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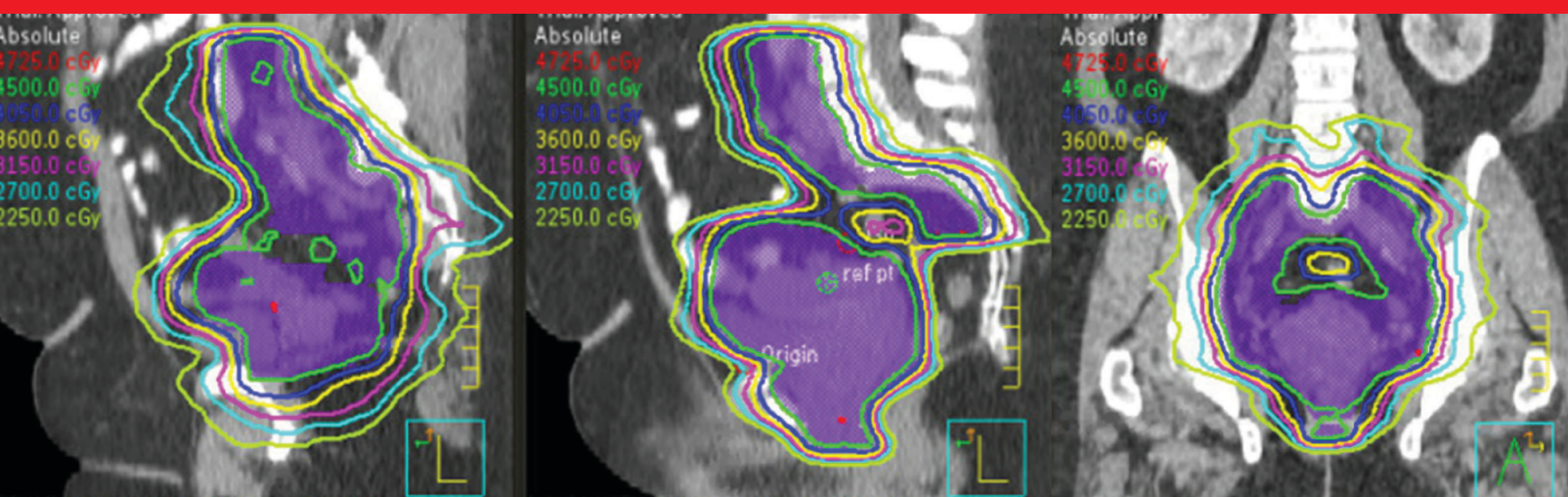

CME
Special Considerations of Pelvic Radiation Therapy in the Adolescent and Young Adult Female Population

Review
Late Effects of Pelvic Radiation Therapy in the Female Patient: A Comprehensive Review

Research
A Novel Framework to Define and Prognosticate Visual Outcomes Following Fractionated Radiation Therapy for Optic Nerve Sheath Meningiomas

Case Report
Radiation-Therapy-Induced Toxicity in a Breast Cancer Patient with Variance of Unknown Significance in Ataxia Telangiectasia Gene

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FOCUS: PELVIC RADIATION THERAPY IN FEMALE PATIENTS

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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.

Pelvic Radiation Therapy: Strides and Strategies

John H. Suh, MD, FASTRO, FACR

Welcome to the fall edition of *Applied Radiation Oncology*! This issue features the theme of pelvic radiation therapy in the female patient, offering two comprehensive review articles on this important, yet challenging, topic.

In the first review, *Special Considerations of Pelvic Radiation Therapy in the Adolescent and Young Adult (AYA) Female Population*, the authors help bridge the communication gap between providers and patients regarding the long-term effects of pelvic radiation treatment on physical, sexual, and mental health. Unfortunately, this communication has historically been lacking, compromising patient satisfaction and outcomes. The CME-approved article also examines the often overlooked but highly valuable resources and subspecialist interventions that can aid this vulnerable group by mitigating side effects and improving quality of life.

The second review, *Late Effects of Pelvic Radiation Therapy in the Female Patient*, offers a thorough, well-written summary of late side effects in this patient population, including gastrointestinal, urinary, gynecologic organ, skin, bone, hematologic/bone marrow, and peripheral nerve toxicities. Understanding these late effects is paramount to creating strategies that can minimize the risk of long-term and life-altering complications.

We are also pleased to present two research articles: *A Novel Framework to Define and Prognosticate Visual Outcomes Following Fractionated Radiation Therapy for Optic Nerve Sheath Meningiomas* and *A Practical Method to Prolong Expiratory Breath Holds (EBHs) for Abdominal Stereotactic Body Radiation Therapy (SBRT)*.

The former article provides groundwork to predict individualized risk of blindness or worsened visual outcomes caused by radiation treatment of this rare meningioma. The results help develop a new standard to guide decision-making and manage expectations for visual outcomes.

The latter research article describes the experience of the first patients treated with abdominal SBRT using a supplemented EBH technique with supplemental oxygen and mild hyperventilation. The authors discuss how this simple, inexpensive, and safe intervention may improve breath-hold times, reduce treatment time, and ultimately increase the number of patients eligible for EBH-based abdominal SBRT.

An enlightening case report is featured as well: *Radiation Therapy-Induced Toxicity in a Breast Cancer Patient with Variance of Unknown Significance in Ataxia Telangiectasia Gene*. We hope you benefit from these novel findings, which help move the field forward bit by bit.

Finally, we are proud to feature this month's thought-provoking Resident Voice Editorial, *Public Relations and Collaborative Support: Claiming a Seat at the Table When No One Else Is Buying It*. The authors shed light on how misconceptions, historical precedents, and financial biases in radiation oncology can obstruct optimal treatment choices.

In other news, we are working diligently behind the pages to bring on-demand publishing to *ARO*, significantly reducing acceptance-to-publication time. Stay tuned for updates, and please enjoy the issue as well as our many online offerings designed to expand education and enrich collaboration throughout the field and beyond the vault.

As always, thank you for your continued support! We wish you a beautiful, bountiful autumn.

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Special Considerations of Pelvic Radiation Therapy in the Adolescent and Young Adult Female Population

Description

This review article describes specific considerations for pelvic radiation therapy in the adolescent and young adult (AYA) cancer population, including fertility and premature ovarian insufficiency, sexual health, financial toxicity, and psychological impact. Awareness of these effects and available resources can help radiation oncologists to better communicate and counsel patients, set clear and realistic expectations, and proactively manage late side effects that can impair quality of life and long-term survivorship.

Learning Objectives

Upon completing this activity:

1. Physicians can improve communication skills when counseling AYA patients to help address specific and unique considerations that AYA cancer patients may face compared with other cancer populations.
2. Physicians can implement more routine and proactive referrals to subspecialists that can help AYA patients with the impact of acute and late side effects of pelvic radiation therapy.

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Target Audience

- Radiation oncologists
- Related oncology professionals

Commercial Support

None.

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Special Considerations of Pelvic Radiation Therapy in the Adolescent and Young Adult (AYA) Female Population

Sudha R. Amarnath, MD*

Abstract

Adolescent and young adult (AYA) patients are a small, but very important, group of cancer patients to focus on because they have historically been underrepresented in clinical trials and they have unique care needs that, if unaddressed, lead to poorer long-term survival outcomes and quality of life. Pelvic radiation therapy (RT) is frequently utilized in treatment paradigms for pelvic cancers, and treatment can lead to several acute and late side effects in patients. Some of these side effects can be especially impactful in AYA female cancer patients, including issues surrounding fertility and premature ovarian insufficiency, sexual health, financial toxicity, and psychological impact on body image, relationships, and other facets of a young person's life. An understanding of how pelvic RT can specifically affect AYA patients can help radiation oncologists to better counsel patients and take proactive steps to help mitigate side effects, as well as make referrals to other specialists who are equipped with resources that may help improve the AYA patient's long-term quality of life and survivorship.

Keywords: pelvic radiation therapy; AYA; adolescent and young adult; late effects; survivorship, education

Introduction

The adolescent and young adult (AYA) cancer population (generally defined as patients ages 15-39) represents an important group of patients with unique needs compared with the pediatric or older adult populations. The National Cancer Institute estimates that almost 86,000 AYA patients are diagnosed with cancer each year, which represents approximately 4% of all cancer diagnoses.[1] The incidence of cancer in this population has also been rising over the last decade, with a 0.3% increase each year from 2010 to 2019, for reasons not well understood at this time.[1] The survival rates of AYA patients have also not incrementally improved over the last decade compared with other cancer populations.[1] Unique challenges identified in this population include delays in initial diagnosis, decreased access to and participation in clinical trials, differences in tumor biology, poorer compliance and adherence to prescribed therapies, lack of communication and resources to address their specific psychosocial needs, negative impact of therapy on body image and sexuality, loss of fertility, and financial toxicity of treatment (**Table 1**).[2,3] Pelvic radiation therapy (RT) is frequently used in the treatment of cancers that can routinely affect the AYA population, including cervical cancer, rectal cancer, and sarcomas. Awareness and understanding of the specific

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Table 1. Specific Considerations for Adolescent and Young Adult Cancer Patients

- Delays in the initial diagnosis
- Decreased access to and participation in clinical trials
- Differences in tumor biology
- Poorer compliance and adherence to prescribed therapies
- Lack of communication and resources to address specific psychosocial needs
- Negative impact of therapy on body image and sexuality
- Loss of fertility
- Financial toxicity of treatment

considerations for pelvic RT in the AYA female population, as described in this article, can help radiation oncologists to better communicate and counsel patients, set clear and realistic expectations, and be proactive in managing late side effects that can impact quality of life and long-term survivorship.

Fertility and Premature Ovarian Insufficiency

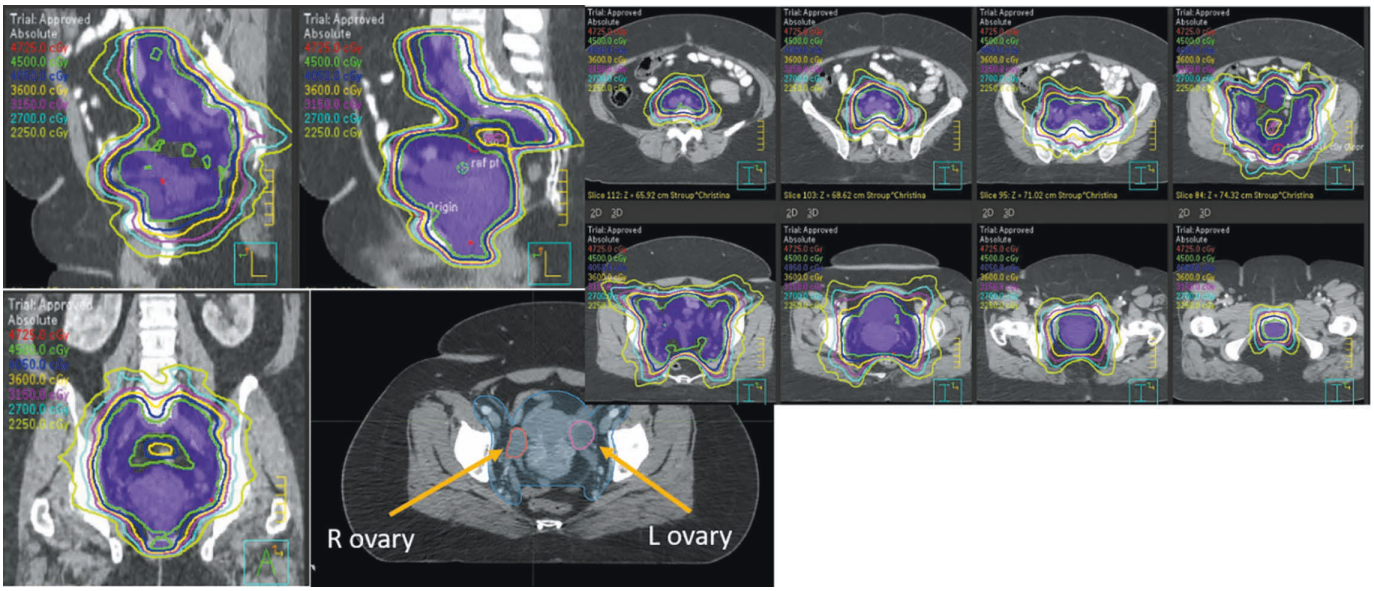
The late side effect that most commonly comes to mind when thinking about AYA patients is loss of fertility. Approximately 50% of cervical cancer patients are premenopausal at diagnosis and 15% of rectal cancer patients are under the age of 50 at diagnosis.[4] Even low doses of pelvic RT can cause a total shutdown of ovarian function in women of this age group, with doses of less than 4 Gy (and even less than 2 Gy) associated with the elimination of 50% of the oocyte pool.[5] Standard pelvic dosing of 45-50 Gy (**Figure 1**) also leads to uterine vascular changes that make future successful gestation of a pregnancy unlikely. When counseling patients, it is important to discuss loss of fertility and premature ovarian insufficiency (POI), also known as premature menopause, at the initial consultation. This includes discussion surrounding ovarian shutdown leading to loss of viable eggs and inability to carry a full-term pregnancy due to uterine changes after radiation.

Loss of Viable Eggs

The loss of viable eggs after low doses of pelvic RT leads to an inability to create embryos later in life. If it is clinically safe to delay cancer treatment, patients should be urgently referred to specialists in reproductive endocrinology and infertility (REI) for counseling and discussion of fertility options. These typically include cryopreservation of embryos (if the patient has a partner or sperm donor they would like to create embryos with), cryopreservation of oocytes, and cryopreservation of ovarian tissue.[6] Data are limited, but according to one retrospective study from the University of Southern California, thawed oocytes had a lower survival rate than embryos (79.1% vs 90.1%), but similar rates of fertilization (76.2% vs 72.8%) and live birth rates (25% in both groups).[7] Another study from New York University showed a live birth rate of 39% from thawed oocytes, with the best outcomes seen in patients less than 38 years old and a higher number of thawed oocytes.[8] Cryopreservation of ovarian tissue led to a live birth rate of 25.0% in a large registry study from the Netherlands, with increased rates of success in women less than 35 years of age at the time of ovarian tissue freezing (28.2%) vs greater than 35 years of age at the time of freezing (16.7%).[9] It is also important to have a discussion of the financial aspects of these preservation procedures, as they are not typically covered by insurance. A limited number of national programs can help provide funding to offset costs, but the upfront cost and ongoing costs of cryotherapy storage can be cost-prohibitive to many AYA patients.

Another option for patients who do not have ovarian involvement by tumor is surgical ovarian transposition.[10] With this procedure, the ovary is surgically transposed with its vascular pedicle to another location, ideally well above the pelvic brim, to minimize the radiation dose to the ovary. The procedure is most often performed laparoscopically, allowing for relatively quick recovery times. Transposition can be performed concurrently with other surgical procedures (such as pelvic node debulking, para-aortic nodal sampling, diverting ostomies, or hysterectomy/trachelectomy) or as stand-alone surgery. The ovaries should ideally be transposed at least 3 cm above the upper border of the radiation field, well above the pelvic brim and as lateral as possible (**Figure 2**). Although the data for ovarian transposition are somewhat limited, a 2021 Italian review of 28 manuscripts (including 699 patients with cervical cancer undergoing ovarian transposition and RT ± chemotherapy) showed that transposition was able to preserve ovarian function in 62% of patients. Ovarian preservation in these studies was defined as FSH < 10 mIU/mL, E2 > 50 pg/mL, and the presence of follicles on ultrasound. The type of treatment had implications on ovarian preservation rates as well, with an 86% preservation rate with brachytherapy alone vs a 55% preservation rate in patients who received external-beam radiation therapy + brachytherapy.[11] Complication rates are typically low, with a reported rate of approximately 8.5%.[12] Laparoscopic ovarian transposition is recommended due to decreased complication rates, reduced time

Figure 1. A typical pelvic radiation therapy plan using intensity-modulated radiation therapy, with ovaries identified on CT.



to starting pelvic RT, and very high ovarian survival rates.[13,14] Studies have shown that in women under age 40 who underwent laparoscopic ovarian transposition, ovarian function preservation rates were as high as 88.6%.[15] There are no consensus guidelines on dose constraints to transposed ovaries, and ideally, the dose to the transposed ovary or ovaries should be as low as possible. However, one study looking at women treated with intensity-modulated radiation therapy after ovarian transposition showed that dose constraints of a maximum dose < 9.985 Gy, mean dose < 5.32 Gy, and V5.5 < 29.65% to the transposed ovary could be better at preventing ovarian dysfunction, especially in women under age 38.[16]

CT simulation can typically be performed within a week of the procedure if the abdominal wall has sufficiently deflated (after surgical insufflation with laparoscopy) for reproducible treatment planning and delivery. The surgeon should mark the location of the transposed ovary or ovaries with a surgical clip and the ovarian tissue should be contoured for dosimetric evaluation. If the ovary is high enough in the abdomen, there should be minimal direct dosing to the ovary; however, the ovary will likely still receive some radiation exposure via internal scatter. This is important to explain when counseling patients, as the risk of ovarian failure remains given the tissue's sensitivity to radiation. Other risks associated with ovarian transposition include complications at the time of surgery, ovarian torsion, vascular injury, fallopian tube infarction, and small bowel obstruction due to postsurgical adhesions. Ovarian cyst formation is common and reported in up to 95% of patients but is unlikely related to the transposition procedure. Patients who undergo successful ovarian transposition with function retained after radiation therapy may retain viable eggs after treatment, which can later be retrieved for in vitro fertilization procedures. Ovarian transposition tends to be more successful in younger women, with the best outcomes seen in patients under age 35 (preservation rates by age: 25-30: 87.5%; 31-35: 62.5%; and 35-40: 42.9%).[17] National guidelines by the American Society of Clinical Oncology and the National Cancer Comprehensive Network[3,18] both recommend offering ovarian transposition to appropriately selected AYA cancer patients (**Table 2**) and referral to psychosocial providers when patients are distressed about potential infertility.

Premature Ovarian Insufficiency

Although fertility is an important consideration, the implications of POI or premature menopause on a young woman's health can often be overlooked by providers. Premature ovarian insufficiency is age dependent, with doses of 16.5 Gy at age 20 vs 10 Gy at age 45 to deplete the ovarian oocyte pool with conventional fractionation of 1.8-2.0 Gy per fraction. The shutdown of ovarian tissue with low doses of RT leads to decreased production of estrogen. Estrogen has many important normal functions in the body unrelated to reproductive health, including maintaining bone mineral density, decreasing the risk of cardiovascular disease by lowering the risk of atherosclerosis, neuroprotective effects due to estrogen-dependent DNA repair

Figure 2. Ideal location of transposed ovaries that are high and lateral in the abdomen (pink). Less ideal locations are also shown (crossed out).

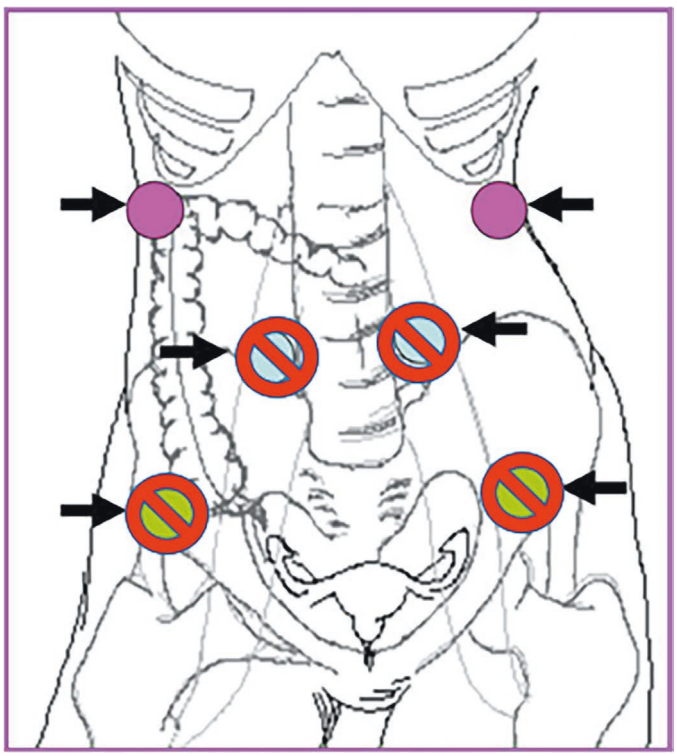


Table 2. Candidacy for Ovarian Transposition

GOOD CANDIDATES FOR TRANSPOSITION	POOR CANDIDATES FOR TRANSPOSITION

• Premenopausal
  • Patients who prefer not to take long-term hormone replacement
  • Best outcomes in patients aged < 35-40
• Low risk of ovarian metastases from primary cancer
• Medically operable
• NOT receiving gonadotoxic chemotherapy
	• Perimenopausal/postmenopausal
	• High risk of ovarian metastases from primary cancer
	  • Imaging can be important to determine the extent of the disease prior to offering the procedure
	• Medically inoperable
	• Receiving gonadotoxic chemotherapy

mechanisms in the brain, as well as effects on cognition and the immune system. The decreased lifetime exposure to estrogen in AYA patients can therefore have other long-term consequences on their overall health and life expectancy.

Menopause also comes with a host of symptoms that can substantially alter the quality of life and affect the body image of AYA patients. These menopausal symptoms include vasomotor symptoms (hot flashes), vaginal changes and decreased libido (see "Sexual Health"), depressed mood/anxiety/mental health changes from the rapid loss of estrogen, and memory changes. Many of these symptoms affect a patient's ability to work and can significantly impact their relationships at a time in life when many patients are building their careers and family lives.

There are treatment options for patients who undergo POI and referral should be made early to a women's health specialist, ideally someone who has more familiarity with POI due to cancer therapies. Options may include hormone replacement (in patients with nonhormonally driven cancers), symptomatic management for hot flashes (eg, venlafaxine, fezolinetant), and antidepressants/antianxiolytics. Patients may also benefit from a referral to a behavioral health specialist. Another option is to prevent POI by performing ovarian transposition prior to pelvic RT. Even if a patient does not desire fertility preservation in the future, successful transposition and protection of the ovary can allow for continued endogenous estrogen production in appropriately selected patients **Table 2**. Patients should be counseled about the risks of POI at the time of consultation and either referred for discussion of transposition (performed by REI or gynecologic oncology physicians at most centers) or hormone replacement therapy, and made aware of proactive steps that can help improve long-term quality of life.

Uterine Changes

The uterus is more resistant to radiation-induced changes than the ovaries; however, at the doses most typically used for gynecologic cancers, colorectal cancers, and sarcomas, long-term vascular changes and fibrosis are common. The decreased vascularity in the uterus translates into an inability to increase blood flow sufficiently to support the gestation of a fetus. The fibrosis that occurs in the wall of the uterus means that the uterus cannot expand as it normally would support a pregnancy.[19] Radiation to the uterus can lead to infertility, an increased risk of miscarriage, low-birth-weight infants, and premature births. It is important to counsel a

patient that even if they choose to undergo cryopreservation or ovarian transposition and can create embryos in the future, depending on the dose of radiation that the uterus received, they may be unable to carry their own pregnancy and may require the use of a gestational carrier.[20] The use of a gestational carrier comes with the potential for considerable financial cost, as well as possible state-dependent legal implications, which can significantly affect a patient and her family planning and decision-making. If a patient would like to pursue carrying her own pregnancy, referral should be made to maternal-fetal medicine providers for counseling and care.

Sexual Health

Pelvic RT can have significant effects on a patient's sexual health.[21] Studies suggest that patients receiving pelvic RT have significantly lower scores of satisfaction with social support and sexual function.[22] Since many AYA patients are often in a stage of trying to understand their sexuality and build and maintain relationships at the time of their cancer diagnosis, treatment that affects their sexual health can have a more devastating impact on body image, relationships, and sexual enjoyment.[23] Unfortunately, female patients routinely rate communication surrounding sexual function changes by physicians to be inadequate. A small study from 2023[24] found that patients felt that (1) they were not properly informed about sexual side effects and felt "blindsided and embarrassed," (2) they were psychologically affected with lower self-esteem and no longer feeling sexy, (3) they were not supported by their physicians and frequently had to turn to the internet for information and community support, and (4) their radiation oncologist could be more proactive in asking about sexual history and identifying individual patient priorities surrounding sexual health after treatment.

Pelvic radiation therapy primarily impacts vulvovaginal health and libido. Vaginal changes after pelvic RT and/or brachytherapy can include vaginal dryness, fibrosis, stenosis, vaginal length shortening, loss of elasticity, and vaginal closure. The reported incidence of vaginal stenosis ranges from 2.5% to 88% depending on a multitude of factors, including cancer type, RT dose, and the volume of vagina treated. Vulvar changes after pelvic RT can include painful labial adhesions and labial fibrosis. Patients may also experience dyspareunia and painful pelvic floor symptoms due to pelvic floor spasms. Patients should be counseled on these potential late effects at the time of consultation, as well as during and after treatment.

Vaginal dilators (**Figure 3**) are widely accepted in the radiation oncology community as an efficacious modality to mitigate vaginal stenosis after pelvic RT for any cancer type, and their use is recommended by international guidelines.[25,26] Although a 2014 Cochrane meta-analysis concluded that no reliable evidence exists that routine regular vaginal dilation prevents stenosis or improves quality of life,[27,28] several observational studies and one randomized controlled study from Brazil suggest that frequent dilation is associated with lower rates of vaginal stenosis.[29] Vaginal dilators are also used by some centers during simulation and treatment for anal and rectal cancers to decrease the dose of radiation to the vagina and potentially decrease the severity of vaginal stenosis. One study out of the MD Anderson Cancer Center showed that, on average, the use of a silicone vaginal dilator during treatment reduced the mean dose to the vagina by 5.5 Gy without compromising tumor coverage.[30] Another study looking at dosimetric predictors of radiation-induced vaginal stenosis after pelvic RT suggested that sparing of vaginal volume to a low dose may be important and that patients who received lower mean vaginal doses (<43 Gy) had a reduction in severe vaginal stenosis.[31] While this is an option, to set appropriate expectations, patients should be counseled that they may have difficulty tolerating dilator use later in treatment due to pain from inflammatory changes in the vulvovaginal area.

Patients should be counseled on how to appropriately use the dilator, lubrication (coconut oil, KY Jelly, or other vaginal moisturizers are recommended), and frequency of use. Dilation should start 4-6 weeks after completion of RT and should likely continue long-term (vaginal stenosis typically occurs 3-5 y after treatment), although no data or consensus exist as to the optimal duration of therapy.[32] Based on a large survey of US-based radiation oncologists, most providers recommend dilating three times per week for 5-10 minutes per session.[25] Vaginal intercourse may be difficult and painful for patients after treatment, but many patients may eventually have more comfortable vaginal intercourse with dilator use. Ongoing counseling and assessment of a patient's sexual health and vaginal tissue by providers can help improve patient compliance with dilator use and increase patient satisfaction and outcomes.[32] Some patients may also benefit from topical hormonal therapy.[26] In patients who have difficulty with dilator use or labial/vaginal adhesions, referral should be made to a urogynecologist for further assessment, as surgical treatment may be needed. Many patients also benefit from a referral for pelvic floor physical therapy to help with pelvic floor laxity (which can lead to incontinence symptoms, in

Figure 3. Examples of silicone and hard plastic vaginal dilators in different sizes.

addition to sexual health changes) or pelvic floor tightness/spasms, which can lead to dyspareunia and vaginismus symptoms.

Decreased libido can result from POI as discussed but can also be caused by diminished views of body image after cancer diagnosis and treatment, decreased sexual enjoyment due to pain/discomfort from vulvovaginal changes, or depression.[23] Patients should be referred to behavioral health specialists and sexual therapists when appropriate.[26] Sexual therapy can help patients discover new ways to experience intimacy and sexual enjoyment, leading to improved relationships and quality of life in AYA patients.

Financial Toxicity

The cost of a cancer diagnosis can be immense and cause significant financial impact and harm to AYA patients who are just starting to build careers and wealth. Patients who have financial toxicity also have inferior outcomes.[33] Direct cancer care-related costs include those of health insurance; copays for appointments, treatments, and prescribed medications; over-the-counter medications recommended for symptom management; and daily transportation costs. Additional costs may also be related to travel, housing, and meals. Indirect costs include time away from school/college and loss of work hours for patients and caregivers.

There are also considerable costs to being a cancer survivor. Approximately 80% of AYA cancer patients are long-term survivors[2] and face significant ongoing costs of maintaining good health insurance with a preexisting condition, copays for follow-up cancer surveillance tests and appointments, in addition to the costs associated with seeing other providers/specialists for the treatment of long-term side effects of cancer treatments. These appointments lead to continued days of missed school and work for patients and caregivers.

Acknowledging the financial impact of a cancer diagnosis and, more specifically, how multiple weeks of daily pelvic RT can affect a patient and her family is an important step in helping patients find resources to manage costs. A recent large cross-sectional study of 1075 patients from Germany who underwent RT revealed that the overall prevalence of financial toxicity was higher than anticipated with subjective financial distress reported by 41% of patients.[34] Prasad et al published a financial toxicity screening tool for radiation oncology that can help identify early-onset, patient-reported financial toxicity after radiation therapy with three variables: age, money owed, and copayment-related concerns.[35] Such tools can help radiation oncologists more easily identify at-risk patients and help provide appropriate resources. Social workers can be helpful in identifying financial grants and funds that a patient may be eligible for to help defray expenses, as well as helping to identify resources for transportation and housing that insurance or other cancer organizations may help cover. Financial navigators and advocates can assist patients in better understanding and managing treatment-related bills, in addition to helping patients with payment plans that they can more easily manage. The medical team can also consider more hypofractionated treatment courses (when clinically appropriate) and support patients with the appropriate letters and paperwork to

help them maintain their jobs while undergoing treatment.

Psychological Impact

A cancer diagnosis has a psychological impact at any age, but a cancer diagnosis in AYA patients can be even more psychologically devastating since the cancer diagnosis and treatment are occurring at a major time for living independent adult lives and building careers and relationships.

After diagnosis, cancer treatments and their short- and long-term side effects can compound the psychological impact. In addition to the side effects discussed, bowel and urinary changes caused by pelvic radiation therapy can have a major psychological impact (see the accompanying article in this issue, "Late Effects of Pelvic Radiation Therapy"). Adams et al surveyed 418 patients who had received pelvic RT 1-11 years previously and measured patient-reported toxicity, psychological morbidity, and quality of life. Female patients reported moderate/severe toxicity with bowel (59% of patients), urine urgency (49% of patients), and the ability to have a sexual relationship (24% of patients). These symptoms were just as frequent 6-11 years after RT compared with 1-5 years after RT, and symptom severity was associated with poorer quality of life and higher levels of depression.[36]

Unfortunately, women treated with pelvic RT routinely report unmet post-treatment psychosexual and psychological needs. It is therefore important to discuss these side effects at each follow-up appointment and support patients with resources. A randomized controlled trial showed that patients who received a psychosexual rehabilitation booklet over standard information were more likely to have higher dilator adherence and be better educated on psychosexual side effects and rehabilitation options.[37] Giving patients tools and information after pelvic RT treatment can help reduce distress and positively affect patients psychologically.

Referral to specific AYA cancer programs can be helpful, if available. These programs typically help patients navigate their diagnosis, testing, and appointments. They are also connected to AYA-specific resources, including behavioral health specialists who can help patients better weather the psychological storm. If an AYA program is not available, early intervention by a social worker or other behavioral health specialist can be instrumental in helping patients access care and increase compliance with treatment. In addition, partners, children, and other caregivers are often negatively impacted. Family counselors, support groups, and psycho-oncologists can help patients and their families in survivorship as well. Proactive support of patients' and their caregivers' mental health during diagnosis, treatment, and survivorship can help create a better therapeutic relationship through the care continuum and improve the quality of life of AYA patients.

Survivorship: Other Considerations

Adolescent and young adult patients should also be counseled and monitored appropriately for late side effects that may affect all patients undergoing pelvic RT, including late bladder and bowel changes (eg, incontinence, functional impairment, cystitis/proctitis), bone and joint changes, and surveillance for secondary malignancies. Referrals should be made to appropriate specialists, if indicated, in reproductive health (REI), maternal-fetal medicine, urogynecology/urology, gastroenterology/colorectal surgery, physical therapy (pelvic floor, lymphedema, functional strength/mobility), behavioral health, and others, to help ensure better long-term quality of life for these young survivors.

Conclusion

Female AYA patients can experience significant impact on their physical and mental health with pelvic RT, including loss of fertility, POI, sexual health changes, financial toxicity, and psychological tolls. Awareness of these effects and available resources can help radiation oncology providers to better communicate and counsel patients, set expectations for the long term, and proactively manage these effects in a vulnerable population, which can positively impact long-term survivorship and quality of life.

References

1) National Cancer Institute. Adolescents and young adults with cancer was originally published by the National Cancer Institute. 2023. Accessed June 10, 2023.

2) Coccia PF. Overview of adolescent and young adult oncology. *J Oncol Pract*. 2019;15(5):235-237. doi:10.1200/JOP.19.00075

3) Bhatia S ea. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Adolescent and Young Adult (AYA) Oncology V.2.2024. National Comprehensive Cancer Network, Inc. All rights reserved. Accessed June 10, 2023. www.NCCN.org

4) Group. USCSW. U.S. Cancer Statistics Data Visualizations Tool, based on 2022 submission data (1999-2020): U.S. Department of Health and Human Services, Centers for Disease Control and Prevention and National Cancer Institute; 2023. Accessed June 15, 2023. https://www.cdc.gov/cancer/dataviz

5) Wallace WHB, Thomson AB, Kelsey TW. The radiosensitivity of the human Oocyte. *Hum Reprod*. 2003;18(1):117-121. doi:10.1093/humrep/deg016

6) Wallace WHB, Anderson RA, Irvine DS. Fertility preservation for young patients with cancer: who is at risk and what can be offered *Lancet Oncol*. 2005;6(4):209-218. doi:10.1016/S1470-2045(05)70092-9

7) Ho JR, Woo I, Louie K, et al. A comparison of live birth rates and perinatal outcomes between cryopreserved oocytes and cryopreserved embryos. *J Assist Reprod Genet*. 2017;34(10):1359-1366. doi:10.1007/s10815-017-0995-2

8) Cascante SD, Blakemore JK, DeVore S, et al. Fifteen years of autologous oocyte thaw outcomes from a large university-based fertility center. *Fertil Steril*. 2022;118(1):158-166: . doi:10.1016/j.fertnstert.2022.04.013

9) Lotz L, Bender-Liebenthron J, Dittrich R, et al. Determinants of transplantation success with cryopreserved ovarian tissue: data from 196 women of the FertiPROTEKT network. *Hum Reprod*. 2022;37(12):2787-2796. doi:10.1093/humrep/deac225

10) Moawad NS, Santamaria E, Rhoton-Vlasak A, Lightsey JL. Laparoscopic ovarian transposition before pelvic cancer treatment: ovarian function and fertility preservation. *J Minim Invasive Gynecol*. 2017;24(1):28-35. doi:10.1016/j.jmig.2016.08.831

11) Hoekman EJ, Broeders E, Louwe LA, et al. Ovarian function after ovarian transposition and additional pelvic radiotherapy: a systematic review. *Eur J Surg Oncol*. 2019;45(8):1328-1340. doi:10.1016/j.ejso.2019.02.017

12) Buonomo B, Multinu F, Casarin J, et al. Ovarian transposition in patients with cervical cancer prior to pelvic radiotherapy: a systematic review. *Int J Gynecol Cancer*. 2021;31(3):360-370. doi:10.1136/ijgc-2020-001774

13) Swift BE, Leung E, Vicus D, Covens A. Laparoscopic ovarian transposition prior to pelvic radiation for gynecologic cancer. *Gynecol Oncol Rep*. 2018;24:78-82. doi:10.1016/j.gore.2018.04.005

14) Morice P, Juncker L, Rey A, et al. Ovarian transposition for patients with cervical carcinoma treated by radiosurgical combination. *Fertil Steril*. 2000;74(4):743-748. doi:10.1016/s0015-0282(00)01500-4

15) Bisharah M, Tulandi T. Laparoscopic preservation of ovarian function: an underused procedure. *Am J Obstet Gynecol*. 2003;188(2):367-370. doi:10.1067/mob.2003.38

16) Yin L, Lu S, Zhu J, Zhang W, Ke G. Ovarian transposition before radiotherapy in cervical cancer patients: functional outcome and the adequate dose constraint. *Radiat Oncol*. 2019;14(1):100. doi:10.1186/s13014-019-1312-2

17) Hoekman EJ, Knoester D, Peters AAW, et al. Ovarian survival after pelvic radiation: transposition until the age of 35 years. *Arch Gynecol Obstet*. 2018;298(5):1001-1007. doi:10.1007/s00404-018-4883-5

18) Oktay K, Harvey BE, Partridge AH, et al. Fertility preservation in patients with cancer: ASCO clinical practice guideline update. *J Clin Oncol*. 2018;36(19):1994-2001. doi:10.1200/JCO.2018.78.1914

19) Critchley HOD, Wallace WHB. Impact of cancer treatment on uterine function. *J Natl Cancer Inst Monogr*. 2005;34:64-68. doi:10.1093/jncimonographs/lgi022

20) Teh WT, Stern C, Chander S, Hickey M. The impact of uterine radiation on subsequent fertility and pregnancy outcomes. *Biomed Res Int*. 2014;2014:482968. doi:10.1155/2014/482968

21) Jensen PT, Froeding LP. Pelvic radiotherapy and sexual function in women. *Transl Androl Urol*. 2015;4(2):186-205. doi:10.3978/j.issn.2223-4683.2015.04.06

22) Rodrigues AC, Teixeira R, Teixeira T, et al. Impact of pelvic radiotherapy on female sexuality. *Arch Gynecol Obstet*. 2012;285(2):505-514. doi:10.1007/s00404-011-1988-5

23) Savoie MB, Paciorek A, Van Loon K, et al. Sexual function remains persistently low in women after treatment for colorectal cancer and anal squamous cell carcinoma. *J Sex Med*. 2023;20(4):439-446. doi:10.1093/jsxmed/qdac047

24) Morgan O, Schnur J, Caban-Martinez AJ, et al. A qualitative analysis of female patient perspectives on physician communication regarding sexual dysfunction associated with pelvic radiotherapy. *J Sex Med*. 2023;20(6):813-820. doi:10.1093/jsxmed/qdad041

25) Kachnic LA, Bruner DW, Qureshi MM, Russo GA. Perceptions and practices regarding women's vaginal health following radiation therapy: a survey of radiation oncologists practicing in the United States. *Pract Radiat Oncol*. 2017;7(5):356-363. doi:10.1016/j.prro.2017.02.003

26) Carter J, Lacchetti C, Andersen BL, et al. Interventions to address sexual problems in people with cancer: American society of clinical oncology clinical practice guideline adaptation of cancer care Ontario guideline. *J Clin Oncol*. 2018;36(5):492-511. doi:10.1200/JCO.2017.75.8995

27) Miles T, Johnson N. Vaginal dilator therapy for women receiving pelvic radiotherapy. *Cochrane Database Syst Rev*. 2010;9. doi:10.1002/14651858.CD007291.pub2

28) Miles T, Johnson N. Vaginal dilator therapy for women receiving pelvic radiotherapy. *Cochrane Database Syst Rev*. 2014;2014(9):CD007291. doi:10.1002/14651858.CD007291.pub3

29) Martins J, Vaz AF, Grion RC, Costa-Paiva L, Baccaro LF. Correction to: topical estrogen, testosterone, and vaginal dilator in the prevention of vaginal stenosis after radiotherapy in women with cervical cancer: a randomized clinical trial. *BMC Cancer*. 2021;21(1):811. doi:10.1186/s12885-021-08543-8

30) Briere TM, Crane CH, Beddar S, et al. Reproducibility and genital sparing with a vaginal dilator used for female anal cancer patients. *Radiother Oncol*. 2012;104(2):161-166. doi:10.1016/j.radonc.2012.05.011

31) Son CH, Law E, Oh JH, et al. Dosimetric predictors of radiation-induced vaginal stenosis after pelvic radiation therapy for rectal and Anal cancer. *Int J Radiat Oncol Biol Phys*. 2015;92(3):548-554. doi:10.1016/j.ijrobp.2015.02.029

32) Damast S, Jeffery DD, Son CH, et al. Literature review of vaginal stenosis and dilator use in radiation oncology. *Pract Radiat Oncol*. 2019;9(6):479-491. doi:10.1016/j.prro.2019.07.001

33) Carrera PM, Kantarjian HM, Blinder VS. The financial burden and distress of patients with cancer: understanding and stepping-up action on the financial toxicity of cancer treatment. *CA Cancer J Clin*. 2018;68(2):153-165. doi:10.3322/caac.21443

34) Fabian A, Rühle A, Domschikowski J, et al. Financial toxicity in cancer patients undergoing radiotherapy in a universal health care system - A prospective multicenter study of 1075 patients. *Radiother Oncol*. 2023;183:109604. doi:10.1016/j.radonc.2023.109604

35) Prasad RN, Patel TT, Keith SW, et al. Development of a financial toxicity screening tool for radiation oncology: a secondary analysis of a pilot prospective patient-reported outcomes study. *Adv Radiat Oncol*. 2021;6(6):100782. doi:10.1016/j.adro.2021.100782

36) Adams E, Boulton MG, Horne A, et al. The effects of pelvic radiotherapy on cancer survivors: symptom profile, psychological morbidity and quality of life. *Clin Oncol (R Coll Radiol)*. 2014;26(1):10-17. doi:10.1016/j.clon.2013.08.003

37) Lubotzky FP, Butow P, Hunt C, et al. A psychosexual rehabilitation booklet increases vaginal dilator adherence and knowledge in women undergoing pelvic radiation therapy for gynaecological or anorectal cancer: a randomised controlled trial. *Clin Oncol (R Coll Radiol)*. 2019;31(2):124-131. doi:10.1016/j.clon.2018.11.035

Late Effects of Pelvic Radiation Therapy in the Female Patient: A Comprehensive Review

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Abstract

Radiation therapy (RT) is a valuable treatment option for gynecologic cancers, but it is also associated with acute and chronic toxicity that can greatly impact a patient's quality of life. The severity and incidence of these side effects depend on various factors, such as the site, volume of tissue within the radiation field, treatment schedule, total dose, dose per fraction, and type of RT. Gastrointestinal (GI) toxicity is the most common side effect of pelvic radiation and late toxicity can include strictures, lower GI bleeding, and fibrosis. Genitourinary complications may include hemorrhagic cystitis, urethral and ureteral strictures, urge incontinence, fistulas, vaginal stenosis, premature ovarian insufficiency, and secondary malignancies. Outside the visceral tissues, insufficiency fractures, bone marrow suppression, and skin changes are also sporadically seen. Overall, advances in RT techniques and the understanding of patient-related factors influencing toxicity have led to improvements in treatment outcomes and reduced rates of late side effects. Understanding the late side effects associated with pelvic RT is critical for developing strategies to both minimize the risk of long-term complications and improve the quality of life of patients. This review aims to summarize the late side effects associated with RT in the pelvis and the respective interventions that may help treat toxicities.

Introduction

Radiation therapy (RT) is an essential treatment option for many gynecologic cancers, prostate cancer, and gastrointestinal (GI) malignancies. It can be used as a definitive, adjuvant, or neoadjuvant therapy. Evidence-based guidelines recommend that most gynecologic cancers can benefit from RT (eg, 60% of cervical, 45% of endometrial, 35% of vulvar, 100% of vaginal, and 5% of patients with ovarian cancer).[1,2] However, RT is associated with acute and late side effects that vary depending on which pelvic organ is targeted.[3]

Acute toxicity of RT typically occurs within a few weeks of starting treatment and is caused by the death of rapidly proliferating cells in normal tissues. Subacute effects may occur 4-12 weeks after treatment and represent a prolonged recovery from acute toxicity. Late effects can take months to years after treatment to develop and may result in fibrosis, vascular injury, or other gradual changes in slowly dividing tissues. These late effects can be long-lasting and irreversible, potentially leading to end-organ damage. In rare cases, residual DNA damage from RT can even cause delayed carcinogenesis, with the development of secondary malignancy years after RT.[4]

The incidence and severity of RT side effects are influenced by multiple factors, such as the site and volume of tissue exposed, treatment schedule, total dose, dose per fraction, and type of RT. Smoking history is a significant predictor of bowel and bladder complications from treatment.[3] Patients with active collagen vascular disease,[5]

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inflammatory bowel disease,[6] and vascular disorders such as diabetes and hypertension[7,8] may also be at higher risk for RT-related toxicity. Obesity,[9] low body mass index, and White ethnicity are also independently associated with increased toxicity.[10]

Several RT options are available for the treatment of pelvic tumors, including 3D conformal radiation therapy (3D-CRT), intensity-modulated RT (IMRT), or brachytherapy (BT).[11] Technological improvements, such as dose reduction and decreased radiation fields, have decreased radiation morbidity since 1990.[12] Furthermore, modern techniques such as IMRT are associated with excellent outcomes and limited rates of toxicity.[13,14] For example, severe late side effects resulting from RT are becoming rare in early stage cervical cancer, and most radiation-related comorbidities identified on imaging scans are clinically silent.[15]

Understanding the late side effects associated with pelvic RT is critical for developing strategies to both minimize the risk of long-term complications and improve the quality of life (QOL) of patients. This review aims to summarize the late side effects associated with RT in the pelvis and the respective interventions that may help treat toxicities.

Gastrointestinal Toxicity

Gastrointestinal toxicity is the most common side effect related to pelvic RT in both acute and late phases. Acute GI symptoms typically resolve within 2-4 weeks after treatment; however, they can sometimes progress to chronic toxicity, which can lead to worsening in QOL, especially in patients receiving definitive RT.[16-18] Chronic RT side effects in the bowel can have a latency period that varies from 6 months to several years. Most of the cases resolve within 12 months; however, lower-grade toxicity or progression to a higher grade is also commonly reported.[18]

Risk Factors

Several risk factors are associated with increased risk of GI toxicity. Age (60 y or older) is associated with a higher cumulative incidence rate of serious small intestinal obstruction or perforation.[19] Diabetes, atherosclerosis, or inflammatory bowel disease are also associated with an increased risk of toxicity from RT. The frequency of side effects in patients with a history of abdominal surgery or adjuvant RT is also increased.[18-20] For example, previous hysterectomy has been shown to increase the risk of RT toxicity due to the anatomic position of bowels deeper in the pelvis with a higher likelihood of being in the radiation field.[17] Additionally, rectal bleeding may be exacerbated in patients using anticoagulants.[20]

Small Bowel Toxicities

Both the small intestine and colon are susceptible to RT toxicity delivered within the pelvis, but the small intestine is more vulnerable due to its high epithelial mitotic rate, leading to more acute side effects. The injury can lead to focal ischemia and fibrosis, with the development of ulcers, strictures, and lower GI bleeding.[11] Severe late small bowel toxicities are rare and can present with fistula, obstruction, or hemorrhage.[21]

Diarrhea and Malabsorption

The mucosal atrophy and loss of mucin-producing goblet cells associated with RT can lead to chronic diarrhea and malabsorption. For chronic diarrhea, a multidisciplinary approach is usually helpful and antidiarrheal medications are often required. Radiation therapy to the distal ileum can cause vitamin B12 deficiency in up to 20% of patients. For malabsorption, vitamin replacement may be needed. Cholestyramine can be used when bile salt malabsorption is present.[22] Dehydration or constipation can occur as a result of impaired water absorption due to colonic radiation injury.[23] Perioperative nutritional therapy is an important intervention to help with chronic malnutrition observed in patients with prolonged chronic radiation enteritis.[24]

Obstruction/Ileus

Fibrosis of the intestinal wall can lead to dysmotility and the risk of obstruction.[7] For recurrent ileus or obstruction, the best option is conservative management, when possible, but sometimes surgery is required.[25]

Radiation Proctitis

Radiation therapy can lead to vascular sclerosis, which can then cause mucosal telangiectasias or ulceration, most commonly in the rectosigmoid colon. Patients most often present with symptoms of painless hematochezia, tenesmus, or pain. A colonoscopy is typically performed to exclude malignancy, and argon plasma coagulation can be performed at that time to help with bleeding vessels.[26] For rectal proctopathy, it is extremely important to avoid constipation. Sucralfate and hydrocortisone enemas can help protect the injured mucosa.[27] Guidelines from the Multinational Association of Supportive Care in Cancer note that hyperbaric oxygen treatment (HBOT) can be helpful for mucosal injury.[28] One study

indicated that topical formalin was as effective as argon plasma coagulation for bleeding control.[29] Topical butyrate is not helpful for chronic proctitis but can be helpful for acute proctitis.[30]

Fecal Incontinence

Fecal incontinence is a rarer late side effect of pelvic RT.[31] Surgical management is not typically indicated due to wound-healing issues postradiation.[31]

Secondary Malignancy

Secondary malignancy is a potential late side effect of RT. A meta-analysis showed an increased risk for rectal cancer after RT for cervical cancer (relative risk [RR] 1.43; 95% CI, 1.18-1.72) and prostate cancer (RR, 1.36; CI, 1.10-1.67). However, no relation was seen in patients with ovarian cancer and the modality of RT did not influence the incidence of rectal cancer postpelvic RT.[32]

Dosimetric and Planning Considerations to Reduce GI Toxicity

Some RT techniques can decrease the total radiation dose delivered to the small bowel, such as IMRT when compared with 3D-CRT,[33,34] reducing the incidence of late severe GI obstruction after postoperative pelvic RT.[35] The 3-year cumulative incidence of grade 2 or higher GI adverse events after image-guided IMRT (21%) was significantly lower than that of 3D-CRT (42%) (hazard ratio, .46), with noninferior clinical efficacy.[36,37]

Chronic rectal toxicity is correlated to the volume of the rectum receiving 70 Gy or more (V70) and should be kept as low as possible.[38] Grade 2 rectal toxicity is lower with IMRT (5%-21%) compared with 3D-CRT.[39,40] Also, the Post Operative Radiation Therapy in Endometrial Carcinoma 2 Trial (PORTEC 2) demonstrated increased levels of GI symptoms and lower QOL in patients receiving postoperative external-beam radiation therapy (EBRT) compared with vaginal BT.[41,42]

The use of image guidance and/or placement of spacers prior to and during planning may also reduce the dose delivered to organs at risk (OARs) and subsequent GI toxicity.[32,43] For example, results from the prospective EMBRACE study, which utilized MRI-guided adaptive BT for cervical cancer, reported that a rectal D2cc equivalent dose in 2 Gy fraction (EQD2)3 < 65 Gy was associated with half the risk of proctitis compared with a rectal D2cc (EQD2)3 ≥ 65 Gy.[43] Hydrogel spacers are employed at some institutions to decrease dose and toxicity by placing a physical spacer to protect OARs in gynecologic and prostate cancer.[42] Pelvic RT is also often delivered with instructions for the patient to have a full bladder, which allows displacement of the bowel superior to the pelvis, reducing the risk of bowel toxicity.

Urinary Toxicity

Genitourinary late side effects usually start 1-3 years after treatment, although higher doses of radiation can prolong latency time.[44] They occur due to epithelial and microvascular changes mediated by fibrosis (lower bladder capacity and loss of compliance) and may include hemorrhagic cystitis, urethral and ureteral strictures, urinary fistulae, and secondary primary malignancies. Radiation therapy has also been linked with infertility, lower urinary tract dysfunction (urge incontinence), bladder fibrosis, and necrosis.[45] Measurable differences in QOL can persist for more than 15 years, specifically because of urinary urgency, incontinence, and limitations in daily activities due to bladder symptoms.[46]

Risk Factors

Some patient-related factors can influence radiation-related toxicity. The use of anticoagulants increases the severity of postradiation hematuria. Obesity and heavy smoking are associated with a higher risk of bladder complications following RT for cervical cancer, especially fistula formation and hemorrhagic cystitis.[3]

Bladder Ulceration

One of the most common and severe effects related to higher doses of radiation is persistent nonhealing tissue, which can lead to bladder ulceration and stone formation. However, even in the definitive treatment of cervical cancer, where higher cumulative doses to the bladder are seen due to the combination of pelvic RT combined with BT, the probability of late genitourinary (GU) grade 3 or 4 side effects (**Table 1**) is still low, at less than 3%.[47]

Hemorrhagic Cystitis

Hemorrhagic cystitis may be a potentially life-threatening complication of pelvic RT. In a study of 1784 patients treated for cervical carcinoma with BT or EBRT, the incidence of hemorrhagic cystitis was 6.5% and the mean interval to the onset of symptoms was 35 months after completing RT. However, some patients developed hemorrhagic cystitis as late as 20 years after treatment; hence, radiation-induced cystitis must be considered at any time following the completion of RT.[48]

Treatment for hemorrhagic cystitis is usually conservative because surgical intervention can precipitate toxicity given the poor vascularity and healing after radiation. Treatment

Table 1. RTOG/EORTC Late Radiation Morbidity for Pelvic Tissues[129]

TISSUE	GRADE			
	1	2	3	4
Skin	Slight atrophy; pigmentation change; some hair loss	Patch atrophy; moderate telangiectasia; total hair loss	Marked atrophy; gross telangiectasia	Ulceration
Subcutaneous tissue	Slight induration (fibrosis) and loss of subcutaneous fat	Moderate fibrosis but asymptomatic; slight field contracture; < 10% linear reduction	Severe induration and loss of subcutaneous tissue; field contracture > 10% linear measurement	Necrosis
Mucous membrane	Slight atrophy and dryness	Moderate atrophy and telangiectasia; little mucous	Marked atrophy with complete dryness	Ulceration
Small/large intestine	Mild diarrhea; mild cramping; bowel movement 5 times daily; slight rectal discharge or bleeding	Moderate diarrhea and colic; bowel movement > 5 times daily; excessive rectal mucus or intermittent bleeding	Obstruction or bleeding, requiring surgery	Necrosis/perforation fistula
Bladder	Slight epithelial atrophy; minor telangiectasia (microscopic hematuria)	Moderate frequency; generalized telangiectasia; intermittent macroscopic hematuria	Severe frequency and dysuria; severe telangiectasia (often with petechiae); frequent hematuria; reduction in bladder capacity (< 150 cc)	Necrosis/contracted bladder (capacity < 100 cc); severe hemorrhagic cystitis
Bone	Asymptomatic; no growth retardation; reduced bone density	Moderate pain or tenderness; growth retardation; irregular bone sclerosis	Severe pain or tenderness; complete arrest of bone growth; dense bone sclerosis	Necrosis/spontaneous fracture

Abbreviations: EORTC, European Organization for Research and Treatment of Cancer; RTOG, Radiation Therapy Oncology Group.

options include hydration, blood transfusions, and bladder irrigation with clot evacuation. In severe cases, embolization can also be considered. Other options include HBOT, intravesical formalin, argon plasma coagulation, endoscopic procedures, botulinum toxin injection, or systemic therapy.[11]

Fistulas

Urethrovaginal and vesicovaginal fistulas are more common with high-dose focal radiation injury and are directly influenced by tumor invasion of GU structures before therapy. In a review of women diagnosed with stage IVA cervical cancer (invasion of the bladder or rectum), 48% developed a fistula at a median time of 2.9 months from cancer diagnosis. In this study, there was no difference between women treated with radiation alone compared with chemoradiation in the incidence of fistula formation.[49]

Hematuria and Radiation Cystitis

Sodium pentosan polysulfate has been tested for radiation-induced hematuria with promising results.[50] Symptomatic improvement with hyperbaric oxygen is reported for late radiation cystitis.[51]

Dosimetric and Planning Considerations to Reduce Toxicity

Localized dose to the bladder neck is a potential predictor of urinary incontinence, whereas weaker associations are observed between urgency and some bladder-wall parameters.[52]

Apart from the primary site of treatment, GU toxicity is also affected by total radiation dose, treatment volume, treatment modality, and treatment technique. With more typical doses of EBRT for gynecologic cancers (40-50 Gy in 1.8-2 Gy fractions), the likelihood of bladder side effects of moderate to severe intensity is low;[53] however, focal therapy with BT is associated with higher GU morbidity.[14,20] For example, the risk of late side effects with the incorporation of 3D treatment planning into BT correlates best with the dose received by bladder D2cc (EQD2)3

per EMBRACE with the complication probability for bladder D2cc (EQD2)3 of 101 Gy (EBRT + BT) being approximately 10%. More recent published data recommend a lower bladder dose constraint of D2cc (EQD2)3 ≤ 80-85 Gy, but only in the absence of bladder involvement by tumor.[37,54,55]

Gynecologic Organ Toxicity

Vagina

Toxicity to the vagina is commonly seen after RT for cervical and uterine cancer, which can lead to sexual dysfunction due to vaginal dryness, dyspareunia, and vaginal stenosis, impairing the QOL.

Risk Factors

The incidence is higher in locally advanced tumors, with more than half of the women reporting sexual dysfunction after RT.[56] Vaginal toxicity is lower when RT is applied as an adjuvant treatment with surgery compared with definitive RT alone.[57] Vaginal shortening is more common in patients with advanced age, concomitant chemotherapy, higher vaginal RT doses, and lack of vaginal dilator use compliance.[25,58-61]

Vaginal Ulceration

Full-thickness vaginal ulceration and necrosis are rare after RT and more frequently occur in patients requiring interstitial BT for vaginal cancers.[25] Necrosis is more common in the acute phase and the distal vagina has less radiation tolerance. For vaginal ulcerations, management is initially conservative. Options for vaginal mucosal injury include hydrogen peroxide douching, pentoxifylline, or HBOT.[62,63]

Fistulas

Uncommon but potential complications of pelvic RT are also rectovaginal and vesicovaginal fistulas.[49] They primarily occur in patients who require high doses of radiation to control gross disease involving the vagina or due to tumor invasion of adjacent organs. Interstitial BT may increase this risk compared with intracavitary BT.[49] Conservative management of fistulas is advised because surgical repair can precipitate complications. Like vaginal ulcerations, HBOT and pentoxifylline can be used.[62,63]

Vaginal Stenosis

The most common late vaginal side effect is vaginal stenosis, which can occur both with EBRT and BT. The incidence of vaginal stenosis varies widely between available studies, with rates between 2.5% and 88%.[61] Dyspareunia (or vaginismus) is a frequent complaint due to the shortening of vaginal length and the narrowing of the vaginal vault or the development of adhesions. It is often accompanied by mucosal pallor and telangiectasias. Vaginal stenosis can interfere with the ability to perform surveillance pelvic exams or the ability to have comfortable vaginal intercourse. Vaginal stenosis is primarily treated, and even prevented, with vaginal dilators.[64]

Dosimetric Considerations to Reduce Toxicity

The biggest risk of vaginal stenosis is the combined treatment of pelvic RT plus BT.[60,61] A planning aim of ≤ 65 Gy EQD2 (EBRT + BT dose) to the rectovaginal reference point was proposed by Kirchheiner et al to reduce the risk of vaginal stenosis.[65]

Secondary Malignancy

Gynecologic radiation-induced secondary malignancies were found to be predominantly more aggressive, poorly differentiated, and had rare histologic types compared with sporadic tumors. The management is influenced by previous radiation doses and the location of the radiation-induced secondary malignancies.[66]

Ovaries

Radiation toxicity to ovaries includes infertility or premature ovarian insufficiency (POI) (defined as menopause before 40 y of age) because ovaries are very sensitive to low doses of radiation, even with small fraction sizes.

Premature Ovarian Insufficiency

Oocytes are the most sensitive cells within the ovary, and even low doses of radiation can lead to hormonal changes, hot flashes, mood changes, and vaginal dryness.[67] POI is expected when ovaries remain within the radiation field for the treatment of adult malignancies, with age-dependent sensitivity to radiation.[67]

The dose predicted to result in POI immediately following treatment is 16.5 Gy at 20 years old and 14.3 Gy at 30 years old,[67] but even ovarian doses of 4 Gy or less have been associated with premature menopause.[68] With lower dose exposures, estrogen levels can recover between 6 and 18 months, but early menopause is still likely to occur.

Menopausal symptoms usually respond to the use of systemic or vaginal hormone replacement therapy. Some studies also show the benefits of serotonin reuptake inhibitors.

Fertility

Doses as low as 1.7-2.5 Gy have been associated with significant but temporary amenorrhea or sterility without ovulation for several years.[69] Women who desire future pregnancy should be evaluated by reproductive endocrinology before initiation of RT to discuss the options of ovarian transposition, ovarian stimulation with oocytes,

or embryo cryopreservation or ovarian tissue preservation, as clinically appropriate.

Ovarian Transposition to Preserve Ovarian Function

Laparoscopic ovarian transposition may be performed in premenopausal women < 40 years old before pelvic radiation to enhance the preservation of ovaries, but the surgeon must understand the radiation field (transposed ovaries should be at least 3 cm above the radiation field). High rates of preservation (80%-88%) have been reported, with an improved likelihood of success when both ovaries are transposed.[70,71] Transposition is only considered if the patient has a low risk that their primary malignancy will have ovarian spread.[70,71]

Uterus

Pelvic radiation is also correlated with increased rates of miscarriage, preterm labor, low birth weight, and placenta accreta due to arteriolar damage, decreased fetoplacental blood flow, and fibrosis, which decreases the uterine distension after pelvic RT.[72,73]

Skin Toxicity

A wide spectrum of injuries can arise as radiation-induced skin toxicities, highly variable in incidence, temporality, and severity.[74-76] Acute dermatitis usually resolves in 1-3 weeks. Late skin side effects can include persistent hyperpigmentation, telangiectasia, and radiation fibrosis. Irradiated skin also presents an increased risk of developing skin cancer.[77,78]

Risk Factors

Patient comorbidities such as vascular compromise (smoking history and diabetes) are associated with increased risk of skin toxicity as well as collagen vascular disease (specifically scleroderma). Obese patients develop skin toxicity more frequently due to increased apposition of skin in the groin and pannus. Immunocompromised patients and HIV-seropositive patients also develop increased toxicity from RT, although the reported literature does not correlate CD4 count with outcomes.[79-81]

Treatment-Related Factors

Factors depending on the type of treatment can also influence the development of skin toxicity. Treatment-related factors, including lower megavoltage photon beam energy, proton therapy, field size, and tangential fields, can increase the risk of skin toxicity.[82-84] Modern pelvic RT using high-energy photons (10-18 MV) and multifield arrangements are associated with skin-sparing effects. Consequently, radiation dermatitis for gynecologic cancer is usually mild. However, when the radiation target volumes are close to or involve the skin surface, the incidence of skin reactions is higher. For example, less than half of patients with endometrial cancer present with skin reactions, while almost all patients treated with RT for vulvar cancer will develop skin toxicity to some degree, and grade 3 skin reactions may become common.[82-84] If inguinal nodal basins are included in the treatment plan, the skin is exposed to higher doses of radiation and the risk of toxicity is higher.[82] Many of the cases are mild or moderate, but serious injury may also develop and result in RT break or disability.[82,85] The use of IMRT may reduce the risk of grade 3 or higher skin toxicities, minimizing skin doses outside the target volume.[74,85] Dose, fractionation, concurrent radiosensitizing systemic therapy, and re-irradiation are also important considerations[86] that may affect the risk of skin toxicity.

Treatment of Skin Toxicities

Skin hygiene and water-based creams are helpful for skin erythema or dry desquamation. Moisturizers can address dry skin.[87] Topical anesthetics can be used for the management of patient discomfort. Silvadene cream may be used to manage moist desquamation. Radiation-induced telangiectasias can be treated with laser intervention if a patient has cosmesis concerns.[26] Radiation fibrosis of the skin can be difficult to treat, but in some cases, may respond to oral pentoxifylline and vitamin E.[88] Management of chronic ulcerations includes wound care with dressing, ointment, debridement, and, if needed, a biopsy to rule out skin cancer.[89]

Bone Toxicity

Radiation therapy side effects within the bones typically occur chronically, over the course of several years. Among the most common changes are osteopenia, increased bone density (osteosclerosis), and changes in the sacroiliac joints.[90]

Pelvic Fractures

Radiation-related insufficiency fractures can develop at the pubic symphysis,[91] the pubic rami, and, most commonly, the sacrum.[92,93] The clinical presentation is usually localized pain.[94]

Risk Factors

Risk factors such as osteoporosis, kidney or vascular disease, and long-term use of steroids are associated with pathological fractures or osteonecrosis.[95-97] The risk of RT-related fractures varies based on the type of malignancy

treated. The rates are the highest for anal and cervical cancers (14% and 8%-20%, respectively).[92,94,98] For rectal cancer, the rates of pathological pelvic fractures are slightly lower, reported between 7% and 11%.[99] In patients with prostate cancer, a small retrospective series in patients primarily treated with 3D-CRT showed a pelvic fracture incidence of 6.8% over the 5 years following whole-pelvic radiation.[100] Other risk factors include older age, pre-existing osteopenia, diabetes mellitus, low body weight, and higher radiation doses (above 50 Gy).[92,101]

Diagnosing Pelvic Fractures and Other Bony Changes

Diagnosis is traditionally made with imaging, with CT showing peripheral sclerotic areas or fracture lines.[97,102] In some cases, an MRI will be warranted, with an acute fracture line showing edema (low T1, high T2).[103] Later findings will include linear sclerosis (low T1, low T2) surrounding the fracture.[103] Bone scintigraphy is also sensitive, showing the characteristic Honda sign.[94,103] It is important to rule out metastatic disease if pathological fracture is suspected, but biopsy should be carefully considered since the findings of healing bone can mimic malignancy.[104]

Prevention and Treatment of PIF

The prevention of osteoporosis is important to preserve bone mineral density. Calcium and vitamin D supplements, as well as weight-bearing exercises, can be helpful. Bisphosphonates, hormonal therapy, and calcitonin can also be used for fracture prevention.[104] The use of IMRT may also help reduce the risk of pelvic insufficiency fractures (PIFs). A systematic review and meta-analysis identified the 5-year incidence of PIFs at 15% following pelvic radiation (59% symptomatic); however, fractures were less likely with IMRT, with an incidence of 4.8%.[105] Patients can typically be managed with pain medication and rest. Pentoxifylline, alone or in combination with other therapies, can be safe and effective for fractures or osteoradionecrosis, but requires further investigation.[95,106]

Secondary Malignancy and Radionecrosis

Secondary malignancies may arise related to radiation, most commonly hematologic malignancies, and bone osteosarcomas.[107,108] Osteosarcomas may have similar features to radiation necrosis, another potential late complication from radiation. Radiation necrosis often has a long latent period and is more common than malignancy. Lack of pain generally favors necrosis alone. Globular calcification may occur in radiation necrosis and usually is not present with malignancy. Lack of progression on serial imaging also favors radiation necrosis.[109] There are several case reports regarding avascular femoral head necrosis from radiation, which is an uncommon but very serious complication that can lead to significant morbidity, especially in older patients.[97]

Hematologic/Bone Marrow Toxicity

Hematologic toxicity is responsible for the overwhelming majority of acute grade 4 radiation toxicity. Given the high replication rates, hematopoietic cells are very sensitive to lower doses of radiation.[110] The pelvis contains at least 25% of the bone marrow reserves. It has also been established that IMRT can minimize the dose of radiation to the bone marrow. Several studies suggest that this lowers the risk of hematologic complications and may improve the likelihood of completing all intended doses of chemotherapy.[107,108,111]

Follow-up with weekly blood counts is usually performed in patients with concurrent chemotherapy. If the absolute neutrophil count drops below 500/µL or platelets are less than 40,000/µL, radiation treatment is suspended. Hemoglobin levels are preferably maintained at more than 10 mg/dL, especially in patients with cervical cancer.[20]

Peripheral Nerve Toxicity

Peripheral nerve toxicity after pelvic RT is a relatively less common toxicity, with radiation-induced lumbosacral plexopathy (RILP) being the most common complication.[112]

Radiation-Induced Lumbosacral Plexopathy

Radiation-induced lumbosacral plexopathy translates into damage to the lumbosacral plexus, which includes the lumbar (L1-L4) and sacral (L5-S5) portions of the lumbar plexus, which has both motor and sensory fibers to the abdominal wall, anteromedial thigh, and leg.[113] The exact mechanism of RILP remains not fully understood, with recent investigations indicating microvascular injury followed by the development of radiation-induced fibrosis as the most accepted pathogenesis.[112,114]

Risk Factors

Several factors are linked with RILP, including larger total delivered doses (>50 Gy to the plexus), higher amounts per fraction (2.5 Gy), heterogeneous high-dose distribution, and possibly BT.[112,114,115]

Presentation and Diagnosis

The onset of RILP is slowly progressive, mostly affecting motor fibers and function. Sensory

impairments and neuropathic pain are typically developed later. Symptoms start usually unilaterally and then progress to bilateral, typically asymmetric, damage. Knee-jerk and ankle reflexes are almost always decreased.[112,114,116] RILP may develop as a very late complication from radiation, with a case report mentioning the condition 36 years after RT for cervical cancer.[117]

Radiation-induced lumbosacral plexopathy is a diagnosis of exclusion, with some other possible diagnoses including metastasis, local tumor growth, or degenerative compression of lumbosacral nerve roots. Axial imaging is valuable for diagnosis. PET scanning using F-18 fluorodeoxyglucose (FDG) can aid in diagnosing recurrent tumors,[118,119] but it has limited potential in identifying intrinsic lumbosacral plexus pathologies.[120] Other potential differential diagnoses to consider include lumbar infection and connective tissue diseases, including systemic vasculitis and polyneuropathy. Workup can also include laboratory studies, cerebrospinal fluid analysis, nerve conduction studies, and needle electromyography.[121,122]

Treatment and Prevention of RILP

Unfortunately, no curative therapy is available for RILP. The therapeutic modalities mostly target symptomatic improvement, with neuropathic pain being the most common type of pain, for which several guidelines have been published.[123,124] Tricyclic antidepressants, serotonin-noradrenaline reuptake inhibitor antidepressants, pregabalin, and gabapentin are the most acceptable.[123] Adjuvant rehabilitation is recommended, especially neurostimulation physical therapy.[124,125] Psychotherapy can be recommended as a second-line therapy.[124] Once the motor deficit is seen, translating into severe axonal damage, recovery is rarely described.[112,114,126,127] Spontaneous recovery is less common.[128]

To prevent RILP, the optimal strategy is to avoid exceeding dose-volume constraints when radiation is delivered. This precludes damage to at-risk organs, for which state-of-the-art RT technologies (eg, volumetric-modulated arc therapy) can be used.[96]

Conclusion

Radiation therapy offers valuable treatment options for gynecologic, prostate, and GI cancers. However, it comes with the potential for acute and chronic toxicity that can significantly impact patients' QOL. The severity and occurrence of these side effects depend on several factors, including the treatment area, tissue volume in the radiation field, treatment schedule, total dose, dose per fraction, and RT type.

There are several options for the prevention and treatment of these late effects, and patients should be appropriately counseled prior to treatment and monitored during and after treatment to assess and treat late toxicities. Referrals should be made to appropriate specialists in other disciplines to help with the long-term management of radiation-induced late toxicities. Patients should also undergo routine surveillance and standard screening for other malignancies.

In conclusion, advancements in RT techniques and our understanding of patient-related factors influencing toxicity have led to improved treatment outcomes and reduced rates of late side effects. Future research should continue to focus on optimizing treatment strategies to minimize toxicity and enhance the QOL of patients undergoing pelvic RT for gynecologic cancers.

References

1) Delaney G, Jacob S, Barton M. Estimation of an optimal radiotherapy utilization rate for gynecologic carcinoma: part I--malignancies of the cervix, ovary, vagina and vulva. *Cancer*. 2004;101(4):671-681. doi:10.1002/cncr.20444

2) Delaney G, Jacob S, Barton M. Estimation of an optimal radiotherapy utilization rate for gynecologic carcinoma: part II--carcinoma of the endometrium. *Cancer*. 2004;101(4):682-692. doi:10.1002/cncr.20445

3) Eifel PJ, Jhingran A, Bodurka DC, Levenback C, Thames H. Correlation of smoking history and other patient characteristics with major complications of pelvic radiation therapy for cervical cancer. *J Clin Oncol*. 2002;20(17):3651-3657. doi:10.1200/JCO.2002.10.128

4) Bentzen SM. Preventing or reducing late side effects of radiation therapy: radiobiology meets molecular pathology. *Nat Rev Cancer*. 2006;6(9):702-713. doi:10.1038/nrc1950

5) Wo J, Taghian A. Radiotherapy in setting of collagen vascular disease. *Int J Radiat Oncol Biol Phys*. 2007;69(5):1347-1353. doi:10.1016/j.ijrobp.2007.07.2357

6) Willett CG, Ooi C-J, Zietman AL, et al. Acute and late toxicity of patients with inflammatory bowel disease undergoing irradiation for abdominal and pelvic neoplasms. *Int J Radiat Oncol Biol Phys*. 2000;46(4):995-998. doi:10.1016/S0360-3016(99)00374-0

7) Maruyama Y, Van Nagell JR, Utley J, Vider ML, Parker JC. Radiation and small bowel complications in cervical carcinoma therapy. *Radiology*. 1974;112(3):699-703. doi:10.1148/112.3.699

8) van Nagell JR, Parker JC, Maruyama Y, Utley J, Luckett P. Bladder or rectal injury following radiation therapy for cervical cancer. *Am J Obstet Gynecol*. 1974;119(6):727-732. doi:10.1016/0002-9378(74)90082-9

9) Mikkelsen TB, Sørensen B, Dieperink KB. Prediction of rehabilitation needs after treatment of cervical cancer: what do late adverse effects tell us. *Support Care Cancer*. 2017;25(3):823-831. doi:10.1007/s00520-016-3466-x

10) Rubinsak LA, Kang L, Fields EC, et al. Treatment-related radiation toxicity among cervical cancer patients. *Int J Gynecol Cancer*. 2018;28(7):1387-1393. doi:10.1097/IGC.0000000000001309

11) Nicholas S, Chen L, Choflet A, et al. Pelvic radiation and normal tissue toxicity. *Semin Radiat Oncol*. 2017;27(4):358-369. doi:10.1016/j.semradonc.2017.04.010

12) Wit EMK, Horenblas S. Urological complications after treatment of cervical cancer. *Nat Rev Urol*. 2014;11(2):110-117. doi:10.1038/nrurol.2013.323

13) Mansha MA, Sadaf T, Waheed A, et al. Long-term toxicity and efficacy of intensity-modulated radiation therapy in cervical cancers: experience of a cancer hospital in Pakistan. *JCO Glob Oncol*. 2020;6:GO.20.00169:1639-1646:. doi:10.1200/GO.20.00169

14) Contreras J, Srivastava A, Chundury A, et al. Long-term outcomes of intensity-modulated radiation therapy (IMRT) and high dose rate brachytherapy as adjuvant therapy after radical hysterectomy for cervical cancer. *Int J Gynecol Cancer*. 2020;30(8):1157-1161. doi:10.1136/ijgc-2020-001412

15) Nadova K, Burghardtova M, Fejfarova K, Reginacova K, Malikova H. Late radiation-related toxicities in patients treated for early-stage cervical carcinoma by surgery and adjuvant radiotherapy: a retrospective imaging study. *Pathol Oncol Res*. 2021;27:1609915. doi:10.3389/pore.2021.1609915

16) Nout RA, Putter H, Jürgenliemk-Schulz IM, et al. Quality of life after pelvic radiotherapy or vaginal brachytherapy for endometrial cancer: first results of the randomized PORTEC-2 trial. *J Clin Oncol*. 2009;27(21):3547-3556. doi:10.1200/JCO.2008.20.2424

17) Wang Y, Kong W, Lv N, et al. Incidence of radiation enteritis in cervical cancer patients treated with definitive radiotherapy versus adjuvant radiotherapy. *J Cancer Res Ther*. 2018;14(suppl 1):S120-S124. doi:10.4103/0973-1482.163762

18) Shejul J, Chopra S, Ranjan N, et al. Temporal course of late rectal toxicity & impact of intervention in patients undergoing radiation for cervical cancer. *Indian J Med Res*. 2021;154(2):375-382. doi:10.4103/ijmr.IJMR_4787_20

19) Yamada T, Ishihara S, Kawai M, et al. Analysis of late adverse events and their chronological changes after radiation therapy for cervical cancer. *Nagoya J Med Sci*. 2018;80(4):487-496. doi:10.18999/nagjms.80.4.487

20) Viswanathan AN, Lee LJ, Eswara JR, et al. Complications of pelvic radiation in patients treated for gynecologic malignancies. *Cancer*. 2014;120(24):3870-3883. doi:10.1002/cncr.28849

21) Taverner D, Talbot IC, Carr-Locke DL, Wicks AC. Massive bleeding from the ileum: a late complication of pelvic radiotherapy. *Am J Gastroenterol*. 1982;77(1):29-31.

22) Vistad I, Kristensen GB, Fosså SD, Dahl AA, Mørkrid L. Intestinal malabsorption in long-term survivors of cervical cancer treated with radiotherapy. *Int J Radiat Oncol Biol Phys*. 2009;73(4):1141-1147. doi:10.1016/j.ijrobp.2008.05.064

23) Shrieve DC, Loeffler JS. *Human Radiation Injury*. Wolters Kluwer Health/Lippincott Williams & Wilkins; 2011:533.

24) Zhang L, Gong J, Ni L, et al. Influence of preoperative nutritional support on surgical outcomes of chronic radiation enteritis patients complicated with intestinal obstruction. *Zhonghua Wei Chang Wai Ke Za Zhi*. 2013;16(4):340-344.

25) Eifel PJ, Levenback C, Wharton JT, Oswald MJ. Time course and incidence of late complications in patients treated with radiation therapy for FIGO stage IB carcinoma of the uterine cervix. *Int J Radiat Oncol Biol Phys*. 1995;32(5):1289-1300. doi:10.1016/0360-3016(95)00118-I

26) Lanigan SW, Joannides T. Pulsed dye laser treatment of telangiectasia after radiotherapy for carcinoma of the breast. *Br J Dermatol*. 2003;148(1):77-79. doi:10.1046/j.1365-2133.2003.04861.x

27) Bansal N, Soni A, Kaur P, Chauhan AK, Kaushal V. Exploring the management of radiation Proctitis in current clinical practice. *J Clin Diagn Res*. 2016;10(6):XE01-XE06. doi:10.7860/JCDR/2016/17524.7906

28) Elad S, Cheng KKF, Lalla RV, et al. MASCC/ISOO clinical practice guidelines for the management of mucositis secondary to cancer therapy. *Cancer*. 2020;126(19):4423-4431. doi:10.1002/cncr.33100

29) Yeoh E, Tam W, Schoeman M, et al. Argon plasma coagulation therapy versus topical formalin for intractable rectal bleeding and anorectal dysfunction after radiation therapy for prostate carcinoma. *Int J Radiat Oncol Biol Phys*. 2013;87(5):954-959. doi:10.1016/j.ijrobp.2013.08.034

30) Talley NA, Chen F, King D, Jones M, Talley NJ. Short-chain fatty acids in the treatment of radiation proctitis: a randomized, double-blind, placebo-controlled, cross-over pilot trial. *Dis Colon Rectum*. 1997;40(9):1046-1050. doi:10.1007/BF02050927

31) Putta S, Andreyev HJN. Faecal incontinence: a late side-effect of pelvic radiotherapy. *Clinical Oncology*. 2005;17(6):469-477. doi:10.1016/j.clon.2005.02.008

32) Wortel RC, Incrocci L, Pos FJ, et al. Acute toxicity after image-guided intensity modulated radiation therapy compared to 3D conformal radiation therapy in prostate cancer patients. *Int J Radiat Oncol Biol Phys*. 2015;91(4):737-744. doi:10.1016/j.ijrobp.2014.12.017

33) Arbea L, Ramos LI, Martínez-Monge R, Moreno M, Aristu J. Intensity-modulated radiation therapy (IMRT) vs. 3D conformal radiotherapy (3DCRT) in locally advanced rectal cancer (LARC): dosimetric comparison and clinical implications. *Radiat Oncol*. 2010;5:17. doi:10.1186/1748-717X-5-17

34) Roeske JC, Lujan A, Rotmensch J, et al. Intensity-modulated whole pelvic radiation therapy in patients with gynecologic malignancies. *Int J Radiat Oncol Biol Phys*. 2000;48(5):1613-1621. doi:10.1016/s0360-3016(00)00771-9

35) Tsuchida K, Murakami N, Kato T, et al. Postoperative pelvic intensity-modulated radiation therapy reduced the incidence of late gastrointestinal complications for uterine cervical cancer patients. *J Radiat Res*. 2019;60(5):650-657. doi:10.1093/jrr/rrz041

36) Chopra S, Gupta S, Kannan S, et al. Late toxicity after adjuvant conventional radiation versus image-guided intensity-modulated radiotherapy for cervical cancer (PARCER): a randomized controlled trial. *J Clin Oncol*. 2021;39(33):3682-3692. doi:10.1200/JCO.20.02530

37) Tanderup K, Nesvacil N, Kirchheiner K, et al. Evidence-based dose planning aims and dose prescription in image-guided brachytherapy combined with radiochemotherapy in locally advanced Cervical cancer. *Semin Radiat Oncol*. 2020;30(4):311-327. doi:10.1016/j.semradonc.2020.05.008

38) Marzi S, Arcangeli G, Saracino B, et al. Relationships between rectal wall dose-volume constraints and radiobiologic indices of toxicity for patients with prostate cancer. *Int J Radiat Oncol Biol Phys*. 2007;68(1):41-49. doi:10.1016/j.ijrobp.2006.12.003

39) Zelefsky MJ, Levin EJ, Hunt M, et al. Incidence of late rectal and urinary toxicities after three-dimensional conformal radiotherapy and intensity-modulated radiotherapy for localized prostate cancer. *Int J Radiat Oncol Biol Phys*. 2008;70(4):1124-1129. doi:10.1016/j.ijrobp.2007.11.044

40) Al-Mamgani A, Heemsbergen WD, Peeters STH, Lebesque JV. Role of intensity-modulated radiotherapy in reducing toxicity in dose escalation for localized prostate cancer. *Int J Radiat Oncol Biol Phys*. 2009;73(3):685-691. doi:10.1016/j.ijrobp.2008.04.063

41) Rombouts AJM, Hugen N, van Beek JJP, et al. Does pelvic radiation increase rectal cancer incidence? - A systematic review and meta-analysis. *Cancer Treat Rev*. 2018;68:136-144. doi:10.1016/j.ctrv.2018.05.008

42) Viswanathan AN, Damato AL, Nguyen PL. Novel use of a hydrogel spacer permits reirradiation in otherwise incurable recurrent gynecologic cancers. *J Clin Oncol*. 2013;31(34):e446-7. doi:10.1200/JCO.2012.47.9931

43) Mazeron R, Fokdal LU, Kirchheiner K, et al. Dose-volume effect relationships for late rectal morbidity in patients treated with chemoradiation and MRI-guided adaptive brachytherapy for locally advanced cervical cancer: results from the prospective multicenter EMBRACE study. *Radiother Oncol*. 2016;120(3):412-419. doi:10.1016/j.radonc.2016.06.006

44) Perez CA, Breaux S, Bedwinek JM, et al. Radiation therapy alone in the treatment of carcinoma of the uterine cervix. *Cancer*. 1984;54(2):235-246. doi:10.1002/1097-0142(19840715)54:2<235::aid-cncr2820540210>3.0.co;2-h

45) Chorbińska J, Krajewski W, Zdrojowy R. Urological complications after radiation therapy-nothing ventured, nothing gained: a narrative review. *Transl Cancer Res*. 2021;10(2):1096-1118. doi:10.21037/tcr-20-2589

46) Nout RA, van de Poll-Franse LV, Lybeert MLM, et al. Long-term outcome and quality of life of patients with endometrial carcinoma treated with or without pelvic radiotherapy in the post operative radiation therapy in endometrial carcinoma 1 (PORTEC-1) trial. *J Clin Oncol*. 2011;29(13):1692-1700. doi:10.1200/JCO.2010.32.4590

47) Morris M, Eifel PJ, Lu J, et al. Pelvic radiation with concurrent chemotherapy compared with pelvic and para-aortic radiation for high-risk cervical cancer. *N Engl J Med*. 1999;340(15):1137-1143. doi:10.1056/NEJM199904153401501

48) Levenback C, Eifel PJ, Burke TW, Morris M, Gershenson DM. Hemorrhagic cystitis following radiotherapy for stage IB cancer of the cervix. *Gynecol Oncol*. 1994;55(2):206-210. doi:10.1006/gyno.1994.1278

49) Moore KN, Gold MA, McMeekin DS, Zorn KK. Vesicovaginal fistula formation in patients with stage IVA cervical carcinoma. *Gynecologic Oncology*. 2007;106(3):498-501. doi:10.1016/j.ygyno.2007.04.030

50) Sandhu SS, Goldstraw M, Woodhouse CRJ. The management of haemorrhagic cystitis with sodium pentosan polysulphate. *BJU Int*. 2004;94(6):845-847. doi:10.1111/j.1464-410X.2004.05044.x

51) Oscarsson N, Arnell P, Lodding P, Ricksten SE, Seeman-Lodding H. Hyperbaric oxygen treatment in radiation-induced cystitis and proctitis: a prospective cohort study on patient-perceived quality of recovery. *Int J Radiat Oncol Biol Phys*. 2013;87(4):670-675. doi:10.1016/j.ijrobp.2013.07.039

52) Zakariaee R, Hamarneh G, Brown CJ, et al. Association of bladder dose with late urinary side effects in cervical cancer high-dose-rate brachytherapy. *Brachytherapy*. 2017;16(6):1175-1183. doi:10.1016/j.brachy.2017.07.001

53) Marks LB, Carroll PR, Dugan TC, Anscher MS. The response of the urinary bladder, urethra, and ureter to radiation and chemotherapy. *Int J Radiat Oncol Biol Phys*. 1995;31(5):1257-1280. doi:10.1016/0360-3016(94)00431-J

54) Georg P, Pötter R, Georg D, et al. Dose effect relationship for late side effects of the rectum and urinary bladder in magnetic resonance image-guided adaptive cervix cancer brachytherapy. *Int J Radiat Oncol Biol Phys*. 2012;82(2):653-657. doi:10.1016/j.ijrobp.2010.12.029

55) Manea E, Escande A, Bockel S, et al. Risk of late urinary complications following image guided adaptive brachytherapy for locally advanced cervical cancer: refining bladder dose-volume parameters. *Int J Radiat Oncol Biol Phys*. 2018;101(2):411-420. doi:10.1016/j.ijrobp.2018.02.004

56) Flay LD, Matthews JH. The effects of radiotherapy and surgery on the sexual function of women treated for cervical cancer. *Int J Radiat Oncol Biol Phys*. 1995;31(2):399-404. doi:10.1016/0360-3016(94)E0139-B

57) Brand AH, Do V, Stenlake A. Can an educational intervention improve compliance with vaginal dilator use in patients treated with radiation for a gynecological malignancy. *Int J Gynecol Cancer*. 2012;22(5):897-904. doi:10.1097/IGC.0b013e31824d7243

58) Brand AH, Bull CA, Cakir B. Vaginal stenosis in patients treated with radiotherapy for carcinoma of the cervix. *Int J Gynecol Cancer*. 2006;16(1):288-293. doi:10.1111/j.1525-1438.2006.00348.x

59) Gondi V, Bentzen SM, Sklenar KL, et al. Severe late toxicities following concomitant chemoradiotherapy compared to radiotherapy alone in cervical cancer: an inter-era analysis. *Int J Radiat Oncol Biol Phys*. 2012;84(4):973-982. doi:10.1016/j.ijrobp.2012.01.064

60) Bruner DW, Lanciano R, Keegan M, et al. Vaginal stenosis and sexual function following intracavitary radiation for the treatment of cervical and endometrial carcinoma. *Int J Radiat Oncol Biol Phys*. 1993;27(4):825-830. doi:10.1016/0360-3016(93)90455-5

61) Mirabeau-Beale K, Hong TS, Niemierko A, et al. Clinical and treatment factors associated with vaginal stenosis after definitive chemoradiation for anal canal cancer. *Pract Radiat Oncol*. 2015;5(3):e113-e118. doi:10.1016/j.prro.2014.09.003

62) Dion MW, Hussey DH, Doornbos JF, et al. Preliminary results of a pilot study of pentoxifylline in the treatment of late radiation soft tissue necrosis. *Int J Radiat Oncol Biol Phys*. 1990;19(2):401-407. doi:10.1016/0360-3016(90)90549-y

63) Williams JA, Clarke D, Dennis WA, Dennis EJ, Smith ST. The treatment of pelvic soft tissue radiation necrosis with hyperbaric oxygen. *Am J Obstet Gynecol*. 1992;167(2):412-415. doi:10.1016/s0002-9378(11)91421-5

64) Denton AS, Maher EJ. Interventions for the physical aspects of sexual dysfunction in women following pelvic radiotherapy. *Cochrane Database Syst Rev*. 2003;2003(1):CD003750. doi:10.1002/14651858.CD003750

65) Kirchheiner K, Nout RA, Lindegaard JC, et al. Dose-effect relationship and risk factors for vaginal stenosis after definitive radio(chemo)therapy with image-guided brachytherapy for locally advanced cervical cancer in the EMBRACE study. *Radiother Oncol*. 2016;118(1):160-166. doi:10.1016/j.radonc.2015.12.025

66) Barcellini A, Dominoni M, Gardella B, Mangili G, Orlandi E. Gynecological radio-induced secondary malignancy after a gynecological primary tumor: a rare entity and a challenge for oncologists. *Int J Gynecol Cancer*. 2022;32(10):1321-1326. doi:10.1136/ijgc-2022-003686

67) Wallace WHB, Thomson AB, Saran F, Kelsey TW. Predicting age of ovarian failure after radiation to a field that includes the ovaries. *Int J Radiat Oncol Biol Phys*. 2005;62(3):738-744. doi:10.1016/j.ijrobp.2004.11.038

68) Rubin P, Casarett GW. *Clinical Radiation Pathology*. Saunders; 1968.

69) Wallace WHB, Thomson AB, Kelsey TW. The Radiosensitivity of the human oocyte. *Hum Reprod*. 2003;18(1):117-121. doi:10.1093/humrep/deg016

70) Bisharah M, Tulandi T. Laparoscopic preservation of ovarian function: an underused procedure. *Am J Obstet Gynecol*. 2003;188(2):367-370. doi:10.1067/mob.2003.38

71) Morice P, Castaigne D, Haie-Meder C, et al. Laparoscopic ovarian transposition for pelvic malignancies: indications and functional outcomes. *Fertil Steril*. 1998;70(5):956-960. doi:10.1016/s0015-0282(98)00284-2

72) Hawkins MM. Is there evidence of a therapy-related increase in germ cell mutation among childhood cancer survivors. *J Natl Cancer Inst*. 1991;83(22):1643-1650. doi:10.1093/jnci/83.22.1643

73) Viswanathan AN. Childhood cancer survivors: stillbirth and neonatal death. *Lancet*. 2010;376(9741):570-572. doi:10.1016/S0140-6736(10)61263-9

74) Pepek JM, Willett CG, Wu QJ, et al. Intensity-modulated radiation therapy for anal malignancies: a preliminary toxicity and disease outcomes analysis. *Int J Radiat Oncol Biol Phys*. 2010;78(5):1413-1419. doi:10.1016/j.ijrobp.2009.09.046

75) Porock D. Factors influencing the severity of radiation skin and oral mucosal reactions: development of a conceptual framework. *Eur J Cancer Care (Engl)*. 2002;11(1):33-43.

76) Agrawal RK, Alhasso A, Barrett-Lee PJ, et al. First results of the randomised UK FAST trial of radiotherapy hypofractionation for treatment of early breast cancer (CRUKE/04/015). *Radiother Oncol*. 2011;100(1):93-100. doi:10.1016/j.radonc.2011.06.026

77) Shore RE. Radiation-induced skin cancer in humans. *Med Pediatr Oncol*. 2001;36(5):549-554. doi:10.1002/mpo.1128

78) Perkins JL, Liu Y, Mitby PA, et al. Nonmelanoma skin cancer in survivors of childhood and adolescent cancer: a report from the childhood cancer survivor study. *J Clin Oncol*. 2005;23(16):3733-3741. doi:10.1200/JCO.2005.06.237

79) Gichangi P, Bwayo J, Estambale B, et al. HIV impact on acute morbidity and pelvic tumor control following radiotherapy for cervical cancer. *Gynecol Oncol*. 2006;100(2):405-411. doi:10.1016/j.ygyno.2005.10.006

80) Shrivastava SK, Engineer R, Rajadhyaksha S, Dinshaw KA. HIV infection and invasive cervical cancers, treatment with radiation therapy: toxicity and outcome. *Radiother Oncol*. 2005;74(1):31-35. doi:10.1016/j.radonc.2004.11.006

81) Housri N, Yarchoan R, Kaushal A. Radiotherapy for patients with the human immunodeficiency virus: are special precautions necessary. *Cancer*. 2010;116(2):273-283. doi:10.1002/cncr.24878

82) Moore DH, Thomas GM, Montana GS, et al. Preoperative chemoradiation for advanced vulvar cancer: a phase II study of the gynecologic oncology group. *Int J Radiat Oncol Biol Phys*. 1998;42(1):79-85. doi:10.1016/S0360-3016(98)00193-X

83) Keys HM, Roberts JA, Brunetto VL, et al. A phase III trial of surgery with or without adjunctive external pelvic radiation therapy in intermediate risk endometrial adenocarcinoma: a gynecologic oncology group study. *Gynecologic Oncol*. 2004;92(3):744-751. doi:10.1016/j.ygyno.2003.11.048

84) Mak RH, Halasz LM, Tanaka CK, et al. Outcomes after radiation therapy with concurrent weekly platinum-based chemotherapy or every-3-4-week 5-fluorouracil-containing regimens for squamous cell carcinoma of the vulva. *Gynecologic Oncol*. 2011;120(1):101-107. doi:10.1016/j.ygyno.2010.09.004

85) Beriwal S, Shukla G, Shinde A, et al. Preoperative intensity modulated radiation therapy and chemotherapy for locally advanced vulvar carcinoma: analysis of pattern of relapse. *Int J Radiat Oncol Biol Phys*. 2013;85(5):1269-1274. doi:10.1016/j.ijrobp.2012.11.012

86) Hopewell JW, Nyman J, Turesson I. Time factor for acute tissue reactions following fractionated irradiation: a balance between repopulation and enhanced radiosensitivity. *Int J Radiat Biol*. 2003;79(7):513-524. doi:10.1080/09553000310001600907

87) McQuestion M. Evidence-based skin care management in radiation therapy: clinical update. *Semin Oncol Nurs*. 2011;27(2):e1-17. doi:10.1016/j.soncn.2011.02.009

88) Gothard L, Cornes P, Brooker S, et al. Phase II study of vitamin E and pentoxifylline in patients with late side effects of pelvic radiotherapy. *Radiother Oncol*. 2005;75(3):334-341. doi:10.1016/j.radonc.2005.02.002

89) Hymes SR, Strom EA, Fife C. Radiation dermatitis: clinical presentation, pathophysiology, and treatment 2006. *J Am Acad Dermatol*. 2006;54(1):28-46. doi:10.1016/j.jaad.2005.08.054

90) Mitchell MJ, Logan PM. Radiation-induced changes in bone. *Radiographics*. 1998;18(5):1125-1136; . doi:10.1148/radiographics.18.5.9747611

91) Papadopoulou I, Stewart V, Barwick TD, et al. Post-radiation therapy imaging appearances in cervical carcinoma. *Radiographics*. 2016;36(2):538-553. doi:10.1148/rg.2016150117

92) Baxter NN, Habermann EB, Tepper JE, Durham SB, Virnig BA. Risk of pelvic fractures in older women following pelvic irradiation. *JAMA*. 2005;294(20):2587-2593. doi:10.1001/jama.294.20.2587

93) Robins CJ, Luten AG. Sociotropy and autonomy: differential patterns of clinical presentation in unipolar depression. *Journal of Abnormal Psychology*. 1991;100(1):74-77. doi:10.1037/0021-843X.100.1.74

94) Oh D, Huh SJ. Insufficiency fracture after radiation therapy. *Radiat Oncol J*. 2014;32(4):213-220. doi:10.3857/roj.2014.32.4.213

95) Delanian S, Chatel C, Porcher R, Depondt J, Lefaix JL. Complete restoration of refractory mandibular osteoradionecrosis by prolonged treatment with a pentoxifylline-tocopherol-clodronate combination (PENTOCLO): a phase II trial. *Int J Radiat Oncol Biol Phys*. 2011;80(3):832-839. doi:10.1016/j.ijrobp.2010.03.029

96) Delanian S, Lefaix JL. Current management for late normal tissue injury: radiation-induced fibrosis and necrosis. *Semin Radiat Oncol*. 2007;17(2):99-107. doi:10.1016/j.semradonc.2006.11.006

97) Michalecki L, Gabryś D, Kulik R, Wydmański J, Trela K. Radiotherapy induced hip joint avascular necrosis-two cases report. *Rep Pract Oncol Radiother*. 2011;16(5):198-201. doi:10.1016/j.rpor.2011.04.004

98) Schmeler KM, Jhingran A, Iyer RB, et al. Pelvic fractures after radiotherapy for cervical cancer: implications for survivors. *Cancer*. 2010;116(3):625-630. doi:10.1002/cncr.24811

99) Kim HJ, Boland PJ, Meredith DS, et al. Fractures of the sacrum after chemoradiation for rectal carcinoma: incidence, risk factors, and radiographic evaluation. *Int J Radiat Oncol Biol Phys*. 2012;84(3):694-699. doi:10.1016/j.ijrobp.2012.01.021

100) Iğdem S, Alço G, Ercan T, et al. Insufficiency fractures after pelvic radiotherapy in patients with prostate cancer. *Int J Radiat Oncol Biol Phys*. 2010;77(3):818-823. doi:10.1016/j.ijrobp.2009.05.059

101) Ikushima H, Osaki K, Furutani S, et al. Pelvic bone complications following radiation therapy of gynecologic malignancies: clinical evaluation of radiation-induced pelvic insufficiency fractures. *Gynecol Oncol*. 2006;103(3):1100-1104. doi:10.1016/j.ygyno.2006.06.038

102) Micha JP, Goldstein BH, Rettenmaier MA, et al. Pelvic radiation necrosis and osteomyelitis following chemoradiation for advanced stage vulvar and cervical carcinoma. *Gynecologic Oncol*. 2006;101(2):349-352. doi:10.1016/j.ygyno.2005.12.007

103) Peh WC, Khong PL, Yin Y, et al. Imaging of pelvic insufficiency fractures. *Radiographics*. 1996;16(2):335-348. doi:10.1148/radiographics.16.2.8966291

104) Henry AP, Lachmann E, Tunkel RS, Nagler W. Pelvic insufficiency fractures after irradiation: diagnosis, management, and rehabilitation. *Arch Phys Med Rehabil*. 1996;77(4):414-416. doi:10.1016/s0003-9993(96)90094-5

105) Razavian N, Laucis A, Sun Y, et al. Radiation-induced insufficiency fractures after pelvic irradiation for gynecologic malignancies: a systematic review. *Int J Radiat Oncol Biol Phys*. 2020;108(3):620-634. doi:10.1016/j.ijrobp.2020.05.013

106) Beşe NS, Ozgüroğlu M, Kamberoğlu K, Karahasanoglu T, Ober A. Pentoxifylline in the treatment of radiation-related pelvic insufficiency fractures of bone. *Radiat Med*. 2003;21(5):223-227.

107) Rose BS, Aydogan B, Liang Y, et al. Normal tissue complication probability modeling of acute hematologic toxicity in cervical cancer patients treated with chemoradiotherapy. *Int J Radiat Oncol Biol Phys*. 2011;79(3):800-807. doi:10.1016/j.ijrobp.2009.11.010

108) Mell LK, Kochanski JD, Roeske JC, et al. Dosimetric predictors of acute hematologic toxicity in cervical cancer patients treated with concurrent cisplatin and intensity-modulated pelvic radiotherapy. *Int J Radiat Oncol Biol Phys*. 2006;66(5):1356-1365. doi:10.1016/j.ijrobp.2006.03.018

109) Dalinka MK, Mazzeo VP. Complications of radiation therapy. *Crit Rev Diagn Imaging*. 1985;23(3):235-267.

110) Peters WA, Liu PY, Barrett RJ, et al. Concurrent chemotherapy and pelvic radiation therapy compared with pelvic radiation therapy alone as adjuvant therapy after radical surgery in high-risk early-stage cancer of the cervix. *JCO*. 2000;18(8):1606-1613. doi:10.1200/JCO.2000.18.8.1606

111) Klopp AH, Moughan J, Portelance L, et al. Hematologic toxicity in RTOG 0418: a phase 2 study of postoperative IMRT for gynecologic cancer. *Int J Radiat Oncol Biol Phys*. 2013;86(1):83-90. doi:10.1016/j.ijrobp.2013.01.017

112) Bourhafour I, Benoulaid M, El Kacemi H, et al. Lumbosacral plexopathy: a rare long term complication of concomitant chemo-radiation for cervical cancer. *Gynecol Oncol Res Pract*. 2015;2:12. doi:10.1186/s40661-015-0019-9

113) Bowen BC, Seidenwurm DJ, Neurologic I. Plexopathy. *AJNR Am J Neuroradiol*. 2008;29(2):400-402.

114) Delanian S, Lefaix JL, Pradat PF. Radiation-induced neuropathy in cancer survivors. *Radiother Oncol*. 2012;105(3):273-282. doi:10.1016/j.radonc.2012.10.012

115) Ashenhurst EM, Quartey GR, Starreveld A. Lumbo-sacral radiculopathy induced by radiation. *Can J Neurol Sci*. 1977;4(4):259-263. doi:10.1017/s0317167100025087

116) Georgiou A, Grigsby PW, Perez CA. Radiation induced lumbosacral plexopathy in gynecologic tumors: clinical findings and dosimetric analysis. *Int J Radiat Oncol Biol Phys*. 1993;26(3):479-482. doi:10.1016/0360-3016(93)90966-y

117) Krkoska P, Kazda T, Vlazna D, Adamova B. Case report: radiation-induced lumbosacral plexopathy - a very late complication of radiotherapy for cervical cancer. *BMC Neurol*. 2022;22(1):475. doi:10.1186/s12883-022-03013-5

118) Moskovic E, Curtis S, A'Hern RP, Harmer CL, Parsons C. The role of diagnostic CT scanning of the brachial plexus and axilla in the follow-up of patients with breast cancer. *Clin Oncol*. 1992;4(2):74-77. doi:10.1016/S0936-6555(05)80969-0

119) Taylor BV, Kimmel DW, Krecke KN, Cascino TL. Magnetic resonance imaging in cancer-related lumbosacral plexopathy. *Mayo Clin Proc*. 1997;72(9):823-829. doi:10.4065/72.9.823

120) Bykowski J, Aulino JM, Berger KL, et al. ACR appropriateness criteria((R)) plexopathy. *J Am Coll Radiol*. 2017;14(5):S225-S233. doi:10.1016/j.jacr.2017.02.002

121) Rubin DI. Brachial and lumbosacral plexopathies: a review. *Clin Neurophysiol Pract*. 2020;5:173-193. doi:10.1016/j.cnp.2020.07.005

122) Ehler E, Vyšata O, Včelák R, Pazdera L. Painful lumbosacral plexopathy: a case report. *Medicine (Baltimore)*. 2015;94(17):e766. doi:10.1097/MD.0000000000000766

123) Finnerup NB, Attal N, Haroutounian S, et al. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. *Lancet Neurol*. 2015;14(2):162-173. doi:10.1016/S1474-4422(14)70251-0

124) Moisset X, Bouhassira D, Avez Couturier J, et al. Pharmacological and non-pharmacological treatments for neuropathic pain: systematic review and French recommendations. *Rev Neurol (Paris)*. 2020;176(5):325-352. doi:10.1016/j.neurol.2020.01.361

125) Bernetti A, Agostini F, de Sire A, et al. Neuropathic pain and rehabilitation: a systematic review of international guidelines. *Diagnostics*. 11(1):74. doi:10.3390/diagnostics11010074

126) Jiang J, Li Y, Shen Q, et al. Effect of Pregabalin on radiotherapy-related neuropathic pain in patients with head and neck cancer: a randomized controlled trial. *J Clin Oncol*. 2019;37(2):135-143. doi:10.1200/JCO.18.00896

127) Klimek M, Kosobucki R, Luczyńska E, Bieda T, Urbański K. Radiotherapy-induced lumbosacral plexopathy in a patient with cervical cancer: a case report and literature review. *Contemp Oncol (Pozn)*. 2012;16(2):194-196. doi:10.5114/wo.2012.28805

128) Enevoldson TP, Scadding JW, Rustin GJ, Senanayake LF. Spontaneous resolution of a postirradiation lumbosacral plexopathy. *Neurology*. 1992;42(11):2224-2225. doi:10.1212/wnl.42.11.2224-a

129) 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. doi:10.1016/0360-3016(95)00060-C

A Novel Framework to Define and Prognosticate Visual Outcomes Following Fractionated Radiation Therapy for Optic Nerve Sheath Meningiomas

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Abstract

Objective: Optic nerve sheath meningiomas (ONSMs) are rare tumors that can cause significant visual problems due to their location along the optic nerve. Fractionated radiation therapy (RT) is the standard treatment, but data related to the discussion of visual outcomes are limited. No comprehensive guidelines exist to classify or define visual outcomes postoncological therapy. We propose the Wills Eye Visual Outcomes (WEVO) classification system to evaluate visual outcomes based on visual acuity, visual fields, and color vision status.

Methods: We retrospectively reviewed visual and radiographic outcomes for 29 ONSMs in 27 patients who were treated with fractionated stereotactic RT between 1997 and 2012.

Results: Median radiation dose of 52.2 Gy (range, 50.4-55.8). Median visual and radiographic follow-ups were 7 years (range, 1-22 y) and 6 years (range, 2-18 y), respectively. Ultimately, progression-free survival was 100% at the last follow-up. Using the WEVO criteria, visual outcomes were determined to be improved, unchanged, or worsened. At the last follow-up, 11 cases had improved vision, 10 cases had unchanged vision, and 8 cases had worsened vision. Patients aged > 46, those presenting with large visual field defects, and those with color vision defects were more likely to have worsened visual outcomes following RT. Poor visual acuity at treatment and an observation time of > 6 months from presenting with symptoms to RT did not significantly correlate with worsening visual outcomes.

Conclusion: We provide groundwork to predict individualized risk of blindness or worsened visual outcomes in the radiation of ONSMs.

Keywords: visual outcomes, radiation therapy, optic nerve sheath meningioma, skull base tumors

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Introduction

Optic nerve sheath meningiomas (ONSMs) are rare tumors located within the orbital canal, accounting for only 1% to 2% of all meningiomas. Despite their rarity, they are the second most common primary tumor found in the orbit, representing a third of all optic nerve tumors.[1] Typically, ONSMs cause a painless and gradual loss of vision, most commonly in middle-aged women. Although a classic triad of vision loss, optic nerve atrophy, and an optociliary shunt is often used to describe ONSM, in practice one or more of these features may be absent at presentation.[2,3] Radiographically, ONSMs can be differentiated from more common gliomas by the presence of calcifications and a "tram-track sign" on fat-suppressed T1 gadolinium-enhanced scans.[4] Due to their characteristic appearance on imaging and well-established clinical presentation, biopsies are generally not necessary for diagnosis or treatment and may even be harmful.[5,6] Intervention may indeed be a cat-and-mouse game with some meningiomas, but when it comes to the management of ONSMs, the most important consideration is unequivocally the preservation of vision.

With regard to the watch-and-wait strategy used in the management of OSNMs, the decision tree for when to proceed with intervention can be tricky. ONSMs are insidious as they can progress slowly and without symptoms. However, if left untreated, they can eventually lead to complete blindness in the affected eye due to compression of the optic nerve.[7] In some cases, patients may retain good vision and have minimal visual field (VF) loss even without prolonged nerve compression. Therefore, serial ophthalmological examinations are necessary to monitor for visual loss and optic nerve atrophy, and most ONSMs can be managed conservatively with a watch-and-wait strategy for a number of years.[2]

Intervention in the form of RT and/or surgery is typically reserved for cases of high-risk tumor progression or deterioration of eyesight.[8] Surgery is usually only considered for cases of morbid proptosis in patients who have experienced severe visual loss as it carries a high risk of compromising the blood supply to the optic nerve and causing iatrogenic visual loss.[1,9,10] Currently, fractionated stereotactic RT (FSRT) is considered the standard of care for ONSMs.

Many studies evaluating FSRT for ONSMs have a relatively short follow-up, and few report outcomes using complete ophthalmological examinations.[11] Therefore, we strongly believe that a comprehensive assessment of visual acuity (VA), VF, and color vision (CV) is necessary to obtain a pertinent picture of the patient's visual status leading up to treatment and in the years following treatment. Currently, no guidelines use comprehensive visual examination outcomes to define a composite visual outcome after definitive treatment of ONSM. Hence, we propose a new standard to categorize visual outcomes after FSRT as improved, worsened, or unchanged. In our cohort, we evaluate factors such as patient age, time to intervention, VF, CV, VA, and radiation specifications to assess visual outcomes. We hope that our framework will contribute to decision-making and serve as a foundation for further meta-analyses and larger cohorts to redefine their visual outcomes and predict outcomes for their patients. The results will provide physicians and patients with information to guide decision-making and manage expectations for visual outcomes following treatment with FSRT.

Materials and Methods

Patient Selection

This retrospective study underwent approval by the institutional review boards of both Thomas Jefferson University and Wills Eye Hospital. The study focused on reviewing radiation records from patients treated for ONSMs between 1997 and 2012, ensuring long-term follow-up. To be considered for analysis, patients had to have been treated with FSRT, with comprehensive follow-up, including both MRI and ophthalmological assessments before and after treatment. Patients who initially presented with blindness or whose meningiomas showed evidence of extra-orbital origin were excluded. A total of 29 primary ONSM cases from 27 patients met the inclusion criteria. One patient received a second course of RT 3.5 years after initial treatment for tumor control, and another patient had bilateral ONSMs (clinically suspected neurofibromatosis) treated simultaneously. An overall summary of each patient is provided in **Supplementary Table 1** (available in the online version of this article at www.appliedradiationoncology.com).

Data Recording

To gather relevant information for the study, patient charts were reviewed in paper and electronic formats. The information collected included demographic, medical, radiographic, and ophthalmologic data such as VF, VA, CV, and proptosis. Radiation therapy information such as dose, fractionation schedule, maximum dose to structure and optic

nerve, and maximum dose to prescription dose ratio (MDPD) was also recorded. Visual acuity was measured using Snellen notation, color recognition was documented by the number of Ishihara plates identified, and visual defects were determined by the ophthalmologist's interpretation of automated VFs using the Humphrey Visual Fields analyzer and Matrix 24-2 program from Zeiss. **Supplementary Table 2** (available in the online version of this article at www.appliedradiation oncology.com), contains details on radiographic and visual follow-up. Any information related to potential confounding factors that could affect visual function, such as cataracts, diabetes, macular degeneration, or glaucoma, was also noted. The RT information collected included tumor volume, maximum dose, mean dose, total dose, number of fractions, treatment frequency (daily or twice daily), and dates of treatment. Additionally, MDPD was calculated as a measure of dose homogeneity and documented in **Supplementary Table 3** (available in the online version of this article at www.appliedradiation oncology.com).

Radiation Treatment Details

Prior to 2004, the X-Knife 3-D planning system (Radionics) was utilized for treatment planning, and a dedicated stereotactic 600SR linear accelerator (Varian) was employed for radiation treatment delivery. Between 2004 and 2013, iPlan (Brainlab) was used for treatment planning, and TrueBeam STx (Varian) equipped with high-definition multileaf collimators and ExacTrac (Brainlab) for onboard imaging was used for treatment delivery. All patients receiving irradiation were immobilized using custom-made Brainlab thermoplastic masks.

For all patients, treatment planning MRI (thin cut [1-1.5 mm] axial fat-suppressed postcontrast MRI) and CT images were obtained and fused. The gadolinium-enhanced T1-weighted series was used to define the gross tumor volume (GTV) on MRI. The planning target volume (PTV) was defined as the GTV with a minimum margin of 0-2 mm, as determined by the treating physician. Critical normal structures, such as the optic nerves, chiasm, and brainstem, were contoured as organs at risk.

Intensity-modulated radiation therapy (IMRT) or hybrid arcs (a combination of dynamic arcs with static IMRT beams) were employed as the radiation planning modality prior to 2004. **Supplementary Table 1** (available in the online version of this article at www.appliedradiation oncology.com), under "Treatment Summary" provides dose and fractionation details, while full radiation details are available in **Supplementary Table 3** (available in the online version of this article at www.appliedradiation oncology.com).

Defining Visual Status and Outcomes

According to the World Health Organization's (WHO's) "Levels of Visual Impairment" guidelines, visual impairment (based on VA only) is categorized as follows using Snellen notation: 20/20 to 20/30 = minimal to no impairment, 20/40 to 20/70 = mild, 20/80 to 20/160 = moderate, 20/200 to light perception = severe, and no light perception = blindness.[12] Visual field defects were categorized as small if they encompassed < 50% of the VF or large if > 50%. Color vision was classified as deficient or full, depending on the presence or absence of a deficit in any of the Ishihara color plates. The VA, VF, and CV of the uninvolved eyes were also evaluated.

As no established criteria are available in the literature to combine VA, VF, and CV into a comprehensive endpoint, we propose a new system to classify "visual outcome" as either worsened, unchanged, or improved. The Wills Eye Visual Outcomes (WEVO) classification system (shown in **Figure 1**) is based on the following criteria:

A. Worsened vision if 1 or more of the following are met:
    1. VA deteriorates by >1 WHO "Level of Visual Impairment."
    2. VF deteriorates from small to large defects.
    3. Deficient in color plate interpretations.

B. Unchanged vision if *all 3* of the following are met:
    1. VA remains within 1 WHO level of visual impairment.
    2. No change in VF, or only develops a small defect.
    3. No change in the number of color plate interpretations.

C. Improved vision if any of the following are met:
    1. VA improvement by 1 or more WHO levels of visual impairment with no change in VF or CV.
    2. Improvement of VA with improvement of VF and CV.
    3. Stable VA within 1 WHO level, but with improvement of either or both VF and CV.

Within our cohort, each case was subsequently classified as

Figure 1. Wills Eye Visual Outcomes (WEVO) classification system. We introduce the WEVO classification system, designed to evaluate the impact of therapy on optic nerve tumors, specifically focusing on visual acuity (VA), visual field (VF), and color vision (CV). The reference criteria for VA, VF, and CV are provided on the right side of the figure. To assess visual outcomes, users can systematically navigate through each column, following the categories from left to right. This framework allows for a comprehensive evaluation of whether visual outcomes have improved, remained unchanged, or worsened after therapy.

<table>
<tr><th colspan="4">Wills Eye Visual Outcomes (WEVO) Classification System</th><th rowspan="2">Reference Criteria:</th></tr>
<tr><th>VA</th><th>VF</th><th>CV</th><th>Outcome</th></tr>
<tr><td rowspan="3">↓ by > 1 WHO LOVI</td><td rowspan="2">Deteriorates from small/no defect to large defect</td><td>↓ in # of color plates</td><td rowspan="4">Worsened</td><td rowspan="5">Visual Acuity (VA) Criteria:
WHO “Levels of Visual Impairment” (LOVI):
1. Minimal to none (20/20 to 20/30)
2. Mild (20/40-20/70) to moderate (20/70-20/100)
3. Severe (20/200 to 20/400)
4. Profound (20/500 to counting fingers only)
5. Blindness (no light perception)

Visual Field (VF) Criteria:
• No VF deficit: Full Humphrey test field intact
• Small VF deficit: < 50% defect in field
• Large VF deficit: >/= 50% defect in field

Color Vision (CV) Criteria:
• Full: all Ishihara plates
• Deficient: at least 1 Ishihara plate incorrectly identified</td></tr>
<tr><td>↑ or no change in # of color plates</td></tr>
<tr><td rowspan="2">Unchanged Visual Field</td><td>↓ in # of color plates</td></tr>
<tr><td rowspan="2">Unchanged or improvement in in WHO LOVI</td><td>↑ or no change in # of color plates</td></tr>
<tr><td>Within 1 level of WHO LOVI</td><td>No change OR from none to small VF defect</td><td>No change in # of color plates</td><td>Unchanged</td></tr>
<tr><td>↑ by 1 or more WHO LOVI</td><td>No change OR from none to small VF defect</td><td>↑ or no change in # of color plates</td><td rowspan="3">Improved</td></tr>
<tr><td rowspan="2">Unchanged WHO LOVI</td><td rowspan="2">Improved Visual Field</td><td rowspan="2">↑ in # of color plates</td></tr>
<tr><td>No change OR from none to small VF defect</td></tr>
</table>

worsened, improved, or unchanged as seen in **Table 1** with individual explanations.

Statistics

Statistical analyses were conducted using GraphPad Prism version 5. Chi-squared tests were utilized to compare the outcomes between the worsened and improved/unchanged categories. For continuous variables such as maximum dose to the tumor or optic nerve, lesion size, and MDPD, a *t*-test was employed to evaluate whether these variables significantly influenced visual outcomes, as defined by a *P* value of < 0.05.

Results

Patient Demographics and Presentation

Table 2 summarizes the demographics of our cohort. The median age of patients at the time of initial treatment was 46 years (range, 33-73). Of the 27 patients, 23 (85%) were women and 4 (15%) were men. Two patients underwent surgery prior to radiation treatment to the tumor bed, and an additional patient underwent a biopsy to confirm ONSM prior to RT. The chief complaint of mild/moderate vision loss was present in 25 of 29 cases (86%). One case of ONSM was visually asymptomatic at presentation and was incidentally discovered during imaging. Eye pain was reported in 4 cases (14%), proptosis in 7 (24%), diplopia in 11 (38%), flashes/scintillation in 3 (10%), and severe subjective visual loss in 8 patients (28%) at presentation.

Radiation Treatment

Most patients were treated with conformal dynamic arcs. The median total radiation dose was

Table 1. Summary of Visual Outcomes

CASE	OVERALL STATUS	RATIONALE	CASE	OVERALL STATUS	RATIONALE
1	=	Unchanged VA; unchanged VF; unchanged CV	14	+	Improved VA; unchanged VF; unchanged CV
2a	+	Unchanged VA; improved VF; unchanged CV	15	+	Improved VA; unchanged VF; unchanged CV
2b	=	Unchanged VA; unchanged VF; unchanged CV	16	–	Worsened VA; mildly improved VF defect; unchanged CV
3	=	Insignificant change in VA; unchanged VF; unchanged CV	17	–	Worsened VA; unchanged VF; unchanged CV
4	=	Unchanged VA; unchanged VF; unchanged CV	18	+	Improved VA; unchanged VF; unchanged CV
5	=	Insignificant change in VA; unchanged VF; unchanged CV	19	+	Improved VA; unchanged VF; improved CV
6a	=	Unchanged VA; unchanged VF; unchanged CV	20	+	Improved VA; unchanged VF; unchanged CV
6b	=	Unchanged VA; unchanged VF; unchanged CV	21	+	Improved VA; improved VF; improved CV
7	–	Worsened VA; worsened VF; unchanged CV	22	–	Worsened VA; unchanged VF; unchanged CV/unable to assess
8	+	Unchanged VA; improved VF; improved CV	23	+	Unchanged VA; improved VF; unchanged CV
9	=	Unchanged VA; unchanged VF; unchanged CV	24	–	Unchanged VA; worsened VF; unchanged CV/inability to assess
10	+	Improved VA; unchanged VF; unchanged CV	25	=	Unchanged VA; unchanged VF; unchanged CV/unable to assess
11	=	Insignificant change in VA; unchanged VF; unchanged CV	26	–	Worsened VA; unchanged VF; unchanged CV/unable to assess
12	+	Improved VA; unchanged VF; unchanged CV	27	–	Worsened VA; worsened VF; unchanged CV/unable to assess
13	–	Worsened VA; worsened VF; worsened CV			

Rationales for improved, unchanged, or worsened vision are given in detail. For more information on the levels of improvement and description of exam findings, see ***Supplementary Table 2*** *(available in the online version of this article at www.appliedradiationoncology.com).*

Abbreviations: CV, color vision; VA, visual acuity; VF, visual field.

52.2 Gy (range, 41.4-55.8) in 23-30 fractions, and the median maximum dose to the PTV was 61.8 Gy (range, 52.44-79.3). The median PTV size was 1.54 cc (range, 0.31-7.36 cc) and the MDPD was 1.18 (range, 1.04-1.48). While a high dose to the involved optic nerve was largely unavoidable given the nature of treating ONSMs, the optic chiasm dose was kept within an acceptable range with a goal of D_{max} > 54 but an absolute limit of 60 Gy (median, 39.8 Gy, range, 2.39-58.5 Gy).

Treatment and Overall Radiographic and Vision Outcomes

Radiation therapy was administered empirically in most cases, as ONSM was primarily diagnosed radiographically. Of the treated patients, 1 had a marginal recurrence and required re-treatment with radiation. The median duration of visual follow-up was 81 months (range, 17-240 mo). Of the 27 patients, 14 were initially observed prior to treatment, with a median observation period of 5 months (range, 0-180 mo) between diagnosis and treatment. The median MRI follow-up period was 77.2 months (range, 10-161 mo). **Supplementary Table 1** (available in

Table 2. Patient Demographics

Patients (*n*)	27
Male (%)	4 (15%)
Female (%)	23 (85%)
Laterality	
Left	9 (with 2 separate courses)
Right	16
Bilateral	1 (each side treated once)
Age (y) at treatment: median (range)	46 (33-73)
Total RT courses	29
Surgery then RT	1
Biopsy then RT	1
Single course of RT	25 patients (25 cases)
Two separate courses of RT (same orbit)	1 patient (2 cases)
Two separate courses of RT (bilateral)	1 patient (2 cases)
Radiographic follow-up (mo) by MRI: median (range)	77.2 (10-161)
Ophthalmological follow-up (mo) by MRI: median (range)	81 (17-240)

This information is a representative breakdown of the 27 patients and 29 cases of ONSM followed in this study, as well as the length of radiographic and visual follow-up.

Abbreviations: ONSM, optic nerve sheath meningioma; RT, radiation therapy.

the online version of this article at www.appliedradiationoncology.com), provides a comprehensive overview of each patient's demographics, treatment particulars, follow-up details, and visual outcomes.

Radiographic control was achieved in 28/29 (96.6%) cases with 1 course of radiation and ultimately, all patients showed complete tumor control following RT, as assessed by MRI. There were no in-field ONSM recurrences. All patients were classified using WEVO criteria, and of the 29 optic nerves treated with FSRT, 11 (39%) showed visual improvement, 10 (34%) remained unchanged, and 8 (27%) experienced worsened vision.

Predictors of Visual Outcome

Time to treatment (TTT), CV, VFs, VA, and age at treatment were all assessed as potential predictors of visual outcomes following radiation treatment. **Figure 2** shows the outcomes following radiation broken down into subgroups and queried for significance using chi-square analysis.

Time to Treatment

Those with a TTT of < 6 months from initial presentation showed worsened visual outcomes in 2 of 13 cases compared with 5 of 9 cases whose TTT was 6 months or greater (P = .1593).

Color Vision

For patients who had CV defects, 6 out of 15 had worsened visual outcomes compared with 1 out of 14 that showed worsening with full CV at presentation (P = .039).

Visual Field

Of the 19 patients who presented with no defect or a small VF defect, none experienced worsened visual outcomes, while 7 of the 10 (70%) cases initially presenting with large visual defects experienced worsened visual outcomes (P < .001).

Visual Acuity

Of the 20 patients whose VA at the onset of treatment was normal to moderate, 4 (20%) experienced worsening of their VA. Among the 9 people who initially presented with severely decreased VA, 3 (33%) experienced a further decline in their vision (P = .4376). However, all other patients showed either stable or improved visual outcomes. Among the 10 cases of ONSMs with no visual change, 90% had minimal to no visual impairment prior to treatment.

Age

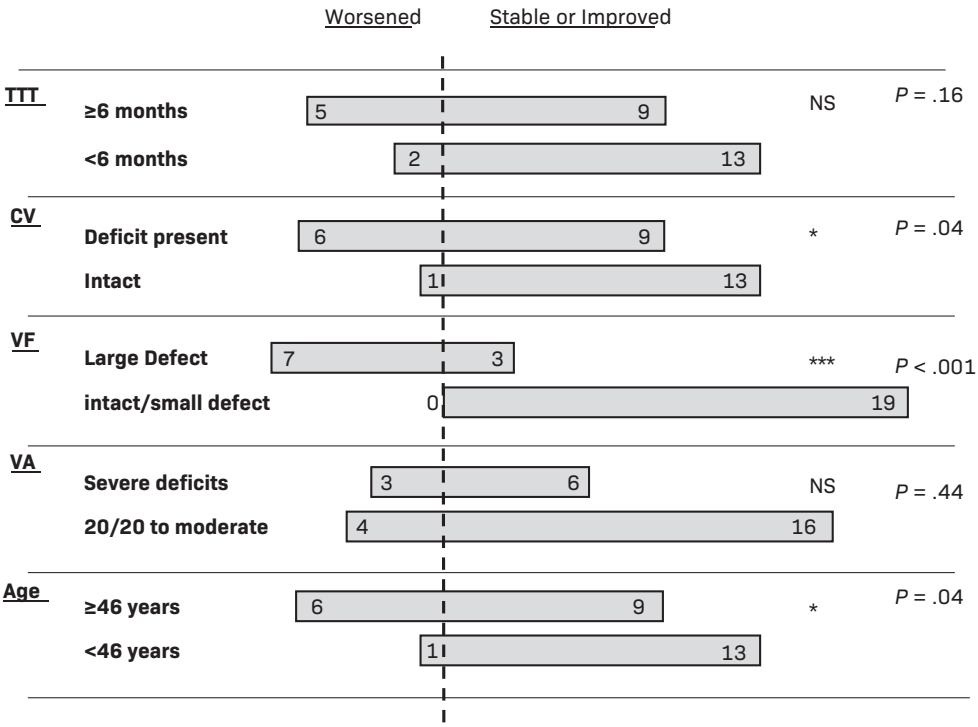
Optic nerve sheath meningiomas in patients > 45 years old had higher rates of vision deterioration compared with younger patients (41% vs 8%). Also, 1 out of 14 patients treated at age < 46 years worsened in terms of overall vision status compared with 6 out of 15 patients treated at age ≥ 46 years who worsened (P = .039).

No significant association was noted between total radiation dose (P = .6236), dose homogeneity (MDPD, P = .39322), PTV D_{max} (P = .6573), uninvolved ipsilateral optic nerve D_{max} (P = .4218), PTV size (P = .0631), or symptom duration prior to treatment (P = .5758), with ultimate visual outcome following RT (**Supplementary Table 4** available in the online version of this article at www.appliedradiationoncology.com).

Discussion

There are currently no established consensus guidelines for the management of ONSMs specifically, although the National Comprehensive Cancer Network

Figure 2. Assessment of time to treatment (TTT), color vision (CV), visual field (VF), visual acuity (VA), and age (in years) as pretreatment predictors of visual outcome. TTT was dichotomized into those who received radiation therapy (RT) ≥ 6 mo after diagnosis vs those who proceeded to treatment within 6 mo of diagnosis. CV was defined as deficient if any Ishihara plate was misread in the pretreatment ophthalmological exam. Intact denotes that all plates were read correctly. For VF, large defect denotes any field cut > 50%. A small defect was < 50%/VA was defined as severe deficits if vision was noted to be 20/200 or worse.



(NCCN) provides recommendations for the treatment of meningiomas in general and stresses the importance of early intervention to preserve visual function in cases involving the optic nerve.[13] In most cases, observation is the preferred approach for asymptomatic or minimally symptomatic patients, while RT is reserved for those with impending vision loss or in cases of progressive or advanced diseases.[14] Since ONSM progression can be unpredictable, it is crucial to ensure that any intervention prioritizes the maintenance or improvement of vision.[15]

Before the development of our proposed system, there was no standardization of visual outcomes following treatment for optic nerve tumors. To address this gap, we have created the WEVO classification system, which we applied to our cohort of 29 closely monitored ONSM cases. Our analyses also aimed to identify any factors within our cohort that may predict a worsened outcome and provide guidance to help maintain or improve vision.

Our patient cohort is consistent with those of other limited series and is highly representative of the ONSM population, thereby increasing the generalizability of our results and making them suitable for future meta-analyses. In their largest known retrospective cohort study of visual outcomes for ONSMs, Dutton conducted a review of nearly 500 cases and characterized ONSMs.[1] The patients in the study were mostly middle-aged women (with a mean age of 47 y) and 5% had bilateral tumors. Additionally, 25% of patients had a VA of counting fingers or worse, while 45% had a VA of 20/40 or better.[1] In our cohort, the median age was 47 years and the mean age was 48.9 years. Of the 29 patients, 83% werewomen, 1 had bilateral disease (3.7%), 24% presented with severe visual deficits, and 45% presented with a VA of 20/40 or better.

Our series of 29 cases had well-documented, comprehensive long-term radiographic and ophthalmologic follow-up, with a median follow-up of 81 months and a mean of 93 months (range, 17-240 mo). To the best of our knowledge, this study has the longest median and most comprehensive visual and radiographic follow-up of primary ONSMs following FSRT in the medical literature. Vanikieti et al reported a cohort of 34 patients

with ONSM with an impressive visual examination range of follow-up of 6 to 251 months; however, only VF and VA were reported and the overall visual function was defined as strictly related to VF and VA. They did not have full radiographic follow-up for their entire cohort.[16] Most studies had similarly small samples (10-45 patients), with shorter follow-up times ranging from a median of 54 weeks to 5 years.[8,17-19] Two studies, Smee et al and Metellus et al, had median follow-ups of 86 months and 90 months, respectively, but had only 15 and 9 patients.[20,21] Paulsen et al followed 109 patients after FSRT; however, long-term ophthalmologic and radiographic outcomes were available for only 38% and 33% of all patients, respectively, and 67% were "secondary" ONSMs.[22] Turbin et al had a mean follow-up of 150.2 months with a range of 51-516 months (SD, 74.7 mo) and followed 64 patients, only 16 of whom had radiation alone and another 16 of whom had RT plus surgery.[5] It is important to note that most studies only reported VA as the measure of visual outcome. With our study's long-term median follow-up of more than 7 years and complete visual outcomes, we were uniquely able to work with ocular oncology at the Wills Eye Institute to develop the WEVO criteria to define visual outcomes for each case.

Multiple studies have attempted to identify predictive factors for outcomes of RT to best stratify patients. Kennerdell et al reported worsened visual outcomes in those with a VA of 20/40 or below or with a constricting VF, although in this study, VA alone was reported in only 9 patients.[10] Similarly, Saeed et al reported worsened visual outcomes in patients with pretreatment VA below 20/50.[23,24] Neither study considered integrated VA, VF, and CV to determine whether visual outcomes improved, remained stable, or worsened, nor did they individually assess pretreatment VF or CV as predictors for visual outcome. Our findings suggested that VF and CV defects, rather than VA, were more predictive of worsened visual outcomes using the WEVO criteria. Our study also noted that patients below age 46 were more likely to have improved or unchanged vision compared with patients at or older than 46 years. Perhaps related to younger patients having better outcomes, Wright et al reported a more active primary ONSM in patients < 40 years old and recommended more active treatment, such as surgery, assuming more active meningothelial cells.[25] Paulsen et al found that a radiation dose of 54 Gy vs < 54 Gy was predictive of radiographic control. They also determined that sex, histology (biopsy taken vs not taken), early RT vs treatment at progression, and tumor size < 5 cm^3 vs > 5 cm^3 were not predictive of VA, ocular motility, VF, or tumor control following RT.[22] Similarly, our study did not find a significant impact from tumor size or time of radiation with respect to visual outcome. Unique to our study is the significance of pretreatment for older age, VF, and CV defects rather than VA or TTT in regard to poor visual outcomes. More recently, in a cohort of 43 patients treated between 2015 and 2021, who underwent external beam radiation therapy (EBRT) for ONSMs, Tang et al observed that patients with severe vision loss at diagnosis or a duration of vision loss exceeding 12 months had a lower likelihood of vision recovery after treatment.[26] This was similar to our findings; however, using our WEVO criteria, we did note that the 6-month duration of vision loss was sufficient to predict worsening visual outcomes after treatment.

Several limitations to our study should be considered. Most importantly, our study was retrospective in design and limited to a single institution. Selection bias may play an important role in the outcomes as there is an urgency to treat patients who present with severe visual loss vs those with mild loss. The overall sample size is relatively limited due to the rarity of the disease (2%-3% of all meningiomas), although our study is similar in size to many published series. Another important limitation is that several radiation treatment parameters were not readily available from paper chart extraction (eg, MDPD was available for 26 cases only). Nevertheless, we felt that all patients who had total dose and fractionation as well as a clearly documented TTT from diagnosis were appropriate to include in our study. Strengths of our study include length of follow-up, inclusion of only primary ONSMs, as well as comprehensive ophthalmologic and radiographic evaluation.

Conclusions

Visual outcomes are of great importance to consider in the treatment strategy and patient discussion surrounding ONSMs. This study, along with others, adds to the literature supporting the efficacy and durability of FSRT for ONSMs with respect to local control and visual preservation.[17,22,27] We propose a classification that defines a comprehensive visual outcome endpoint based on the WEVO criteria as improved, worsened, or unchanged. Using these criteria, we found that age at treatment, CV defect, and large VF defect were associated with poor visual outcomes. However, we did not observe any correlation between

VA, radiation dose statistics (total dose, maximum dose to the optic nerve and the tumor, and MDPD), lesion size, and the ultimate visual outcomes. In the future, we recommend using the WEVO classification to further contribute to studies that can predict visual outcomes and lead to decisions that preserve vision for patients with ONSM.

References

1) Dutton JJ. Optic nerve sheath meningiomas. *Surv Ophthalmol*. 1992;37(3):167-183. doi:10.1016/0039-6257(92)90135-g

2) Spencer WH. Primary neoplasms of the optic nerve and its sheaths: clinical features and current concepts of pathogenetic mechanisms. *Trans Am Ophthalmol Soc*. 1972;70:490-528.

3) Carrasco JR, Penne RB. Optic nerve sheath meningiomas and advanced treatment options. *Curr Opin Ophthalmol*. 2004;15(5):406-410. doi:10.1097/01.icu.0000138617.53435.d9

4) Fineman MS, Augsburger JJ. A new approach to an old problem. *Surv Ophthalmol*. 1999;43(6):519-524. doi:10.1016/s0039-6257(99)00038-7

5) Turbin RE, Thompson CR, Kennerdell JS, Cockerham KP, Kupersmith MJ. A long-term visual outcome comparison in patients with optic nerve sheath meningioma managed with observation, surgery, radiotherapy, or surgery and radiotherapy. *Ophthalmology*. 2002;109(5):890-899. doi:10.1016/S0161-6420(02)01017-5

6) Turbin RE, Pokorny K. Diagnosis and treatment of orbital optic nerve sheath meningioma. *Cancer Control*. 2004;11(5):334-341. doi:10.1177/107327480401100508

7) Egan RA, Lessell S. A contribution to the natural history of optic nerve sheath meningiomas. *Arch Ophthalmol*. 2002;120(11):1505-1508. doi:10.1001/archopht.120.11.1505

8) Pitz S, Becker G, Schiefer U, et al. Stereotactic fractionated irradiation of optic nerve sheath meningioma: a new treatment alternative. *Br J Ophthalmol*. 2002;86(11):1265-1268. doi:10.1136/BJO.86.11.1265

9) Miller NR. New concepts in the diagnosis and management of optic nerve sheath meningioma. *J Neuroophthalmol*. 2006;26(3):200-208. doi:10.1097/01.wno.0000235569.19131.ac

10) Kennerdell JS, Maroon JC, Malton M, Warren FA. The management of optic nerve sheath meningiomas. *Am J Ophthalmol*. 1988;106(4):450-457. doi:10.1016/0002-9394(88)90882-3

11) Shapey J, Sabin HI, Danesh-Meyer HV, Kaye AH. Diagnosis and management of optic nerve sheath meningiomas. *J Clin Neurosci*. 2013;20(8):1045-1056. doi:10.1016/j.jocn.2013.03.008

12) Colenbrander A. *Visual standards, aspects and ranges of vision loss with emphasis on population surveys*. International Council of Ophthalmology (ICO); 2002.

13) Nath SK, Trifiletti DM, Zaorsky NG, Rusthoven CG. Central nervous system cancers. *Absol Clin Radiat Oncol Rev*. 2019:83-131. doi:10.1007/978-3-319-96809-4

14) Falardeau J. Current Diagnosis and Management of Optic Nerve Sheath Meningioma - American Academy of Ophthalmology. American Academy of Opthalmology; 2007. Accessed January 4, 2019. https://www.aao.org/current-insight/current-diagnosis-management-of-optic-nerve-sheath.

15) Egan RA, Lessell S. A contribution to the natural history of optic nerve sheath meningiomas. *Arch Ophthalmol*. 2002;120(11):1505-1508. doi:10.1001/archopht.120.11.1505

16) Vanikieti K, Chaiwithooanukul C, Puataweepong P, Jindahra P, Padungkiatsagul T. Long-term visual function after fractionated stereotactic radiotherapy for primary optic nerve sheath meningioma: a retrospective analysis of 34 subjects. *Clin Ophthalmol*. 2022;16:3119-3128. doi:10.2147/OPTH.S383702

17) Andrews DW, Faroozan R, Yang BP, et al. Fractionated stereotactic radiotherapy for the treatment of optic nerve sheath meningiomas: preliminary observations of 33 optic nerves in 30 patients with historical comparison to observation with or without prior surgery. *Neurosurgery*. 2002;51(4):890-902. doi:10.1097/00006123-200210000-00007

18) Narayan S, Cornblath WT, Sandler HM, Elner V, Hayman JA. Preliminary visual outcomes after three-dimensional Conformal radiation therapy for optic nerve sheath meningioma. *Int J Radiat Oncol Biol Phys*. 2003;56(2):537-543. doi:10.1016/s0360-3016(03)00005-1

19) Becker G, Jeremic B, Pitz S, et al. Stereotactic fractionated radiotherapy in patients with optic nerve sheath meningioma. *Int J Radiat Oncol Biol Phys*. 2002;54(5):1422-1429. doi:10.1016/s0360-3016(02)03753-7

20) Smee RI, Schneider M, Williams JR. Optic nerve sheath meningiomas—non-surgical treatment. *Clin Oncol (R Coll Radiol)*. 2009;21(1):8-13. doi:10.1016/j.clon.2008.10.010

21) Metellus P, Kapoor S, Kharkar S, et al. Fractionated Conformal radiotherapy for management of optic nerve sheath Meningiomas: long-term outcomes of tumor control and visual function at a single institution. *Int J Radiat Oncol Biol Phys*. 2011;80(1):185-192. doi:10.1016/j.ijrobp.2010.01.034

22) Paulsen F, Doerr S, Wilhelm H, et al. Fractionated stereotactic radiotherapy in patients with optic nerve sheath meningioma. *Int J Radiat Oncol Biol Phys*. 2012;82(2):773-778. doi:10.1016/j.ijrobp.2010.11.018

23) Kim JW, Rizzo JF, Lessell S. Controversies in the management of optic nerve sheath meningiomas. *Int Ophthalmol Clin*. 2005;45(4):15-23. doi:10.1097/01.iio.0000176367.16758.f4

24) Saeed P, Rootman J, Nugent RA, White VA, Mackenzie IR, Koornneef L. Optic nerve sheath meningiomas. *Ophthalmology*. 2003;110(10):2019-2030. doi:10.1016/S0161-6420(03)00787-5

25) Wright JE, McNab AA, McDonald WI. Primary optic nerve sheath meningioma. *Br J Ophthalmol*. 1989;73(12):960-966. doi:10.1136/bjo.73.12.960

26) Tang T, Wang J, Lin T, Zhai Z, Song X. The treatment efficacy of radiotherapy for optic nerve sheath meningioma. *Eye (Lond)*. 2023. doi:10.1038/s41433-023-02640-7

27) Hamilton S, Nichol A, Hsu F, et al. Visual outcomes and local control after fractionated stereotactic radiation therapy for optic nerve sheath meningioma. *Int J Radiat Oncol Biol Phys*. 2015;93(3):E63-E64. doi:10.1016/j.ijrobp.2015.07.705

RESEARCH

A Practical Method to Prolong Expiratory Breath Holds for Abdominal Stereotactic Body Radiation Therapy

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Abstract

Objective: Motion management is crucial to safe and efficacious abdominal stereotactic body radiation therapy (SBRT). Expiratory breath hold (EBH) treatment is attractive as it minimizes target motion compared with other techniques; however, only a proportion of patients can perform an EBH to permit efficient treatment. We implemented a technique utilizing supplemental oxygen and mild hyperventilation in patients receiving abdominal SBRT, with the hypothesis that it may prolong EBHs and reduce treatment times.

Materials and Methods: Starting in August 2020, we provided patients supplemental oxygen (50% F_iO_2) and encouraged mild hyperventilation at 18 breaths/min with a metronome to improve EBHs for patients undergoing abdominal SBRT. We evaluated all completed treatments with this supplemented procedure (EBH_{supp}) as well as historical controls treated with EBH prior to this new procedure (EBH_{RA}, where RA signifies room air). EBH durations and treatment times were assessed. Statistical comparisons were made with chi-square test, Student *t*-test, and Mann-Whitney *U* test.

Results: For 20 patients treated with SBRT via EBH_{supp} and 26 patients treated with SBRT via EBH_{RA}, there were no statistical differences in baseline patient characteristics or treatment planning characteristics between the groups. The EBH_{supp} group had significantly increased maximum (52.8 s vs 34.5 s, $P < .001$) and median (24.9 s vs 18.7 s, $P = .002$) EBH times and required less EBH per treatment (8.9 vs 12.7, $P < .001$). The mean treatment time was 3 minutes less for EBH_{supp} compared with EBH_{RA} (17.6 min vs 20.8 min, $P = .025$).

Conclusion: Patients receiving supplemental oxygen and mild hyperventilation exhibited prolonged EBH time and reduced overall treatment time during abdominal SBRT. This intervention may improve individual patient breath-hold times, reduce treatment times, and increase the number of patients eligible for EBH-based abdominal SBRT.

Keywords: abdominal stereotactic body radiation therapy, expiratory breath hold, supplemental oxygen, hyperventilation

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Data sharing statement: Data are available upon reasonable request. De-identified patient data are stored in a departmental database and will be shared upon request with the corresponding author.

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Introduction

Stereotactic body radiation therapy (SBRT) is an increasingly utilized radiation technique that enables accurate delivery of ablative radiation doses with a steep dose fall-off to surrounding tissues. However, the utilization of SBRT for moving targets can be a significant challenge. Failure to account for respiratory motion can lead to underdosing targets and overdosing normal tissues.[1,2] Motion management is especially important for abdominal SBRT cases given the high dose per fraction and steep dose gradients between the tumor target and nearby gastrointestinal viscera (such as the stomach and the bowel). Various strategies have been utilized to minimize the effects of respiratory motion during abdominal/thoracic SBRT, such as abdominal compression, amplitude- and phased-based gating, and breath-hold techniques, among others.[1,3-5]

Voluntary breath-hold techniques are attractive for motion management during abdominal SBRT. With this strategy, the beam is intermittently enabled only when the patient is holding their breath, which is coordinated via instructions from the radiation therapists. As the tumor and target tissue are effectively stationary during beam-on, there is no need for an internal target volume margin, which minimizes the volume of irradiated normal tissue to achieve adequate tumor target coverage. This reduction in motion translates to improved on-board cone-beam CT (CBCT) image quality, allowing more accurate patient alignment prior to SBRT treatment.[6-8]

Both inspiratory breath-hold (IBH)[5,9,10] and expiratory breath hold (EBH)[11-13] techniques have been successfully utilized for SBRT treatments. While EBH is more reproducible and minimizes target motion compared with IBH,[13-19] it is generally more challenging for patients to perform an EBH of sufficient duration compared with IBH.[20] Physiological studies of breath holding have shown that supplemental oxygen and mild hyperventilation can significantly improve breath-hold durations,[20] with each technique adding incrementally to the improvement in breath-hold duration. Several pilot studies have demonstrated the clinical effectiveness of supplemental oxygen and mild hyperventilation for deep-inspiratory breath hold (DIBH) treatment in patients with breast cancer,[21-23] but the effectiveness of this technique for patients undergoing EBH is unknown.

In this article, we report the experience of the first 20 patients treated with abdominal SBRT using a supplemented EBH technique (EBH_{supp}) with supplemental oxygen and mild hyperventilation. We evaluated data on individual patient EBH durations and treatment times, and we compared this data with a cohort of similar patients treated with EBHs without supplementation (EBH_{RA}, room air, no mild hyperventilation). We hypothesized that the EBH_{supp} technique would prolong EBHs and reduce overall treatment time compared with EBH_{RA}.

Materials and Methods

Patient Inclusion/Exclusion Criteria

All patients receiving 3-fraction abdominal SBRT treated with an EBH technique in our department from January 2018 onward receiving between 1300 cGy and 1500 cGy per fraction were included (Institutional Review Board 120703005). Other SBRT fractionation schemes were not included to reduce heterogeneity in treatment characteristics that might influence overall treatment time (eg, reduced monitor units [MUs] per treatment for 5-fraction plans or for 3-fraction plans with lower prescription doses, increased patient practice/experience with 5-fraction treatments). Patient demographic and clinicopathologic information (age, gender, diagnosis, and comorbidities) were obtained from the medical record, and treatment details (dose per fraction, number of treatment arcs, MUs delivered per treatment) were obtained from the oncology information system (OIS) (ARIA; Varian).

Treatment Procedure Details

Prior to August 2020, patients were treated with standard EBH without oxygen supplementation or coaching/prompting of their respiratory rate (RR) prior to EBH (designated EBH_{RA}, where RA signifies room air). After August 2020, as part of a quality improvement initiative in our department and after a successful proof-of-concept study in healthy volunteers (see **Supplementary Figure 1**, available in the online version of this article at www.appliedradiationoncology.com), patients were offered treatment with a supplemented oxygen, mild hyperventilation EBH technique (EBH_{supp}). During both CT simulation and treatment, patients received 50% supplemental oxygen (50% fraction inspired oxygen or F_iO_2) via Venturi mask with an appropriate adapter and were instructed to synchronize their breathing at an RR of 18 breaths/min (ie, mild hyperventilation) with audio cues from an online metronome that was beamed into the simulation or treatment room (see **Figure 1** and **Supplementary Figure 2**, available in the online version of this article at www.appliedradiationoncology.com,

an online metronome available at https://www.imusic-school.com/en/tools/online-metronome, set at 36 beats/min with stress on the first beat to give a different audio cue for inhalation vs exhalation). The oxygen content of 50% F_iO_2 and RR of 18 breaths/min were chosen based on the known safety of these parameters in humans and the fact that similar parameters have been utilized in cancer patients performing inspiratory breath holds during radiation treatments.[21,22] While breathing to the beat of the metronome was encouraged by radiation therapists, there were no measures to forcibly maintain the patient at a strict RR of 18 breaths/min prior to EBH. Initiation of supplemental oxygen and mild hyperventilation in patients undergoing EBH_{supp} was initiated just prior to setup imaging and stopped right after treatment beam-off (with no prolonged time for oxygenation prior to treatment start).

For both EBH_{RA} and EBH_{supp}, patients were screened at the time of CT simulation, per standard departmental protocol, to verify their ability to perform repeated EBHs of more than 20 seconds' duration. This was assessed by radiation therapy staff with the patient on the CT simulation table and in the treatment position with full immobilization gear and tracking of abdominal excursion via Varian's Real-Time Position Management system (RPM). Completion of 2 consecutive, 20+ second EBHs within a 5-mm-amplitude window (as tracked by RPM) was required for the patient to move forward with EBH CT simulation and treatment. Patients not able to complete EBH simulation were treated with phased-based respiratory gating and are not described in this article. To be eligible for EBH-based SBRT treatments at our institution, all patients (both for EBH_{RA} and EBH_{supp}) were required to have either implanted fiducials or radio-opaque transarterial chemoembolization (TACE) material within or directly adjacent to the target to allow for intrafraction kV x-ray real-time monitoring of motion in addition to RPM amplitude gating.

CT Simulation and Target Delineation

Following EBH CT simulation, contouring and planning were performed on the EBH CT simulation scans. Gross tumor volumes (GTVs) were defined on the EBH CT simulation scan with assistance from fused diagnostic images (eg, triple-phase MRI). For post-TACE targets without residual enhancing tumors, a clinical target volume (CTV) encompassing the TACE volume was contoured in lieu of a GTV. Otherwise, CTV was a 3- to 4-mm isotropic expansion from the GTV with cropping at natural boundaries (eg, edge of the liver). The planning target volume was generated via an isotropic 5-mm expansion of the CTV. Tracking structures (fiducials or TACE) were contoured with the bone window. Two planning organ-at-risk (PRV) volumes were generated for these tracking structures via 3-mm and 5-mm isotropic expansions for PRV3 and PRV5 structures, respectively, to allow for intrafraction kV assessment of tracking structure displacement during treatments. Volumetric-modulated arc therapy (VMAT) plans consisting of 2 or 3 coplanar arcs were generated for all patients.

Treatment Delivery

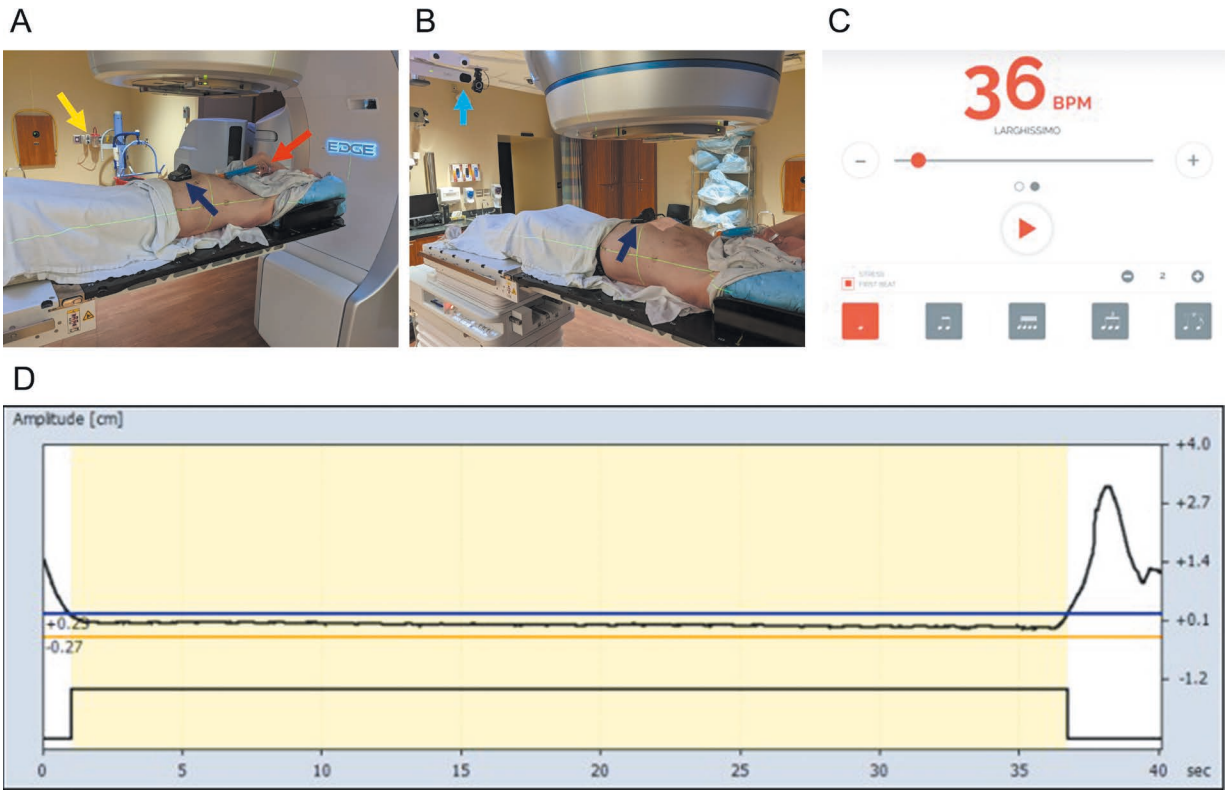
On the days of treatment, the general treatment workflow for both EBH_{RA} and EBH_{supp} treatments was as follows (see **Figure 2**): initial alignment to bony structures with orthogonal EBH kV images, EBH CBCT for final target/fiducial alignment, and finally delivery of the treatment with 2-3 coplanar arcs. For EBH_{supp} patients, supplemental oxygen and metronome-cued breathing started right before setup imaging and stopped right after treatment beam-off, with no prolonged oxygenation prior to therapy.

The RPM amplitude gating (5 mm) and intrafraction fiducial/TACE tracking with triggered kV images obtained every 10/20 degrees of gantry rotation were used to confirm breath-hold position during treatment (see **Figure 1**). Patients were instructed by therapy staff to breathe to the beat of the metronome in between EBH. A minimum of 6 breaths was recommended between each attempted EBH, but the timing of EBH attempts was left to the discretion of the radiation therapy staff. Additional images (eg, repeat kV or CBCT) were acquired as clinically necessary. All data regarding EBH duration and treatment time were automatically logged into the OIS.

Data Extraction

Individual patient EBH duration data for every breath hold for all treatments were extracted from the OIS in text file form, including beam on/off times during EBH (**Figure 2**). Individual patient EBH durations were penalized for beam holds (the time the beam was off during breath hold due to either excursion outside RPM amplitude window or fiducial excursion outside PRV5; see **Figure 2** and **Supplementary Figure S3**, available in the online version of this article at www.appliedradiationoncology.com, for examples) so that only EBH time while the beam was on was counted. Total treatment time, time

Figure 1. Implementation details of the supplemented expiratory breath hold technique (EBH_{supp}). Supplemental oxygen was delivered at 50% F_iO_2 via a Venturi mask and appropriate adapter (red arrow) connected to in-house oxygen flowmeters (yellow arrow) in the treatment delivery vault (A). Varian's Real-Time Position Management (RPM) system was used to track patient respiratory motion with an infrared tracking camera (light blue arrow) and reflective marker (dark blue arrow) placed on the patient's abdomen (B). Patients were encouraged to breathe at a respiratory rate of 18 breaths/min with the use of an online metronome. The metronome was set at 36 beats/min with stress on the first beat so there would be a distinct sound cue for both the start of inhalation and the start of exhalation (C). An example of breath-hold tracing during patient treatment via the RPM system is shown (D). Permission was given by a patient volunteer for the use of photographs in this article.

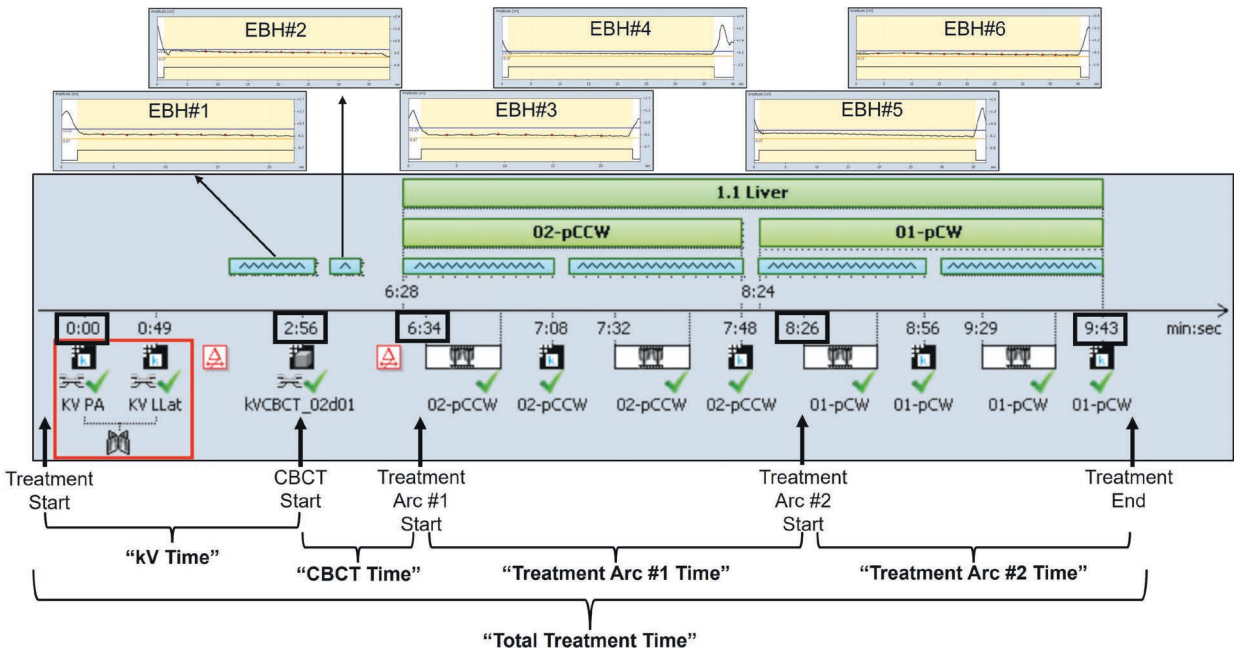


for completion of EBH orthogonal kV images, time for completion of EBH CBCT, and time for completion of each treatment arc were also extracted from the OIS and defined as illustrated in **Figure 2**. Briefly, the "kV Time" was defined as the time from Treatment Start (start of first kV acquisition) until CBCT Start (start of CBCT acquisition). The "CBCT Time" was defined as the time from CBCT Start until the time of Treatment Arc #1 Start (start of delivery of first treatment arc). The "Treatment Arc #1 Time" was defined as the time from Treatment Arc #1 Start until the time of Treatment Arc #2 Start (start of delivery of second treatment arc). The "Treatment Arc #2 Time" was defined as the time from Treatment Arc #2 Start until Treatment End (completion of second treatment arc). The "Total Treatment Time" was defined as the time from Treatment Start until Treatment End.

Statistical Analysis

Patient demographic, clinical, and treatment characteristics were compared between the EBH_{RA} and EBH_{supp} groups via Student *t*-test (continuous variables) and the chi-square test (categorical variables). For categorical variables with more than 2 categories, variables were dichotomized prior to performing the chi-square test. Specifically, the "Diagnosis" variable was dichotomized as hepatocellular carcinoma or nonhepatocellular carcinoma and the "Dose per Fraction" variable was dichotomized as 1500 or more cGy or less than 1500 cGy. Individual patient max EBH, mean EBH, median EBH, and the number of EBHs required to complete treatment were compared between the EBH_{RA} and EBH_{supp} groups via unpaired Student *t*-test. Individual patient EBH percentiles (10th, 25th, 50th, 75th, and 90th) were also determined and compared between groups via the Student *t*-test. Total treatment time and time for completion of individual treatment components (eg, time for completion of CBCT) were determined and compared between groups via Mann-Whitney *U* test given the non-normal distribution

Figure 2. Treatment timeline example and definition of time points. The shaded gray area shows an example "Session Timeline" screenshot from Varian Eclipse treatment planning software from a patient treated with a supplemented expiratory breath-hold (EBH) technique. The individual EBHs performed by the patient during cone-beam CT (CBCT) and delivery of treatment arcs are shown in the amplitude tracings at the top of the figure (EBH#1 to EBH#6). Treatment time definitions are shown toward the bottom of the figure (and are described in the "Materials and Methods" section).



of the data. For all statistical tests, a P value < 0.05 was considered statistically significant.

Results

We identified a total of 46 patients meeting inclusion criteria who received 3-fraction SBRT with EBH treatment in our department after January 2018. Prior to the initiation of the EBH_{supp} technique in August 2020, 26 patients were treated with 28 treatment plans via standard EBH_{RA} (2 patients had 2 liver tumors that were treated with separate treatment plans), accounting for a total of 83 EBH_{RA} treatments (28 treatment plans × 3 fractions = 84 treatments minus 1 patient who received a liver transplant after the completion of only 2 fractions). At the time of this analysis, 20 patients were treated with the EBH_{supp} technique with 24 treatment plans (4 patients had 2 liver tumors who were treated with separate treatment plans) for a total of 72 EBH_{supp} treatments (24 treatment plans × 3 fractions = 72 treatments).

Patient demographic, clinicopathologic, and treatment parameters are shown in **Table 1**. Overall, there were no significant differences in any parameter between patients in the EBH_{RA} and EBH_{supp} groups. The mean patient age was approximately 62 years old in both groups (62.4 vs 63.2, P = .788), and most patients were male (76.9% vs 90.0%, P = .246) and carried a diagnosis of hepatocellular carcinoma (73% vs 70%, P = .883). In all cases, patients received EBH SBRT to the liver. Patient comorbidity burden was similar between the groups as judged by the Charlson comorbidity index (CCI, 7.31 vs 7.60, P = .590). Treatment parameters, including dose per fraction and MU delivered per treatment, were similar between the groups, with nearly all patients receiving treatment with 2 co-planar arc VMAT plans (2 patients in the EBH_{supp} group were treated with 3 co-planar arc VMAT plans).

A total of 1735 individual EBHs were extracted from the OIS (**Supplementary Figure S3**, available in the online version of this article at www.appliedradiationoncology.com) and showed a significant increase in EBH duration for patients treated with the EBH_{supp} technique (**Figure 3**, **Table 2**). Maximum EBH for patients was significantly increased for patients treated with EBH_{supp}, with a difference in maximum EBH of ~18 seconds (34.5 s vs 52.8 s, P < .001). Mean (18.2 s vs 25.1 s, P < .001) and median (18.7 s vs 24.9 s, P = .002) EBH were also significantly increased for patients treated with EBH_{supp} compared with EBH_{RA}. There was a corresponding decrease in the number of EBHs required to complete each treatment (12.7 vs 8.9, P < .001). **Table 2** shows a percentile breakdown of patient EBH between the 2 groups

Table 1. Patient Clinicopathologic Characteristics and Relevant Treatment Parameters

VARIABLE	EBH_{RA} (*N* = 26)	EBH_{SUPP} (*N* = 20)	*P* VALUE
Age (mean {SD})	62.4 {11.1}	63.2 {10.0}	.7881
Gender			
Female	6 (23.1)	2 (10.0)	.246
Male	20 (76.9)	18 (90.0)	
Diagnosis			
Hepatocellular carcinoma	19 (73.1)	15 (70.0)	.883
Intrahepatic cholangiocarcinoma	1 (3.8)	1 (5.0)	
Liver metastasis	6 (23.1)	4 (20.0)	
CCI (mean {SD})	7.31 {1.52}	7.60 {2.14}	.590
Current smoker (%)	9 (34.6)	5 (25.0)	.482
Dose per fraction (cGy)			.415
1300	3 (11.5)	5 (25.0)	
1400	1 (3.8)	0 (.0)	
1500	22 (84.6)	15 (75.0)	
Number of treatment arcs			.099
2	26 (100.0)	18 (90.0)	
3	0 (.0)	2 (10.0)	
MU per treatment (mean {SD})	4162 {967}	4058 {950}	.695

For continuous variables, the mean value and standard deviation are shown. For categorical variables, the number of patients is presented, with the number in parentheses representing the percentage of patients. P values were calculated via Student t-test and the χ^2 test for continuous and categorical variables, respectively.

Abbreviations: CCI, Charlson comorbidity index; EBH, expiratory breath hold; MU, monitor units; RA, room air.

with a statistically increased EBH observed with EBH_{supp} treatment for all individual patient EBH percentiles except for the lowest (10th) percentile (10th percentile: 6.4 s vs 7.8 s, $P = .219$).

Examination of treatment times between the 2 groups (**Figure 4**) showed a significant reduction in the time required for completion of treatment in patients treated with EBH_{supp} compared with EBH_{RA}, with a mean reduction of ~5 minutes (21.8 min vs 16.7 min, $P = .025$) and a median reduction of ~2 minutes (18.1 min vs 16.2 min). While the time required for completion of kV radiographs ("kV Time") was not different between the 2 groups ($P = .325$), the time required for completion of CBCT ("CBCT Time," $P < .001$) and each treatment arc ("Treatment Arc Time," $P < .001$) was significantly reduced in patients treated with the EBH_{supp} technique.

Discussion

Expiratory breath hold is an effective method for motion management in patients undergoing abdominal SBRT treatments but is underutilized due to patients' difficulty in performing repeated EBH of sufficient duration.[1] In this study, we found that patients undergoing abdominal SBRT with supplemental oxygen and mild hyperventilation exhibited prolonged EBH durations compared with patients treated with nonsupplemented EBH. Patients in the EBH_{supp} group performed EBH of longer duration by all reported metrics (maximum EBH, mean EBH, and median EBH) and required less total EBH to complete treatments. These results agree with previously published experiences utilizing similar techniques in patients undergoing DIBH for breast cancer treatments[20-22] as well as a recent randomized study of volunteers undergoing EBH that showed an improvement in median EBH duration from 24 seconds to 49 seconds with supplemental oxygen and mild hyperventilation.[24]

The reduction in treatment times observed in the EBH_{supp} group compared with the EBH_{RA} group is likely related to improve EBH using the supplemented technique. This is supported by significant improvements in time to complete tasks that required prolonged EBH (eg, CBCT, treatment arcs) and a lack of significant improvement in tasks that did not require prolonged EBH (eg, kV acquisition/alignment). There were no significant differences in patient clinical/pathological characteristics between the groups (eg, age, diagnosis, and comorbidity index) nor in treatment-related parameters that might be expected to influence treatment time (eg, dose per fraction, MU delivered, and number of treatment arcs). During the study period, there were no other changes in departmental protocols or treatment-planning techniques as an alternate explanation for the reduction in treatment time observed. While the EBH_{supp} technique reduced treatment times in our study, there was an initial time investment (~10-15 min) at the time of CT simulation for added patient training for breathing with

Figure 3. Duration and number of individual expiratory breath holds (EBHs) during stereotactic body radiation therapy treatments. The data illustrate the average maximum (Max EBH) (A), mean (Mean EBH) (B), median (Median EBH) (C), expiratory breath-hold duration of individual patients, as well as the average of the total number of expiratory breath holds required for individual patients to complete treatment for patients treated with standard (EBH_{RA}) or supplemented (EBH_{supp}) EBH technique (D). Error bars in the box and whisker plot represent the range (min to max), bars represent the interquartile range, and line represents the median. *P* values were calculated via a Student *t*-test.

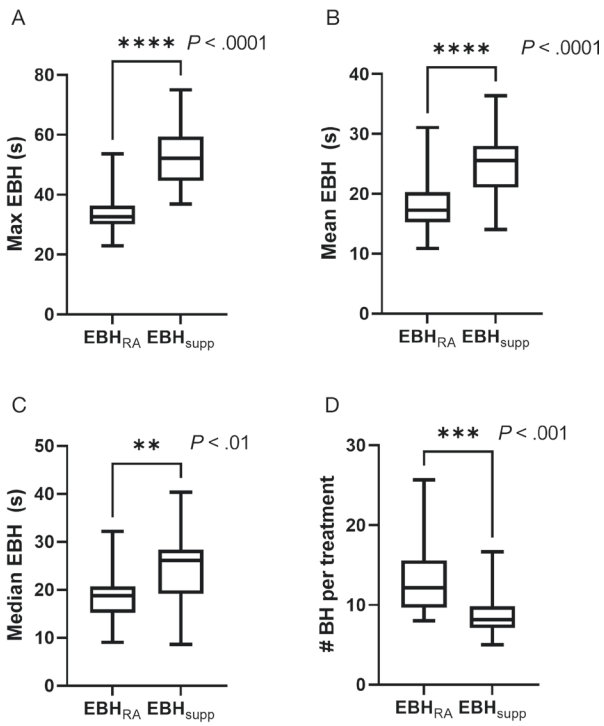


Table 2. Descriptive Statistics of Expiratory Breath-Hold (EBH) Times

STATISTIC	EBH_{RA} (S)	EBH_{SUPP} (S)	*P* VALUE
10th percentile	6.4	7.8	.219
25th percentile	11.3	14.7	.031
50th percentile	18.7	24.9	.002
75th percentile	24.6	34.7	<.001
90th percentile	29.3	43.1	<.001
Max	34.5	52.8	<.001
Mean	18.2	25.1	<.001

Values reported are the mean values for each EBH statistic computed for patients in the control group (EHB_{RA}) and the supplemented group (EBH_{supp}). P values reported were calculated via Student t-test.

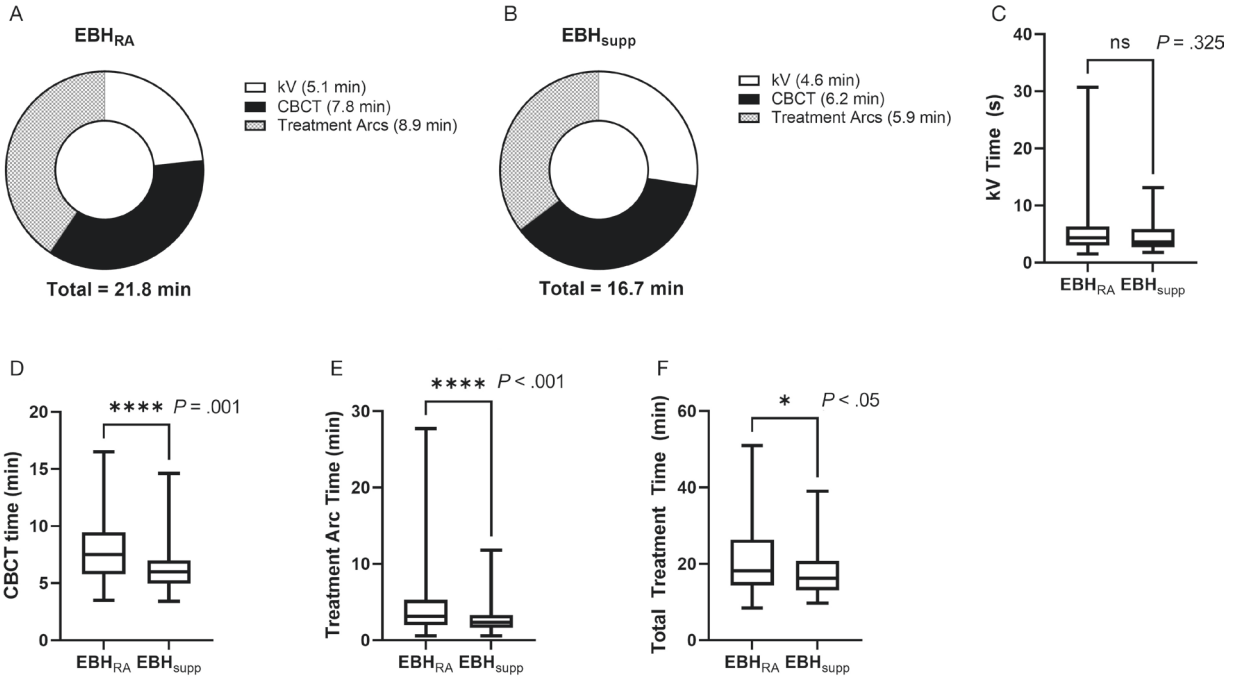
Abbreviation: RA, room air.

a metronome and the use of a Venturi mask.

The reported EBH_{supp} technique was safe in our study population. We had no patients who had any issues or symptoms related to the breath-hold component of their treatments (eg, no lightheadedness, syncope, tingling, tetany, or other concerns), which is in agreement with other studies that have shown the safety of breath holds (both inspiratory and expiratory) with mild hyperventilation and supplemental oxygen.[20-25] The mild hyperventilation used in this study was chosen based on the RRs previously utilized and found to be safe in breast cancer patients undergoing DIBH treatment with prolonged hyperventilation.[22,23] We specifically avoided more rapid hyperventilation given the theoretical increased risk of tetany that can occur with more aggressive hyperventilation and associated hypocapnia.[26] Similarly, the level of supplemental oxygen of 50% F_iO_2 was selected based on safety as supplemental oxygen levels above 60% are associated with an increased risk of absorptive atelectasis.[25,27-30]

One safety issue that should be mentioned for all breath-hold treatments (not just supplemented ones such as the EBH_{supp} method) is the well-established increase in blood pressure during prolonged breath holds.[25,31,32] However, the risk and severity of blood pressure rise during breath holds do not appear to be worsened by supplemented techniques, including a similar technique with mild hyperventilation and supplemental oxygen.[25] Further, a recent randomized study of EBHs in volunteers did not find a significant change in blood pressure during EBH, possibly due to the relatively modest prolongation of EBHs with supplemented techniques (< 1 min) compared with DIBH (up to 5 min prolonged breath holds reported).[24] In general, patient cardiopulmonary comorbidities should be considered by the treating radiation oncologist prior to proceeding with breath-hold treatment with discussion of

Figure 4. Times for completion of individual treatment components and for total treatment. Pie charts showing the mean times required for each component of treatment and the total treatment time for individual patients treated with standard expiratory breath hold (EBH) (EBH_{RA}) (A) or supplemented EBH (EBH_{supp}) techniques (B). Box and whisker plots of time to completion of orthogonal kVs (kV Time) (C), time to completion of cone-beam CT (CBCT Time) (D), time to completion of treatment arcs (Treatment Arc Time) (E), and total treatment time (F). Error bars in the box and whisker plot represent the range (min to max), bars represent the interquartile range, and line represents the median. *P* values were calculated via Mann-Whitney *U* test.



the technique with the patient's other involved physicians (eg, cardiologist and pulmonologist) for those with significant cardiopulmonary comorbidities.

There are several limitations to this study. First, this was not a randomized trial and. therefore, there is a possibility of biases (eg, selection bias) that could have partially influenced the results between the EBH_{RA} and EBH_{supp} groups, though patient groups were well balanced overall with respect to both clinical parameters and treatment parameters. Second, all the patients described here received liver SBRT and, therefore, the results may not be generalizable to all patients receiving abdominal SBRT, though we have additionally treated several patients with primary pancreatic cancer with pancreas SBRT with the EBH_{supp} method with similar experience to those treated with liver SBRT. Lastly, this was a "real-world" study of EBH_{supp} implementation in a busy radiation oncology clinic, and we did not attempt to capture nor control all aspects of respiratory physiology that govern breath-hold capacity. While we encouraged patients to breathe at a rate that would normally correspond to mild hyperventilation, we did not forcibly control patient RR or tidal volumes and did not measure partial pressures of carbon dioxide; therefore, whether hyperventilation/hypocapnia was achieved for each patient is unknown. Future mechanistic studies of patients undergoing repeated, supplemented EBH with real-time measurement of these parameters will be helpful in further optimizing supplementation/hyperventilation protocols and ensuring uniformity of technique among individual patients.

Conclusions

Patients receiving supplemental oxygen and mild hyperventilation exhibited prolonged EBH time and reduced overall treatment time during abdominal SBRT. This intervention is simple, inexpensive, safe, and may improve individual patient breath-hold times, reduce treatment time, and increase the number of patients eligible for EBH-based abdominal SBRT.

References

1) Brandner ED, Chetty IJ, Giaddui TG, Xiao Y, Huq MS. Motion management strategies and technical issues associated with stereotactic body radiotherapy of thoracic and upper abdominal tumors: a review from NRG oncology. *Med Phys.* 2017;44(6):2595-2612. doi:10.1002/mp.12227

2) Caillet V, Booth JT, Keall P. IGRT and motion management during lung SBRT delivery. *Phys Med*. 2017;44:113-122. doi:10.1016/j.ejmp.2017.06.006

3) Campbell WG, Jones BL, Schefter T, Goodman KA, Miften M. An evaluation of motion mitigation techniques for pancreatic SBRT. *Radiother Oncol*. 2017;124(1):168-173. doi:10.1016/j.radonc.2017.05.013

4) Dieterich S, Green O, Booth J. SBRT targets that move with respiration. *Phys Med*. 2018;56:19-24. doi:10.1016/j.ejmp.2018.10.021

5) Boda-Heggemann J, Knopf A-C, Simeonova-Chergou A, et al. Deep inspiration breath hold-based radiation therapy: a clinical review. *Int J Radiat Oncol Biol Phys*. 2016;94(3):478-492. doi:10.1016/j.ijrobp.2015.11.049

6) Shen S, Duan J, Fiveash JB, et al. Validation of target volume and position in respiratory gated CT planning and treatment. *Med Phys*. 2003;30(12):3196-3205. doi:10.1118/1.1626121

7) Shimizu S, Shirato H, Kagei K, et al. Impact of respiratory movement on the computed tomographic images of small lung tumors in three-dimensional (3D) radiotherapy. *Int J Radiat Oncol Biol Phys*. 2000;46(5):1127-1133. doi:10.1016/s0360-3016(99)00352-1

8) Mageras GS, Pevsner A, Yorke ED, et al. Measurement of lung tumor motion using respiration-correlated CT. *Int J Radiat Oncol Biol Phys*. 2004;60(3):933-941. doi:10.1016/j.ijrobp.2004.06.021

9) Hanley J, Debois MM, Mah D, et al. Deep inspiration breath-hold technique for lung tumors: the potential value of target immobilization and reduced lung density in dose escalation. *Int J Radiat Oncol Biol Phys*. 1999;45(3):603-611. doi:10.1016/s0360-3016(99)00154-6

10) Murphy MJ, Martin D, Whyte R, et al. The effectiveness of breath-holding to stabilize lung and pancreas tumors during radiosurgery. *Int J Radiat Oncol Biol Phys*. 2002;53(2):475-482. doi:10.1016/s0360-3016(01)02822-x

11) Lin YH, Ozawa S, Miura H, et al. Split-VMAT technique to control the expiratory breath-hold time in liver stereotactic body radiation therapy. *Phys Med*. 2017;40:17-23. doi:10.1016/j.ejmp.2017.06.022

12) Yang W, Fraass BA, Reznik R, et al. Adequacy of inhale/exhale breathhold CT based ITV margins and image-guided registration for free-breathing pancreas and liver SBRT. *Radiat Oncol*. 2014;9:11. doi:10.1186/1748-717X-9-11

13) Oliver PAK, Yewondwossen M, Summers C, et al. Influence of intra- and interfraction motion on planning target volume margin in liver stereotactic body radiation therapy using breath hold. *Adv Radiat Oncol*. 2021;6(1):100610. doi:10.1016/j.adro.2020.10.023

14) Seppenwoolde Y, Shirato H, Kitamura K, et al. Precise and real-time measurement of 3D tumor motion in lung due to breathing and heartbeat, measured during radiotherapy. *Int J Radiat Oncol Biol Phys*. 2002;53(4):822-834. doi:10.1016/s0360-3016(02)02803-1

15) George R, Chung TD, Vedam SS, et al. Audio-visual biofeedback for respiratory-gated radiotherapy: impact of audio instruction and audio-visual biofeedback on respiratory-gated radiotherapy. *Int J Radiat Oncol Biol Phys*. 2006;65(3):924-933. doi:10.1016/j.ijrobp.2006.02.035

16) Vedam SS, Keall PJ, Kini VR, Mohan R. Determining parameters for respiration-gated radiotherapy. *Med Phys*. 2001;28(10):2139-2146. doi:10.1118/1.1406524

17) Goossens S, Senny F, Lee JA, Janssens G, Geets X. Assessment of tumor motion reproducibility with audio-visual coaching through successive 4D CT sessions. *J Appl Clin Med Phys*. 2014;15(1):4332. doi:10.1120/jacmp.v15i1.4332

18) Lens E, Gurney-Champion OJ, Tekelenburg DR, et al. Abdominal organ motion during inhalation and exhalation breath-holds: pancreatic motion at different lung volumes compared. *Radiother Oncol*. 2016;121(2):268-275. doi:10.1016/j.radonc.2016.09.012

19) Holland AE, Goldfarb JW, Edelman RR. Diaphragmatic and cardiac motion during suspended breathing: preliminary experience and implications for breath-hold MR imaging. *Radiology*. 209(2):483-489. doi:10.1148/radiology.209.2.9807578

20) Parkes MJ. Breath-holding and its breakpoint. *Exp Physiol*. 2006;91:1-15. doi:10.1113/expphysiol.2005.031625

21) Parkes MJ, Green S, Kilby W, et al. The feasibility, safety and optimization of multiple prolonged breath-holds for radiotherapy. *Radiother Oncol*. 2019;141:296-303. doi:10.1016/j.radonc.2019.06.014

22) Parkes MJ, Green S, Stevens AM, et al. Safely prolonging single breath-holds to >5 min in patients with cancer; feasibility and applications for radiotherapy. *Br J Radiol*. 2016;89(1063):20160194. doi:10.1259/bjr.20160194

23) Parkes MJ, Green S, Cashmore J, Ghafoor Q, Clutton-Brock T. Shortening the preparation time of the single prolonged breath-hold for radiotherapy sessions. *Br J Radiol*. 2022;95(1130):20210408. doi:10.1259/bjr.20210408

24) Towell V, Gysen KV, Cross S, Kk Low G. Efficacy of preoxygenation administration in volunteers, in extending the end-expiration breath-hold duration for application to abdominal radiotherapy. *Tech Innov Patient Support Radiat Oncol*. 2023;26:100208. doi:10.1016/j.tipsro.2023.100208

25) Parkes MJ, Green S, Stevens AM, Clutton-Brock TH. Assessing and ensuring patient safety during breath-holding for radiotherapy. *Br J Radiol*. 2014;87(1043):20140454. doi:10.1259/bjr.20140454

26) Macefield G, Burke D. Paraesthesiae and tetany induced by voluntary hyperventilation. Increased excitability of human cutaneous and motor axons. *Brain*. 1991;114 (Pt 1B):527-540. doi:10.1093/brain/114.1.527

27) O'Brien J. Absorption atelectasis: incidence and clinical implications. *AANA J*. 2013;81(3):205-208.

28) Kim HI, Min JY, Lee J-R, et al. The effect of oxygen concentration on atelectasis formation during induction of general anesthesia in children: a prospective randomized controlled trial. *Paediatr Anaesth*. 2021;31(12):1276-1281. doi:10.1111/pan.14304

29) Rothen HU, Sporre B, Engberg G, et al. Prevention of atelectasis during general anaesthesia. *Lancet*. 1995;345(8962):1387-1391. doi:10.1016/s0140-6736(95)92595-3

30) Edmark L, Kostova-Aherdan K, Enlund M, Hedenstierna G. Optimal oxygen concentration during induction of general anesthesia. *Anesthesiology*. 2003;98(1):28-33. doi:10.1097/00000542-200301000-00008

31) Pingitore A, Gemignani A, Menicucci D, et al. Cardiovascular response to acute hypoxemia induced by prolonged breath holding in air. *Am J Physiol Heart Circ Physiol*. 2008;294(1):H449-55. doi:10.1152/ajpheart.00607.2007

32) Heusser K, Dzamonja G, Tank J, et al. Cardiovascular regulation during apnea in elite divers. *Hypertension*. 2009;53(4):719-724. doi:10.1161/HYPERTENSIONAHA.108.127530

Radiation Therapy-Induced Toxicity in a Breast Cancer Patient With Variance of Unknown Significance in the Ataxia Telangiectasia Gene

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Abstract

Breast conservation has been an effective part of the multimodality treatment of localized breast cancer. Appropriate candidates for breast conservation include patients with early stage disease. However, there are certain absolute contraindications for breast cancer, including radiation during pregnancy, multiple positive margins, and homozygosity mutations in the ataxia telangiectasia mutated (*ATM*) gene. *ATM*, an autosomal-recessive disorder, is associated with the childhood onset of neurologic impairment, immunodeficiency, and ocular and cutaneous telangiectasias. Typically, patients with heterozygous *ATM* mutations remain candidates for breast conservation. However, *ATM* mutations have been linked to increased sensitivity to radiation therapy and, in some cases, to severe toxicity. We present a case of a 51-year-old woman with variance of unknown significance (VUS) in her *ATM* gene, who was treated with adjuvant radiation and subsequently developed fibrosis, reduced shoulder movement, and telangiectasias. Thus, our case highlights the need for patients with VUS to be appropriately counseled on radiotoxicity.

Keywords: ataxia telangiectasia, telangiectasias, fibrosis, breast radiation, radiation pneumonitis, dermatitis, toxicity, side effects

Case Summary

A 51-year-old woman presented in 2018 after a screening mammogram discovered asymmetry in the right subareolar region with a 15 × 13 × 14 mm mass on ultrasonography. Breast biopsies revealed triple-positive infiltrating ductal carcinoma. She had no history of collagen vascular diseases or prior radiation. Genetic testing revealed a heterozygous variance of unknown significance (VUS) in the ataxia telangiectasia (*ATM*) gene (c.3158A>T(p.Asp1053Val)) and negative BReast CAncer gene *(BRCA)* testing. She underwent neoadjuvant chemotherapy with Adriamycin and cyclophosphamide, followed by Taxol, Herceptin, and pertuzumab. Subsequent right partial mastectomy showed grade 2 residual invasive ductal carcinoma. She received a total dose of 5000 cGy of 3D radiation therapy to the right breast and the supraclavicular and axillary lymph nodes with a boost.

The patient developed cutaneous symptoms, which progressed to telangiectasias and significant fibrosis (**Figure 1**). In addition, she developed radiographically detected asymptomatic radiation pneumonitis (**Figure 2A-B**).

Platelet-rich infusions, used for fibrosis treatment, were ineffective. The patient subsequently underwent a mastectomy.

Discussion

By facilitating DNA double-stranded breaks, ionizing radiation is known to cause damage to both

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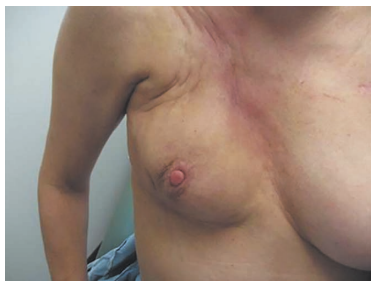
Figure 1. Significant fibrosis and poor cosmesis seen following radiation.



malignant and nonmalignant cells. In patients with mutant *ATM* genes, DNA repair via nonhomologous DNA end-joining is impaired, which raises concern for an increased sensitivity to radiation therapy[1,2]. The data regarding increased toxicity from radiation therapy in heterozygous carriers of *ATM* mutations are unclear. Furthermore, it is also unclear whether there is a correlation between VUS mutations and an increased sensitivity to radiation. An extensive database regarding VUS mutations across several genes is available on the ClinVar website. Of the 8945 submitted variants of the *ATM* gene, more than 50% (4742) were deemed to be VUS mutations.[3]

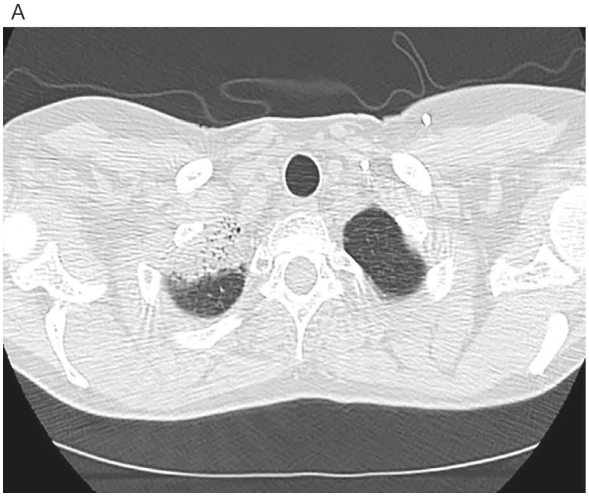
Clinical investigations attempting to assess the link between VUS and increased radiation sensitivity have been unclear, with different studies yielding contradictory results. In a study assessing 91 evaluable carriers of *ATM* variants, of whom 23 harbored a pathological variant while 68 harbored VUS, researchers determined no evidence of increased radiation-associated toxicity among carriers of pathogenic *ATM* germline variants.[4] Another study assessed 357 pan-cancer patients who received a cumulative total of 727 courses of radiation therapy, determining that genetic inactivation of *ATM* was associated with an improved radiotherapeutic efficacy.[5]

However, one case series demonstrated that patients with heterozygous germline *ATM* mutations can have widely varying clinical responses to radiation therapy, ranging from benign to severe,[6] as was seen in our patient's case. Moreover, the landmark WECARE study discovered increased contralateral breast cancers in radiated patients possessing otherwise nonpathologic *ATM* variants.[7]

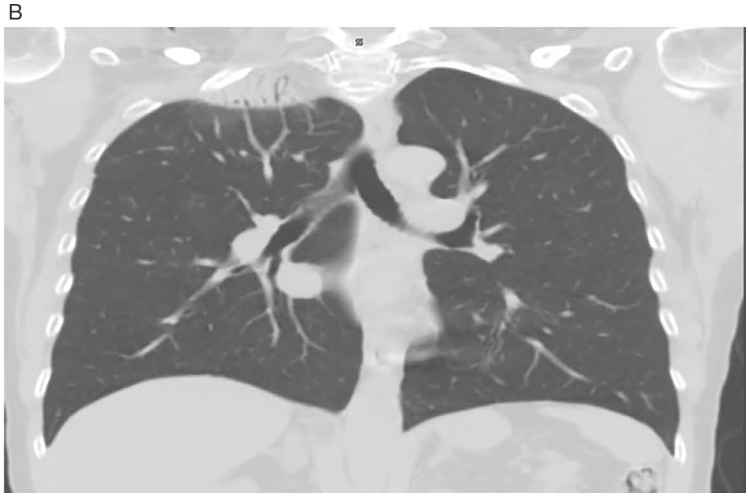
ATM heterozygotes make up approximately 1% of the general population, and it has been shown in epidemiologic studies that this mutation confers a 3- to 5-fold increase in the risk of developing breast cancer. However, understanding the clinical significance of VUS in the *ATM* gene is vital for patients undergoing radiation treatment. While it has been discussed that VUS should be considered normal and should not confer increased radiosensitivity to patients,[8] our patient's severe cutaneous toxicity serves as a reminder that adverse radiation-induced effects can be seen in patients with VUS. Recent guidelines recommend that radiation therapy should be offered when clinically indicated for women with breast cancer who are carriers of an *ATM* mutation.[9] Therefore, more investigation is needed into VUS mutations to determine the significance of single-nucleotide alterations. We present this case so that it can be added to the ClinVar website and future patients could be counseled and avoid the severe side effects seen in this patient.

Figure 2. Apical scarring of the right lung following radiation as seen on an axial view (A). Apical scarring of the right lung following radiation as seen on a coronal view (B).

A



B



Conclusions

The *ATM* gene is a critical regulator of DNA double-strand breaks and ensures appropriate mismatch repair. We present a case of a patient with triple-positive breast cancer and a VUS *ATM* gene, who developed significant fibrosis and cutaneous scarring following radiation therapy. Certainly, it is possible that there is a subset of VUS in which some patients may develop more deleterious side effects than others. Nevertheless, our case underscores the need for further analysis of VUS mutations and appropriate patient counseling, determining the risk of radiation toxicity in these patients.

References

1) Dosani M, Schrader KA, Nichol A, et al. Severe late toxicity after adjuvant breast radiotherapy in a patient with a germline ataxia telangiectasia mutated gene: future treatment decisions. *Cureus*. 2017;9(7):e1458. doi:10.7759/cureus.1458

2) Ho AY, Fan G, Atencio DP, et al. Possession of ATM sequence variants as predictor for late normal tissue responses in breast cancer patients treated with radiotherapy. *Int J Radiat Oncol Biol Phys*. 2007;69(3):677-684. doi:10.1016/j.ijrobp.2007.04.012

3) Hosoya N, Miyagawa K. Implications of the germline variants of DNA damage response genes detected by cancer precision medicine for radiological risk communication and cancer therapy decisions. *J Radiat Res*. 2021;62(supplement_1):i44-i52. doi:10.1093/jrr/rrab009

4) Modlin LA, Flynn J, Zhang Z, et al. Tolerability of breast radiotherapy among carriers of ATM germline variants. *JCO Precis Oncol*. 2021;5:PO.20.00334. doi:10.1200/PO.20.00334

5) Pitter KL, Casey DL, Lu YC, et al. Pathogenic ATM mutations in cancer and a genetic basis for radiotherapeutic efficacy. *J Natl Cancer Inst*. 2021;113(3):266-273. doi:10.1093/jnci/djaa095

6) Mullins BT, Gupta G. Increased radiation toxicity with germline ATM variant of uncertain clinical significance. *Rep Pract Oncol Radiother*. 2019;24(6):672-680. doi:10.1016/j.rpor.2019.09.008

7) Reiner AS, Robson ME, Mellemkjær L, et al. Radiation treatment, ATM, BRCA1/2, and CHEK2*1100delC pathogenic variants and risk of contralateral breast cancer. *J Natl Cancer Inst*. 2020;112(12):1275-1279. doi:10.1093/jnci/djaa031

8) Bergom C, West CM, Higginson DS, et al. The implications of genetic testing on radiation therapy decisions: a guide for radiation oncologists. *Int J Radiat Oncol Biol Phys*. 2019;105(4):698-712. doi:10.1016/j.ijrobp.2019.07.026

9) McGuire KP, Mamounas EP. Management of hereditary breast cancer: ASCO, ASTRO, and SSO guideline. *Ann Surg Oncol*. 2020;27(6):1721-1723. doi:10.1245/s10434-020-08396-8

Public Relations and Collaborative Support: Claiming a Seat at the Table When No One Else Is Buying It

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Before embarking upon a career in medicine, we assumed that scientific research aiming to save lives by elucidating optimal treatment paradigms would be largely unaffected by outside factors such as public relations and financial influences. As we have continued on in oncology, which remains at the forefront of scientific discovery in medicine, that assumption has proven idealistic and erroneous.

While treatment has advanced throughout the decades, public perception of the severity of deleterious side effects from yesteryear has lingered. Furthermore, there seemingly is always a cost to doing business. Funding, which is integral to scientific advancement, now often serves as the basis for determining just how distinguished and decorated an academic career is.[1,2] Even with the advent of cutting-edge techniques and expanding indications of treatment modalities, with radiation therapy having neither historical precedent as a primary treatment modality for treating many disease sites nor the financial support of the booming pharmaceutical industry, is radiation oncology getting its voice heard at the proverbial table?

Unfortunately, recent interactions between the media and publications by *The New England Journal of Medicine*, an esteemed journal with one of the highest impact factors worldwide, suggest that the answer is no. In February 2023, 10-year outcomes from the PRIME II study were published. The study involved randomizing patients aged ≥ 65 years with early stage breast cancer treated with breast-conserving surgery and adjuvant endocrine therapy to whole-breast radiation therapy (WBRT) vs omission of radiation therapy.[3] Despite results demonstrating a nearly 10% risk of local recurrence at 10 years with omission of radiation (vs 1% for those who received WBRT), *The Wall Street Journal* soon after published an article titled "More Women with Breast Cancer Could Skip Harsh Radiation, Study Says."[4] Harsh radiation? Modern treatment planning and patient positioning techniques—coupled, of course, with a thoughtful radiation oncologist—have markedly reduced the risk and severity of side effects.[5] The media influences perception, and we care what patients think. Even if patients are not attending tumor boards or sitting on specialty-specific editorial boards, their perceptions of treatment options matter if they are choosing for themselves. Patients and their loved ones sit on institutional review boards, read articles, invest in companies that drive investigational funding, and donate to cancer research. Their choices drive investigation.

A few months later in May 2023, *The New York Times* came under fire from radiation oncologists

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worldwide, objecting to their description of findings of the PROSPECT trial, stating that "brutal" neoadjuvant radiation can be avoided for rectal cancer,[6] in spite of the study looking at a select population of patients with more favorable risk features, including T2N1, T3N0, or T3N1 rectal cancers located 5-12 cm from the anal verge without circumferential resection margin positivity.[7] (Of note, that article underwent a name change after publication due to backlash.) This oversimplified title is dangerous, particularly if readers look beyond the abstract and see that the acute grade 3+ toxicity rate of 22.8% for the arm including radiation is actually less than the 41% grade 3+ toxicity rate for patients receiving chemotherapy alone.[7]

Of greater concern from the standpoint of scientific methodology was the recent publication of the INDIGO trial in June 2023. The trial sought to compare the isocitrate dehydrogenase (IDH) inhibitor vorasidenib with a placebo in the management of residual or recurrent low-grade gliomas after surgical resection alone.[8] Although the standard management would incorporate radiation therapy,[9] no radiation was used in either treatment arm. When discussing this trial, one author reported, "This will [allow] our patients to delay the use of radiation, particularly in this IDH mutant tumor population enriched with younger patients."[10] However, the study design eliminating the use of chemoradiation therapy ignores data supporting enhanced longevity with this standard-of-care regimen—also important for younger patients—in favor of a placebo. We believe that this unfounded study design illustrates how pharmaceutical funding has the power to trump an established treatment paradigm for a phase III study if the paradigm does not promise lucrative revenue.

How does radiation oncology overcome historical strongholds in perception and the lack of a third party "buying" a seat at the table? Along with potential assistance from the American Society for Radiation Oncology (ASTRO), teamwork is needed, both in establishing strong partnerships with referring providers and patients, as well as providing open communication and education on the benefits and risks of radiation treatment. Truly collaborative multidisciplinary input may go a long way in eliminating misconceptions, historical precedents, or financial biases that impede optimal treatment paradigms.

We must also collaborate with our own. As the old quote goes, "United we stand; divided we fall." While critical analysis and spirited discussion on topics such as photons vs protons, extent of heterogeneity or hypofractionation, and the use of adaptive treatment or not are essential for optimizing care, we must be wary of the optics that our patients and colleagues outside of radiation oncology perceive. In a unique specialty where myriad approaches often exist for a clinical situation, mutual respect among radiation, surgical, and medical oncologists, and heartfelt support to investigators in the trenches could enlighten attitudes in the media and within academia.

References

1) Zaorsky NG, Ahmed AA, Zhu J, et al. Industry funding is correlated with publication productivity of US academic radiation oncologists. *J Am Coll Radiol*. 2019;16(2):244-251. doi: 10.1016/j.jacr.2018.07.024

2) Connelly MT, Sullivan AM, Chinchilla M, et al. The impact of a junior faculty fellowship award on academic advancement and retention. *Acad Med*. 2017;92(8):1160-1167. doi:10.1097/ACM.0000000000001541

3) Kunkler IH, Williams LJ, Jack WJL, Cameron DA, Dixon JM. Breast-conserving surgery with or without irradiation in early breast cancer. *N Engl J Med*. 2023;388(7):585-594. doi:10.1056/NEJMoa2207586

4) Abbot B. More women with breast cancer could skip harsh radiation, study says. The Wall Street Journal; 2023. Accessed July 19, 2023. https://www.wsj.com/articles/breast-cancer-women-radiation-study-8391efd9.

5) Arsenault J, Parpia S, Goldberg M, et al. Acute toxicity and quality of life of hypofractionated radiation therapy for breast cancer. *Int J Radiat Oncol Biol Phys*. 2020;107(5):943-948. doi: 10.1016/j.ijrobp.2020.03.049

6) Kolata G. Rectal cancer patients could be spared the effects of radiation. The New York Times; 2023. Accessed July 19, 2023. https://www.nytimes.com/2023/06/04/health/rectal-cancer-radiation-treatment.html.

7) Schrag D, Shi Q, Weiser MR, et al. Preoperative treatment of locally advanced rectal cancer. *N Engl J Med*. 2023;389(4):322-334. doi:10.1056/NEJMoa2303269

8) Mellinghoff IK, van den Bent MJ, Blumenthal DT, et al. Vorasidenib in IDH1- or IDH2-mutant low-grade glioma. *N Engl J Med*. 2023;389(7):589-601. doi:10.1056/NEJMoa2304194

9) National Comprehensive Cancer Network. Central Nervous System Cancers (Version 1. 2023); 2023. Accessed July 19, 2023. https://www.nccn.org/professionals/physician_gls/pdf/cns.pdf.

10) Tucker N. Vorasidenib delays disease progression or death in IDH+ low-grade glioma Targeted Oncol; 2023. Accessed September 13, 2023. https://www.targetedonc.com/view/vorasidenib-delays-disease-progression-or-death-in-idh-low-grade-glioma.

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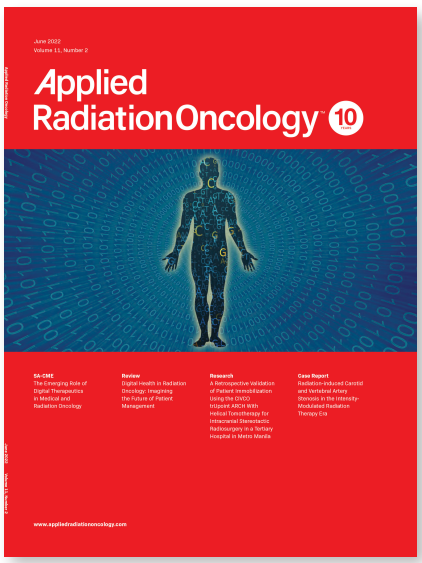

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