning algorithms.

Smart Patches

Smart patches such as vital sign patches are designed to wirelessly track and monitor heart rate, respiratory rate, sleep cycle, stress levels, temperature, step counts, and falls/incapacitation.[60] Temperature-tracking smart patches (TempTraq) are being used in CAR T cell therapy clinical trials.[61] In a recent proof-of-concept study, smart patches were used to monitor dyspnea in the palliative care setting.[62] Transdermal delivery of chemotherapeutics utilizing smart patches may be a possibility in the future.[63] Smart patches have also been used to biopsy skin cells on the

skin surface.[64,65] Despite these promising applications, patients may be wary of wearing a patch sensor, and instead opt for biosensors embedded in armbands or wrist-worn devices.[66] For example, patients who are receiving concurrent chemoradiation therapy may be at higher risk of hospitalization due to toxicities[67] and could benefit from smart patch technology to seamlessly evaluate vital signs and distress in real-time using remote patient monitoring evaluated by a centralized virtual care team.[68]

Smart Cameras

Smart cameras, such as smartphones or standalone technology that includes camera and smart technology infrastructure, can capture changes in the environment. Smart cameras may support a machine vision system by digitizing and transferring frames for computer analysis although some smart cameras can also serve as self-contained vision systems without relying on external processing equipment.[69] Such technology can be used to diagnose, monitor, or evaluate skin conditions including assisting with wound care in patients with diabetes and skin cancer.[70-74] Smart cameras can also enhance privacy by using video analytics to hide sensitive health data on displays; enhance patient/resident safety through fall monitoring and prevention; and enhance efficiency of patient check-in, admission, and patient flow through the clinic.[75] Within the radiation oncology clinic, smart cameras may capture patient check-in, waiting times, clinic visit times, location of family members, and help monitor safety at the linac and brachytherapy consoles, among other applications.

Smart Voice Assistants

Smart voice assistants can be installed in a private setting (such as the home or car) and provide AI-supported conversation agents, including Amazon's Alexa, Google Assistant, and Apple's Siri, to answer a specific set of health-related questions without human contact. Examples include evaluation and management of depression and anxiety; autism; sexual, substance, and physical harassment issues; language impairment; obstructive sleep apnea; hypertension; breast cancer; type 2 diabetes; and pain management.[76] Smart voice assistants may also improve access to in-home virtual care.[77] Applications have included scheduling appointments; offering chatbots, web browser searches, and phone calls; educating cancer patients about treatments; providing feedback on pain management options; refilling medications; locating practitioners; assisting with documentation through ambient clinical intelligence; and other applications.[78-82] Specifically for radiation oncology, a smart voice assistant could remind patients about the day of their weekly treatment management visit, the time of their scheduled daily radiation treatment (with special reminders when schedules change); record notes prior to, during, and after visits; and help find high-quality education for patients and caregivers.

Digital Medications

Digital medications include an ingestible sensor (typically made from magnesium, copper, or silicon) that can communicate with an external body sensor such as a wearable patch or mobile app. Information is stored on the cloud and used to measure medication adherence, absorption, activity, and heart rate.[83] In 2019, Proteus Digital Health introduced digital chemotherapy for stage 3 or stage 4 colorectal cancer.[84] When a patient swallows the capsule, a sensor activates when it reaches the stomach, which then transmits data to a smart patch with the time of day, the dose, and the type of medication. Unfortunately, Proteus recently filed for bankruptcy, driven by an expensive technology without a clear business model and uneven patient acceptance of ingestible sensors.[85] This example illustrates the importance of demonstrating a clear value proposition and product-market fit. In radiation oncology, these technologies (linked with smart patches) can assess patient compliance and toxicities with concurrent chemotherapies (such as capecitabine or temozolomide).

Artificial Intelligence

Overall, AI is a promising medical application leveraging IoT. Narrow AI applications include natural language processing, image analysis, drug discovery development, and computational genomics. Recently, Google Health and Meditech have announced a collaboration to improve clinical search functionality in Expanse electronic health record, which would be another practical use of AI technology.[86] With data generated from mobile health apps and IoT devices, AI and deep learning can also optimize disease management and provide big data analysis.[86] Big data in health care has rapidly grown to include genomics, metabolomics, proteomics, lipomics, transcriptomics, immunomics, glycomics and imageomics.[88-90]

Deep learning, a subset of AI, is now being used in decision-making, autosegmentation, radiation treatment planning, and adaptive radiation therapy, but may be limited by access to the internet, web-based cloud solutions, or high-performance computing hardware; and lack of protocols for clinical commissioning, validation, implementation, and maintenance.[91] Ultimately, AI holds promise of augmenting or improving efficiencies rather than replacing radiation oncologists' toolsets, although it may refocus tasks performed by the treatment planning team.[91,92]

Robotics

Robots using AI technology can interact with humans in various health care settings. Examples have

included robots assisting patients with hospital navigation, collecting patient data and assisting with physical therapy and rehabilitation.[93,94] Robotic surgery has gained acceptance in minimally invasive surgery,[95] and AI in surgery has shaped preoperative planning and intraoperative guidance.[96,97] AI-powered robotics could also have applications in brachytherapy, including placement of applicators/needles, and chemotherapeutic and other systemic therapy delivery.

IoT and Improving Cancer Care Delivery

IoT can enable smart devices to transform traditional cancer care in the radiation oncology clinic into a more efficient, higher-quality, technology-enabled service. IoT will be able to impact health care delivery across the full spectrum of care delivery, from primary care to tertiary/quaternary care.

Oncology patients are not only grappling with acute care for their cancer diagnosis but also with competing risks with comorbidities. Primary care focuses on disease prevention, reducing disease burden, modifying risk factors, and caring for patient populations. Unfortunately, 28% of men and 17% of women do not have a primary care provider and lack chronic care services, which will also impact compliance and outcomes from oncologic therapies.[98] IoT will enable patients to better self-manage conditions and allow providers to assess modifiable risk factors in real-time.[99] It will also increase capacity and access to primary care using AI (including chatbots) and smart voice assistants. However, there is no well-defined pathway for regulatory approval of smart apps, and data on safety and efficacy is lacking.[100,101] IoT will also be able to help integrate nonhealth data through data from smart homes, including data from independent living units, grocery/refrigeration, wearable devices, power, appliances, security, and entertainment, to provide a more holistic view of patients and their unique needs. When applied over the population level, it will enhance disease surveillance and assessment of environmental risk factors. During the COVID-19 pandemic, big data analytics have been applied to credit card payments, television surveillance, and geographic location to contact trace and identify close contacts.[102]

IoT will also directly improve cancer care delivery. Better integration of IoT data with EHRs and nonhealth data will lead to more coordinated and proactive care, as opposed to the current piecemeal, uncoordinated care within the traditional health care system. For instance, IoT can better connect physicians with patients in their home, allowing physicians to better understand patients, better assess toxicities from systemic therapies and radiation, assess treatment compliance, reduce costs, and improve quality of care. IoT will also encourage self-monitoring of data uploaded to the cloud and allow for continuous feedback from providers; create alerts when intervention is needed; help emergency departments and urgent care facilities better triage patients; and increase the number of point-of-care tests rather than outsource to centralized locations.[8,10,103]

Within the radiation oncology clinic, IoT will allow for broader communication with cloud platforms, data centers, and remote monitoring and control systems. It will facilitate clinic workflows, automation of narrow tasks such as contouring,[104,105] treatment and adaptive planning,[106,107] quality assurance and quality control procedures,[108,109] patient positioning with sensors, intelligent image-guided radiation therapy and intelligent robotics, and communication with radiation information systems potentially even in remote settings with limited availability of trained on-site staffing. Data from smart homes can be integrated with wearable sensors and digital medications/pillboxes to provide contextual data to radiation oncologists and multidisciplinary teams.

Challenges

To further support the growth and use of IoT in cancer care delivery, health care policy will need to support mobile and eHealth technologies. This will require government and private sector investment in IoT hardware and software infrastructure and a transparent and efficient regulatory pathway for approval with the US Food and Drug Administration (FDA). Several countries already have policies for IoT.[110] Despite ongoing evidence development in other industries, there are still limited use cases in health care, and limited government (including FDA) regulations and approval.

IoT technology will also need to become more usable and cost effective for consumers of all socioeconomic backgrounds in order to increase user acceptability and confidence in the technology. For instance, a much lower percentage of 55- to 64-year-olds use smart devices compared with those ages 18 to 29 years.[111] Only 15% of Americans with an annual household income below $30,000 own a smart speaker while that number rises to 34% for those who earn above $75,000.[111] There is also limited understanding from both patients and physicians of the value of cloud-based storage systems, an unfamiliarity with IoT technology, and limited organizational readiness to adopting such technology.[112] Patients and physicians may also be reluctant to adopt these technologies if they are intrusive, difficult to use with current daily schedules or workflows, or associated with an overwhelming amount of data.

Furthermore, cybersecurity risks remain an obstacle of growth and

integration of IoT technologies with existing technologies, especially as the number of entry points with each internet-connected device increases. This is especially the case in health care where protected health information (PHI) is being transmitted across machines and must abide by the Health Insurance Portability and Accountability Act of 1996 (HIPAA). IoT communications are wireless and most utilize low energies, both of which increase the difficulty in ensuring security. Although draft security feature recommendations for IoT devices have been released, the level to which these will be adopted or how they can be enforced is unclear.[113]

Transparency of data governance and ownership will also be needed for IoT applications. Cloud-based aggregation of IoT data has resulted in centralized cloud storage, which has raised questions about who owns the health care data, and who can view, edit or delete the data. Sharing of this data between states, nations, and organizations is also an important consideration.

Lack of standardization of protocols has also created issues about interoperability of IoT devices with each other or existing legacy technologies. There is not yet consensus regarding wireless communication protocols and standards for machine-to-machine communication. Even existing EHR technology lacks full semantic interoperability, although a push toward Fast Healthcare Interoperability Resources (FHIR) holds promise.[114]

Finally, there may be an increased resource and information burden to health care providers without adequate reimbursement. In traditional health care systems, health care staff lack expertise to assist with data monitoring and there is an increased burden to clinicians for reviewing large volumes of data. There may also be increased malpractice liability associated with data monitoring. The COVID-19 pandemic has improved reimbursement for telehealth services (commensurate with its increased utilization), but reimbursement for IoT applications will need a concerted effort across governmental and private payers.[115]

Summary and Conclusions

IoT applications hold great potential to improve the quality and efficiency of cancer care with several practical applications to radiation oncology. As health care systems transform from traditional care delivery models to digital health models, IoT will enable integration of EHR and nonhealth care data with therapeutic augmented reality, wearable technologies, smart voice assistants, digital medicines, robots with AI capabilities, continuous and Bluetooth-enabled monitors, and smart cameras. However, implementation and full realization of the value of IoT will require more robust policy measures, enhancements in usability and cost effectiveness of IoT devices, improvements in cybersecurity and privacy, transparency of data governance, standardization of protocols to enhance interoperability, and more favorable reimbursement. These innovations will improve disease prevention and population health initiatives as well as high-acuity care such as cancer care.

References

1) World Health Organization. Ageing and health. 2021. Accessed July 4, 2022. https://www.who.int/news-room/fact-sheets/detail/ageing-and-health

2) GBD 2017 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet.* 2018;392:1789-1858.

3) Mariotto AB, Enewold L, Zhao J, Zeruto CA, Yabroff KR. Medical care costs associated with cancer survivorship in the United States. *Cancer Epidemiol Biomarkers Prev.* 2020;29:1304-1312.

4) Osarogiagbon RU, Mullangi S, Schrag D. Medicare spending, utilization, and quality in the oncology care model. *JAMA.* 2021;326:1805-1806.

5) Richards MK, Goldin AB. Patient-centered care and quality: activating the system and the patient. *Semin Pediatr Surg.* 2015;24:319-322.

6) Monaghesh E, Hajizadeh A. The role of telehealth during COVID-19 outbreak: a systematic review based on current evidence. *BMC Public Health.* 2020;20:1193.

7) Lee P, Abernethy A, Shaywitz D, et al. Digital health COVID-19 impact assessment: lessons learned and compelling needs. *NAM Perspect.* 2022;2022.

8) Mitchell M, Kan L. Digital technology and the future of health systems. *Health Syst Reform.* 2019;5:113-20.

9) Kelly JT, Campbell KL, Gong E, Scuffham P. The internet of things: impact and implications for health care delivery. *J Med Internet Res.* 2020;22:e20135.

10) Dang LM, Piran MJ, Han D, Min K, Moon H. A survey on internet of things and cloud computing for healthcare. *Electronics.* 2019:768.

11) Torous J, Jan Myrick K, Rauseo-Ricupero N, Firth J. Digital mental health and COVID-19: using technology today to accelerate the curve on access and quality tomorrow. *JMIR Ment Health.* 2020;7:e18848.

12) Appleby C, Wurz J, Hendricks J, Shudes C. Digital transformation. 2021. Accessed July 4, 2022. https://www2.deloitte.com/us/en/insights/industry/health-care/digital-transformation-in-healthcare.html

13) Reddy M. Digital Transformation in Healthcare in 2022: 7 Key Trends. 2022. Accessed July 4, 2022. https://www.digitalauthority.me/resources/state-of-digital-transformation-healthcare/

14) Shah Nazir YA, Naeem Ullah, Iván García-Magariño. Internet of things for healthcare using effects of mobile computing: a systematic literature review. *Wireless Com Mobile Comp.* 2019;2019:20.

15) Sethi P, Sarangi SR. Internet of things: architectures, protocols, and applications. *J Elec Comp Eng.* 2017;2017:9324035.

16) Mashal I, Alsaryrah O, Chung T-Y, Yang C-Z, Kuo W-H, Agrawal DP. Choices for interaction with things on Internet and underlying issues. *Ad Hoc Net.* 2015;28:68-90.

17) Miao W, Ting-Jie L, Fei-Yang L, Jing S, Hui-Ying D. Research on the architecture of internet of things. 2010 3rd International Conference on Advanced Computer Theory and Engineering (ICACTE). 2010;V5-484-V5-7.

18) Said O, Masud M. Towards internet of things: survey and future vision. *Int J Comp Net.* 2013;5:1-17.

19) Li S, Xu LD, Zhao S. 5G Internet of things: a survey. *J Indust Info Integrat.* 2018;10:1-9.

20) Pan J, McElhannon J. Future edge cloud and edge computing for internet of things applications. *IEEE Intern Things J.* 2018;5:439-449.

21) Chen HS, Jarrell JT, Carpenter KA, Cohen DS, Huang X. Blockchain in healthcare: a patient-centered model. *Biomed J Sci Tech Res.* 2019;20:15017-22.

22) Williams CL, Kovtun KA. The future of virtual reality in radiation oncology. *Int J Radiat Oncol Biol Phys.* 2018;102:1162-1164.

23) Gerup J, Soerensen CB, Dieckmann P. Augmented reality and mixed reality for healthcare education beyond surgery: an integrative review. *Int J Med Ed.* 2020;11:1-18.

24) Valmaggia LR, Latif L, Kempton MJ, Rus-Calafell M. Virtual reality in the psychological treatment for mental health problems: a systematic review of recent evidence. *Psychiat Res.* 2016;236:189-195.

25) Lohse KR, Hilderman CG, Cheung KL, Tatla S, Van der Loos HF. Virtual reality therapy for adults post-stroke: a systematic review and meta-analysis exploring virtual environments and commercial games in therapy. *PLoS One.* 2014;9:e93318.

26) Chirico A, Lucidi F, De Laurentiis M, Milanese C, Napoli A, Giordano A. Virtual reality in health system: beyond entertainment. a mini-review on the efficacy of VR during cancer treatment. *J Cell Physiol.* 2016;231:275-287.

27) Tashjian VC, Mosadeghi S, Howard AR, et al. Virtual reality for management of pain in hospitalized patients: results of a controlled trial. *JMIR Ment Health.* 2017;4:e9.

28) Persky S. Application of virtual reality methods to obesity prevention and management research. *J Diabetes Sci Technol.* 2011;5:333-339.

29) Gouveia PF, Costa J, Morgado P, et al. Breast cancer surgery with augmented reality. *Breast.* 2021;56:14-17.

30) Sahovaler A, Chan HHL, Gualtieri T, et al. Augmented reality and intraoperative navigation in sinonasal malignancies: a preclinical study. *Front Oncol.* 2021;11:723509.

31) Tagaytayan R, Kelemen A, Sik-Lanyi C. Augmented reality in neurosurgery. *Arch Med Sci.* 2018;14:572-578.

32) Wang LJ, Casto B, Luh JY, Wang SJ. Virtual reality-based education for patients undergoing radiation therapy. *J Cancer Ed.* 2022;37:694-700.

33) van der Kruk SR, Zielinski R, MacDougall H, Hughes-Barton D, Gunn KM. Virtual reality as a patient education tool in healthcare: a scoping review. *Patient Educ Couns.*2022;105:1928-1942.

34) Reynolds LM, Cavadino A, Chin S, et al. The benefits and acceptability of virtual reality interventions for women with metastatic breast cancer in their homes; a pilot randomised trial. *BMC Cancer.* 2022;22:360.

35) Herbst R, Rybak T, Meisman A, et al. A virtual reality resident training curriculum on behavioral health anticipatory guidance: development and usability study. *JMIR Ped Parent.* 2021;4:e29518.

36) Hooper J, Tsiridis E, Feng JE, et al. Virtual reality simulation facilitates resident training in total hip arthroplasty: a randomized controlled trial. *J Arthroplasty.* 2019;34:2278-2283.

37) Taunk NK, Shah NK, Hubley E, Anamalayil S, Trotter JW, Li T. Virtual reality-based simulation improves gynecologic brachytherapy proficiency, engagement, and trainee self-confidence. *Brachytherapy.* 2021;20:695-700.

38) Penn Radiation Oncology VR Experience. 2022. Accessed July 4, 2022. https://www.oncolink.org/penn-radiation-oncology-vr-experience

39) Johnson K, Liszewski B, Dawdy K, Lai Y, McGuffin M. Learning in 360 degrees: a pilot study on the use of virtual reality for radiation therapy patient education. *J Med Imag Radiat Sci.* 2020;51:221-226.

40) Chamunyonga C, Burbery J, Caldwell P, Rutledge P, Fielding A, Crowe S. Utilising the virtual environment for radiotherapy training system to support undergraduate teaching of IMRT, VMAT, DCAT treatment planning, and QA concepts. *J Med Imag Radiat Sci.* 2018;49:31-38.

41) Kane P. Simulation-based education: a narrative review of the use of VERT in radiation therapy education. *J Med Imag Radiat Sci.* 2018;65:131-136.

42) Low CA. Harnessing consumer smartphone and wearable sensors for clinical cancer research. *NPJ Digit Med.* 2020;3:140.

43) Sangave NA, Aungst TD, Patel DK. Smart connected insulin pens, caps, and attachments: a review of the future of diabetes technology. *Diabetes Spectr.* 2019;32:378-384.

44) Doryab A, Villalba DK, Chikersal P, et al. Identifying behavioral phenotypes of loneliness and social isolation with passive sensing: statistical analysis, data mining and machine learning of smartphone and Fitbit data. *JMIR Mhealth Uhealth.* 2019;7:e13209.

45) Kakria P, Tripathi NK, Kitipawang P. A real-time health monitoring system for remote cardiac patients using smartphone and wearable sensors. *Int J Telemed Appl.* 2015;2015:373474.

46) Merchant RK, Inamdar R, Quade RC. Effectiveness of population health management using the propeller health asthma platform: a randomized clinical trial. *J Allergy Clin Immunol Pract.* 2016;4:455-463.

47) Ballard-Barbash R, Friedenreich CM, et al. Physical activity, biomarkers, and disease outcomes in cancer survivors: a systematic review. *J Natl Cancer Inst.* 2012;104:815-840.

48) Ferrer RA, Huedo-Medina TB, Johnson BT, Ryan S, Pescatello LS. Exercise interventions for cancer survivors: a meta-analysis of quality of life outcomes. *Ann Behav Med.* 2011;41:32-47.

49) Ohri N, Halmos B, Bodner WR, et al. Daily step counts: a new prognostic factor in locally advanced non-small cell lung cancer? *Int J Radiat Oncol Biol Phys.* 2019;105:745-751.

50) Ohri N, Kabarriti R, Bodner WR, et al. Continuous activity monitoring during concurrent chemoradiotherapy. *Int J Radiat Oncol Biol Phys.* 2017;97:1061-1065.

51) Sun V, Dumitra S, Ruel N, et al. Wireless monitoring program of patient-centered outcomes and recovery before and after major abdominal cancer surgery. *JAMA Surg.* 2017;152:852-859.

52) Bennett AV, Reeve BB, Basch EM, et al. Evaluation of pedometry as a patient-centered outcome in patients undergoing hematopoietic cell transplant (HCT): a comparison of pedometry and patient reports of symptoms, health, and quality of life. *Qual Life Res.* 2016;25:535-546.

53) Soto-Perez-De-Celis E, Kim H, Rojo-Castillo MP, et al. A pilot study of an accelerometer-equipped smartphone to monitor older adults with cancer receiving chemotherapy in Mexico. *J Geriat Oncol.* 2018;9:145-151.

54) Wright AA, Raman N, Staples P, et al. The HOPE Pilot Study: harnessing patient-reported outcomes and biometric data to enhance cancer care. *JCO Clin Cancer Inform.* 2018;2:1-12.

55) Bade BC, Brooks MC, et al. Assessing the correlation between physical activity and quality of life in advanced lung cancer. *Integrat Cancer Ther.* 2018;17:73-79.

56) Low CA, Bovbjerg DH, Ahrendt S, et al. Fitbit step counts during inpatient recovery from cancer surgery as a predictor of readmission. *Ann Behav Med.* 2018;52:88-92.

57) Pavic M, Klaas V, Theile G, et al. Mobile health technologies for continuous monitoring of cancer patients in palliative care aiming to predict health status deterioration: a feasibility study. *J Palliat Med.* 2020;23:678-685.

58) Panda N, Solsky I, Huang EJ, et al. Using smartphones to capture novel recovery metrics after cancer surgery. *JAMA Surg.* 2020;155:123-129.

59) Less Downtime, More Insights with Varian Smart Services. 2022. Accessed July 4, 2022. https://www.varian.com/resources-support/blogs/clinical-oncology-news/less-downtime-more-insights-varian-smart-services

60) Levine DM, Ouchi K, Blanchfield B, et al. Hospital-level care at home for acutely ill adults: a pilot randomized controlled trial. *J Gen Intern Med.* 2018;33:729-736.

61) Brown B. Temperature Tracking Smart Patch Aids New Cancer Treatment Trials. 2021. Accessed July 4, 2022. https://healthtechinsider.com/2021/06/30/temperature-tracking-smart-patch-aids-new-cancer-treatment-trials/

62) Mallick MK, Biser S, Haridas A, et al. Improving dyspnoea symptom control of patients in palliative care using a smart patch – a proof of concept study. *Front Dig Health.* 2021;3:765867.

63) Neupane R, Boddu SHS, Abou-Dahech MS, et al. Transdermal delivery of chemotherapeutics: strategies, requirements, and opportunities. *Pharmaceutics.* 2021;13.

64) Gerami P, Yao Z, Polsky D, et al. Development and validation of a noninvasive 2-gene molecular assay for cutaneous melanoma. *J Am Acad Dermatol.* 2017;76:114-20.e2.

65) DermTech. 2022. Accessed July 4, 2022. https://dermtech.com/

66) Wong CK, Ho DTY, Tam AR, et al. Artificial intelligence mobile health platform for early detection of COVID-19 in quarantine subjects using a wearable biosensor: protocol for a randomised controlled trial. *BMJ Open.* 2020;10:e038555.

67) Tonse R, Ramamoorthy V, Rubens M, et al. Hospitalization rates from radiotherapy complications in the United States. *Sci Rep.* 2022;12:4371.

68) Pritchett JC, Borah BJ, Desai AP, et al. Association of a remote patient monitoring (RPM) program with reduced hospitalizations in cancer patients with COVID-19. *JCO Oncol Pract.* 2021;17:e1293-e302.

69) Smart Camera Integration in Machine Vision Systems. 2022. Accessed July 4, 2022. https://www.thomasnet.com/articles/automation-electronics/smart-camera-machine-vision-system/

70) Ashique KT, Kaliyadan F, Aurangabadkar SJ. Clinical photography in dermatology using smartphones: an overview. *Indian Dermatol Online J.* 2015;6:158-163.

71) Bhelonde A, Didolkar N, Jangale S, Kulkarni NL. Flexible wound assessment system for diabetic patient using android smartphone. 2015 International Conference on Green Computing and Internet of Things (ICGCIoT); 2015;466-469.

72) Rat C, Hild S, Rault Sérandour J, et al. Use of smartphones for early detection of melanoma: systematic review. *J Med Internet Res.* 2018;20:e135.

73) Das K, Cockerell CJ, Patil A, et al. Machine learning and its application in skin cancer. *Int J Environ Res Public Health.* 2021;18.

74) Wu Y, Chen B, Zeng A, Pan D, Wang R, Zhao S. Skin cancer classification with deep learning: a systematic review. *Front Oncol.* 2022;12:893972.

75) Thorpe J. Three ways healthcare can be improved with smart cameras. 2021. Accessed July 4, 2022. https://internationalsecurityjournal.com/healthcare-smart-cameras/

76) Laranjo L, Dunn AG, Tong HL, et al. Conversational agents in healthcare: a systematic review. *J Am Med Inform Assoc.* 2018;25:1248-58.

77) Teladoc Health and Amazon Team Up to Launch Teladoc on Alexa. 2022. Accessed July 4, 2022. https://www.teladochealth.com/newsroom/press/release/Teladoc-Health-and-Amazon-Team-Up-to-Launch-Teladoc-on-Alexa/

78) McDonald R. 'Alexa For Health Care': New Virtual Assistant Helps Patients with Cancer at Home. 2020. Accessed July 4, 2022. https://www.curetoday.com/view/alexa-for-health-care-new-virtual-assistant-helps-patients-with-cancer-at-home

79) Schwartz E. New Portable Smart Speaker Helps Oncologists Treat Cancer Patients. 2021. Accessed July 4, 2022. https://voicebot.ai/2021/01/19/new-portable-smart-speaker-helps-oncologists-treat-cancer-patients/

80) Baertsch M-A, Decker S, Probst L, et al. Convenient access to expert-reviewed health information via an Alexa voice assistant skill for patients with multiple myeloma: development study. *JMIR Cancer.* 2022;8:e35500.

81) Martinez-Martin N, Luo Z, Kaushal A, et al. Ethical issues in using ambient intelligence in health-care settings. *Lancet. Dig Health.* 2021;3:e115-e23.

82) Avendano JP, Gallagher DO, Hawes JD, et al. Interfacing with the electronic health record (EHR): a comparative review of modes of documentation. *Cureus.* 2022;14:e26330.

83) Plowman RS, Peters-Strickland T, Savage GM. Digital medicines: clinical review on the safety of tablets with sensors. *Expert Opin Drug Saf.* 2018;17:849-852.

84) Robbins R. A 'digital pill' for cancer patients is rolled out for the first time, in hopes of improving outcomes. 2019. Accessed July 4, 2022. https://www.statnews.com/2019/01/17/a-digital-pill-for-cancer-patients-is-rolled-out-for-the-first-time-in-hopes-of-improving-outcomes/

85) Landi H. From big deals to bankruptcy, a digital health unicorn falls short. Here's what other startups can learn from Proteus. 2020. Accessed July 4, 2022. https://www.fiercehealthcare.com/tech/from-billions-to-bankruptcy-proteus-digital-health-fell-short-its-promise-here-s-what-other

86) Siwicki B. Meditech and Google Health to collaborate on clinical search in Expanse EHR. 2022. Accessed July 4, 2022. https://www.healthcareitnews.com/news/meditech-and-google-health-collaborate-clinical-search-expanse-ehr

87) Tobore I, Li J, Yuhang L, et al. Deep learning intervention for health care challenges: some biomedical domain considerations. *JMIR Mhealth Uhealth.* 2019;7:e11966.

88) Morrison JJ, Hostetter J, Wang K, Siegel EL. Data-driven decision support for radiologists: re-using the national lung screening trial dataset for pulmonary nodule management. *J Dig Imag.* 2015;28:18-23.

89) Chen RC, Gabriel PE, Kavanagh BD, McNutt TR. How will big data impact clinical decision making and precision medicine in radiation therapy? *Int J Radiat Oncol Biol Phys.* 2016;95:880-884.

90) Chen G, Cui J, Qian J, et al. Rapid progress in intelligent radiotherapy and future implementation. *Cancer Investig.* 2022;40:425-436.

91) Netherton TJ, Cardenas CE, Rhee DJ, Court LE, Beadle BM. The emergence of artificial intelligence within radiation oncology treatment planning. *Oncology.* 2021;99:124-134.

92) Mesko B. Doctors Reject Support From A.I. – Here's Why. 2021. Accessed July 4, 2022. https://www.linkedin.com/pulse/doctors-reject-support-from-ai-heres-why-bertalan-mesk%C3%B3-md-phd/

93) Wan S, Gu Z, Ni Q. Cognitive computing and wireless communications on the edge for healthcare service robots. *Comp Com.* 2020;149:99-106.

94) Putte Dvd, Boumans R, Neerincx M, Rikkert MO, Mul Md. A social robot for autonomous health data acquisition among hospitalized patients: an exploratory field study. 2019 14th ACM/IEEE International Conference on Human-Robot Interaction (HRI); 2019;658-659.

95) Vijayakumar M, Shetty R. Robotic surgery in oncology. *Indian J Surg Oncol.* 2020;11:549-551.

96) Kwo L. Contributed: The power of AI in surgery. 2021. Accessed July 4, 2022. https://www.mobihealthnews.com/news/contributed-power-ai-surgery

97) Feizi N, Tavakoli M, Patel RV, Atashzar SF. Robotics and AI for teleoperation, tele-assessment, and tele-training for surgery in the era of COVID-19: existing challenges, and future vision. *Front Robot AI.* 2021;8:610677.

98) Finnegan J. Many Americans don't have a primary care doctor. 2017. Accessed July 4, 2022. https://www.fiercehealthcare.com/practices/many-americans-don-t-have-a-primary-care-doctor

99) Vickery DM, Kalmer H, Lowry D, Constantine M, Wright E, Loren W. Effect of a self-care education program on medical visits. *JAMA.* 1983;250:2952-2956.

100) Borycki E. Quality and safety in eHealth: the need to build the evidence base. *J Med Internet Res.* 2019;21:e16689.

101) Bates DW, Landman A, Levine DM. Health apps and health policy: What is needed? *JAMA.* 2018;320:1975-1976.

102) Chen CM, Jyan HW, Chien SC, et al. Containing COVID-19 among 627,386 persons in contact with the diamond princess cruise ship passengers who disembarked in Taiwan: big data analytics. *J Med Internet Res.* 2020;22:e19540.

103) Palmieri F, Ficco M, Pardi S, Castiglione A. A cloud-based architecture for emergency management and first responders localization in smart city environments. *Comput Elec Engin.* 2016;56:810-830.

104) Siddique S, Chow JCL. Artificial intelligence in radiotherapy. *Reports Pract Oncol Radiother.* 2020;25:656-666.

105) Song Y, Hu J, Wu Q, et al. Automatic delineation of the clinical target volume and organs at risk by deep learning for rectal cancer postoperative radiotherapy. *Radiother Oncol.* 2020;145:186-192.

106) Fung NTC, Hung WM, Sze CK, Lee MCH, Ng WT. Automatic segmentation for adaptive planning in nasopharyngeal carcinoma IMRT: time, geometrical, and dosimetric analysis. *Med Dosim.* 2020;45:60-65.

107) Han EY, Kim GY, Rebueno N, Yeboa DN, Briere TM. End-to-end testing of automatic plan optimization using RayStation scripting for hypofractionated multimetastatic brain stereotactic radiosurgery. *Med Dosim.* 2019;44:e44-e50.

108) McNutt TR, Moore KL, Wu B, Wright JL. Use of big data for quality assurance in radiation therapy. *Sem Rad Onc.* 2019;29:326-332.

109) Kalet AM, Luk SMH, Phillips MH. Radiation therapy quality assurance tasks and tools: the many roles of machine learning. *Med Phys.* 2020;47:e168-e77.

110) Global Internet of Things Policies 2018-2019. 2019. Accessed July 4, 2022. https://www.globenewswire.com/news-release/2019/05/30/1859482/0/en/Global-Internet-of-Things-Policies-2018-2019.html

111) Stasha S. Amazon Alexa Statistics, Facts, and Trends. 2021. Accessed July 4, 2022. https://policyadvice.net/insurance/insights/amazon-alexa-statistics/

112) Gagnon MP, Ngangue P, Payne-Gagnon J, Desmartis M. m-Health adoption by healthcare professionals: a systematic review. *J Am Med Inform Assoc.* 2016;23:212-220.

113) NIST. NIST Releases Draft Security Feature Recommendations for IoT Devices. 2019. Accessed July 4, 2022. https://www.nist.gov/news-events/news/2019/08/nist-releases-draft-security-feature-recommendations-iot-devices

114) Office of the National Coordinator for Health Information Technology. What Is FHIR? 2019. Accessed July 4, 2022. https://www.healthit.gov/sites/default/files/2019-08/ONCFHIRFSWhatIsFHIR.pdf

115) Samson LW TW, Turrini G, Sheingold S. Medicare Beneficiaries' Use of Telehealth in 2020: Trends by Beneficiary Characteristics and Location. 2020. Accessed July 4, 2022. https://www.aspe.hhs.gov/sites/default/files/documents/a1d5d810fe3433e18b192be42dbf2351/medicare-telehealth-report.pdf?_ga=2.263152908.1288477598.1638811694-1417522139.1637192937

The Evidence and Rationale for a Coronary Brachytherapy Dose-Response

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Abstract

Background: Multiple prospective, randomized trials have confirmed that vascular brachytherapy can prevent in-stent restenosis (ISR) after percutaneous coronary intervention (PCI). Although several observational studies suggest short-term effectiveness, the rate of long-term ISR after salvage intravascular brachytherapy (IVBT) is approximately 40% at 3 years' follow-up. While moderately effective, there is clearly room to improve IVBT.

Methods: We used the PubMed search engine with the terms *coronary, intravascular brachytherapy, dose,* and *response.*

Results: A positive dose-response relationship has been shown for IVBT, based on preclinical, retrospective and prospective randomized clinical trials. There has been remarkably little toxicity of IVBT, despite many thousands of patients being treated on and off trials. Considering the lack of reported complications despite meticulous follow-up of hundreds of patients enrolled in studies, it seems that coronary vessel tolerance to radiation may be higher than the current prescription doses.

Conclusion: Given the high rate of failure in patients with recurrent ISR, and a fairly consistent dose-response relationship in most studies, further clinical investigation of higher prescription doses seems warranted.

Keywords: radiation, oncology, coronary, brachytherapy, heart, cardiac, intravascular

Radiation is routinely used for a variety of noncancerous conditions, including keloids, heterotopic bone formation, Dupuytren's contracture, and arteriovenous malformations.[1-4] Its use against atherosclerotic vascular disease was first explored in the 1960s.[5] By the 1990s, intravascular brachytherapy (IVBT) techniques were developed to prevent restenosis after coronary angioplasty or stent placement.[6] At least 6 prospective, randomized trials have confirmed the clinical efficacy of IVBT, which reduces the restenosis rate from approximately 40% to 20%, depending on patient characteristics and the length of follow-up.[7-12]

For several years, brachytherapy was the most effective treatment to prevent restenosis inside coronary stents (**Figure 1**). Early studies were done with iridium-192 (Ir-192), a high-energy photon emitter. Strontium-90 (Sr-90), a pure beta emitter, was later adopted to limit shielding requirements. Retrospective and prospective randomized trials showed similar outcomes with Ir-192 vs Sr-90.[11,13]

Drug-eluting stents (DESs) were developed in the late 1990s. In 2 randomized studies, they proved somewhat more effective than brachytherapy for treating restenosis within bare-metal stents.[14,15] DES largely replaced IVBT for treatment of in-stent restenosis (ISR) after 2006.

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Disclosure: 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.

Although no study has compared IVBT for treatment of ISR specifically in DES, the convenience of stent placement led to their nearly universal adoption for ISR in DES.

First-time DESs have only about a 1% to 2% ISR rate of 1 year.[15] But patients who need a second DES for same-site ISR may have a 15% to 20% chance of developing a second restenosis at 1 year.[16] Factors that might account for a higher subsequent restenosis rate include drug resistance, metal hypersensitivity, stent underexpansion, barotrauma stent gap, and residual uncovered atherosclerotic plaque.[17] Additionally, subsequent restenosis becomes progressively more likely as additional stents-inside-stents are placed.[18,19] With an increasing chance of restenosis with more stent layers, the proper treatment for ISR of a DES has become a subject of some controversy.[20] Placing additional stents in an occluded DES has been the most common solution.

IVBT is a potential alternative to angioplasty alone or inserting additional stents inside of stenosed stents. Three retrospective, uncontrolled studies suggest that IVBT may be a preferable choice for recurrent ISR, with 1-year target lesion revascularization rates of 10% to 20.[21-23] These studies have led to a gradual resurgence of IVBT for patients with a second episode of ISR. IVBT was available in 45 US institutions as of 2020 (Best Vascular, email, August 29, 2022).

Although several observational studies suggest short-term effectiveness, the rate of late ISR after salvage IVBT remains up to 40% at 3 years, and potentially higher with longer follow-up (**Figure 2**).[22] While moderately effective, there is clearly room to improve IVBT for multiple-recurrent ISR inside of DESs. As part of an effort to improve our institution's program, we reviewed the published literature regarding a dose-response relationship for IVBT.

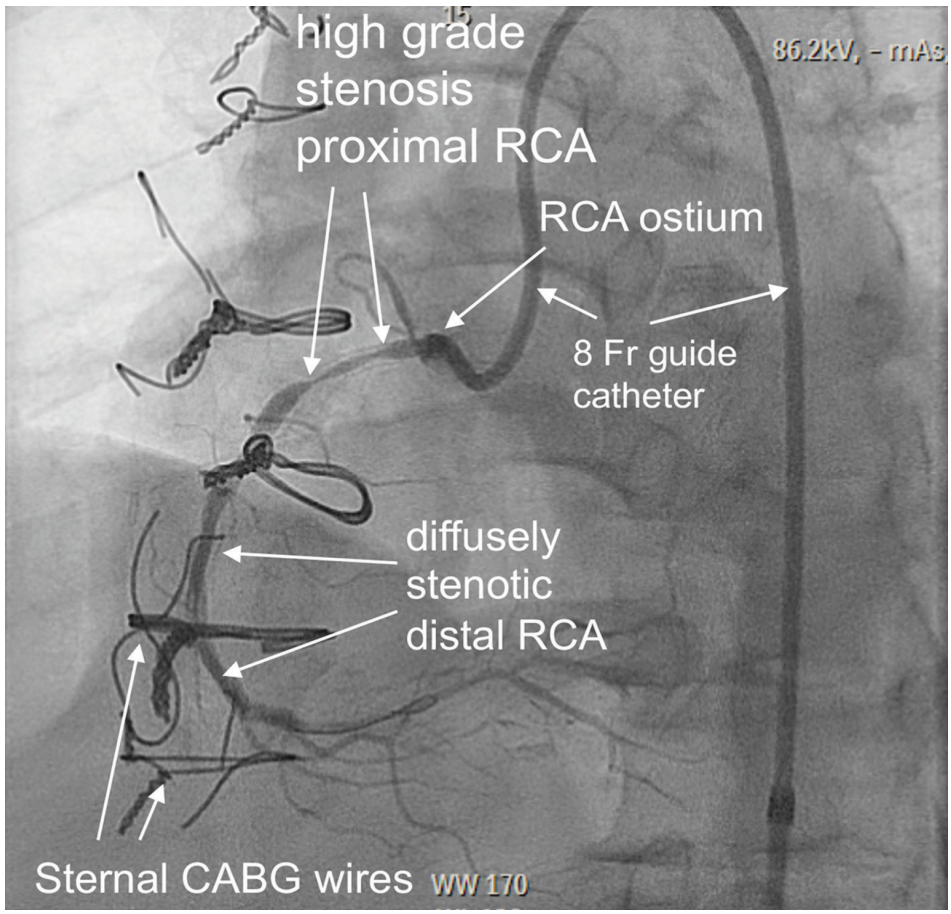

Figure 1. Example of short stenotic lesion involving the proximal right coronary artery (RCA). Note the myriad pathologies in addition to the stenotic lesion. CABG = coronary artery bypass graft.

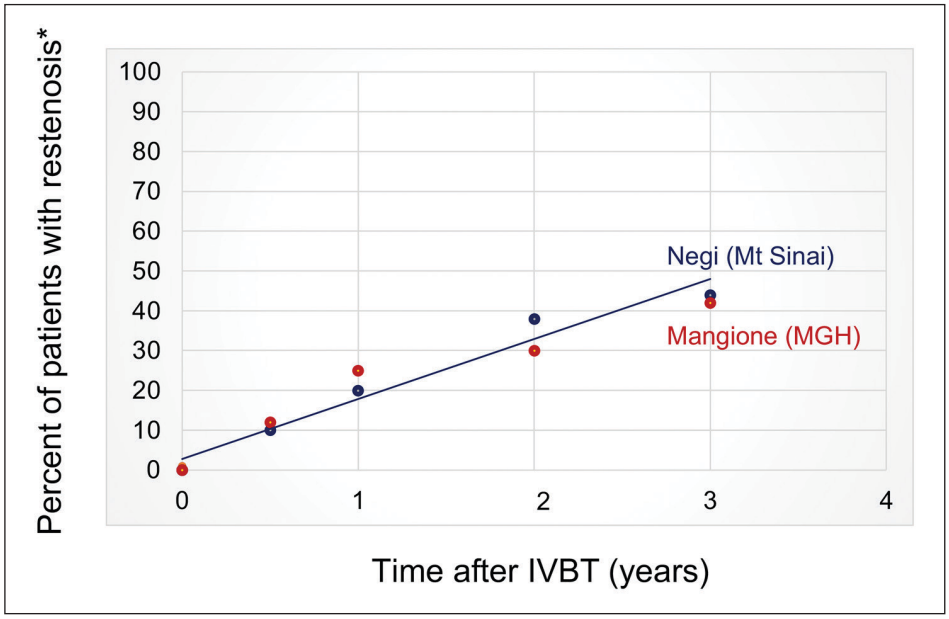

Figure 2. The target vessel revascularization (TVR) rate after intravascular brachytherapy (IVBT) increased to approximately 40% at 3 years in the 2 series with longest follow-up. It appears likely to continue increasing thereafter. *Restenosis was defined as target vessel revascularization. MGH = Massachusetts General Hospital.

Table 1. Preclinical Studies Addressing IVBT Dose-Response in Animals

AUTHOR	MODEL	RADIATION SOURCE	DOSE TESTED	ENDPOINT	DOSE-RESPONSE
Waksman (1995)[41]	Swine	Sr-90	7-56 Gy	Neointima formation	Yes
Verin (1995)[53]	Rabbits	Y-90	6-18 Gy	Stenosis	Yes
Weinberger (1996)[40]	Swine	Ir-192	10-20 Gy	Neointima formation	Yes (?)
Mazur (1996)[39]	Swine	Ir-192	10-25 Gy	Intimal proliferation	Yes (?)
Waksman (1997)[54]	Swine	Sr-90/Ir-192	14, 28 Gy	Cell proliferation	Yes
Carter (1999)[55]	Swine	P-32		Neointima	Yes
Kaluza (2001)[56]	Swine	P-32	7-36 Gy	Neontimal growth	Yes

Table 2. Clinical Studies Addressing Dose-Response in Humans

AUTHOR (YEAR)	PATIENTS	RADIATION SOURCE	RANDOMIZED	DOSES TESTED	DOSE-RESPONSE
Teirstein (1998)[42]	52	Ir-192	No	< 8 Gy and > 8 Gy	Yes
Coen (2000)[51]		variable	No	various	?
Albiero (2000)[57]	82	P-32	No	0.75 uCi-12.0 uCi	Yes
Witkowski (2000)[46]	48	P-32	Yes	20 Gy (?)	Yes
Sabate (2000)[43]	18	Sr-90	No	adventitial D90	Yes
Verin (2001)[47]	181	Sr-90	Yes	9, 12, 15,18 Gy	Yes
Ahmed (2001)[58]	180	Ir-192	No	15 vs 18 Gy	Yes
Morino (2002)[44]	30	Sr-90	No	18 vs 23 Gy	No
Singh (2004)[45]	42	Sr-90, Ir-192	No	< 8.4 Gy and > 8.4 Gy	Yes
Kuchulakanti (2005)[59]	167	Ir-192	No	18 vs 21 Gy	No
Price (2006)[26]	336	Ir-192	Yes	14 vs 17 Gy	Yes

Methods

We used the PubMed search engine with the terms *coronary, intravascular brachytherapy, dose,* and *response*. The search yielded 104 articles or abstracts, 90 of which dealt with coronary brachytherapy. Of those, only 4 mentioned dose-response in the title or keywords. Starting with those, we were able to identify a total of 15 publications that considered some aspect of a dose-response relationship. The 15 studies are listed in **Tables 1 and 2**.

Radionuclides and Delivery Systems

Clinical studies primarily employed catheter-based temporary delivery systems, using Ir-192 or Sr-90 (**Table 3**). A wide variety of other isotopes and delivery systems have been considered for development, but were not extensively pursued.[24] To minimize shielding requirements, the beta-emitting Sr-90 source system has been universally adopted (for now).[25] Clinical studies verified comparable outcomes with gamma or beta sources.[13,26]

Table 3. Isotopes Used (Extensively) Clinically for IVBT[24]

ISOTOPE	PRIMARY (THERAPEUTIC) DECAY MODE	HALF LIFE	AVERAGE ENERGY
Ir-192	Gamma	74 days	0.375 MeV
Sr-90*	Beta (pure)	28 years	0.970 MeV
P-32	Beta (pure)	14 days	0.695 MeV

**Sr-90 is also referred to as Sr-90/Y-90.*

Murky Dosimetry

While there is substantial in vivo evidence of a dose-response relationship for IVBT (see below), myriad impediments remain to our understanding and manipulation of the relationship, starting with uncertainty over the intended radiation target(s), and the dose actually delivered to that target.

Smooth muscle cells (SMCs) or their progenitors are generally believed to be the effectors of restenosis.[27-29] Labeling studies in pigs have shown that vascular damage (catheter-based stretching or plaque destruction) induces SMC migration from the outer to the inner vascular wall, where they generate an extracellular matrix,

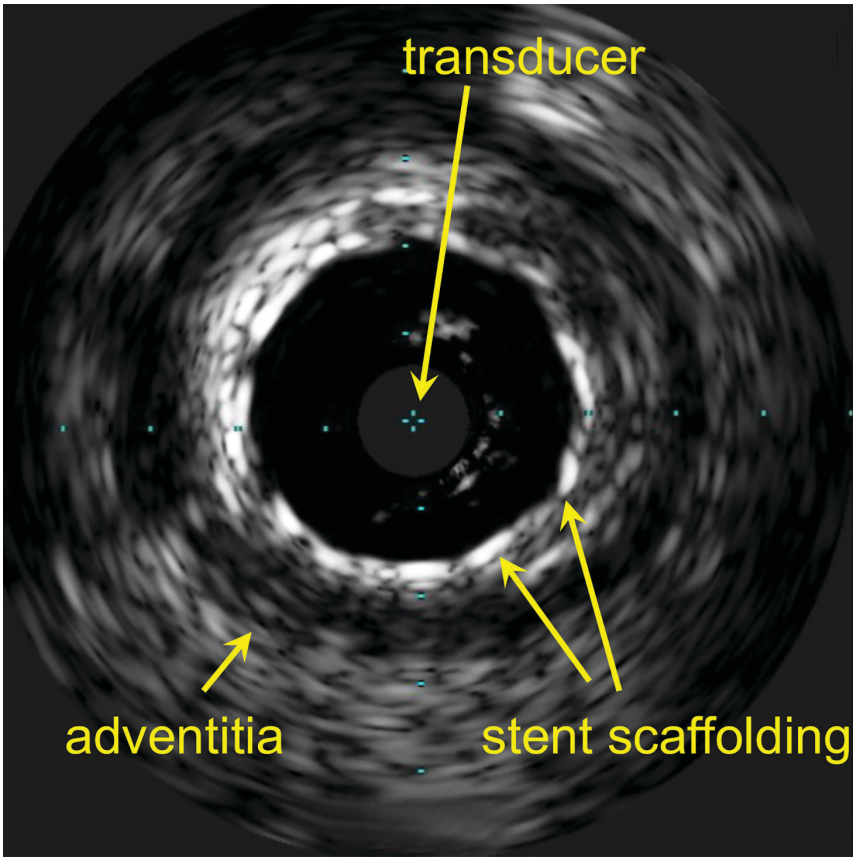

Figure 3. In situ stent lattice visible on intravascular ultrasound (IVUS). Calcium deposits are often visible on IVUS, permitting quasi-quantitative identification. As with ultrasound in general, a bit of imagination often aids image interpretation.

leading to neointimal build-up and repeat occlusion. It is generally held that radiation prevents re-occlusion by limiting SMC migration.[25] The simplest mechanistic explanation is that the outer vascular wall is the radiation target, being the site of resting SMCs. However, it is unclear whether radiation's antistenotic effect is a result of direct action on SMCs. Postradiation SMCs do not exhibit apoptosis, suggesting that direct radiation killing is not the mechanism by which radiation works.[25] Instead, the anti-ISR effect may be mediated by radiation-induced cytokine release.[27,30]

In addition to questions about the actual radiation target, there is substantial uncertainty regarding geographic dose distribution within the vessel wall. Compared with external beam techniques, the quantification of IVBT doses is crude, complicated and undoubtedly inaccurate. By its nature, brachytherapy's rapid dose fall-off leads to extreme heterogeneity longitudinally and circumferentially across the vessel wall, exacerbated by stents and calcium.[31,32]

Metal stents and calcium deposits both interfere with radiation penetration of the vessel wall.[33,34] Stent lattice decreases dose transmission by approximately 20% to 30% behind the metal lattice itself.[33-35] And patients commonly have had additional stents-within-stents to treat prior sites of restenosis, so the cumulative dose reduction could be far greater and complex.

Coronary calcifications also diminish dose transmission through the vessel walls. The thickness of calcium is typically highly variable along the vessel. In a heavily calcified section, the adventitial beta dose could easily be reduced twofold.[33]

Quantifying and correcting for dose perturbations in atherosclerotic vessels is further hindered by the lack of high-quality imaging. Intravascular ultrasound (IVUS) or optical coherence tomography (OCT) are the most common modalities used. IVUS gives a fair image of vessel wall thickness in healthier vessels.[36] However, metal stents and thick calcium deposits are poorly imaged, at best (**Figure 3**).

Geometric Obstacles

In addition to interference by stents and calcium, geometric factors substantially alter vessel wall doses. The rapid dose fall-off of Sr-90 beta leads to dramatic dose inhomogeneity in the confines of a 4-mm diameter coronary artery. There is approximately a 50% dose fall-off over 1 mm of tissue, about the thickness of a coronary vessel wall.[31] Source wire asymmetry inside the vessel exacerbates fall-off by increasing dose to the near wall and decreasing dose to the far wall (**Figure 4**).[37] Additionally,

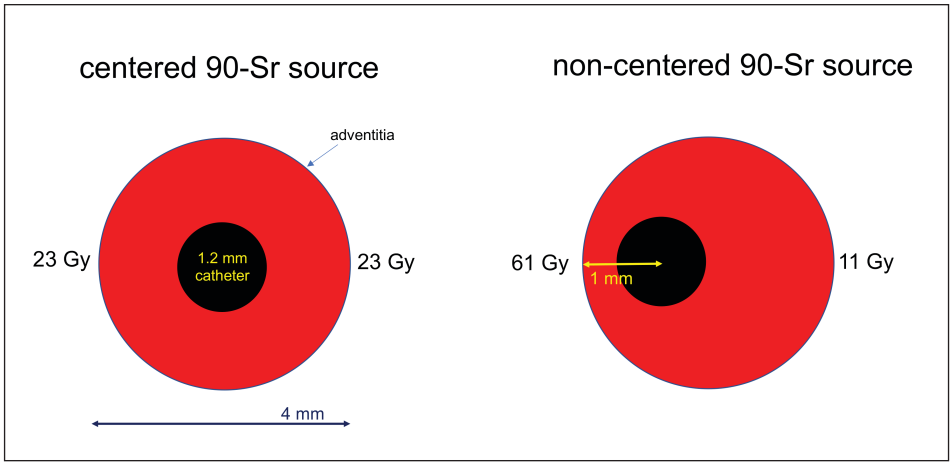

Figure 4. Schematic showing marked dose asymmetry at the outer vessel wall, which occurs with 90-Sr source train asymmetry inside the vessel.

asymmetry is exacerbated by vessel curvature.[32,35]

Taken together, rapid dose fall-off, stents, calcium, suboptimal imaging and source asymmetry lead to great uncertainty about minimal (or maximal) doses to the vessel wall.[31] Considering the doses employed over the narrow range of 10 to 25 Gy, these dose-lowering effects might significantly limit the effect of IVBT – or maybe not.

Does Dose Matter?

Where radiation is used against benign disease, a dose-response relationship is typically demonstrable. Conditions for which a relationship has been established include keloids and arteriovenous malformations.[1,2] Similarly, a positive dose-response relationship has generally been shown for IVBT based on preclinical, retrospective and prospective randomized clinical trials (see below). Additionally, smooth muscle cellularity is decreased in a DES vs bare-metal stent, a phenomenon that might render DES ISR less sensitive to radiation inhibition.[38] Accordingly, a dearth of SMCs might require a higher radiation dose to disrupt SMC-based restenosis.

Animal Models

There are at least 8 pre-clinical animal studies of Ir-192 or Sr-90 IVBT to prevent restenosis, 3 of which investigated a dose-response relationship.[25] The results are mixed. In one of the earliest pre-clinical IVBT dose-response studies, Mazur and colleagues used a miniature swine coronary overstretch model to search for an Ir-192 dose-response for maintaining coronary patency. For such studies, the coronary vessels are damaged by overdilation with a balloon or wire stent, preceded or followed by intravascular radiation. Their results were inconclusive. Brachytherapy's anti-stenotic effect for the left anterior descending artery increased steadily from 10 to 25 Gy at 1.5 mm from the source center. However, results were mixed for the right coronary artery (RCA) and circumflex (Cx).[39]

Weinberger and colleagues, also using a miniature swine model, showed increased inhibition of neointima as the dose was increased from 15 to 20 Gy (Ir-192, at the "vessel wall"). A dose of 10 Gy was associated with accelerated stenosis, a puzzling phenomenon of some concern.[40] A stimulatory effect of lower doses has not been consistently reported by other investigators and may have been an artifact

In the largest pre-clinical study, Waksman and colleagues studied 42 swine treated to doses ranging from 7 Gy to 56 Gy (Sr-90 at 2 mm from center). There was a progressive loss of maximal intimal thickness from 7 Gy to 56 Gy, with no clear limit to the anti-stenotic effect with increasing dose (**Figure 5**).[41] There was only 1 animal in each of the 2 highest dose groups, making the statistical validity uncertain.

Retrospective Clinical Studies

Two retrospective human studies have also revealed an IVBT dose-response relationship. Teirstein and colleagues analyzed the relationship between vessel wall doses and restenosis in a prospective placebo-controlled study, using Ir-192 for ISR of bare-metal stents.[42] Their nominal prescription dose was planned for 8 Gy to the most distal vessel wall, governed by a maximum dose of 30 Gy to any point on the inner vessel wall (intima). Sixteen patients received a minimal dose less than 8 Gy to the outer wall due to the 30 Gy intimal dose constraint. There was no demonstrable treatment effect in patients with a minimum vessel wall dose below 8 Gy ($P = 0.72$). Patients whose outer coronary wall received at least 8 Gy minimum did show a trend to a beneficial treatment effect ($P = 0.081$).

Sabate and colleagues looked retrospectively at vessel wall Sr-90 doses, showing lesser plaque build-up in patients with a higher adventitial dose.[43] Their method of calculating the integral dose to the adventitia is not readily comparable to the point doses used by other investigators. Despite

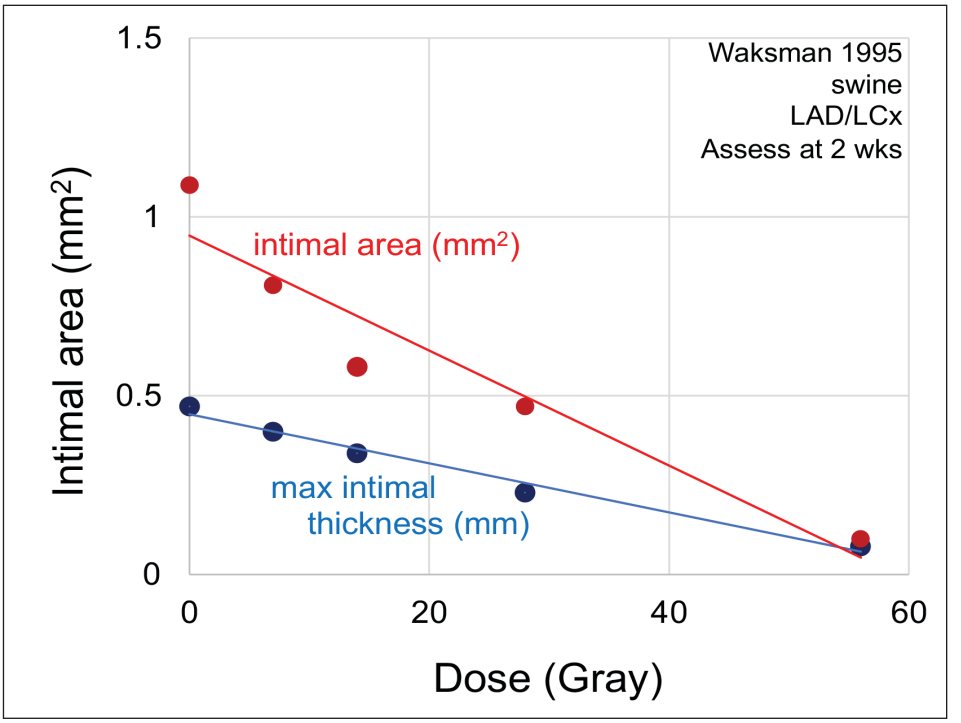

Figure 5. The intimal area and the maximal intimal thickness – parameters that reflect restenosis – were increasingly diminished with higher intravascular brachytherapy (IVBT) doses in swine.

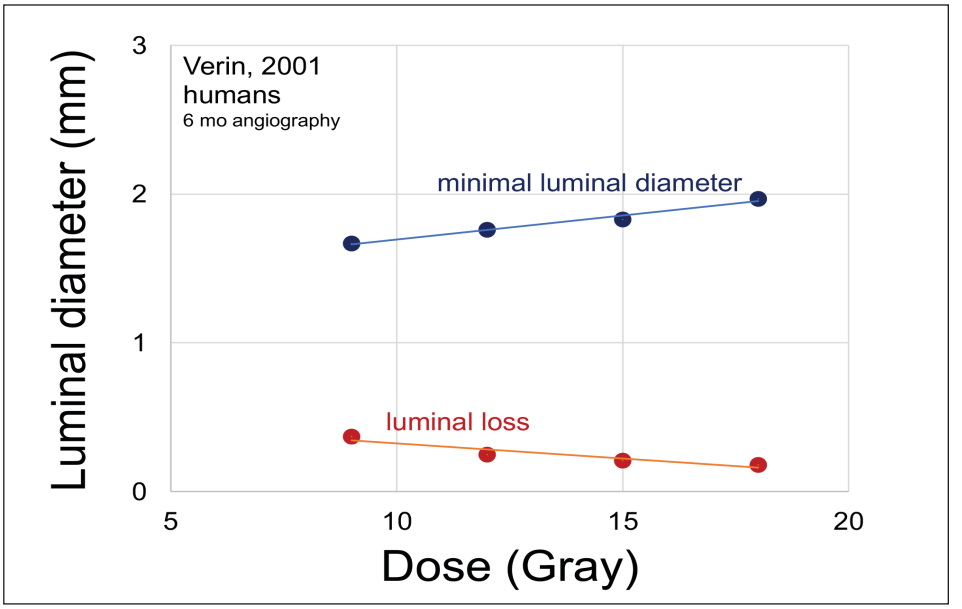

Figure 6. The minimal luminal diameter and the luminal loss – parameters that reflect restenosis – were steadily improved with higher doses of intravascular brachytherapy (IVBT) in humans.

the noncomparable dose calculation methodologies and endpoints, the Teirstein and Sabate studies were consistent in suggesting a positive clinical dose-response relationship.

Other investigators have compared more sophisticated imaging-based dose metrics with revascularization success.[44-46] While these efforts point to future methodology, interpretation of the studies is hampered by the poorly defined geometric and compositional complexity of the diseased vascular wall.

Prospective Clinical Studies

In a meticulous prospective clinical dose-response study, Verin and colleagues randomized 183 patients with de novo stenosis to Sr-90 doses of 9, 12, 15 and 18 Gy at 1 mm tissue depth. The percent of stenosis after intervention was in a narrow range of 31% to 33% among the 4 groups. Patients did not receive long-term dual antiplatelet therapy. Regardless, higher radiation doses led to progressively greater minimal luminal diameter at 6-month follow-up (**Figure 6**).[47]

Multiple angiographic indices of restenosis were increasingly improved with higher IVBT doses. There was no consistent indication of a maximal response, up to 18 Gy.

Price and colleagues randomized 336 patients to 14 vs 17 Gy (Ir-192 at 2 mm from source) for bare-metal stent ISR. The average postintervention stenosis was 37% and 35% in the 14 Gy and 17 Gy groups, respectively. Patients who received a new stent at the time of irradiation were placed on long-term dual antiplatelet therapy. At 8-month follow-up angiography, minimal luminal diameter was 1.48 for patients treated to 17 Gy vs 1.32 mm for those treated to 14 Gy ($P = 0.007$). In-stent stenosis as a percent of the luminal diameter decreased from 46% to 37% with the higher radiation dose ($P = 0.009$). Overall adverse cardiac events decreased from 28% to 17% in patients who received the higher dose ($P = 0.018$).[26]

Like the retrospective studies, the 2 prospective randomized clinical studies are not readily comparable, as they used different source types (Sr-90 vs Ir-192), dose specification (1 vs 2 mm from center) and endpoints. Nonetheless, they both showed a consistent relationship between higher prescription dose and greater effectiveness at preventing restenosis. Not known is whether prescription doses higher than the currently used 18 to 23 Gy are more effective (and safe). Had the popularity of IVBT not plummeted abruptly with the introduction of DES, the upper limit of the dose-response would likely have been studied years ago.

Does Dosimetry Matter?

It is hard to reconcile the extreme technical challenges of IVBT dosimetry with the surprisingly consistent clinical evidence of effectiveness and of a dose-response relationship. Even though we cannot quantify the dose well, the procedure works, and there *is* a dose-response relationship. Perhaps precise dosimetry is not necessary.

In planning radiation therapy treatments, great effort is made to achieve dose uniformity, with the intention of delivering a minimal tumoricidal dose to all potential sites of malignant cells. If the antistenotic effect of IVBT were analogous to cancer eradication, dose perturbations behind metal stent lattice and calcium deposits would severely limit its effectiveness. But dosimetric goals may be different for vascular brachytherapy. If cytokine perturbations rather than direct SMC killing are the mechanism of radiation-suppressed restenosis, dose heterogeneity may not be so important.

The generation of effector cytokines in higher-dosed parts of the vessel wall would presumably not be substantially compromised by dose heterogeneity. And cytokine diffusion within the vessel wall could minimize the effect of radiation dose inhomogeneity resulting from stents, calcium and source asymmetry. In other words, underdosed areas in the vessel wall would not limit radiation effectiveness in the way that underdosed regions can spare cancer cells. This could explain the consistent effectiveness and dose responsiveness of IVBT despite the heterogeneous, unpredictable dosimetry. It would also still allow for a dose-response relationship, despite unpredictable dosimetry, and would be a rationale for increasing the current prescription dose(s).

Are Higher Prescription Doses Safe?

Despite early animal studies predicting late radiation injury, remarkably little clinically evident toxicity has been reported after IVBT.[48] There were early reports of excessive late thrombosis after IVBT, leading to longer use of dual antiplatelet therapy (DAPT). DAPT may decrease the late thrombosis rate, at least in patients who have additional stents placed at the time of IVBT.[49,50] In current practice, placement of additional stents at the time of IVBT is not routine, but use of prolonged DAPT is commonly recommended.

Candado and colleagues raised some early concern about vessel tolerance when they reported a pseudoaneurysm in a series of 19 patients.[6] It was not clear if the aneurysm was related to radiation or the angioplasty procedure. Regardless, no reports of excessive or unusual radiation-related complications have emerged, despite many thousands of patients being treated on and off trials. Nor have reports from multiple series suggested a higher incidence of major cardiac events in IVBT patients compared with those treated with angioplasty or repeat stenting. With higher doses used in some series, radiation-related complications have not emerged. Coen and colleagues treated 28 patients with 28 to 42 Gy prescription doses (P-32 at 2 mm from the source center), substantially higher than the current 18 to 23 Gy typically prescribed with Sr-90. They did not report excess toxicity.[51]

More reassuring of the safety of higher doses is a re-treatment series published by Waksman and colleagues.[52] They retreated 51 patients with a second IVBT, 6 months or more after an initial IVBT, with no apparent complications. Even a doubling of dose by adding a second treatment seems to not be accompanied by complications, again suggesting that doses well above the current maximum of 18 to 23 Gy are relatively safe. Considering the lack of reported complications despite meticulous follow-up of hundreds of patients enrolled in studies, it seems likely that coronary vessel tolerance to radiation is higher than the current 18 to 23 Gy. Just how much higher the prescription doses can safely go to is a matter of conjecture, considering the lack of radiation-related complications to date.

Conclusion – Where to From Here?

Despite dosimetric uncertainties, coronary brachytherapy has repeatedly proven effective, decreasing restenosis by half.[7] This effectiveness comes despite the unavoidable dose uncertainties and inhomogeneities with current technology. But considering the 40% recurrence rate at 3 years, there is clearly room for improvement. Better methods to tailor dose delivery to individual patients' vessel walls seem possible, and may offer increased effectiveness.[35]

In summary, dose-response studies mostly point to increasing effect with increasing dose. Prior investigators have not found an upper limit to the dose-response relationship, and there have been remarkably few complications at current doses. Despite far-from-perfect dosimetry, it seems that the most logical, simple way to increase IVBT effectiveness is by increasing the prescription dose or prescription depth, even using the crude system we have now. Given the high rate of target lesion failure in patients with recalcitrant, recurrent in-stent restenosis, the paucity of options for such patients, and the modest benefit of current brachytherapy protocols, further clinical studies with higher prescription doses seem warranted. The authors choose not to speculate specifically at this time as to how high the doses should be raised. However, a substantial increase would seem justifiable, given the lack of clinically evident complications with current doses.

References

1) Flickinger JC, Pollock BE, Kondziolka D, Lunsford LD. A dose-response analysis of arteriovenous malformation obliteration after radiosurgery. *Int J Radiat Oncol Biol Phys.* 1996;36(4):873-879.

2) Kal HB, Veen RE, Jurgenliemk-Schulz IM. Dose-effect relationships for recurrence of keloid and pterygium after surgery and radiotherapy. *Int J Radiat Oncol Biol Phys.* 2009;74(1):245-251.

3) de Haan A, van Nes JGH, Werker PMN, Langendijk JA, Steenbakkers R. Radiotherapy for patients with Ledderhose disease: long-term effects, side effects and patient-rated outcome. *Radiother Oncol.* 2022;168:83-88.

4) Popovic M, Agarwal A, Zhang L, et al. Radiotherapy for the prophylaxis of heterotopic ossification: a systematic review and meta-analysis of published data. *Radiother Oncol.* 2014;113(1):10-17.

5) Friedman M, Felton L, Byers S. The antiatherogenic effect of iridium-192 upon the cholesterol-fed rabbit. *J Clin Invest.* 1964;43:185-192.

6) Condado JA, Waksman R, Gurdiel O, et al. Long-term angiographic and clinical outcome after percutaneous transluminal coronary angioplasty and intracoronary radiation therapy in humans. *Circulation.* 1997;96(3):727-732.

7) Bhargava B, Tripuraneni P. Role of intracoronary brachytherapy for in-stent restenosis? *Lancet.* 2002;359(9306):543-544.

8) Teirstein PS, Massullo V, Jani S, et al. Catheter-based radiotherapy to inhibit restenosis after coronary stenting. *N Engl J Med.* 1997;336(24):1697-1703.

9) Leon MB, Teirstein P, Moses JW. Localized intracoronary gamma-radiation therapy to inhibit the recurrence of restenosis after stenting. *N Engl J Med.* 2001;344:250-256.

10) Waksman R, White LR. intracoronary gamma radiation therapy after angioplasty inhibits recurrence in patients with in-stent restenosis. *Circulation.* 2000;101:2165-2171.

11) Popma JJ, Suntharalingam M, Lansky AJ, et al. Randomized trial of 90Sr/90Y beta-radiation versus placebo control for treatment of in-stent restenosis. *Circulation.* 2002;106(9):1090-1096.

12) Waksman R, Raizner AE, Yeung AC, Lansky A. Use of localised intracoronary beta radiatoion in treatment of in-stent restenosis: the INHIBIT randomised controlled trial. lancet. 2002;359:551-557.

13) Shirai K, Lansky AJ, Mintz GS, et al. Comparison of the angiographic outcomes after beta versus gamma vascular brachytherapy for treatment of in-stent restenosis. *Am J Cardiol.* 2003;92(12):1409-1413.

14) Holmes DR, Jr., Teirstein P, Satler L, et al. Sirolimus-eluting stents vs vascular brachytherapy for in-stent restenosis within bare-metal stents: the SISR randomized trial. *JAMA.* 2006;295(11):1264-1273.

15) Stone GW, Ellis SG, O'Shaughnessy CD, et al. Paclitaxel-eluting stents vs vascular brachytherapy for in-stent restenosis within bare-metal stents: the TAXUS V ISR randomized trial. *JAMA.* 2006;295(11):1253-1263.

16) Mehilli J, Byrne RA, Tiroch K, et al. Randomized trial of paclitaxel- versus sirolimus-eluting stents for treatment of coronary restenosis in sirolimus-eluting stents: the ISAR-DESIRE 2 (Intracoronary Stenting and Angiographic Results: Drug Eluting Stents for In-Stent Restenosis 2) study. *J Am Coll Cardiol.* 2010;55(24):2710-2716.

17) Dangas GD, Claessen BE, Caixeta A, Sanidas EA, Mintz GS, Mehran R. In-stent restenosis in the drug-eluting stent era. *J Am Coll Cardiol.* 2010;56(23):1897-1907.

18) Raber L, Juni P, Loffel L, et al. Impact of stent overlap on angiographic and long-term clinical outcome in patients undergoing drug-eluting stent implantation. *J Am Coll Cardiol.* 2010;55(12):1178-1188.

19) Cheneau E, Wu Z, Leborgne L, et al. Additional stenting promotes intimal proliferation and compromises the results of intravascular radiation therapy: an intravascular ultrasound study. *Am Heart J.* 2003;146(1):142-145.

20) Siontis GC, Stefanini GG, Mavridis D, et al. Percutaneous coronary interventional strategies for treatment of in-stent restenosis: a network meta-analysis. *Lancet.* 2015;386(9994):655-664.

21) Negi SI, Torguson R, Gai J, et al. Intracoronary brachytherapy for recurrent drug-eluting stent failure. *Cardiovasc Interv.* 2016;9(12):1259-1265.

22) Mangione FM, Jatene T, Badr Eslam R, et al. Usefulness of intracoronary brachytherapy for patients with resistant drug-eluting stent restenosis. *Am J Cardiol.* 2017;120(3):369-373.

23) Varghese MJ, Bhatheja S, Baber U, et al. Intravascular brachytherapy for the management of repeated multimetal-layered drug-eluting coronary stent restenosis. *Circ Cardiovasc Interv.* 2018;11(10):e006832.

24) Chiu-Tsao ST, Schaart DR, Soares CG, Nath R, No ATPCTG. Dose calculation formalisms and consensus dosimetry parameters for intravascular brachytherapy dosimetry: recommendations of the AAPM Therapy Physics Committee Task Group No. 149. *Med Phys.* 2007;34(11):4126-4157.

25) Sims EC, Rothman MT, Warner TD, Powell ME. Coronary artery brachytherapy. *Clin Oncol.* 2002;14(4):313-326.

26) Price MJ, Moses JW, Leon MB, et al. A multicenter, randomized, dose-finding study of gamma intracoronary radiation therapy to inhibit recurrent restenosis after stenting. *J Invasive Cardiol.* 2006;18(4):169-173.

27) Rubin P, Williams JP, Riggs PN, et al. Cellular and molecular mechanisms of radiation inhibition of restenosis. Part I: role of the macrophage and platelet-derived growth factor. *Int J Radiat Oncol Biol Phys.* 1998;40(4):929-941.

28) Casscells W. Migration of smooth muscle and endothelial cells. Critical events in restenosis. *Circulation.* 1992;86(3):723-729.

29) Wilcox JN, Waksman R, King SB, Scott NA. The role of the adventitia in the arterial response to angioplasty: the effect of intravascular radiation. *Int J Radiat Oncol Biol Phys.* 1996;36(4):789-796.

30) Scott NA. Restenosis following implantation of bare metal coronary stents: pathophysiology and pathways involved in the vascular response to injury. *Adv Drug Deliv Rev.* 2006;58(3):358-376.

31) DeCunha J, Janicki C, Enger SA. A retrospective analysis of catheter-based sources in intravascular brachytherapy. *Brachytherapy.* 2017;16(3):586-596.

32) DeCunha JM, Enger SA. A new delivery system to resolve dosimetric issues in intravascular brachytherapy. *Brachytherapy.* 2018;17(3):634-643.

33) Li XA, Wang R, Yu C, Suntharalingam M. Beta versus gamma for catheter-based intravascular brachytherapy: dosimetric perspectives in the presence of metallic stents and calcified plaques. *Int J Radiat Oncol Biol Phys.* 2000;46(4):1043-1049.

34) Fan P, Chiu-Tsao ST, Patel NS, et al. Effect of stent on radiation dosimetry in an in-stent restenosis model. *Cardiovasc Radiat Med.* 2000;2(1):18-25.

35) Li XA, O'Neill M, Suntharalingam M. Improving patient-specific dosimetry for intravascular brachytherapy. *Brachytherapy.* 2005;4(4):291-297.

36) Carlier SG, Coen VL, Sabate M, et al. The role of intravascular ultrasound imaging in vascular brachytherapy. *Int J Cardiovasc Intervent.* 2000;3(1):3-12.

37) Sehgal V, Li Z, Palta JR, Bolch WE. Dosimetric effect of source centering and residual plaque for beta-emitting catheter based intravascular brachytherapy sources. *Med Phys.* 2001;28(10):2162-2171.

38) Byrne RA, Joner M, Kastrati A. Stent thrombosis and restenosis: what have we learned and where are we going? The Andreas Gruntzig Lecture ESC 2014. *Eur Heart J.* 2015;36(47):3320-3331.

39) Mazur W, Ali MN, Khan MM, et al. High dose rate intracoronary radiation for inhibition of neointimal formation in the stented and balloon-injured porcine models of restenosis: angiographic, morphometric, and histopathologic analyses. *Int J Radiat Oncol Biol Phys.* 1996;36(4):777-788.

40) Weinberger J, Amols H, Ennis RD, Schwartz A, Wiedermann JG, Marboe C. Intracoronary irradiation: dose response for the prevention of restenosis in swine. *Int J Radiat Oncol Biol Phys.* 1996;36(4):767-775.

41) Waksman R, Robinson KA, Crocker IR, et al. Intracoronary low-dose beta-irradiation inhibits neointima formation after coronary artery balloon injury in the swine restenosis model. *Circulation.* 1995;92(10):3025-3031.

42) Teirstein PS, Massullo V, Jani S, et al. A subgroup analysis of the Scripps Coronary Radiation to Inhibit Proliferation Post-stenting Trial. *Int J Radiat Oncol Biol Phys.* 1998;42(5):1097-1104.

43) Sabate M, Marijnissen JP, Carlier SG, Kay IP, van der Giessen WJ, Coen VL, et al. Residual plaque burden, delivered dose, and tissue composition predict 6-month outcome after balloon angioplasty and beta-radiation therapy. *Circulation.* 2000;101(21):2472-2477.

44) Morino Y, Kaneda H, Fox T, et al. Delivered dose and vascular response after beta-radiation for in-stent restenosis: retrospective dosimetry and volumetric intravascular ultrasound analysis. *Circulation.* 2002;106(18):2334-2339.

45) Singh HS, Yue N, Azimi N, Nath R, Roberts KB, Pfau S. Relation of clinical success in coronary brachytherapy to dose. *Am J Cardiol.* 2004;94(7):847-852.

46) Witkowski A, Chmielak Z, Kalinczuk L, et al. Optimization of dose prescription protocol and its impact on delivered dose and vascular response after beta-radiation for in-stent restenosis. A randomized trial with serial volumetric intravascular ultrasound and dose volume histograms. *Cardiovasc Revasc Med.* 2006;7(1):34-40.

47) Verin V, Popowski Y, de Bruyne B, et al. Endoluminal beta-radiation therapy for the prevention of coronary restenosis after balloon angioplasty. The Dose-Finding Study Group. *N Engl J Med.* 2001;344(4):243-249.

48) Powers BE, Thames HD, Gillette EL. Long-term adverse effects of radiation inhibition of restenosis: radiation injury to the aorta and branch arteries in a canine model. *Int J Radiat Oncol Biol Phys.* 1999;45(3):753-759.

49) Costa MA, Sabate M, van der Giessen WJ, et al. Late coronary occlusion after intracoronary brachytherapy. *Circulation.* 1999;100(8):789-792.

50) Waksman R, Ajani AE, White RL, et al. Two-year follow-up after beta and gamma intracoronary radiation therapy for patients with diffuse in-stent restenosis. *Am J Cardiol.* 2001;88(4):425-428.

51) Coen VL, Knook AH, Wardeh AJ, et al. Endovascular brachytherapy in coronary arteries: the Rotterdam experience. *Cardiovasc Radiat Med.* 2000;2(1):42-50.

52) Waksman R, Lew R, Ajani AE, et al. Repeat intracoronary radiation for recurrent in-stent restenosis in patients who failed intracoronary radiation. *Circulation.* 2003;108(6):654-656.

53) Verin V, Popowski Y, Urban P, et al. Intra-arterial beta irradiation prevents neointimal hyperplasia in a hypercholesterolemic rabbit restenosis model. *Circulation.* 1995;92(8):2284-2290.

54) Waksman R, Rodriguez JC, Robinson KA, et al. Effect of intravascular irradiation on cell proliferation, apoptosis, and vascular remodeling after balloon overstretch injury of porcine coronary arteries. *Circulation.* 1997;96(6):1944-1952.

55) Carter AJ, Scott D, Bailey L. Dose-response effects of 32P radioactive stents in an atherosclerotic porcine coronary model. *Circulation.* 1999;100(14):1548-1554.

56) Kaluza GL, Raizner AE, Mazur W, et al. Dose-response study of intracoronary beta-radiation with 32P in balloon- and stent-injured coronary arteries in swine. *Cardiovasc Radiat Med.* 2001;2(4):225-230.

57) Albiero R, Adamian M, Kobayashi N, et al. Short- and intermediate-term results of (32)P radioactive beta-emitting stent implantation in patients with coronary artery disease: The Milan Dose-Response Study. *Circulation.* 2000;101(1):18-26.

58) Ahmed JM, Mintz GS, Waksman R, et al. Serial intravascular ultrasound assessment of the efficacy of intracoronary gamma-radiation therapy for preventing recurrence in very long, diffuse, in-stent restenosis lesions. *Circulation.* 2001;104(8):856-859.

59) Kuchulakanti P, Torguson R, Canos D, et al. Optimizing dosimetry with high-dose intracoronary gamma radiation (21 Gy) for patients with diffuse in-stent restenosis. *Cardiovasc Revasc Med.* 2005;6(3):108-112.

Radiation Therapy Techniques in the Management of Locally Advanced, High-Grade, Soft-Tissue Sarcoma

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Abstract

Objective: We sought to assess which prognostic factors are associated with local recurrence (LR) rates and wound complications of locally advanced, high-grade, soft-tissue sarcoma (STS).

Methods: Retrospective analysis was performed on patient data from 2005 to 2018, with high-grade STS of extremity or trunk, > 5 cm, histology-specific, with central pathology review. Wide-excision was performed in 100 patients along with radiation, whose radiation fields and dose plans were available for review, of which 31 also received ifosfamide-doxorubicin, with a minimum follow-up of 1 year. Multivariable analysis (MVA) of prognostic factors was calculated to see which variables were associated with LR, and nonhealing wound rates.

Results: Median follow-up was 5.8 years. Univariate analysis revealed that trunk location, distal and radial clinical-target-volume (CTV) margins of 1.5 cm had higher rates of LR vs ≥ 2 cm or presence of fascial boundary. MVA of these prognostic factors revealed that trunk location ($P = 0.048$), and radial CTV of 1.5 cm ($P = 0.006$) were independently associated with higher LR, as 10 of 15 LRs were at the edge of the radial margin. The bolus did not affect LR. The odds ratio for nonhealing wounds at 3 months was higher for subcutaneous (T2a) disease, larger tumor size, proximal CTV ≥ 2 cm, wider field size, bolus technique, and lack of chemotherapy.

Conclusion: Longitudinal CTV margins of 3 cm seem adequate, but high-grade STS ≥ 5 cm may benefit from increased radial CTV margins of 2 to 2.5 cm in the absence of a fascial boundary, although larger CTV may increase nonhealing wound rates. Bolus techniques may increase wound complications in T2a-b STS and should not be routinely employed.

Keywords: soft-tissue sarcoma, radiation therapy, bolus, margins, complications

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Disclosure: The authors have no conflicts of interest to disclose. None of the authors received outside funding for the production of this original manuscript and no part of this article has been previously published elsewhere. Abstract accepted for presentation October 24, 2022, at the American Society for Oncology Annual Meeting, San Antonio.
Data availability and disclaimer: The interpretation and reporting of these data are the sole responsibility of the authors. All data relevant to the study are provided in the article. Dr. Goy: conceptualization, data curation, formal analysis, investigation, methodology, project administration, resources, software, supervision, validation, visualization, original and final draft writing and editing. Dr. Helmstedter: conceptualization, data curation, editing of final draft. Ms. Yao: statistical analysis, software, validation, editing of final draft. Dr. Syed: pathology review validation, investigation, editing of final draft. The views expressed in the submitted article are the author's own and are not an official position of the Southern California Kaiser Permanente Medical Group. Kaiser Permanente IRB# 11646.

Introduction

Limb-salvage therapy using external-beam radiation therapy (EBRT) to reduce local recurrence (LR) allows surgeons to perform wide-excision of soft-tissue sarcoma (STS), allowing less radical surgery such as amputation.[1,2] In 2011, the Radiation Therapy Oncology Group (RTOG) published guidelines for designing clinical target volume (CTV) margins in the treatment of extremity soft-tissue sarcoma (ESTS), which was verified by subsequent publications, where longitudinal proximal/distal CTV recommendations were 3 to 5 cm, but radial CTV was 1.5 cm.[3-6] One question was whether these guidelines can be applied to STS involving subcutaneous tissues, and the trunk, where space is more limited. Large treatment volumes can increase a patient's risk of long-term complications.[7] However, this must be balanced against risks of LR when treatment volumes are too small, and thus our goal was to assess prognostic factors associated with higher LR rates and wound complications of locally advanced, high-grade, STS, and see which CTV margins may be optimal.

Methods

Retrospective analysis was performed on data from 100 adult patients from January 2005 to December 2018, who had primary high-grade STS of the extremity or trunk, > 5 cm, localized to the muscle or subcutaneous tissue, that were either synovial (16 patients), dedifferentiated liposarcoma (16), myxofibrosarcoma (13), round cell liposarcoma (7), undifferentiated pleomorphic sarcoma (39), or undifferentiated sarcoma not otherwise specified (9). We defined locally advanced as > 5 cm in size. Patients were T2 if the tumor was > 5 cm in maximal dimension, T2a for subcutaneous tumor, and T2b for muscle-invasive tumor.[8] Patients had to have their radiation fields and dose plans available for review, with a minimum of 1 year of follow-up. Bone sarcomas, gastrointestinal stromal tumors, pediatric sarcomas, and retroperitoneal sarcomas were excluded from this analysis. Central pathology review was performed by our soft-tissue pathologist (S.S.) and graded according to the Federation Nationale des Centres de Lutte Contra le Cancer (FNCLCC);[9] our study included only grade 3 or high-grade sarcomas. Radiation therapy was delivered using megavoltage photons, using either 6 MV or 15 MV, with the majority (78%) undergoing preoperative radiation to 4400-5000 cGy in 200 cGy fractions to the gross tumor with margin, followed by wide excision, which occurred about 6 weeks after radiation. Twenty-two percent underwent postoperative radiation to 4500-5040 cGy with a shrinking field boost to a total of 5940-6660 cGy in 180-200 cGy fractions. Additional boost was not performed on preoperative radiation patients who had a positive margin after wide excision.[10] All patients underwent immobilization using a polystyrene-filled vacuum cradle. Gross tumor volume (GTV) contours included T1-weighted images with gadolinium enhancement of the tumor on MRI, and T2-weighted edema included in the CTV. CTV volumes were determined by the prescribing physician. CTV to planning target volume (PTV) expansion was 1 cm, as image guidance was not performed. A bolus was used in select cases at the discretion of the prescribing physician due to concern about scar/cutaneous recurrence. During the timeframe these patients were treated, there was no effort to treat the skin as an organ at risk (OAR). Three-dimensional conformal radiation therapy (3DCRT) was performed in 91 patients, and intensity-modulated radiation therapy (IMRT) was performed in 9 patients. The radiation planning images (digitally reconstructed radiographs) and isodose plans were scaled and compared to MRI evidence of LR, which was categorized as out of field if > 80% of the volume was outside of the irradiated volume, in field if > 80% of the volume was inside the irradiated volume, and marginal if recurrence was at the edge of the irradiated volume between the out-of-field and in-field parameters, listed above. Binary classification of CTV margins was performed. The first was a CTV of 1.5 cm. The second was a CTV margin ≥ 2 cm or if the CTV extended to a fascial boundary, as a fascial boundary is equivalent to a wide margin. For postoperative patients, CTV margins were recorded based on the original fields taken to 4500-5040 cGy, and not based on the boost margins.

The Charlson Comorbidity Index score is a method of categorizing comorbidities of patients based on the International Classification of Diseases, and was assessed for each patient, and tabulated in **Table 1**.[11] After therapy, patients without wound complications were generally followed every 6 months for 5 years, and yearly thereafter, with MRI of the local area and computed tomography (CT) of the chest.

Date of surgery was established as time zero, and Kaplan-Meier estimates were used to calculate local recurrence-free survival (LRFS).[12] Characteristics of patients were reported as percentages for categorical factors, and median with ranges was used for continuous factors. Fisher's exact tests were used to test for categorical differences in treatment groups. Wilcoxon rank-sum tests were used to calculate differences on continuous factors. Multivariable analysis (MVA) of prognostic factors using the Cox proportional hazards models was used to estimate hazard ratios on LR.[13] Multivariate logistic regression was performed and odds ratios were calculated to detect the factors associated with the probability of wound

Table 1. Patient Cohort Characteristics

	LOCAL CONTROL (N = 85)	LOCAL RECURRENCE (N = 15)	P VALUE
Age (years)			0.10
median	58.5	64.8	
range	18.3-87.4	34.9-86.1	
Gender			0.65
Female	40 (47.1%)	8 (53.3%)	
Male	45 (52.9%)	7 (46.7%)	
Race			0.09
Asian	5 (5.9%)	4 (26.7%)	
Black	7 (8.2%)	2 (13.3%)	
Hispanic	27 (31.8%)	3 (20.0%)	
White	42 (49.4%)	6 (40.0%)	
Other/unknown	4 (4.7%)	0 (0.0%)	
Charlson			0.31
median	6	7	
range	2-15	3-11	
Stage - clinical			0.25
T2a	17 (20.0%)	5 (33.3%)	
T2b	68 (80.0%)	10 (66.7%)	
Size (cm)			0.36
median	10.0	9.3	
range	5.2-33.4	5.5-15.3	
Location			0.001
Upper extremity	14 (16.5%)	2 (13.3%)	
Lower extremity	53 (62.4%)	3 (20.0%)	
Trunk	18 (21.2%)	10 (66.7%)	
Margin positive	9 (10.6%)	3 (20.0%)	0.30
Preop XRT	66 (77.6%)	12 (80.0%)	0.84
Postop XRT	19 (22.4%)	3 (20.0%)	
Unintended surgery	4 (4.7%)	2 (13.3%)	0.19
Bolus	17 (20%)	1 (6.7%)	0.54
IMRT	8 (9.4%)	1 (3.73%)	0.73
Chemotherapy	26 (30.6%)	5 (33.3%)	0.83
Long-Proximal CTV ≥ 2 cm or fascial	77 (90.6%)	11 (73.3%)	0.058
Long-Proximal CTV 1.5 cm	8 (9.4%)	4 (26.7%)	
Long-Distal CTV ≥ 2 cm or fascial	76 (89.4%)	10 (66.7%)	0.019
Long-Distal CTV 1.5 cm	9 (10.6%)	5 (33.3%)	0.019
Radial CTV ≥ 2 cm or fascial	73 (85.9%)	5 (33.3%)	< 0.001
Radial CTV 1.5 cm	12 (14.1%)	10 (66.7%)	< 0.001
Median field length	23.5 cm (10.1-40.0)	20.0 cm (13.8-38.0)	0.09
Median field width	10.5 cm (4.2-22.0)	10.0 cm (4.2-17.0)	0.46

Abbreviations: XRT, radiation therapy; CTV, clinical tumor volume; Long, longitudinal

Table 2. Multivariable Analysis of Prognostic Factors

PROGNOSTIC FACTOR	HAZARD RATIO	CONFIDENCE INTERVAL	P VALUE
Location (trunk vs extremity)	3.54	1.01-12.40	0.048
Long-Proximal CTV 1.5 cm vs > 2 cm or fascial	0.93	0.21-4.04	0.92
Long-Distal CTV 1.5 cm vs > 2 cm or fascial	1.05	0.26-4.30	0.95
Radial CTV 1.5cm vs > 2 cm or fascial	5.40	1.63-17.84	0.006

Abbreviations: CTV, clinical tumor volume; Long, longitudinal

complications or the presence of a wound vacuum device at 3 months after surgery. The forest plot was produced to display the results graphically. The Wald test was used to calculate *P* value for the odds ratio.[14] Statistical significance utilized a 2-sided $P < 0.05$. All analyses were conducted using SAS EG 7.13 (SAS Institute Inc.).

Results

Median follow-up was 5.8 years (range 1.0 to 15.0 years). Ifosfamide-doxorubicin was given in 31 patients, and 69 received radiation therapy alone as adjuvant therapy. Ifosfamide-doxorubicin was usually prescribed neoadjuvantly for 5 cycles followed by radiation, then followed by wide excision; whereas for postoperative radiation, ifosfamide-doxorubicin was administered after the completion of radiation. All patients underwent en bloc wide excision, but 6 patients had unintended excision, where the surgeon had violated the tissue planes. These 6 patients subsequently underwent en bloc wide re-excision.

Cohort characteristics using univariate comparisons revealed that trunk location ($P = 0.001$), longitudinal-distal CTV 1.5 cm ($P = 0.019$), and radial CTV 1.5 cm ($P < 0.001$) were associated with higher rates of LR, but longitudinal-proximal CTV 1.5 cm did not quite make statistical significance ($P = 0.058$) (**Table 1**). MVA of these factors revealed that trunk location ($P = 0.048$), and radial CTV 1.5 cm ($P = 0.006$) were independently associated with higher rates of LR (**Table 2**). No significant difference in LR was found with preoperative radiation, margin status, tumor size, unintended initial surgery, use of bolus, or chemotherapy (**Table 1**). Of the patients with LR, 10 out of 15 had a trunk location, and 10 of 15 were muscle-invasive (T2b). In relation to the field of radiation, 10 out of 15 were marginal at the radial edge of the field, 4 out of 15 were in-field recurrences (1 of which had a positive margin), and 1 in 15 recurred marginally at the longitudinal-proximal edge of the radiation field in which the CTV margin was 2 cm (**Table 3**). None of the LRs were completely outside the field of radiation. Most local recurrences (14 out of 15) correlated with the depth of their initial stage, and only 1 patient with T2a disease experienced a cutaneous recurrence, which had also recurred at the marginal edge of the radial margin, despite having a bolus applied. Most of the patients were treated with 3DCRT (91%), and only 9 (9%) patients were treated with IMRT.

There were 15 patients with LR, with an estimated 5-year LRFS of 83.0%. Sixty-nine percent of patients had a wide radial margin since the field edge was beyond the fascial boundary with 7.2% LR. Of these with a wide fascial margin, those with a positive margin had 20% LR, whereas those with a negative margin had 5.1% LR. Patients with a 1.5 cm radial CTV that was not beyond the fascial boundary experienced 45.4% LR, but those with radial CTV $\geq$ 2.5 cm did not experience LR, despite not having a fascial boundary (**Table 4**).

Requirement of a wound vacuum device and/or open wounds occurred in 27 (27%) patients, ranging from 3 days to 29.7 months, with the median duration of wound vacuum devices/open wounds being 4.7 months. The odds ratio for open wounds at 3 months or the presence of a wound vacuum device showed a higher risk for patients with larger tumor size ($P = 0.02$), larger field width ($P = 0.02$), and use of a bolus ($P = 0.02$). Patients with muscle-invasive disease had a lower odds ratio of wound complications compared with subcutaneous disease ($P = 0.008$). Also, patients with a smaller proximal CTV of 1.5 cm ($P = 0.046$) and those who underwent chemotherapy ($P = 0.044$) experienced a lower risk of wound complications (**Figure 1**).

Discussion

CTV Margins

RTOG Guidelines for ESTS published in 2011 recommended using CTV of 3-5 cm longitudinally, but only 1.5 cm radially.[3-5] At that time, it was unclear if this could be extrapolated to trunk lesions, where space is more limited, or to subcutaneous tumors. In the current study, although longitudinal proximal/distal CTV of 1.5 cm was only associated with increased LR on univariate analysis, the reason may be that the standard of care based on RTOG guidelines was already a CTV of 3 cm. This resulted in only a small percentage of our patients undergoing a longitudinal CTV of 1.5 cm, as 11% of patients had a longitudinal CTV of 1.5 cm, making statistical significance more difficult on MVA. Thus, it seems that a longitudinal proximal/distal CTV of 3 cm should be adequate, although this can be reduced in the presence of a fascial boundary. However, for high-grade sarcomas > 5 cm, a radial

Table 3. Characteristics of Local Recurrence

#	SITE	T-STAGE	DEPTH OF LR	TYPE OF LR	PREOP	+SURG MARG	RADIAL MARG (CM)	LONG MARG (CM)
1	Upper extremity	2a	subcut	radial-marginal	N	N	1.5	4.0
2	Lower extremity	2b	muscle	radial-marginal	Y	N	1.5	3.0
3	Trunk	2b	muscle	radial-marginal	Y	N	1.5	4.0
4	Trunk	2b	muscle	in-field	N	Y	fascial	4.0
5	Upper extremity	2a	subcut	radial-marginal	Y	N	1.5	4.0
6	Lower extremity	2a	cutan	radial-marginal	Y	N	1.5	3.0
7	Trunk	2b	muscle	in-field	Y	N	fascial	3.5
8	Trunk	2b	muscle	radial-marginal	Y	N	1.5	1.5
9	Trunk	2b	muscle	radial-marginal	N	Y	1.5	7.5
10	Trunk	2b	muscle	in-field	Y	Y	fascial	3.0
11	Trunk	2b	muscle	radial-marginal	Y	N	1.5	5.5
12	Trunk	2a	subcut	radial-marginal	Y	N	1.5	3.0
13	Trunk	2b	muscle	radial-marginal	Y	N	1.5	3.0
14	Lower extremity	2b	muscle	in-field	Y	N	fascial	3.0
15	Trunk	2a	subcut	long- proximal marginal	Y	N	fascial	2.0

Abbreviations: LR, local recurrence; surg, surgical; marg, margins; long, longitudinal; subcut, subcutaneous; cutan, cutaneous

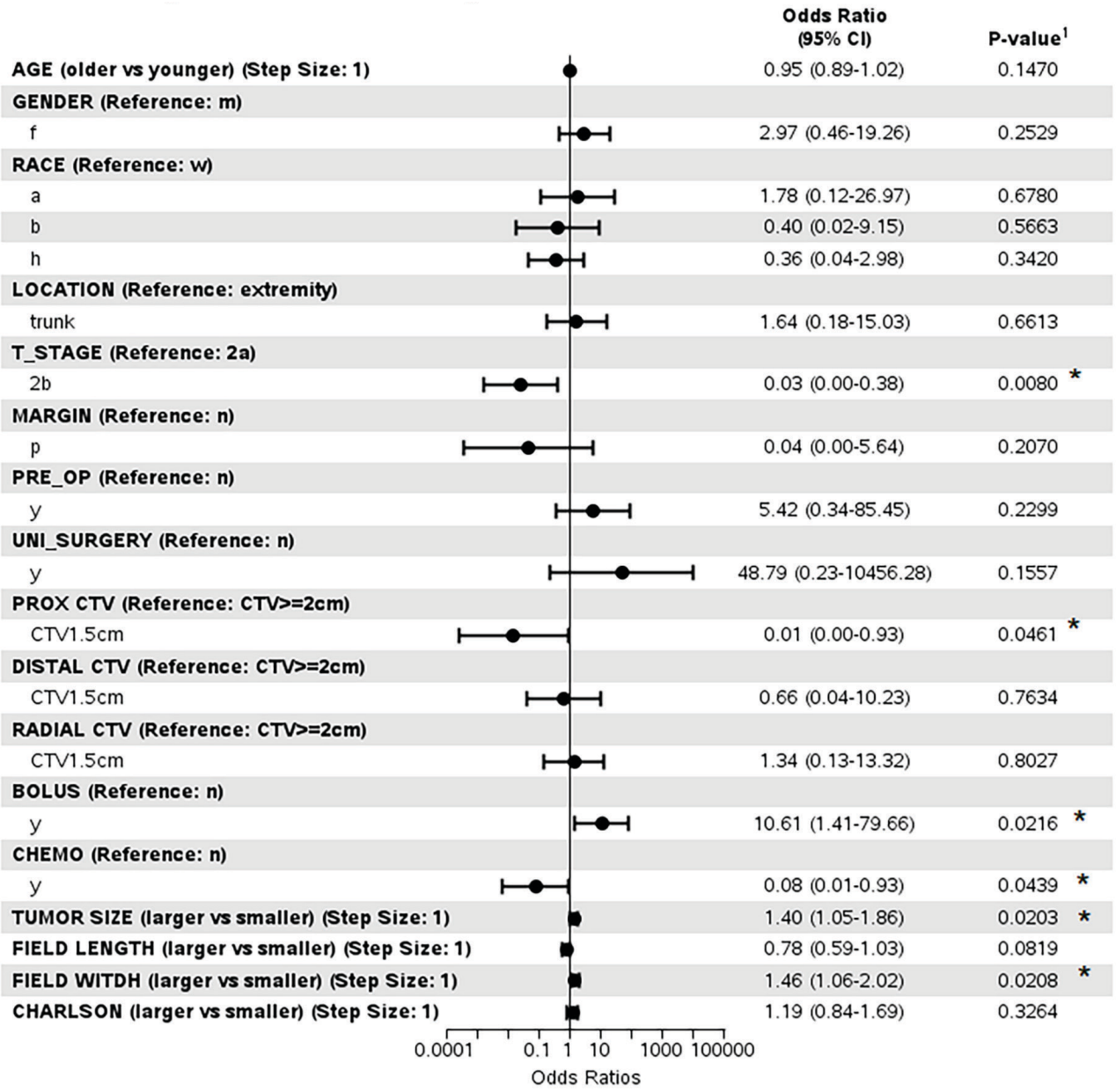
CTV of 1.5 cm may not be sufficient without a fascial boundary. American Society for Radiation Oncology (ASTRO) guidelines published in 2021 concluded that radial CTV of 3-4 cm is now recommended for subcutaneous disease; so why not for muscle-invasive disease?[15] In our study, we found a significant rate of LR using a CTV of 1.5 cm for both subcutaneous and muscle-invasive disease, in the absence of a fascial boundary, with the majority being marginal field-edge recurrences. Without a fascial boundary, high-grade sarcomas can easily extend radially to adjacent musculature for T2b disease, and thus we would only recommend a radial CTV of 1.5 cm only in the presence of a fascial boundary. It may be that a radial CTV of 1.5 cm is adequate for low-intermediate grade sarcomas or smaller high-grade sarcomas ≤ 5 cm, but a one-size-fits-all approach may not be suitable, especially for high-grade sarcomas > 5 cm. There was a slightly higher LR for positive margins, but this was not significant, possibly due to the small number of patients with positive margins, and that radiation may have some role in making up for positive margins.[16,17] Despite findings of increased LR with a radial CTV of 1.5 cm in the current study, there are studies that support reducing field size when using radiation as part of limb-salvage therapy. A randomized study using brachytherapy has led to the possibility of using smaller CTV margins, although the magnitude of the benefit seemed smaller than the randomized study using EBRT, where larger margins were used.[2,18] RTOG 0630 performed a phase II trial on STS, utilizing 3 cm longitudinal proximal/distal CTV, and 1.5 cm radial CTV, in which 74 patients underwent preoperative radiation followed by surgery. There were 5 patients with LR, and all were in-field. However, only 48.1% had high-grade histology, and 11.4% had smaller T1 lesions, so only about 32 patients had sarcomas > 5 cm of high grade, with a shorter median follow-up of 3.6 years.[19]

Table 4. Local Recurrence Based on Clinical Tumor Volume (CTV) Radial Margin

CTV RADIAL MARGIN	# PATIENTS	LOCAL RECURRENCE (%)
Beyond fascial boundary	69	5/69 (7.2%)
Beyond fascial boundary, but positive surgical margins	10	2/10 (20.0%)
Beyond fascial boundary, but negative surgical margins	59	3/59 (5.1%)
1.5 cm without fascial boundary	22	10/22 (45.4%)
2.5 cm without fascial boundary	2	0%
3.0 cm without fascial boundary	6	0%
4.0 cm without fascial boundary	1	0%

ASTRO published updated guidelines in 2021, which recommend a

Figure 1. Odds ratio of nonhealing wounds and/or wound vacuum device at 3 months. Abbreviations: a, Asian; b, Black; chemo, chemotherapy; CTV, clinical tumor volume; distal, distal longitudinal; f, female; h, Hispanic; m, male; n, no; p, positive; prox, proximal longitudinal; uni, unintended surgery; w, White: y, yes



[1]Covariate Wald p-value;
* p<0.05

Abbreviations: a-asian, b-black, chemo-chemotherapy, CTV-clinical tumor volume, distal-distal longitudinal, f-female, h-hispanic, m-male, n-no, p-positive, prox-proximal longitudinal, uni-unintended surgery, w-white, y-yes

longitudinal proximal/distal CTV of 3 cm, but still maintain a radial CTV of 1.5 cm for muscle-invasive disease. However, for subcutaneous disease, ASTRO now recommends radial CTV margins of 3-4 cm.[15] Our data support these guidelines for subcutaneous disease, although our data suggest also expanding radial CTV to at least 2-2.5 cm for muscle-invasive disease, due to higher marginal LR rates at the radial margin when a 1.5 cm radial CTV is applied, in the absence of a fascial boundary. Most of our patients (69%) had a radial margin that was beyond a fascial boundary, so a 1.5 cm CTV was considered adequate in these patients, but in the absence of a fascial boundary, we found a higher LR with a 1.5 cm radial CTV margin.

Wound Complications

The presence of an open wound at 3 months or the use of a wound vacuum device were significantly higher when using wider fields, and so an attempt to make radiation fields smaller is an important goal. In our study, utilizing a smaller longitudinal proximal CTV reduced wound complications (**Figure 1**). Interestingly, chemotherapy also reduced wound complication rates. Most of our patients underwent neoadjuvant sequential chemotherapy, in which preoperative radiation followed chemotherapy, despite it causing immune suppression. By the time radiation started, patient blood counts had time to recover, and the neoadjuvant chemotherapy caused shrinkage of these large sarcomas. It may be this cytoreduction that led to lower wound complications from chemotherapy, as we only included the most chemotherapy-sensitive STS histology in our study (**Figure 1**).[20]

Lastly, we found that the use of a bolus was associated with higher wound complications. In our experience, only 1 patient with T2a disease had a cutaneous recurrence, which recurred at the radial edge in which the CTV was 1.5 cm, and the skin was part of the CTV where the bolus was applied. However, in most cases our soft-tissue surgeon will remove the overlying skin when sarcomas are close to the dermis. The majority of our LRs were not cutaneous, making it less likely for a bolus to impact LR rates. Thus, we concur with the most recent ASTRO guidelines from 2021, which do not recommend the use of a bolus in the treatment of STS with radiation.[15]

Limitations and Final Thoughts

One limitation of this study is that the majority of our patients were treated with 3DCRT techniques, mostly using opposed fields. This leads to a more rapid falloff in radiation dose at the radial edge. One study published that IMRT had a lower rate of LR, and this may be due to the more gradual falloff of radial dose, which can still be effective in controlling subclinical disease, and thus it's possible that a smaller radial CTV, such as 1.5 cm, could be achievable with IMRT, and that the current study utilized older techniques of treatment.[21,22] Thus, we anticipate the VORTEX trial results (randomized trial of volume of postoperative radiation therapy given to adult patients with ESTS), although our study predominantly used preoperative radiation. Another limitation of our study was the omission of image-guided radiation therapy (IGRT), in which studies have suggested a reduction in the CTV to PTV expansion from 1.0 cm to 0.5 cm and relatively lower complications with the use of IGRT.[19,23]

Thirdly, none of the patients had a radial CTV of 2.0 cm, although we did have some with a longitudinal CTV of 2.0 cm **(Tables 3,4)**. Due to the influence of the RTOG and ASTRO guidelines, it appears that there was a significant application of the use of a radial CTV of 1.5 cm.[3-5,15]

We suggest when using 3DCRT that radial CTV for subcutaneous lesions can be extended to 2.0-2.5 cm, as this would be similar to 3 cm longitudinally due to lower scatter contribution at the proximal and distal edges of the radiation field.[24] For muscle-invasive disease, we also think that a 2.0-2.5 cm radial margin would be appropriate, although this must be balanced with the possibility of a slightly higher risk of wound complications. By increasing the CTV by a small amount, we can potentially reduce marginal recurrences, as there is evidence of higher LR rates leading to a decline in overall survival in STS.[25]

Conclusion

Longitudinal proximal/distal CTV margins of 3 cm seem adequate, but high-grade STS $\geq$ 5 cm may benefit from increased radial CTV margins of 2-2.5 cm in the absence of a fascial boundary, although larger CTV may increase nonhealing wound rates. Bolus techniques may increase wound complications in T2a-b STS, and should not be routinely employed.

References

1) Rosenberg SA, Tepper J, Glatstein E, et al. The treatment of soft-tissue sarcomas of the extremities: prospective randomized evaluations of (1) limb-sparing surgery plus radiation therapy compared with amputation and (2) the role of adjuvant chemotherapy. *Ann Surg.* 1982;196:305-315.

2) Yang JC, Chang AE, Baker AR, et al. Randomized prospective study of the benefit of adjuvant radiation therapy in the treatment of soft tissue sarcomas of the extremity. *J Clin Oncol.* 1998;16:197-203.

3) Wang D, Bosch W, Roberge D, et al. RTOG sarcoma radiation oncologists reach consensus on gross tumor volume and clinical target volume on computed tomographic images for preoperative radiotherapy of primary soft tissue sarcoma of extremity in radiation therapy oncology group studies. *Int J Radiat Oncol Biol Phys.* 2011;81:e525-e528.

4) Dickie CI, Griffin AM, Parent AL, et al. The relationship between local recurrence and radiotherapy treatment volume for soft tissue sarcomas treated with external beam radiotherapy and function preservation surgery. *Int J Radiat Oncol Biol Phys.* 2012;82:1528-1534.

5) Haas RL, DeLaney TF, O'Sullivan B, et al. Radiotherapy for management of extremity soft tissue sarcomas: why, when, and where? *Int J Radiat Oncol Biol Phys.* 2012;84:572-580.

6) ICRU Report 50. Prescribing, recording, and reporting of photon beam theapy. Bethesda, MD: International Commission on Radiation Units and Measurement; 1993.

7) Davis AM, O'Sullivan B, Turcotte R, et al. Late radiation morbidity following randomization to preoperative vs postoperative radiotherapy in extremity soft tissue sarcoma. *Radiother Oncol.* 2005;75:48-53.

8) Edge SB, Byrd DR, Compton CC, et al. AJCC Cancer Staging Handbook, 7th ed. Springer; 2010.

9) Coindre JM, Bertrand G, Chateau MD, et.al. Recommandations pour la prise en charge anatomo-pathologique des sarcomes des tissus mous de l'adulte. *Ann Pathol.* 1998;18:505-511.

10) Yami AA, Griffin AM, Ferguson PC, et al. Positive surgical margins in soft tissue sarcoma treated with preoperative radiation: Is a postoperative boost necessary? *Int J Radiat Oncol Biol Phys.* 2010;77:1191-1197.

11) Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis.* 1987;40:373-383.

12) Kaplan EL, Meier P. Non-parametric estimation from incomplete observations. *J Am Stat Assoc.* 1958;53:457-500.

13) Cox DR. Regression models and life tables. *JR Stat Soc B.* 1972;34:187-189.

14) Tests for the Odds Ratio in Logistic Regression with One Normal X (Wald Test). NCSS.com. https://ncss-wpengine.netdna-ssl.com/wpcontent/themes/ncss/pdf/Procedures/PASS/Tests_for_the_Odds_Ratio_in_Logistic_Regression_with_Two_Binary_XsWald_Test.pdf

15) Salerno KE, Alektiar KM, Baldini EH, et al. Radiation therapy for treatment of soft tissue sarcoma in adults: executive summary of an ASTRO clinical practice guideline. *Pract Radiat Oncol.* 2021;11:339-351.

16) Gronchi A, Casali PG, Mariani L, et al. Status of surgical margins and prognosis in adult soft tissue sarcomas of the extremities: a series of patients treated at a single institution. *J Clin Oncol.* 2005;23:96-104.

17) Jebsen NL, Trovik CS, Bauer HC, et al. Radiotherapy to improve local control regardless of surgical margin and malignancy grade in extremity and trunk wall soft tissue sarcoma: a scandinavian sarcoma group study. *Int J Radiat Oncol Biol Phys.* 2008;71:1196-1203.

18) Pister PW, Harrison LB, Leung DH, et al. Long-term results of a prospective randomized trial of adjuvant brachytherapy in soft tissue sarcoma. *J Clin Oncol.* 1996;14:859-868.

19) Wang D, Zhang Q, Eisenberg JM, et al. Significant reduction of late toxicities in patients with extremity sarcomas treated with image-guided radiation therapy to a reduced target volume: results of radiation therapy oncology group RTOG-0630 trial. *J Clin Oncol.* 2015;33:2231-2238.

20) Goy BW, Syed S, Padmanabhan A, et al. The role of Ifosfamide-Doxorubicin chemotherapy in histology-specific, high grade, locally advanced soft tissue sarcoma, a 14-year experience. *Radiother and Oncol.* 2021;165:174-178.

21) Folkert MR, Singer S, Brennan MF, et al. Comparison of local recurrence with conventional and intensity-modulated radiation therapy for primary soft-tissue sarcomas of the extremity. *J Clin Oncol.* 2014;32:3236-3241.

22) Withers HR, Peters LJ, Taylor JM. Dose-response relationship for radiation therapy of subclinical disease. *Int J Radiat Oncol Biol Phys.* 1995;31:353-359.

23) O'Sullivan BO, Griffin AM, Dickie CI, et al. Phase 2 study of preoperative image-guided intensity-modulated radiation therapy to reduce wound and combined modality morbidities in lower extremity soft tissue sarcoma. *Cancer.* 2013;119:1878-1884.

24) Merredith WJ. *Radium Dosage: The Manchester System.* Livingstone, Ltd;1967.

25) Lewis JJ, Leung D, Heslin M, et al. Association of local recurrence with subsequent survival in extremity soft tissue sarcoma. *J Clin Oncol.* 1997;15:646-652.

Shingles After a Single Fraction of Radiation for Ewing Sarcoma

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Abstract

Reactivation of human herpes viruses is a feared complication for immunosuppressed cancer patients. We present the first reported case of varicella-zoster virus (VZV) reactivation after a single fraction of radiation. This 61-year-old woman began radiation therapy for Ewing sarcoma and within 24 hours complained of lower back pain in the dermatome of the dorsal root ganglion (DRG) that was within the radiation field. Antiviral therapy was initiated, and appropriate patient isolation was prioritized. Within 48 hours of radiation therapy (RT), vesicles erupted within the painful dermatome. All symptoms resolved following a course of valacyclovir, and no long-term neurologic symptoms were noted. We recommend that clinicians closely monitor patients receiving radiation therapy for symptoms of herpes zoster reactivation, provide swift and appropriate interventions when needed, and consider prophylactic antiviral treatment prior to cancer treatment.

Keywords: Radiation toxicity, varicella zoster, shingles, reactivation, side effects, immunosuppression, skin toxicity

Case Summary

A 61-year-old woman with a history of diffuse large B-cell lymphoma treated with R-CHOP for 6 cycles, and no evidence of disease for 10 years, presented to the local emergency department with progressive left lower extremity weakness. MR imaging showed an L4 vertebral body lesion with canal and foraminal stenosis, and bone biopsy revealed Ewing sarcoma. Dexamethasone therapy was initiated, and due to neurologic symptoms, RT was started upfront. Chemotherapy was added concurrently and continued following RT completion. One day after the radiation began, the patient noted lower back pain in a right-sided band-like distribution corresponding to the dermatome of the dorsal root ganglion (DRG) that was in the radiation field, with no vesicles or other dermatological lesions visible. She was started on valacyclovir 3 times daily due to concerns of VZV reactivation and an immunocompromised state. Two days after radiation began, right-sided lesions concerning for VZV were visible and appropriate isolation precautions were made. The diagnosis was visual and confirmed by PCR swab of the vesicular lesion. The patient has recovered without any postherpetic pain or scarring.

Imaging and Radiation Plans

MRI lumbar spine was notable for diffuse neoplastic marrow replacement at L4, epidural neoplastic extension with moderate to severe canal stenosis, extraosseous extension into the left paraspinal space at L4 measuring 4.7 × 3.7 × 1.4 cm, abutment of the left psoas muscle, and encroachment into the left L4-5 neural foramen with severe stenosis (**Figure 1**).

Due to neurologic symptoms, RT was started upfront and chemotherapy was added concurrently and continued following RT completion. Treatment consisted of a mixed proton/photon plan to a total of 56 Gy in 24 fractions. The initial plan was a simple 2-beam photon plan, anterior to posterior

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Disclosure/informed consent: The authors have no conflicts of interest to disclose. None of the authors received outside funding for the production of this original manuscript and no part of this article has been previously published elsewhere. The patient has provided informed consent for the publication of this case report.

Figure 1. T2-weighted axial MRI lumbar spine (A) and T2-weighted right sagittal lumbar spine (B). These images demonstrate an abnormal L4 vertebral body with severe central canal and foraminal stenosis at L4-L5. L4 is completely replaced by tumor and there is paraspinal tumor visible next to the left psoas muscle.

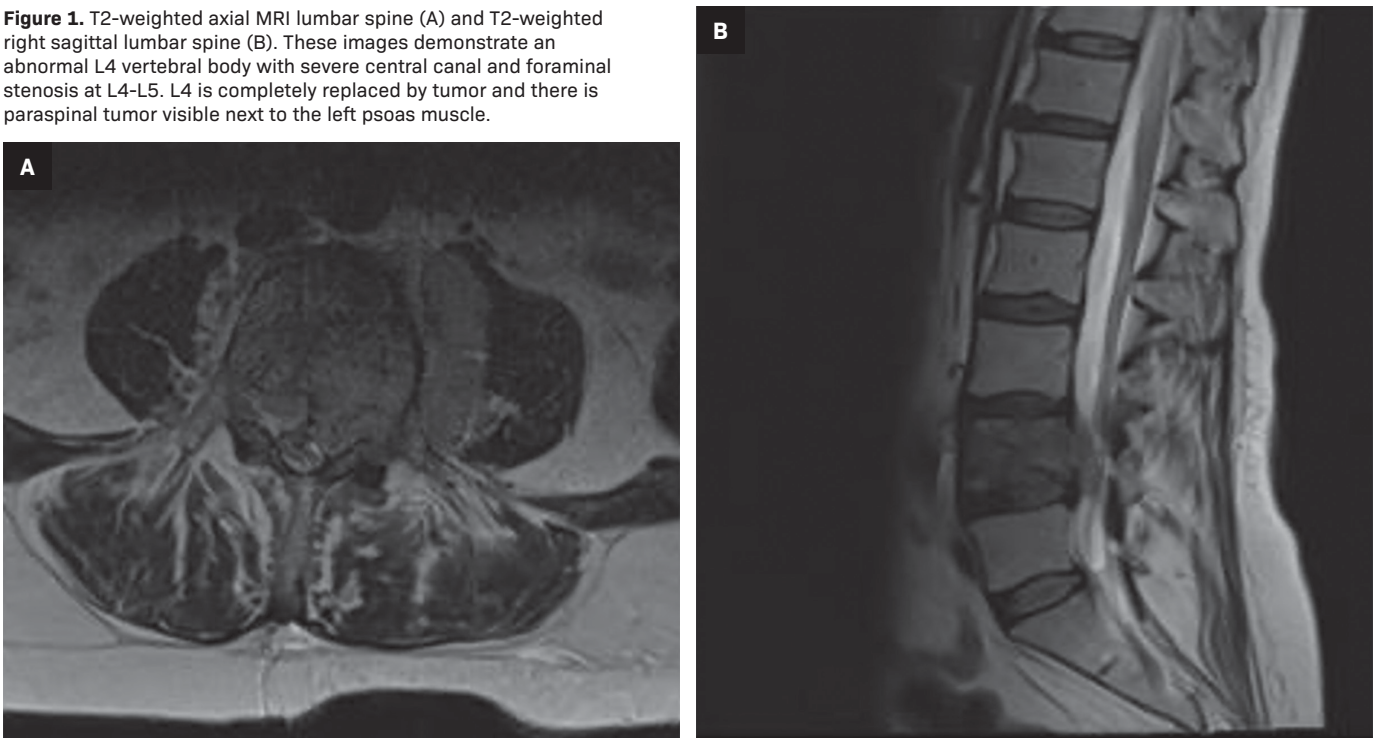


Figure 2. Plan for radiation therapy showing anatomical targets and a color map describing dose color wash with axial (A), sagittal (B), and coronal (C) views. The first dose was 5600 Gy. It started with photons, anterior-posterior/posterior-anterior (AP/PA), and then switched to protons for the final 12 fractions with a posterior beam and a left posterior oblique (LPO) beam.

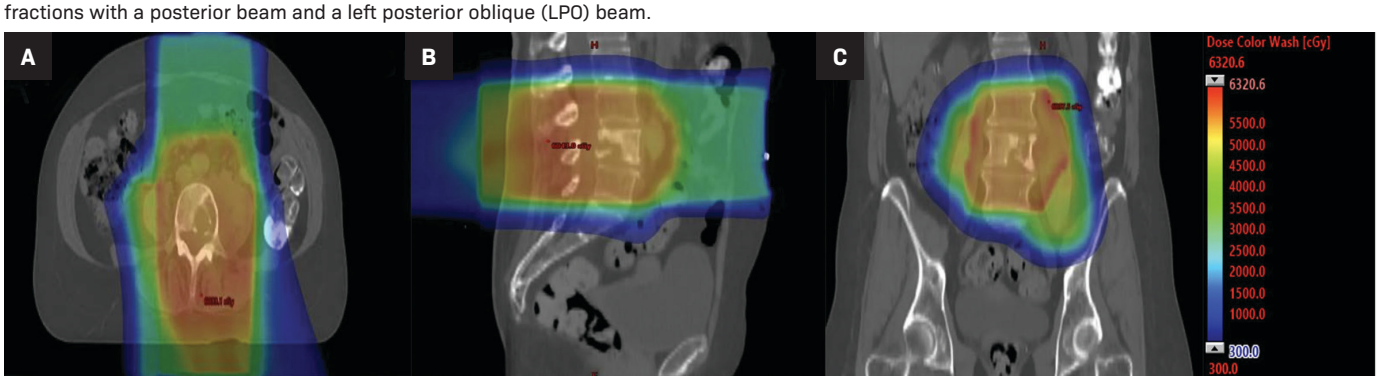
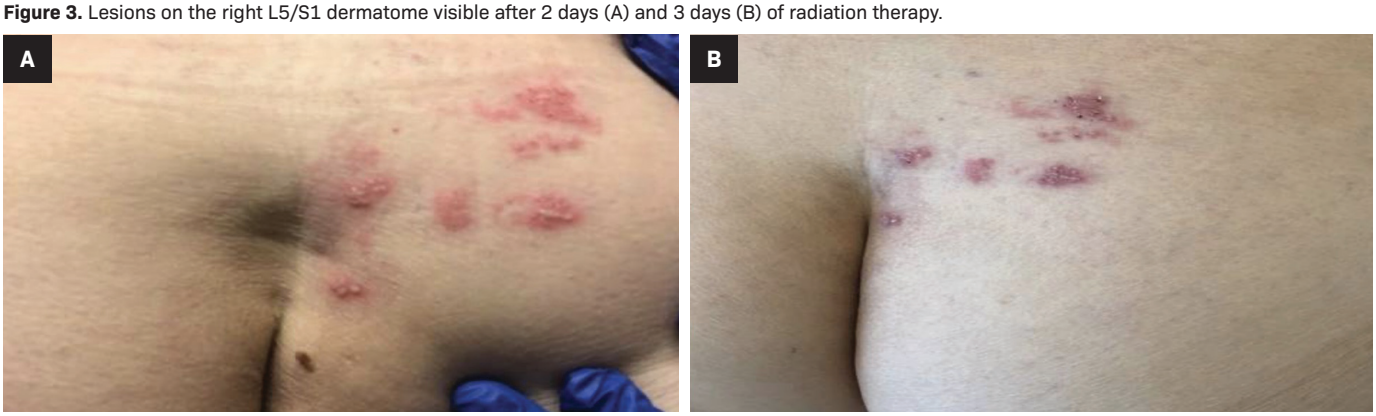


Figure 3. Lesions on the right L5/S1 dermatome visible after 2 days (A) and 3 days (B) of radiation therapy.



and posterior to anterior beams. For the final 12 fractions, the patient was switched to a proton plan with a posterior beam and a left posterior oblique beam to spare bowel toxicity (**Figure 2**). See **Supplementary Figure 1** (available as a PDF in the online version of this article at www.appliedradiationoncology.com) for relevant dose statistics of the safe, effective, and peer-reviewed plan sum used to treat this patient.

One day after the radiation began, the patient noted right-sided lower back pain. Within 48 hours, right-sided lesions concerning for VZV were visible and appropriate isolation precautions were made. Although there is variability regarding specific dermatomes, these vesicles were likely in the DRG of her L5/S1 dermatome, which corresponds to the area where she received radiation therapy. The lesions are seen in **Figure 3**.

Diagnosis

Physical examination and routine labs were otherwise unremarkable and there was no stigmata of VZV reactivation at this point. Possible diagnoses including atopic dermatitis, trauma, autoimmune dermatologic manifestations, and pain from musculoskeletal or neurogenic origin were considered and ruled out. The infectious diseases team was consulted and suspected VZV reactivation even prior to the appearance of lesions, particularly given the immunocompromised state of the patient. Of note, the patient received her second dose of the SHINGRIX (GlaxoSmithKline) vaccine in 2018 and had no prior history of shingles/VZV reactivation.

Discussion

Our patient is the first reported patient to have developed reactivation of an alphaherpesvirus varicella zoster virus (VZV) after only a single fraction of radiation.[1] Reactivation of latent VZV, also known as herpes zoster or shingles, is most often seen with waning T cell immunity (eg, older or immunocompromised individuals). The first sign of herpes zoster is often superficial pain followed by a maculopapular rash in a unilateral dermatomal distribution that transitions into a vesicular rash. More concerning neurological complications include inflammation of the cranial nerves, encephalitis, meningitis, and significant ophthalmological complications. In addition, gastrointestinal manifestations such as pancreatitis and gastritis have been reported.[2] Among the more concerning side effects, postherpetic neuralgia can develop in approximately 1 out of 5 patients who experience a Zoster outbreak.[3] Those with postherpetic neuralgia experience significant decline in quality of life, and therapies such as tricyclic antidepressants, analgesics, and interventional therapies have notable drawbacks and often do not provide full relief.[4,5] Therefore, it is best to ensure infection does not occur and to prioritize prevention, particularly in immunocompromised patients. It is important to note that previously reported cases of herpes zoster in cancer patients occurred much later in the course of radiation therapy or even months after completing treatment, and never after a single fraction of radiation therapy. Moreover, to our knowledge no direct investigation into the mechanism linking radiation therapy to alphaherpesvirus reactivation has been conducted. In this case report, we present a detailed overview of the case at hand, offer potential explanations, and discuss the implications of the clinical findings.

Both cancer as well as cancer treatments (including radiation therapy) have been shown to be independent risk factors for VZV reactivation. Multiple studies have demonstrated an increased risk of herpes zoster reactivation in breast cancer patients receiving radiation to the chest.[6,7] Shimizuguchi et al reported a significantly increased incidence of herpes zoster in patients receiving radiation therapy over 5 years compared with those who did not receive radiation therapy (hazard ratio, 2.59, 95% CI, 1.84-3.66), leading the authors to recommend Shingrix vaccination and possible VZV prophylaxis prior to radiation therapy.[8] Hodgkin's lymphoma patients have demonstrated decreased cell-mediated immune response to VZV in vitro. Moreover, when treated with both radiation therapy and chemotherapy, these patients had decreased overall immune capacity compared with those treated with a single modality.[9,10] Small-cell lung carcinoma patients have also experienced high occurrence of herpes zoster following combined radiation and chemotherapy.[11]

We postulate that in this scenario, the location of radiation therapy may have caused or lowered the threshold for a VZV outbreak. Since the radiation for this specific patient was directed near the spinal cord and VZV often lays latent in the sensory DRG,[3] this may have increased risk for VZV reactivation. We suspect that the right lower lumbar/sacral DRG in this patient was harboring dormant virus.

Previous work has proposed mechanisms for how radiation therapy can reshape the tumor microenvironment, such as through inducing cell death and subsequently priming cytotoxic T lymphocytes to further attack tumor cells.[12] Proposed mechanisms for radiation-therapy-induced immunosuppression leading to herpetic reactivation include immune dysfunction in the treatment region and disruption of the body's ability to contain latent virus, both of which increase viral load and make reactivation more likely.[13,14]

As the patient had a known history of cancer and a nearby tumor prior to any reported clinical manifestations, we cannot rule out that the cause of VZV reactivation may have been the tumor microenvironment and that the timeline of radiation and VZV reactivation was coincidental. However, the symptoms of herpes zoster presented exclusively on the right side of the

patient's spine that was away from the left-sided tumor, making the tumor a less likely agent in the sequence of reactivation. Additionally, the VZV reactivation occurred only after radiation and was in the dermatome of the DRG corresponding to the precise target of radiation therapy.

We also note that although she was on concurrent steroids when this VZV outbreak occurred, the immunosuppression this caused was unlikely to have contributed to her Zoster outbreak, since she had taken multiple courses of steroids during prior cancer treatments and even during prior episodes of pain leading up to this hospital admission without such a complication. Moreover, while Qian et al showed that the incidence of VZV was higher in patients taking systemic corticosteroids, this increased incidence was mostly seen 1 to 3 months after initiation of the prolonged steroid regimen.[15] Our patient showed reactivation after a single day of dexamethasone treatment, making dexamethasone an unlikely agent in VZV reactivation.

We postulate that there may be a common mechanism by which radiation therapy lowers the threshold for reactivation of latent alphaherpesviruses that has yet been to be elucidated, and that this mechanism may be distinct from immunosuppression. In addition, multiple factors may contribute to reactivation of VZV in patients receiving radiation therapy, such as the type of cancer, the type of radiation therapy provided, and the anatomical location of the radiation (eg, proximity to spinal cord). Ultimately, we can only posit that any perturbation may increase the likelihood of VZV reactivation.

VZV reactivation, which is typically dermatomal, can be associated with more severe disease or complications in immunocompromised patients, including those undergoing cancer treatment. Radiation oncologists must be vigilant when treating patients with a past history of VZV as the virus lies dormant and can seemingly be reactivated after a single dose of radiation therapy. In addition to VZV symptoms, complications of reactivation may hinder the patient's cancer treatment.[16] As a result, it is imperative that radiation oncologists closely monitor radiation therapy patients for VZV symptoms — especially if they have not received the Shingrix vaccine — and inform them about this possible side effect. Early detection and treatment can mitigate the course of reactivation. Given the relationship between viral load and likelihood of reactivation,[14] there may be use for viral load estimation and/or VZV prophylaxis[8] prior to patients undergoing radiation treatment. Future randomized clinical trials comparing the rates of VZV reactivation in radiation fields containing dorsal root ganglia and intervention in the form of antiviral prophylaxis would be a welcomed next step.

Conclusion

This interesting and concerning finding should spark more investigation into the pathogenesis of the reactivation of this disease in the setting of radiation therapy. Moreover, it is imperative to increase awareness among radiation oncologists of the possibility of alphaherpesvirus reactivation in their patients and to be more vigilant in screening patients who may be susceptible, as well as counseling patients on this rare but potentially serious side effect. Future clinical trials investigating the reliability of viral load estimation and/or VZV prophylaxis prior to radiation therapy could improve patient outcomes.

References

1) Kennedy PG, Rovnak J, Badani H, Cohrs RJ. A comparison of herpes simplex virus type 1 and varicella-zoster virus latency and reactivation. *J Gen Virol.* 2015;96(Pt 7):1581-602. doi:10.1099/vir.0.000128. Epub 2015 Mar 20.

2) John AR, Canaday DH. Herpes zoster in the older adult. *Infect Dis Clin North Am.* 2017;31(4):811-826. doi:10.1016/j.idc.2017.07.016.

3) Macomber MW, Mullane KM, Liauw SL. Herpes zoster and radiation therapy: what radiation oncologists need to know about diagnosing, preventing, and treating herpes zoster. *Pract Radiat Oncol.* 2014;4(1):58-64. doi:10.1016/j.prro.2013.02.004.

4) Lin CS, Lin YC, Lao HC, Chen CC. Interventional treatments for postherpetic neuralgia: a systematic review. *Pain Physician.* 2019;22(3):209-228.

5) Hadley GR, Gayle JA, Ripoll J, et al. Post-herpetic neuralgia: a review. *Curr Pain Headache Rep.* 2016;20(3):17. doi: 10.1007/s11916-016-0548-x. Erratum in: *Curr Pain Headache Rep.* 2016;20(4):28.

6) Ellis, F. Herpes zoster after irradiation. *Br Med J.* 1949;2(4640):1323-1328. doi:10.1136/bmj.2.4640.1323

7) Lai Y et al. Increased risk of Varicella-Zoster Virus infection in patients with breast cancer after adjuvant radiotherapy: a population-based cohort study. *PLoS ONE.* 2019;14(1):1-10. doi:10.1371/journal.pone.0209365

8) Shimizuguchi T, Sekiya N, Hara K, et al. Radiation therapy and the risk of Herpes zoster in patients with cancer. *Cancer.* 2020;126(15):3552-3559. doi:10.1002/cncr.32926

9) Ruckdeschel JC, Schimpff SC, Smyth AC, Mardiney Jr. MR. Herpes zoster and impaired cell-associated immunity to the Varicella-zoster Virus in patients with Hodgkin's disease. *Am J Med.* 1977;62(1):77-85.

10) Guinee VF et al. The incidence of Herpes zoster in patients with Hodgkin's disease. An analysis of prognostic factors. *Cancer.* 1985;56(3):642-648.

11) Feld R, Evans WK, DeBoer G. Herpes zoster in patients with small-cell carcinoma of the lung receiving combined modality Treatment. *Ann. Intern Med.* 1980;93(2):282–283. doi:10.7326/0003-4819-93-2-282

12) Ruckert M, Flohr A, Hecht M, Gaipl US. Radiotherapy and the immune system: more than just immune suppression. *Stem Cells.* 2021;39(9):1155-1165.

13) Ruocco V, Ruocco E, Piccolo V, Brunetti G, Guerrera LP, Wolf R. The immunocompromised district in dermatology: a unifying pathogenic view of the regional immune dysregulation. *Clin Dermatol.* 2014;32(5):569-576.

14) Schiffer JT, Corey L. Rapid host immune response and viral dynamics in herpes simplex virus-2 infection. *Nat. Med.* 2013;19(3):280-290.

15) Qian J, Banks E, Macartney K, Heywood AE, Lassere MN, Liu B. Corticosteroid use and risk of Herpes zoster in a population-based cohort. *Mayo Clinic Proceed.* 2021;96(11):2843-2853. doi:10.1016/j.mayocp.2021.05.029

16) Ramirez-Fort MK, Zeng J, Feily A, et al. Radiotherapy-induced reactivation of neurotrophic human herpes viruses: overview and management. *J Clin Virol.* 2018;98:18-27.

Aggressive Multimodality Therapy for Treatment of a Locally Advanced Radiation-Related Chest Wall Sarcoma

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Abstract

Radiation-induced soft-tissue sarcoma (STS) is a rare but serious long-term complication following radiation therapy. Management of these aggressive malignancies includes surgical resection with wide margins, as margin status has been consistently correlated with outcomes. Given the proximity to critical structures contained within the thoracic cavity, adequate margins are often difficult to achieve. Neoadjuvant therapy has become important to improve the probability of local control following surgical resection in locally advanced cases. Current clinical practice guidelines for STS recommend neoadjuvant therapy with radiation therapy, chemotherapy, or combination chemoradiation. While some studies have evaluated regional hyperthermia with chemotherapy or radiation, data regarding the efficacy of neoadjuvant thermochemoradiation are sparse. Specifically, treatment of chest wall STS with this multimodality regimen is not well documented. Here we present a patient who developed a 14-cm undifferentiated pleomorphic sarcoma of the chest wall 10 years after MammoSite (Cytyc/Hologic) accelerated partial breast radiation. Due to the locally advanced nature of the primary tumor, neoadjuvant thermochemoradiation was delivered followed by an extensive chest wall resection with reconstruction.

Keywords: chest wall sarcoma, hyperthermia, chemoradiation, neoadjuvant radiation, radiation-induced sarcoma

Background

Breast-conserving therapy is a well-established treatment paradigm for early stage breast cancer, and accelerated partial breast irradiation (APBI) following lumpectomy has become a standard of care for many women.[1,2] MammoSite was the first FDA-approved device to deliver APBI, but due to the initial single lumen design, dose distribution could not be well optimized to limit chest wall and skin dose.[3] In a retrospective review, patients with a higher median chest wall dose were found to have a significantly higher risk of chest wall and rib pain following high dose rate brachytherapy, and newer multicatheter devices have been developed to permit improved dose optimization.[4] A late but serious complication of any radiation therapy includes the risk of secondary malignancy, a stochastic effect with a probability that is proportional to dose.[5,6] The incidence of radiation-induced sarcoma following breast radiation therapy is approximately 0.32% at 15 years compared with 0.23% in breast cancer patients not treated with radiation (P = 0.001).[7] Radiation-induced sarcomas are associated with poorer clinical

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Disclosures: Dr. Shah: Imedimed (consultant, speaker), Prelude (consultant, grants), Veraform (consultant), Varian (grant), VisionRT (grant), PrecisCA (speaker). Dr. Mesko: ONKOS Surgical (consultant), Bone Support (advisor), Stryker (consultant). Dr. Scott: Cvergenx (consultant, advisor), Radiogenomics (IP). Dr. Raymond: KLS Martin (consultant). The authors have no other conflicts of interest to disclose. None of the authors received outside funding for the production of this original manuscript and no part of this article has been previously published elsewhere. The patient has provided informed consent for the publication of this case report.

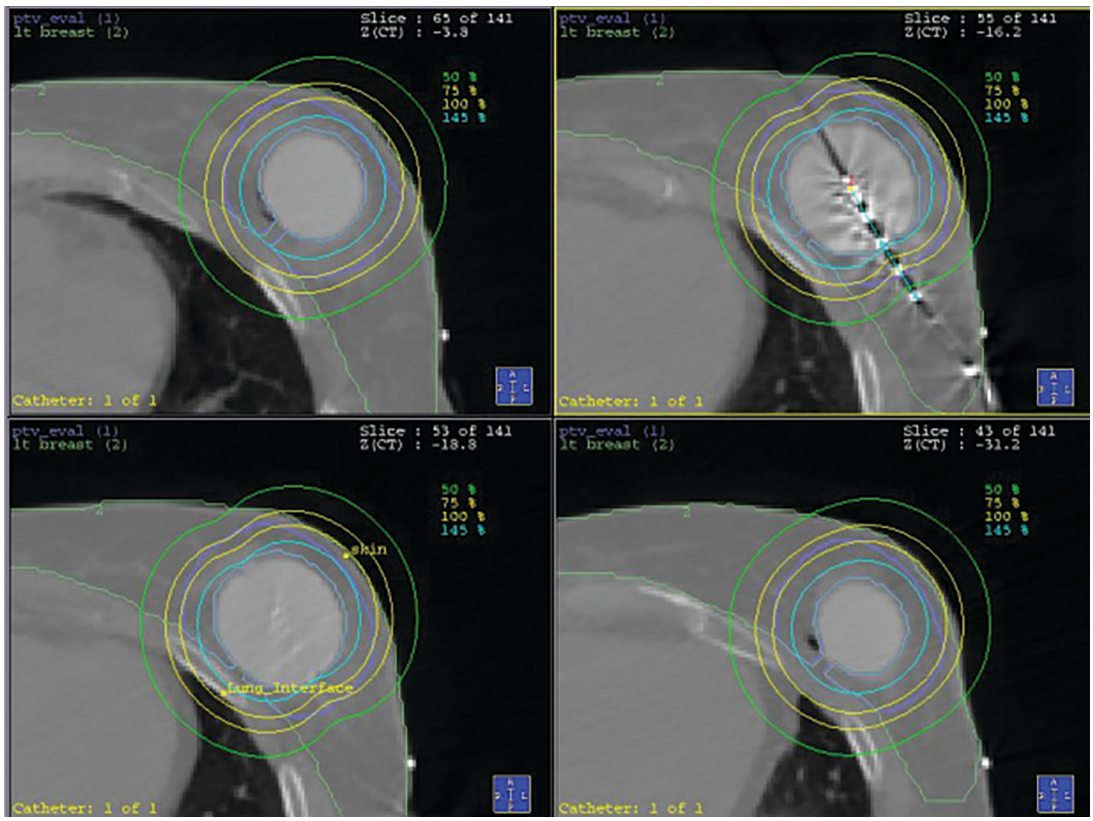

Figure 1. MammoSite plan for treatment of T1bN0M0 invasive ductal carcinoma 10 years prior to presentation.

outcomes when compared with sporadic cases, and local control can be challenging for locally advanced cases.[8] In one case-control series, the 5-year survival of patients with radiation-induced sarcoma was 32%, compared with 51% for sporadic sarcomas ($P < 0.001$).[9]

Management of radiation-induced soft-tissue sarcoma (STS) largely depends on surgical resectability, with neoadjuvant chemotherapy and/or radiation therapy utilized to decrease the risk of local recurrence following surgery. For unresectable cases, definitive radiation therapy with or without chemotherapy can be used.[10] Hyperthermia is a known sensitizer that provides a synergistic effect when used in conjunction with radiation and chemotherapy. In this case study, we present a patient with a 14-cm radiation-induced undifferentiated pleomorphic sarcoma of the chest wall that was successfully resected following neoadjuvant thermochemoradiation with excellent outcomes.

Case Summary

This is a case of a 66-year-old woman who presented with a 1-year history of burning left upper quadrant abdominal and chest discomfort. Past medical history was significant for a T1bN0M0 invasive ductal carcinoma of the left breast, grade 1, ER 90%, PR 80%, and HER-2/neu negative 10 years prior. The patient was treated with standard breast-conserving therapy with partial mastectomy and sentinel lymph node biopsy followed by APBI and 5 years of anastrazole. APBI was delivered using the single lumen MammoSite applicator with iridium 192 high dose rate brachytherapy of 34 Gy in 10 fractions delivered twice per day over 5 consecutive days. Due to the cavity size and location, a portion of the chest wall was within the 145% isodose line (**Figure 1**). The patient underwent routine annual mammogram screening for surveillance after treatment.

Workup of the patient's upper abdominal/chest wall pain was initially limited as it was attributed to gastroesophageal reflux disease. The patient then noticed palpable changes at the site of prior lumpectomy, which were initially attributed to radiation fibrosis. On routine screening mammogram, an 8-cm mass of the left breast lower outer aspect was noted, which had not been seen on the mammogram from 16 months prior. Core needle biopsy of the left breast mass demonstrated a large cell malignant neoplasm, with immunostains favoring undifferentiated pleomorphic sarcoma, although a sarcomatoid carcinoma could not be excluded. MRI of the bilateral breasts with and without contrast demonstrated a 14 × 9 × 9-cm mass centered within the left chest wall, with invasion through the chest wall and suspected to be involving the pleura, pericardium, and left hemi-diaphragm (**Figure 2**). Positron emission tomography/

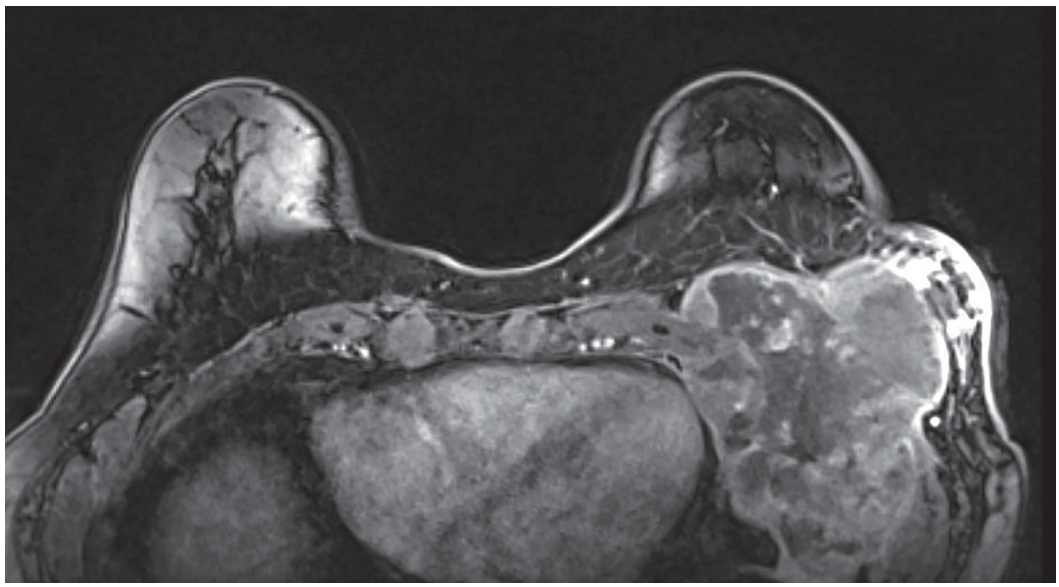

Figure 2. Pretreatment diagnostic MRI of breasts with contrast. T1 postcontrast spectral attenuated inversion recovery (SPAIR) sequence – axial view. Large heterogeneously enhancing mass with mixed vascular kinetics.

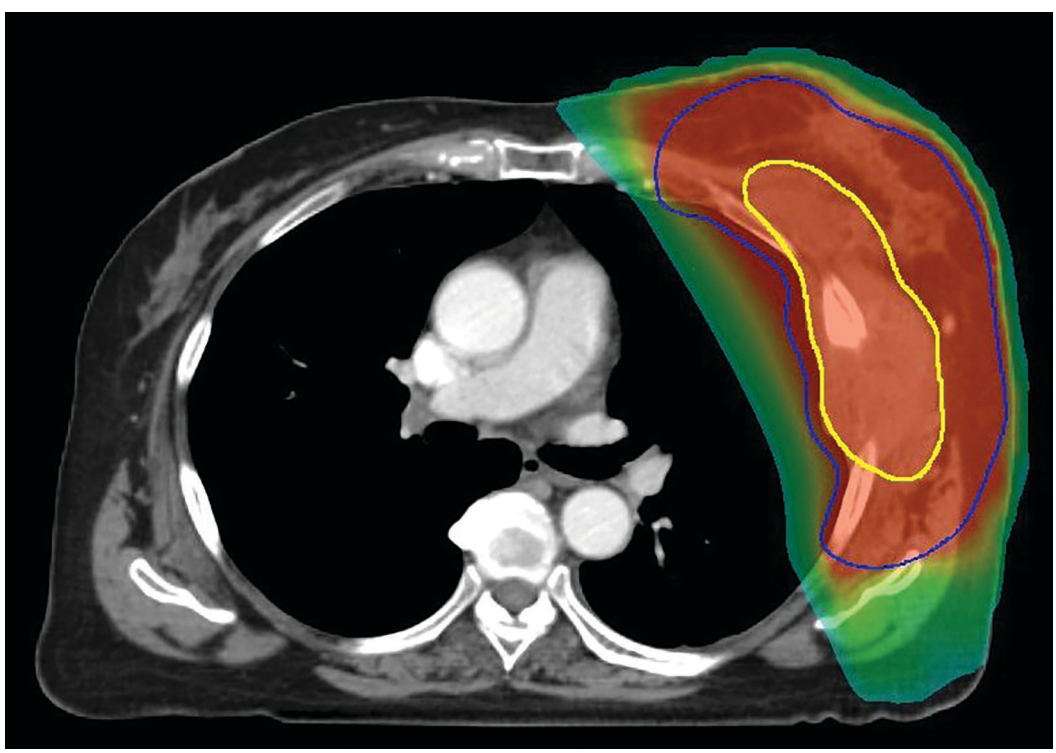

Figure 3. Neoadjuvant radiation therapy plan – axial view. Yellow outline denotes gross tumor volume (GTV). Blue outline denotes planning target volume (PTV). Red color wash denotes area receiving 50 Gy, while color wash to peripheral teal represents 25 Gy.

CT (PET/CT) demonstrated the known primary mass with maximum standardized uptake value (SUV) of 25.5 and an internal mammary and prevascular lymph node with maximum SUV uptake of 2.5. Due to the architecture and low SUV uptake, the lymph nodes were favored to be reactive in nature. A follow-up MRI of the brachial plexus demonstrated no evidence of infiltration.

After multidisciplinary evaluation, we proceeded with neoadjuvant thermochemoradiation to improve likelihood of achieving local control following an anticipated close margin resection. Neoadjuvant radiation was planned to 50 Gy in 25 fractions delivered once daily with a 1-cm bolus applied to the chest wall for the first 13 fractions. Treatment was delivered with 3 coplanar volumetric-modulated arc therapy (VMAT) 10-MV arcs prescribed to the 97.3% planning target volume (PTV) mean (**Figure 3**). Active breathing control was utilized for motion management, and image guidance was provided with daily cone-beam computed tomography (CT) and surface-guided radiation therapy to monitor intrafraction motion.[11] Superficial hyperthermia was administered

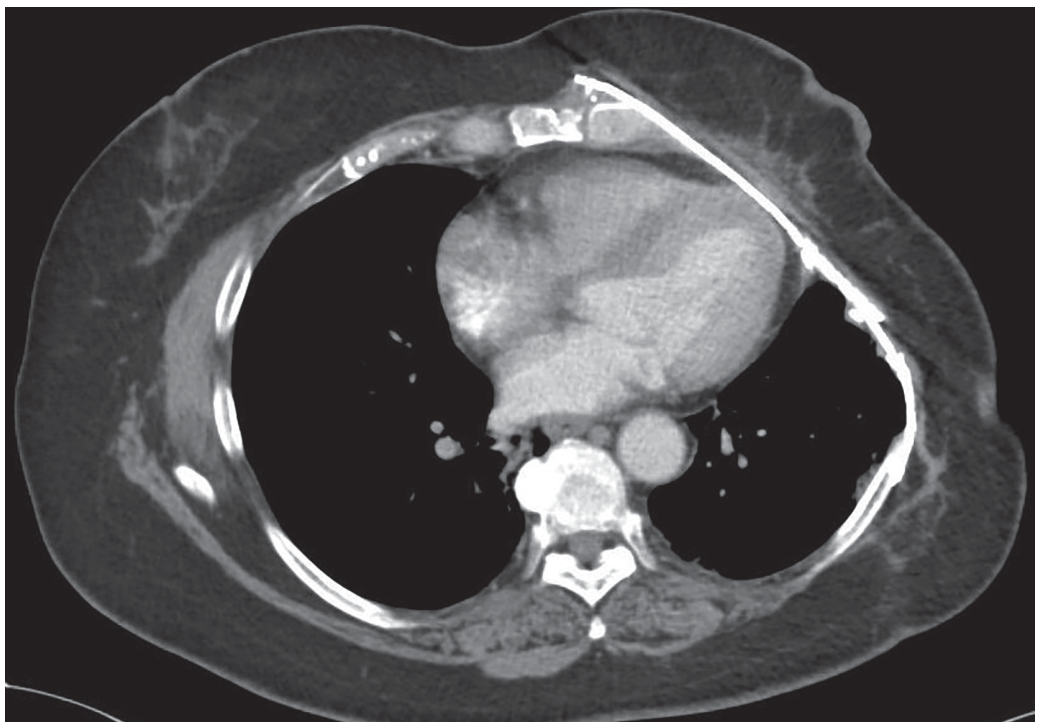

Figure 4. Axial slice of contrast-enhanced computed tomography (3 months postoperative) demonstrating successfully reconstructed chest wall. No radiographic evidence of residual disease was noted.

with a 915-MHz microwave applicator twice per week, separated by 72 hours, with the target temperature of 40 degrees Celsius for 60 minutes immediately prior to radiation. A large 20 × 20-cm applicator was used. Concurrent chemotherapy was administered with weekly gemcitabine at 500mg/m^2. The patient tolerated thermochemoradiation well with toxicity limited to grade 1 radiation dermatitis and fatigue.

Five weeks following completion of thermochemoradiation, repeat CT of the chest with IV contrast demonstrated the known primary mass without a significant change in size. There was radiographic evidence of radiation pneumonitis in the left upper lung, for which the patient was asymptomatic, and a small pleural effusion. The imaging findings represented expected postradiation changes and there was no definitive evidence of distant metastatic disease, so the decision was made to proceed with surgical resection.

Seven weeks following the completion of neoadjuvant therapy, the patient underwent surgical resection of the large chest wall mass. Due to the locally advanced nature, resection of the chest wall – portions of ribs 3 to 8 – and wedge resection of the lung lingula were required**.** The postoperative defect measured 18 cm and was reconstructed with a 20 ×-20 cm titanium mesh; a small residual defect was covered with prolene mesh (**Figure 4**). The titanium mesh has been increasingly used in our institution to provide a more rigid mechanical construct for large chest wall defects, which allows for improved ventilation mechanics. After the chest wall defect was closed, the plastic surgery team performed multisite reconstruction with latissimus dorsi myocutaneous flap, pectoralis minor muscle flap advancement, pectoralis major muscle flap advancement, and serratus muscle flap advancement. Pathological analysis was remarkable for ypT3 primary tumor with 70% necrosis, and final margins were negative with the closest margin at 0.3 cm (mediastinum). The patient tolerated the surgery well and was discharged home on postoperative day 5. There were no infectious, pulmonary, cardiac, or wound-healing complications. She underwent routine surveillance with CT imaging of the chest and physical examination every 3 months for the first 2 years and every 6 months to date. The patient is now 3.5 years post treatment, has resumed normal activities and has no evidence of disease. She was initially treated with gabapentin for mild chest wall pain, which was discontinued 1 year postoperatively. Currently, there is mild episodic nerve pain of the chest wall that lasts seconds and does not require any medical therapy.

Discussion

STS arising in a previously irradiated field often poses a therapeutic challenge, but neoadjuvant therapy can be critical in achieving an R0 resection for large tumors, providing the highest likelihood of local control. This patient's tumor was initially deemed unresectable by multiple practitioners due to its extensive size. However, after detailed imaging, critical structures were determined

to be tumor free and, although it was high-risk, a chest wall resection was deemed possible. Neoadjuvant therapy was crucial as the resection would be completed with limited margins and it also provided an opportunity to assess the biologic behavior of the tumor. It is important to note that the decision to proceed with aggressive therapy was made only after extensive discussion among the multidisciplinary tumor board. Sarcoma tumor board discussions can be particularly valuable, as comprehensive multidisciplinary treatment planning and care has been shown to be associated with improved 2-year, relapse-free survival in sarcoma patients (46.6% vs 51.7%, $P < 0.001$).[10] Additionally, treatment at higher volume centers has been associated with improved median survival (40 months vs 37 months, $P = 0.002$), highlighting the importance of multidisciplinary evaluation at tertiary care centers.

Gemcitabine was chosen as the concurrent chemotherapy agent as it is a well-known radiosensitizer, and phase I data from high-risk extremity and trunk STS demonstrated a major pathologic response (> 90% necrosis) in 47% of patients at a maximum tolerated dose of 700 mg/m^2. This study reported 5-year overall survival of 86%, but the maximum tolerated dose was associated with 24% grade 4 toxicity.[13] This study also did not have many trunk STSs, so there was additional concern for an increased risk of radiation pneumonitis that has been seen with gemcitabine and high-dose thoracic radiation in non-small cell lung cancer.[14,15] To provide the maximum benefit but limit risk of complications, which could delay or prevent surgery, gemcitabine was ultimately given at 500 mg/m^2 weekly, which was well tolerated. Previous literature suggests that gemcitabine acts as a potent radiosensitizer even at doses 1000 times lower than that normally achieved in plasma.[16]

Due to the partially superficial nature of this chest wall tumor, the addition of moderate temperature hyperthermia was used as a complementary therapy. Hyperthermia results in enhanced perfusion improving oxygenation and, potentially, the effectiveness of chemoradiation.[17-20] Both hypoxia and radiation are known to induce expression of proteins, such as HIF-1α, which prevent activation of signaling cascades necessary to induce cellular apoptosis. Driving down expression of these proteins via oxygenation is thought to alleviate this blockade, increasing overall apoptosis from radiation-induced DNA damage.[20] In addition to enhanced perfusion and oxygenation, as intracellular temperature rises, tertiary and quaternary protein structure can be interrupted, resulting in denaturation and subsequent loss of function. Cytoskeletal elements, centrioles, and DNA repair proteins have been shown to be particularly sensitive to this form of damage.[21] Interruption of DNA repair mechanisms diminishes target cells' ability to recover from both direct and indirect radiation-induced DNA damage.[22] This concept has been extended to DNA damage-based chemotherapeutic agents.[23] Specifically, hyperthermia has been shown to decrease cells' ability to recover from gemcitabine-induced halted replication forks.[24] Our institution has a superficial microwave applicator that has a typical penetration of 3 cm and, although the entire tumor could not be completely heated, we felt that the possible benefit from heating the majority of the tumor with a low risk of toxicity justified its use.

The extensive chest wall resection that would be required to completely remove the tumor was the driving factor that led most providers to believe this tumor was not resectable. Any defect larger than 5 cm and involving multiple ribs must be carefully reconstructed to restore pulmonary function, protect the intrathoracic organs, and support soft-tissue reconstruction for wound closure. In this case, the resulting chest wall defect measured 18 cm and was reconstructed with titanium mesh and a complex multisite flap closure. Titanium mesh was chosen based on the biomechanical characteristics that create a stable and rigid anatomical chest wall contour while maintaining mechanical ventilation.

While these modalities have been studied in limited combination, the efficacy of thermochemoradiation prior to a large surgical resection requiring extensive reconstruction has not been well explored. In a phase III randomized study, the addition of regional hyperthermia to neoadjuvant systemic therapy for high-risk STS was shown to prolong median disease-free survival by 15.9 months and subsequently improve 5- and 10-year overall survival by 11% and 10%, respectively.[25] Hyperthermia with neoadjuvant chemoradiation was also found to double 3-year overall survival for patients with squamous cell carcinoma of the esophagus, and also resulted in a significantly higher rate of pathologic complete response (25% vs 5.9%, $P < 0.05$).[26] Hyperthermia can be particularly helpful for patients with unresectable disease, as the thermal enhancement ratio can result in a higher likelihood of local control with definitive radiation. In the meta-analysis of radiation with hyperthermia for locally recurrent breast cancer, the addition of hyperthermia increased the likelihood of achieving a complete response by 22% without significant morbidity; hyperthermia was also associated with improved locoregional control in approximately two-thirds of patients receiving reirradiation.[27] In a more recent randomized control trial in cervical cancer, thermochemoradiation outperformed chemoradiation alone with higher 5-year overall survival rates (81.9% vs 72.3%, $P < 0.05$).[28] This case provides evidence that the successes seen with this aggressive multimodality approach

have potential to extend to STS of the chest wall in patients with acceptable comorbidities.

Conclusion

This case report demonstrates the successful treatment of a patient with locally advanced radiation-induced chest wall sarcoma using neoadjuvant thermochemoradiation, surgical resection, and complex reconstruction with a titanium mesh implant and multisite flap closure. The aggressive treatment approach resulted in a microscopic complete resection and the patient remains disease free 3.5 years post treatment. While radiation-induced sarcomas present significant therapeutic challenges, it is important that otherwise fit patients without metastatic disease receive multidisciplinary evaluation at tertiary care centers, because with aggressive multimodality therapy they have potential for long-term survival.

References

1) Vicini FA, Cecchini RS, White JR, et al. Long-term primary results of accelerated partial breast irradiation after breast-conserving surgery for early-stage breast cancer: a randomised, phase 3, equivalence trial. *Lancet.* 2019;394:2155-2164. doi:10.1016/S0140-6736(19)32514-0

2) Whelan TJ, Julian JA, Berrang TS, et al. External beam accelerated partial breast irradiation versus whole breast irradiation after breast conserving surgery in women with ductal carcinoma in situ and node-negative breast cancer (RAPID): a randomised controlled trial. *Lancet*. 2019;394:2165-2172. doi:10.1016/S0140-6736(19)32515-2

3) Vicini FA, Douglas A, Todor D, Julian T, Lyden M. Dosimetric improvements in balloon-based brachytherapy using the contura R multi-lumen balloon (MLB) catheter to deliver accelerated partial breast irradiation. *J Contemp Brachytherapy*. 2010;2:1-8. doi:10.5114/jcb.2010.13716

4) Brown S, Vicini F, Vanapalli JR, et al. Factors associated with chest wall toxicity after accelerated partial breast irradiation using high-dose-rate brachytherapy. *Int J Radiat Oncol Biol Phys*. 2012;83:801-805. doi:10.1016/j.ijrobp.2011.08.033

5) Chang DS, Lasley FD, Das IJ, Mendonca MS, Dynlacht JR. Basic radiotherapy physics and biology. *Basic Radiother Phys Biol.* 2014;303-311. FF:10.1007/978-3-319-06841-1

6) Santos AM, Marcu LG, Wong CM, Bezak E. Risk estimation of second primary cancers after breast radiotherapy. *Acta Oncol*. 2016;55:1331-1337. doi:10.1080/0284186X.2016.1185150

7) Yap J, Chuba PJ, Thomas R, et al. Sarcoma as a second malignancy after treatment for breast cancer. *Int J Radiat Oncol Biol Phys.* 2002;52(5):1231-1237. doi:10.1016/s0360-3016(01)02799-7

8) Dineen SP, Roland CL, Feig R, et al. Radiation-associated undifferentiated pleomorphic sarcoma is associated with worse clinical outcomes than sporadic lesions. *Annals Surg Oncol*. 2015;22:3913-3920. doi:10.1245/s10434-015-4453-z

9) Bjerkehagen B, Småstuen M, Hall K, et al. Why do patients with radiation-induced sarcomas have a poor sarcoma-related survival? *Br J Cancer*. 2012;106:297-306. doi:10.1038/bjc.2011.559

10) Mehren MV, Randall RL, Benjamin RS, et al. Soft Tissue Sarcoma, Version 2.2018: Clinical Practice Guidelines in Oncology. *J Natl Compr Cancer Netw.* 2018;16:536-563. doi:10.6004/jnccn.2018.0025

11) Eldredge-Hindy H, Lockamy V, Crawford A, et al. Active Breathing Coordinator reduces radiation dose to the heart and preserves local control in patients with left breast cancer: report of a prospective trial. *Pract Radiat Oncol.* 2015;5:4-10. doi:10.1016/j.prro.2014.06.004.Active

12) Blay J-Y, Soibinet P, Penel N, et al. Improved survival using specialized multidisciplinary board in sarcoma patients. *Ann Oncol.* 2017;28:2852-2859. doi:10.1093/annonc/mdx484

13) Tseng WW, Zhou S, To CA, et al. Phase 1 adaptive dose-finding study of neoadjuvant gemcitabine combined with radiation therapy for patients with high-risk extremity and trunk soft tissue sarcoma. 2015;121(20):3659-3667. doi:10.1002/cncr.29544

14) Arrieta O, Gallardo-Rincon D, Villarreal-Garza C, et al. High frequency of radiation pneumonitis in patients with locally advanced non-small cell lung cancer treated with concurrent radiotherapy and gemcitabine after induction with gemcitabine and carboplatin. *J Thorac Oncol.* 2009;4:845-852. doi:10.1097/JTO.0b013e3181a97e17

15) Socinski MA, Blackstock AW, Bogart JA, et al. Randomized phase II trial of induction chemotherapy followed by concurrent chemotherapy and dose-escalated thoracic conformal radiotherapy (74 Gy) in stage III non-small-cell lung cancer: CALGB 30105. *J Clin Oncol.* 2008;26:2457-2463. doi:10.1200/JCO.2007.14.7371

16) Shewach DS, Lawrence TS. Gemcitabine and radiosensitization in human tumor cells. *Investig New Drugs.* 1996;14:257-263. doi:10.1007/BF00194528

17) Song CW. Effect of local hyperthermia on blood flow and microenvironment: a review. *Cancer Res.* 1984;44(10 Suppl):4721s-4730s.

18) Brizel DM, Scully SP, Harrelson JM, et al. Radiation therapy and hyperthermia improve the oxygenation of human soft tissue sarcomas. *Cancer Res.* 1996;56:5347-5350.

19) Sun X, Xing L, Clifton Ling C, Li GC. The effect of mild temperature hyperthermia on tumour hypoxia and blood perfusion: relevance for radiotherapy, vascular targeting and imaging. *Int J Hyperth.* 2010;26:224-231. doi:10.3109/02656730903479855

20) Moeller BJ, Cao Y, Li CY, Dewhirst MW. Radiation activates HIF-1 to regulate vascular radiosensitivity in tumors: role of reoxygenation, free radicals, and stress granules. *Cancer Cell.* 2004;5:429-441. doi:10.1016/S1535-6108(04)00115-1

21) Vidair CA, Doxsey SJ, Dewey WC. Heat shock alters centrosome organization leading to mitotic dysfunction and cell death. *J Cell Physiol.* 1993;54:443-455. doi:10.1002/jcp.1041540302

22) Kampinga HH, Dikomey E. Hyperthermic radiosensitization: mode of action and clinical relevance. *Int J Radiat Biol.*2001;77:399-408. doi:10.1080/09553000010024687

23) Mantso T, Goussetis G, Franco R, Botaitis S, Pappa A, Panayiotidis M. Effects of hyperthermia as a mitigation strategy in DNA damage-based cancer therapies. *Semin Cancer Biol.* 2016;37-38:96-105. doi:10.1016/j.semcancer.2016.03.004

24) Raoof M, Zhu C, Cisneros BT, et al. Hyperthermia inhibits recombination repair of gemcitabine-stalled replication forks. *J Natl Cancer Inst.* 2014;106(8). doi10.1093/jnci/dju183

25) Issels R, Linder LH, Verweij J, et al. Effect of neoadjuvant chemotherapy plus regional hyperthermia on long-term outcomes among patients with localized high-risk soft tissue sarcoma. 2018;4:483-492. doi:10.1001/jamaoncol.2017.4996

26) Kitamura K, Kuwano M, Watanabe M, et al. Prospective randomized study of hyperthermia combined with chemoradiotherapy for esophageal carcinoma. *J Surg Oncol.* 1995;60;55-58. doi:10.1002/jso.2930600111

27) Datta NR, Puric E, Klingbiel D, Gomez S, Bodis S. Hyperthermia and radiation therapy in locoregional recurrent breast cancers: a systematic review and meta-analysis. *Int J Radiat Oncol Biol Phys*. 2016;94:1073-1087. doi:10.1016/j.ijrobp.2015.12.361

28) Wang Y, Hong W, Che S, et al. Outcomes for hyperthermia combined with concurrent radiochemotherapy for patients with cervical cancer. *Int J Radiat Oncol Biol Phys*. 2020;107(3):499-511. doi:10.1016/j.ijrobp.2020.03.006

ARO Introduces Four Medical Student Committees

Applied Radiation Oncology is excited to announce the development of four medical student committees to help increase student exposure to radiation oncology and provide publishing-related experience in the field. We look forward to working with this aspiring and talented group for the 2022-2023 academic year, focusing on peer reviews, podcasts/webinars, blog and article submissions, and social media engagement.

Special thanks to our dedicated board member, Sarah Hoffe, MD, section head of GI Radiation Oncology at Moffitt Cancer Center for serving as the faculty advisor for the committees.

Please join us in welcoming the new committee members and co-chairs, and stay tuned online and in print for developments surrounding their efforts!

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Environmentally Sustainable Radiation Oncology: Can We Turn the Tides?

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It is irrefutable that our planet and human health are increasingly impacted by a changing climate. Around the world, numerous sectors are actively participating in adaptation and mitigation efforts to reduce the environmental impact of daily practices and lessen the burden on human health.[1] In the US, the health care sector accounts for approximately 8.5% of greenhouse gas (GHG) emissions, with hospitals consuming, on average, more than any other type of nonresidential building.[2] Governments, hospitals and health systems, domestically and around the globe, have committed to reduce health care emissions and address issues of environmental injustice.[3] Accordant actions include: analyzing waste streams and segregation practices, monitoring operating room temperatures, creating "green" travel policies, developing device-reprocessing programs, recycling electronic waste, implementing climate-smart supply chains, using locally sourced food services, and establishing climate resiliency community-based programs.[1,4]

As radiation oncologists in training, we feel obligated to not only advocate but actively participate in transitioning to sustainable practices within our field and the broader oncology community. The Global Health Subcommittee within the Association of Residents in Radiation Oncology has established the Climate Health, Equity, and Sustainability Taskforce (CHEST) to foster united awareness, action, and collaboration. Broad-reaching opportunities and areas for future focus include, but are not limited to the following:

1. Develop and disseminate climate health and oncology educational tools.
2. Quantify GHG emissions associated with current radiation therapy.
3. Reduce clinical and procedural waste.
4. Practice sustainable resource consumption.
5. Advocate for decarbonization of energy sources within the health system.
6. Identify opportunities for improved equipment/departmental energy efficiency (eg, machine idle time and sequence of treatment delivery).
7. Collaborate with industry partners to align machine design, production, and operations with sustainability goals.

Disclosure: The authors have no conflicts of interest to disclose. None of the authors received outside funding for the production of this original manuscript and no part of this article has been previously published elsewhere.
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8. Partner with suppliers to increase the availability of reusable products when possible (eg, immobilization devices and procedural equipment).
9. Address issues of environmental injustice and health inequities exacerbated by climate change.
10. Design and implement programs to promote climate health equity and build climate resiliency among vulnerable populations.[5]

In accordance with national and international societies and other medical specialties (including the American Board of Radiology) who have declared commitments toward environmental stewardship, we as residents make this call to action within radiation oncology and our professional society.[3] We aim to bring climate health, equity and sustainability to the forefront of current discussions. Radiation oncologists have an urgent but timely opportunity to actively engage and become leaders in creating a more equitable, sustainable, and healthy future for our communities, patients, colleagues, and generations to come.

References

1) IPCC, 2022: Climate Change 2022: Impacts, Adaptation, and Vulnerability. Contribution of Working Group II to the Sixth Assessment Report of the Intergovernmental Panel on Climate Change. Pörtner HO, Roberts DC, Tignor M, et al, eds. Cambridge University Press. In Press.

2) Eckelman MJ, Huang K, Lagasse R, Senay E, Dubrow R, Sherman JD. Health care pollution and public health damage in the United States: an update. *Health Aff (Millwood)*. 2020;39(12):2071-2079.

3) Countries commit to develop climate-smart health care at COP26 UN climate conference. Accessed June 13, 2022. https://www.who.int/news/item/09-11-2021-countries-commit-to-develop-climate-smart-health-care-at-cop26-un-climate-conference

4) Lichter K, Baniel C, Anderson J, Bhatia R. Environmentally sustainable brachytherapy care. *Brachytherapy*. 2022;S1538-4721(22)00089-7. doi:10.1016/j.brachy.2022.06.002

5) Balbus JM, Luber G. Human health. In: D'Onofrio D, ed. *Fourth National Climate Assessment*. U.S. Global Change Research Program; 2018.

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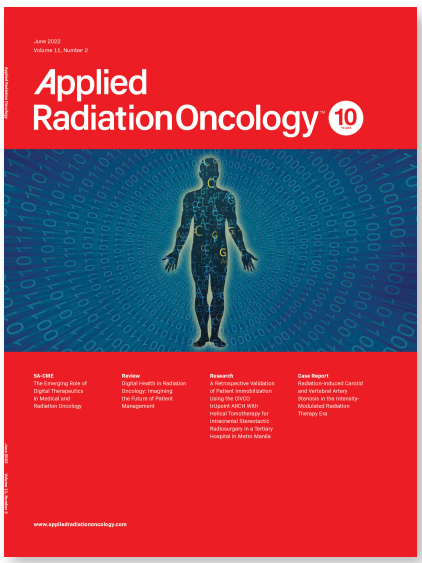

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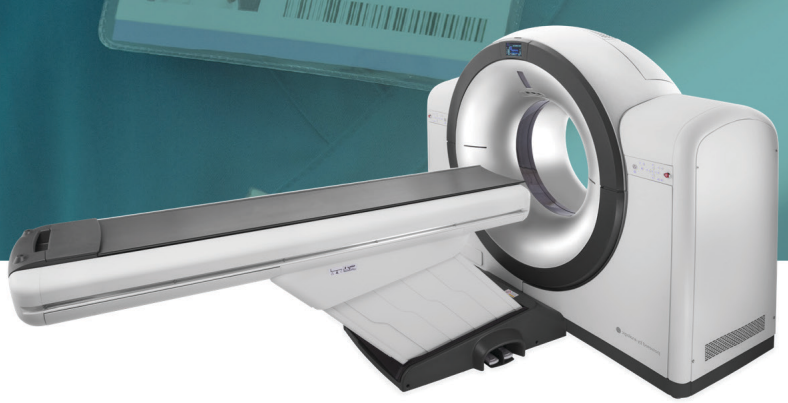

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