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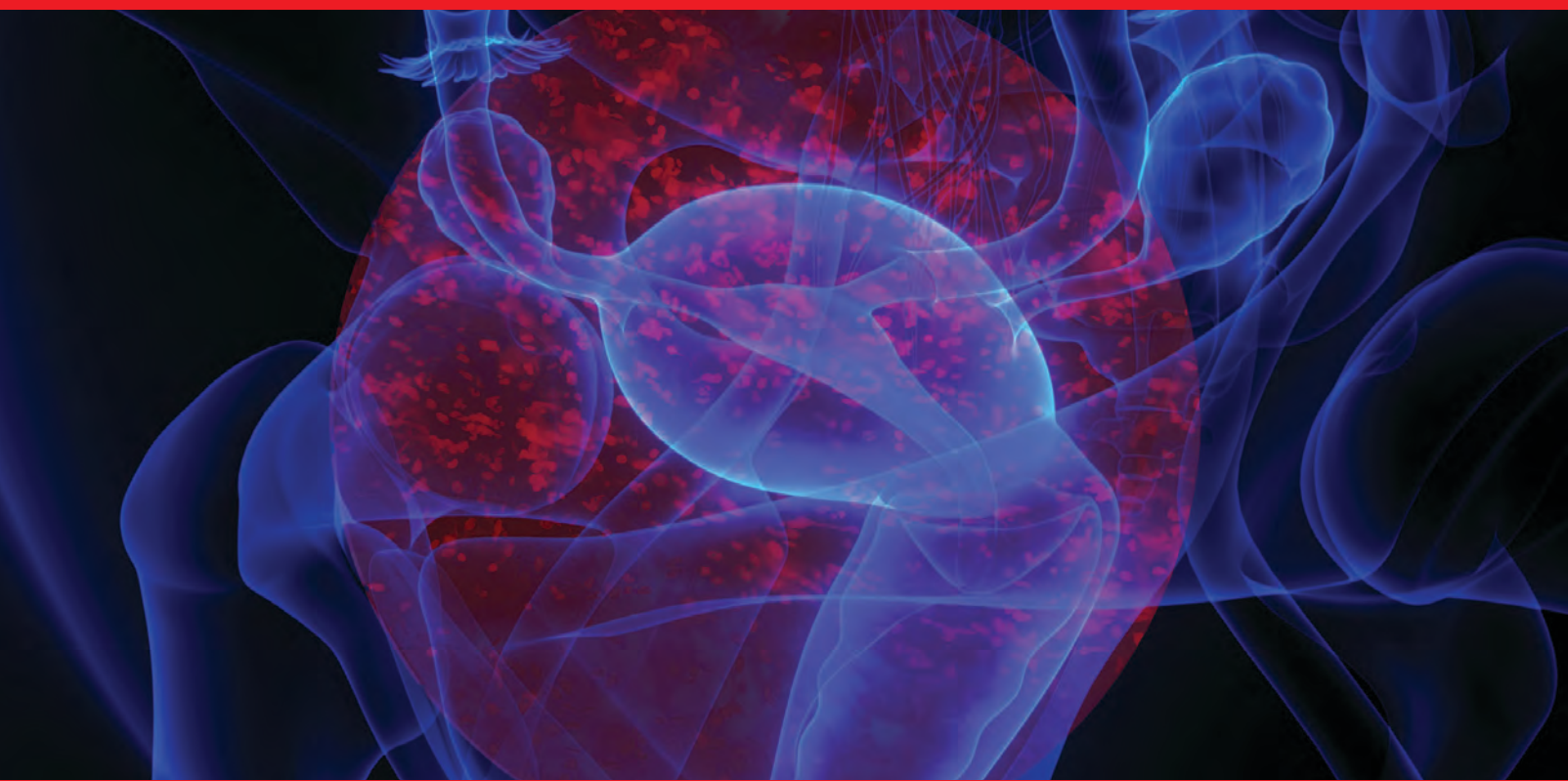

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A Proposed Way Forward From the Prior Authorization Crisis in Radiation Oncology

Review
Adjuvant Radiation in Early Stage Vulvar Cancer: A Review of Indications and Optimal Dose

Research
Real-time Prostate Gland Motion and Deformation During CyberKnife Stereotactic Body Radiation Therapy

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FOCUS: GYNECOLOGIC CANCER

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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.

Goals and Gains in Gynecologic Radiation Therapy

John Suh, MD, FASTRO, FACR

Welcome to the March 2022 issue of *ARO*! We are pleased to begin our 11th year in operation with a focus on gynecologic cancer featuring articles on cervical, vulvar and ovarian malignancies.

Kicking off the issue is the guest editorial, *Efforts to Support Cervical Cancer Treatment During the COVID-19 Pandemic,* which describes resourceful steps taken during the crisis to foster the essential role of radiation therapy (RT) in low- and middle-income countries (LMICs). Hosting virtual RT training and webinars in multiple languages are just a few ways groups mobilized resources to improve cervical cancer management in LMICs, which are disproportionately burdened by this disease. Such global initiatives showcase the power of a collective momentum, providing progress and much-needed hope in times of upheaval.

Next, we present the comprehensive article, *Adjuvant Radiation in Early Stage Vulvar Cancer: A Review of Indications and Optimal Dose*. This excellent review examines why patients with vulvar cancer with positive or close margins should consider adjuvant radiation therapy as long as the potential advantages of reducing local recurrence and improving progress-free survival outweigh morbidity-related concerns.

The case report, *Whole Abdominal Radiation Therapy (WART) for Chemo-Refractory Adult Granulosa Cell Tumor of the Ovary*, is also presented as part of the focus to illustrate how WART delivered with modern radiation techniques can produce excellent clinical and radiological response rates with acceptable toxicity and potential long-term disease control.

In addition to gynecologic oncology, we offer a variety of other timely, important topics, including the terrific SA-CME-approved review, *A Proposed Way Forward From the Prior Authorization Crisis in Radiation Oncology*. Also featured is the Resident Voice column, *Improving Well-Being and Combating Burnout in Radiation Oncology Training,* a needed reminder – especially in today's tumultuous times – that public health emergencies and social unrest require heightened support for trainee well-being in particular.

We also are excited to offer additional thought-provoking articles on global health gaps and growth, namely *Quality Assurance in Radiation Oncology: Addressing a Changing Treatment Landscape*, and *Radiation Therapy in Indonesia: Estimating Demand as Part of a National Cancer Control Strategy*. Finally, we hope you enjoy the research article, *Real-time Prostate Gland Motion and Deformation During CyberKnife Stereotactic Body Radiation Therapy*, which analyzes intrafraction prostate motion in a small cohort of patients and calculates the planning target volume margins needed to address related errors when delivering prostate SBRT.

In closing, I would like to sincerely thank and acknowledge the dedicated team of peer reviewers (see p. 43) who were instrumental in helping *ARO* deliver strong, engaging content throughout 2021, which was a very difficult year for all of us. Peer reviewers are a special group who volunteer hours of time amidst busy schedules to provide thoughtful, constructive feedback in their areas of expertise. Without their efforts, *ARO* would not be able to publish the various research and review articles, case reports, and editorials.

As spring settles in, we wish you a season of renewal and hope, especially as we face a new chapter of global distress stemming from the war in Ukraine. We hope for a swift, peaceful resolution, and offer our sincerest thoughts and support to all of those who are affected. Please continue to be kind during these uncertain times.

Efforts to Support Cervical Cancer Treatment During the COVID-19 Pandemic

Megan E. Kassick, MD, MPH; Alfredo Polo, MD, PhD; May Abdel-Wahab, MD, PhD

Dr. Kassick is a PGY5 radiation oncology resident at Yale University School of Medicine, and former intern in the Division of Human Health, Department of Nuclear Sciences and Applications, International Atomic Energy Agency, (IAEA), Vienna, Austria.

Dr. Polo is a radiation oncologist in the Division of Human Health, IAEA.

Dr. Abdel-Wahab is director of the Division of Human Health, IAEA.

Disclosure: Dr. Abdel-Wahab is the chair of the International Committee of the American Society for Radiation Oncology (ASTRO). The authors have no other conflicts of interest to disclose.

Radiation therapy is a mainstay of treatment in cervical cancer, with both external-beam radiation therapy and brachytherapy required for curative intent treatment in all but the earliest stages of the disease.[1] With appropriate treatment, cure can be achieved even in patients with locally advanced disease. Including brachytherapy is essential for cure and significantly increases survival.[1] Detriments in survival, however, are seen if treatment is extended beyond an overall treatment time of 8 weeks.[2] Therefore, decreased access to treatment, including during the COVID-19 pandemic, has a recognized significant impact. While the International Atomic Energy Agency (IAEA) has been active in supporting cervical cancer management, the COVID-19 pandemic resulted in additional challenges that had to be addressed.

In 2020, cervical cancer estimates revealed 600,000 new cases and 340,000 deaths, with a disproportionate burden in low- and middle-income countries (LMICs).[3] In response to this public health crisis, the United Nations Joint Global Programme on Cervical Cancer Prevention and Control (Joint Programme) was launched in 2017, which involves 7 United Nations agencies including the IAEA, and provides global leadership and technical assistance to governments and their partners to build national comprehensive cervical cancer control programs.[4] Subsequently, a World Health Assembly resolution was passed in 2020 with the global strategy to accelerate the elimination of cervical cancer adopted at that time, demonstrating a continued commitment to tackling cervical cancer, even in the face of a global pandemic.[5]

The global strategy calls for specific targets by 2030; the 90-70-90 targets indicate goals for vaccination, screening, and treatment of both pre-invasive and invasive cervical disease.[5] While immunization and screening are of critical importance, especially in the long-term for the millions of women who will continue to be diagnosed with cervical cancer, access to treatment will more immediately impact individual patient survival. The combined strategy will be effective since it allows the treatment of current cervical cancer patients, while preventing cervical cancer in decades to come.

The significant role that the IAEA plays in the Joint Programme focuses on initiatives related to radiation therapy, nuclear medicine, and diagnostic radiology. Joint missions were conducted by the United Nations agencies and partners in 6 initial countries and resulted in work plans to address gaps in cervical cancer control. The IAEA has been supporting these countries through its programs.[6,7] Further IAEA actions through the Joint Programme include providing training on radiation therapy for cervical cancer, the most recent of which were initially planned to be held on site in Tanzania and Morocco. The multiday training was designed to focus on practical aspects of delivering high-quality radiation therapy for cervical cancer, including both external beam and brachytherapy techniques. With travel put on hold, the IAEA converted the training to virtual sessions. While these were not meant to replace the in-person training that will come later, it allowed the continuation of support to experts on the ground during a time with limited options. The multiday sessions were conducted in December 2020 and March 2021. Tanzania had more than 40 participants, and Morocco had over 70 participants from 5 different sites in the country. The sessions included relevant lectures, review and critique of treatment plans, and interactive hands-on tumor and normal tissue contouring activities.

Another way in which the IAEA has continued to support countries during the pandemic

is through a series of COVID-19 webinars in multiple UN languages. These webinars have convened professional societies in radiation therapy and nuclear medicine to guide centers on the ground to continue safe delivery of these essential services to patients (https://www.iaea.org/topics/health/infectious-diseases/covid-19/webinars). In addition, virtual tumor boards with Africa (AFRONET) and Asia (ASPRONET) allow for case discussions and educational lectures among oncology team members regionally.

In addition to education and training, the IAEA plays a role in many other aspects of ensuring continued access to radiation therapy and particularly brachytherapy for cervical cancer, including through mapping resources for radiation therapy and radiology in the Directory of Radiotherapy Centres (DIRAC) (https://dirac.iaea.org) and Medical imAGIng and Nuclear mEdicine (IMAGINE) (https://humanhealth.iaea.org/HHW/DBStatistics/IMAGINE.html) databases. Safety and quality are important and can be enhanced through comprehensive quality assurance audits implemented through the Quality Assurance Team for Radiation Oncology (QUATRO).[8] Dosimetry laboratory calibration services for radiation therapy sources used in high-dose-rate and low-dose-rate brachytherapy are provided as another method of quality control.[9] Research efforts through the IAEA's coordinated research activities represent another way to promote cervical cancer treatment for patients. These include clinical trials, cost-effectiveness studies, dosimetric studies, and implementation studies, among others. Examples of these coordinated research efforts include a study examining brachytherapy fractionation and radiobiology and an implementation study for image-guided brachytherapy for cervical cancer.[10] In addition, the IAEA provides support to set up radiation therapy and nuclear medicine centers worldwide.[6]

Now, nearly 2 years into the pandemic, it remains more important than ever to continue efforts to increase access to life-saving radiation therapy for patients diagnosed with cervical cancer. IAEA efforts and the recently launched global initiatives illustrate that the collective momentum is unprecedented. Such measures to increase access to cancer treatment are essential to achieve our goals.

References

1) Viswanathan AN, Thomadsen B. American Brachytherapy Society consensus guidelines for locally advanced carcinoma of the cervix. Part I: general principles. *Brachytherapy.* 2012;11:33-46.

2) Girinsky T, Rey A, Roche B, et al. Overall treatment time in advanced cervical carcinomas: a critical parameter in treatment outcome. *Int J Radiat Oncol Biol Phys.* 1993;27:1051-1056.

3) Ferlay J, Ervik M, Lam F, et al. Global Cancer Observatory: Cancer Today. *International Agency for Research on Cancer.* Accessed April 1, 2021. https://gco.iarc.fr/today

4) World Health Organization. *UN Joint Global Programme on Cervical Cancer Prevention and Control.* World Health Organization, Geneva; 2016.

5) World Health Organization. *Global Strategy to Accelerate the Elimination of Cervical Cancer as a Public Health Problem*. World Health Organization, Geneva; 2020.

6) Abdel-Wahab M, Zubizarreta E, Polo A, et al. Improving quality and access to radiation therapy – an IAEA perspective. *Semin Radiat Oncol.* 2017;27:109-117.

7) Abdel-Wahab M, Gondhowiardjo S, Accioly Rosa A, et al. Global radiotherapy: current status and future directions – white paper. *J Glob Oncol.* 2021;7:827-842.

8) International Atomic Energy Agency. *Comprehensive audits of radiotherapy practices: a tool for quality improvement*. International Atomic Energy Agency, Vienna; 2007.

9) Izewska J, Lechner W, Wesolowska P. Global availability of dosimetry audits in radiotherapy: the IAEA dosimetry audit networks database. *Phys Imaging Radiat Oncol.* 2018;5:1-4.

10) Hendy J, Jones GW, Mahantshetty UM, et al. Radiobiological analysis of outcomes using external beam radiotherapy plus high dose rate brachytherapy (4×7 Gy) or (2×9 Gy) for cervical cancer in a multi-institution trial. *Int J Radiat Oncol Biol Phys.* 2017;99:313-1314.

A Proposed Way Forward From the Prior Authorization Crisis in Radiation Oncology

Description

The authors review the rationale behind the establishment of prior authorization (PA) by health care payers, discuss issues with the current system with a focus on radiation oncology, and propose multiple changes that could improve the system for clinicians, payers, and patients.

Learning Objectives

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

- understand the initial intentions behind the establishment of prior authorization and how its use has expanded beyond these initial intentions;
- recognize the specific flaws and burdens associated with the current system, especially as it pertains to the practice of radiation oncology; and
- appreciate the potential of systems-based changes to streamline the process and improve transparency as a potential way forward.

Accreditation/ Designation Statement

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

Authors

Praveen Pendyala, MD;[1]
Alexander G. Goglia, MD, PhD;[2]
Ronald D. Ennis, MD[3]

Affiliations: [1]Department of Radiation Oncology, Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH; [2]Department of Radiation Oncology, Memorial Sloan-Kettering Cancer Center, New York, NY; [3]Department of Radiation Oncology, Rutgers Cancer Institute of New Jersey, New Brunswick, NJ.

Target Audience

- Radiation Oncologists
- Related Oncology Professionals

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A Proposed Way Forward From the Prior Authorization Crisis in Radiation Oncology

Praveen Pendyala, MD;[1] Alexander G. Goglia, MD, PhD;[2] Ronald D. Ennis, MD[3]

Abstract

The use of prior authorization (PA) by medical payers has expanded in recent years beyond its initial focus on limiting the use of unproven, high-cost treatments and is now more frequently being used to limit access to guideline-concordant treatments and generic medications. This has been accompanied by a similar expansion of administrative demands for physicians to comply with PA requests, requiring hours of additional time per week, especially for resource-intensive specialties like radiation oncology. Here, we discuss the current landscape of PA use in radiation oncology and propose actionable steps that can be taken to improve the process for patients, clinicians, and payers alike. By streamlining electronic practitioner-payer communication, increasing transparency around payers' PA requirements, and providing a path to waiving PA requirements for select cases, we can establish a system in which patients are able to receive the best possible care in a timely, cost-efficient, and evidence-based fashion.

Keywords: radiation oncology, prior authorization, preauthorization, medical economics, health care spending, advocacy, insurance, reimbursement

Introduction: Prior Authorization Defined

Prior authorization (PA) is a management process applied by health care insurers to a list of services and medications that requires case-by-case review to determine whether a proposed treatment will be covered.[1] The expanding set of services subject to PA is determined unilaterally by the payer. These policies vary by insurer and are changed frequently, creating a system of low predictability for physicians and their patients.[2] Given the burdens this process also creates for the insurers themselves, many have turned to third-party businesses known as resource benefits managers (RBMs) to carry out their policies.[3]

The ubiquitous PA requirements of the current practice environment have created a medical system where, for each patient, physicians must first determine whether a proposed service will require PA and, if so, whether it is likely to qualify for payment through the particular insurer.[2,4,5] If a proposed service is unlikely to be approved, physicians might decide not to pursue the medically superior treatment and instead pivot to a more easily approved alternative. If they do elect to pursue PA for a service, physicians are generally required to submit documentation — in some circumstances, remarkably, on paper via fax — regarding the patient's characteristics and proposed treatment. This will often include completing forms or entering data that is already present in the medical record, creating a wasteful burden on clinicians and their staff without providing reimbursement for additional time spent.[2] The required information, the timeliness of its submission, and the timeliness of payer's response are all unilaterally decided by the insurers/RBMs and vary across the industry, creating a chaotic experience for clinicians and patients alike.

Affiliations: [1]Department of Radiation Oncology, Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH; [2]Department of Radiation Oncology, Memorial Sloan-Kettering Cancer Center, New York, NY; [3]Department of Radiation Oncology, Rutgers Cancer Institute of New Jersey, New Brunswick, NJ.
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If authorization is denied, a peer-to-peer consultation is often the next step.[6] In this process, the physician will discuss the case with a physician employee of the insurer or an RBM to explain the justification of the proposed treatment. However, the effectiveness and collaborative nature of this process varies widely. First, the scheduling of this conversation is often established by the insurers without regard for the physician's availability. Physicians may be expected to interrupt a sensitive consultation with a patient, an important meeting, or an after-hours family gathering to accommodate the payer's schedule. In addition, the qualifications of the "peer" with whom the provider discusses the case can be highly variable and may not even be from the same field (eg, primary care doctors reviewing radiation oncology requests), which obviously makes the review far less substantive and representative of the state-of-the-art. Lastly, the authority of the "peer" to authorize treatment also varies greatly, with some simply able to reiterate that the proposed care is not covered without any insight into the individual case, creating only a façade of case review.

Finally, if the proposed care is still not approved after peer-to-peer review, the physician can either file an appeal or pursue an alternative treatment option. Again, this appeals process is unilaterally under the control of payers and is inconsistently defined and managed across the industry. This phase of the process can be exceptionally long and creates a dilemma: since a delay in treatment can negatively impact prognosis,[2] physicians must weigh whether fighting for their perceived optimal care is worth the impact of delays on patient outcomes.

Radiation oncology is a resource-intensive field that is heavily impacted by PA, causing professional societies like the American Society for Radiation Oncology (ASTRO) and American College of Radiation Oncology (ACRO) to devote significant efforts to highlight the burden of PA in the field and to engage with government stakeholders to advocate for PA reform.[7-10] To illustrate the extent of this impact, a recent study analyzing claims from a wide variety of specialties found that radiation oncology had the highest rate (97%) of services that require PA.[4] Here, we review the background behind the establishment of PA, detail the radiation-oncology-specific burdens and consequences associated with the current system, and present concrete proposals for improving the PA process so that payers and practitioners are better aligned to support patient access to timely, cost-effective, and high-quality cancer care.

Seamless coordination and cooperation between physicians and payers in this process is crucial to optimizing outcomes, allowing patients to receive the best possible care without concern for treatment delays or financial toxicity. However, PA continues to drive a deepening wedge between physicians and payers, becoming increasingly burdensome for both from year to year[11] and frequently delaying initiation of treatment, which results in direct patient harm.[12] PA thus challenges clinicians' autonomy to enact the shared medical decisions they make with their patients and instead implies that payers are the final decision-makers on how care is delivered, in many ways allowing payers themselves to practice medicine.

Background and Payer Rationale for PA

Overuse of expensive, unnecessary medical services has been a key driver of the ongoing unsustainable growth seen in US health care costs. Berwick et al listed the overuse of low-value tests and treatments as one of the 6 primary domains of health care waste, accounting for $75.7 to 101.2 billion in excess costs per year.[13] Thus, limiting or eliminating the delivery of low-value care through strict third-party oversight of health care practices or "utilization management" (UM) is logically accepted by the payer community as a fundamental cost-containment strategy. Prior authorization (PA) has become an increasingly common form of UM, defined as a "set of techniques designed to manage health care costs by influencing patient care decision-making through case-by-case assessments of the appropriateness of care prior to its provision."[14] In addition to bending the cost curve, UM is also viewed by payers as an essential tool to maximize patient safety and promote evidence-based care. UM initially emerged in the 1960s and saw rapid adoption by private payers early in the managed care era of the 1980s.[14] Among the largest 776 employers in the US, the proportion of employers who worked with payers to implement UM had increased from 47% in 1985 to 75% by 1990.[15]

Despite mounting pressure from health care practitioners to scale back PA, payers have remained committed to the necessity and effectiveness of a robust PA process in optimizing value. In 2014, after UnitedHealthcare instituted a PA process specifically for cancer treatments in Florida, they found that Florida chemotherapy costs decreased by 9% that year.[5] Because average chemotherapy expenditures across the US increased by 11% in 2014, United credits the PA program with the savings generated in Florida. In a 2019 survey from the advocacy group America's Health Insurance Providers (AHIP), 91% of payers felt their PA programs had a positive impact on the quality and affordability of care, while 84% felt PA improved patient safety.[16]

Challenges With Navigating the PA Process

While payers clearly have a strong rationale for developing and adopting PA (ie, limiting wasteful spending and

promoting evidence-based practice), PA as it is currently employed has evolved beyond its well-intentioned origins into an intrusive, inconsistent, resource-intensive system that does not promote evidenced-based, state-of-the-art care. To wit, PA was named as "the greatest challenge facing the field" by radiation oncologists in the ASTRO annual survey.[7] Moreover, 94% of physicians in a 2020 American Medical Association (AMA) survey reported that PA can lead to treatment delays and 79% reported that PA can lead to treatment abandonment.[17] The current PA system has multiple flaws that cause frustration and fatigue for all stakeholders, with 2 of the most prominent being its poor transparency and its drain on time and resources.

Lack of Transparency

Payers' policies typically state that it is the clinician's responsibility to know whether a particular service will require PA. However, each payer's unique coverage guidelines are often not available at the point of care. Accordingly, 58% of physicians polled in a recent AMA survey report that it is challenging to determine whether a given medical service requires PA.[17] Predicting when PA will be required can also be complicated by inconsistencies between payer coverage guidelines and professional society recommendations. To illustrate, a recent single-institution study examining PA determinations for proton therapy found no significant association between insurance approval and compliance with ASTRO guidelines on clinically appropriate uses of proton therapy.[18] Similarly, while the use of endocrine therapy in hormone-receptor positive breast cancer is supported by level 1 evidence, generic endocrine therapies accounted for 15% of 2015 PA requests submitted by the breast oncology division at Dana-Farber Cancer Institute,[2] further suggesting that PA requests are not simply serving to rein in wasteful medical spending.

As a result of this unpredictability, physicians are often unable to prepare their patients when a treatment will be subject to PA and thus potentially delayed by appeals, denied by their insurer, or both. Instead, physicians are routinely alerted after having already engaged in thoughtful shared decision-making with the patient. Physicians at this point must then inform patients that they are unable to offer the agreed-upon treatment, undermining patients' trust and confidence in their physicians. In addition, practitioners and patients are typically not provided with regular updates on the status of PA requests, adding anxiety and uncertainty to an already challenging diagnosis.

Drain on Time and Resources

Prior authorization ranked as the no. 1 burden reported by physicians in a survey by the Medical Group Management Association (MGMA), with 88% of respondents describing PA as a "very" or "extremely" burdensome process hampered by increasing requirements and delays.[19] Another recent survey found that physicians average 1 hour per week on PA, while nurses average over 13 hours.[20] Nearly one-fifth of physicians in the ASTRO survey reported that at least 10% of their workday is spent addressing PA issues, which represents valuable time diverted away from direct patient care.[7]

A major factor underlying the burden of PA is the highly manual nature of completing and submitting PA requests. Even when payers adopt electronic PA (ePA), physicians must still access each payer's unique web portal, manually input answers to each inquiry, and then pull individual notes and reports from the patient's medical record, because ePA systems and electronic medical records (EMRs) frequently lack integration.[21] A 2020 survey by AHIP found that 58% of physicians do not use EMRs integrated with ePA.[16] Furthermore, the significant variation in coverage guidelines and PA processes between different payers limits the ability of physicians and staff to achieve efficiency in completing PA requests. Beyond the burden of submitting multiple nonstandardized forms, 85% of ASTRO survey respondents reported that they were required to generate multiple distinct treatment plans for individual PA requests, demanding a significant amount of unreimbursed time and resources from physicians, dosimetrists, and physicists.[7]

Even once a PA request is successfully submitted, communication between payers and physicians regarding the status of the submission is often slow and inefficient, adding to treatment delays. Notably, only 21% of medical plans have adopted fully electronic PA communication, with 79% of plans still requiring communication by fax or phone.[22] In addition, the current system of peer-to-peer phone calls serves as another major burden for clinicians. Despite the significant time commitment required to schedule these calls, the discussions themselves may be quite short and unproductive. This is because peer physicians often lack the specialty-specific knowledge and expertise required to engage in a thoughtful dialogue or to appreciate the rationale for a treatment approach that may on its surface appear inconsistent with coverage guidelines. Specifically, 44% of radiation oncologists responding to the ASTRO survey indicated that peer reviews typically are not conducted by a licensed radiation oncologist.[7]

Long-term Consequences

The most critical concern with the current PA system is its potential to adversely impact patient health. First, the time required for a PA process — which can be prolonged if a denial must be appealed — can

significantly delay or deny access to necessary care. In the ASTRO survey, 93% of the participants reported PA-related delays in life-saving treatments, with 31% indicating that the average delay lasts longer than 5 days.[7] In a study examining the insurance approval process for proton therapy, 2/3 of PA denials were ultimately reversed on appeal, suggesting that the majority of PA-related care delays are avoidable.[23]

Unfortunately, delayed care directly translates into harm for cancer patients. The AMA survey showed that PA-related care delays lead to increased morbidity, with 39% of respondents indicating that delays led to either hospitalization or an intervention preventing permanent impairment.[17] PA-related delays can also mean the difference between life and death for cancer patients: A National Cancer Database study showed that each 1-week delay in the initiation of cancer treatment was associated with a 3.2% increase in absolute risk of mortality for early stage breast, lung, renal, and pancreas cancers.[12] Thus, these delays in cancer care are not merely an inconvenience; they have a life-and-death impact.

The burdens of the PA system may also exacerbate pre-existing socioeconomic and racial disparities in access to high-quality oncologic care. For example, smaller community practices and freestanding hospitals caring for rural or underserved populations may lack the resources to efficiently navigate the PA process, ultimately limiting access to treatment options available at large health systems with full-time staff dedicated to the PA process. The ASTRO survey found that, relative to academic physicians, a significantly higher percentage of community practice physicians reported PA-related treatment delays lasting longer than 1 week (34% vs 28%).[7] In cardiology, another resource-intensive medical specialty subject to significant PA burden, PA rejection rates have been shown to be higher for minorities and low-income groups.[24] As ASTRO, ACRO, and other professional medical societies have prioritized reducing health care disparities, tackling the flaws in the current PA system will be an important step toward health equity.

In addition to delaying access to existing evidence-based treatment options, the PA process also frequently stands in the way of innovation in radiation oncology by hindering clinical trial enrollment. Because payers do not automatically waive PA requirements for new treatments being investigated on clinical trials, the time-intensive process of submitting PA requests and appealing coverage denials serves as a major barrier to patient accrual, leading to premature trial closures. A recent study on phase 3 clinical trials of proton therapy found that 64% of PA requests were initially denied, and that 67% of these initial denials remained denied after appeal.[18] This creates a catch-22 whereby payers inhibit the generation of the very evidence needed to demonstrate value and justify payment coverage of the latest treatments. More importantly, these practices prevent the improvement of cancer care, causing progress to stagnate and resulting in unnecessary continued patient suffering that potentially could have been prevented by research had it continued uninhibited.

Finally, while strict PA policies were intended to control health care costs by limiting use of expensive treatments, there is evidence that their burdensome requirements and rigid coverage guidelines may ultimately increase overall health care expenditures. Excessive administrative costs – driven in part by the complex, inefficient PA system – are a top reason the US spends significantly more per capita on health care than any other higher-income country.[25] In the 2020 AMA survey, 40% of physicians report having at least 2 full-time staff dedicated entirely to PA.[17] Moreover, it is estimated that practices spend $31 billion per year on PA-related tasks.[26] Another recent study estimated the total annual PA-related spending for all US academic radiation oncology centers to be more than $40 million, of which 86% is associated with navigating the PA process for treatments that are ultimately approved.[27] Thus, the current PA system paradoxically generates new waste in the form of unnecessary administrative time and costs.

Excessively stringent PA practices may also further increase health expenditures in the long-term if the savings generated from treatment denials are offset or surpassed by the downstream costs of treating complications that arise from delayed or inferior care. An analysis of PA claims for type 2 diabetes medications found that plans spent significantly more on patients who did not receive a requested drug (either via denial or delays) vs patients approved for the medication.[28] A similar analysis of patients with bipolar disorder or schizophrenia found that prescription prior authorization led to significantly increased hospitalizations, 23% higher inpatient costs, and 16% higher spending overall.[29]

Fixing the Prior Authorization Crisis

Leveraging Technology to Streamline PA

If the purpose of PA is truly to decrease waste in medicine — and not simply to delay or deny care — increased automation of the intricate, multistep PA process is critical to reduce clinician burden and minimize delays in care. Ideally, software can be designed to accomplish this either as an integrated part of the EMR or as a stand-alone app that can communicate with the EMR.

For example, the steps required to achieve payment coverage could be seamlessly integrated into clinical workflows in the EMR. Specifically, physicians could be alerted at the point of care if a given service requires PA and be informed upfront of all necessary supporting documentation, based on the unique coverage requirements of the payer. If PA is required, the EMR could communicate the pertinent clinical data from the patient's chart to the payer. Similarly, the payer could communicate its response to the physician though the EMR. These capabilities are eminently achievable with software capabilities and should be developed; however, realistically, a government mandate will likely be required to achieve this.

Some progress has been made to enable an integrated health IT ecosystem that permits secure communication between a practitioner's EMR and payers' ePA systems. One approach to facilitate interoperability between traditionally siloed health information systems has been the development of a new common language or "standard" for health data exchange called Fast Healthcare Interoperability Resources (FHIR).[30] Under the FHIR standard, discrete data elements such as individual diagnostic reports or medications can be communicated between different health information systems via web-based application programming interfaces (APIs). These APIs allow a particular software program, such as a practitioner's EMR, to access data or content generated and housed by another program, such as an insurance plan's coverage policy rules.

The CMS Interoperability and Prior Authorization proposed rule (CMS-9123-P) is a landmark policy effort that seeks to accelerate PA automation by promoting FHIR-enabled APIs.[31] The proposed rule requires payers in Medicaid, the Children's Health Insurance Program, and qualified health plans on federal exchanges to build and maintain an FHIR-enabled document requirement look-up service API, which would allow providers to retrieve the unique PA requirements of specific payers directly within the EMR. CMS-9123-P also requires payers to build and maintain an FHIR-enabled prior authorization support API that will allow clinicians to "send PA requests and receive responses electronically within their existing workflow," while complying with HIPAA standards. CMS-9123-P is proposed to take effect January 1, 2023.

The bipartisan Improving Seniors' Timely Access to Care Act of 2021 also seeks to streamline the PA process by mandating that Medicare Advantage plans establish ePA programs that meet specified standards, including coverage determination decisions, in real time for routinely approved services.[32] Close collaboration between policymakers, practitioners, health plans, and EMR vendors will be essential to ensure that the technological solutions promoted by the above policy initiatives are deployed in the private market as well to spur broad PA automation.

Increasing Transparency of the PA Process

In addition to streamlining the documentation process, another key step to ease the current PA burden will be to increase transparency around payers' coverage determination requirements and processes. Physicians should be aware of different treatments' PA requirements before engaging with patients to formulate a management plan. Insight into the PA process empowers physicians to set appropriate expectations regarding the potential hurdles to overcome prior to arriving at the optimal treatment. Greater clarity can help avoid patients' frustration and anxiety stemming from abrupt and unexpected delays or changes in the initial care plan. If a treatment is held up by the PA process, both the patient and physician should be able to conveniently obtain status updates and receive a specific deadline by which a coverage decision will be made.

The Improving Seniors' Timely Access to Care Act of 2021 also aims to increase transparency in the PA process by mandating that Medicare Advantage plans grant physicians and patients with upfront access to criteria used for making coverage decisions along with details regarding the supporting documentation that must be submitted as part of the PA request.[32] Private health technology companies are also developing machine learning solutions that continuously scan the dynamic coverage policies and medical necessity rules of different health plans, so physicians can be accurately informed of a plan's most up-to-date coverage requirements for a particular service.[33]

Once PA requests are submitted, the CMS-9123-P rule requires participating plans to enable patients and physicians to track all pending and active PA decisions through FHIR-enabled APIs. Multipayer, web-based portals are also being developed in the private market to serve as a one-stop hub for practitioners to monitor the status of all PA requests in real time, eliminating the need for inefficient and repeated phone calls to insurance companies for updates.[34]

Both the CMS-9123-P proposed rule and the Improving Seniors' Timely Access to Care Act of 2021 will also open a window into how plans manage the use of different services by mandating that plans publish PA metrics, including rates of initial PA approval, denial, and approval after appeal. The Improving Seniors' Timely Access to Care Act of 2021 also strives to increase transparency by requiring Medicare Advantage plans to provide data on the extent to which software decision support tools and clinical evidence standards are being factored into PA coverage determinations. This information will enable patients and

practitioners to hold plans accountable for ensuring a clear and consistent application of their internal coverage guidelines during the PA process.

Shortening Turnaround Times for PA Approvals

A central goal of streamlining the PA process through ePA systems is to accelerate time to PA approval. New technologies have shown promise, as a new machine-learning-based solution was shown to reduce PA approval time by 60% at a regional medical center.[33] Similarly, the FASTPATH initiative, which enabled clinicians to navigate the PA process electronically through a multipayer web-based portal, reduced the median time to a PA decision by threefold.[34]

Regulatory measures are an equally (if not more) important strategy for shortening the PA process. The CMS-9123-P proposed rule applies strict time-frame constraints for decisions, requiring participating health plans to respond within 72 hours of urgent requests and within 7 calendar days of standard requests. ASTRO's commentary on the proposed rule encourages CMS to update the maximum response time to urgent requests to 48 hours. Rather than imposing fixed deadlines on PA decisions, the Improving Seniors' Timely Access to Care Act of 2021 aims to incentivize timely PA determinations by requiring Medicare Advantage plans to report average response times to PA requests. This allows patients and practitioners to hold payers accountable for PA practices that result in unacceptably long delays in care.

Selective Waiving of PA Requirements

While the prospect of eliminating PA is unrealistic, expanding the services and physicians that are selectively exempted from PA requirements has greater buy-in from health plans based on a consensus statement signed by multiple stakeholder groups including the AMA and AHIP.[35] Plans can significantly cut their own administrative costs by adopting the practice of "gold carding," in which practitioners with historically high PA approval rates for certain services are exempted from having to repeat the PA process for those services in the future. A Texas law, H.B. No. 3459, that took effect in October 2021, gold cards physicians who have a 90% PA approval rate over 6 months on certain services.[36] Ideally, future legislation should also look to award gold card status to medical groups that establish their own utilization management process and demonstrate high compliance with internal, evidence-based care pathways. In addition to rewarding practitioners who have a proven record of high-value, guideline-concordant care, physicians who have embraced value-based payment models are already assuming financial risk and should be exempt from restrictive utilization management practices.

Thought should also be given to exempting certain services from PA regardless of the ordering physician. For example, in Sunset PA programs, specific services with particularly high rates of initial or ultimate approval are phased out of the PA process completely.[6] Treatments being investigated in well-designed prospective clinical research trials should also be exempt from PA requirements to facilitate trial accrual, which is crucial for innovation and for aligning payer coverage policies with up-to-date practice guidelines.

Advocacy of Practicing Physicians

Finally, it is important to note that the major PA-related policy changes that have been enacted[36] or proposed thus far[32,33] have been achieved in large part by the political advocacy efforts of radiation oncologists in professional societies like ASTRO and ACRO.[8-10,37] Notably, the additional systems-level changes proposed in this article are unlikely to be implemented without further advocacy efforts at the state or federal level. Thus, it is essential to recognize that additional effort and involvement of practicing radiation oncologists and affiliated stakeholders will be needed to bring ongoing issues to the attention of government officials and to advocate for change.

Conclusion

Ultimately, physicians and payers are ideally both working to ensure that patients receive the best possible care that is grounded in evidence and delivered cost-effectively. When applied appropriately, PA is an invaluable tool for payers to limit medical waste and ensure that patients receive guideline-concordant care. However, there is valid concern that the current PA system has expanded its scope beyond medical waste and is now being used as a general cost-containment tool, particularly within specialties like radiation oncology.[7] When PA is applied broadly and with limited transparency, patients face frequent delays and denials for proven treatments while physicians face ever-expanding administrative burdens. We hope the solutions offered here – with a focus on leveraging technology to make the process more efficient and more transparent – can help practitioners and payers find a balance that provides reasonable oversight where appropriate while limiting unnecessary treatment delays/denials and minimizing administrative burden.

References

1) Wickizer TM, Lessler D. Utilization management: issues, effects, and future prospects. *Annu Rev Public Health.* 2002;23;233-254.

2) Lin NU, Bichkoff H, Hassett MJ. Increasing burden of prior authorizations in the delivery of oncology care in the United States. *J Oncol Pract.* 2018;14:525-528.

3) Lee DW, Rawson JV, Wade S. W. Radiology benefit managers: Cost saving or cost shifting? *J Am Coll Radiol.* 2011;8:393-401.

4) Schwartz A., Brennan TA, Verbrugge DJ,

Newhouse JP. Measuring the scope of prior authorization policies: applying private insurer rules to Medicare Part B. *JAMA Health Forum.* 2021;2:e210859-e210859.

5) Kirkwood MK, Hanley A, Bruinooge SS, et al. The state of oncology practice in America, 2018: results of the ASCO Practice Census Survey. *J Oncol Pract.* 2018;14:e412-e420.

6) Psotka MA, Singletary EA, Bleser WK, et al. Streamlining and reimagining prior authorization under value-based contracts: a call to action from the Value in Healthcare Initiative's Prior Authorization Learning Collaborative. *Circ Cardiovasc Qual Outcomes.* 2020;13:e006564.

7) American Society for Radiation Oncology. Prior authorization and cancer patient care. Accessed December 9, 2021. https://www.astro.org/ASTRO/media/ASTRO/News and Publications/PDFs/ASTROPriorAuthorization-Physician-SurveyBrief.pdf

8) American Society for Radiation Oncology. ASTRO applauds new prior authorization legislation to reduce cancer patient burden and delays. Accessed January 19, 2022. https://www.astro.org/News-and-Publications/News-and-Media-Center/News-Releases/2019/ASTRO-applauds-new-prior-authorization-legislation

9) American Society for Radiation Oncology. ASTRO Advocacy Accomplishments 2021. Accessed January 20, 2022. https://www.astro.org/ASTRO/media/ASTRO/Advocacy/PDFs/20_AdvocacyAccomplishments.pdf

10) American College of Radiation Oncology. ACRO leadership meets with EviCore to address concerns. Accessed January 20, 2022. https://acro.org/news/news.asp?id=584912.

11) Resneck JS Jr. Refocusing medication prior authorization on its intended purpose. *JAMA*. 2020;323:703-704. doi:10.1001/jama.2019.21428

12) Khorana AA, Tullio K, Elson P, et al. Time to initial cancer treatment in the United States and association with survival over time: an observational study. *PLoS One*. 2019;14:e0213209. doi:10.1371/journal.pone.0213209.

13) Berwick DM, Hackbarth AD. Eliminating waste in US health care. *JAMA*. 2012;307,1513-1516.

14) Institute of Medicine (US) Committee on Utilization Management by Third Parties. *Controlling Costs and Changing Patient Care? The Role of Utilization Management.* National Academies Press, 1989.

15) Oehm MJ. Private utilization review. *Seattle Univ Law Rev.* 1991;14:527.

16) America's Health Insurance Plans (AHIP). Key results of industry survey on prior authorization. 2020. Accessed December 9, 2021. https://www.ahip.org/wp-content/uploads/Prior-Authorization-Survey-Results.pdf.

17) American Medical Association. Measuring progress in improving prior authorization. 2021. Accessed December 9, 2021. https://www.ama-assn.org/system/files/2021-05/prior-authorization-reform-progress-update.pdf

18) Gupta A, Khan AJ, Goyal S, et al. Insurance approval for proton beam therapy and its impact on delays in treatment. *Int J Radiat Oncol Biol Phys.* 2019;104:714-723. doi:10.1016/j.ijrobp.2018.12.021

19) Medical Group Management Association. MGMA Annual Regulatory Burden Report. October 2021. Accessed December 9, 2021. https://www.mgma.com/getattachment/22ca835f-b90e-4b54-ad93-9c77dfed3bcb/MGMA-Annual-Regulatory-Burden-Report-October-2021.pdf.aspx?lang=en-US&ext=.pdf

20) Howell S, Yin PT, Robinson JC. Quantifying the economic burden of drug utilization management on payers, manufacturers, physicians, and patients. *Health Aff.* 2021;40:1206-1214.

21) Cognizant. Automated prior authorization: a high-value opportunity. 2019. Accessed December 9, 2021. https://www.cognizant.com/whitepapers/automated-prior-authorization-a-high-value-opportunity-codex4505.pdf

22) Council for Affordable and Quality Healthcare (CAHQ). 2020 CAQH INDEX. Closing the Gap: The Industry Continues to Improve, But Opportunities for Automation Remain. 2020. Accessed December 10, 2021. https://www.caqh.org/sites/default/files/explorations/index/2020-caqh-index.pdf

23) Ning MS, Gomez DR, Shah AK, et al. The insurance approval process for proton radiation therapy: a significant barrier to patient care. *Int J Radiat Oncol Biol Phys.* 2019;104:724-733.

24) Association of Black Cardiologists. Identifying How Prior Authorization Impacts Treatment of Underserved and Minority Patients. 2019. Accessed December 9, 2021. http://abcardio.org/wp-content/uploads/2019/03/AB-20190227-PA-White-Paper-Survey-Results-final.pdf

25) Himmelstein DU, Campbell T, Woolhandler S. Health care administrative costs in the United States and Canada, 2017. *Ann Intern* Med. 2020;172:134-142.

26) Casalino LP, Nicholson S, Dans GN, et al. What does it cost physician practices to interact with health insurance plans? *Health Aff.* 2009;28:w533-w543.

27) Bingham BS, Chennupati S, Osmundson EC. Time driven activity based costing as a method for estimating the practice-level and national cost burden of treatment-related prior authorization for academic radiation oncology practices. *Int J Radiat Oncol Biol Phys.* 2021;111:S70-S71.

28) Bergeson JG, Worley K, Louder A, Ward M, Graham J. Retrospective database analysis of the impact of prior authorization for type 2 diabetes medications on health care costs in a Medicare Advantage prescription drug plan population. *J Manag Care Pharm.* 2013;19:374-384.

29) Seabury SA, Goldman DP, Kalsekar I, et al. Formulary restrictions on atypical antipsychotics: impact on costs for patients with schizophrenia and bipolar disorder in Medicaid. *Am J Manag Care.* 2014;20:52-60.

30) HL7 International. HL7 Annual Report, 2020. Accessed December 9, 2021. http://www.hl7.org/documentcenter/public/HL7/HL7 2020 Annual Report v5.pdf

31) Centers for Medicare & Medicaid Services. Reducing Provider and Patient Burden by Improving Prior Authorization Processes, and Promoting Patients Electronic Access to Health Information CMS-9123-P: Fact Sheet. Centers for Medicare & Medicaid Services Newsroom. 2020. Accessed December 9, 2021. https://www.cms.gov/newsroom/fact-sheets/reducing-provider-and-patient-burden-improving-prior-authorization-processes-and-promoting-patients

32) 117th Congress (2021-2022). Summary: H.R.3173 – 117th Congress (2021-2022). Improving Seniors' Timely Access to Care Act of 2021. Congress.gov (2021). Accessed December 9, 2021. https://www.congress.gov/bill/117th-congress/house-bill/3173?s=1&r=92

33) Olive. Leveraging AI to solve prior authorization. 2021. Accessed December 9, 2021. https://oliveai.com/resources/whitepapers/leveraging-ai-to-solve-prior-authorization

34) Center for Health Care Advancement. Evaluation of the Fast Prior Authorization Technology Highway Demonstration: Final Report. 2021. Accessed December 9, 2021. https://www.ahip.org/wp-content/uploads/Fast-PATH-Evaluation.pdf

35) American Hospital Association, America's Health Insurance Plans, American Medical Association, American Pharmacists Association, BlueCross BlueShield Association, M. G. M. A. Consensus Statement on Improving the Prior Authorization Process. 2018. Accessed December 9, 2021. https://edhub.ama-assn.org/data/multimedia/10.1001ama.2018.0080supp1.pdf

36) 87th Legislature (Texas). HB 3459 - Relating to preauthorization requirements for certain health care services and utilization review for certain health benefit plans, 2021. Accessed December 9, 2021. https://capitol.texas.gov/tlodocs/87R/billtext/html/HB03459F.htm

37) American Society for Radiation Oncology. Protecting Patients' Access to Health Care. 2021. Accessed January 20, 2022. https://www.astro.org/ASTRO/media/ASTRO/Meetings and Education/PDFs/ADay20/ADay-20HealthReformPolicies.pdf

Adjuvant Radiation in Early Stage Vulvar Cancer: A Review of Indications and Optimal Dose

Karishma Khullar, MD;[1] Tomas Patrich, BA;[2] Salma K. Jabbour, MD;[1] Lara Hathout, MD[1]

Abstract

Vulvar cancer is a relatively rare gynecologic malignancy for which surgery remains the cornerstone of treatment. A wide local excision with curative intent in patients with early stage vulvar cancer is the gold standard. Adverse pathologic features have been shown to increase risk of local recurrence. Specifically, the presence of positive or close margins of < 8 mm or 2 or more positive nodes have been shown to significantly increase the risk of recurrence and have informed guidelines for risk-adapted adjuvant radiation, although the optimal dose for adjuvant radiation is yet to be established. Given the rarity of vulvar cancer, guidelines regarding the indications and dose for adjuvant radiation are based largely on retrospective studies. The purpose of this review is to summarize the evidence underlying the current indications for adjuvant radiation in early stage vulvar cancer as well as to determine the optimal dose for adjuvant radiation.

Keywords: vulvar cancer, early stage, management, radiation dose, adjuvant radiation

Vulvar cancer is a relatively rare malignancy accounting for 5% of gynecologic tumors, with an incidence of 6,120 cases and 1,550 deaths in the United States in 2021.[1] While the incidence of vulvar cancer increases with age, there has been an increase in younger patients in recent years, likely due to the association with human papillomavirus (HPV) infections.[2] One of the most common presenting symptoms of vulvar cancer is pruritis, but other less commonly reported symptoms include bleeding, dysuria, discharge, and pain.[3] Many patients experience a delay in diagnosis due to misdiagnosis as an inflammatory condition due to the lack of specificity in presenting symptoms.[4] Squamous cell carcinoma is the predominant histology of vulvar cancer, accounting for 95% of all histological types. Approximately 30% of patients who present with early stage vulvar cancer have existing lymph node metastases — most commonly to the inguinal and femoral nodes followed by metastases to the pelvic nodes.[3] Lymph node status has been shown to be the most important independent prognostic factor for disease-free survival in vulvar cancer.[5,6]

Early stage vulvar cancer is generally considered to be T1 or T2 disease with clinically nonsuspicious lymph nodes.[7] The cornerstone of treatment for early stage vulvar cancer remains surgery with the goal of achieving a wide-margin resection. Historically, the standard surgical approach was an en bloc radical vulvectomy with a bilateral lymph node dissection.[8] However, this surgery was associated with significant morbidity and mortality, with up to 70% to 85% of patients reporting chronic lymphedema and wound breakdown[9] and an operative mortality rate of up to 16%.[10] In recent years, this radical surgical approach has been largely replaced by a wide local excision and modified radical vulvectomy with a 1 cm margin.[11] Furthermore, a separate skin vulvar-groin incision can be performed for nodal assessment rather than an en bloc groin dissection,[12]

Affiliations: [1]Department of Radiation Oncology, Rutgers Cancer Institute of New Jersey, Rutgers University, New Brunswick, NJ. [2]Rutgers Robert Wood Johnson Medical School, Piscataway, NJ. **Disclosure:** The authors have no conflicts of interest to disclose. This work is supported in part by a grant from the National Cancer Institute (P30CA072720). No part of this article has been previously published elsewhere.

Table 1. Studies of Vulvar Cancer Patients With Close or Positive Margin

AUTHOR	YEAR	NUMBER OF VULVAR CANCER PATIENTS S/P SURGERY	MARGIN STATUS	INTERVENTION	RESULTS
Heaps et al[19]	1990	135 patients	91 patients with ≥ 8 mm margins and 44 patients with < 8 mm margins	LR examined by margin status	LR 0% in patients with ≥ 8 mm margins and 50% in patients with < 8 mm margins
Faul et al[20]	1997	62 patients	All patients had positive or < 8 mm margins	31 patients were observed and 31 patients received adjuvant radiation	LR 58% in observed vs 16% in the radiation group, *P* = 0.036
Chan et al[21]	2007	90 patients	30 patients with > 8 mm and 53 patients with ≤ 8 mm margins	Differences in recurrence examined	LR 0% with a margin > 8 mm and 23% with ≤ 8 mm margins
Viswanathan et al[22]	2013	205 patients	69 patients (negative margins), 116 (< 1 cm margins), 20 patients (positive margins)	Freedom from vulvar relapse was examined	4-year freedom from vulvar relapse rates: 82% (negative margins), 63% (close margins), 37% (positive margins), *P* = .005
Ignatov et al[24]	2016	257 patients	65 patients had close or positive margins ≤ 10 mm	34 patients received postoperative brachytherapy and 31 were observed	5-year overall survival improved with adjuvant radiation (67.6% vs 29%, *P* < .0001)
Groenen et al[26]	2010	93 patients	54% of the patients had < 8 mm margin	LR was examined by margin status	No significant difference in LR (23% vs 22%) between those with close margins or clear margins
Nooij et al[25]	2016	148 patients	122 patients with margins < 8 mm	40% patients with close margins received either local excision or radiation	No difference in LR between those who received treatment and those who did not (14% vs 7%, *P* = 0.323)
Barlow et al[23]	2020	122 patients	All had close or positive margins	146 patients were treated with re-excision or adjuvant radiation and 76 patients were observed	LR significantly decreased in those who were treated (8.7% vs 30.2%, *P* = 0.005)
Nomura et al[27]	2021	34 patients	10 patients positive, 3 with < 3 mm, 4 with < 5 mm, 5 with < 8 mm, 12 with ≥ 8 mm margins	Differences in recurrence patterns in patients based on margin status were examined	LR-free survival increased with narrower surgical margins: 32%, 30.3%, 42.5%, 55.5%, and 73% for positive, < 3 mm, < 5 mm, < 8 mm, and ≥ 8 mm margins, respectively

Key: s/p = status post, LR = local recurrence

and an ipsilateral node dissection can be considered in well-lateralized tumors.[13] However, given that an inguinofemoral nodal dissection can be associated with significant morbidity, sentinel lymph node biopsy is becoming integrated into standard treatment for early stage vulvar cancers on the basis of two major trials. Specifically, GOG 173 found that sentinel lymph node biopsy was a viable alternative to an inguinofemoral lymphadenectomy with a sensitivity of 91.7%,[14] and GROINSS-V showed that the recurrence rate with a negative sentinel node assessment was 2.3% with significantly lower complications than those with a positive sentinel node who ultimately underwent an inguinofemoral lymphadenectomy.[15]

Radiation therapy is often used in the adjuvant setting in vulvar cancer to reduce local recurrence and improve survival in patients who have adverse pathologic features. However, given the relative rarity of vulvar cancer, there are limited randomized controlled trials to inform the use and optimal dose of adjuvant radiation. Current treatment guidelines are largely based on retrospective studies and extrapolated from cervical and anal canal cancers. The purpose of this review is to determine the indications for adjuvant radiation in early stage vulvar cancer as well as to report the evidence regarding the optimal dose for adjuvant radiation.

Indications for Adjuvant Radiation in Early Stage Vulvar Cancer

The role of adjuvant radiation in vulvar cancer is to reduce local recurrence. The two strongest predictors of local recurrence, which have informed current guidelines, include margin status and nodal involvement:

Adjuvant Radiation for Close or Positive Margins

One of the indications for adjuvant radiation in early stage vulvar cancer is a close or positive margin. While re-excision can be considered for close or positive margins, it can often have significant morbidity and psychosocial impact on the patient in terms of lymphedema and sexual function.[16] Thus, adjuvant radiation is often recommended in situations where re-excision would result in excessive morbidity.[17] While there is some variation in the definition of margin status, much of the literature traditionally defines margins of < 8 mm as close margins – corresponding to a 1 cm surgical margin given the 20% shrinkage in formalin – and classifies any tumor at the surgical edge of the specimen as positive margins.[18] Studies addressing the impact of margin status and/or adjuvant radiation on local recurrence in vulvar cancer patients are summarized in **Table 1**. A study by Heaps et al reviewed 135 patients with squamous cell carcinoma of the vulva; among the 91 patients with a margin ≥ 8 mm, none had a local recurrence. By contrast, among 44 patients with margins < 8 mm, 50% of patients had a local recurrence.[19] In a subsequent study, 62 patients with vulvar cancer with positive or close margins defined as < 8 mm were retrospectively reviewed. Thirty-one patients were observed after surgery and 31 patients received adjuvant radiation to a mean dose of 5,654 cGy for those with positive margins and 4,867 cGy for those with close margins. The local recurrence rate in the observation group was 58% vs 16% in the radiation group, and adjuvant radiation significantly decreased local recurrence rates in both the close margin (≤ 8 mm, $P = 0.036$) and positive margin groups ($P = 0.0048$). On multivariate analysis, adjuvant radiation and margin status were significant predictors for local control ($P = 0.009$ and $P = 0.0001$ respectively).[20] Finally, a study by Chan et al examined 90 vulvar cancer patients who underwent surgery and found margin status to be an important predictor of recurrence. Specifically, among the 30 patients with a margin > 8 mm, none had a local recurrence, whereas 23% of the women with ≤ 8 mm had a recurrence.[21]

In a large retrospective study by Viswanathan et al, 205 vulvar cancer patients who underwent surgery were categorized by margin status as follows: negative margins, close margins of < 1 cm, and positive margins. The 4-year freedom from vulvar relapse rates for the groups were 82%, 63% and 37% respectively ($P = 0.005$). Additionally, while recurrences were seen with margins up to 9 mm, the risk of recurrence was significantly increased with margins < 5 mm ($P = 0.002$).[22] Barlow et al examined 122 vulvar cancer patients who underwent surgery with close or positive margins — defined as between 0.1 mm and 8 mm or tumor on any surgical skin edge, respectively — of which 46 patients underwent re-excision or adjuvant radiation and 76 patients were observed. Local recurrence was significantly decreased in patients who underwent re-excision or adjuvant radiation compared with those who were observed (8.7% vs 30.2%, $P = 0.005$).[23] In addition, in a retrospective review of 257 patients with vulvar squamous cell carcinoma by Ignatov et al, 65 patients had close or positive margins — defined as ≤ 10 mm — of which 34 patients received postoperative brachytherapy (median dose of 50 Gy) and 31 patients did not receive adjuvant therapy. The 5-year overall survival was significantly improved in patients with close or positive margins who received adjuvant brachytherapy compared with those who did not receive adjuvant treatment (67.6% vs 29%, $P < 0.0001$).[24] In a meta-analysis of 10 studies consisting of 1,276 vulvar cancer patients and 255 local recurrences, the risk of recurrence nearly doubled for patients with margins < 8 mm compared with those with margins > 8 mm (RR 1.99, CI: 1.1 to 3.5).[25]

While the aforementioned studies have demonstrated that margin status is an important predictor of local recurrence and have largely focused on 8 mm as an appropriate margin, other studies have challenged the association between margin status and local recurrence and have shown that narrower margins may be appropriate. In a study by Groenen et al, 93 patients who underwent surgery for squamous cell carcinoma of the vulva were retrospectively reviewed and 54% of these patients had a margin of < 8 mm. After a median follow-up of 31 months, the recurrence rate did not significantly differ between patients with margins > 8 mm or < 8 mm (23% vs 22%), respectively. However, it is important to note that among patients with < 8 mm margins, 48% received additional treatment with either radiation or re-excision. Thus, the results should be interpreted with caution, since the additional treatment may have impacted the findings of this study.[26] Furthermore, Nooij et al conducted a cohort study of 148 patients with vulvar squamous cell carcinoma and found no significant difference in local recurrence between those who had < 8 mm margins vs those who had > 8 mm margins (HR 1.18, CI: 0.32 to 4.35). Additionally, among the 122 patients who had margins

< 8 mm, 40% received either local excision or radiation, and there was no significant reduction in recurrence between those who received additional treatment compared with those who received no additional treatment (14% vs 7%, $P = 0.323$).[25]

Furthermore, a Japanese study examined 34 patients with vulvar cancer who underwent surgery with curative intent. On univariate analysis, local recurrence-free survival generally increased with wider surgical margins, with rates of 32%, 30.3%, 42.5%, 55.5%, and 73% for positive, < 3 mm, < 5 mm, < 8 mm, and ≥ 8 mm margins, respectively. However, on multivariate analysis, only a tumor size of > 2 cm and a positive surgical margin — defined as tumor at the edge of the specimen — were risk factors for local recurrence (HR 17.7, 95% CI: 1.39 to 226 and HR 0.0092, 95% CI: 0.011 to 0.53, respectively), thereby suggesting that narrower surgical margins may be acceptable.[27] Lastly, a review by Milliken et al examined articles from 2005 to 2020 and concluded that a 2- to 3-mm margin was not associated with higher local recurrence rates compared with an 8-mm margin.[28]

While earlier literature has traditionally classified < 8 mm margin as close margins requiring adjuvant radiation to reduce local recurrence, some series have questioned the adequate width of surgical margin and its impact on local recurrence. In a systematic review by te Grootenhuis et al, 11 studies examined the role of margin status and local recurrence and only 6 studies showed a decreased local recurrence with margins > 8 mm vs ≤ 8 mm.[29] Nevertheless, the most conservative recommendation put forth in the ACR Appropriateness Criteria for adjuvant therapy in vulvar cancer is to continue to offer adjuvant radiation in vulvar cancer patients with margins < 8 mm,[17] although if there is concern for a patient's ability to tolerate the radiation or for significant morbidity then omission is reasonable in light of recent studies.

Nodal Involvement

Adjuvant Radiation With 2 or More Positive Nodes or Extracapsular Extension

The role of adjuvant radiation for patients with ≥ 2 positive lymph nodes or fixed ulcerated groin nodes has been supported by a randomized trial. Specifically, GOG 37 randomized 114 patients with invasive vulvar cancer and positive nodal status post radical vulvectomy and bilateral groin lymphadenectomy between pelvic node resection or adjuvant radiation therapy to a dose of 45 to 50 Gy bilaterally to the groins. The 2-year overall survival rates were significantly improved in the adjuvant radiation arm compared with pelvic resection (68% vs 54%, $P = 0.03$),[30] but at 6 years, the overall survival did not remain significant for the entire cohort (51% vs 41%, $P = 0.18$). The incidence of cancer-related death, however, significantly favored the radiation arm (29% vs 51%, $P = 0.015$), and the overall survival benefit persisted for patients with fixed ulcerated groin nodes and 2 or more positive groin nodes ($P = 0.004$ and $P = < 0.001$ respectively), or those with ≥ 20% lymph node positivity.[31]

The AGO-CaRE-1, a large retrospective study, evaluated the role of adjuvant radiation in patients with node-positive vulvar cancer. A total of 1,249 patients were included of which 447 patients had node-positive disease, with 38.5% of patients having 1 positive node, 22.8% having 2 positive nodes, 33.3% having ≥ 3 positive nodes, and 5.4% having an unknown number of positive nodes. Among the node-positive patients, 54.6% received adjuvant therapy: 183 patients had inguinal nodal irradiation and 117 patients had inguinal and pelvic nodal irradiation. For all node-positive patients, regardless of the field irradiated, the median dose was 50.4 Gy. After a median follow-up of 39.4 months, adjuvant radiation in node-positive patients significantly improved the progression-free survival (PFS) compared with observation (39.6% vs 25.9%, $P = 0.004$, respectively). On multivariate analysis, adjuvant radiation was significantly associated with superior PFS in patients with 2 or 3 positive nodes. Although the overall survival was also improved, it was not statistically significant (57.7% vs 51.4%, $P = 0.17$).[32]

A subset analysis of this study examined 360 patients with positive nodes, known radiation status, and known radiation volumes. In this cohort, 15.8% received adjuvant radiation to the inguinal and pelvic nodes, 40.5% received adjuvant radiation to the vulva in addition to the inguinal and pelvic nodes, and 43.6% of patients did not receive any adjuvant treatment. After a median follow-up of 17.2 months, local recurrence was significantly higher in node-positive patients without adjuvant radiation compared with those who received adjuvant radiation to the vulva in addition to the groins and pelvis (HR 1.79, CI: 1.09 to 2.91, $P = 0.019$). Additionally, median disease-free survival was significantly improved (18.3 months vs 12.7 months) in node-positive patients who received radiation to the vulva, groins, and pelvis compared with those who did not receive adjuvant radiation ($HR_{withoutradiation}$ 1.53, CI: 1.10 to 2.13, $P = 0.010$). Thus, this study concluded that node-positive patients benefit from adjuvant radiation, particularly in the case of comprehensive radiation to the vulva, groins and pelvis.[33]

Finally, a study by van der Velden et al also substantiated the role of adjuvant radiation not only for those with 2 or more positive nodes, but also for patients who have nodes with extracapsular extension. Specifically, 71 patients with squamous

cell carcinoma of the vulva were reviewed, and extracapsular extension, 2 or more positive nodes, and > 50% replacement of lymph nodes by tumor were found to be independent predictors of poor survival ($P = 0.00$, $P = 0.02$, and $P = 0.03$, respectively). Moreover, extracapsular extension was found to be the most significant independent predictor of survival, thereby underscoring the potential benefit of adjuvant radiation in these patients.[34]

Adjuvant Radiation with 1 Positive Node

While the role of radiation in patients with 2 or more positive nodes is well-supported by the literature, the role of radiation in patients with a single positive node remains controversial. In a small retrospective review, 75 vulvar cancer patients with lymph node metastasis underwent radical vulvectomy and an inguino-femoral lymphadenectomy, of which 31 patients were treated with adjuvant radiation therapy to a dose of 46 Gy. There was no significant difference in the 5-year disease-free survival and disease-specific survival between those who received radiation therapy and those who did not receive radiation therapy (63% and 69%, $P = 0.97$ vs 62% and 68%, $P = 0.96$ respectively).[35] Van der Velden et al further supported the omission of radiation therapy for vulvar cancer patients with a single intracapsular positive node. A total of 96 patients with vulvar cancer with a single positive intracapsular node who did not receive radiation therapy were reviewed. After a median follow-up of 64 months, only 1 patient (1%) had an isolated groin recurrence in a contralateral groin that had been assessed as node-negative at the time of surgery, and 2 patients (2.1%) had a local and groin recurrence. Of the patients with a combined local and groin recurrence, 1 patient had a large vulvar recurrence with lymphangitis carcinomatosa of the skin in the groin and the other had a vulvar recurrence and a groin nodal recurrence in the undissected left groin. The risk of recurrence or survival did not depend on the size of the node or lymph node ratio. Furthermore, the 5-year disease-specific survival, overall survival, and recurrence-free survival were 79%, 62.5%, and 97%, respectively. Given the low risk of groin recurrence, the authors concluded that radiation therapy could be omitted in this patient cohort.[36]

By contrast, Parthasarathy et al suggested a potential benefit from adjuvant radiation in vulvar cancer patients with a single positive node. This study examined 490 patients with node-positive vulvar cancer of which 208 patients had a single positive node. Radiation therapy significantly improved survival in the subset of patients with ≤ 12 lymph nodes removed (76.6% vs 55.1%, $P = 0.035$), but the improvement in survival did not reach significance in those with >12 lymph nodes removed (77.3% vs 66.7%, $P = 0.23$). However, an important limitation of this study was that the size and characteristics of the nodal metastases were not reported.[37] Finally, a multicenter study examined 176 patients with vulvar cancer and 1 positive node. While there were significant differences in 5-year overall survival between women with no lymph node metastases and women with 1 intracapsular metastasis ($P < 0.0001$), 1 extracapsular metastasis ($P = 0.0006$) and with 3 node metastases ($P < 0.0001$), there were no significant differences in survival between women with 1 intracapsular, 1 extracapsular, or 2 nodal metastases. Additionally, lymphovascular space invasion (LVSI) was a negative predictor of recurrence-free survival while adjuvant radiation was a positive predictor of recurrence-free survival (HR 0.10, CI: 0.01 to 0.90, $P = 0.04$ and HR 5.87, CI: 1.21 to 28.5, $P = 0.02$, respectively). These results suggest that adjuvant radiation would be beneficial regardless of the number of positive nodes, particularly if negative risk factors such as LVSI are present.[38]

Thus, adjuvant radiation should be recommended in patients with > 2 positive nodes and in those with extracapsular extension, and could be considered in patients with 1 positive

Adjuvant Radiation in Early Stage Vulvar Cancer: Highlights

- Early stage vulvar cancer is managed with wide local excision and nodal assessment followed by risk-adapted adjuvant radiation.
- Indications for adjuvant radiation are based on factors shown to increase risk of local recurrence.
- Close (< 8 mm) or positive margins (tumor on the edge of the surgical specimen) are an indication for adjuvant radiation.
- Two or more positive lymph nodes, extracapsular extension, or gross residual nodal disease are also indications for adjuvant radiation.
- The role of adjuvant radiation for a single positive node remains controversial.
- Dose escalation to > 56 Gy has been shown to reduce local recurrence compared with 45 to 50 Gy in patients with close or positive margins.
- Prospective trials are needed to validate the use of adjuvant radiation and to clarify the role of systemic therapy in patients with early stage vulvar cancer.

node in the presence of additional negative risk factors such as LVSI.

Optimal Dose for Adjuvant Radiation

With regard to radiation technique and volumes for postoperative vulvar cancer, intensity-modulated radiation therapy has become a standard option for vulvar cancer and consensus recommendations have been developed. Specifically, for a vulvar primary with negative margins, the CTV should encompass the entire operative bed, while if a case has positive margins, the CTV should have a margin of approximately 2 cm. Furthermore, the lymph node volumes for lesions involving the vulva or distal vagina include bilateral inguinofemoral, bilateral obturator, bilateral internal, and external iliac groups, with perirectal and presacral nodes added for anal involvement.[39] While adjuvant radiation has been shown to decrease the risk of local recurrence in vulvar cancer, relatively few studies have been conducted to ascertain the optimal dose of adjuvant radiation. The randomized study by Homesley et al established the dose of 45 to 50 Gy as standard dose for adjuvant pelvic and inguinal nodal irradiation.[30] More recent studies explored the benefit of dose escalation particularly in the presence of close or positive margins. The aforementioned study by Viswanathan et al not only found that margins ≤ 5 mm were significantly associated with an increased risk of local recurrence but also examined the relationship between radiation dose and recurrence. A total of 61 patients received adjuvant radiation of which 25% had negative margins, 66% had close margins, and 10% had positive margins.[22] The median vulvar radiation dose was 50.4 Gy, 47.4 Gy, and 47.6 Gy for those with negative, close, and positive margins, respectively. The vaginal recurrence rates were 21% and 34% for patients who received ≥ 56 Gy and ≤ 50.4 Gy, respectively. There were significantly more recurrences in patients who received < 56 Gy compared with those who received ≥ 56 Gy ($P = 0.046$).[22]

A study published in 2017 examined 3,075 patients with vulvar squamous cell carcinoma with positive margins of which 35.3% received adjuvant radiation to a median cumulative dose of 54.0 Gy. Patients were stratified by the following radiation dose categories: 30.0 to 45.0 Gy, 45.1 to 53.9 Gy, 54.0 to 59.9 Gy, and ≥ 60 Gy. The unadjusted 3-year overall survival in these groups was 54.3%, 55.7%, 70.1%, and 65.3%, respectively, ($P < 0.001$). On multivariate analysis, patients receiving 54 Gy to 59.9 Gy and ≥ 60 Gy had the greatest mortality reduction compared with patients receiving < 54 Gy (HR 0.75, $P = 0.024$ and HR 0.71, $P = 0.015$, respectively). This mortality reduction for patients receiving ≥ 54 Gy persisted for both node-positive and node-negative patients (HR 0.73, $P < 0.001$ and HR 0.79, $P = 0.001$, respectively). However, there was no significant overall survival benefit between patients who received ≥ 60 Gy compared with those who received 54.0 to 59.9 Gy (HR 0.95, $P = .779$).[40]

In summary, while early literature suggested that doses of 45 to 50 Gy were appropriate for adjuvant radiation, recent studies support dose escalation to > 56 Gy in patients with close or positive margins as mentioned in the ACR Appropriateness Criteria.[17]

Conclusion

Early stage vulvar cancer is managed by wide local excision with nodal assessment followed by risk-adapted adjuvant radiation. Despite the lack of large, randomized trials in vulvar cancer, a multitude of retrospective studies has shown benefits of adjuvant radiation therapy, including lower recurrence rates, improved PFS, and improved overall survival. The strongest indications for adjuvant radiation are close or positive margins – often defined in the literature as margins < 8 mm and tumor on the edge of the surgical specimen, respectively – and positive nodes due to the increased risk of local recurrence with the presence of these factors. Thus, patients with vulvar cancer with positive or close margins should undergo adjuvant radiation therapy unless concerns for excessive morbidity would outweigh potential benefit of decreasing local recurrence and improving PFS. Additionally, patients with 2 or more positive nodes or ≥ 1 node with extracapsular extension should undergo adjuvant radiation therapy, with radiation for patients with 1 intracapsular positive node reserved for those with additional risk factors such as LVSI. Future trials are needed to investigate the role of adjuvant radiation therapy in patients with a single positive node. Moreover, while optimal dose of adjuvant radiation is still being defined, dose escalation to > 56 Gy has shown a benefit in the presence of close or positive margins and should be utilized in cases where adjuvant radiation is indicated. Although adjuvant radiation has shown benefit in patients with close or positive margins and in node-positive disease, prognosis still remains relatively poor. Intensification of adjuvant therapy with the addition of chemotherapy to radiation may be a potential strategy to improve outcomes analogous to anal or cervical cancers. Prospective trials are needed to further inform the use of appropriate adjuvant therapy in patients with early stage vulvar cancer.

References

1) Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2021. *CA Cancer J Clin*. 2021;71(1):7-33. doi:10.3322/caac.21654

2) Hampl M, Deckers-Figiel S, Hampl JA, Rein D, Bender HG. New aspects of vulvar cancer: changes in localization and age of onset. *Gynecol Oncol*. 2008;109(3):340-345. doi:10.1016/j.ygyno.2008.01.041

3) Alkatout I, Schubert M, Garbrecht N, et al. Vulvar cancer: epidemiology, clinical presentation, and management options. *Int J Womens Health*. 2015;7:305-313. doi:10.2147/ijwh.S68979

4) Muigai J, Jacob L, Dinas K, Kostev K, Kalder M. Potential delay in the diagnosis of vulvar cancer and associated risk factors in women treated in German gynecological practices. *Oncotarget*. 2018;9(9):8725-8730. doi:10.18632/oncotarget.23848

5) Woelber L, Eulenburg C, Choschzick M, et al. Prognostic role of lymph node metastases in vulvar cancer and implications for adjuvant treatment. *Int J Gynecol Cancer*. 2012;22(3):503-508. doi:10.1097/IGC.0b013e31823eed4c

6) Woelber L, Mahner S, Voelker K, et al. Clinicopathological prognostic factors and patterns of recurrence in vulvar cancer. *Anticancer Res*. 2009;29(2):545-552.

7) Pecorelli S. Revised FIGO staging for carcinoma of the vulva, cervix, and endometrium. *Int J Gynaecol Obstet*. 2009;105(2):103-4. doi:10.1016/j.ijgo.2009.02.012

8) Way S. The anatomy of the lymphatic drainage of the vulva and its influence on the radical operation for carcinoma. *Ann R Coll Surg Engl*. 1948;3(4):187-209.

9) Podratz KC, Symmonds RE, Taylor WF, Williams TJ. Carcinoma of the vulva: analysis of treatment and survival. *Obstet Gynecol*. 1983;61(1):63-74.

10) Twombly GH. The technique of radical vulvectomy for carcinoma of the vulva. *Cancer*. 1953;6(3):516-30. doi:10.1002/1097-0142(195305)6:3<516::aid-cncr2820060310>3.0.co;2-#

11) Micheletti L, Preti M. Surgery of the vulva in vulvar cancer. *Best Pract Res Clin Obstet Gynaecol*. 2014;28(7):1074-1087. doi:10.1016/j.bpobgyn.2014.07.011

12) Hacker NF, Leuchter RS, Berek JS, Castaldo TW, Lagasse LD. Radical vulvectomy and bilateral inguinal lymphadenectomy through separate groin incisions. *Obstet Gynecol*. 1981;58(5):574-579.

13) Burke TW, Stringer CA, Gershenson DM, Edwards CL, Morris M, Wharton JT. Radical wide excision and selective inguinal node dissection for squamous cell carcinoma of the vulva. *Gynecol Oncol*. 1990;38(3):328-332. doi:10.1016/0090-8258(90)90067-u

14) Levenback CF, Ali S, Coleman RL, et al. Lymphatic mapping and sentinel lymph node biopsy in women with squamous cell carcinoma of the vulva: a gynecologic oncology group study. *J Clin Oncol*. 2012;30(31):3786-3791. doi:10.1200/jco.2011.41.2528

15) Van der Zee AG, Oonk MH, De Hullu JA, et al. Sentinel node dissection is safe in the treatment of early-stage vulvar cancer. *J Clin Oncol*. 2008;26(6):884-889. doi:10.1200/jco.2007.14.0566

16) Jones GL, Jacques RM, Thompson J, et al. The impact of surgery for vulval cancer upon health-related quality of life and pelvic floor outcomes during the first year of treatment: a longitudinal, mixed methods study. *Psychooncology*. 2016;25(6):656-662. doi:10.1002/pon.3992

17) Jolly S, Soni P, Gaffney DK, et al. ACR Appropriateness Criteria® Adjuvant Therapy in Vulvar Cancer. *Oncology (Williston Park)*. 2015;29(11):867-72, 874-587.

18) Fuh KC, Berek JS. Current management of vulvar cancer. *Hematol Oncol Clin North Am*. 2012;26(1):45-62. doi:10.1016/j.hoc.2011.10.006

19) Heaps JM, Fu YS, Montz FJ, Hacker NF, Berek JS. Surgical-pathologic variables predictive of local recurrence in squamous cell carcinoma of the vulva. *Gynecol Oncol*. 1990;38(3):309-314. doi:10.1016/0090-8258(90)90064-r

20) Faul CM, Mirmow D, Huang Q, Gerszten K, Day R, Jones MW. Adjuvant radiation for vulvar carcinoma: improved local control. *Int J Radiat Oncol Biol Phys*. 1997;38(2):381-389. doi:10.1016/s0360-3016(97)82500-x

21) Chan JK, Sugiyama V, Pham H, et al. Margin distance and other clinico-pathologic prognostic factors in vulvar carcinoma: a multivariate analysis. *Gynecol Oncol*. 2007;104(3):636-641. doi:10.1016/j.ygyno.2006.10.004

22) Viswanathan AN, Pinto AP, Schultz D, Berkowitz R, Crum CP. Relationship of margin status and radiation dose to recurrence in post-operative vulvar carcinoma. *Gynecol Oncol*. 2013;130(3):545-549. doi:10.1016/j.ygyno.2013.05.036

23) Barlow EL, Jackson M, Hacker NF. The prognostic role of the surgical margins in squamous vulvar cancer: a retrospective Australian study. *Cancers (Basel)*. 2020;12(11). doi:10.3390/cancers12113375

24) Ignatov T, Eggemann H, Burger E, Costa SD, Ignatov A. Adjuvant radiotherapy for vulvar cancer with close or positive surgical margins. *J Cancer Res Clin Oncol*. 2016;142(2):489-495. doi:10.1007/s00432-015-2060-9

25) Nooij LS, van der Slot MA, Dekkers OM, et al. Tumour-free margins in vulvar squamous cell carcinoma: Does distance really matter? *Eur J Cancer*. 2016;65:139-149. doi:10.1016/j.ejca.2016.07.006

26) Groenen SM, Timmers PJ, Burger CW. Recurrence rate in vulvar carcinoma in relation to pathological margin distance. *Int J Gynecol Cancer*. 2010;20(5):869-873. doi:10.1111/IGC.0b013e3181df7423

27) Nomura H, Omi M, Netsu S, et al. Positive surgical margin is an independent predictor of overall survival of patients with vulvar squamous cell carcinoma. *J Obstet Gynaecol Res*. 2021;47(11):3990-3997. doi:10.1111/jog.14962

28) Milliken S, May J, Sanderson PA, et al. Reducing the radicality of surgery for vulvar cancer: are smaller margins safer? *Minerva Obstet Gynecol*. 2021;73(2):160-165. doi:10.23736/s0026-4784.20.04743-7

29) Te Grootenhuis NC, Pouwer AW, de Bock GH, et al. Prognostic factors for local recurrence of squamous cell carcinoma of the vulva: a systematic review. *Gynecol Oncol*. 2018;148(3):622-631. doi:10.1016/j.ygyno.2017.11.006

30) Homesley HD, Bundy BN, Sedlis A, Adcock L. Radiation therapy versus pelvic node resection for carcinoma of the vulva with positive groin nodes. *Obstet Gynecol*. 1986;68(6):733-740.

31) Kunos C, Simpkins F, Gibbons H, Tian C, Homesley H. Radiation therapy compared with pelvic node resection for node-positive vulvar cancer: a randomized controlled trial. *Obstet Gynecol*. 2009;114(3):537-546. doi:10.1097/AOG.0b013e3181b12f99

32) Mahner S, Jueckstock J, Hilpert F, et al. Adjuvant therapy in lymph node-positive vulvar cancer: the AGO-CaRE-1 study. *J Natl Cancer Inst*. 2015;107(3)doi:10.1093/jnci/dju426

33) Woelber L, Prieske K, Eulenburg CZ, et al. Adjuvant radiotherapy and local recurrence in vulvar cancer - a subset analysis of the AGO-CaRE-1 study. *Gynecol Oncol*. 2022;164(1):68-75. doi:10.1016/j.ygyno.2021.11.004

34) van der Velden J, van Lindert AC, Lammes FB, et al. Extracapsular growth of lymph node metastases in squamous cell carcinoma of the vulva. The impact on recurrence and survival. *Cancer*. 1995;75(12):2885-2890. doi:10.1002/1097-0142(19950615)75:12<2885::aid-cncr2820751215>3.0.co;2-3

35) Fons G, Groenen SM, Oonk MH, et al. Adjuvant radiotherapy in patients with vulvar cancer and one intra capsular lymph node metastasis is not beneficial. *Gynecol Oncol*. 2009;114(2):343-345. doi:10.1016/j.ygyno.2009.05.017

36) van der Velden J, Pleunis N, Barlow E, et al. Radiotherapy is not indicated in patients with vulvar squamous cell carcinoma and only one occult intracapsular groin node metastasis. *Gynecol Oncol*. 2021;160(1):128-133. doi:10.1016/j.ygyno.2020.10.008

37) Parthasarathy A, Cheung MK, Osann K, et al. The benefit of adjuvant radiation therapy in single-node-positive squamous cell vulvar carcinoma. *Gynecol Oncol*. 2006;103(3):1095-1099. doi:10.1016/j.ygyno.2006.06.030

38) Serre E, Raimond E, Diguisto C, et al. Inguino-femoral radiotherapy in vulvar squamous cell carcinoma: clues to revised indications in patients with only one intracapsular lymph node metastasis. *Acta Oncol*. 2020;59(5):518-524. doi:10.1080/0284186x.2019.1687934

39) Gaffney DK, King B, Viswanathan AN, et al. Consensus recommendations for radiation therapy contouring and treatment of vulvar carcinoma. *Int J Radiat Oncol Biol Phys*. 2016;95(4):1191-1200. doi:10.1016/j.ijrobp.2016.02.043

40) Chapman BV, Gill BS, Viswanathan AN, Balasubramani GK, Sukumvanich P, Beriwal S. Adjuvant radiation therapy for margin-positive vulvar squamous cell carcinoma: defining the ideal dose-response using the National Cancer Data Base. *Int J Radiat Oncol Biol Phys*. 2017;97(1):107-117. doi:10.1016/j.ijrobp.2016.09.023

Real-time Prostate Gland Motion and Deformation During CyberKnife Stereotactic Body Radiation Therapy

Deepak Gupta, MD;[1] Venkatesan Kaliyaperumal, MSc;[1] Shyam Singh Bisht, MD;[1] Susovan Banerjee, MD;[1] Shikha Goyal, MD, DNB;[2] Kushal Narang, MD;[1] Anurita Srivastava, MD;[3] Saumya Ranjan Mishra, MD;[1] Tejinder Kataria, MD, DNB[1]

Abstract

Purpose: To analyze intrafraction prostate motion during radical CyberKnife stereotactic body radiation therapy (SBRT) and calculate the planning target volume margins needed to ameliorate errors related to this intrafraction motion.

Materials and Methods: We analyzed the data for 10 consecutive patients with prostate cancer treated with the Accuray CyberKnife (54 fractions, 5,465 alignment shifts in target position). Real-time alignment shifts during delivery of SBRT fractions were obtained by in-room image tracking of 3 to 5 (minimum 3 required for tracking) gold seed fiducials implanted in the prostate. The intrafraction target motion was analyzed, and the margins required to compensate for the real-time motion were calculated using margin recipe formulae.

Results: The translational mean ± standard deviation (SD) in left-right (LR), anterior-posterior (AP), and superior-inferior (SI) directions was 1.65 ± 2.17 mm, 1.24 ± 1.55 mm and 1.13 ± 2.1 mm, respectively. The rotational mean ± SD was 1.2 ± 1.33, 2.17 ± 2.14, and 0.99 ± 0.87 degrees in roll, pitch, and yaw, respectively. Motion in LR, AP, and SI directions was less than 2.0 mm in 78.1%, 86.73%, and 92.21% of readings, respectively, and less than 3.0 mm in 85.9%, 96.5%, and 95.7% of readings, respectively. A margin of 5 mm in LR, 4 mm in both SI and AP directions would ensure that ≥ 95% of patients receive at least 95% of the prescribed dose.

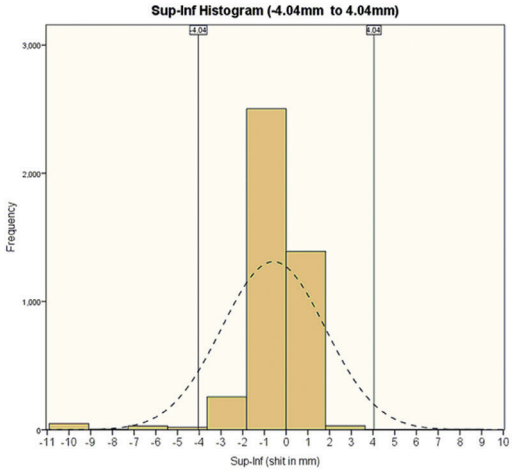
Conclusions: Our dataset constitutes among the largest series of intrafraction prostatic motion during SBRT. The observed intrafraction prostate motion is highest in the LR and SI directions, and least in the AP direction.

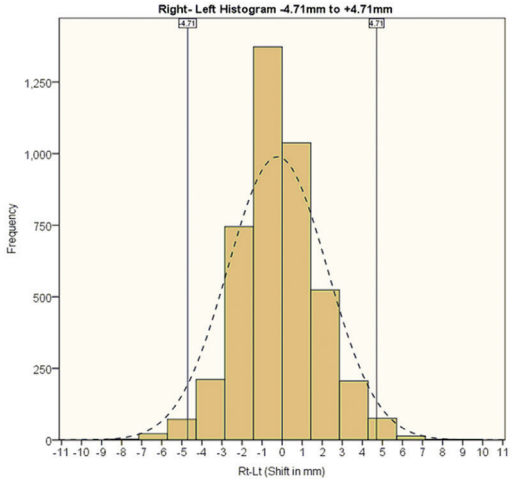
Keywords: CyberKnife, intrafraction motion, prostate, stereotactic body radiation therapy

Radiation therapy (RT) dose escalation in curative treatment of prostate cancer has yielded better disease control, but with a corresponding higher probability of organ-at-risk (OAR) complications.[1-3] Image guidance before each treatment fraction using various in-room imaging technologies (electronic portal imaging device [EPID], cone-beam computed tomography [CBCT], etc.) may help reduce the interfraction set-up errors. However, the prostate gland undergoes significant physiological spatial motion and volumetric deformation during the course of a radiation fraction. Both these interfraction and intrafraction variations are accounted for by adding a planning target volume (PTV) margin during RT planning. Hypofractionated treatments or dose escalation studies involve a relatively higher fractional dose and need a much sharper peripheral dose fall-off compared with conventional fractionation and delivery techniques, thus necessitating a reduction in PTV margins to minimize normal tissue adverse effects.[4,5] This requirement is addressed by various techniques that measure variations

Affiliations: [1]Radiation Oncology, Medanta – The Medicity, Gurgaon, Haryana, India; [2]Department of Radiotherapy and Oncology, PGIMER, Chandigarh; [3]Radiation Oncology, Maulana Azad Medical College, New Delhi. **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. **Data availability statement:** The deidentified patient data supporting the findings of this study are available from the corresponding author Deepak Gupta, MD, (deepakonco@gmail.com) upon reasonable request. The study protocol and statistical analysis performed during the study by physicist Venkatesan Kaliyaperumal, MSc, are included in this manuscript.

Figure 1. Histogram of translation motions in all patients. Data consist of 5,465 events. A) Superior-inferior directions. Confidence interval 97.68% and 2.32% is out of margin. B) Right-left directions. Confidence interval 96.75% and 3.25% is out of margin. C) Anterior-posterior directions. Confidence interval 97.49% and 2.51% is out of margin.





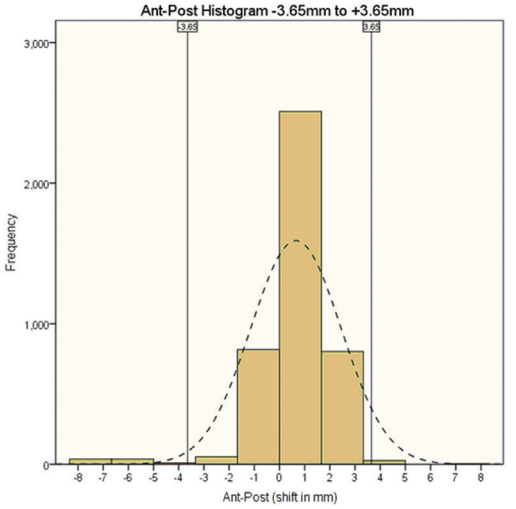


Table 1. Margin Calculation

	SUPERIOR-INFERIOR	RIGHT-LEFT	ANTERIOR-POSTERIOR
∑	.14 mm	.67 mm	.35 mm
σ	2.2 mm	1.89 mm	1.51 mm
Angular component	1.71 mm		
Margin	4.04 mm	4.71 mm	3.65 mm
Margin (rounded off)	4 mm	5 mm	4 mm

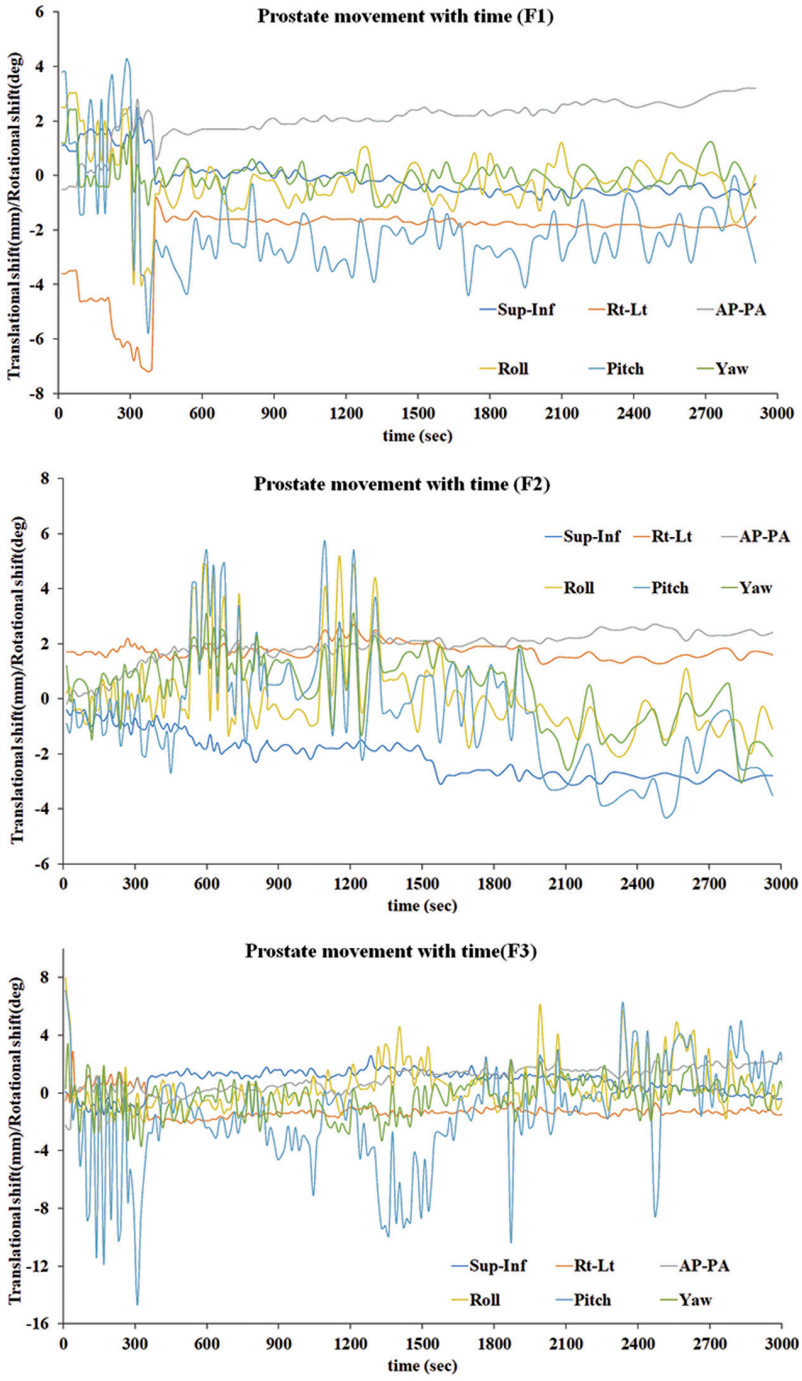
in daily setup and internal organ motion during a treatment fraction, either by assessing organ motion directly or through surrogates such as implanted fiducials (ultrasound, EPID, CBCT, electromagnetic transponders in Calypso [Varian]).[6-13] Strict and efficient image guidance may help limit PTV margins considerably, and thus enable the dual goals of dose escalation and normal tissue sparing. Although techniques such as volumetric-modulated arc therapy (VMAT) and the current hot-topic FLASH radiation therapy have potential to reduce these uncertainties by lowering the fraction duration, we will not be discussing this aspect as the present study deals only with a specific SBRT system and related real-time intrafraction motion not adequately explored in the aforementioned strategies.

At our institution, we use the CyberKnife system (Accuray Inc.) for stereotactic body radiation therapy (SBRT). This system uses frequent real-time stereoscopic x-ray imaging of implanted fiducials during treatment delivery to monitor changes in prostate position. Each pair of stereoscopic images acquired is used to compute the center of mass (CM) of implanted fiducials, and this forms a surrogate for intrafraction prostatic movement. This study is an analysis of individual patient data of 10 consecutive patients treated with CyberKnife for definitive prostate cancer radiation and seeks to quantify intrafraction prostate motion. The purpose of presenting this data is to guide PTV margins based on observed translational and rotation motion. We also calculated the deformation of the prostate gland during the treatment.

Materials and Methods

All 10 patients (54 fractions) received SBRT with the CyberKnife VSI System using gold-seed fiducial-based tracking between December 2018 and December 2019. SBRT was used as monotherapy or in combination therapy as a prostate boost with standard pelvic radiation (using conventional fractionation) on a linear accelerator (linac). Following informed consent, 3 to 5 (minimum 3 required for tracking) gold fiducials were placed in the periphery of the prostate gland (1 at the prostate apex, 2 near the base on the right and left side, 1 to 2 fiducials in the transverse plane midway between the apex and base on the right and left sides) under transrectal ultrasound guidance per CyberKnife protocol (> 2 cm and > 15 degrees apart, within 6 cm of each other). Usually, at least 3 of these fiducials would be usable for tracking the prostate during SBRT. After waiting to 5 to 7 days to allow for any possible fiducial movement/migration, noncontrast RT planning CT scans (slice thickness 1 mm, no superposition of slices, 512 × 512 pixel matrix, pitch 1) with the patient immobilized in the supine position with a customized full-body vacuum cushion (empty bladder, optimal rectal emptying) were obtained and co-registered with thin section volumetric MR

Figure 2. Prostate movement of one patient's fractions with respect to time.



images (T2-weighted and T1 contrast sequences) acquired in the supine position for target delineation. This step was undertaken first regardless of whether an SBRT boost preceded or followed the linac-based RT. Adequate bowel preparation was ensured prior to simulation and before delivery of each fraction to minimize errors in prostate localization and to prevent interference with daily imaging during treatment. Specifically, the patients were counseled for a low-residue diet during the first consultation and advised to have adequate hydration throughout the day. Those with pre-existing constipation were additionally advised to take laxatives and a charcoal-simethicone combination to allow a regular bowel movement and minimize bowel gas, starting 3 to 4 days before simulation and continuing until the last fraction. Occasionally, a phosphate enema was given if the simulation topographic scan showed the rectum loaded with feces, in which case simulation was re-attempted after an hour of the enema. The prostate clinical target volume (CTV) was delineated on the primary CT dataset (co-registered with axial T2- and T1-contrast sequence volumetric MRI with 1-mm slice thickness) with the help of a radiologist specializing in prostate imaging. An isotropic 3-mm margin around the CTV was given to generate a final PTV, which was prescribed to receive a dose of 1,650 to 1,800 Gy in 3 fractions for an SBRT boost (4 patients, 3 fractions per patient), or 3,500 to 4,200 cGy in 7 fractions when delivering radical SBRT to the prostate (6 patients, 7 fractions per patient).

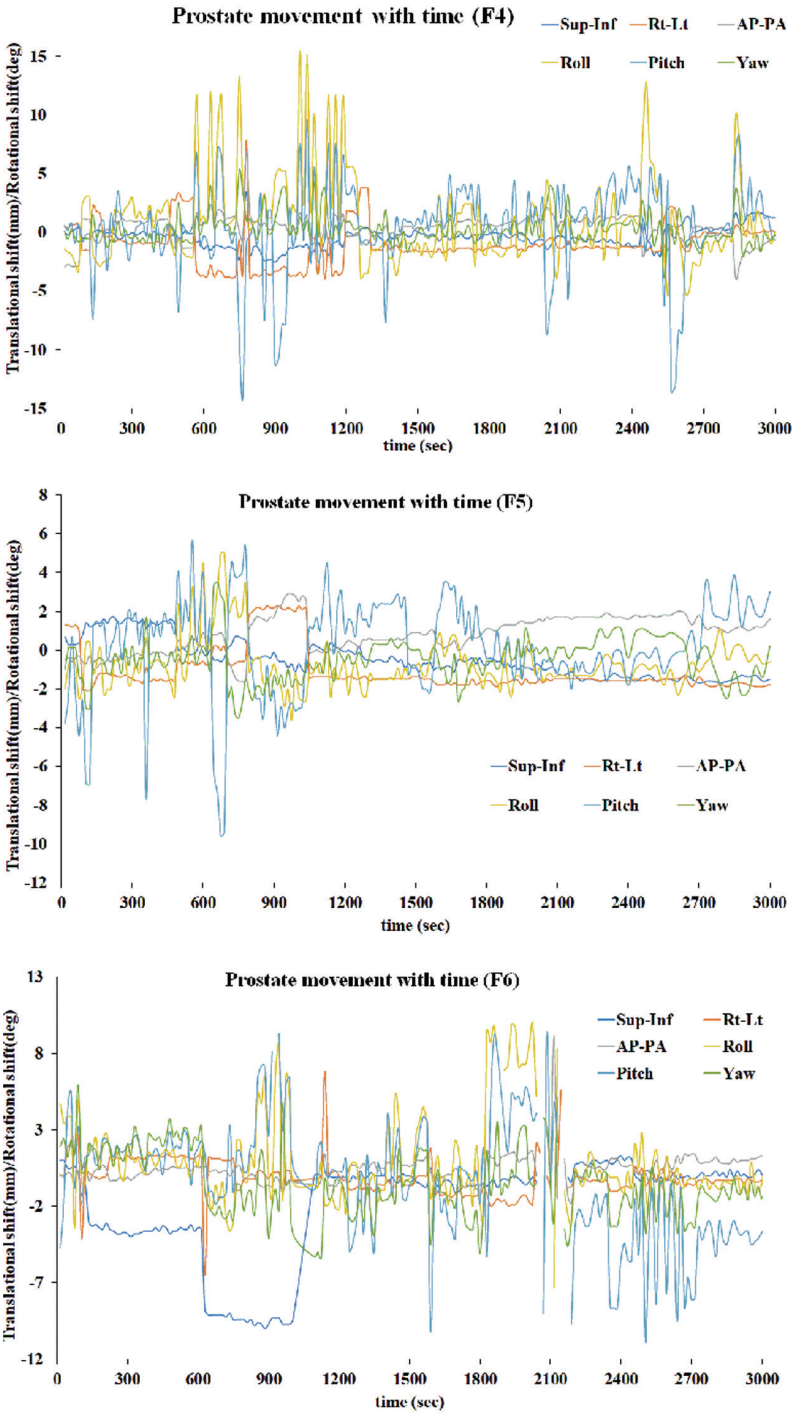
The 2 Gy equivalent dose (EQD2) for the SBRT plan was calculated using the formula, $EQD2 = n \times d \times (\alpha/\beta + d)/(\alpha/\beta + 2)$, keeping in mind the limitations of dose equivalence in high fractional doses. MultiPlan software (Accuray Inc.) was used for treatment planning whereby inverse planning helped achieve the prescribed target dose while respecting normal tissue constraints for the given dose fractionation. Plans were then evaluated for adequate target coverage, dose heterogeneity and conformality index. Strict patient-specific quality assurance was ensured for accurate and smooth treatment delivery.

The CyberKnife SBRT system employs a robotic, arm-mounted, miniaturized 6 MV linac with 6 degrees of freedom. Translations from

0.6 to 10.0 mm, and rotations in roll (2.0 degrees), pitch (5.0 degrees) and yaw (3.0 degrees), in either direction, can be corrected by the robotic arm without needing to move the patient couch. The planning system generates multiple pairs of digitally reconstructed radiographs (DRRs) after plan approval, which are used as references for treatment verification. The treatment room has 2 in-room, ceiling-mounted kV x-ray sources placed at 45 degrees to the vertical along with 2 flat-panel detectors on the floor. These aid real-time imaging of the implanted fiducials during treatment delivery, thus allowing detection and subsequent correction of intrafraction shifts. In tempo adaptive imaging system of CyberKnife (time-based adaptive image guidance) is used for prostate SBRT to assist in the frequency of tracking (minimum interval between 2 consecutive image acquisitions from 5 to 150 seconds) and thereby corrects nonpredictable intrafraction target motion. In tempo imaging helps determine the best frequency of imaging depending on the instability in the prostate position. Every projection pair acquired by the cameras is co-registered in 6-dimensional space with a reference DRR image pair using a complex tracking algorithm, and intrafraction target motion data are generated.

Once the patient is set up in the treatment position using in-room lasers, verification images are acquired and, within seconds, co-registered with the planning DRRs to detect set-up errors and correct them by couch movement before initiating treatment. During treatment, real-time set-up errors are continuously recorded, and appropriate adjustments are performed by the robotic arm, without needing to move the patient. However, larger deviations lead to greater uncertainties in the accuracy of correction by the robot; hence, it is advisable that these deviations are kept to a minimum

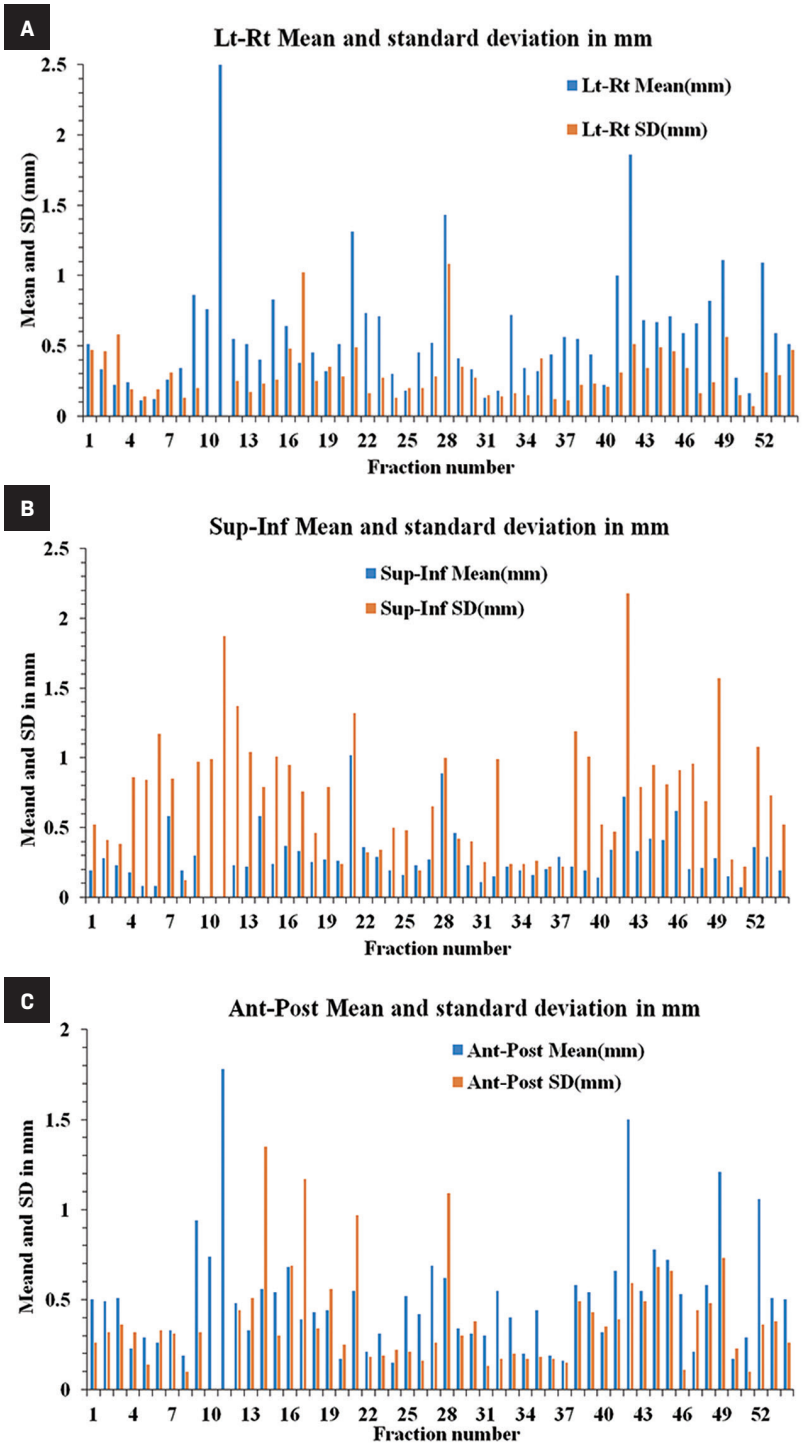
Figure 2 (continued). Prostate movement of one patient's fractions with respect to time.



during treatment. At our institution, we use a threshold of 5.0 mm for translational shifts. If the calculated shift exceeds this threshold, the robot automatically pauses the treatment, and remote-assisted couch movement is performed to correct gross movements, so the robot can continue fine adjustments once the shift is within the threshold limit.

To analyze our data on prostate motion, we retrieved the treatment

Figure 3. Rigid Body Error: A) left-right, b) superior-inferior, c) anterior-posterior



log files (containing data on fiducial tracking with time) from the CyberKnife treatment localizer system for 10 patients, accounting for a total of 5,465 intrafraction shift datasets; these were reviewed for this study.

By using in-house MATLAB version R2015a (MathWorks) programming, the translational, rotational and deformation shifts of the fiducials were obtained with respect to the fiducial position on the RT planning CT scan.

Statistical analysis was done using IBM SPSS software (version 24). Histograms in descriptive statistics were obtained with Gaussian distribution trendline for translational and rotational shifts. A scatter line graph was plotted between fiducial position and time through the treatment duration for the entire dataset of 1 patient with 7 fractions.

Margin Calculation

Standard deviation (SD) of the mean for the individual shifts was calculated for systematic uncertainty (Σ). For random errors (σ), root mean square of the individual patient's SD was used. The traditional Van Herk margin recipe was modified to include the margin for the angular component.

For angular margin, the following formula was used:

Angular margin (mm) =
$x\sin(\Theta)+y\cos(\Delta)+(z/xy)*\tan(\Gamma)$

Θ- roll; Δ- pitch; Γ- yaw (all in degrees)

Total Margin =
$2.5\Sigma+0.7\sigma$+ angular component

We took the initial 5 minutes of each fraction for systematic error, and the rest of the variation during treatment for random error calculations.[14] Mean value of the angular linear component was added to individual translational margin to account for the rotational movement of the fiducials.

The CyberKnife system records the rigid body error (RBE) data for every fiducial used for tracking at every time stamp. The RBE at a particular time is defined as "the distance of a fiducial from its corresponding position on planning CT after the system has assessed the best translational and rotational transformation through a rigid registration of the acquired in-room projection images with CT-generated DRRs."[15]

Results

The translational mean (± SD) for intrafraction motion of the prostate in superior-inferior (SI), anterior-posterior (AP) and left-right (LR) directions was 1.24 mm (± 1.55 mm), 1.65 mm (± 2.17 mm), and 1.13 mm (± 2.10 mm), respectively. The rotational mean (± SD) for roll, pitch, and yaw was 1.20 (± 1.33), 2.17 (± 2.14) and 0.99 (± 0.87) degrees, respectively. Intrafraction prostate motion for > 97% readings was ± 4.01 mm (SI), ± 3.65 mm (AP) and ± 4.71 mm (LR). **Figure 1** shows the histograms depicting the range of intrafraction translational movement of the COM of the fiducials in all 3 dimensions (**1A** SI, **1B** LR, **1C** AP).

We observed intrafraction prostate motion under 2 mm in 92.21% (SI), 86.73% (AP), and 78.10% (LR) readings, and less than 3 mm in 95.7% (SI), 96.50% (AP) and 85.90% (LR) readings, respectively. We observed intrafraction prostate motion of over 5 mm only in 1.8% readings, and this was only in the SI direction.

It is important to note that in our patients, treatment delivery began only after the computed shift was lower than the preset 5 mm threshold for fiducial tracking. Throughout treatment, automatic adjustments to incident beam were made by the robot to compensate for deviation in target localization. If the deviation exceeded 5 mm, then treatment stopped automatically, and the patient realigned such that translational error returned within the threshold limit before restarting treatment. Hence, the observed values do not represent the mean target motion magnitude during the entire treatment fraction. However, it is also important to note that the frequency of such erratic larger magnitude shifts is significantly less compared with the majority of the motion recorded during the treatment time of a single fraction. This practice may be responsible for < 2% incidence of > 5 mm translational shift in our study. These shifts account for the actual prostate motion during most of the treatment duration, barring a few erratic large movements.

Based on the above data, the calculated margins for translational motion were 4.04 mm (SI), and 3.65 mm (AP), and 4.71 mm (LR), respectively. On the other hand, rotational prostate movement as noted from fiducials is random; it is observed during the initial part of treatment in most patients and midtreatment in others. The detailed contribution to the margin from systematic and random errors and the angular component (deformation) are depicted in **Table 1**. **Figure 2** represents the prostate movement for a representative patient's treatment fractions over time (F1 through F7 represent fractions 1-7 for a patient). From our analysis, we surmised that time interval between 2 consecutive intrafraction image acquisitions should preferably be less than 20 seconds for the first 380 seconds of treatment and not exceed 35 seconds throughout the treatment.

RBE calculated for the fiducial shifts was 0.59 mm (± 0.29 mm) for fiducials 1-2, 0.51 mm (± 0.29 mm) for fiducials 1-3, and 0.73 mm (± 0.38 mm) for fiducials 2-3. **Figure 3** shows the rigid body error for our patients in A) SI, B) LR, and C) AP directions. Average treatment time for all patients per fraction was 48.29 +/- 5.31 min (range, 45 to 56 min).

Discussion

Most protocols for prostate SBRT use PTV margins of 5 mm circumferentially (and 3 mm posteriorly toward the rectum). Assuming that real-time determination of intrafraction movement of the target during CyberKnife may help reduce PTV margins and make dose escalation safer, we used a 3 mm circumferential margin for our patients based on the study by Litzenberg et al who demonstrated a reduction in PTV margin to less than 2 mm if intrabeam adjustments or continuous tracking were performed.[16] However, we observed in our study that although a 3 mm PTV margin may cover more than 95% of intrafraction motion in SI and AP directions, it served less than 90% motion in the LR direction. We determined that a margin of 4 mm in SI and AP directions and 5 mm in the LR direction (after correction of setup errors at the outset) would ensure that 95% of the planned dose would be delivered to at least 95% patients. It is possible that other factors such as positioning and immobilization techniques, bowel and bladder protocol variations, or patient weight and general fitness may contribute to differences in target motion between various intrafraction motion monitoring techniques.

Table 2 lists several studies that assessed intrafraction prostate displacements and reported on PTV margins based on their observations.[13,15-26]

A large patient database of a VMAT study using 4 half arcs with an average treatment duration of 15.6 minutes showed that a 3-mm margin is desirable for intrafraction translational motion correction. Rotational motion was not studied, and in this study, the relative displacements decreased over subsequent arcs after the first correction.[17]

Langen et al tracked the real-time prostate motion during intensity-modulated radiation therapy (IMRT). They noted a slow posterior and inferior drift in prostate position with time during a fraction, possibly due to muscle relaxation or change in rectal contents. Sudden and transient anterior and superior movements were seen, possibly attributable to peristalsis. Lateral movements were infrequent. Large interpatient variations were noted. Frequency of displacements grew

with increasing time from start of treatment, with only 2% of the observations with displacement exceeding 3 mm during the first minute, increasing to 23% during the tenth minute. They recommended that the gap between initial setup and treatment initiation should be minimized as far as possible.[13] Kron et al made similar observations on the rise in intrafraction motion according to increasing treatment duration.[18] We did not notice a similar drift, possibly due to couch adjustments whenever the motion was out of range (preset 5 mm limit) but this is an important observation suggesting that a shorter treatment time would minimize additional errors.

The CyberKnife study by Gottschalk et al reported that a PTV margin of 2 mm would give at least 95% target coverage for more than 90% patients.[19] Another study of CyberKnife SBRT by Xie et al also used a preset threshold of 5 mm for couch correction, as in our study. They reported intrafraction motion similar to our results with average shift vector length of 2.61 ± 1.94 mm.[15] However, they studied only translations and deformations; rotational shifts were not considered. Additionally, their dataset was much smaller compared with our dataset. Similar to the findings of Langen et al,[13] they noted increasing motion with time since treatment initiation. Motion > 2 mm increased with increasing time since initiation of therapy, reiterating the need to start treatment quickly after setup. Their RBE value was within 1.5 mm, suggesting a relatively smaller contribution from deformation. Our data also notes the RBE value of the fiducials to be well within 1.5 mm. Yu et al, based on their experience with Synchrony (Accuray Inc.) tracking, have suggested respiratory motion tracking of implanted fiducials to mitigate errors due to respiratory motion, although none of the other CyberKnife studies including ours have used respiratory tracking for the prostate.[20]

Shimizu et al classified patients as those with large motion (> 5 mm displacement within 10 minutes), increasing (> 5 mm displacement noted after 10 minutes) or steady (no displacement > 5 mm) based on magnitude and timing of observed intrafraction movement during real-time tumor tracking (RTRT), and recommended that monitoring duration may be tailored to type of motion.[21]

Aubry et al used video-based EPID to determine intrafraction prostate motion during IMRT (average treatment time 5 minutes).[22] Rotational data were recorded but not corrected. Our study noted relatively larger rotations than their study in coronal (LR), sagittal (SI) and transverse (AP) planes at 1.20 (± 1.33), 2.17 (± 2.14) and 0.99 (± 0.87) degrees, respectively. Rotation exceeding 3 degrees in the Y axis was found in 10.9% readings, suggesting a significant rotational component of intrafraction motion in our dataset.

van de Water et al, in their CyberKnife simulation study, determined a 60- to 180-second imaging interval as optimum for maintaining CTV coverage, with little contribution of adaptive imaging.[23] In contrast, a much shorter imaging interval of 35 seconds throughout treatment and in tempo imaging were found useful for motion management in our patients. Simulations of in tempo imaging were possibly not able to fully determine the true impact of variations that occur during an actual treatment session. Our study also assessed the impact of deformation and its correction, though RBE was < 1 mm for our patients.

Several studies have tried to assess the impact of intrafraction motion on organ-at-risk doses although we have not been able to address that with the CyberKnife system.[24-26] Wu et al studied intrafraction translational motion and sagittal rotation during 3DCRT, and determined that intrafraction motion compromised PTV coverage and reduced rectal dose.[24] Rijkhorst et al, in their simulation study, also showed the increasing probability of tumor underdose with uncorrected rotations while rectal and bladder doses remained the same or reduced.[25] Another study on CyberKnife using only translational corrections, showed significant reduction in D98 and D50 of PTV, although the absolute reduction was not clinically relevant. There was no significant impact on bladder/rectum/urethra dose volume histogram indices.[26]

Several MRI studies have correlated the AP intrafraction motion with rectal distension and peristalsis, although there seems to be minimal additional value over conventional tracking methods in determining PTV margins.[27,28] In addition to motion tracking, use of an air-filled endorectal balloon or Foley catheter to immobilize the prostate have helped further reduce the positional uncertainty and PTV margins to < 2 mm, with variations within 1 mm for 95% of treatment sessions in the extreme hypofractionation study by Greco et al.[29] Hydrogel spacers during CyberKnife treatment have also shown promise, especially over long treatment durations.[30]

Our dataset on intrafraction motion and deformation is among the largest reported datasets, and we conclude that there is differential motion, the highest being in longitudinal and lateral aspects, and the least in the AP aspect. Our study confines itself to the impact of intrafraction motion assessment after initial setup and correction of set-up error. Our findings of nearly similar motion in all 3 translational directions may be attributable to strict adherence to a rectal protocol as well as treating patients with an empty bladder such that AP motion seen in other studies was largely overcome. In contrast to the other literature reported on CyberKnife and other methods of tracking intrafraction motion, tracking and correction encompassed

Table 2. Contemporary Studies Reporting Intrafraction Prostate Displacements and PTV Margins Based on Observations[13,15-26]

S. NO.	STUDY	NO. OF PATIENTS	SETUP	MONITORING TECHNIQUE	DETERMINED PTV MARGINS	OTHER OBSERVATIONS
1	Litzenberg et al[16]	11	3 implanted gold fiducials; Supine, knee rest, feet fixed together; No bladder or bowel protocol; Initial alignment with skin tattoos and set-up error correction with orthogonal DRR	Electromagnetic transponders (monitored for 8 minutes)	LR 1.3 mm AP 1.5 mm SI 1.5 mm	2 patients had deviations >3 mm (maximum in SI direction)
2	Levin-Epstein et al[17]	205		Planar orthogonal imaging or ExacTrac (Brainlab) imaging prior to each treatment arc	PTV margin for intrafraction motion LR 1.9 mm SI 2.7 mm AP 3.1 mm	Shifts > 3 mm were seen in SI direction in 2% and in AP direction in 5.4% patients
3	Langen et al[13]	17 (550 sessions)	3 electromagnetic transponders implanted; Supine, knee cushion, rubber band around feet for immobilization; No bowel or bladder preparation; PTV margin 6 mm (4 mm posteriorly)	Electromagnetic transponders (monitored for 10 minutes)	5 mm – covered 96.7% displacements averaged over all patients	Slow posterior & inferior drift with time during each fraction; 3D vector displacement > 3 mm seen in 13.2% of observation time and > 5 mm in 3.1% of observation time; For 5/17 patients, displacement of > 5 mm occurred for 5% -10% of treatment time
4	Kron et al[18]	184 (5778 image pairs)	3 gold fiducials implanted; Verification using orthogonal kV x-rays and correction before treatment; Another set of x-rays at treatment completion Treatment with 3DCRT or IMRT; PTV margin 10 mm (7 mm posteriorly)	No intrafraction monitoring; Data for first 5 fractions used for calculations	Margins varied according to treatment time; Under 9 minutes AP 3 mm LR 2 mm SI 3 mm Over 9 minutes AP 4 mm LR 3 mm SI 4 mm	Only 4.7% displacements were above 5 mm and 0.4% above 10 mm; Increase in average displacement of 3D vector by 0.2 mm for every 5 minutes of treatment time; Probability of a shift of > 5 mm increased by 10% after 18 minutes of initial setup in the absence of continuous tracking or correction
5	Gottschalk et al[19]	13 (2,438 alignment shifts)	3 gold fiducials implanted; Other set-up details not mentioned	Intrafraction monitoring with a pair of in-room kV x-ray imagers during CyberKnife; Images taken every 1-2 min	PTV margin of 2 mm would ensure that 90% of patients receive at least 95% prescribed dose to CTV	< 2 mm shift in 80% (SI), 80% (AP) and 92% (LR); <3 mm shift in 89% (SI), 90%, (AP) and 97% (LR); > 5 mm shift in 3% readings for SI and AP and only 1% readings in LR
6	Xie et al[15]	21 (4,439 timestamps)	3 gold fiducials implanted; Other set-up details not mentioned	Intrafraction monitoring with a pair of in-room kV x-ray imagers during CyberKnife; Images taken every 40 seconds	PTV margins were not calculated Average shifts in each direction were: SI: 1.55 ±1.28 mm LR: 0.87 ± 1.17 mm AP: 1.80 ±1.44 mm	Motion of > 2 mm increased from 5% datasets at 30 seconds to 14% datasets at 120 seconds
7	Yu et al[20]	9	3 gold fiducials implanted; Other set-up details not mentioned	Intrafraction monitoring with a pair of in-room kV X-ray imagers during CyberKnife; Synchrony tracking system was additionally used	PTV margin 2.7 mm	Largest single axis deviation in AP; LR 2.5 mm translation, 1.7° rotation SI 2.0 mm translation, 0.82° rotation AP 1.65 mm translation, 0.74° rotation

Table 2. continued

S. NO.	STUDY	NO. OF PATIENTS	SETUP	MONITORING TECHNIQUE	DETERMINED PTV MARGINS	OTHER OBSERVATIONS
8	Shimizu et al[21]	20 (4,541 observations)	3 gold fiducials implanted; PTV margin: 3 mm; Other positioning details not mentioned; No specific bladder or rectal rectal protocol–patients were asked to void 1 hour before the treatment time	Table position correction using the RTRT system		To maintain a treatment accuracy within 2 mm, more frequent table position adjustments were needed after 10 min. than at 2 min. for AP and SI directions. At 10 min., adjustments were needed for 14.2% observations in AP, 12.3% in SI and 5.0% in LR directions. Adjustment > 5 mm was needed at least once during treatment in 11/20 patients.
9	Aubry et al[22]	18 (282 intrafraction movements)	2-3 implanted fiducials	Video-based EPID	PTV margin of 3 mm ensured > 98% volume received the desired dose for average treatment duration of 5 min.	Mean intrafractional translational movements: SI 0.0 ± 1.1 mm AP 0.2 ± 1.6 mm LR 0.2 ± 0.8 mm Rotational movements: SI: 0.5 ± 3.8° AP: 0.4±2.0° LR: -0.5±5.8° Random & systematic SD of intrafraction rotations: LR: 1.8° & 1.0° SI: 1.1° & 0.8° AP: 0.6° & 0.3°
10	van de Water at al[23]	17 (548 prostate motion tracks)	Various CyberKnife treatment scenarios were simulated - such as timing of correction (fixed intervals between imaging and correction of 15/60/180/360 seconds vs adaptive timing based on extent of prostate motion during a short interval), extent of correction (none, translation only, translation with variable rotation correction) and PTV margin (0-3 mm) to assess target coverage variations	Real-time motion data captured through electromagnetic transponders; Used for dosimetric simulations of CyberKnife therapy	PTV margin of 3 mm: sufficient for up to 5-degree rotational error in addition to translational motion, to achieve 98% CTV coverage over 98% treatment sessions	For intervals smaller than 60-180 seconds, benefit of reducing time interval was minimal. Benefit of adaptive timing was also miniscule.
11	Wu et al[24]	28	PTV margin 7 mm in AP and LR, 12 mm in SI direction	Coregistration of planning and treatment CT images	PTV margin of 3 mm allows 90% of patients to receive at least 98% of planned D99	Prostate motion was largest in AP direction followed by SI and LR direction Organ motion reduces target coverage as well as rectal dose
12	Rijkhorst et al[25]	19	2 simulated plans generated per patient – based on margins of 7 mm/4 mm for primary and boost treatment in first plan set and 4 mm/1 mm in second plan set	Coregistration of planning and treatment CT images	PTV margin – If only translational correction: 7 mm If both trnaslational and rotational correction: 4 mm	There were marginal reductions in bladder and rectal doses (2-3%) with reduction of PTV margins
13	Koike et al[26]	16 (1,929 timestamps)	3 implanted fiducials PTV margin around prostate was 5 mm except 3 mm posteriorly	Intrafraction monitoring with a pair of in-room kV x-ray imagers during CyberKnife		Mean absolute shifts per timestamp: SI: 1.54 ± 1.37 mm RL: 0.59 ± 0.56 mm AP: 1.59 ± 1.44 mm Mean 3D vector length: 2.57 ± 1.77 mm. 3D vector length >3 mm in 31.3% and > 5 mm in 9.1% cases

Key: S = study, PTV = planning target volume, DRR = digitally reconstructed radiograph, LR = left-right, AP = anterior-posterior, SI = superior-inferior, IMRT = intensity-modulated radiation therapy, CTV = clinical target volume, RTRT = real-time tumor tracking, EPID = electronic portal imaging device, CT = computed tomography, 3D = 3 dimensional

all 3 aspects of position variation (translation, rotation, deformation) and our margin recipe also included all of these.

Limitations of Fiducial-Based Tracking

Fiducial-based image-guided tracking in prostate SBRT carries several limitations. Fiducial implantation is an invasive procedure and may not be looked at favorably by patients and some physicians. Additionally, the tracking algorithm for CyberKnife, similar to the Calypso system, is best suited for rigid tumors. There is no option for tracking the movement and shape of adjacent critical structures, such as the bladder and rectum, which may also vary during treatment in addition to their relationship with the target (prostate). This, in turn, may alter the dose distribution and real-time irradiated volume during an RT fraction. Real-time tracking also substantially adds to treatment time, increasing the duration of a fraction to 30 to 45 minutes in contrast to 7 to 10 minutes for linac-based IMRT or VMAT. This increases the probability of prostate motion during the latter half of treatment, which is counterproductive.

Conclusions

Intrafraction motion and deformation are among the most important and challenging aspects of prostate external-beam radiation, and become even more relevant in the setting of dose escalation, hypofractionation, and SBRT due to the narrow therapeutic window. The interpatient, interfraction and intrafraction variability necessitate an individualized margin recipe for each image-guidance technique. We were able to achieve acceptable coverage for most patients despite the lower CTV to PTV margin of 3 mm in our study. Based on our findings, we suggest a differential margin of 5 mm in LR, and 4 mm in both craniocaudal and AP directions to ensure that at least 95% of the prescribed dose is delivered to at least 95% patients, thus maximizing the target coverage and minimizing the irradiated OAR volumes.

References

1) Zietman AL, DeSilvio ML, Slater JD, et al. Comparison of conventional – dose vs high-dose conformal radiation therapy in clinically localized adenocarcinoma of the prostate: a randomized controlled trial. *JAMA.* 2005;294:1233-1239. doi:10.1001/jama.294.10.1233

2) Pollack A, Zagars GK, Starkschall G, et al. Prostate cancer radiation dose response: results of the M.D. Anderson phase III randomized trial. *Int J Radiat Oncol Biol Phys.* 2002;53:1097-1105. doi:10.1016/s0360-3016(02)02829-8

3) King CR, Lehmann J, Adler JR, et al. CyberKnife radiotherapy for localized prostate cancer: rationale and technical feasibility. *Technol Cancer Res Treat.* 2003;2:25-30. doi:10.1177/153303460300200104

4) Chen Z, Yang Z, Wang J, et al. Dosimetric impact of different bladder and rectum filling during prostate cancer radiotherapy. *Radiat Oncol.* 2016;11:103.

5) Wong JR, Grimm L, Uematsu M, et al. Image-guided radiotherapy for prostate cancer by CT-linear accelerator combination: prostate movements and dosimetric considerations. *Int J Radiat Oncol Biol Phys.* 2005;61:561-569. doi:10.1016/j.ijrobp.2004.06.010

6) Chen J, Lee RJ, Handrahan D, et al. Intensity-modulated radiotherapy using implanted fiducial markers with daily portal imaging: assessment of prostate organ motion. *Int J Radiat Oncol Biol Phys.* 2007;68:912-919. doi:10.1016/j.ijrobp.2007.02.024

7) Langen KM, Meeks SL, Poole DO, et al. The use of megavoltage CT (MVCT) images for dose recomputations. *Phys Med Biol.* 2005;50:4259-4276. doi:10.1088/0031-9155/50/18/002

8) Litzenberg DW, Balter JM, Lam KL, et al. Retrospective analysis of prostate cancer patients with implanted gold markers using off-line and adaptive therapy protocols. *Int J Radiat Oncol Biol Phys.* 2005;63:123-133. doi:10.1016/j.ijrobp.2005.02.013

9) Poulsen PR, Muren LP, Hoyer M. Residual set-up errors and margins in on-line image-guided prostate localization in radiotherapy. *Radiother Oncol.* 2007;85:201-206. doi:10.1016/j.radonc.2007.08.006

10) Kupelian P, Willoughby T, Mahadevan A, et al. Multiinstitutional clinical experience with the Calypso System in localization and continuous, real-time monitoring of the prostate gland during external radiotherapy. *Int J Radiat Oncol Biol Phys.* 2007;67:1088-1098. doi:10.1016/j.ijrobp.2006.10.026

11) Balter JM, Wright JN, Newell LJ, et al. Accuracy of a wireless localization system for radiotherapy. *Int J Radiat Oncol Biol Phys.* 2005;61:933-937. doi:10.1016/j.ijrobp.2004.11.009

12) King CR, Brooks JD, Gill H, et al. Stereotactic body radiotherapy for localized prostate cancer: interim results of a prospective phase II clinical trial. *Int J Radiat Oncol Biol Phys.* 2009;73:1043-1048. doi:10.1016/j.ijrobp.2008.05.059

13) Langen KM, Willoughby TR, Meeks SL, et al. Observations on real-time prostate gland motion using electromagnetic tracking. *Int J Radiat Oncol Biol Phys.* 2008;71:1084-1090. doi:10.1016/j.ijrobp.2007.11.054

14) Herschtal A, Kron T, Fox C. Radiotherapy margin design with particular consideration of high curvature CTVs. *Med Phys.* 2009;36:684-697. doi:10.1118/1.3070539

15) Xie Y, Djajaputra D, King CR, et al. Intrafractional motion of the prostate during hypofractionated radiotherapy. *Int J Radiat Oncol Biol Phys.* 2008;72:236-246. doi:10.1016/j.ijrobp.2008.04.051

16) Litzenberg DW, Balter JM, Hadley SW, et al. Influence of intrafraction motion on margins for prostate radiotherapy. *Int J Radiat Oncol Biol Phys.* 2006;65:548-553. doi:10.1016/j.ijrobp.2005.12.033

17) Levin-Epstein R, Qiao-Guan G, Juarez JE, et al. Clinical assessment of prostate displacement and planning target volume margins for stereotactic body radiotherapy of prostate cancer. *Front Oncol.* 2020;10:539. doi:10.3389/fonc.2020.00539

18) Kron T, Thomas J, Fox C, et al. Intrafraction prostate displacement in radiotherapy estimated from pre- and post-treatment imaging of patients with implanted fiducial markers. *Radiother Oncol.* 2010;95:191-197. doi:10.1016/j.radonc.2010.01.010

19) Gottschalk AR, Hossain S, Chuang C, Descovich, Ma L. Intrafraction prostate motion during CyberKnife radiosurgery: implications on planning margins. *Int J Radiat Oncol Biol Phys.* 2008;72:S569. doi:10.1016/j.ijrobp.2008.06.147

20) Yu H, Chen C, Tsai J, et al. Quantifying the accuracy of intrafractional internal target volume margin in stereotactic body radiotherapy for prostate cancer using CyberKnife Tumor Tracking System. *Int J Radiat Oncol Biol Phys.* 2011;81:874. doi:10.1016/j.ijrobp.2011.06.1561

21) Shimizu S, Osaka Y, Shinohara N, et al. Use of implanted markers and inter-portal adjustment with real-time tracking radiotherapy system to reduce intrafraction prostate motion. *Int J Radiat Oncol Biol Phys.* 2011;81:393-399. doi:10.1016/j.ijrobp.2011.04.043

22) Aubry JF, Beaulieu L, Girouard LM, et al. Measurements of intrafraction motion and interfraction and intrafraction rotation of prostate by three-dimensional analysis of daily portal imaging with radiopaque markers. *Int J Radiat Oncol Biol Phys.* 2004;60:30-39. doi:10.1016/j.ijrobp.2004.02.045

23) Van de Water S, Valli L, Aluwini S, et al. Intrafraction prostate translations and rotations during hypofractionated robotic radiation surgery: dosimetric impact of correction strategies and margins. *Int J Radiat Oncol Biol Phys.* 2014;88:1154-1160. doi:10.1016/j.ijrobp.2013.12.045

24) Wu Q, Ivaldi G, Liang J, et al. Geometric and dosimetric evaluations of an online image-guidance strategy for 3D-CRT of prostate cancer. *Int J Radiat Oncol Biol Phys.* 2006;64:1596-1609. doi:10.1016/j.ijrobp.2005.12.029

25) Rijkhorst EJ, Lakeman A, Nijkamp J, et al. Strategies for online organ motion correction for intensity-modulated radiotherapy of prostate cancer: prostate, rectum, and bladder dose effects. *Int J Radiat Oncol Biol Phys.* 2009;75:1254-1260. doi:10.1016/j.ijrobp.2009.04.034

26) Koike Y, Sumida I, Mizuno H, et al. Dosimetric impact of intrafraction prostate motion under a tumour-tracking system in hypofractionated robotic radiosurgery. *PLoS One.* 2018;13:0195296. doi:10.1371/journal.pone.0195296

27) Padhani AR, Khoo VS, Suckling J, et al. Evaluating the effect of rectal distension and rectal movement on prostate gland position using cine MRI. *Int J Radiat Oncol Biol Phys.* 1999; 44:525-533. doi:10.1016/s0360-3016(99)00040-1

28) Mah D, Freedman G, Milestone B, et al. Measurement of intrafractional prostate motion using magnetic resonance imaging. *Int J Radiat Oncol Biol Phys.* 2002;54:568-575. doi:10.1016/s0360-3016(02)03008-0

29) Greco C, Pares O, Pimentel N, et al. Target motion mitigation promotes high-precision treatment planning and delivery of extreme hypofractionated prostate cancer radiotherapy: Results from a phase II study. *Radiother Oncol.* 2020;146:21-28. doi:10.1016/j.radonc.2020.01.029.

30) Sumila M, Mack A, Schneider U, et al. Long-term intrafractional motion of the prostate using hydrogel spacer during Cyberknife treatment for prostate cancer – a case report. *Radiat Oncol.* 2014;9:186. doi:10.1186/1748-717X-9-186

Quality Assurance in Radiation Oncology: Addressing a Changing Treatment Landscape

Ryan Kraus, MD;[1] Christopher Weil, MD;[1] May Abdel-Wahab, MD, PhD[2]

Abstract

Innovation within the field of radiation oncology has led to new and complex treatment techniques that require increasing coordination among care teams. Quality assurance and quality improvement initiatives must keep pace with this ever-changing treatment landscape to ensure that quality of care remains high as new technology and treatment processes are adopted. Physicians should be engaged in these quality assurance and quality improvement initiatives and need updated resources to fulfill this essential role. With this in mind, the updated Quality Assurance Team for Radiation Oncology (QUATRO) guidelines by the International Atomic Energy Agency (IAEA) provide a resource for radiation oncology treatment centers. The QUATRO guidelines have served as a detailed template for performing health care audits and establishing quality assurance measures and plans specific to resources available across low-, middle-, and high-income countries. The new QUATRO guidelines provide additional tools focused on treatment delivery, reporting, and management of deviations in treatment delivery, oncology information systems, academic education, and brachytherapy. Radiation oncologists, physicists, and radiation therapists are encouraged to familiarize themselves with these quality assurance tools and use them to guide quality assurance initiatives tailored to the needs and resources of their institution.

Key words: radiation oncology, quality assurance, quality improvement, health care audits

As the field of radiation oncology continues to advance, the use of more complex treatment modalities involving larger multidisciplinary teams is increasing. As treatment complexity grows, there is a greater need for appropriate and sophisticated quality assurance measures.[1] This has led to quality improvement initiatives becoming an increasingly integral part of modern medical practice.

The highly specialized technology, equipment and professional training requirements that are essential to safe and effective radiation therapy procedures cannot be overstated. The regular review and verification of the elements of treatment processes, as well as patient-specific decision-making and procedures, are necessary for continuous quality improvement.

The spectrum of activities in the patient care process must be undertaken under an umbrella of continuous quality improvement. The process of care includes the evaluation and development of a clinical plan, preparation for treatment through simulation dosimetry and pretreatment review and verification, treatment including set-up, delivery, and on-treatment evaluation, as well as post-treatment verification and follow-up care. These processes should all be coordinated within a quality management and improvement framework that also includes quality management of equipment and software.[2] The benefits of these activities extend beyond direct patient care

Affiliations: [1]Department of Radiation Oncology, Huntsman Cancer Institute, University of Utah, Salt Lake City, UT; [2]Division of Human Health, International Atomic Energy Agency, Vienna, Austria. **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.

and can enhance the robustness of clinical research trial results.

Health Care Audits

One of the most common methodologies utilized in quality assurance programs is a health care audit, which involves observing and analyzing clinical performance over a specified time frame, followed by observer feedback regarding ways to improve the care delivery. Physician engagement is central to the success of health care audits as physician involvement lends credibility to any recommended improvements and has been associated with higher rates of successful implementation of quality improvement plans. Beyond improving the quality of care at an institution, physician engagement in quality assurance initiatives is also associated with improved communication between interdisciplinary colleagues and higher job satisfaction. In addition, it provides an opportunity to create a more collaborative environment between physicians and hospital administrators, putting physicians on more equal footing with administrators and flattening the hierarchy of leadership.[3]

Quality Assurance Team in Radiation Oncology Guidelines

Within radiation oncology, the International Atomic Energy Agency (IAEA) has created opportunities for physicians, medical physicists, and radiation therapists to become actively involved in a variety of quality assurance initiatives.[4] The IAEA has a history of quality assurance projects dating back to 1969 when a postal audit program was created using thermoluminescence dosimetry to confirm the appropriate calibration of radiation therapy machines.[5] The IAEA has now completed more than 15,500 dosimetric audits involving 2,500 radiation therapy treatment centers across 139 countries. Given the widespread utilization of these dosimetric audits, the IAEA was approached by multiple countries and treatment organizations about preforming more comprehensive health care audits. In response, the IAEA crafted a comprehensive quality assurance protocol, known as the Quality Assurance Team in Radiation Oncology (QUATRO) guidelines. These guidelines were the product of the IAEA QUATRO workshop held in Vienna in May 2005, which culminated in the 2007 publication of the recommended procedures for auditors participating in quality assurance missions.[6] The published QUATRO guidelines have been extensively field tested by expert teams and found to be effective in systematically identifying clinical inadequacies and facilitating collaboration between international experts and local physician leaders to implement changes to improve the quality of care delivered.[7,8] To date, more than 100 QUATRO missions have been performed involving 51 countries and 84 treatment facilities. The success of the QUATRO guidelines has resulted in multiple endorsements from professional societies and several countries creating their own national radiation quality assurance programs based on the QUATRO methodology. One example is B-QUATRO in Belgium where QUATRO audits were adapted to the Belgian context.[9] In addition, QUATRO guidelines have been referred to by the European Commission in its guidelines for clinical audit.[10]

QUATRO audits are performed at the voluntary request of individual institutions and vary in scope from comprehensive audits of an entire department to partial audits focused on specific aspects of treatment delivery. A comprehensive audit consists of staff interviews; review of documentation, infrastructure, and dosimetric measurements; and observation of radiation therapy practices. The scope of a comprehensive audit covers the appropriateness of diagnosis, treatment, and follow-up of patients, as well as dosimetry, medical radiation physics, machine calibration, infrastructure, staffing, and training programs.

The auditing team is composed of an experienced radiation oncologist, radiation therapy medical physicist, and a radiation therapist. When needed, an additional specialist, such as a radiation protection officer, may also be involved depending on the scope of the audit requested by the institution. The 2007 QUATRO guidelines consist of 37 checklists that guide the auditing team in performing a systematic and standardized assessment of the aforementioned aspects of clinical care. QUATRO audits culminate in confidential reports delivered to the requesting institution with recommendations on how to optimize the quality of patient care based on each institution's available resources.

Updated Guidelines

Since 2007, treatment modalities such as 3D conformal radiation, intensity-modulated radiation, volumetric-modulated arc therapy, stereotactic radiosurgery, and 3D high-dose-rate brachytherapy have become more widely utilized. Additionally, more advanced imaging modalities are playing a larger role in diagnosis, staging, and treatment planning. Given the continued innovation within radiation oncology, updated QUATRO guidelines are needed. In 2018, the IAEA began collaborating with a group of international experts to revise the QUATRO guidelines incorporating lessons gleaned from the prior decade of QUATRO missions and accounting for advances in technology.

The update of the QUATRO guidelines now includes a section dedicated to the introduction of new

technologies at radiation therapy centers, which builds upon more recent IAEA publications.[11-14] New technologies include treatment machines, physical infrastructure, hardware, software, updated processes, and changes in workflow including new treatment regimens. In addition to improving and modernizing the original 37 checklists, 5 new checklists have been incorporated into the guidelines to assist auditing teams in completing an audit. These 5 new checklists cover daily patient identification, treatment delivery, reporting and management of deviations in radiation therapy administration; brachytherapy procedures and planning; oncology information systems; and academic education. The emphasis on academic education and training helps ensure that individual facilities can sustainably and adequately train new staff to meet their needs as the communities they serve grow.

Conclusion

The second edition of the QUATRO guidelines will serve as an indispensable resource for radiation therapy health care audits. The publication reflects modern practice and technological challenges and provides guidance on implementation of future innovations in radiation oncology. Radiation oncologists, medical physicists, and radiation therapists are encouraged to familiarize themselves with these quality management tools and use them to guide quality assurance initiatives tailored to the needs and resources of their institution. QUATRO audits may be requested in anticipation of implementing new technology to ensure adequate training, staffing, budgeting, quality assurance protocols, and a plan for its sustainable use. Physicians should continue to play a leading role in quality improvement, as their engagement remains key to the successful implementation and sustainability of quality assurance and improvement initiatives.

References

1) Huq MS, Frass BA, Dunscombe PB, et al. A method for evaluating quality assurance needs in radiation therapy. *Int J Radiat Oncol Biol Phys.* 2008;71(1 Suppl):S170-173. doi:10.1016/j.ijrobp.2007.06.081

2) Safety is No accident: A framework for quality radiation oncology care. American Society for Radiation Oncology. 2019. Accessed February 7, 2022. https://www.astro.org/Patient-Care-and-Research/Patient-Safety/Safety-is-no-Accident

3) Hut-Mossel L, Ahaus K, Welker G, Gans R. Understanding how and why audits work in improving the quality of hospital care: a systematic realist review. *PLoS One.* 2021;16(3):e0248677.

4) Abdel-Wahab M, Rosenblatt E, Holmberg O, Meghzifene A. Safety in radiation oncology: the role of international initiatives by the International Atomic Energy Agency. *J Am Coll Radiol.* 2011;8(11):789-794. doi:10.1016/j.jacr.2011.07.014

5) Izewska J, Bokulic T, Kazantsev P, Wesolowska P, van der Merwe D. 50 years of the IAEA/WHO postal dose audit programme for radiotherapy: what can we learn from 13756 results? *Acta Oncol.* 2020;59(5):495-502. doi:10.1080/0284186X.2020.1723162

6) Comprehensive Audits of Radiotherapy Practices: A Tool for Quality Improvement. Quality Assurance Team for Radiation Oncology (QUATRO). 2007, Vienna: International Atomic Energy Agency.

7) Rosenblatt E, Zubizarreta E, Izewska J, Binia S, Garcia-Yip F, Jimenez P. Quality audits of radiotherapy centres in Latin America: a pilot experience of the International Atomic Energy Agency. *Radiat Oncol.* 2015;10:169. https://doi.org/10.1186/s13014-015-0476-7

8) Izewska J, Coffey M, Scalliet P, et al. Improving the quality of radiation oncology: 10 years' experience of QUATRO audits in the IAEA Europe Region. *Radiother Oncol.* 2018;126(2):183-190. doi:10.1016/j.radonc.2017.09.011

9) B-QUATRO - Comprehensive Audits of Radiotherapy Practices: A Tool for Quality Improvement adapted to the Belgian context. Accessed Feb 10, 2022. https://fank.fgov.be/de/system/files/2020-01-23-b-quatro2.6vcomp.pdf

10) European Commission guidelines on clinical audit for medical radiological practices (diagnostic radiology, nuclear medicine and radiotherapy). Luxembourg: Publications Office of the European Union; 2009. Accessed Feb 10, 2022. https://data.europa.eu/doi/10.2768/20266

11) Transition from 2-D Radiotherapy to 3-D Conformal and Intensity Modulated Radiotherapy. IAEA TECDOC Series No. 1588. 2008: International Atomic Energy Agency.

12) The Transition from 2-D Brachytherapy to 3-D High Dose Rate Brachytherapy, IAEA Human Health Reports No. 12. 2015: International Atomic Energy Agency.

13) Wesolowska P, Georg D, Lechner W, et al. Testing the methodology for a dosimetric end-to-end audit of IMRT/VMAT: results of IAEA multicentre and national studies. *Acta Oncol.* 2019;58(12):1731-1739. doi:10.1080/0284186X.2019.1648859

14) Introduction of Image Guided Radiotherapy into Clinical Practice. 2019. IAEA Human Health Reports No. 16. Accessed February 7, 2022. https://www.iaea.org/publications/12264/introduction-of-image-guided-radiotherapy-into-clinical-practice

Radiation Therapy in Indonesia: Estimating Demand as Part of a National Cancer Control Strategy

Steven Octavianus, MD;[1] Soehartati Gondhowiardjo, MD, PhD[1]

Abstract

Purpose: The International Agency for Research on Cancer (IARC) predicts that the burden of cancer will continue to increase over the next few decades. Based on the Indonesia Basic National Health Survey (RISKESDAS) in 2018, cancer prevalence has increased 28% from 1.4 per 1,000 (2013) to 1.8 per 1,000 in 2018. Given the burden and challenges of the problems resulting from cancer over time, a comprehensive and systematic effort and response from various sectors is needed in the form of a National Cancer Control Plan (NCCP). Cancer treatment is the most expensive part of a cancer control program, and cancer-specific health facilities, human resources, specialized equipment, and therapy all contribute a high cost. Radiation therapy (RT) is a primary and priority medical treatment needed for cancer care; more than 50% of cancer patients will need RT.

Methods: Cancer incidences were extracted from the International Agency for Research on Cancer GLOBOCAN database. The total population was based on the Central Bureau of Statistics of Indonesia. Several models based on published literature were used to estimate the number of patients requiring RT in each province and the demand for megavoltage machines in Indonesia.

Results: Based on these models, the need for additional RT centers is evident. Through various estimation methods, Indonesia is expected to need 265 to 427 megavoltage machines to provide RT access to all cancer patients in the country. Using the Indonesian Radiation Oncology Society (IROS) estimation model (conventional and hypofractionated RT) and megavoltage/million, with the 82 megavoltage machines available in 2020, the coverage of RT services in Indonesia (available RT machines / RT required) is 21.7% (conventional RT), 27.7% (hypofractionated RT) and 31% (megavoltage/million).

Conclusions: Access to RT is a necessity and global priority. In addition to more facilities, implementing high-quality and safe RT services is essential. Hypofractionated radiation therapy (HRT) may be one innovation and solution for overcoming the RT shortage and preparing for a growing number of cancer cases in the future.

Keywords: Cancer, radiation therapy, access, cancer control

Cancer is one of the most prevalent noncommunicable diseases after cardiovascular disease, and is a worldwide problem.[1] Data from the Institute for Health Metrics and Evaluation (IHME) have shown that cancer prevalence ranked fourth among diseases in 2007 and second in 2017, excluding maternal and childhood diseases and infectious diseases.[1] A World Health Organization analysis concluded that 1 in 6 deaths is caused by cancer.[2] Also alarming is that a new case of cancer arises every 1.5 seconds and every 2 seconds is a cancer death. More than 50% of cancer cases occur in people from low- to middle-income countries (LMICs) where health systems are not well prepared or equipped to manage this growing burden,

Affiliation: [1]Department of Radiation Oncology, Faculty of Medicine Universitas Indonesia - Dr. Cipto Mangunkusumo Hospital, Jakarta, Indonesia. **Disclosure:** Dr. Gondhowiardjo is a past chair of the National Cancer Control Committee of Indonesia and president of the Indonesian Radiation Oncology Society. The authors have no additional disclosures or conflicts of interest. 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.

and where budget allocations and resource mobilization are severely insufficient.[3-5]

The International Agency for Research on Cancer (IARC) has assessed and estimated cancer incidence and mortality in Indonesia. In 2018, Indonesia was estimated to have 348,809 new cancer cases annually, which will increase by 65.1% to 575,814 in 2040. In addition, cancer deaths will increase by 76.9% from 207,210 to 366,567 in 2040.[6] This increase is also in line with a Basic Health Research (RISKESDAS) analysis that shows a significant rise of 28% in cancer prevalence from 1.4 per 1,000 in 2013, to 1.8 per 1,000 in 2018.[7] According to the national population-based cancer registry report in 2017 from the National Cancer Control Committee, which collected cancer data in Indonesia from 2008 to 2012, breast cancer and cervical cancer were the most common cancers in women, and lung cancer and nasopharyngeal cancer were the most common in men. Additionally, pediatric cancers represent 3% to 5% of all cancers in Indonesia.[8]

Cancer costs also increase annually, according to the National Health Insurance system, part of the Health Insurance Administration Agency. Reaching 1.5 trillion rupiah (110 million USD) in 2014 and 4.15 trillion rupiah (300 million USD) in 2019, these costs directly result from services at health facilities in collaboration with BPJS Health (Indonesian national health insurance) and do not include the cost of health services at private health facilities.[9] In addition, many indirect costs stem from the loss of productivity of patients and families, and travel expenses required due to lack of health facilities and facility infrastructure.

Radiation therapy (RT) is one of the main components of multidisciplinary cancer treatment. Recent data suggest that more than 50% of cancer patients will require RT throughout their disease, either as a single treatment or in combination with other treatment modalities.[10] RT may be given preoperatively to allow for less extensive surgical procedures to preserve organ function and to produce better results, or postoperatively to improve local control. For palliative purposes, RT can relieve symptoms associated with advanced or metastatic disease, improving quality of life.[11] As these benefits suggest, RT has an essential and indispensable role in the multidisciplinary management of cancer. Unfortunately, many barriers remain. Many countries or communities in various parts of the world have not been able to provide RT as one of the main therapeutic modalities in the course of disease management. Research by Abdel-Wahab et al has shown that only 9 out of 31 (29%) low-income countries and 34 out of 52 (65%) LMICs have RT services.[12]

Addressing the growing burden of cancer as a public health priority remains a challenge, and requires a flexible approach and strategies adapted to local circumstances. This is because cancer is not a single disease but is complex and multifactorial with an extensive impact. All strategic plans and decisions must be prepared and based on the best available evidence and accurate epidemiological data, and addressed in a cancer control program or a national cancer control program (NCCP). The International Atomic Energy Agency (IAEA) states in its publication, "Inequity in Cancer Care: A Global Perspective," that only through a well-designed, managed, and funded NCCP, with universal reach and accessibility, will these efforts impact cancer control.[13] Thus, it can be concluded that an NCCP is an excellent example of a whole-of-government and whole-of-society approach through leadership and cross-sectoral engagement. This is because cancer cannot be prevented or controlled by the health sector alone. In this literature review, we will discuss the role and strategy of RT in the NCCP to enable available resources to be used more rationally, with more optimal medical and social benefits.

Current Status of Cancer Care and Radiation Therapy Services in Indonesia

Indonesia is one of the largest archipelago countries in the world that has a decentralized government system divided into central, provincial and district governments with specific roles and responsibilities.[14] The Indonesian health system is a mix of government/public and private health facilities. The public system is managed in line with the decentralized government system in Indonesia, with the responsibility of the central, provincial and district governments. The Ministry of Health is responsible for managing several vertical/tertiary and specialized hospitals, providing strategic direction, standards, regulations, and ensuring the availability of financial and human resources. The provincial government is responsible for managing the provincial-level hospitals, providing technical supervision and monitoring of district health services, and coordinating cross-district health problems within the province. District/city governments are responsible for managing district/city hospitals, district public health networks from Puskesmas (Primary Health Care [PHC]), and other related health facilities. Several private service providers, including a network of hospitals and clinics, are managed by nonprofit and charitable organizations.[13]

This decentralization also affects how health services in Indonesia are carried out in its referral system. This referral system refers to staging according to medical needs, with Puskesmas acting as the first contact of access

Figure 1. Access to radiation therapy services at the end of 2020. (IROS database 2020)

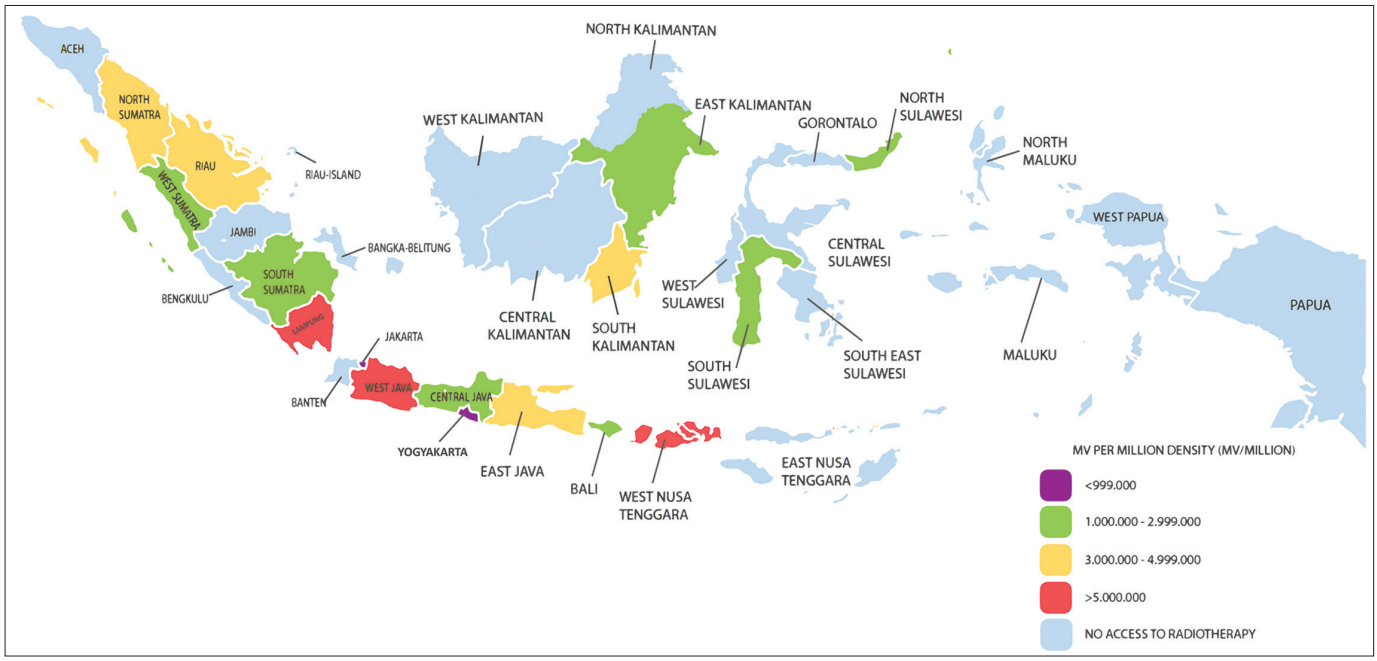


Table 1. Example of Calculating the Need for Radiation Therapy Using Mv/M

COUNTRY/PROVINCE	POPULATION*	NUMBER OF RT NEEDS MV/M#
Indonesia	265,015,300	265
North Borneo	716,400	1
West Java	48,638,700	48
Jakarta Capital Special Region	10,467,600	10

**Population data based on the Central Statistics Agency 2019;[17]*
#Number of Mv/M RT needs: population/1 million.
Key: Mv/M = megavoltage/million, RT = radiation therapy

to public health services. According to the Ministry of Health, there are approximately 9,993 PHCs, 8,841 clinics, and 2,724 hospitals, with most health care systems centralized around Java. The second or third contact of access consists of 15 specialized vertical hospitals with the capability of providing a broad spectrum of cancer care, including Dr. Cipto Mangunkusumo Hospital or Dharmais National Cancer Centers as top referral hospitals for cancer treatment in Indonesia.[15] This referral system in Indonesia was created due to geographical challenges and a widespread population. Distribution in rural areas appears to be the biggest challenge to the referral system, causing negative implications for time, and travel expenses that, in turn, hamper the overall process and adherence to treatment and follow-up care.

Along with its geographical situation (ie, Indonesia being the largest archipelago in the world), lack of supporting infrastructure poses a steep challenge in supporting the availability of RT centers, causing uneven and concentrated availability. In 2000, only 20 RT treatment units and 31 radiation oncologists were available in Indonesia. At the end of 2020, 16 out of 34 provinces had access to RT services, with 47 centers in operation. Currently, there are 82 megavoltage machines including 60 linear accelerators, 21 cobalt systems, and 1 tomotherapy unit. In addition, there are 135 radiation oncologists and 54 residents in training (**Figure 1,** IROS Database, 2020).

Estimating the Need for Radiation Therapy in Indonesia

The total population and population per province in Indonesia were obtained from the Central Bureau of Statistics of Indonesia. Cancer incidences were extracted from the International Agency for Research on Cancer (IARC) GLOBOCAN database. The number of existing machines was primarily obtained from the Indonesian Radiation Oncology Society (IROS) database. Several models based on published literature, as described below, were used to estimate the number of patients in the densest and less dense provinces and the capital of Indonesia, and estimate the demand for megavoltage machines.

Megavoltage/Million

The megavoltage/million (Mv/M) calculation method or 1 unit of radiation therapy/1 million population is the most common and easy-to-use RT availability indicator.[16] This calculation uses a simple method based

Table 2. The Estimated Need for Radiation Therapy

COUNTRY/ PROVINCE	POPULATION*	CANCER INCIDENCE BY GLOBOCAN 2020[20]@	NUMBER OF NEW CANCER PATIENTS/YEAR#	NUMBER OF CANCER PATIENTS REQUIRING RT^	RT REQUIREMENTS§
Indonesia	265,015,300	1.45	384,272	192,136	427
North Borneo	716,400	1.45	1,038	519	1
West Java	48,638, 700	1.45	70,526	35,263	78
Jakarta Capital Special Region	10,467, 600	1.45	15,178	7,589	16

**Population data based on the Central Statistics Agency 2019.[17]*
@Indonesian Cancer Incidence based on GLOBOCAN 2020[20]: 273,523,621/396,914 = 1.45/1,000.
#Number of new cancer patients/year: (Population) × (Indonesian cancer incidence/1,000 population).
^Number of cancer patients requiring RT: RTU 50%.
§RT requirement: (Number of cancer patients requiring RT)/450. Key: RT = radiation therapy

Table 3. Estimated Radiation Therapy Needs Based on Optimal Fractionation

COUNTRY/ PROVINCE	POPULATION*	CANCER INCIDENCE BY GLOBOCAN 2020[20]@	NUMBER OF NEW CANCER PATIENTS/YEAR#	REQUIRED AMOUNT OF FRACTIONATION 9,768/1,000^	NUMBER OF RT EQUIPMENT (8 WORKING HOURS/DAY)¢	NUMBER OF RT EQUIPMENT (10 WORKING HOURS/DAY)¥
Indonesia	265,015,300	1.45	384,272	3,753,569	361	289
North Borneo	716,400	1.45	1,038	10,139	1	1
West Java	48,638,700	1.45	70,526	688,898	66	53
Jakarta Capital Special Region	10,467,600	1.45	15,178	148,259	14	11

**Population data based on the Central Statistics Agency 2019.[17]*
@Indonesian Cancer Incidence based on GLOBOCAN 2020[20]: 273,523,621/396,914 = 1.45/1,000.
#Number of new cancer patients/year: (population) × (Indonesian cancer incidence/1,000 population).
^Number of required fractionation: (number of new cancer patients/year) × 9,768/1,000[21].
¢Number of fractions per year/1 linac (8 hours/day): (1 linac) × (5 fractions/hour) × (8 hours/day) × (5 days/week) × (52 weeks) = 10,400.
¥Number of fractions per year/1 linac (8 hours/day): (1 linac) × (5 fractions/hour) × (8 hours/day) × (5 days/week) × (52 weeks) = 13,000.
Number of RT equipment (8 working hours/day): (amount of fractionation needed) / 10,400.
Number of RT equipment (10 working hours/day): (amount of fractionation needed) / 13,000.
Key: RT = radiation therapy

on the latest population data without considering incidence of cancer or radiation therapy utilization units (RTUs) (**Table 1**). Provinces/local governments can use this method as the initial stage of planning the construction of RT facilities in their area. However, it is also necessary to consider access and geographical distribution as the next significant factors to assess.

ESTRO-QUARTS Method

The European Society of Radiotherapy and Oncology (ESTRO) developed a guideline for calculating RT needs through the Quantification of Radiation Therapy Infrastructure and Staffing needs (QUARTS).[18,19] The project compiled guidelines for infrastructure and staffing throughout Europe and formulated it into a general guideline. The result is a standard that suggests having 1 linear accelerator (linac) for 450 cancer patients, 1 radiation oncologist per 200 to 250 patients, and 1 medical physicist per 450 to 500 patients (population as follows in **Table 2**).

Use of Fractionation Needs Calculation

Another method for estimating RT need is to use the optimal number of fractions. Wong et al developed a model combining the calculation of the radiation therapy utilization rate (RUR) and the need for retreatment. RUR is defined as the proportion of a given population of cancer patients who received at least 1 course of RT during their lifetime.[21] From these results, it was found that 9,768 RT fractions were required for every 1,000 cancer patients. Estimating the optimal number of fractions has been recognized as valuable in planning RT services. The Global Taskforce on Radiotherapy for Cancer Control, founded by the Union for International Cancer, estimates that 119 million fractions were needed for all cancer patients worldwide in 2012.

From this amount, the need can be extrapolated to describe a population. In this scheme, the number of needs is greatly influenced by the addition of working hours. The higher the number of working hours per day, the higher the fractionation capacity of an RT device. **Table 3** estimates the need

Table 4. Estimated RT Needs Based on Zubizarreta et al Calculations

		INDONESIA	NORTH BORNEO	WEST JAVA	JAKARTA CAPITAL SPECIAL REGION
Population*	A	265,015,300	716,400	48,638,700	10,467,600
Number of new cancer patients/year#	B	384,272	1,038	70,526	15,178
Number of cases requiring RT/year%	C = B × (49.49%) × 1.25	237,720	642	43,629	9,389
Number of fractions/year	D = C × 16. 29	3,872,463	10,460	710,719	152,955
Number of fractions/1 linac	E	9,600 fractions/year with 10 hours/day[17] [applies to all columns]			
Total RT needed	F = D/E	403	1	74	16

**Population data based on the Central Statistics Agency 2019.[17]*
#Number of new cancer patients/year: (population)
**(Indonesian cancer incidence/1,000 population). Indonesian cancer incidence based on GLOBOCAN 2020[20]: 273,523,621/396,914 = 1.45/1,000.*
%RTUs (49.49%), mean fraction (16.29), and 25% retreatment rate in the Asia Pacific based on Zubizarreta et al.[16]
Key: RT = radiation therapy, RTUs = radiation therapy utilization units

Table 5. Estimated RT Needs Based on IROS Calculations (Standard Fractionation Scheme)

		INDONESIA	NORTH BORNEO	WEST JAVA	JAKARTA CAPITAL SPECIAL REGION
Population*	A	265,015,300	716,400	48,638,700	10,467,600
Number of new cancer patients/year#	B	384,272	1,038	70,526	15,178
Number of cases requiring RT/year%	C = B × (50%)	192,136	519	35,263	7,589
Number of fractions/year	D = C × (25.6)	4,918,682	13,286	902,733	194,278
Number of fractions/1 linac	E	13,000 (50 fractions/day × 5 days/week × 52 weeks) [applies to all columns]			
Total RT needed	F = D/E	378	1	69	15

*Population data based on the Central Statistics Agency 2019.[17]
#number of new cancer patients/year: (population)
*(Indonesian cancer incidence/1,000 population).
Indonesian cancer incidence by GLOBOCAN 2020[21]: 273,523,621/396,914 = 1.45/1,000. %RTU (50%), mean fraction (25.6)
Key: RT = radiation therapy, RTUs = radiation therapy utilization units

Table 6. Estimated RT Needs Based on IROS Hypofractionation Scheme

		INDONESIA	NORTH BORNEO	WEST JAVA	JAKARTA CAPITAL SPECIAL REGION
Population*	A	265,015,300	716,400	48,638,700	10,467,600
Number of new cancer patients/year#	B	384,272	1,038	70,526	15,178
Number of cases requiring RT/year%	C = B × (50%)	192,136	519	35,263	7,589
Number of fractions/year	D = C × (20)	3,842,720	10,380	705,260	151,780
Number of fractions/1 linac	E	13,000 (50 fractions/day × 5 days/week × 52 weeks) [applies to all columns]			
Total RT needed	F = D/E	296	1	54	12

**Population data based on the 2019 Central Statistics Agency.[17]*
#number of new cancer patients/year: (population) × (Indonesian cancer incidence/1,000 population).
Indonesian Cancer Incidence by GLOBOCAN 2020[20]: 273,523,621/396,914 = 1.45/1,000.
%RTU (50%), mean fraction (20).
Key: RT = radiation therapy, IROS = Indonesian Radiation Oncology Society

Table 7. Comparison of RT Needs Based on Estimated Calculations

	INDONESIA	NORTH BORNEO	WEST JAVA	JAKARTA CAPITAL SPECIAL REGION
Population*	265,015,300	716,400	48,638,700	10,467,600
Number of new cancer patients/year#	384,272	1,038	70,526	15,178
Mv/M Method[16]	265	1	48	10
ESTRO-QUARTS Method[18,19]	427	1	78	16
RT Optimal Fraction Method[21]	289	1	53	11
Zubizarreta et al Method[16]	403	1	74	16
IROS Method (standard fractionation)	378	1	69	15
IROS Method (hypofractionation)	296	1	54	12

**Population data based on the Central Statistics Agency 2019.[17]*
#Number of new cancer patients/year: (Population) × (Indonesian cancer incidence/1,000 population);
Indonesian cancer incidence by GLOBOCAN 2020[20]: 273,523,621/396,914 = 1.45/1,000.
Key: RT = radiation therapy; Mv/M = megavoltage/million,
ESTRO-QUARTS = European Society of Radiotherapy and Oncology - Quantification of Radiation Therapy Infrastructure and Staffing

for RT in several sample populations throughout Indonesia.

Use of Mean Fraction

Another method is to calculate the mean fraction of RT in an area. Zubizarreta et al in their publication, "Need for Radiotherapy in Low- and Middle-Income Countries: The Silent Crisis Continues," compiled a model that combines different RTUs, retreatment rates, and mean fractions on each continent. For example, there are differences in RTUs on each continent, namely Europe and Central Asia (50.05%), Africa (54.3%), Asia Pacific (49.49%), Latin America (53.27%), and for all LMICs (50.53%). There are also differences in the mean fraction on each continent, particularly Europe and Central Asia (15.95), Africa (16.44), Asia Pacific (16.29), Latin America (16.56), and for all LMICs (16.31).[16] This method can help determine the needs of RT in the population (**Table 4**).

Calculation Model of the Indonesian Radiation Oncology Society

The Indonesian Radiation Oncology Society (IROS) also analyzed RT needs using specific characteristics of Indonesia. This model explicitly utilized the reference from Zubizarreta et al,[12] using the mean fraction based on the internal IROS survey,[6,26] the mean fraction with the hypofractionated scheme (HRT), and RTU (50%) without considering the retreatment rate. **Tables 5 and 6** are a model and calculation of RT needs based on the scheme.

Table 7 is a summary of the need for RT in Indonesia from the various methods described above.

Hypofractionated RT as a Solution to Improve RT Access

Technology has an important role in the continuous development of RT. The long road to modern, high-tech radiation oncology has become a reality with technological discoveries and innovations resulting from the interaction of various disciplines (biology, physics, mathematics, computer science, and engineering).[22] Innovations in these fields enable faster, more customized radiation treatment, increasing the effectiveness, safety, and accessibility of RT.

From an economic point of view, Aneja et al provide an overview of the estimated cost of RT driven mostly by the total treatment time, calculated as daily treatment time multiplied by the number of fractions. As this suggests, hypofractionation can reduce the burden of increasing health care costs in the field of RT.[23,24] In a study of breast cancer treatment at the Leuven Radiotherapy Department in Belgium, there was a 60% reduction in the total cost of treatment with hypofractionated radiation therapy (HRT) compared with scheduled conventional fractionated (CF) therapy in the Belgian health treatment system. The decrease is a direct consequence of the decline in daily radiation costs. An Australian study reported a 24% to 32% reduction in medical costs in the Australian health care system for breast cancer patients on an HRT schedule and an increase in capacity of an additional 14 patients each month.[23,25,26] The same study was also conducted in Africa by Irabor et al, which reported a 40% reduction in the cost of providing whole-breast RT per patient for those receiving HRT compared with conventional fractions, and an increase in RT capacity of 25.4%.[24]

According to the IROS estimation methods, RT coverage in Indonesia (available RT machines / RT required) improves when using HRT (27.7%) vs conventional RT (21.7%). Among

benefits, HRT utilization increases RT capacity and savings with regard to National Health Insurance. Reduced waiting lists and the resultant increase in capacity for access to RT are other notable advantages of HRT. In addition, HRT increases patient convenience by requiring fewer trips to the radiation therapy center. Thus, there is potential for reduced patient costs, including travel/parking costs and lost income/productivity associated with longer treatment schedules. Further savings on the care provision can be attributed to the reduced need for patient accommodations, nurse/doctor consultations, and transport schemes.[26] However, implementing HRT in daily practice requires support from all stages of RT services and a large investment, from RT equipment to human resources. This requires consistent and careful planning and transition.

Radiation Therapy and the National Cancer Control Plan

The National Cancer Control Program or National Cancer Control Plan (NCCP) refers to the broad implementation of programs and evidence-based strategies to actively address the national cancer burden. Methods based on the cancer continuum include health promotion, prevention, early detection (including early diagnosis and screening), management, rehabilitation, palliation and research support. Each stage of the cancer continuum also requires specific interventions and special support. Another component is use of a cancer registry as a basis for identifying cancer burdens and providing support for setting priorities for comprehensive cancer control policies and being the key to effective cancer program implementation and monitoring.[27]

Optimal estimates of RT need within the NCCP necessitate monitoring of both the national cancer burden (sites and staging) and determination of RUR. The shortfall in RT refers to the difference between currently available RT and what would be needed within the country to optimally deliver necessary RT services to cancer patients.[3]

As stated, access to RT for LMICs is a global concern. The 66th General Assembly of the United Nations (UN) has described cancer as an "increasing epidemic" of noncommunicable diseases and has determined that there is a shortage of RT service facilities, especially in developing countries.[28] Samiei et al in their publication, "Challenges of Making Radiotherapy Accessible in Developing Countries," stated that the reality in LMICs is very worrying. LMICs, despite being home to 85% of the world's population, have only about 4,400 megavoltage machines, fewer than 35% of the world's RT facilities, leaving most cancer patients in LMICs without access to potentially life-saving RT treatments.[29] The implication: RT access is a must. Zubizarreta et al said that it is impossible to establish a cancer control program in a country if RT facilities are not available.[16] In addition, in planning an NCCP, the accessibility of RT services in that country must be carefully considered. Atun et al also noted that RT is an important health care investment and should be embedded as a key part of an NCCP or broader national health strategy.[3]

In addition to RT, other services in the cancer care continuum must be considered, such as screening, early detection, surgery, and chemotherapy – the type and amount of which must be provided according to community needs. Having adequate and equitable services in a community is crucial to preventing waiting lists for cancer management. Waiting lists cause delays that can significantly impact tumor control probability (TCP) and ultimately survival. Wyatt et al predicted that delaying cancer treatment resulted in a decrease in TCP of 0.2 to 0.3% per week for small tumors (T1), and 0.5 to 0.7% delay per week for larger tumors. In a multidisciplinary treatment approach, the impact of delaying postoperative radiation initiation will reduce TCP by up to 1.5% per week in head and neck cancer patients.[30] Deviations during the cancer continuum such as delays in access to diagnosis and treatment, substandard cancer drugs, unavailability, and poor quality of RT can cause unnecessary suffering, death, and wasted resources.

National professional societies are key advocates and have specific roles in expanding RT access and implementing an NCCP. A society should have a roadmap and vision for increasing RT accessibility and affordability in its country. For example, to close the gap of RT services in Indonesia, IROS, as the only radiation oncology society in Indonesia, developed a roadmap in 2010 to incorporate into the NCCP and provide guidance for key stakeholders. IROS also established a reimbursement tariff for national health insurance to foster an investment in RT services. For now, IROS consistently advocates a framework of investment in RT (public-private partnership) and the need for RT to health facilities in Indonesia.[31]

The ability to estimate the demand for access to cancer services and understand the type and number of cancers in the community is crucial. However, problems related to RT are not only limited to availability of RT facilities; analysis of RT needs often focuses solely on equipment. A new RT department requires a significant investment in qualified human resources to run the RT department, and lack of resources remains a pressing challenge in LMICs. Forming and training RT teams takes years and is an expensive investment. As such, the construction of RT facilities, long-term planning, and careful analysis are critically important.[16]

Conclusion

Given the burden and challenges of cancer problems over time, a comprehensive and systematic effort and response are needed from various sectors; they are not the sole responsibility of the health system. Effective cancer control planning requires strategies appropriate to the needs and circumstances of a country's situation. Cancer control plans and interventions also must be integrated in a multisectoral, multidisciplinary manner and adapt to the capacity of available health services.

Optimal treatment can significantly improve cancer survival and quality of life. As such, access to RT is a global priority and a must. Availability of RT centers and technology is highly important. Additionally, the use of HRT and longer working hours can help overcome the shortage of RT facilities and increase access to RT in developing countries with a limited number of such centers.

References

1) Institute for Health Metrics and Evaluation. Global Burden of Disease. 2020. Accessed April 23, 2021. https://vizhub.healthdata.org/gbd-compare/

2) World Health Organization. WHO Report on Cancer. 2020.

3) Atun R, Jaffray DA, Barton MB, et al. Expanding global access to radiotherapy. *Lancet Oncol.* 2015;16(10):1153-1186.

4) Barton MB, Frommer M, Shafiq J. Role of radiotherapy in cancer control in low-income and middle-income countries. *Lancet Oncol.* 2006;7(7):584-595.

5) Prager GW, Braga S, Bystricky B, et al. Global cancer control: responding to the growing burden, rising costs and inequalities in access. *ESMO Open.* 2018;3(2).

6) Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: a Cancer Journal for Clinicians.* 2018;68(6):394-424.

7) Balitbang Kemenkes RI. Hasil Utama Riset Kesehatan Dasar Tahun 2018. Kementrian Kesehatan Republik Indonesia. Jakarta; 2019. Accessed March 9, 2021. http://labdata.litbang.kemkes.go.id/images/download/laporan/RKD/2018/Laporan_Nasional_RKD2018_FINAL.pdf

8) Agustina J, Sinulingga DT, Suzanna E, Tehuteru E, Ramadhan R, Kadir A. Epidemiology of childhood cancer in Indonesia: study of 14 population based cancer registries. *J Glob Oncol*. 2018;(4_suppl_2):67s-67s.

9) BPJS Kesehatan. Accessed March 8, 2022. https://bpjs-kesehatan.go.id/bpjs/post/read/2021/2061/BPJS-Kesehatan-Dorong-Faskes-Optimalkan-Pelayanan-untuk-Pasien-Kanker

10) Barton MB, Jacob S, Shafiq J, et al. Estimating the demand for radiotherapy from the evidence: a review of changes from 2003 to 2012. *Radiother Oncol.* 2014;112(1):140-144.

11) Valentini V, Boldrini L, Mariani S, Massaccesi M. Role of radiation oncology in modern multidisciplinary cancer treatment. *Molec Oncol*. 2020;14(7):1431-1441.

12) Abdel-Wahab M, Fidarova E, Polo A. Global access to radiotherapy in low- and middle-income countries. *Clin Oncol.* 2017;29(2):99-104.

13) International Atomic Energy Agency. Inequity in Cancer Care: A Global Perspective. IAEA, editor. Vienna: IAEA; 2011.

14) Mahendradhata Y, Trisnantoro L, Listyadewi S, et al. The Republic of Indonesia health system review Asia Pacific observatory on health systems and policies. Vol. 7, Health Systems in Transition. World Health Organization; 2017. p.328.

15) Ministry of Health Indonesia. Profil Kesehatan Indonesia 2018 [Indonesia Health Profile 2018]. 2019;207-207.

16) Zubizarreta EH, Fidarova E, Healy B, Rosenblatt E. Need for radiotherapy in low and middle income countries - the silent crisis continues. *Clin Oncol.* 2015;27(2):107-114.

17) Badan Pusat Statistik. Statistik Indonesia 2019. Jakarta: Badan Pusat Statistik; 2019.

18) Bentzen SM, Heeren G, Cottier B, et al. Towards evidence-based guidelines for radiotherapy infrastructure and staffing needs in Europe: the ESTRO QUARTS project. *Radiother Oncol.* 2005;75(3):355-365.

19) Slotman BJ, Cottier B, Bentzen SM, Heeren G, Lievens Y, van den Bogaert W. Overview of national guidelines for infrastructure and staffing of radiotherapy. ESTRO-QUARTS: work package 1. *Radiother Oncol.* 2005;75(3):349.E1-349.E6.

20) Ferlay J, Ervik M, Lam F, et al. Global Cancer Observatory: Cancer Today. International Agency for Research on Cancer. Lyon, France; 2020.

21) Wong K, Delaney GP, Barton MB. Evidence-based optimal number of radiotherapy fractions for cancer: a useful tool to estimate radiotherapy demand. *Radiother Oncol.* 2016;119(1):145-149.

22) Fiorino C, Guckemberger M, Schwarz M, van der Heide UA, Heijmen B. Technology-driven research for radiotherapy innovation. *Molec Oncol.* 2020;14(7):1500-1513.

23) Aneja S, Pratiwadi RR, Yu JB. Hypofractionated radiation therapy for prostate cancer: risks and potential benefits in a fiscally conservative health care system. *Oncology.* 2012;26(6):512-518.

24) Irabor OC, Swanson W, Shaukat F, et al. Can the adoption of hypofractionation guidelines expand global radiotherapy access? An analysis for breast and prostate radiotherapy. *JCO Global Oncol.* 2020;(6):667-678.

25) Dwyer P, Hickey B, Burmeister E, Burmeister B. Hypofractionated whole-breast radiotherapy: impact on departmental waiting times and cost. *J Med Imag Radiat Oncol.* 2010 9;54(3):229-234.

26) Hunter D, Mauldon E, Anderson N. Cost-containment in hypofractionated radiation therapy: a literature review. *J Med Radiat Sci.* 2018;65(2):148-157.

27) World Health Organization. National cancer control programmes: policies and managerial guidelines. 2nd ed. World Health Organization. Geneva: World Health Organization; 2002.

28) Datta NR, Samiei M, Bodis S. Radiation therapy infrastructure and human resources in low- and middle-income countries: Present status and projections for 2020. *Int J Radiat Oncol Biol Phys.* 2014;89(3):448-457.

29) Samiei M. Challenges of Making Radiotherapy Accessible in Developing Countries Cancer Control. 2013. p. 85-94. Accessed December 19, 2021. http://cancercontrol.info/wp-content/uploads/2014/08/cc2013_83-96-Samiei-varian-tpage-incld-T-page_2012.pdf

30) Wyatt RM, Jones BJ, Dale RG. Radiotherapy treatment delays and their influence on tumour control achieved by various fractionation schedules. *Brit J Radiol.* 2008;81(967):549-563.

31) Indonesian Radiation Oncology Society. About Perhimpunan Onkologi Radiasi Indonesia. Accessed March 2, 2021. http://www.pori.or.id/about/

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Whole Abdominal Radiation Therapy for Chemo-Refractory Adult Granulosa Cell Tumor of the Ovary: A Case Report

Sheen Cherian, MD;[1] Sudha Amarnath, MD;[1] Anthony Mastroianni, MD;[1] Mariam AlHilli, MD[2]

Abstract

Granulosa cell tumors (GCTs) emerging from sex-cord stromal cells of the ovary represent less than 5% of all ovarian cancers. This report discusses a case of primary chemotherapy refractory adult GCT of the ovary with widespread abdomino-pelvic metastasis. Because GCTs are radiosensitive, whole abdominal radiation therapy (WART) is a useful treatment when surgical and systemic options have been exhausted. WART delivered with modern radiation techniques results in excellent clinical and radiological response rates with acceptable toxicity and the possibility of long-term disease control.

Keywords: Granulosa cell tumors, whole abdominal radiation therapy, ovarian cancer, volumetric-modulated arc therapy

Case Summary

A 43-year-old White woman was referred for consideration of whole abdominal radiation therapy (WART) in July 2019. Her history dates to May 2018 when the patient developed intermenstrual bleeding and intermittent abdominal pain. Initial imaging revealed a left ovarian cyst. She underwent a left salpingo-oophorectomy (LSO) with uterine dilation and curettage (D&C). At the time of surgery, left ovarian cyst rupture was noted. Pathology was consistent with adult type granulosa cell tumor (GCT). On immunohistochemical stains, the tumor cells were SF-1 positive, calretinin positive, and negative for epithelial membrane antigen (EMA) and synaptophysin, confirming the diagnosis. The patient then underwent a total laparoscopic hysterectomy, right salpingo-oophorectomy, bilateral pelvic and para-aortic lymphadenectomy, omentectomy, peritoneal biopsies, and cystoscopy in June 2018. Her final surgical staging was FIGO stage IIA. She then underwent 6 cycles of adjuvant carboplatin and paclitaxel chemotherapy, and her inhibin A and B levels were normal at completion of adjuvant therapy in November 2018.

In April 2019, rising inhibin levels prompted a computed tomography (CT) scan that revealed 1 pelvic, 2 hepatic surface and 2 peritoneal lesions. The hepatic lesion was biopsied and a relapse was confirmed. The multidisciplinary tumor board recommended systemic therapy with letrozole and bevacizumab for 3 months and then proceeding with maximal cytoreductive surgery (MCS). In October 2019, the patient underwent MCS. Her postoperative period was uneventful, with minimal residual disease (< 1 cm^3) and normal inhibin A and B levels. Letrozole and bevacizumab were re-initiated 8 weeks later. Unfortunately, small-volume disease progression was identified within 6 months of surgery and eventually the patient was switched

Affiliations: [1]Department of Radiation Oncology, Taussig Cancer Institute, Cleveland Clinic, Cleveland, Ohio; [2]Subspeciality Care for Women's Health, Cleveland Clinic, Cleveland, Ohio. **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

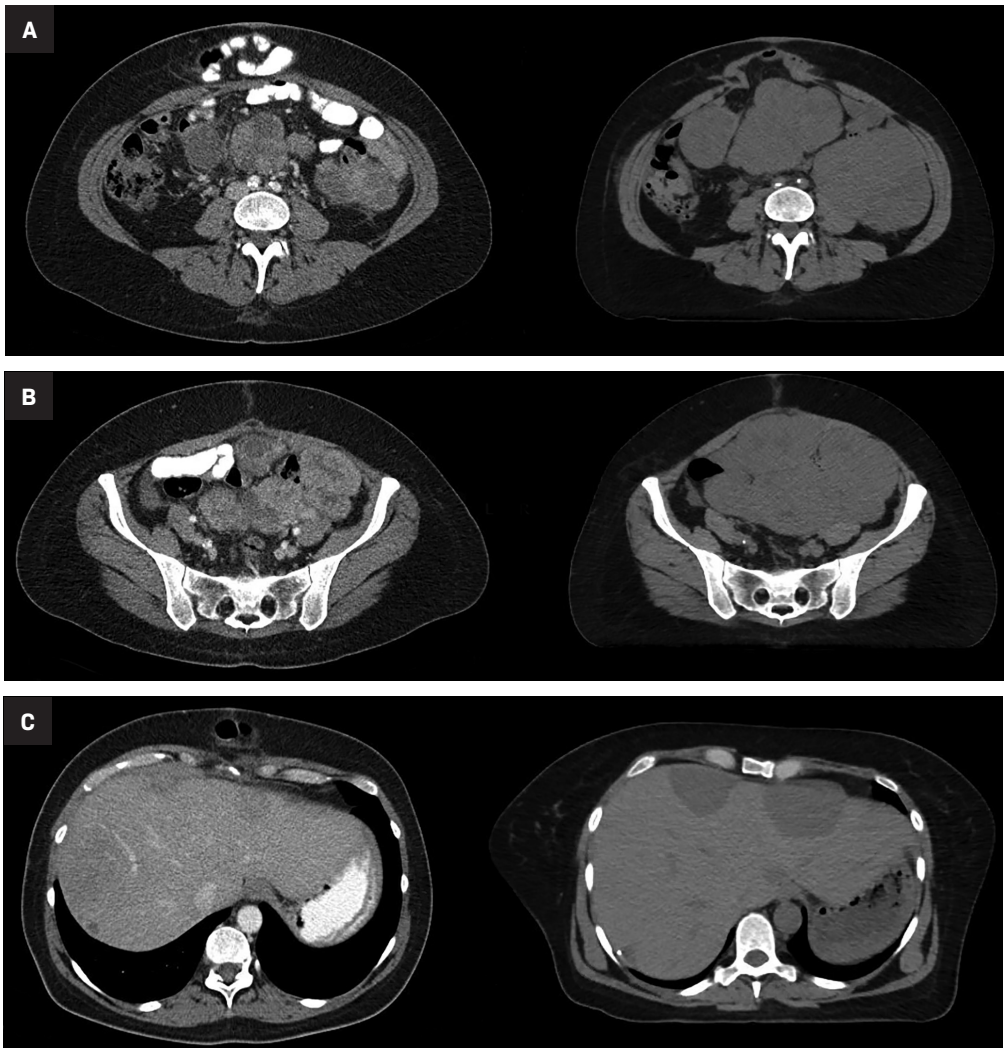

Figure 1. Post and pre whole abdominal radiation therapy for A) abdominal disease, B) pelvic disease, and C) hepatic disease.

to liposomal doxorubicin, followed by tamoxifen/megestrol, then paclitaxel, and finally etoposide/cisplatin. All of the aforementioned systemic agents were stopped prematurely due to disease progression while on therapy.

Although the patient was initially referred to us for radiation therapy in July 2019, it was our collective decision to exhaust all systemic options before embarking on whole abdominal radiation therapy (WART). In November 2021, the patient started WART utilizing multi-isocentric, image-guided, volumetric-modulated arc therapy (VMAT). At the time, her disease burden involved multiple hepatic surface and parenchymal metastasis, and multiple large soft-tissue masses throughout the abdomen and pelvis (average size of 8 cm and the largest measuring 11 cm). She received a total dose of 30 Gy in 20 fractions, over 4 weeks. The organs-at-risk dose constraints were as follows: kidney mean dose < 18 Gy and small bowel max point dose < 110%. The patient tolerated treatment well with acute RTOG grade-1 gastrointestinal side effects.[1] At last follow-up, 6 weeks post WART, she had no residual acute side effects and had a Karnofsky Performance Status (KPS) of 90. CT scan confirmed good partial response (all lesions including index lesion ≥ 50% decrease) by RECIST criteria (Figures 1 A-C).[2] Since her first relapse, she has been on 5 systemic agents and her disease was primary refractory to all agents. WART has been the only therapy modality able to induce a response.

Imaging Findings

A CT scan prior to WART showed multiple large hepatic, abdominal and pelvic masses, which had significantly reduced in size 6 weeks after radiation therapy (**Figures 1 A-C**). WART was planned using VMAT techniques to spare the renal parenchyma (**Figure 2**).

Diagnosis

Primary chemotherapy refractory adult GCT of the ovary with widespread abdomino-pelvic metastasis.

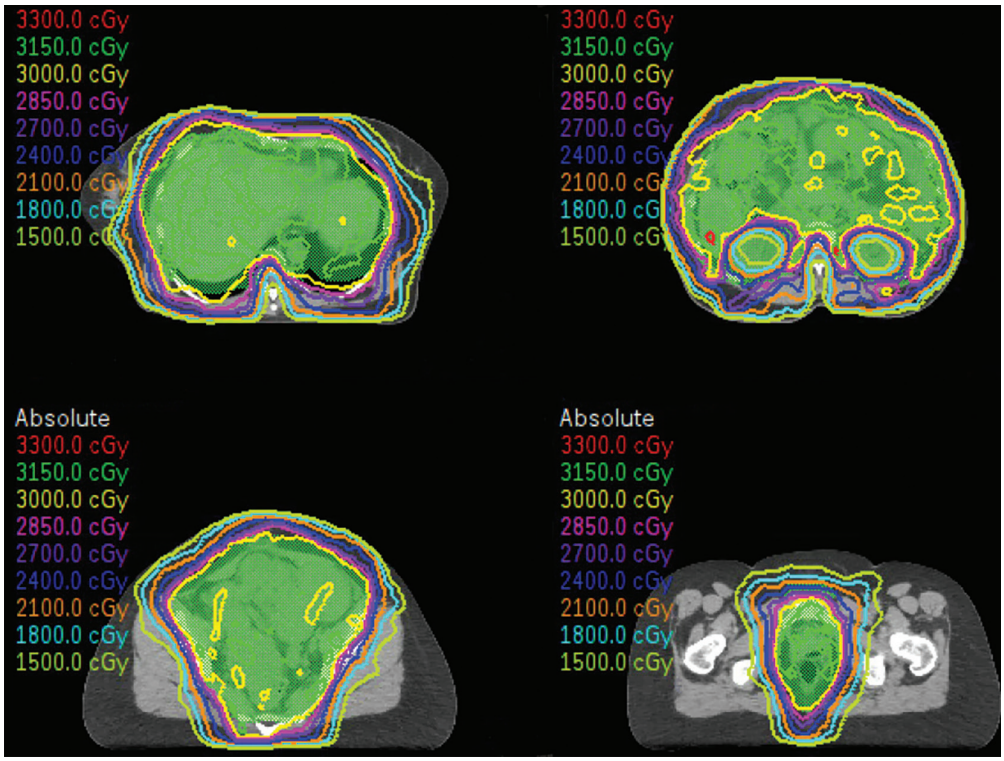

Figure 2. Kidney-sparing volumetric-modulated arc therapy plan for whole abdominal radiation therapy.

Discussion

GCTs arising from sex-cord stromal cells of the ovary are rare and represent under 5% of all ovarian cancers.[3] They occur most commonly in women in the reproductive age group. They are characterized by a long natural history and have a tendency to relapse late.[3] Based on clinical presentation and histological characteristics, GCTs are classified into juvenile and adult GCTs. The majority are adult GCTs and 5% are juvenile.[4] Nearly all GCTs are secretory, producing estradiol, leading to precocious puberty in juvenile patients, and menstrual irregularities and virilization in adults.[5] GCTs are also known to increase the risk of endometrial and breast cancers due to a hyperestrogenic state.[6,7] Under microscopy, the adult GCTs appear round to oblong with scant cytoplasm and classic "coffee-bean" grooved nuclei. The cells arrange themselves in rosettes around a central cavity and this pattern is called "Call-Exner bodies," which is pathognomonic for GCTs. Somatic mutations in FOXL2 are identified in 97% of cases.[8] On immunohistochemistry, they are commonly positive for inhibin, calretinin, CD56 and CD99.[9]

Surgery remains the mainstay for early stage GCTs and late-stage tumors if maximal debulking is feasible.[10,11] Stage I disease has an excellent prognosis and no adjuvant therapy is recommended.[3] Residual disease after surgery is associated with poor prognosis and chemotherapy has not been found to increase disease-free interval.[3,12] Multiple retrospective studies have shown a survival benefit with radiation therapy when used in the adjuvant setting as well as for recurrent disease.[3,13,14] A retrospective study from MD Anderson identified 10 patients treated with WART to a total dose of 27 to 28 Gy, 4 of whom had a complete clinical response to WART. The patients lived for 5, 10, 13 and 21 years.[13]

With the advent of modern radiation techniques like VMAT, safe and precise delivery of WART is possible. Acceptable acute and late toxicity has been reported at doses of 30 Gy when WART was used for gynecological cancers.[15,16] We plan to monitor our patient with periodic CT scans. A sequential boost was decided against due to the presence of complicating ventral hernias from abdominal tumor burden.

Conclusion

GCTs should be aggressively considered for surgery as it remains the standard of care. When appropriate, adjuvant chemotherapy should be considered, especially for large tumors or if a tumor ruptures at surgery. For advanced disease, maximal debulking surgery should be contemplated, followed by systemic agents. WART delivered with modern radiation techniques results in excellent clinical and radiological response rates with acceptable toxicity and the possibility of long-term disease control. In the future, pro-

spective studies to further investigate the timing of WART, adjuvant vs late, may help guide therapeutic options for patients with advanced GCTs.

References

1) Cox JD, Stetz J, Pajak TF. Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). *Int J Radiat Oncol Biol Phys.* 1995;31(5):1341-1346.

2) Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer.* 2009;45(2):228-247.

3) Pectasides D, Pectasides E, Psyrri A. Granulosa cell tumor of the ovary. *Cancer Treat Rev.* 2008;34(1):1-12.

4) Young RH. Sex cord-stromal tumors of the ovary and testis: their similarities and differences with consideration of selected problems. *Mod Pathol.* 2005;18 Suppl2:S81-98.

5) Vassal G, Flamant F, Caillaud JM, Demeocq F, Nihoul-Fekete C, Lemerle J. Juvenile granulosa cell tumor of the ovary in children: a clinical study of 15 cases. *J Clin Oncol.* 1988;6(6):990-995.

6) Hammer A, Lauszus FF, Petersen AC. Ovarian granulosa cell tumor and increased risk of breast cancer. *Acta Obstet Gynecol Scand.* 2013;92(12):1422-1425.

7) Nasioudis D, Wilson E, Mastroyannis SA, et al. Increased risk of breast and uterine cancer among women with ovarian granulosa cell tumors. *Anticancer Res.* 2019;39(9):4971-4975.

8) Shah SP, Kobel M, Senz J, et al. Mutation of FOXL2 in granulosa-cell tumors of the ovary. *N Engl J Med.* 2009;360(26):2719-2729.

9) Nofech-Mozes S, Ismiil N, Dube V, et al. Immunohistochemical characterization of primary and recurrent adult granulosa cell tumors. *Int J Gynecol Pathol.* 2012;31(1):80-90.

10) Belz J, Wakker R, Hoepffner J, Caselitz J. Metastasis surgery in granulosa cell tumor--determining indications and tumor after care. *Langenbecks Arch Chir.* 1992;377(1):25-27.

11) Lauszus FF, Petersen AC, Neumann G, et al. Less extensive surgery compared to extensive surgery: survival seems similar in young women with adult ovarian granulosa cell tumor. *Eur J Obstet Gynecol Reprod Biol.* 2014;177:61-66.

12) Meisel JL, Hyman DM, Jotwani A, et al. The role of systemic chemotherapy in the management of granulosa cell tumors. *Gynecol Oncol.* 2015;136(3):505-511.

13) Wolf JK, Mullen J, Eifel PJ, Burke TW, Levenback C, Gershenson DM. Radiation treatment of advanced or recurrent granulosa cell tumor of the ovary. *Gynecol Oncol.* 1999;73(1):35-41.

14) Hauspy J, Beiner ME, Harley I, et al. Role of adjuvant radiotherapy in granulosa cell tumors of the ovary. *Int J Radiat Oncol Biol Phys.* 2011;79(3):770-774.

15) Randall ME, Filiaci VL, Muss H, et al. Randomized phase III trial of whole-abdominal irradiation versus doxorubicin and cisplatin chemotherapy in advanced endometrial carcinoma: a Gynecologic Oncology Group Study. *J Clin Oncol.* 2006;24(1):36-44.

16) Arians N, Kieser M, Benner L, et al. Adjuvant intensity modulated whole-abdominal radiation therapy for high-risk patients with ovarian cancer FIGO stage III: final results of a prospective phase 2 study. *Radiat Oncol.* 2019;14(1):179.

Dr. Gergelis is a PGY5 resident, Department of Radiation Oncology, Mayo Clinic,Rochester, MN.

Dr. Laughlin is a PGY3 resident, Department of Radiation Oncology, Mayo Clinic, Phoenix, AZ.

Improving Well-Being and Combating Burnout in Radiation Oncology Training

Kimberly Gergelis, MD; Brady Laughlin, MD

Crises in public health and social unrest have heightened the need to support trainee well-being. External factors coupled with oncology-specific factors, such as regularly facing mortality, balancing palliation with toxicity, the rapid pace of treatment advances, and engaging in emotionally charged conversations with patients, can lead to burnout.[1] Burnout is characterized by emotional exhaustion, depersonalization, and a sense of reduced personal accomplishment; it affects physicians and physicians-in-training at greater rates than the general population.[2] Emotional exhaustion, depersonalization, and burnout affected 28%, 17%, and 33% of radiation oncology residents, respectively, in the United States in 2016.[3] Consequences may include inadequate patient care, professional ineffectiveness, and physician harm, including substance abuse, clinical depression, and suicidality.[4]

Building community is important for increasing professional fulfillment, while decreasing burnout. A recent study described the implementation of a well-being curriculum for residents within a radiation oncology department, which allowed residents to openly discuss topics that cause distress in a supportive environment.[5] This intervention led to a decrease in burnout among residents.

Strong relationships among colleagues are essential to identify residents at risk for burnout or depression. Mayo Clinic has proposed 5 steps to recognize and support learners in distress:[6]

1) Be on the lookout: Burnout and depressive symptoms are prevalent among medical students and residents. Keep your eyes open for signs of mental distress in colleagues.
2) Recognize the signs: Watch for changes in hygiene and behavior, including mood swings, sadness, irritability, and social isolation.
3) Trust your gut: Follow your intuition when concerned about someone. If you think something may be troubling them, do not hesitate to ask.
4) Ask questions: Assume you are the only one who will reach out. Be direct with colleagues when red flag behaviors are present. Asking them about their emotional health is the most helpful thing you can do.
5) React to the answer: Provide support to your colleague. Do not minimize their problems or feelings. Take on the role of encourager, not a clinical role of assessment, diagnosis, and referral.

With the changing state of radiation oncology and the challenges of the COVID-19 pandemic, residents are now more vulnerable than ever to burnout and stress. Establishing well-being programming and identifying learners in need are crucial steps to improve overall professional fulfillment and education.

References

1) Shanafelt T, Dyrbye L. Oncologist burnout: causes, consequences, and responses. *J Clin Oncol.* 2012;30(11):1235-1241. doi:10.1200/JCO.2011.39.7380

2) Shanafelt TD, Boone S, Tan L, et al. Burnout and satisfaction with work-life balance among US physicians relative to the general US population. *Arch Intern Med.* 2012;172(18):1377-13785. doi:10.1001/archinternmed.2012.3199

3) Ramey SJ, Ahmed AA, Takita C, Wilson LD, Thomas CR, Jr., Yechieli R. Burnout evaluation of radiation residents nationwide: results of a survey of United States residents. *Int J Radiat Oncol Biol Phys.* 2017;99(3):530-538. doi:10.1016/j.ijrobp.2017.06.014

4) West CP, Dyrbye LN, Erwin PJ, Shanafelt TD. Interventions to prevent and reduce physician burnout: a systematic review and meta-analysis. *Lancet.* 2016;388(10057):2272-2281. doi:10.1016/S0140-6736(16)31279-X

5) Gergelis KR, Anand US, Rian JS, et al. Integrating a grassroots well-being curriculum into a radiation oncology residency program. *Adv Radiat Oncol.* 2022;7(1):100837. doi:10.1016/j.adro.2021.100837

6) Wolanskyj-Spinner A, Rackley S. Take 5 takeaways: how to support a learner in distress. Identifying and acting on signs of struggle. Mayo Clinic. 2019.

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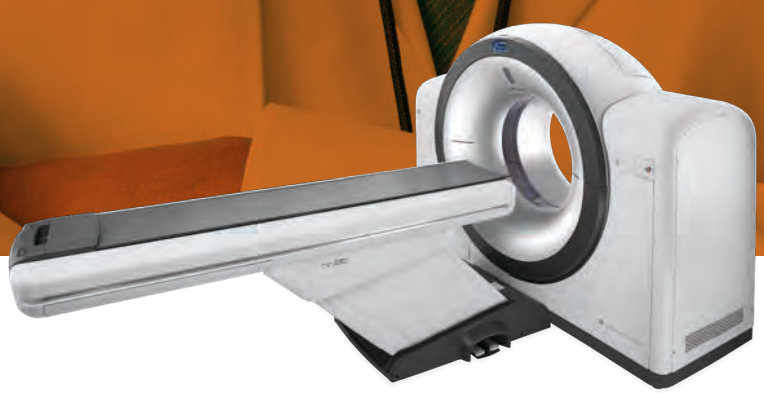

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