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Disparities in Colorectal Cancer Outcomes Among Young Adults and African Americans in the US

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Disparities in Lung Cancer for Black Patients in the US

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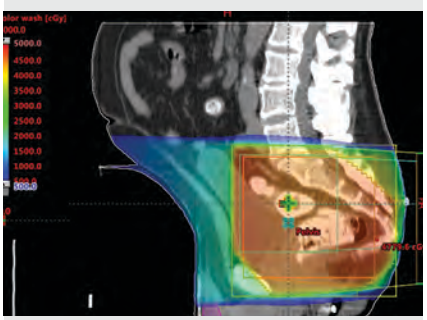

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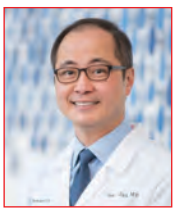

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FOCUS: RACIAL DISPARITIES IN CANCER CARE

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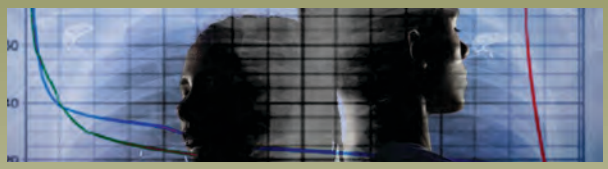

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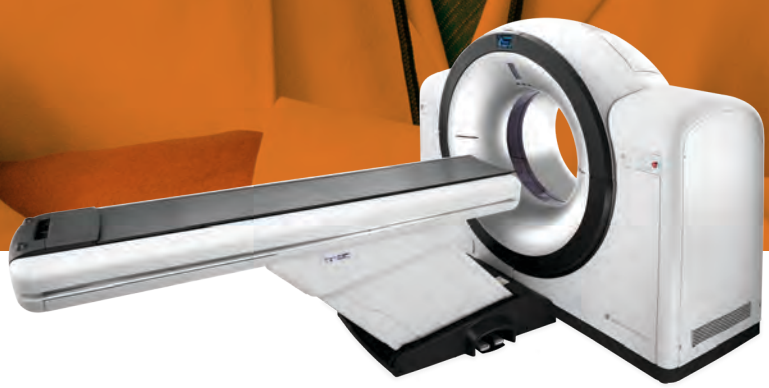

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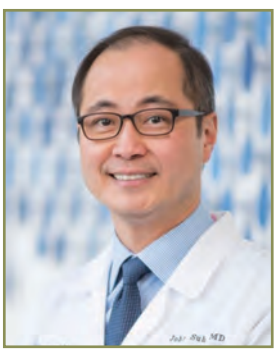
EDITORIAL

Breaking Barriers to Racial Disparities in Cancer Care



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

With more than 300,000 US lives lost to COVID-19 and months of egregious racial injustice, 2020 is a year that we will always remember given the magnitude of its volatility, uncertainty, complexity, and ambiguity. Unfortunately, COVID-19 and race also share more than just an unprecedented year: Growing evidence shows that various racial and ethnic minority groups are disproportionately impacted by the coronavirus.[1] These disparities, which are evident throughout the entire health care system, magnify its impact on cancer detection and treatment and accentuate our obligation to be part of the solution, especially for those who are most vulnerable.

Earlier this year, we postponed our original June lineup to provide timely coverage of COVID-19 and radiation oncology. We have taken similar steps for the December edition to focus on racial disparities in cancer care, underscoring the critical need to raise awareness and the need for action.

The first article presented, *Disparities in Lung Cancer for Black Patients in the US: An Overview of Contributing Factors and Potential Strategies for Radiation Oncologists to Bridge the Gap*, offers an important literature review and key strategies to help reduce and overcome shortcomings relating to incidence, screening, treatment and outcomes for Black patients. The second review, *Disparities in Colorectal Cancer Outcomes Among Young Adults and African Americans in the United States*, is a well-written update that examines screening options, disproportionate surges in diagnosis, and trends to aid groups with the worst colorectal outcomes. Both reviews offer free SA-CME credit.

We are also pleased to feature the thoughtful Resident Voice editorial, *Health Disparities in Radiation Oncology: Our Call to Action,* discussing financial toxicity, delayed access, lack of diversity in radiation oncology, and implicit physician bias, as well as the dire need for social accountability, equality and ultimately, justice.

Beyond health care disparities, our December issue presents several novel case reports, research articles, and additional content that we hope will enrich your knowledge base and provide pragmatic applications.

As we head into 2021, we look forward to greater safety, stability, and health, and offer sincere gratitude for those working tirelessly to achieve those goals, especially health care workers who have clearly epitomized the definition of being a hero. I also extend my deepest thanks to our Editorial Advisory Board for their time, direction, and tremendous support of *ARO*. They have been instrumental in our efforts to offer SA-CME credit, create specialty sections, build a robust Peer Review Panel, and so much more. We also offer special thanks to our knowledgeable reviewers who offer detailed, constructive and punctual feedback to authors, ensuring our high-quality content. Finally, thank you, our subscribers, for your feedback, social media callouts, and staunch support over the past nine years. You are the reason for our journal, and it is an honor to serve you.

As we transition to a New Year filled with hope, promise, and growth, we wish you an abundance of joy, health and purpose. Please continue to mask up, socially distance, and wash your hands so we can overcome this pandemic together and see each other in person very soon. Happy holidays!

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.*

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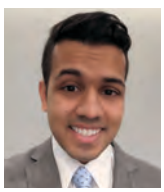
RESIDENT VOICE

Health Disparities in Radiation Oncology: Our Call to Action

Avinash R. Chaurasia, MD; Rohini Bhatia, MD; Michael C. LeCompte, MD; Kekoa Taparra, MD, PhD; Idalid "Ivy" Franco, MD, MPH; Allison Garda, MD; Benjamin Li, MD, MBA; Ian J. Pereira, MD



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Radiation oncology has made tremendous strides to establish itself as a vital discipline for the cure and palliation of cancer. However, as society has demonstrated increasing demands for fairness, equity, and dignity, we have lagged behind the forefront of these movements. Historically, our social accountability has been to those with means for the right care. From the perspective of the next generation of clinicians, we attempt to address these disparities and highlight potential ways our specialty can experience progress in these domains moving forward.

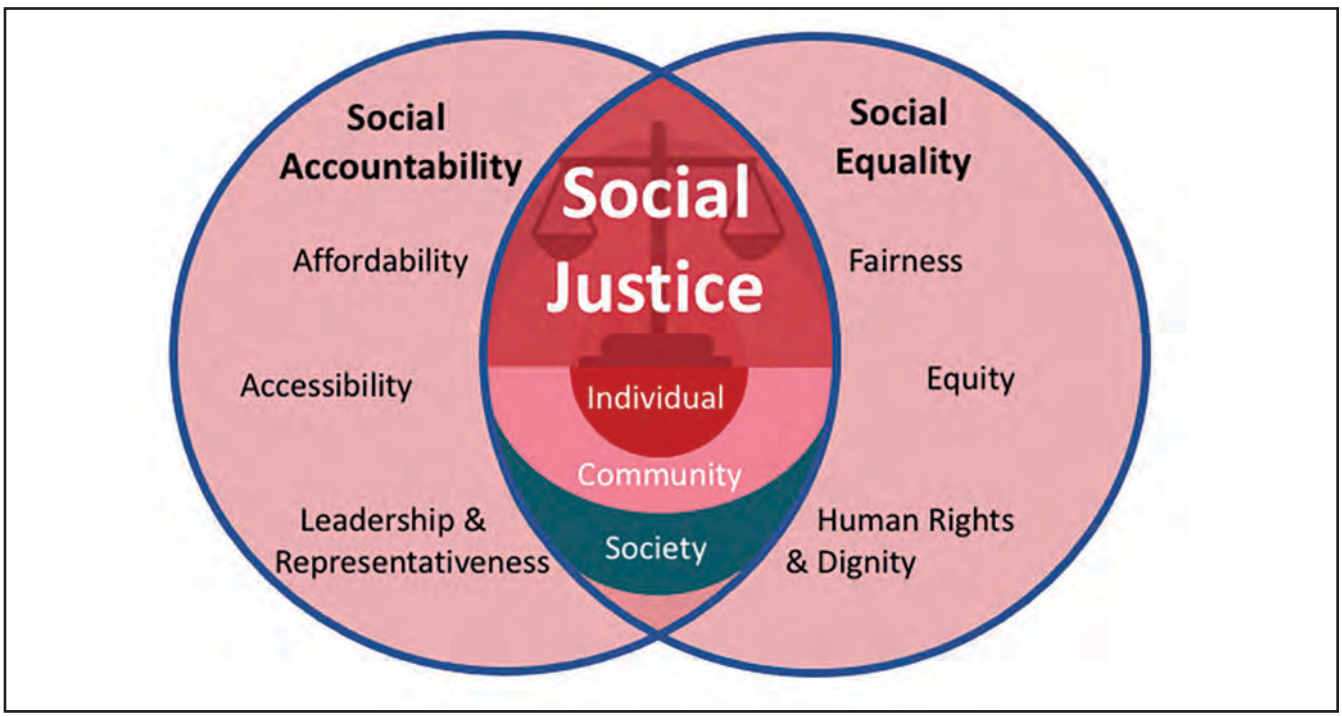
Financial Toxicity: When Less Really Can Be More

Increasing financial costs for our treatments, especially for our most vulnerable patients, limits quality of life, compliance, and survival.[1,2] Financial toxicity (FT) impacts multiple domains by hindering ability to access medications, attend appointments, afford living expenses, and adhere to recommendations for care. This disproportionately impacts patients with cancer[3] and nearly 1 in 6 undergoing radiation therapy (RT) experience moderate or severe FT.[4,5] FT follows racial and ethnic divides – 1 in 20 Black or Latina women with early stage breast cancer lose their home as a consequence and nearly half of these patients cut back on basic needs such as food.[6] Simple solutions may go a long way toward bridging this gap, starting at measuring the problem and increasing FT awareness for patients and providers.[1] More dynamic interventions can include increased cost transparency and accessibility to financial counseling, as well as sustainable policies to incentivize cost reduction.

Improving Access to Quality Care

Financial cost may only be the tip of the iceberg – there are also large disparities in the delivery of quality cancer care. African Americans with prostate cancer experience a longer time from diagnosis to treatment, even after controlling for socioeconomic factors.[7] Palliative care, integral to quality cancer care, is disproportionately utilized by Black patients who are 20% to 30% less likely to receive palliative RT.[8] Black pediatric patients are also less likely to receive proton therapy, despite equal enrollment in national prospective trials.[9] These data highlight that systemic and structural racism ingrained in society is experienced by our patients throughout the spectrum of cancer care.

Moreover, other socioeconomic barriers impede quality cancer care. It has been well-established that rural and remote communities have decreased rates



of RT utilization;[10] however, even urban urban populations lack access to newer technologies, especially among those with less insurance, lower socioeconomic status, and less education.[11] In the realm of research, younger, poorer, underinsured, non-White patients are underrepresented in cancer trial enrollment.[12] Dishearteningly, African American and Hispanic cancer trial enrollment has actually decreased over the past several decades.[13] Potential avenues to solvency include expanding trial access to underrepresented communities, guaranteeing insurance coverage for all standard-of-care treatment, and responsible financial incentives and assistance to defray costs. A targeted increase in accessibility to patient navigation programs has also shown promise in achieving quality cancer care.[14]

Leading Change

A diverse oncology workforce helps meet the complex needs of all Americans. Regrettably, diversity within our specialty does not reflect the populations we need to serve. The gender gap and its drivers continue to be an issue as women persistently face an uphill climb toward gender equity.[15] Underrepresented minorities (URMs) are also underrepresented in radiation oncology at the trainee (6.9%) and faculty levels (7.2% to 8.1%).[16,17] This is critical because racial and ethnic representativeness improves outcomes.[18] African American patients treated by physicians of the same race have more active shared decision making and improved overall satisfaction.[19] Similar results are seen among Latinx[20] and indigenous communities.[21] In addition, sociocultural-based programs involving Native Hawaiian physicians that leveraged shared language, culture, and values forged strong patient-physician relationships and improved cancer screening in rural and medically underserved areas.[22]

Ethnic and racial differences between physician and patient are well-defined barriers to care. Implicit bias may unintentionally dictate their relationship and undermine trust.[18] Well-intentioned providers have unknowingly incorporated their biases to limit person-centered care. Although the evidence base is growing for the benefit of increasing URMs in oncology, many groups are left out including LGBTQ populations and individuals with disabilities. Cultural sensitivity can be adopted through recruitment and retention with pipeline programs, but also inculcated through conscientious unlearning to eliminate unconscious bias. This grassroots effort will also require proactive development and recognition of diverse faculty and young leaders at all levels.

The Way Forward

Cancer control can only be achieved for all by addressing health disparities. For our most vulnerable populations, there are interventions that no medication, radiation treatment, or technology can achieve, yet will have the unseen impact of strengthening our society. We must demand more social accountability from our policy makers, institutions, and ourselves. We must create solutions that address it at its roots including affordability, accessibility, and lack of leadership

and representativeness in our workforce. Social justice in radiation oncology is not achieved until we achieve social accountability and social equality for all.

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SA–CME Information

Disparities in Colorectal Cancer Outcomes Among Young Adults and African Americans in the United States

Description

This article reviews current literature continuing to highlight persistent disparities in the diagnosis, treatment and survival outcomes in colorectal cancer in young adults and Black individuals. Topics discussed include screening recommendations, age disparity, racial disparity, and differences in outcomes between Black and White patients and within the growing cohort of young adult patients

Learning Objectives

After completing this activity, participants will be able to:

1. Readers will be able to learn and apply the screening options appropriate to aid in the early detection of colon cancer
2. Readers will learn what patient population group, besides African Americans, is experiencing a disproportionate increase in incidence in colorectal cancer diagnosis
3. Readers will understand which groups of patients have the worse colorectal cancer outcomes and use awareness of these trends to improve best practices

Authors

Maya C. Graves, MS, *is a medical student at New York University Grossman School of Medicine, New York, NY.* ***Janna Z. Andrews, MD,*** *is an associate professor at Zucker School of Medicine at Hoftstra/Northwell, Phelps Hospital, Sleepy Hollow, NY.*

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Disparities in Colorectal Cancer Outcomes Among Young Adults and African Americans in the United States

Maya C. Graves, MS; Janna Z. Andrews, MD

Disparities in colorectal cancer outcomes for young adults (YA) and African Americans (AA) have been long acknowledged within the medical community. Colorectal cancer (CRC) is the third most common cancer in men and women, and a leading cause of cancer-related death throughout the United States. In 2020, it is projected that 147,950 individuals will be newly diagnosed with CRC, with 104,610 of these cases presenting as colon cancer (CC) and 43,340 as rectal cancer (RC).[1] Presentation with advanced-stage disease attributable to delayed diagnosis leads to less favorable outcomes; thus, early detection is considered a means to decrease deaths associated with CRC.[2] Additionally, modifiable risk factors like physical inactivity, smoking, obesity and poor diet are responsible for a proportion of the cancer recurrences and deaths in patients diagnosed with CRC.[3]

While the incidence of CRC in people over age 50 has declined from 2001 to 2012, the incidence rates of CRC in YAs (< 50 years) have continued to increase since the mid-1990s.[4-6] By the turn of the century, most notable changes in this uptrend were highlighted in the youngest age group (20 to 35 years).[4-6] Analyses of the most recent data years (2012 to 2016) have found that incidence rates increased by 2.2% and 1.1% annually in individuals younger than 50 and 50–64, respectively.[7] This data is in contrast to adults aged 65 and older, whose incidence rates have decreased by 3.3% annually.[7] These rising incidences will account for an estimated 12% of the total projected 147,950 cases in 2020 to be diagnosed in patients younger than 50.[1] In terms of mortality rates, YAs diagnosed with CRC will contribute to 7% of CRC-related deaths this year.[1]

Age group differences are not the only disparity observed when looking at outcomes in CRC treatment and survival. The American Cancer Society (ACS) reports that during the most recent data-gathering period (2012 to 2016) CRC incidence rates in AA were 20% higher than those in non-Hispanic Whites, and mortality rates were double the incidence, 40% in AA compared to non-Hispanic Whites.[7] In this article, we review current literature continuing to highlight persistent disparities in the diagnosis, treatment and survival outcomes in CRC in YAs and AAs.

Ms. Graves *is a medical student at New York University Grossman School of Medicine, New York, NY.* ***Dr. Andrews*** *is an associate professor at Zucker School of Medicine at Hoftstra/Northwell, Phelps Hospital, Sleepy Hollow, NY.* *Disclosure: The authors have no conflicts of interest to disclose. None of the authors received outside funding for the production of this original manuscript and no part of this article has been previously published elsewhere.*

Screening Recommendations

The U.S. Preventive Services Task Force (USPSTF) and Centers for Disease Control and Prevention (CDC) recommend CRC screening for average-risk people aged 50 to 75 years. Average risk includes adults who do not have a personal or family history of CRC or certain types of polyps, no history of inflammatory bowel diseases (ulcerative colitis or Crohn's disease), no confirmed or suspected hereditary CRC syndrome, and no personal history of previous radiation therapy in the abdomen or pelvis.[8] Screening can include: fecal occult blood test (FOBT), fecal immunochemical test (FIT), a combination of stool DNA and FIT test (FIT-DNA), computed tomography (CT) colonography, flexible sigmoidoscopy, or colonoscopy.[9] From 2009 to 2015, the CDC implemented the first public health program focused solely on increasing the use of CRC screening tests at a population-based level, the Colorectal Cancer Control Program (CRCCP).[9] However, 2016 data continued to highlight that only 67% of adults ages 50 to 75 were up to date with screening, and 26% of this age cohort had never been screened.[9]

The U.S. Multi-Society Task Force (MSTF) recommends that CRC screening should begin at age 50 in average-risk persons, except AAs in whom limited evidence supports screening at age 45 years.[10] The MSTF-recommended tests are ranked into 3 successive tiers based

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on performance features, costs and practical considerations. Tier 1: colonoscopy every 10 years and annual FIT. Tier 2: CT colonography every 5 years, FIT-fecal DNA every 3 years and flexible sigmoidoscopy every 5-10 years. Tier 3: capsule colonoscopy every 5 years.[10]

The American Cancer Society (ACS) offers a qualified recommendation for patients aged 45 and a strong recommendation for patients aged 50 years, that adults with an average risk of CRC should undergo regular screening. CRC screening options include annual FIT, annual guaiac-based fecal occult blood test, multitarget stool DNA test every 3 years, colonoscopy every 10 years, CT colonography every 5 years, and flexible sigmoidoscopy every 5 years.[8] With acknowledgement of variability in test type availability, effectiveness, and patient burden, the ACS endorses that screening with any of these methods is associated with a significant reduction in CRC incidence through early detection and removal of polyps and other precancerous lesions.[8] By involving patients in decision-making, the ACS hopes to increase the likelihood of long-term adherence.[8]

Age Disparity

Since 2000, the increasing rates of CRC diagnoses have been documented in patients younger than 50, with the greatest increase in patients 20 to 35 years.[6] With a growing incidence of 2.2% annually for this age group, models projected by Bailey et al expect the incidence rates of CRC in YA to nearly double by 2030.[6,11] Clinicopathologic and molecular features of CRC in YA differ from those who develop CRC after age 50. Patients < 50 more often present with advanced disease characterized by tumors with aggressive histologic features and synchronous metastases.[12-14] Additionally, primary tumors in YA are normally localized in the rectum and distal (left) colon.[14] Colorectal cancers are classified by major histological subtypes: adenocarcinoma, mucinous adenocarcinomas, signet-ring cell carcinomas and several additional rare subtypes. In patients > 50 years, adenomatous polyps and adenomatous polyposis coli (APC) mutations are more common, while in young patients (18 to 29 years), signet-ring cell cancer is more prevalent.[14,15] In the realm of all CRC cancer types, signet-ring cell carcinoma is rare and associated with poor prognostic factors.[16]

Inherited syndromes associated with abnormal genes passing from generation to generation are known to increase the likelihood of certain cancers in YAs. Polyposis and nonpolyposis syndromes are inherited syndromes recognized to predispose YAs to CRC. The most common polyposis syndrome, familial adenomatous polyposis (FAP), is an autosomal dominant syndrome affecting the APC tumor suppressor gene.[17] Loss of function in APC causes polyps to develop in hundreds to thousands throughout the colon and rectum. Polyp development typically begins at ages 20 to 30, and without prophylactic colectomy, the lifetime risk of developing CRC approaches 100%.[17] Lynch syndrome (LS) is the most common nonpolyposis hereditary cancer syndrome associated with CRC and endometrial cancer predominantly.[17] LS is caused by an autosomal dominant heterozygous germline mutation in the DNA mismatch repair genes. Polyps developing in patients with LS progress to carcinoma often faster than sporadic cases, and these patients have a CRC lifetime risk reaching 70%, with 40% of LS patients diagnosed with CRC before age 40.[17] Microsatellite instability (MSI) phenotype is present in many cancers, but has been extensively characterized in CRC and is a diagnostic feature of LS.[18,19] MSIs result from a germline mutation in mismatch repair (MMR) genes MLH1, MLH2, MLH6, PMS2 or a germline deletion in epithelial cell adhesion molecule (EPCAM).[17,18] A retrospective review of > 36,000 CRC patients found that patients with recognized hereditary syndromes were more likely to have a high level of microsatellites and to be diagnosed under age 50.[12] In conjunction with family history, microsatellite identification is a first step when diagnosis of LS is suspected.[19] Guidelines supported by the National Comprehensive Cancer Network recommend universal testing for all patients with newly diagnosed CRC to identify deficient MMR or MSI to determine LS association.[20] While the outlook for LS-associated CRC may be promising, heritable syndromes (including LS and FAP among others) only account for roughly 35% of CRC cases in YAs, leaving a greater proportion of colorectal malignancies in this age group presenting with sporadic cases.[15,17] Therefore, risk factors associated with sporadic CRC in the YA population warrant further investigation.

Evaluation of recent studies conducted by Burnett-Hartman et al suggests that stage-specific survival among YAs diagnosed with CRC is equivalent to, or better than, survival outcomes for patients > 50 years.[14] When evaluating the treatment and outcomes of young CRC patients in community-based health care systems, this study found that a majority (83%) of YAs with CRC receive surgery at comparable rates to patients > 50. Additionally, YAs were more likely to receive systemic therapy within 6 months of diagnosis as compared to counterparts > 50 years.[14] Risk of all-cause mortality and mortality due to CRC was lower in early onset patients than older patients (all cause = HR O.66 CI 0.58-0.75; CRC specific = HR 0.66 CI 0.56-0.79).[14] These findings align with another population-based study using the Surveillance, Epidemiology, and End Results (SEER) database to determine treatment plans for average-risk patients who presented with CRC before the recommended screening age (37,847 patients, 14.7% of cohort).[21] They found that younger patients with distant metastases were more likely to still receive surgical

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Table 1. American Cancer Society Reported Trends of Colorectal Cancer Incidence and Mortality Rates

Year	Race	Incidence Rate		Mortality Rate		% Increases (Blacks Compared With Whites)
		Male	*Female*	*Male*	*Female*	
1997-2001	Black	72.9	56.6	34.3	24.5	Incidence 15%; Mortality 40%
	White	63.1	45.9	24.8	17.1	
2001-2005	Black	71.2	54.5	31.8	22,4	Incidence 20%; Mortality 45%
	White	58.9	43.2	22.1	15.3	
2003-2007	Black	68.3	51.5	30.5	21.0	Incidence 20%; Mortality 45%
	White	56.8	41.9	20.9	14.6	
2006-2010	Black	63.8	47.6	29.4	19.4	Incidence 25%; Mortality 50%
	White	50.9	38.6	19.2	13.6	
2009-2014	Black	58.3	42.7	25.9	16.9	Incidence 20%; Mortality 40%
	White	46.1	35.2	17.3	12.3	
2013-2017	Black	53.8	39.9	23.8	15.6	Incidence 20%; Mortality 40%
	White	44.0	33.9	16.3	11.7	

Incidence rates in the table are per 100,000 people and age adjusted to the 2000 US standard population. Source: American Cancer Society Facts and Figures 2005-2020

therapy for the primary tumor followed by radiation therapy.[21] Aggressive treatment methods in patients < 50 have supported better overall disease-specific survival. Adjusted 5-year cancer-specific survival for patients < 50 was better for localized (95.1% vs 91.9% $P < 0.001$), regional (76% vs 70.1% $P < 0.001$), and distant disease (21.3% vs 14.1% $P < 0.001$), despite a larger percentage of YA presenting with more advanced disease.[14,21]

Racial Disparity

Historically, AAs have had higher incidence rates of CRC and poorer survival outcomes than those of White counterparts.[8,22] According to the ACS, in 2005 the incidence rate of CRC in AAs was 15% higher than in Whites, and mortality rate for AAs was 40% higher than in Whites[7] — trends that have continued (**Table 1**). Most recent data reported in 2020 show the relative difference in CRC incidence rates between Whites and AAs is now 20% higher for AAs.[7] Relative differences in mortality rates have remained at 40%.[7] These growing and persistent disparities are problematic because CRC is a treatable cancer when detected as precancerous or localized malignant lesions.[23] In 2010, racial disparities were thought to be explained by differences in socioeconomic status between AAs and Whites.[22] Yet today, many intrinsic and extrinsic factors are recognized contributors to the disparate incidence rates and outcomes of CRC in AAs. Intrinsic factors may include comorbidities, lifestyle choices, medical mistrust, and tumor characteristics. Extrinsic factors may include poverty, insurance status, accessibility to quality health care (medical treatment, surgical treatment) and implicit bias among physicians and established US health care systems.[24–29] Each factor contributes to lower rates of CRC detection and inferior cancer-specific outcomes in AAs as compared to Whites. As mentioned, overall CRC screening rates for the entire population are estimated to be 60% to 70%.[30] A recent prospective cohort study of 47,596 adults > 50 years looked at the use of CRC screening among AAs.[30] Baseline colonoscopy rates were significantly lower among AAs (67.3% vs 75.5%) than Whites; meanwhile, sigmoidoscopy usage rates were similar across the racial groups.[30] For patients who had undergone colonoscopy or sigmoidoscopy at the time of baseline screening, a 46% decreased risk of CRC was detected.[30]

A systematic review from 2011 identifying gaps in CRC screening among AAs concluded that three levels of modifiable barriers can potentially improve screening rates. These include issues at the level of patient barriers, provider barriers, and systemic barriers.[24,31] Patient barriers included psychological factors (fear) and low health literacy regarding CRC risk and perceived susceptibility.[31] Provider barriers included confusion about age recommendations, low acknowledgement of patient barriers and lack of provider recommendation for colonoscopy (the most frequently reported provider barrier to CRC screening in AA of those listed).[31] Systemic barriers included costs, insurance coverage, fewer specialist referrals and limited primary care visits.[31] From 2008 to 2016, implementation of the Affordable Care Act (ACA) and expansions in Medicaid increased access to CRC screening.[32]

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During this period, screening in Whites increased by 0.76% ($P < 0.001$) while for AAs, the rate increased significantly by 1.14% ($P < 0.001$) per year from 2008 to 2014 and then remained stagnant from 2014 to 2016.[32] While these numbers are encouraging, the change did not surpass the previously reported disparity in screening, and screening numbers for Whites continued to exceed AAs and all other racial groups. Overall they found that the absolute difference in screening rates for Whites became smaller, while for Blacks, the disparity in screening slightly increased (3.3% to 4.0%).[32]

Another barrier to equitable health outcomes identified by a National Cancer Institute study was poor recruitment, enrollment and retention levels of AA patients in clinical trials.[33] The study noted that the numbers of AAs enrolled and retained in clinical trials were not representative of the minority population numbers across the US,[33] thus decreasing generalizability. Not surprisingly, at a study center where special recruitment efforts (including additional recruitment costs) for AAs were implemented, levels of minority representation for this study equaled or exceeded the levels of the catchment population.[33] In order to engage AA participants, two studies concluded that the most effective mechanism was to address cultural factors.[24,33] This was achieved by providing accurate information to help overcome a sense of mistrust about clinical trials, promoting community outreach via trusted organizations, and by having Black staff and investigators available to interact with participants.[33]

As highlighted by the ACA, CRC outcomes for AA patients are worse than those of Whites.[1] One study of 199,098 CRC patients from the National Cancer Database (NCDB) from 2004-2012 compared overall 5-year survival across non-Hispanic Black and non-Hispanic White patients.[28] They found that AA patients were more likely to be diagnosed at a younger age (28.1% vs 26.2%), have right-sided colon cancer (33.3% vs 24.1%), and present with stage IV disease (27.6% vs 22.6%).[28] Upon matching by insurance status, the proportional difference in AA and Whites presenting with metastatic disease decreased by 2.2%.[28] Unmatched 5-year survival outcomes for this cohort showed a 9.2% difference (95% CI, 57.3% [56.6 to 57.9] for AAs and 66.5% [66.3 to 66.8] for Whites).[28] After matching by insurance status, the difference decreased to 4.9%.[28] Insurance also played an important role in CRC outcomes based on surgical intervention. While patients across all races undergoing surgical treatment were equally likely to receive colorectal resection by laparoscopic surgical technique, AAs as compared to White patients were more likely to have postoperative complications (OR 1.23, 95% CI 1.17-1.29), including bleeding, cardiac failure, renal failure and respiratory failure.[29] When the data was stratified by insurance type, patients with private insurance were more likely to have laparoscopic procedures as compared to all other insurance types.[29] Patients with Medicare or Medicaid were more likely to have postoperative complications (OR 1.30, 95% CI 1.24 to 1.37, OR 1.40, 95% CI 1.31 to 1.50, respectively).[29]

Physician bias is an emerging field of study without clear recommended methodology. Despite the conceptual nature of bias, disparate health outcomes due to implicit biases are tangible and therefore this factor must be addressed. A systematic review evaluating 27 articles found evidence for implicit bias among physicians and nurses, manifested at levels to a similar degree as the general population.[27] This is concerning as variability in rates of CRC screening and treatment recommendations for AAs are likely influenced by this phenomenon.

Racial and Age Disparity

In addition to existing disparities for CRC incidence and outcomes for age and race independently, differences in outcomes are reported between AA and White patients in the growing cohort of YA patients. A population-based study utilizing SEER data from 2004 to 2011 found that in all patients under age 50, 19% were diagnosed in AA patients, compared to 16% in Whites.[34] Furthermore, young AA patients continue to be diagnosed at later tumor stages and have poorer outcomes.[34,35] Since differences in screening cannot be attributed to an age group < 45 years, differences in tumor biology have been considered as a potential association with poorer outcomes for this race group.[35] While AAs have lower median survival for proximal, distal and rectal disease,[34] primary tumor location differs for AA and White patients. Cancer arising in the colon is found in a higher proportion of AA patients (71.6%) than White (58.2%), and AA patients are more likely to develop proximal CC, which is an independent risk factor for poor outcomes across all ethnic and racial groups.[34] The median time from diagnosis to treatment, surgery and chemotherapy are comparable across race groups, but AAs had the lowest frequency of radiation therapy use.[35] Despite comparable treatment efforts, AAs have significantly lower median and 5-year survival rates (Blacks 58.8% vs Non-Hispanic Whites 66.9%, $P < 0.001$).[35]

Conclusion

Disparities in CRC detection, diagnosis and survival outcomes continue to persist on the basis of age and race. The growing issue of YAs being diagnosed with CRC raises concern as only a fraction of these cases can be attributed to hereditary syndromes with a predictable clinical sequalae. Despite the predicted surge of CRC cases in YAs by 2030, there has been no updated screening guidance or qualified recommendation to address the growing cohort of CRC patients < 45 years old. The choice to not screen adults under age 45 is based on a lack of supporting evidence that screening average-age-risk individuals < 50 years will translate to increased

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early detection of CRC or increased patient survival.[36] Similarly, without full understanding of CRC biology in young adults, clear benefit vs increased risk in early screening cannot be guaranteed.[37] Fortunately, YAs diagnosed with CRC can often withstand more aggressive treatment regimens, and reported staged-based survival outcomes are comparable to older counterparts.

These considerations further support the importance of heightened awareness among both physicians and the general population about the CRC uptrend in YAs. Beginning education early with medical students and positioning continued awareness toward primary health personnel may help to improve this emerging epidemiological trend.[38]

To alleviate the burden of CRC on AA communities, changes are needed to narrow the gap in access, prevention and treatment. Despite targeted efforts to promote screening and engagement of AA populations in research trials, comparable utilization rates to Whites have not yet been achieved. Culturally based interventions and health policy changes[24,33] have proven useful; however, these are only addressing one element of the greater issue. Since tumor characteristics and genetics cannot solely account for the disparities, structural barriers such as insurance and access to care play a role in the treatment of AAs and overall patient outcomes. Furthermore, investigation into the impact of physician bias on patient prevention counseling, time to treatment, and recommended therapy options is warranted.

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SA–CME Information

Disparities in Lung Cancer for Black Patients in the U.S.: An Overview of Contributing Factors and Potential Strategies for Radiation Oncologists to Bridge the Gap

Description

This review article describes key factors that contribute to lung cancer disparities for Black patients and discusses strategies and future directions for radiation oncologists to bridge the gap. Topics discussed are contributing factors for disparities in lung cancer incidence, disparities in lung cancer prevention, disparities in lung cancer treatment and outcomes, and potential strategies to overcome barriers.

Learning Objectives

After completing this activity, participants will be able to:

1. Understand the roles that socioeconomic status, smoking, genetics, and resilience factors play in contributing to disparities in lung cancer incidence in Black/African American individuals
2. Understand how current lung cancer prevention strategies and disparities in treatment lead to worse outcomes for Blacks with lung cancer
3. Adopt strategies in the clinic to reduce cancer disparities and address barriers to social equity

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Disparities in Lung Cancer for Black Patients in the US: An Overview of Contributing Factors and Potential Strategies for Radiation Oncologists to Bridge the Gap

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The tragic death of George Floyd from asphyxiation has fueled a movement against social injustice and racism that has highlighted inequities that exist in all sectors of the United States. The ongoing coronavirus disease 2019 (COVID-19) pandemic has also increasingly brought to light the disparate health outcomes that exist among racial and ethnic minorities. The field of oncology is not immune to such inequities, as racial and socioeconomic factors play a pivotal role in cancer control.

Black individuals comprise 13% of the United States population and assume a disproportionate burden of cancer with the worst outcomes of all racial and ethnic groups for most cancers.[1,2] Lung cancer is the second most common cancer in the United States.[3] Black men are approximately 15% more likely to develop lung cancer compared to White men and have the highest lung cancer mortality of all racial and ethnic groups.[4,5] Lung cancer in the Black population is a multifactorial problem and to reduce such disparities, an understanding of all contributing variables in cancer prevention, diagnosis, and treatment is imperative. Furthermore, the care of lung cancer patients is multidisciplinary, and radiation oncologists play an important role in delivering individualized care. This review article provides background on key factors that contribute to lung cancer disparities for Black patients and discusses strategies and future directions for radiation oncologists to bridge the gap.

Contributing Factors for Disparities in Lung Cancer Incidence

Socioeconomic Status

Socioeconomic status (SES), which is strongly correlated with race in the United States, is the most critical driving force for lung cancer disparities.[2,5] Household income and education status are key determinants of SES. In 2018, the poverty rate for Blacks (20.8%) was more than double that of Whites (8.1%), and in 2019, 26.1% of Blacks vs 40.2% of Whites had obtained at least a 4-year college degree.[2,5-7] Individuals with a lower SES encounter several barriers to accessing health care due to difficulties obtaining adequate health insurance coverage, which frequently contributes to more advanced cancer diagnoses and a higher risk of cancer death.[2,5,8-10] In 2019, 10.1% of Blacks were uninsured compared to 6.3% of Whites, although notable strides by the passage of the Patient Protection and Affordable Care Act in 2010 and the expansion of Medicaid reduced the number of uninsured Blacks by 50%.[2,11] However, healthcare in the United States remains in flux, and the accessibility of health care in the future remains uncertain, which in turn may disproportionally affect the Black community.

The interaction of SES with race/ethnicity, gender, and tobacco use is complex. It is well established that patients in lower socioeconomic brackets smoke more; however, studies have shown that despite matching for socioeconomic status, Blacks still have a higher incidence of lung cancer.[12-14] Interestingly, the increased lung cancer mortality rate in Blacks vs Whites is most pronounced when examining only males at higher education levels, likely because this is one of the only subcategories where Blacks actually have higher smoking rates than Whites.[15] On the other hand, Black

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women are less likely to smoke than White women for every SES level.[16]

Smoking

As smoking is one of the strongest risk factors for lung cancer development, differences in smoking exposure could potentially lead to the observed disparities in lung cancer incidence and outcomes in Black patients. Blacks diagnosed with lung cancer tend to be light or intermittent smokers that start smoking later in life. However, when matching smoking rates across racial groups, Blacks still have a higher lung cancer incidence, suggesting that Blacks are more susceptible to lung cancer at lower levels of tobacco use.[17,18] Furthermore, racial, ethnic, and generational trends in smoking are constantly evolving and the prevalence of smoking depends on the age at which it is measured. For example, Whites are more likely to be current smokers up to age 50, after which Blacks have a higher smoking prevalence; in addition, the intensity of smoking varies between Blacks and Whites, with Blacks being more likely to be lower-intensity, longer-duration smokers.[19] Cigarette preferences are also different among Black vs White smokers as approximately 70% to 85% of Blacks vs 20% to 30% of Whites use mentholated cigarettes that counter the irritant toxins of the tobacco product.[20] It is theorized that mentholation may affect individual smoking behavior and thereby potentially increase cancer risk.[21]

Segregation and other geographic factors are also important influencers of smoking habits. Segregated neighborhoods where living conditions are challenging impose additional stressors on those living within them, thereby facilitating the onset of smoking, making smoking cessation more difficult, and deterring individuals from seeking medical care or adhering to treatment regimens.[16]

Genetics

To date, no genetic mutations specific to Black people have been identified as a risk factor for lung cancer; in fact, African-born Black men and women were found to have an approximately 65% lower frequency of lung cancer compared with Blacks born in the United States.[22] Although some heterogeneity in cancer incidence has been documented between regions of birth in Africa, additional studies are warranted to compare the rate of lung cancer in Blacks, Whites, and native Africans.[22] Kytola et al examined tumor genomics and found a significantly higher mutation rate in the *TP53* gene in the Black patient subgroup, suggesting that genomic instability caused by tobacco may contribute to cancer outcome disparities among different racial/ethnic groups.[23] Other studies have proposed that racial differences in nicotine metabolism may add to the observed disparities in lung cancer incidence. Although the link to malignancy has not been clarified, it has been shown that Blacks have higher circulating levels of urinary and blood cotinine concentration; cotinine is a major metabolite of nicotine, as more than 70% of nicotine is converted to cotinine by the CYP2A6 enzyme.[24]

Resilience Factors

Protective resources and coping mechanisms may potentially mitigate the negative effects of risk factors for developing lung cancer. Higher levels of religious engagement by Black women compared to White women may partially explain why Black women have a lower smoking rate.[16] A study by Alexander et al showed that Black adolescents have significantly stronger religious beliefs against smoking than do White adolescents, although the protective effect of religious beliefs on initiating smoking was stronger for Whites than for Blacks.[25]

Disparities in Lung Cancer Prevention

Currently, the U.S. Preventive Services Taskforce (USPSTF) has drafted new lung cancer screening criteria using low-dose computed tomography (LDCT) for adults ages 50 to 80 years with a 20 pack-year smoking history and who either smoke or quit within the last 15 years.[26,27] These recommendations were formed based on the findings of the National Lung Screening Trial (NLST), in which a 20% reduction in lung cancer mortality was found in those screened with LDCT vs chest x-rays in a largely White cohort with < 5% of Black patients included. The recommendations were recently modified in draft form in 2020 based on the results of a USPSTF-commissioned systematic review.[26,28]

Blacks are typically diagnosed with lung cancer at earlier ages compared to Whites; for example, Black men between ages 40 and 54 are two to four times more likely than White men to develop lung cancer, even after adjusting for smoking.[29] Furthermore, as noted previously, Blacks with lung cancer often have lower overall tobacco exposure. As age and smoking history comprise the main eligibility criteria for LDCT screening, this may contribute to racial disparities in lung cancer outcomes. A recent study of lung cancer cases diagnosed between 1998 and 2014 found that Blacks were more likely to be deemed ineligible for LDCT screening compared to Whites,[30] although the recently drafted USPSTF guidelines have decreased the smoking age and pack-year requirement, which may help reduce future disparities. Alternatively, an individualized lung cancer risk model has also been proposed that includes additional demographic, clinical, and smoking variables, which would significantly increase eligibility of Blacks for lung cancer screening and reduce mortality as well.[31]

Disparities in Lung Cancer Treatment and Outcomes

The 5-year survival rate for lung cancer is lower for Black patients vs White patients (16% vs 19%) and Black men have the highest lung cancer death rate of any racial or ethnic group.[2] Despite the lung cancer mortality gap, studies

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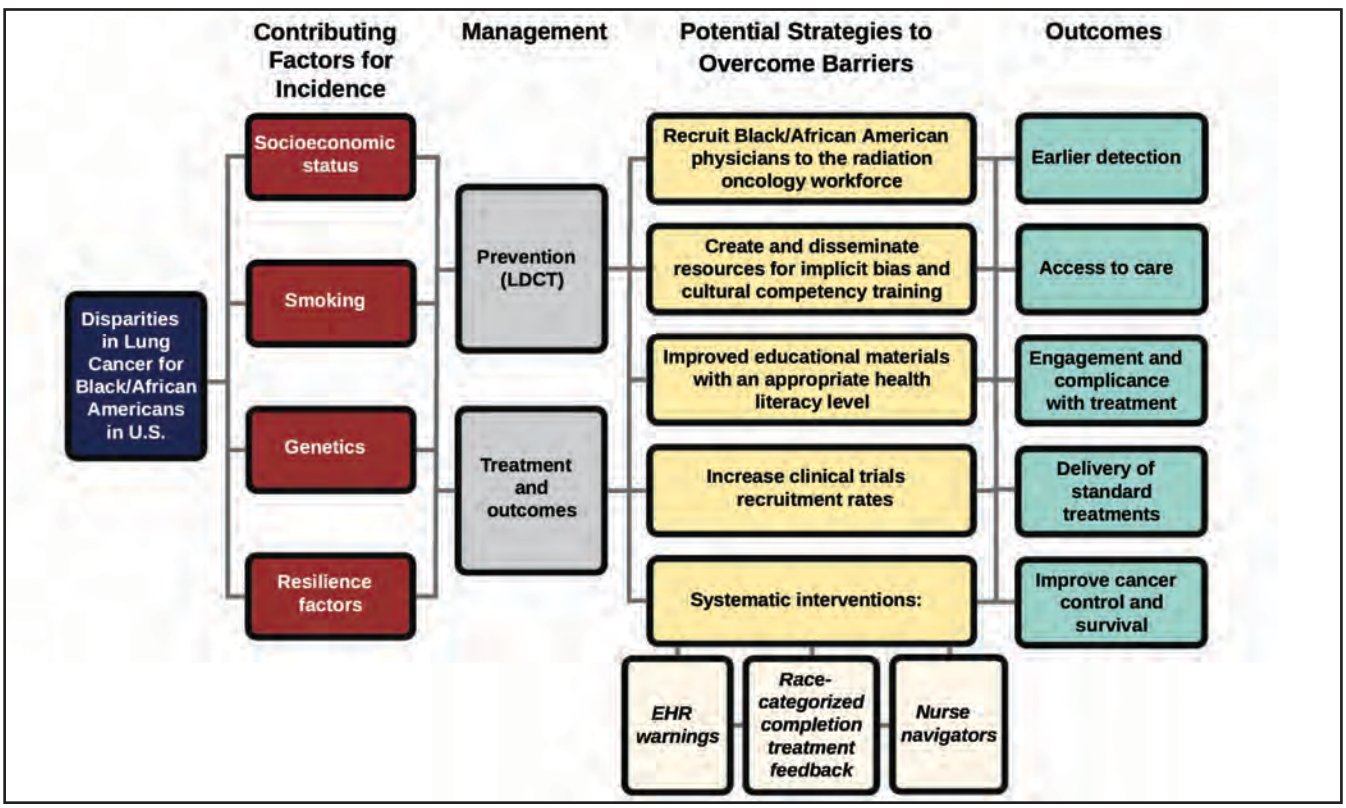

FIGURE 1. *Lung cancer disparities in Black patients is a multifactorial problem across the cancer care continuum. LDCT = low-dose computed tomography; EHR = electronic health record.*

have shown that when access to care is controlled for, much of the racial survival difference disappears.[5] Because over 50% of all lung cancer cases nationwide are diagnosed as either locally advanced or metastatic, where treatments are unlikely to be curative, diagnosing lung cancer early is critical.[4] Blacks are more likely to present with advanced disease, at least partially due to lower socioeconomic status and the corresponding increase in difficulty in accessing appropriate care.[32] Insurance status has also been linked to survival as lung cancer patients with private insurance have higher rates of surgical intervention and overall survival.[4] Nevertheless, access to care does not completely explain the disparity in lung cancer treatment. Even with equal access to care, Black patients are less likely to receive radiation treatment and systemic therapy or undergo surgical resection as compared to White patients, implying that access to high-quality care remains a challenge.[33]

Despite the disparities in lung cancer treatment outcomes for Black patients, the lung cancer incidence for Blacks has been on the decline since 1990, which in turn has coincided with a decline in lung cancer death rates for both Black men and women.[2] The decline in lung cancer death rates are due to the decreased prevalence of smoking, which has been notably more rapid in Blacks than in Whites.[2]

Potential Strategies to Overcome Barriers

Population health strategies for cancer screening and treatment have improved greatly over time; however, an unacceptable health inequity remains. Overcoming disparities in lung cancer is difficult, but data suggest potentially effective strategies can be utilized by radiation oncology departments.

Lack of physician diversity is a potential contributor for disparities, especially when caring for cancer patients.[34] Studies have demonstrated that Black academic faculty are more likely to perform health disparities research than White faculty, and minority physicians are more likely to practice in underserved communities and treat uninsured patients.[35,36] Despite a doubling of Black US graduate medical education trainees from 1984 to 2016, a disproportionate exclusion of Black physicians continues in the radiation oncology workforce.[37] Increased efforts are needed to understand barriers to radiation oncology training for Black physicians in order to develop evidence-based interventions.[37]

A cancer diagnosis is a difficult journey, and many patients find it challenging to understand and navigate the various aspects of care. Patient navigators are trained to offer support and enable completion of cancer workup and appropriate treatment in a timely manner.[38] Studies show that interventions, including use of navigators, can improve the gap in health disparities and are important to improve treatment

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compliance resulting in better outcomes; radiation oncology nurse navigators can play a vital role in facilitating care for minority patients.[39,40]

The attitude and behaviors of health care providers contribute to health disparities.[41] Physicians can look to improve the trust, communication, and overall patient relationships through implicit bias and cultural competency education. Implicit bias is a set of attitudes and beliefs that exist outside of conscious awareness and are difficult to control; prior work has suggested that most health care providers appear to have implicit bias, with a positive attitude toward White patients and a negative attitude toward Black patients.[41] Recognizing these biases and developing appropriate interventions is necessary to deliver equitable care for Black patients. Understanding what influences one's health care decisions is also important, as it opens the door to greater communication and trust, thereby decreasing barriers to health equity. Continuing to expand cultural competency training and education to all areas of health care may help improve racial and ethnic health disparities.[42] Radiation oncology professional organizations have the opportunity to champion significant change by leading the way in developing implicit bias and cultural competency training resources that are accessible to all physicians. Academic centers can also promote change by developing a focused curriculum to address these issues directed toward radiation oncology faculty and residents.

An additional area of improvement is educating lung cancer patients at an appropriate health literacy level. Health literacy is the degree to which individuals have the capacity to obtain, process, and understand basic health information needed to make appropriate health decisions.[43] Low health literacy is associated with a decreased likelihood of seeking cancer information from a health care professional, an increased sense of fatalism about cancer, decreased participation in cancer control programs, later stage of cancer diagnosis, and worsened quality of life.[44] Explaining radiation treatment to patients in simple terms can pose a challenge, and studies have demonstrated that most radiation oncology websites have patient education materials that require a high school graduate's comprehension level.[45] More readable radiation patient education materials that also consider cultural sensitivity need to be developed. Improved patient education materials could increase health literacy and allow for more productive physician-patient interactions.

Clinical trials are vital to advance cancer care, and Black patients are disproportionately not included. The primary barrier for lack of enrollment is medical distrust, although other factors such as dislike of randomization, general lack of understanding of the trial process, and increased costs also exist.[46] Physician barriers to enrollment include needing additional time and resources to potentially enroll minority patients.[46] Prior research has found that initiating an education and tailored support program increased Black enrollment in clinical trials from 9% to 16%, which potentially could be implemented in radiation oncology departments.[47]

Unfortunately, there is a paucity of data overall regarding specific evidence-based interventions that can be implemented in a radiation oncology clinic to improve the disparity that exists for Black patients with lung cancer. Cykert et al examined systemic interventions to reduce the Black-White disparity in patients with early stage lung cancer.[39] They implemented three system interventions – a real-time electronic health record (EHR) warning system, race-categorized provider feedback on their patients' completion of treatment, and a nurse navigator – and followed stage I and II lung cancer patients for five years.[39] After analyzing data from 2,841 patients enrolled in the trial, the researchers showed that these systemic interventions improved the percentage of patients who completed curative treatment (surgery or stereotactic body radiation) for both White and Black patients, while reducing the racial differences in treatment and outcome.[39] Further efforts utilizing technology such as the EHR or mobile applications will be critical to flag patients at risk for not completing treatment and notify providers not offering standard-of-care therapies for a patient based on their documented stage. Additional studies also must be completed to qualify and categorize the barriers that lung cancer patients face with radiation treatments to allow for development of more evidence-based interventions.

Conclusion

Lung cancer disparities in Black patients is a multifactorial problem in all areas of cancer control (**Figure 1**). To decrease disparities, health care providers require a fundamental understanding of the various contributing factors. In the field of radiation oncology, there are many opportunities to help bridge the gap. Recent events have brought to light the dismal impact of systemic racism on the Black community; as radiation oncologists, we can also take a stand against social inequity and work toward reducing cancer disparities.

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Virtual Radiation Oncology Resident Rotations: Preserving Learning During a Pandemic

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Amidst the coronavirus 2019 (COVID-19) pandemic, residents in graduate medical education (GME) face unique challenges. Radiation oncology (RO) residents must balance caseload requirements, board exams, and personal obligations. Decreased clinic volumes and social distancing measures have necessitated new adaptations such as virtual learning.

The American Council on GME (ACGME) allows for "participating sites" in addition to a "sponsoring institution."[1] Even before COVID-19, smaller RO residencies may rely on external rotations to meet ACGME requirements and achieve clinical competency. Survey-based data reveals that 38% of RO residency programs require external rotations.[2]

In the face of an unprecedented global pandemic, institutions may implement varying policies regarding visiting residents. RO residency program directors (PDs) and the participating site directors (PSDs) must balance resident education with patient safety and institutional policies. We report our initial experience in rapidly converting a visiting rotation into a virtual resident rotation (VRR).

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Methods

The goal of the VRR was to preserve the in-person experience, requiring a dynamic re-thinking of how to incorporate the key components of patient encounters, simulation, contouring, treatment planning, and didactics. VRR was piloted by 2 of 6 RO residents between April and July 2020. An example of a typical schedule is in **Table 1**. This study did not require internal review board (IRB) submission as deemed by authors according to institutional policy.

Remote Access

Residents were responsible for operability of a virtual private network (VPN) to access on-site resources.

Patient Encounters

Residents participated in patient encounters over telehealth software to include initial consultation, on-treatment visits (OTV), and follow-ups. Residents pre-wrote the consultation note. Participating actively in the patient encounter was dependent on their ability to maintain a professional home environment (suitable for patient interaction). They could join the actual consultation or conduct a postconsult review session, which focused on relevant findings and learning points.

Residents participated in OTVs and follow-ups based on level of training. Generally, salient learning points for all cases were discussed at the end of each day to prevent disruption to clinic flow. To augment learning, residents reviewed each case in advance (to include treatment plans) in detail.

Simulation

Residents discussed simulation techniques prior to the encounter and reviewed any relevant findings after simulation. Residents also coordinated the fusion of relevant imaging.

Contouring

Residents contoured all normal structures and target volumes using the treatment planning system (TPS) over VPN. All contours were reviewed jointly using screen share capabilities of a virtual meeting platform.

Treatment Planning

All patients contoured had their treatment planning and evaluation coordinated with dosimetry/physics virtually, including use of screen share and video-enabled calls. All treatment plans were evaluated jointly using a virtual meeting platform.

Table 1. Sample Schedule for A Typical Day in Virtual Resident Rotation (VRR)

Time	Activity	Participants (besides rotating resident)
7:30 am – 8 am	Pre-clinic morning huddle*	Attending physician
8 am – 9 am	Virtual chart rounds or grand rounds	Radiation oncology department
9 am – 11 am	Consults	Attending physician, patient
11 am – 12 pm	Coordination of simulation(s)	Physicists, dosimetrists contouring, treatment planning
12 pm – 1 pm	Lunch & mid-day review*	Attending physician
1 pm – 2 pm	Consult	Attending physician, patient
2 pm – 4 pm	Follow-ups, on-treatment visits	Attending physician (resident may or may not participate)
4 pm – 5 pm	Contour review, treatment plan review*	Attending physician, physicists and dosimetrists (as required)
5 pm – 6 pm	End of day review*, resident preparation time for next day	Attending physician (as required)

*All interactions between attending and resident physicians present opportunities for Socratic-method-based teaching. Formal didactics are typically performed virtually (during the COVID-19 pandemic), during one dedicated half day per week.

Didactics

Residents had residency didactics, which were converted to a virtual format. Additionally, residents participated in informal, Socratic-method-based teaching. This included review of relevant clinical trials and case-based learning. In addition, a "mini-journal club" was held once weekly.

Results

In our small residency of 6 residents, 2 participated in the VRR experience at a single participating institution. A post-VRR survey was conducted assessing the VRR and included 3 of 4 attending physicians at the participating site, and 2 of 2 rotating residents. Contouring, treatment planning, and didactics/teaching were reported to have the same learning value as an in-person rotation, while patient encounters were reported to have less learning value than an in-person rotation. The time commitment for teaching/learning was reported to be less or the same as compared to an in-person rotation for both staff and residents. The level of existing technology infrastructure was unanimously felt to be adequate to support the VRR. All participants reported a positive overall experience with the VRR, and all participants felt that it could be implemented for access to unique learning opportunities (such as global health, proton therapy experiences, etc.).

Discussion

While there have been several recent efforts to implement a virtual curriculum for medical students[3] and incoming RO residents,[4] there are no reports in the literature regarding RO visiting resident rotations. While 38% of residency programs require external rotations 1-12 months in duration, there was no policy governing external rotations at 30% of these programs.[2] The burden of these required external rotations likely falls disproportionately on smaller training programs. These programs already face the challenge of balancing resident time and caseload, as they have less protected nonclinical time.[5]

The most analogous situation is the implementation of a virtual medical student RO clerkship.[3] Pollom et al implemented a 2-week virtual rotation conducted in small teams, which allowed for virtual patient interaction, multidisciplinary didactics, and exposure to treatment planning. In their early report, they felt the virtual clerkship broadened the reach of an RO clerkship, particularly in the era of COVID-19.[3] These endeavors are being continued in a multi-institutional effort called Radiation Oncology Virtual Education Rotation (ROVER).

Our initial experience demonstrates the adaptability of RO GME in the face of an unprecedented pandemic. As virtual platforms are now used routinely in RO clinical care, we were able to rapidly restructure a rotation using existing virtual technologies. This experience may also be beneficial in other contexts, such as those facing financial difficulty in travel, increasing accessibility to global health RO experiences, etc. Common applications could include proton therapy VRRs and rotations in subsites where case numbers may be limited (eg, pediatric malignancies).

Global health has gained interest in RO as a career opportunity; nonetheless, it has been shown to have little formalized training and restricted leadership opportunities.[6] Recent efforts to establish a global health track[6] include offering a competency profile[7] and multiple perspectives on how to increase trainee engagement.[8,9] Leveraging such technologies amidst COVID-19 show the possibilities of creating an analogous experience to increase accessibility to global RO.

Table 2. Pros vs Cons of Implementing a Virtual Resident Rotation (VRR)

Pros	Cons
Allows for preservation of learning during times of difficulty (ie, COVID-19 pandemic)	Learning experience may not capture full scope of in-person rotation education
Can help supplement resident case volume in disease sites referred to extremely specialized centers and/or with limited case numbers (eg, pediatrics)	Significantly decreased learning of procedural and/or hands-on skills, particularly brachytherapy (but also fiberoptic laryngoscopy, physical exam, etc.)
Creates new opportunities/rotations for residents at smaller institutions and/or those facing difficulty obtaining funding for such in-person experiences	Cannot completely substitute for fully immersive experience that can come with in-person experiences (ie, mentoring, teaching of "soft skills" of oncology, etc.)
Can serve as an easily accessible way for a senior resident to obtain unique learning experiences	Junior residents may face a steeper learning curve and may not be able to derive as much educational value from such an experience
Increases accessibility to global health experiences	Global health VRR lacks cultural immersion and face-to-face interaction with local staff and patients
Increases accessibility to advanced radiation modalities (particle therapy, etc.)	Difficulty virtually accessing staff, dosimetry/physics, etc., which may limit depth of treatment planning learning
Fully capitalizes on existing remote learning/work infrastructure to maximize learning	Information technology (IT) problems, credentialing issues, etc., may be more difficult to overcome and can hamper learning

The residents who participated in the VRR focused most of their time on head and neck cancer, genitourinary cancer, and breast cancer. It was largely felt that most of the learning related to external-beam radiation therapy (EBRT) treatment planning was preserved for rotating residents on the VRR. Due to COVID-19, no brachytherapy was conducted; however, this is a shortfall of the VRR. While many institutions rely on external rotations to gain brachytherapy experience, especially in prostate and gynecologic cancers, a VRR would not adequately substitute for this learning experience. **Table 2** provides a comprehensive list of VRR pros and cons.

VRR has multiple limitations as a direct replacement to a critical clinical rotation. A VRR cannot incorporate all aspects of RO clinical care, such as hands-on clinical skills (eg, physical examination, fiberoptic laryngoscopy, real-time image verification, etc.), tools to run a busy clinic, etc. Additionally, the virtual nature places a burden on both the resident and attending to prioritize learning opportunities proactively. We therefore recommend that such experiences be pursued by senior residents, as junior residents may face a steep learning curve that may portend a suboptimal educational experience.

Limitations specific to this report include a small sample size (2 residents); however, this is a pilot experience from a small residency program. Additionally, no objective metrics were used to evaluate the VRR prospectively, and this may be the subject of future RO GME efforts.

Conclusions

Our initial experience of a VRR demonstrates how implementing the latest technology can preserve most aspects of clinical learning in RO resident education in light of COVID-19. In addition, it presents an exciting way to allow for broadened accessibility to global health experiences and advanced radiation modalities.

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Metastatic Castrate-Resistant Prostate Cancer (mCRPC)

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CASE SUMMARY

A 69-year-old man presented with a persistent rising prostate specific antigen (PSA) of 15.8 ng/mL in September 2019. The patient's previous PSA readings were 11.4 ng/mL in November 2018 and 12.9 ng/mL in May 2019.

The patient had a known history of prostate cancer and was treated initially with Radical Retropubic Prostatectomy (RRP) for Gleason 3 + 4 = 7. The patient subsequently experienced biochemical recurrences and was treated with salvage external beam radiation therapy, intermittent hormone therapy with leuprolide, and 3 cycles of Provenge.

In early 2017, the patient developed castrate-resistant prostate cancer and was started on abiraterone with prednisone. In November 2018, the patient experienced disease relapse in the iliac bones bilaterally on his choline PET/CT scan with a PSA of 11.4 ng/mL After detailed discussion of his treatment options, the patient opted to change to enzalutamide. In May 2019, the patient underwent repeat evaluation with C-11 choline PET/CT scan and MRI abdomen and pelvis; both imaging showed no dramatic lesions that have been identified associated with the current state of prostate cancer on this individual. As such, the patient was offered to undergo extensive radiographic evaluation with PSMA-PET scan, C-11 choline PET scan and MRI abdomen and pelvis on his subsequent follow-up visit. Surprisingly, while MRI and choline PET scan once again revealed very little evidence of metastatic recurrence of prostate cancer, PSMA PET scan showed innumerable intense PSMA positive metastases throughout the axial and appendicular skeleton (Figure 1). Subsequently, the patient underwent treatment with 6 cycles of docetaxel plus carboplatin, to which he responded very favorably. In June 2020, the patient's PSA decreased markedly to 3.4 ng/mL with only 2 or 3 skeletal lesions on his PSMA-PET scan.

IMAGING FINDINGS

The patient underwent Ga 68 PSMA PET/CT scan with CT fusion imaging for attenuation correction and anatomic co-registration only, with imaging beginning approximately 60 minutes after radiotracer injection. Ga 68 PSMA PET/CT scan revealed innumerable PSMA-avid metastatic lesions throughout the axial and appendicular skeleton, including the sternum, ribs, and spine (Figure 2). There were also multiple

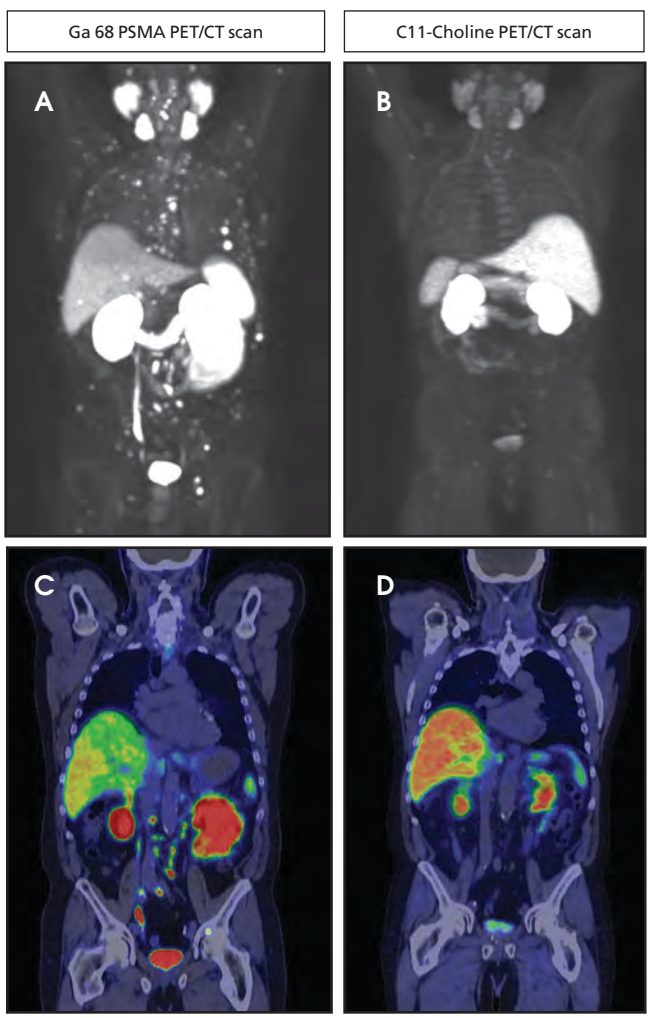

FIGURE 1. *Axial view showing innumerable lesions on Ga68 PSMA PET/CT scan with minimal- to low-level disease on the comparison C-11 choline PET/CT scan.*

tiny, bilateral common iliac and retroperitoneal lymph nodes concerning for metastatic disease. Additionally, there was a solitary aortoesophageal PSMA-avid lymph node. Notably, there was no definitive evidence of PSMA-avid locally recurrent disease within the prostatectomy bed.

DIAGNOSIS:

Metastatic Castrate-Resistant Prostate Cancer (mCRPC)

DISCUSSION

Despite advances in treatment and management, prostate cancer is the second-most common cause of cancer deaths in men, ranking only behind lung cancer. Approximately 192,000 new prostate cancer cases, and nearly 33,000 deaths are expected in 2020.[1] While primary prostate cancer has an indolent nature, most patients will eventually develop castration-resistant prostate cancer, which accounts for the majority of prostate cancer deaths.[2] In contrast to restaging of primary localized disease, restaging of mCRPC requires more advanced radiographic evaluation C-11 choline PET/CT, and/or PSMA PET/CT. Mitchell et al reported better sensitivity to disease relapse after primary treatment in patients with low PSA level with C-11 choline PET/CT scan than with conventional imaging, with an optimum PSA level of ≥2.0 ng/mL. Additionally, current reports suggest better sensitivity with PSMA PET/CT with the ability to detect disease relapse at very low levels of PSA at 0.2 – 0.5 ng/mL[3]

We noted in our case, however, a clear discrepancy between both scans despite a high PSA level of 15.8 ng/ml. This could be explained in part by the patient's extensive history of systemic treatment, including Provenge and novel androgen receptor inhibitors. It has been reported that treatment with novel androgen receptor inhibitors could result in a treatment-induced lineage crisis and cellular plasticity.[4]

Beltran et al described treatment-induced neuroendocrine disease in mCRPC patients undergoing treatment with abiraterone.[5] Therefore, patients with advanced mCRPC may require meticulous evaluation with the multi-imaging modality to detect disease relapse and receive individualized treatment plans based on location of their disease relapse.

CONCLUSION

Ga 68 PSMA PET/CT scan constitutes the most advanced imaging modality for prostate cancer among all currently available scans, even in cases of extremely low PSA levels (0.2ng/mL). The use of Ga 68 PSMA PET/CT scanning to evaluate CRPC patients would constitute an invaluable advance in prostate cancer diagnosis and management.

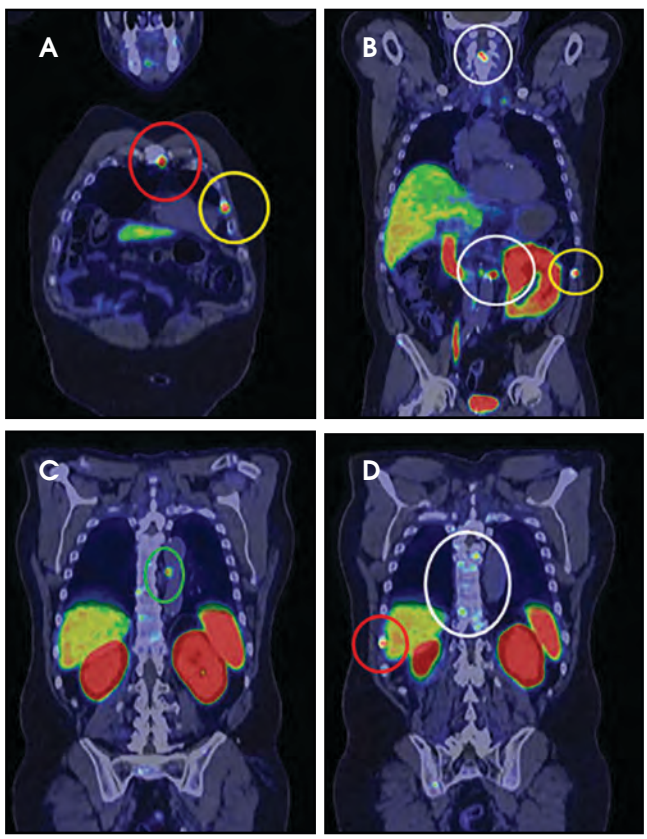

FIGURE 2. *Ga68 PSMA PET/CT scan revealed PSMAavid metastatic lesions throughout the axial and appendicular skeleton, including the sternum (A), ribs (A, B, and D), and spine (B and D). Additionally, there was a solitary aortoesophageal PSMA avid lymph node (C).*

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Prevalence of Pediatric Advanced Life Support Training Among Radiation Oncology Residency Programs

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Abstract

Purpose: Cardiac arrest is a recognized complication of pediatric oncology management, and timely and correct administration of Pediatric Advanced Life Support (PALS) improves return of spontaneous circulation (ROSC).

Methods and Materials: We designed a 6-item internet-based survey, distributed to the 92 program coordinators at US radiation oncology residency programs, which assessed the prevalence of PALS training and potential associated factors among residents. Ordinal and categorical variables were obtained; tests for association with the PALS requirement included Fisher's exact and Spearman's rank correlation.

Results: Sixty-two of 92 residency programs responded in full (67.4%). PALS training is required at 11 of 62 programs (17.7%). Fifty of 62 programs see pediatric patients in-house (80.6%); 38 of these 50 programs also utilize away sites. Forty of 62 programs (64.5%) are associated with a dedicated pediatric hospital. The most common number of residents per program is 7 to 10 (38.7% of programs). Residency programs most commonly (38.7%) have residents focus on pediatric cases for at least 4 months. Most commonly, residents see 12 to 16 pediatric cases over their 4-year training period (40.3% of programs). Of the 15 programs that see pediatric cases intradepartmentally and are not affiliated with a dedicated pediatric hospital, none require PALS training ($P = 0.052$). Neither the size of the residency program, number of months focused on pediatric cases, nor number of total pediatric cases seen by residents over the 4-year training period is significantly associated with the requirement of PALS certification.

Conclusion: Despite the preponderance of intradepartmental pediatric visits and the presence of on-site pediatric hospitals, results suggest that fewer than 1 in 5 US radiation oncology residency programs require PALS certification. Given radiation oncology residents' significant exposure to ill children, we recommend that the requirement for PALS certification during training be reconsidered.

Each year in the United States, an estimated 15,000 pediatric hospital patients experience cardiac arrest and require cardiopulmonary resuscitation (CPR).[1] The CPR algorithm designated for the peri-arrest management of children was designed in 1983 by the American Heart Association (AHA), and integrated into the first Pediatric Advanced Life Support (PALS) courses in 1988.[2] Most recent updates to PALS guidelines were published by the AHA in 2018, alongside corresponding updates to its Advanced Cardiovascular Life Support (ACLS) program designed for adults. Fundamental distinctions in life support delivery are highlighted in these guidelines, reinforcing that delaying proper PALS administration lowers the incidence of return of spontaneous circulation (ROSC).[3]

While ACLS is generally regarded as a prerequisite for radiation oncology credentialing in American hospital systems, PALS is not. This shortcoming is concerning given that pediatric radiation oncology patients are typically seen in a clinic that is separate from designated pediatric staff. We hypothesized that despite the significant pediatric population among radiation oncology patients, as well as the nationally prescribed requirement of a minimum of

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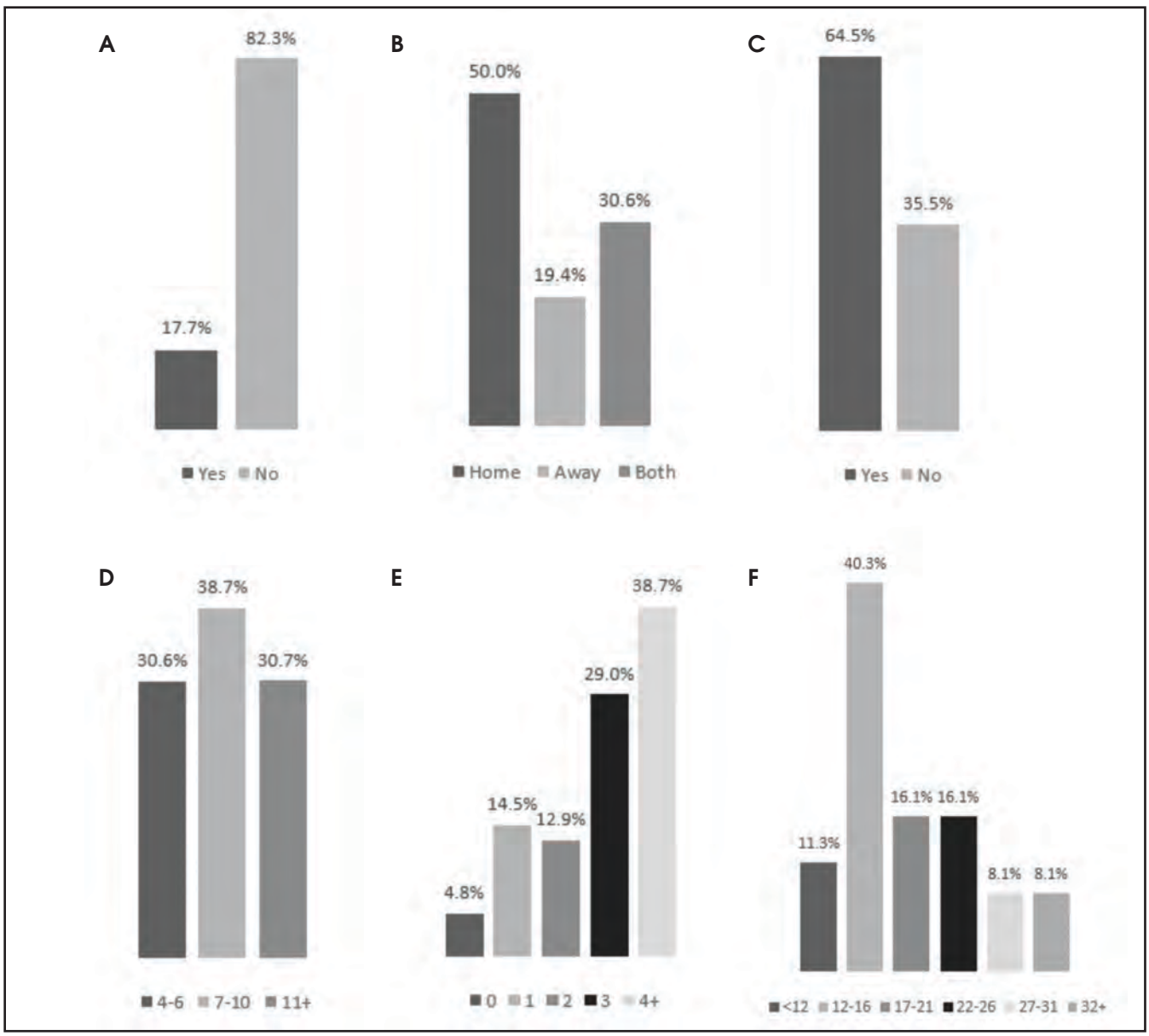

FIGURE 1. *Breakdown of responses to survey questions based on data from 62 programs. A) Programs requiring Pediatric Advanced Life Support (PALS) training. B) Pediatric radiation treatment location. C) Presence of onsite dedicated pediatric hospital. D) Number of residents in program. E) Months focused on pediatric cases. F) Number of pediatric cases per resident over 4 years.*

12 pediatric cases for graduation, PALS training is rarely required within radiation oncology residency programs. To examine this proposition, we designed and distributed a survey that assesses the prevalence of PALS training at radiation oncology residency programs, as well as potential factors associated with programs requiring PALS training for residents in the United States.

Methods and Materials

Survey Instrument

We designed an internet-based survey, managed and distributed by Qualtrics, which consisted of 6 multiple choice questions designed to be completed within 5 minutes (**See Supplement**). The questions assessed the requirement for radiation oncology resident PALS training, number of residents in the program, total number of pediatric patients, total months specifically focusing on pediatric cases, whether the department is associated with a dedicated pediatric hospital, and whether pediatric patients are seen by residents intradepartmentally or at an away site.

The Columbia University Irving Medical Center Institutional Review Board (IRB) reviewed our application

and determined our project did not qualify as human subjects research; therefore, IRB-approval was granted yet not required.

Survey Procedure

Radiation oncology residencies and their associated program coordinators (PC) were identified through the American Council for Graduate Medical Education (ACGME) public search for accredited American programs as of October 2019. Beginning November 2019, each PC was contacted via his/her work email address and provided a link to a Qualtrics-based online survey. There were no exclusion criteria. All email correspondences to potential participants consisted of non-individualized form letters and were distributed by the residency program coordinator at the authors' institution. Approximately every 8 weeks, the same original recipients were sent a reminder to participate in the survey if not yet completed; this reminder email was sent twice over 4 months. No other intervention was undertaken to improve the response rate.

Statistical Analysis

Data were analyzed with SPSS version 26.0 (IMB Corp). Responses were compiled as categorical or ordinal variables. In lieu of numerical variables, the survey grouped quantitative data into groups for ordinal analysis. Tests for association with PALS training included Fisher's exact test with Freeman-Halton extension and Spearman's rank correlation. Statistical significance was two-tailed and defined as a P-value < 0.05.

Results

The survey accrued responses from November 2019 through March 2020. Replies were received from 66 of 92 programs surveyed (71.4%); however, 4 of these contained no responses past the consent page. Therefore, this study examines 62 of 92 analyzable surveys (67.4%). PALS training is required at 11 of 62 residency programs (17.7%). Fifty of 62 programs see pediatric patients in-house (80.6%), with 38.0% of these 50 programs also utilizing away sites. Forty of 62 programs (64.5%) are associated with a dedicated pediatric hospital.

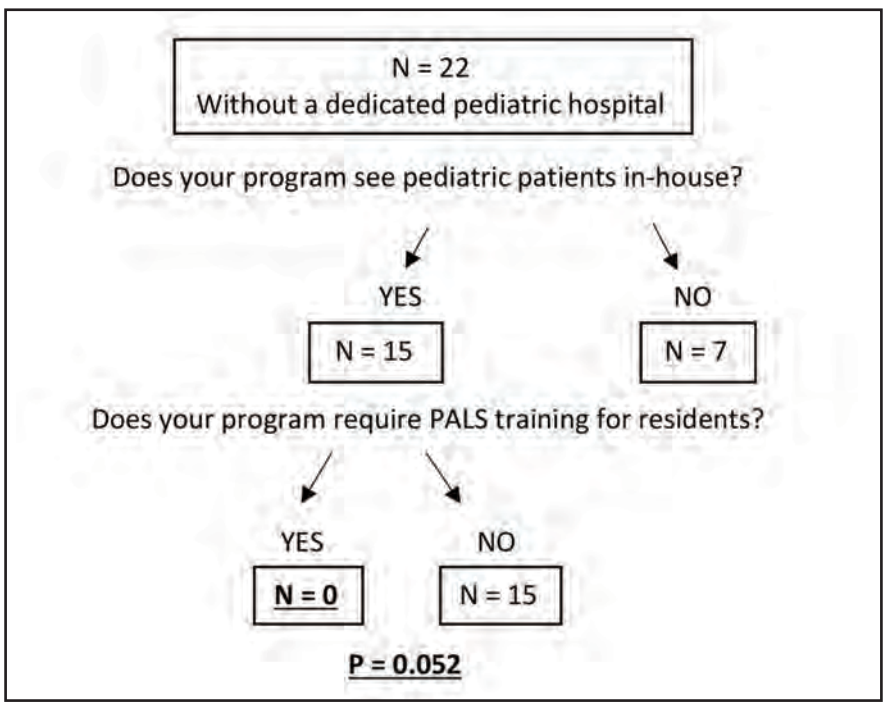

FIGURE 2. *Negative correlation (approaching statistical significance) between Pediatric Advanced Life Support (PALS) training and radiation oncology programs that see pediatric patients in-house and are not affiliated with a dedicated pediatric hospital.*

Twenty-four of 62 programs (38.7%) have 7 to10 residents, 19 of 62 programs (30.6%) have 4 to 6 residents, and the remainder have 11-plus residents. (30.6%). Twenty-four of 62 programs (38.7%) have residents focus on pediatric cases for 4-plus months, 29.0% for 3 months, 12.9% for 2 months, 14.5% for 1 month, and 4.8% for 0 months. Twenty-five of 62 programs (40.3%) have residents see 12 to 16 pediatric cases over their 4-year training period, 16.1% each for 17 to 21 or 22 to 26 cases, 11.3% for < 12 cases, and 8.1% each for 27 to 31 or 32-plus cases (**Figure 1**).

A requirement of PALS training among residents is not associated with residents seeing pediatric patients at their home institution (or both home and away) vs away sites only (P = 0.907), nor with presence of a dedicated pediatric hospital (P = 0.300). No association with PALS was seen with number of residents within the program (rs = 0, P = 1.00), number of months focused on pediatric cases (rs = 0.088, P = 0.498), or number of total pediatric cases (rs = 0.166, P = 0.198).

In the subgroup of 15 residency programs (24.2% of cohort) that both saw patients in-house yet were not affiliated with a dedicated pediatric hospital, none of the 15 programs required PALS training (P = 0.052) (**Figure 2**). PALS training was additionally not associated with the combination of in-house pediatric visits plus the presence of a pediatric hospital (35 of 62 programs (56.4%), P = 0.094), nor was the number of pediatric cases seen by this subgroup shown to be correlated with PALS training (rs = 0.259, P = 0.133).

Discussion

Current evidence-based recommendations highlight fundamental distinctions

Table 1. Differences in Resuscitation Techniques Between Advanced Cardiovascular Life Support (ACLS) and Pediatric Advanced Life Support (PALS)

Intervention	ACLS	PALS
Depth of chest compression	2.0-2.4 in	1.0 in (infants), 2.0 in (children)
Compression-to-breath ratio	30:2	15:2 (2 rescuers), 30:2 (1 rescuer)
Defibrillation energy	120-200 J, may go higher	2 J/kg, then 4 J/kg, max 10 J/kg
Epinephrine dose	1.0 mg every 3-5 min	IV/IO: 0.01 mg/kg every 3-5 min Endotracheal: 0.1mg/kg every 3-5 min
Amiodarone dose	300 mg initial, then 150 mg	5 mg/kg, may repeat twice
Lidocaine dose	1.0-1.5 mg/kg, then 0.5-0.75 mg/kg, can repeat, max 3 mg total	1 mg/kg bolus, then 20-50 mcg/kg/min infusion

in cardiac arrest management between children and adults. Owing to intrinsic differences in anatomy and mass, adjustments in chest compression techniques are required for children, as well as energy reductions in defibrillation shocks and dose reductions in systemic sympathetic agonists such as epinephrine and antiarrhythmics such as amiodarone.[4] Delay in proper administration of PALS leads to a lower incidence of the return of spontaneous circulation (ROSC)[3] (**Table 1**).

For multiple reasons, cancer patients are at increased risk for cardiac arrest as compared to the general population. The hypercoagulable state associated with malignancy significantly increases the risk of thromboembolic events, and exposure to nephro-, hepato-, and cardiotoxic chemotherapies, additionally, are associated with higher incidence of cardiac arrest.[5] Chronic kidney disease precipitates fibrosis and coronary artery calcification and, thus, is an independent risk factor for cardiac death. As a population, cancer patients have worsened kidney function due to exposure to nephrotoxic chemotherapeutic agents.[6] Additionally, use of anesthesia, which is required for pediatric patients far more frequently than for adult patients receiving radiation therapy, is associated with respiratory arrest that requires

1. Do the Radiation Oncology residents at your institution undergo training and certification in Pediatric Advanced Life Support (PALS)?
   a. Yes
   b. No
2. Do the Radiation Oncology residents at your institution treat pediatric patients at your institution or at an away site?
   a. At the home institution
   b. At an away site
   c. Both
3. Does your institution have a dedicated pediatric hospital?
   a. Yes
   b. No
4. How many Radiation Oncology residents are in your program?
   a. 4-6
   b. 7-10
   c. 11+
5. How many months in total over the course of the training program are Radiation Oncology residents at your institution focusing on pediatric cases?
   a. 0
   b. 1
   c. 2
   d. 3
   e. 4+
6. How many pediatric cases does each Radiation Oncology resident have over the 4-year training period?
   a. <12
   b. 12-16
   c. 17-21
   d. 22-26
   e. 27-31
   f. 32+

SUPPLEMENT: *Survey distributed to 62 Program Coordinators*

management with PALS or ACLS algorithms. A recent study showed that nearly 20% of anesthesia-related pediatric cardiac arrests occurred in the emergence or recovery period; these arrests occurred despite the patients being within a dedicated post anesthesia care unit (PACU) setting.[7] While the total number of arrests was low, this study blamed inadequate supervision and provider inexperience. Many radiation oncology patients recover from anesthesia in a clinic setting vs a dedicated PACU, with the final stages of recovery occurring after the anesthesiologist and support technicians have departed. Further research into the logistics of pediatric anesthesia in radiation oncology is needed to identify best practices regarding induction and recovery locations.

To our knowledge, this project is the first survey to assess the prevalence of the requirement for PALS training at radiation oncology residencies throughout the United States. The results suggest that < 1 in 5 American radiation oncology residency programs requires PALS certification for resident physicians. This low representation exists despite the preponderance of intradepartmental pediatric visits and the presence (or lack) of on-site pediatric hospitals.

Our results highlight a particularly dangerous situation in programs where pediatric cancer patients are seen intradepartmentally and yet without support of a dedicated pediatric hospital. Of the 15 such programs, none required PALS training; this finding approached statistical significance ($P = 0.052$) despite the small sample size.

We hypothesized that programs seeing greater numbers of pediatric patients or that have greater numbers of residents would be more likely to require PALS; however, our findings suggest that a requirement for resident training in PALS is not associated with greater numbers of pediatric cases, months dedicated to pediatric patients, or number of residents in a residency program.

In the era of COVID-19, with potentially reduced staff and with multiple reports of catastrophic cardiac events in critically ill children, and especially given the short period required for PALS training and its potential benefit to improve the rate of ROSC, training of radiation oncology residents in PALS may represent a high-value quality improvement initiative.[8] Given the team-based nature of PALS and other advanced life support algorithms, training and proficiency in multiple members of the care team contribute to optimal outcomes. Therefore, while this survey did not assess the prevalence of PALS certification among other members of the radiation oncology care team such as attending physicians and nurses, the fact that radiation oncology residents are routinely trained in ACLS but not PALS identifies a training domain that may improve outcomes for patients. Further, in due time many of these residents will give rise to new attending physicians who are already PALS-certified. Ultimately, the question of who makes the policy decision toward or against implementing PALS training in a radiation oncology program, and for what reasons, is beyond the scope of our survey.

The strength of this small study is the strong response rate of nearly 70%. Curiously, however, 7 programs (11.3%) indicated that their residents see < 12 pediatric patients during their residency; nationally prescribed residency guidelines mandate a minimum of 12 patients for graduation. This dilemma might call into question the validity of their responses. A limitation of our study is that the absolute risk reduction for incorporating PALS training into radiation oncology residency programs is unknown.

Conclusion

Few radiation oncology residency programs require PALS training. Given radiation oncology residents' significant exposure to ill children at elevated risk of cardiopulmonary arrest, radiation oncology residency program directors and graduate medical education leadership should evaluate implementation of PALS training among radiation oncology residents.

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A Just Enough Interaction Segmentation Tool Improves Consistency and Efficiency for Radiation Therapy Contouring of Meningiomas

Weiren Liu; Zhi Chen, PhD; Honghai Zhang, PhD; Dongxu Wang PhD; Brian J. Smith, PhD; Kristin Plichta, MD, PhD; Mark Smith, MD; Milan Sonka, PhD; and John M. Buatti, MD

Abstract

Purpose: To develop a user-friendly segmentation tool requiring minimal expert interaction to reduce physician workload and improve reproducibility.

Methods: Sixteen treated meningiomas cases were manually contoured, then contoured using the JEI-LOGISMOS (just-enough-interaction layered optimal graph image segmentation for multiple objects and surfaces) segmentation tool by two central nervous system experts. Cases were randomly displayed for both manual and JEI-LOGISMOS analyses in several sessions to avoid bias. Segmentation accuracy indices were determined as continuous variables: mean (± standard deviations) or median (and interquartile ranges [IQR]) where appropriate. Computer-analysis accuracy was evaluated using point-wise 3-dimensional (3D) surface distance errors and volumetric linear regression. To assess reproducibility, the Dice coefficient along with 3D relative volume difference (RVD) were obtained. To evaluate the efficiency of the automated method, time required for automated contouring with JEI and manual contouring was compared using Wilcoxon signed-rank test.

Results: Our 3D LOGISMOS segmentations using JEI with both experts achieved subvoxel precision (voxel size ~1 mm) for meningioma tumor surfaces (JEI signed error: 0.86 ± 1.82 mm for expert 1, 0.24 ± 1.26 mm for expert 2) and provided accurate volume measurements in comparison to manual contouring (volume regression: $R2 = 0.93$, $P < 0.001$ for expert 1, $R2 = 0.96$, $P < 0.001$ for expert 2). The interobserver variability of automated contouring showed better reproducibility compared with manual contouring (Dice: 87.4% vs 83.6%; RVD: -1.1% vs 14.9%). Median time required for contouring cases was significantly reduced for both experts (-204 seconds per case, $P = 0.01$, 46.5% faster for expert 1 and -228 seconds per case, $P = 0.04$, 35.8% faster for expert 2).

Conclusion: Automated contouring using a JEI approach following the automated 3D LOGISMOS segmentation improves reproducibility and efficiency of contouring for meningiomas. Volumes obtained using manual tracing and JEI-LOGISMOS were highly comparable.

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Meningiomas are benign neoplasms that originate from the arachnoid layer of the meninges surrounding the brain. They are the fourth most common primary brain tumor with a female predilection (2:1) associated with hormonal stimulation of these tumors.[1,2] Radiographically, meningiomas appear as conspicuous contrast-enhancing masses on computed tomography (CT) and MRI with relatively smooth borders, and are attached to dural surfaces surrounding brain. They may be calcified and occasionally can invade or remodel the surrounding bone. They can present with neurologic symptoms generally caused by mass effect on adjacent brain structures rather than invasion into normal central nervous system tissue. Meningioma mass effect symptoms are usually dictated by location and can include headaches and seizures, as well as focal neurologic symptoms such as weakness, numbness, pain or cranial nerve deficits. They may also rarely result in global neurologic deterioration from hydrocephalus or extreme mass effect.[1] Unlike benign meningiomas, atypical or malignant variants can invade surrounding brain tissues directly.[3] Meningiomas are also frequently found incidentally on scans and, therefore, may have no symptoms.

Surgical resection is the standard treatment for meningiomas and results in cure in more than 90% of cases when complete excision is achieved.[1] However, when meningiomas are around or directly involve critical neurologic structures and cranial nerves of the skull base, surgical resection can result in profound morbidity. Direct involvement of dural venous sinuses or the cavernous sinus may complicate surgical approaches.[4,5] Hence, when meningiomas are poorly resectable or the patient is a poor candidate for resection, radiosurgery has been shown to achieve long-term control rates approaching surgical excision outcomes.[6] Radiosurgery is a more convenient outpatient procedure that may be particularly well-suited for elderly or infirm patients. Radiation is also used after incomplete resection to prevent tumor regrowth or if meningiomas are atypical or malignant and, thus, have greater potential for recurrence.[7] Therefore, radiation therapy and radiosurgery are important therapeutic modalities for these more difficult-to-manage meningiomas and are associated with control rates between 80% to 95% depending on the size and subtype of meningioma.

Accurate identification of the tumor target and anatomy through manual contouring is a critical step in planning radiosurgery or radiation therapy. Since most meningiomas are benign, the gross tumor volume (GTV) effectively defines the target. Treatments generally use minimal margins around meningioma targets and radiation is most often stereotactically delivered (single or multifraction) or treatments use maximal precision image guidance for daily fractionation. Currently, radiation oncologists manually identify and define target lesions in a treatment planning system based on MR imaging in the vast majority of cases. Manually defined tumor targets require significant physician time and effort. Furthermore, many fine points of tumor growth along dural surfaces may be overestimated or underestimated based on physician interpretation of the MR. Even the same physician contouring the same lesion on different occasions will show inconsistency in these subtle interpretations while contouring.[8-10] When lesions are complex in shape and location, there is increased variability in target definition among different physicians as well as with the same physician. Additionally, larger and more complex lesions may take the physician an hour or more to contour manually and are also usually less consistently well reproduced.

The development of an automated segmentation tool has the potential to both improve the consistency of contouring between and among different radiation oncologists and improve the efficiency of contouring for radiation therapy planning. While MR is used for this contouring, these MR images are generally fused to a contrasted CT for dose calculation. Primary contouring tasks occur on the MR data set. Over the past several years, algorithms, including atlas-based contouring, machine learning and shape/appearance methods became the basis for the development of many institution-specific segmentation tools.[11] These tools have shown the potential to improve the workflow of head and neck, breast, lung and abdomen cancer radiation therapy planning.[12-16]

In this study, we present a rapid, robust and highly accurate semi-automatic tumor lesion contouring solution based on layered optimal graph image segmentation for multiple objects and surfaces (LOGISMOS) with an optional just enough interaction (JEI) postsegmentation editing of target surfaces.[17] The algorithm works through identification of a lesion bounded by a spherical volume of interest in which to establish the contour. Using the imaging features or central identified tumor, the algorithm performs a graph-search optimization for surfaces to identify the surface of the lesion where the maximum change in intensity occurs. In performing this function, a change at one point may be propagated to redefine the surface in 3 dimensions (3D) and thereby avert the requirement for manual slice-by-slice editing of contours. An additional motivation for developing this tool is the daily application of imaging for treatment set-up accuracy using MR linear accelerator (MR-linac) devices. The ability to rapidly adapt contours in 3D planes simultaneously will be critical for on-line segmentation that is essential for treatment plan adaptation at several anatomic sites. While not directly applied to this meningioma model, the method may be applied to other images with or without contrast. The approach

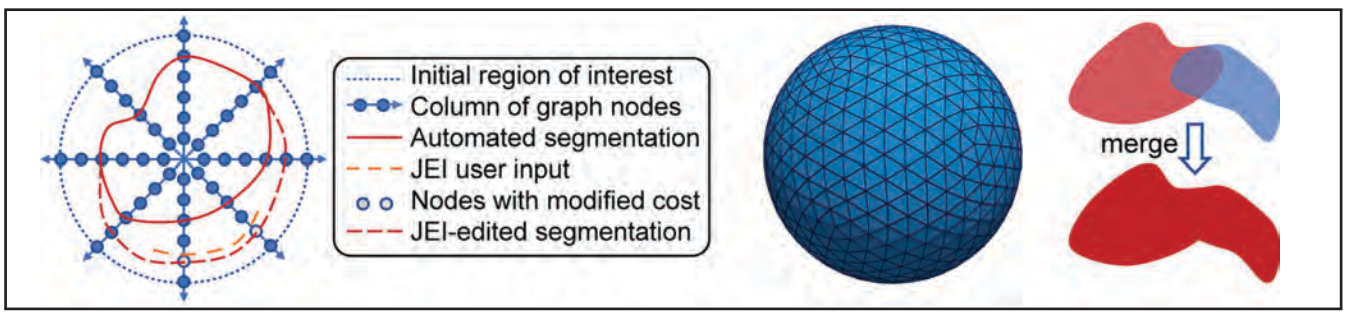

FIGURE 1. *LOGISMOS segmentation with just enough interaction (JEI). (A) A 2D example initialized by a circle. (B) 3D segmentation is initialized by a geodesic sphere. (C) Merging of two 3D contours to form a complex new contour*

has substantial capability to address these needs for rapid adaptation of these non-contrasted images although this is not the primary goal of this report. Select optimization of the algorithm for specific applications will likely be needed. Our current report addresses the capability in the complex model of skull base, highly irregular meningiomas with contrast MR. The development of a framework for this work through a JEI-LOGISMOS method can fully leverage this new MR-linac potential.

Developed at the Iowa Institute for Biomedical Imaging, the LOGISMOS segmentation framework facilitates highly efficient multidimensional, multilayered, and multiobject optimum graph-based segmentation and surface editing on image data from various modalities (CT, MR, ultrasound, optical coherence tomography [OCT], etc.) with the current report using MR. LOGISMOS has previously demonstrated successful applications in cardiology, ophthalmology, neuroscience, pulmonology, radiation oncology and other areas.[18-22]

Methods

Patient Selection and Task Randomization

Sixteen patients treated for radiographically presumed benign meningioma with radiation therapy at the authors' institution were enrolled in this IRB-approved retrospective imaging study. T1-weighted MRI data were used. Each subject's MR image was contoured twice by each of three physicians, once using manual contouring (Monaco, Elekta) and once using JEI-LOGISMOS semi-automatic segmentation. A total of 32 contouring tasks per physician were generated for this patient cohort. Manual or semi-automated segmentation tasks were assigned to each physician in random order (manual vs semi-automated). Manual and semi-automatic contouring sessions for each case by the same radiation oncologist were separated temporally to minimize bias from the radiation oncologist's previous contouring session. After completing sessions, significant agreement was noted in manual contours between two more experienced radiation oncologists specializing in central nervous system (CNS) radiation therapy compared with their non-CNS specializing colleague. The manually traced contours from this non-CNS specializing physician were not used for results reporting, and related findings are presented in the discussion.

Overview of LOGISMOS and JEI-LOGISMOS Algorithms

The automated LOGISMOS method is initialized by the physician interactively placing a sphere encompassing the tumor. Starting from the center of the sphere, columns of graph nodes are constructed. Each graph node is assigned a cost that represents the unlikeness of the node being on the object boundary. The LOGISMOS segmentation finds the optimal set of graph nodes, one per column, with minimum total cost, thus defining the object surface. During the search for the optimal solution, prior knowledge such as the shape and anatomy of the target constrains the segmentation so that it is the one with minimum total cost among all possible solutions that meet the constraints. If needed, errors in the automated segmentation may be corrected by the user's interaction with the 3D LOGISMOS algorithm rather than by slice-by-slice manual retracing (**Figures 1A, 1B**). This process uses our JEI approach that considers the expert hints pointing to the correct boundary locations to modify the underlying segmentation cost functions as needed and searches for a new optimal solution in 3D under the modified cost. If a significant amount is felt lacking an alternative, the JEI approach is used to identify the center of the area missed and a sphere is placed over this area subsequently, followed by repeating the process above. Once this second overlapping area is identified, a merge of the contours can be accomplished (**Figure 1C**). The completed contour of the complex skull base meningioma is shown in **Figure 2**.

Manual Contouring

Manual contouring was performed in a Monaco Treatment Planning System v5.19.03d (Elekta). The T1-weighted contrast-enhanced MRI for each subject was loaded in the contouring session. The participating radiation

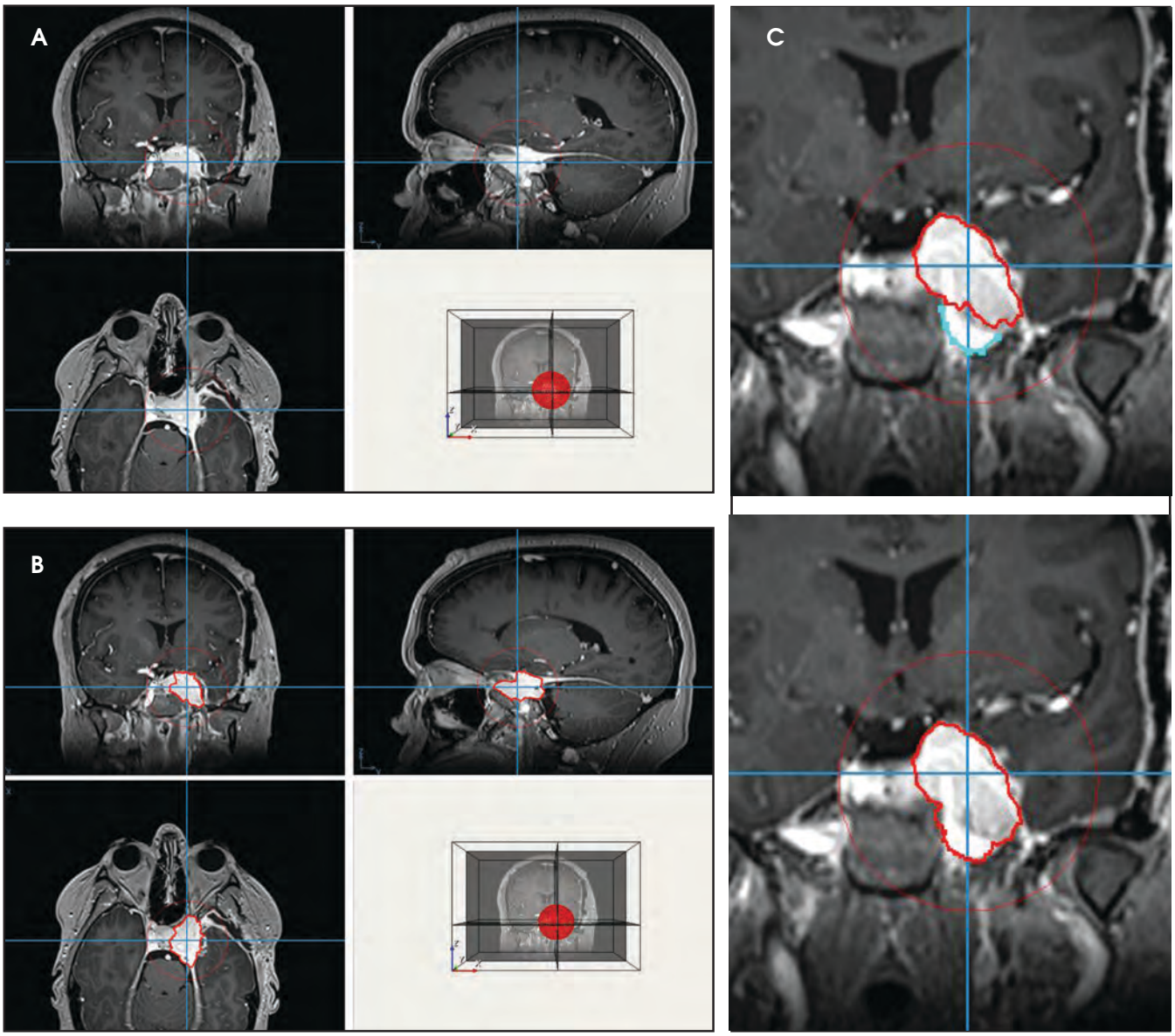

FIGURE 2. *(A) Manually placed sphere encompassing the target tumor by specifying the spherical region of interest. (B) Automated 3D segmentation of the meningioma tumor surface. (C) Surface modification via just enough interaction. Top: The user manually identifies several points in vicinity of which the correct surface should pass, defining a 2D line (cyan). The 2D line affects surface segmentation in 3D. Lower: The resulting contour after JEI correction. Note that the contours on neighboring 2D slices (not shown) are also corrected.*

oncologist used the manual contouring tools, such as a paint brush or polygon generation tool, as they would clinically, on each axial slice of the MRI image. The manual contouring was self-timed using a watch or timed by a colleague using a stopwatch; timing started when the radiation oncologist made the first mouse click on the image, and ended when the radiation oncologist declared the contouring concluded and clicked the "save" button. The manual contours were exported in DICOM format as local files for further processing and analysis.

Semi-automatic Contouring

Semi-automatic contouring was performed in RadOnco Analyzer, an in-house software based on the JEI-LOGISMO) algorithm as described above. The preprocessed T1-weighted contrast-enhanced MRI for each subject was loaded in this software. The participating radiation oncologist searched the approximate volumetric center of meningioma using cross hairs, dropped a "Center" point, set the maximum extent of contour search region using a sphere visible in three planar views (axial, sagittal and coronal)

Table1. Mean Signed and Unsigned Surface Errors, Volume Dice and Relative Volume Differences of Segmentations in Comparison

	Surface Metrics		Volume Metrics	
	Signed Errors (mm)	Unsigned Errors (mm)	Dice	RVD
Accuracy				
Semi-automated vs Manual – Expert 1	0.86 ± 1.82	1.30 ± 1.61	80.5 ± 8.1%	-6.6 ± 19.6%
Semi-automated vs Manual – Expert 2	0.24 ± 1.26	0.86 ±1.02	83.8 ± 8.1%	8.5 ± 19.8%
Reproducibility				
Manual – Expert 1 vs Expert 2	-0.04 ± 0.97	0.71 ± 0.73	83.6 ± 5.8%	14.9 ± 18.0%
Semi-automated – Expert 1 vs Expert 2	0.61 ± 1.31	0.94 ± 1.20	87.4 ± 8.4%	-1.1 ± 16.6%
Manual vs Semi-automated (*P* value)	0.235	0.650	0.08	0.029

P values provide statistical significance of manual and semi-automated reproducibility associated with specific comparison metrics, bold font depicts statistical significance. RVD = relative volume differences.

(**Figure 2A**), and requested the software to automatically find the boundary of the meningioma (**Figure 2B**). JEI editing was then performed if necessary (**Figure 2C**). If additional regions were needed as alternatives, this was also included in the time. The timing of the automatic contouring was also recorded by stopwatch: timing started after the radiation oncologist clicked on the cross hairs to find the "Center" point and stopped when the radiation oncologist clicked the "Finish" button. The contours were automatically saved in an analyzable format by the software.

Continuous variables are described as mean (± standard deviations) or median (and interquartile ranges [IQR]) where appropriate. To evaluate computer-analysis accuracy and reproducibility, point-wise distance errors of 3D surfaces and Dice coefficient along with relative volume difference (RVD) of 3D volumes were reported and compared with manual contouring by paired t-test. To evaluate efficiency of the semi-automated method, times required for automated contouring with JEI-LOGISMOS and manual contouring were compared using a mixed effects regression analysis with random effects for experts and patients. The R coding environment was employed for statistical computing, while a *P*-value of 0.05 denoted statistical significance.

Results

Accuracy and Reproducibility of Automated Contouring

Both surface-positioning and volume interobserver comparisons of obtained segmentations (manual vs semi-automated) are given in **Table 1**. Segmentations of cases using semi-automated contouring achieved subvoxel precision on average (voxel size ~1 mm) for surface differences compared with manual contouring. When pairwise comparing the reproducibility of manual and semi-automated segmentations, surface-positioning differences showed no statistical differences ($P > 0.2$). The same pairwise comparisons of Dice coefficients of volumetric agreement showed less strong but still no statistical differences ($P = 0.08$). There was, however, a statistically significant improvement in relative volume reproducibility assessed as RVD, showing the superiority of our semi-automated approach (14.9 ± 18.0 % vs 1.1 ± 16.6 %, $P < 0.03$).

Efficiency of Automated Contouring

The required time to contour a single meningioma using our automated system with JEI editing and a Monaco Treatment Planning System are given in **Table 2**. The semi-automated contouring process was significantly faster than manual contouring for both experts ($P < 0.001$). To quantify the effort associated with the semi-automated method, the median numbers of JEI edits used by the two expert analysts were 1.5 and 13.6, respectively – correlating with the longer analysis times of both the manual and semi-automated segmentations (but not better segmentation results) of Expert 2 compared with Expert 1.

Discussion

Application of semi-automatic contouring tools can aid radiation oncologists in radiation therapy treatment planning by improving consistency and efficiency of contouring tumor lesions. In this study, we demonstrate the utility of the LOGISMOS-based segmentation tool with JEI postprocessing in contouring complex meningiomas in T1-weighted contrast-enhanced MRI.

Precision and Accuracy

The gold standard to measure tumor contouring accuracy would be comparison with and confirmation by pathology. This, however, is not feasible in most cases, particularly in patients with CNS

Table 2. Semi-Automated and Manual Contouring Time (IQR) Required to Contour a Single Meningioma Lesion

	Semi-automated Time (IQR) in seconds	Manual Time (IQR) in seconds	Semi-automated vs. manual *P* value
Expert 1	235 (137 ~ 400)	439 (343 ~ 694)	< 0.001
Expert 2	408 (224 ~ 617)	636 (384 ~ 776)	< 0.001

All comparisons are statistically significant. IQR = interquartile ranges

tumors such as meningiomas. In similar studies evaluating autosegmentation solutions, the consensus of manually segmented volumes by expert physicians is defined as the ground truths and is used for validation.[11] To evaluate the accuracy and efficiency of our LOGISMOS-JEI semi-automatic segmentation tool, the consensus of the manual contours of experienced radiation oncologists (Expert 1 and 2) is built for each segmentation task and used as ground truth for each case to validate the respective autosegmentations. Our study compared the accuracy and reproducibility of semi-automated segmentation vs manual segmentation of a cohort with variably complex skull-based and convexity meningiomas. Even though the morphologies of the 16 analyzed lesions were complex and diverse, our segmentation tool remained robust, achieving surface positioning errors and Dice agreements indistinguishable between manual tracing and semi-automated analysis. Hence semi-automated JEI contours produced were clinically identical to that of standard-of-care manually produced contours. At the same time, the reproducibility of the semi-automated approach outperformed that of manual tracing when comparing relative volume differences. This demonstrates an ability of the semi-automated segmentation tool to improve inter-observer variability in RVD in a case when tumor volume delineation is performed by different radiation oncologists. This feature of the semi-automated approach will lead to more consistent treatment planning and potentially improved patient outcomes.

We believe we were able to achieve such accuracy and precision due to our base LOGISMOS algorithm coupled with the JEI algorithm postprocessing. LOGISMOS guarantees a volumetrically optimal solution with respect to the employed cost function in 3D (or nD in general) will be produced. The associated JEI steps provide an intuitive and efficient mechanism that allows the user to interact with the LOGISMOS algorithm and thus affect the segmentation result in a volumetric fashion rather than in a slice-by-slice fashion, thus yielding the adjudicated surfaces with minimal interaction efforts.

Improvements in automatic segmentation to delineate meningiomas for radiation therapy planning have not been widely reported. There have been different groups that investigated automatic segmentation algorithms for meningioma detection and recognition. In Hsieh et al a meningioma automated segmentation tool was developed to diagnose brain tumors using MRI images. This tool used an algorithm integrating fuzzy-c-mean and region-growing technique.[23] Similarly in Laukamp et al the authors adapted a deep learning model used for glioblastoma tumor detection in MRI to detect meningiomas.[24,25] Their results yielded similar segmentation accuracy statistics as our segmentation tool in this study.

Efficiency

Manual contouring for radiation treatment planning is a time-consuming process that can bottleneck therapy delivery.[11] The development of a semi-automated tool that can produce accurate segmentations can help radiation oncologists drastically reduce the time spent contouring. The two experts who performed the contouring had different levels of contouring experience as evidenced by their different average contouring time. Using the automated segmentation tool, both individuals reliably reduced the average amount of time spent contouring while improving reproducibility, demonstrating the tool's consistent ability to decrease the time to segment a tumor. The number of specific types of contour-editing instances (surface point vs a region needing an alternative JEI segmentation for a region that was felt to be missed) using the JEI approach were not specifically tracked as there was a clear decrease in the total time spent on each segmentation task compared with manual segmentation. All times included the entire process of editing. In future studies, it is would be interesting to track JEI contour editing occurrences and evaluate the use of JEI editing in different tumor pathologies and different imaging modalities.

When compared to manual contouring, consistent but varying degrees of reduction in segmentation time were reported by other organ-specific automated segmentation tools.[14,15,26-30] As mentioned, while automatic segmentation tools developed for meningioma detection by other groups have been reported, the efficiency of these tools was not specifically studied. In a separate but similar experiment, Oguz et al investigated the efficiency of the LOGISMOS algorithm in automated segmentation of rat brains and found drastically decreased segmentation time compared to neural network-based methods or atlas-based methods.[20]

Table 3. Segmentation Performance Improvement of Expert 3 when Using the JEI-LOGISMOS Semi-Automated Tool

	Signed Errors (mm)	Unsigned Errors (mm)	Dice	RVD
Manual analysis: Expert 3 vs Experts 1 & 2	0.22 ± 1.10	0.84 ± 0.86	**81.4% ± 6.2%**	**8.2% ± 8.3%**
Semi-automated analysis: Expert 3 vs Experts 1 & 2	-0.27 ± 1.20	0.80 ± 1.08	**88.0% ± 7.2%**	**-0.1% ± 7.4%**
P-value	0.107	0.886	**< 0.001**	**0.017**

Bold font depicts statistical significance. RVD = relative volume difference.

Advantages

The algorithm in the segmentation tool presented in this study is packaged in in-house software called RadOnco Analyzer. This software is specifically designed and optimized for radiation oncologists to improve radiation therapy planning. It features an intuitive user interface that allowed users to easily navigate the contouring process despite varied levels of experience. Another advantage of our algorithm is it takes full advantage of the increased use of MR-linacs in radiation treatment delivery. MR produces images with high soft-tissue contrast that particularly lends itself to tumor lesion identification.[11] Because we are studying meningiomas in the skull base, convexity, soft-tissue contrast and anatomy variability are less affected by daily deformities caused by a patient's position during treatment. Lastly, the incorporation of JEI volumetric editing with our LOGISMOS auto-segmentation tool presents a distinct advantage over other segmentation tools for real time adaptation although this specific premise is not tested in the current study. While many commercial and institution-specific segmentation tools perform efficiently and accurately, most also require significant additional time to edit the contours separately and manually after segmentations are completed by the algorithm.[14,31] With JEI-LOGISMOS, fast and intuitive editing occurs at the same time with each segmentation and further complements the time saved by automatic segmentation.

Impact on Performance of Less Experienced Analysts

As mentioned earlier, one of the recruited analysts (Expert 3) was a non-CNS specializing radiation oncologist (also less experienced) and the analyses were not included in the above summarizing results due to the observed tracing differences of manual analysis when compared to more experienced CNS specialist colleagues. We have, however, compared the level of agreement of Expert 3 when using fully manual and semi-automated analysis with the analyses provided by Experts 1 and 2. **Table 3** shows that our semi-automated approach applied by the less expert radiation oncologist had statistically significantly improved agreement with more expert contours compared with manual efforts. These metrics were improved using the semi-automated method with analyses using Dice or RVD metrics for comparison ($P < 0.001$ and $P < 0.02$, respectively). This is an important secondary outcome of our study, demonstrating that our JEI-LOGISMOS semi-automated analysis tool is likely to have a highly positive impact on accuracy as well as reproducibility of volumetric analyses performed by less expert colleagues.

Limitations

While our analysis achieved statistical significance, we believe we can continue to improve the validity of our study by increasing the sample size of our cohort of meningioma patients as well as adding the experience of other physicians. Potential bias in case selection and potential relative benefit for skull-base lesions vs other lesions could also be considered. In addition, the issue of applying in-house software in a noncommercial non-FDA approved tool will require additional levels of validation for broad applicability and to achieve full clinical relevance. The application of specific tools to specific disease sites and imaging modalities including multiparametric imaging is also a challenge for radiation therapy planning. Treatment planning software currently does not comprehensively address the needs for improved automated and semi-automated routines for contouring and the best method to integrate such tools is poorly defined.

The proposed approach is not free of real-world technical limitations resulting in logistical difficulty to incorporate a tool like this in an established clinical workflow. Incorporation in any established clinical workflow involves many steps and the described tool replaces just one of them. As a result, the JEI-LOGISMOS semi-automated segmentation must be properly interfaced with the adjacent modules of the workflow. Such a step, however, requires

cooperation by manufacturers of the respective modules and workflows potentially impacting regulatory approvals of the entire workflow pipeline.

Future Work

Application of our semi-automated algorithms for treatment planning tasks with physician supervision is an important next step furthering the implementation of these tools. We believe the MR-linac environment is ideal for this application since the need for increased efficiency and consistency is compounded by the daily requirements of treatment modifications. Expansion of the patient cohort and testing group of physicians will also be important. While the LOGISMOS framework has been successfully used to segment structures known to have poor contrast uptake including knee cartilage and the basal ganglia, it would be important in the future to evaluate our algorithm in a noncontrast MRI environment.

Conclusion

Automated contouring using a JEI approach following the automated LOGISMOS segmentation markedly improves reproducibility and efficiency of contouring for meningiomas. Evidence also suggests that it may positively improve segmentation performance of less-expert analysts. Our study presents a user-friendly and versatile tool with a robust base algorithm allowing radiation oncologists to efficiently plan radiation treatment while improving accuracy.

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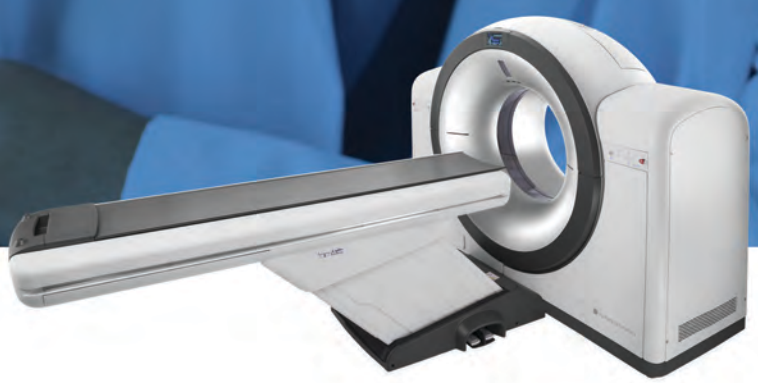

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Equipment Launches and Updates from ASTRO 2020

McKenna Bryant

Hosted virtually at the Miami Convention Center in October, the 62nd annual meeting of the American Society for Radiation Oncology (ASTRO) featured the theme "Global Oncology: Radiation Therapy in a Changing World," and shared timely COVID-19 experiences as well as an array of new attendee options, from Storytelling Sessions and ASTRO Voices, to Master Classes providing a deeper dive on topics.

The meeting also showcased a robust lineup of keynotes, posters, scientific sessions, networking zones, SA-CME opportunities and more, as well as updates from roughly 100 vendors in the virtual exhibit hall. Following is a recap of equipment news and vendor highlights that continue to shape the path of radiation therapy treatment:

Palo Alto, California-based **Varian** presented innovations that deliver more data-driven insights to improve efficiencies and outcomes, making cancer care more personalized. Presentations included data from the use of Varian's adaptive radiation therapy system, Ethos, for lung, prostate, bladder, upper abdomen, head and neck cancers, and first-look data from the recently formed artificial intelligence (AI)-driven Adaptive Intelligence Consortium.

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"Ethos is the world's first AI-powered linear accelerator. It segments both the tumor volume and the associated surrounding healthy tissue to personalize and adapt treatment so therapy can be focused on the tumor and avoid the healthy tissue," said Chris Toth, president and COO of Varian. "That's the Holy Grail of what we've been chasing for two decades within radiation oncology, so we can personalize and adapt treatments in a standard time slot."

The company also is transitioning its training approach to on-demand resources and tools with Varian Think, an online repository for individualized educational content. "We've doubled the investment in this area to support our customers not only with the best technology, but also the best service and support," said Toth.

The company's remote connectivity and telehealth telemedicine support services help clinicians keep cancer patients safe, especially during COVID-19. "This highlights the flexibility of our software applications and how we can keep centers and clinics powered in the midst of the pandemic. It shows how we make sure that that patient care doesn't skip a beat," he said.

Empowering clinicians to see more during radiation therapy planning, **Canon Medical Systems USA, Inc.** introduced the Aquilion Exceed LB CT system (pending 510[k] clearance), (**Figure 1**) an AI-powered premium scanner featuring the industry's largest bore and widest field of view. It enables better contouring using AI with sharp, clear and distinct images from Canon's Advanced intelligent Clear-IQ Engine (AiCE) deep-learning reconstruction technology.

"We're excited to release a system that has AiCE DLR technology with a huge bore opening. This is the first system in the radiation oncology space that has deep-learning reconstruction technology," said Erin Angel, managing director of Canon's CT Business Unit. "It improves low-contrast detectability and the visibility of small details so clinicians can make sure the contours of low-contrast lesions are accurate."

The Aquilion Exceed LB delivers accuracy in complex simulations with a 90-cm bore opening, edge-to-edge extended 90-cm field-of-view reconstruction, and the widest detector coverage (4 cm) in radiation oncology. "It's a spec monster. In every aspect of the system, we've surpassed what the industry expects in a radiation oncology system," said Dhruv Mehta, leader of stra-

FIGURE 1. *Aquilion Exceed LB CT system by Canon Medical Systems USA, Inc.*

tegic development for CT at Canon. "In radiation oncology, it's all about patient positioning. With a 90-cm bore, you're able to ensure accurate positioning of the patient, with AI to improve image quality, because that's the one thing that will matter for every single patient on every single study."

Reinforcing its commitment to innovation, **GE Healthcare** rolled out a roadmap for its portfolio of scanner solutions, including the new Revolution Apex ultra-premium CT and the Discovery RT CT scanner for radiation therapy planning.

Revolution Apex combines a powerful new imaging chain with TrueFidelity CT images created by deep-learning image reconstruction. It gives clinicians access to outstanding coverage, spatial resolution, temporal resolution and spectral imaging capabilities in one system, with the power of the Quantix 160 tube for excellent image quality.

Discovery RT offers a streamlined workflow and submillimetric images with motion and metal artifacts significantly reduced.

On the simulation side, the company presented AIR Recon DL (not CE marked), a deep-learning-based reconstruction algorithm that shortens scan times while delivering better image quality across all anatomies. Developed on GE Healthcare's Edison intelligence platform, the technology generates AIR Recon DL images in real-time at the operator's console.

"By leveraging AI technology, AIR Recon DL helps improve signal-to-noise ratio for better delineation. It supports radiation therapy planning by precisely targeting tumors and minimizing collateral damage for efficacy and optimization of the outcome," said Ben Newton, general manager, oncology business for GE Healthcare.

The company complements those technologies with digital solutions, such as AdvantageSim MD, an integrated simulation and localization software suite that helps improve and streamline treatment planning.

"AdvantageSim allows access to those technologies across the fleet to enable easy radiation, oncology, simulation, and planning," said Newton.

FUJIFILM Medical Systems USA, Inc. highlighted the FCT Embrace CT system. Powered by Analogic, the FCT Embrace was the first 85-cm wide-bore CT imaging unit with 64- or 128-slice configurations. Optimized for oncology and radiology applications, the FCT Embrace, combined with other oncology solutions, offers CT simulation with radiation therapy treatment planning capabilities.

The company has enhanced the platform with the addition of FCT PixelShine (may not be commercially available in all countries), a novel deep-learning technique that improves the image quality of low-dose CT images, reducing the side effects of increased quantum mottle and image noise.

RaySearch Laboratories AB presented advances in machine learning and support for brachytherapy with online demos of its latest oncology software, including its treatment planning system RayStation and oncology information system RayCare. (Both products are subject to regulatory clearance in some markets.)

Among highlights in RayStation treatment planning system are support for brachytherapy planning and robust proton planning using machine learning. The upcoming release of RayStation 10B is expected in December 2020 (subject to regulatory clearance in some markets) and will add support for brachytherapy planning. It will feature automatic channel reconstruction in combination with dwell-time optimization to make the creation of high-quality brachytherapy plans faster and more consistent. Attendees experienced demos of machine-learning planning for photons and robust proton planning, as well as deep-learning organ segmentation.

"For machine learning, the big news is the support for robust proton planning. RayStation 10B now has the functionality to automatically generate proton plans by combining the machine-learning-based dose prediction with the robust optimization framework in RayStation. This [allows] for automatically generating both photon and proton plans that can be used for decision support," said Fredrik Löfman, director of machine learning at RaySearch.

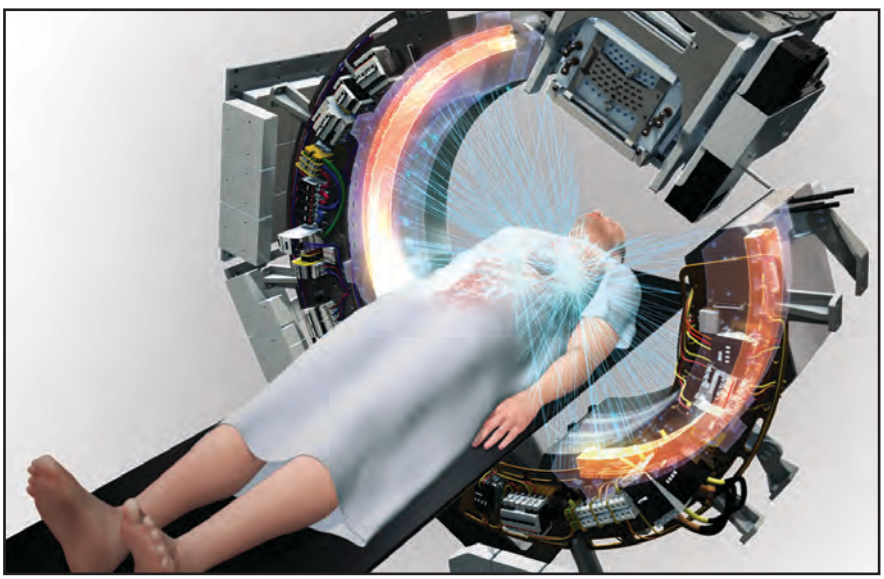

FIGURE 2. *RefleXion X1 by RefleXion Medical*

In the RayCare oncology information system, additional automation capabilities support scripting and enhanced workflow management tools. Released in June 2020, RayCare 4A promotes efficiency and safety by reducing routine manual tasks and handovers. Its workflow management capabilities are enhanced by the introduction of task management for clinical teams. Further functionalities in RayCare 4A include support for scripting as well as automated support for running RayStation scripts from tasks with forks – as well as several new patient chart features. RayCare 4B is expected in December 2020 (subject to regulatory clearance in some markets).

A therapeutic oncology company pioneering biology-guided radiation therapy (BgRT) for treating all stages of cancer, **RefleXion Medical** highlighted new research evaluating feasibility of BgRT to treat metastatic cancer. (The RefleXion X1 BgRT capability requires 510[k] clearance; this feature is not available for sale.)

RefleXion developed the first BgRT machine, which is cleared for the delivery of stereotactic body radiation therapy (SBRT), stereotactic radiosurgery (SRS) and intensity-modulated radiation therapy (IMRT). The first installation at Stanford University was completed in November, with plans to treat patients in early 2021.

"The ring gantry system rotates 60 revolutions per minute. Because of that speed, it can deliver IMRT, SBRT and SRS with exceptional accuracy," said Sean Shirvani, MD, senior vice president of Clinical and Medical Affairs at RefleXion. "On top of that architecture, we are adding a new functionality called BgRT, which uses [positron emission tomography] PET emission signals emanating from tumors to direct therapeutic radiation." (**Figure 2**)

The BgRT technology will synchronize PET data with the linear accelerator to direct radiation therapy to tumors with sub-second latency.

RefleXion also entered into strategic collaborations in 2020 with Merck and Telix Pharmaceuticals, among others. "Our goal is to run clinical trials in collaboration with Merck that combine our technology with their immunotherapy agents to potentially enhance anti-tumor immunity," said Dr. Shirvani. "As we look forward to incorporating other PET tracers besides FDG on our device, Telix will be at the forefront of those explorations with their cancer-cell-specific tracers for renal cell and prostate cancer."

To address some of the most common challenges in radiation therapy, **Siemens Healthineers AG** featured two new CT simulators, AI technologies, and MR- and PET-based planning solutions.

Somatom go.Sim and Somatom go.Open Pro both feature an 85-cm bore and a 60-cm true scan field of view. To meet the challenge of precise 4D CT imaging, Somatom.go Open Pro features Direct i4D(1), the first 4D CT sequence that intelligently adapts to the patient's breathing.

The MAGNETOM RT Pro includes optimized RT imaging protocols with features that allow the patient to be imaged in the treatment position. Dedicated quality assurance (QA) recommendations ensure consistent and geometric accurate MRI imaging. The system can provide important imaging applications to support accurate RT planning, including diffusion-weighted imaging to visualize tumor activity, MR-only planning with synthetic CT, and 4D MRI imaging to manage patient motion.

The company also showcased its Biograph mCT Sim PET/CT scanner, which features a large bore and gives clinicians access to intelligent AI-powered imaging applications to standardize protocols, personalize treatment, and perform respiratory motion correction for PET imaging. Earlier this year, Siemens announced a merger with Varian to create a multidisciplinary global health care company with a comprehensive cancer care portfolio. The transaction is expected to close in the first half of calendar year 2021.

"With Varian, we have the most comprehensive portfolio and multidisciplinary expertise in the industry to address the entire continuum of cancer care," said Bernd Montag, CEO of Siemens Healthineers. "We want to help reduce the fear of cancer by ensuring that patients get the best chance right from the start."

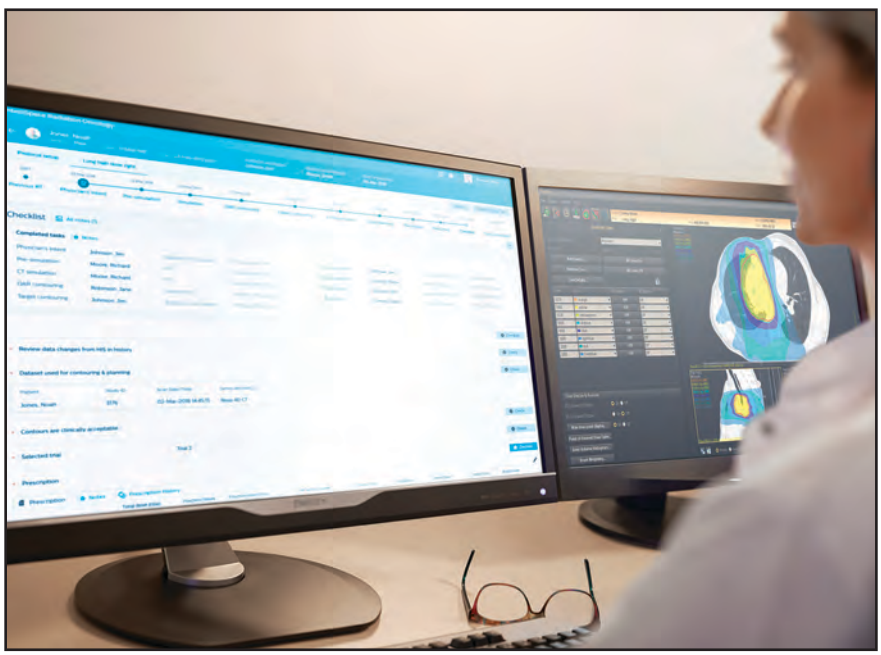

FIGURE 3. *IntelliSpace Radiation Oncology workflow platform by Philips*

Belgium-based IBA (Ion Beam Applications S.A.) discussed how its Proteus solutions and network of clinical and industrial partners are shaping the future of proton therapy.

The latest developments for its Proteus systems address the current and future needs of proton therapy centers. IBA's comprehensive motion management package will help clinicians treat more indications. IBA's proton arc therapy will enable clinicians to treat patients precisely, faster and more easily. IBA systems are also capable of delivering FLASH proton therapy, which the company believes can radically change the radiation therapy landscape, revolutionizing cancer care in general. (Arc Therapy is a work in progress and FLASH therapy is in the research stage; neither are available for sale.)

"We believe that proton therapy systems need to be ready to manage motion and deliver ARC and FLASH therapy as soon as clinically released," said Aymeric Harmant, global marketing director of proton therapy at IBA, noting that the company recently reached the milestone of treating 100,000 patients on IBA proton therapy systems.

With its open-vendor platform, IBA also integrates solutions of leading industrial partners to improve clinical workflow, integration and user experience. IBA has a long-term collaboration with Philips in imaging, diagnostics and radiation therapy for comprehensive cancer treatment. Additionally, its collaboration with Elekta is allowing both companies to offer a full set of treatment modalities in radiation therapy. Close collaboration with RaySearch Laboratories has demonstrated a fully integrated proton therapy workflow integrating IBA's Proteus solution with advanced treatment planning system (TPS) RayStation and next-generation oncology information system (OIS) RayCare (subject to regulatory clearance in some markets).

Philips presented its dedicated radiation oncology line-up, including the Big Bore RT CT scanner and simulator for radiation oncology and therapy, and simulation platform and Ingenia MR-RT, the comprehensive MR simulation platform. Big Bore RT uses iterative model reconstruction (IMR) technology to help visualize fine detail and improve clinical accuracy for detecting and delineating small, subtle structures.

"One of the biggest things we hear from clinicians is that their image quality with our IMR feature has really improved. This is really helpful for better contouring, and also for better image quality in general," said Ardie Ermers, vice president and general manager of Radiation Oncology at Philips.

The highlight of this year's ASTRO meeting was the IntelliSpace Radiation Oncology workflow platform (**Figure 3**) (not available for sale in all markets), which enables radiation therapy departments to accelerate the time from patient referral to the start of treatment. The South West Wales Cancer Centre (SWWCC) in the UK believes it will help reduce its 14-step breast pathway referral-to-first treatment from 32 days to 14 days.

"The referral time to the radiation therapy department to start treatment is, on average, 15 to 20 days. With IntelliSpace, some of our customers are improving that workflow by 50%," said Ermers.

Philips also continues to advance its leading MR-only radiation therapy portfolio with its AI-based MRCAT Brain application. MRCAT reduces the organization and coordination of scans involved in MR-CT registration, saving the patient from undergoing another imaging procedure.

"We used AI to speed up how the algorithm trains itself and to improve the quality of the MR-only simulation process," Ermers said. "We know that AI for the sake of AI doesn't really do much. So we make sure our AI can either make the workflow easier, more automated, or more streamlined, and remove the tedious manual tasks. We believe that applying AI should make life easier for users."

To help address the worldwide cancer burden, **Elekta** introduced the

FIGURE 4. *The Harmony linear accelerator by Elekta*

Elekta Harmony linear accelerator, (**Figure 4**) a cancer treatment system designed to meet the need for a productive, precise and versatile radiation therapy treatment system. Harmony recently received a CE mark, clearing the technology for commercial sales in Europe. (Elekta Harmony is not available in all markets.)

Harmony enables clinicians to treat most indications, including breast, lung, pelvic and head-and-neck cancers. With its comprehensive capabilities – combined with a shorter treatment slot of up to 25 percent, and a 30 percent smaller footprint than Elekta's other linacs – Harmony is a practical system for developing and well-established markets.

"Elekta pioneered linear accelerators and we're taking that technology to the next level, both in precision and personalization," said Ioannis Panagiotelis, chief marketing and sales officer and executive vice president of Elekta. "We believe that real-time, high-quality diagnostic imaging is the way to go forward, and I feel very confident about the promise that this technology is bringing to the radiation oncology community."

Elekta has enhanced its MOSAIQ radiation oncology portfolio with MOSAIQ Voice, a voice-enabled documentation and automation platform that uses speech recognition engines to reduce the time to create accurate patient notes. "Data demonstrate that by using MOSAIQ Voice, clinicians have saved on average 125 hours every year," said Panagiotelis.

Elekta also acquired Kaiku Health, a cloud-based solution that monitors patient-reported outcomes, providing intelligent symptom tracking and management for health care providers in routine oncology care and studies. "Measuring what matters to patients is important in value-based health care, and we can demonstrate that we can improve the quality of life and also reduce potential additional costs."

Innovations in hardware and software solutions and clinical data continue to support the use of **Accuray Incorporated's** CyberKnife and TomoTherapy platforms, including the next-generation Radixact System, to deliver (ultra) hypofractionated radiation treatments. Hypofractionated radiation therapy — a shorter course of radiation therapy with higher radiation doses per fraction — provides an efficient and effective treatment option for an increasing number of indications.

With more than a decade of clinical proof behind Synchrony motion synchronization and real-time adaptive radiation therapy technology for the CyberKnife System, Accuray brought this advanced capability to the Radixact System. The AI-driven Synchrony technology corrects for tumors that move as a result of bodily processes, including respiration and digestion, as well as patient movement, without uncomfortable patient restraints, breath-hold techniques, or human intervention. It's the only technology to use image guidance during radiation delivery to automatically adapt and synchronize radiation treatment in real-time with the movement of the tumor.

"With Synchrony, we can deliver dose to the target very efficiently because we follow it throughout its full cycle of motion, then we're able to create tight margins around the tumor itself. So there's no tradeoff between treatment delivery speed and quality," said Corey Lawson, vice president of product strategy at Accuray.

The CyberKnife S7 System is a robotic, noninvasive radiation therapy device capable of treating cancerous and benign tumors throughout the body, as well as neurological disorders. The system supports SRS and SBRT techniques used to deliver (ultra) hypofractionated radiation therapy. New data presented at ASTRO showed that SBRT delivered with CyberKnife provides excellent control rates in men with early stage prostate cancer followed for at least 10 years. Treatment was also well-tolerated and efficacious in patients with early stage breast cancer.

The most recent innovation for the Radixact system, ClearRT Helical kVCT Imaging, is intended to quickly and cost-effectively produce clear, high-fidelity kVCT images that enhance soft-tissue visualization. (ClearRT helical kVCT imaging for the Radixact treatment delivery system is 510[k] pending and is not available for sale in any market.) The Radixact system is the only radiation therapy device with helical imaging, helical delivery, and intrafraction motion synchronization functionality using Synchrony, with the longest continuous imaging and treatment fields in the industry, up to 135 cm. "We can acquire very long field lengths very quickly, upwards of a meter in a minute," said Lawson.

Balanitis: An Unexpected Adverse Reaction to Pelvic Radiation or to Chemotherapy? Two Cases and a Review of the Literature

Jason Liu, MD; Yi-Jen Chen, MD, PhD

Skin changes caused by ionizing radiation are one of the most common side effects of radiation treatment, with radiation dermatitis occurring in about 85% to 95% of cancer patients receiving radiation treatment.[1] Severity can range from mild erythema to moist desquamation and ulceration.

Radiation is often combined with chemotherapy for concurrent chemoradiation treatment. As a result, it can often be difficult to distinguish whether an adverse reaction to treatment is due to radiation or chemotherapy. It is important to properly identify the causative agent for an adverse reaction, and failure to do so may not only worsen patients' quality of life, but also delay or interrupt treatment.

Generally, when patients have a skin reaction near the area of radiation treatment it is attributed to radiation. However, closer inspection may show this is not always the case. Here, we present 2 cases of patients receiving concurrent

Dr. Liu *is a PGY2 resident physician and* ***Dr. Chen*** *is a clinical professor and residency program director, City of Hope National Medical Center, Duarte, CA.*
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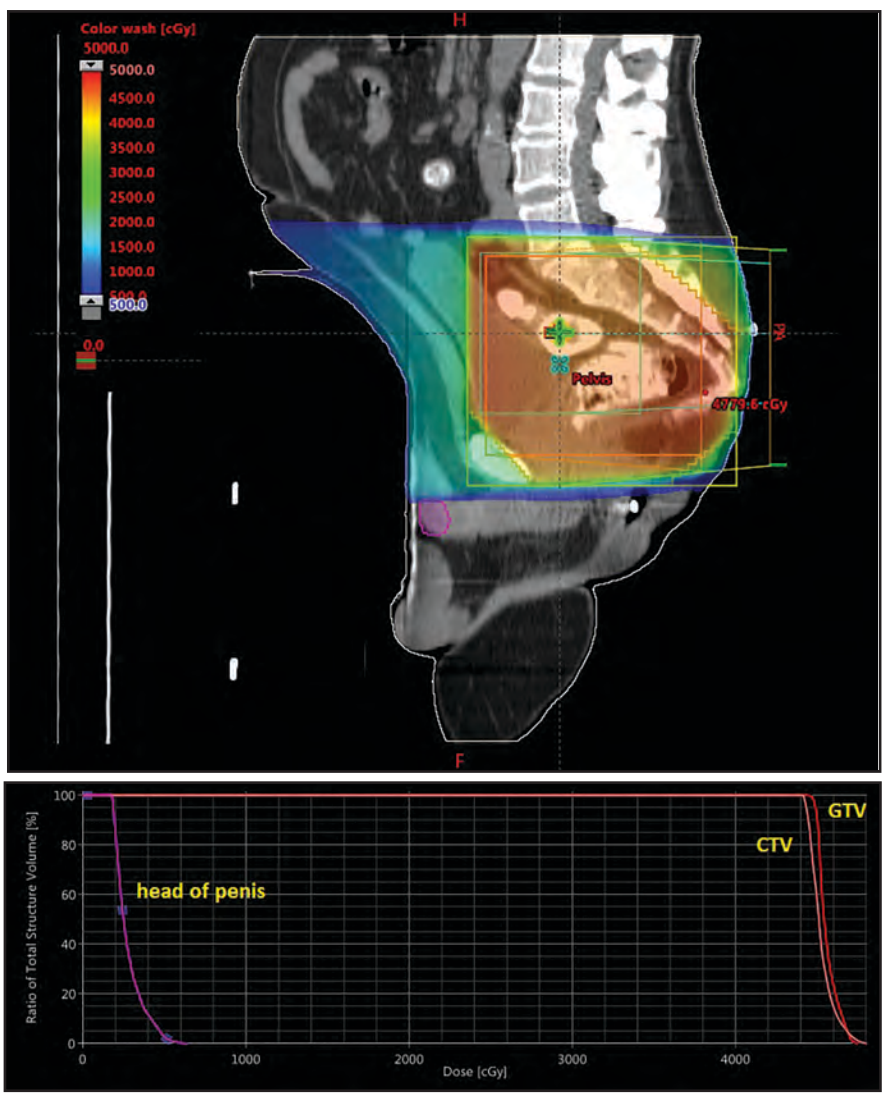

FIGURE 1. *Radiation treatment plan to the rectum using a 4-field box technique with dose represented by color wash. The dose-volume histogram shows only 20% of the head of the penis receiving 4 Gy or more.*

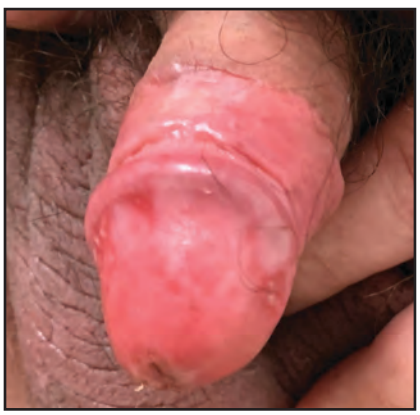

FIGURE 2. *Inflammation and blistering seen at the head of the penis for patient 2. This skin reaction occurred around week 5 out of 6 of radiation treatment (39.6 Gy out of 54 Gy).*

chemoradiation to the pelvis who developed blistering at the head of the penis. The immediate assumption was that this adverse reaction was caused by radiation. Further review of the treatment plan and the literature suggest that this rare adverse effect—also known as balanitis, inflammation of the head of the penis—is associated with chemotherapy, specifically 5-FU and capecitabine.[2-5]

CASE SUMMARIES

Patient 1

Patient 1 is a 59-year-old man with a diagnosis of T3N0M0 rectal cancer. He underwent a screening colonoscopy examination in 2009 and was found to have cancer in situ in a resected polyp in the rectum. He did well until August 2019 when a follow-up screening colonoscopy examination identified a 1.5-cm sessile lesion at about 10 cm from anal verge; biopsy confirmed invasive carcinoma. A computed tomography (CT) scan of the chest/abdomen/pelvis showed no evidence of distant metastases. MRI of the pelvis showed a mass-like lesion over the proximal and midrectum with a cranial caudal extension about 2.4 cm involving the proximal and midrectum with transmural involvement and without evidence of enlarged lymphadenopathy. Based on imaging findings, his rectal cancer was considered T3N0M0.

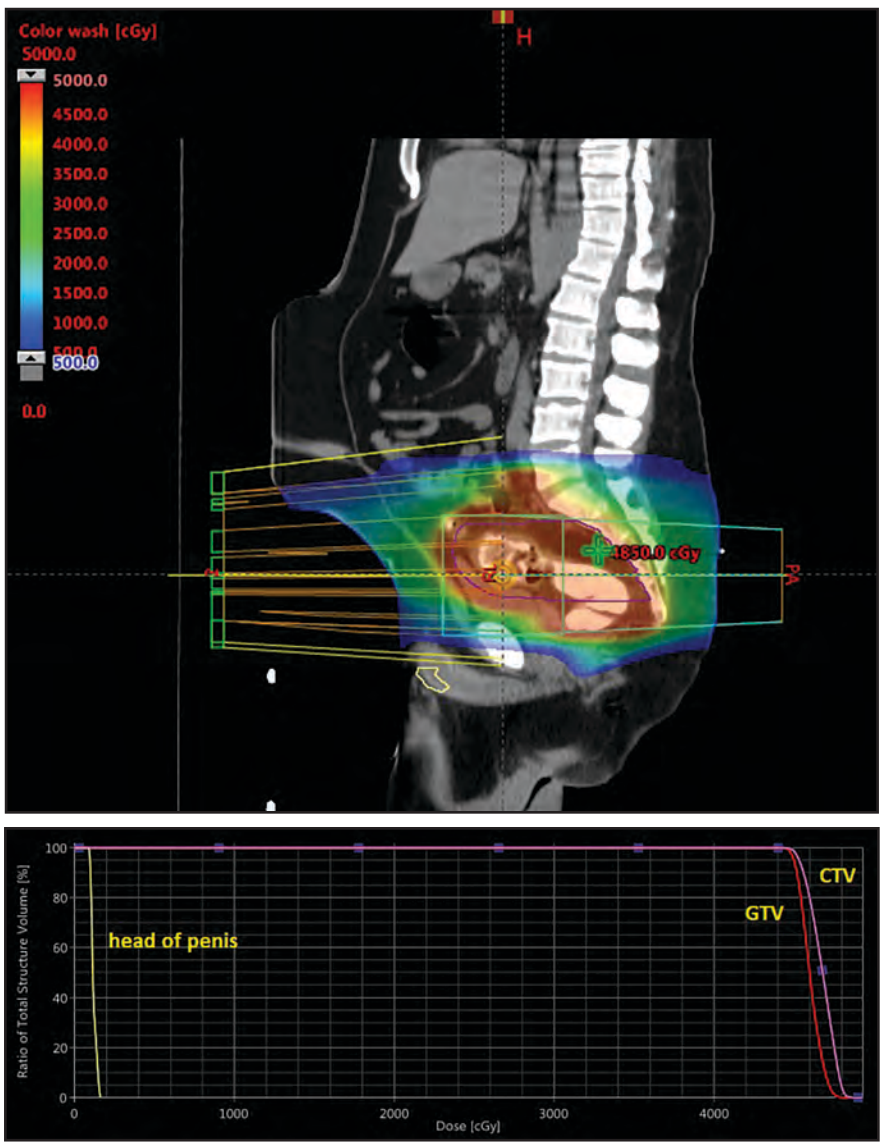

FIGURE 3. *Radiation treatment plan to the rectum using intensity-modulated radiation therapy (IMRT) with dose represented by color wash. The dose-volume histogram shows the entire head of penis receiving < 2 Gy.*

Patient 1 was offered total neoadjuvant therapy followed by surgery to treat his rectal cancer. He was initially started on CAPEOX, but he was unable to tolerate capecitabine due to an adverse skin reaction on his hands and feet, and CAPEOX was stopped after 2 cycles. His chemotherapy was subsequently changed to FOLFOX for 4 more cycles, which the patient tolerated well. A follow-up CT scan of his chest, abdomen, and pelvis showed no evidence of distant metastases. Patient 1 then underwent chemoradiation with infusional 5-FU (2,250 mg weekly) and 54 Gy in 30 fractions to the pelvis using a 4-field box technique.

Around week 5 out of 6 of radiation treatment (after 41.4 Gy out of 54 Gy), he was noted to have erythema with minor blistering lesions over the head of the penis. There was some concern that this may be an adverse reaction to radiation, but reviewing his radiation

Table 1. Documented Cases of Balanitis Associated With 5-FU or Capecitabine

Author	Age/Sex	Diagnosis	Treatment	Severity	Symptom onset
Present case, patient 1	59M	T3N0M0 rectal cancer	Neoadjuvant CAPEOX q3 weeks for 2 cycles followed by FOLFOX q2 weeks for 4 cycles followed by radiation with 5-FU (2250 mg q1 week)	Grade 1	13 weeks (8 weeks of FOLFOX and 5 weeks of chemoradiation with 5-FU)
F Tas, et al[2]	58M	T4NxM1 esophageal cancer	Palliative 5-FU (600 mg/m2 continuous infusion) with cisplatin (75 mg/m2 q3 weeks) for 6 cycles	Grade 1	16 weeks
G Micevic, et al[4]	50M	esophageal cancer	FOLFIRI q2 weeks for unclear number of cycles	Grade 2	3 weeks
Present case, patient 2	41M	T3N1M0 rectal cancer	Neoadjuvant FOLFOX q2 weeks for 8 cycles followed by radiation with capecitabine (2000 mg twice daily)	Grade 1	5 weeks
C Sapp, et al[3]	67M	T3N1M1 colon cancer	Palliative capecitabine (1g twice daily for 14 days followed by 2 weeks of rest) for unclear number of cycles	Grade 2	12 weeks
C Sapp, et al[3]	63M	T4N1M0 colon cancer and T4N1M0 gastric cancer	Adjuvant CAPEOX q3 weeks for unclear number of cycles	Grade 1	2 weeks
Hu, et al[5]	43M	T3cN2bM0 rectal cancer	Neoadjuvant radiation with capecitabine (825 mg/m2 twice daily)	Grade 1	4 weeks

treatment plan did not show significant radiation dose to the head of the penis (**Figure 1**). Further literature review showed an association between 5-FU and inflammation at the head of the penis. His medical oncologist was informed, and it was decided to continue treatment and monitor. He was able to complete the rest of treatment without interruption, although his penile toxicity did not improve until after completion of treatment. MRI and endoscopic evaluation 3 months post-treatment showed that the patient achieved clinical complete response and he is currently on a "watch and wait" protocol.

Patient 2

Patient 2 is a 41-year-old man with a diagnosis of T3N1M0 rectal cancer. He initially presented with changes in bowel habits, intermittent rectal bleeding, and urgency for several months. He eventually underwent an esophagogastroduodenoscopy (EGD) and colonoscopy in early 2020, which showed a circumferential mass approximately 12 cm from the anal verge, which biopsy confirmed to be invasive carcinoma. The tumor was obstructing and could not be passed. Patient 2 underwent a staging CT scan of the chest, abdomen, and pelvis, which showed no evidence of metastatic disease. He also underwent an MRI of the pelvis, which was concerning for possible regional adenopathy. Based on imaging findings, his rectal cancer was considered T3N1M0.

Patient 2 was offered total neoadjuvant therapy followed by surgery to treat his rectal cancer. He completed 8 cycles of FOLFOX without any issues. Follow-up CT scan of his chest, abdomen, and pelvis showed no evidence of distant metastases. Patient 2 then underwent chemoradiation with capecitabine (2,000 mg twice daily) and 54 Gy in 30 fractions to the pelvis using intensity-modulated radiation therapy (IMRT).

Around week 5 out of 6 of radiation treatment (after 39.6 Gy out of 54), he developed blistering over the head of the penis (**Figure 2**). Again, reviewing his radiation treatment plan did not show any radiation dose to the penis (**Figure 3**). Further literature review showed an association between capecitabine and inflammation at the head of the penis. His medical oncologist was informed, and his dose of capecitabine was decreased from 2,000 mg twice daily to 1,500 mg twice daily. Patient 2 was able to complete the rest of treatment without interruption and is currently pending evaluation to assess his response after therapy. Surgical intervention will be followed.

DISCUSSION

One of the most common skin reactions caused by capecitabine and 5-FU is hand-foot syndrome, also known as palmar-plantar erythrodysesthesia. This reaction mostly affects the palms of the hands and soles of the feet, causing inflammation and blistering. Other cytotoxic drugs linked to hand-foot syndrome include pegylated liposomal doxorubicin, docetaxel, vinorelbine, gemcitabine, and sorafenib.[6] Severity can range from National Cancer Institute (NCI) grade 1 (dermatitis, redness, swelling, and hyperkeratosis without pain) to NCI grade 3 (peeling, blisters, bleeding, fissures, swelling, hyperkeratosis with pain, and limiting self-care activities).[7]

Generally, the management for hand-foot syndrome is delaying treatment for up to 2 weeks until symptoms resolve to grade 0-1.[8] Local supportive measures such as cooling and moisturizing the affected areas have been shown to be helpful.[9] Systemic therapy may be considered for severe cases, with systemic corticosteroids and pyridoxine showing varying degrees of efficacy in treating hand-foot syndrome.[10] Symptoms typically resolve within 2 to 4 weeks.

While hand-foot syndrome is a well-known side effect of capecitabine and 5-FU, manifestations outside the hands and feet are uncommon. Skin toxicity involving the genitals is even less common, and only a few case reports document this rare adverse reaction.[2-5] Upon reviewing the literature, we have identified 2 cases of 5-FU-associated balanitis and 2 cases of capecitabine-associated balanitis. **Table 1** summarizes reported cases of chemotherapy-induced balanitis including the patients in this case series to better represent how this unexpected skin toxicity may present.

Based on the literature, it appears that most cases of balanitis are grade 1 to 2 with a symptom onset between 2 to 16 weeks after initiating treatment. All cases of balanitis resolved 2 weeks after decreasing the dose or taking a break from the offending agent. The 2 cases we present in this case report are consistent with previous case reports.

We acknowledge that the penis is a free mobile organ, and the case report findings could be limited by the fact that the penis could be in various positions (in or outside the radiation fields) during daily setup. However, examining the sagittal views in **Figures 1 and 3** show that even with the penis head in the most superior position, it is unlikely to receive any more than 5-10 Gy based on the dose color wash. Also, for patients being treated with IMRT, daily imaging with cone-beam CT (CBCT) could help in tracking the penile tissue during daily treatment. Patient 2 was treated with IMRT, and after he developed balanitis, we actively tracked his penile tissue with CBCT to see if it was inside the radiation field.

Several strategies can help radiation oncologists manage balanitis whether it is caused by chemotherapy or radiation. For mild dermatitis and focal pruritis, skin care products such as Aquaphor and Eucerin cream may be used. For more severe moist desquamation, skin care products containing antibiotics such as Silvadene may be used. For daily set-up considerations, if the patient is receiving IMRT, checking to see whether the head of the penis is in the field of radiation with CBCT is important. As always, it is important to communicate with the medical oncologist to see if any treatment-related issues are related to the chemotherapy or radiation.

CONCLUSION

Balanitis is a rare skin toxicity associated with chemotherapy. For patients receiving concurrent chemoradiation, especially to the pelvic area, it can be easy to misattribute the cause of balanitis to radiation. Incorrectly attributing the cause of this adverse reaction may worsen patient outcomes and prolong patient suffering. It is thus important to showcase these two cases to help clinicians make more informed decisions when encountering these types of reactions in their practice.

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Spontaneous Pregnancy Following Pelvic Irradiation for Anal Cancer: A Case Report

Charlotte Murphy, MB, BCh, BAO, MRCPI; Charles Gillham, MBBS, MRCP, FRCR, MD, FFR, RCSI

CASE SUMMARY

A 26-year-old woman, para 1 and on triple therapy for HIV, was treated with pelvic radiation therapy to 50.4 Gy (30.6 Gy/17 fractions [phase 1], 19.8 Gy/11 fractions [phase 2]). The left ovary mean dose was 1 Gy, right ovary 31.5 Gy, and uterus 34.5 Gy (**Figure 1, 2**) with concurrent 5-FU and mitomycin C for grade 1, cT1N0M0 squamous cell cancer of the anus. Her left ovary was transposed into the abdomen prior to treatment to maintain premenopausal status. Her right ovary received more than double the effective sterilizing dose of radiation. Her treatment response was excellent with no evidence of disease on post-treatment imaging. Somewhat unexpectedly, she continued to menstruate with a regular cycle post-treatment.

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Hysteroscopy to investigate this bleeding demonstrated a small uterine cavity of normal appearance. Endometrial curettings were normal histologically. Colposcopy was also normal. Five years later she spontaneously conceived and vaginally delivered a small-for-dates, but otherwise healthy baby, requiring a significant episiotomy during delivery.

IMAGING FINDINGS

Transverse and sagittal plane images of planning computed tomography (CT) demonstrate radiation dose delivered to pelvic structures (**Figure 1A**). Images of radiation therapy planning CT with both ovaries outlined show that the left ovary has been transposed into the abdomen prior to commencing radiation therapy (**Figure 1B**). Dose-volume histogram for ovaries and uterus is shown in **Figure 2**.

DIAGNOSIS

Grade 1, cT1N0M0 squamous cell cancer of the anus

DISCUSSION

Anal cancer is associated with the human papillomavirus (HPV) and is recognized as a common non-AIDS-defining cancer in HIV-positive individuals.[1] Chemoradiotherapy using 5-FU and mitomycin has been the standard treatment for anal cancer since the Anal Cancer Trial (ACT1) trial.[2]

Unfortunately, the dose of radiation therapy used to treat anal cancer is generally high enough to sterilize the ovaries. Furthermore, current trials are using higher doses of pelvic irradiation (to larger volumes) in certain anal cancers (ACT5 of PLATO);[3] thus, the probability of conception post-treatment will reduce even further. The Faddy-Gosden model, which is a mathematical model of natural oocyte decline, has estimated that a dose of < 2 Gy will destroy half of the immature oocytes following pelvic irradiation.[4] The effective sterilizing dose (ESD) is the dose of fractionated radiation therapy that causes premature ovarian failure immediately after treatment in 97.5% of patients. Naturally, the ESD decreases with increasing age at the time of treatment, due to physiological factors of female reproduction. The ESD at birth is 20.3 Gy, decreasing to 16.5 Gy at 20 years and 14.3 Gy at 30 years.[5]

Previous studies regarding changes seen on dynamic contrast-enhanced MRI in premenopausal women undergoing pelvic RT have demonstrated that the blood vessels of the irradiated uteri

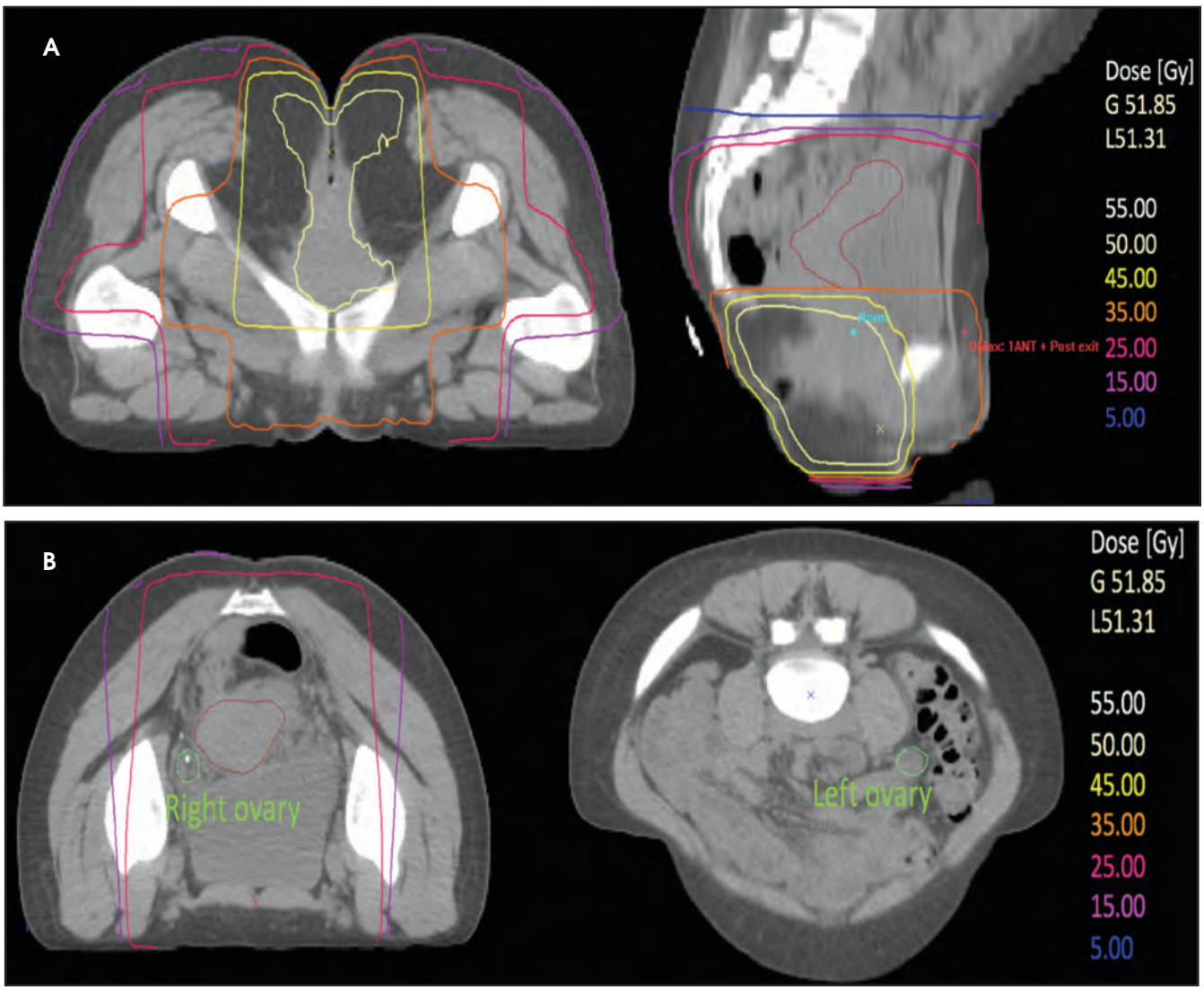

FIGURE 1. *Transverse and sagittal plane images of planning computed tomography (CT) demonstrating radiation dose delivered to pelvic structures (A). Images of a radiation therapy planning CT with both ovaries outlined; note the left ovary has been transposed into the abdomen prior to commencing radiation therapy (B).*

contained marked circumferential intimal thickening and decreased luminal diameter. Furthermore, changes in cervical length, loss of uterine junctional zone anatomy and myometrial atrophy and fibrosis were seen following RT treatment.[6] Although this patient was not offered the use of a vaginal dilator, it is something that should be considered as part of treatment in all women receiving pelvic radiation therapy.[7] Studies are underway to improve compliance with dilator use.[8]

Three factors in this case are interesting due to the rarity of their occurrence. First, the probability of spontaneous conception was extremely low considering this patient received more than twice the effective sterilizing dose to her right ovary (ESD at 26 years old is approximately 15 Gy) during treatment for her anal cancer.[5] Furthermore, although a previous hysteroscopy in this patient had described a small uterine cavity, she successfully carried the fetus to 36 weeks of gestation. It is unclear as to how the uterus was able to maintain a fetus for this length of time, but we can only presume that the dose it received (mean 34.5 Gy) was, in this woman, below the threshold beyond which significant vascular compromise occurred. Finally, her vaginal delivery of a 3.5-pound baby is remarkable considering that radiation therapy often renders the vaginal canal fibrosed and stenosed. We presume that the transposed ovary helped maintain this patient's premenopausal state but it

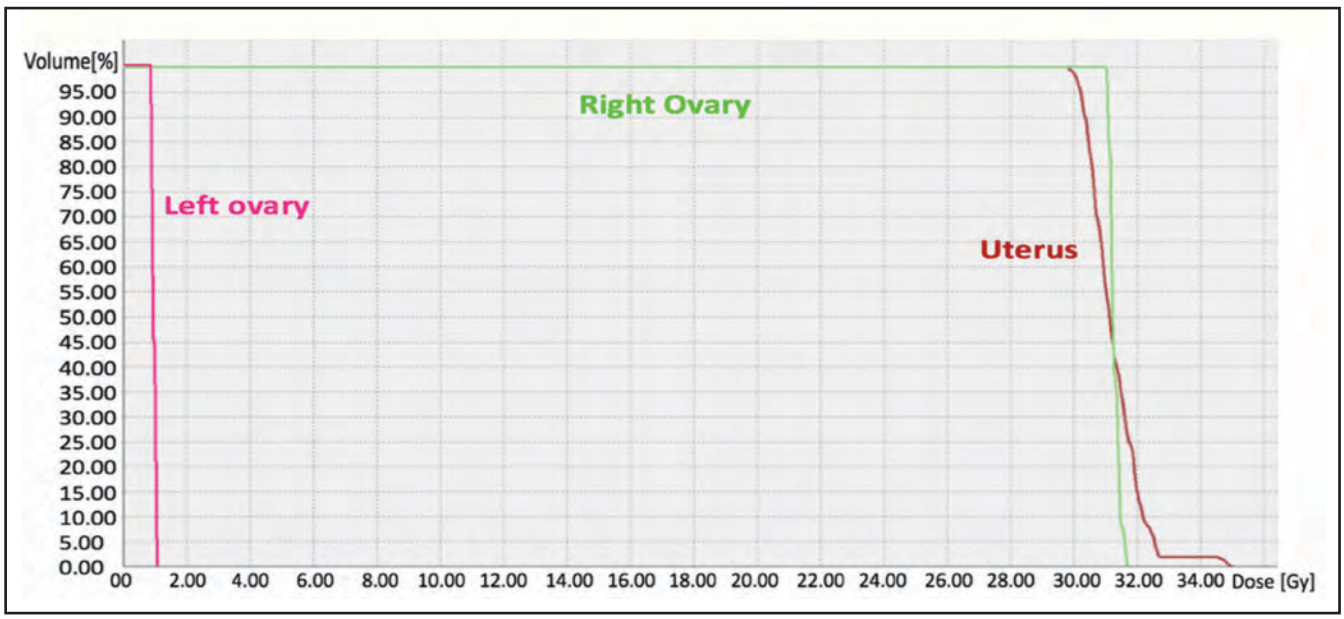

FIGURE 2. *Dose-volume histogram (Phase 1 and Phase 2) demonstrating dose to each ovary and the uterus.*

was the ovary left within the pelvis that must have released the egg that was fertilized.

To our knowledge, this is the only reported case of a woman having a vaginal delivery following pelvic radiation therapy for anal cancer. The only other published case describes a woman who became pregnant but underwent elective caesarean section due to vaginal stenosis.[9] Wald et al describe a spontaneous twin pregnancy following radiation therapy for rectal cancer; however, one child died due to premature labor with a complicated delivery.[10] A case of a woman successfully conceiving and delivering vaginally following radiation therapy to the rectum for rectal MALT lymphoma has also been described.[11] Although the ESD causes premature ovarian failure in 97.5% of patients, it is clear that in extremely rare cases, some ovarian function can remain and subsequent pregnancies can occur.

CONCLUSION

Transposing an ovary (or two) outside of the pelvis should be considered in all premenopausal women prior to anal cancer radiation therapy. The primary aim of this would be to maintain premenopausal status and minimize complications associated with premature ovarian failure. Despite the case highlighted here, it would be difficult to argue that one ovary should remain (attached to its fallopian tube) within the pelvis to maintain fertility. This case highlights the need to remind patients that, although rare, pregnancy is still possible after pelvic radiation therapy and contraception should be considered where necessary. Furthermore, both gestation and delivery carry high risk to the fetus due to the radiation effects on the pelvic anatomy and, if pregnancy occurs, close collaboration between obstetrics and oncology is essential and a vaginal delivery should be avoided.

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RADIATION ONCOLOGY CASE

Mediastinal Epithelioid Hemangioendothelioma in a Patient With Concurrent Early Stage Right Breast Cancer

Masaki Bannai, MBBS; Zaeem Ahmed, MBBS; Marie Bertrand-Philippe, MBBS, PhD; Pankaj Saxena, MBBS, FRACS; Ariyanto Pramana, MBBS, FRANZCR

CASE SUMMARY

A 47-year-old woman initially presented with cancer in her right breast, detected during screening. A core biopsy was suspicious for intraductal carcinoma. She underwent a guide-wire localized lumpectomy, which unexpectedly showed at least 10 tumors ranging 0.5 to 32 mm, grade 2 invasive ductal carcinoma with positive margins, and no lymphovascular space invasion. Re-excision with sentinel lymph node biopsy achieved clear margins and revealed 1 out of 5 sentinel lymph nodes containing 8 isolated tumor cells. Hormone receptors were strongly positive while HER 2 was 1+ and DISH was negative. The final pathological staging was multifocal pT2N0 (i+).

Staging computed tomography (CT) revealed a left anterior mediastinal mass with intense fluorodeoxyglucose (FDG) avidity on subsequent FDG positron emission tomography (PET) **(Figure 1 A-C)**. Tumor markers including alpha-fetoprotein and beta human chorionic gonadotropin were negative. CT-guided biopsy of the mediastinal mass revealed epithelioid hemangioendothelioma (EHE).

Upper hemisternotomy and en bloc resection revealed involvement of the left brachiocephalic vein and left phrenic nerve. It was suspected on the preoperative imaging, which demonstrated an elevated left hemi-diaphragm with a clinical manifestation in mild dyspnea. Histopathological examination revealed a 45-x-25-mm tumor composed of round to spindle-shaped cells with eosinophilic cytoplasm and intracytoplasmic vacuolation in hyalinized stroma (**Figure 2A**). The tumor showed positive staining for endothelial and vascular markers CD31, CD34 and ERG on immunohistochemistry (**Figure 2B** and **2C**). The tumor cells exhibited 4 mitoses per 50 high-power field with no severe atypia. There were no features of an epithelioid angiosarcoma.

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Due to the prolonged time post breast surgery and the need for adjuvant radiation therapy (RT) for both EHE and breast cancer, adjuvant chemotherapy for breast cancer was omitted and endocrine therapy was initiated. Complex planning of adjuvant RT to two adjacent anatomical sites with two distinct malignancies was undertaken using 2-dimensional (2D) tangential and partial arc volumetric-modulated arc therapy (VMAT). Phase I delivered 50.4 Gy in 28 fractions to the right breast and anterior mediastinum. Phase II delivered further 10 Gy in 5 fractions to the surgical cavity in the breast and 9 Gy in 5 fractions to the surgical bed within the anterior mediastinum.

IMAGE FINDINGS

CT/FDG-PET revealed a well-defined 3.8-x-2.3-cm partially calcified soft-tissue mass in the left anterior upper mediastinum with a standard uptake value max of 11.1 (**Figure 1**).

DIAGNOSIS

EHE with R0 resection and multifocal pT2N0 (i+) right breast cancer (ER 90%, PR 95%, HER2 DISH negative)

DISCUSSION

EHE is a rare malignant vascular tumor representing < 1% of all vascular tumors and has been reported to occur in a variety of locations including the mediastinum, head and neck,

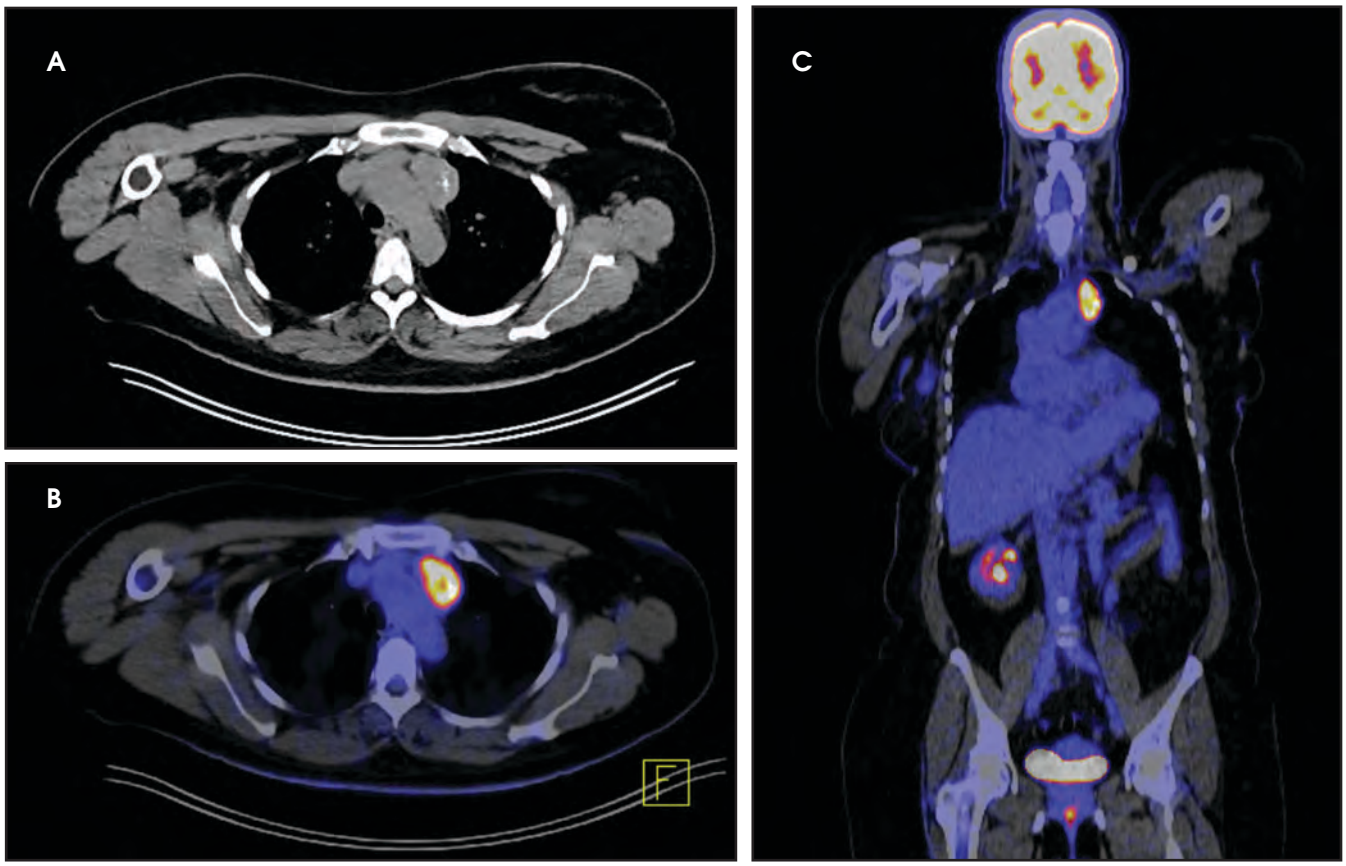

FIGURE 1. *Axial computed tomography (CT) illustrating calcifications within the lesion (A). Coronal (B) and axial (C) staging positron emission tomography (PET) demonstrating FDG-avid mediastinal mass.*

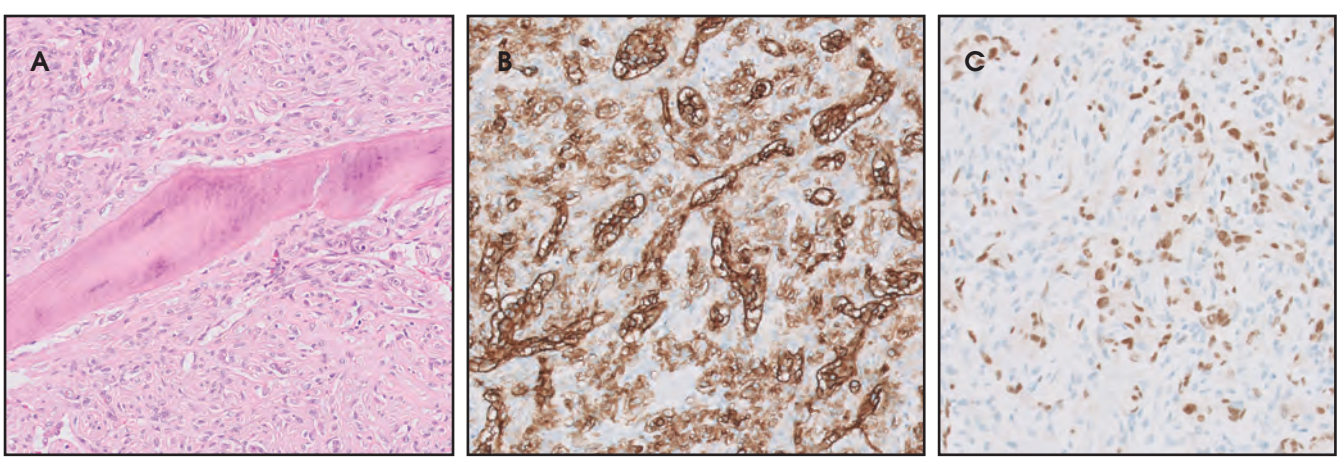

FIGURE 2. *Numerous round to short spindle cells with eosinophilic cytoplasm (H&Ex100) and metaplastic ossification within resected tumor (H&Ex100) (A). Immunohistochemical (IHC) positivity for vascular differentiation markers CD34 (B) and ERG (C), respectively (x100).*

lungs, liver, breast and bone.[1-3] EHE is composed of epithelioid endothelial cells with distinctive myxohyaline stroma and a characteristic WWTR1-CAMTA1 fusion as described in the 2013 WHO classification.[3] Although reported rates of recurrence, metastasis and tumor-related death vary, most soft-tissue EHE has an indolent course in contrast to angiosarcoma.[4,5] EHE involving soft-tissue sites have overall better prognosis than skeletal, hepatic or pulmonary EHE.[6]

Due to its rarity, there are no management guidelines for EHE. Surgical

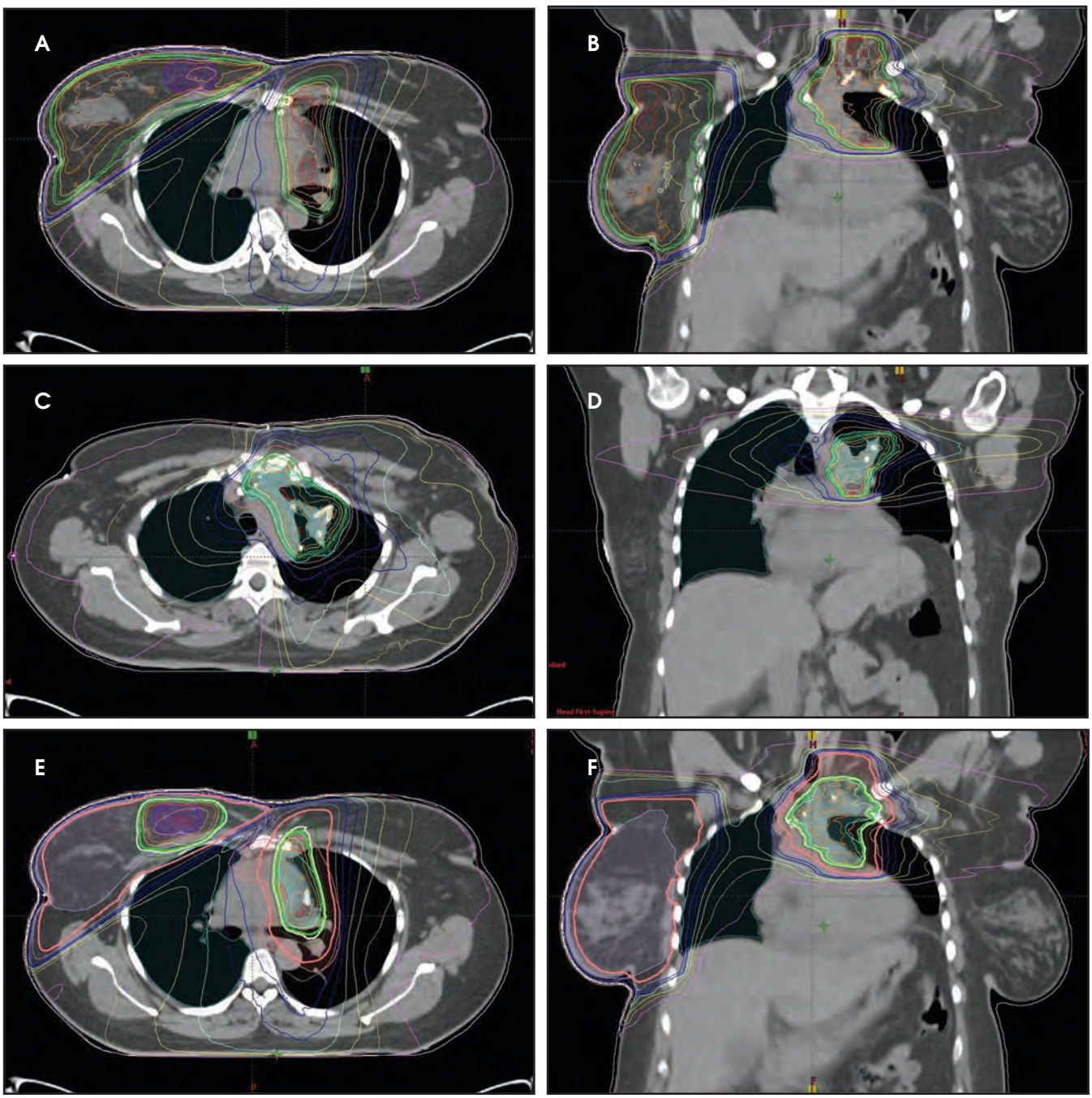

FIGURE 3. *Radiation treatment plan. Phase I delivered 50.4 Gy/28#, 1.8 Gy/# to the right breast and mediastinum using 2-dimensional (2D) tangents and partial-arc volumetric-modulated arc therapy (VMAT) technique (A,B). Phase II delivered 9 Gy/5#, 1.8 Gy/# boost to the mediastinum using partial arc VMAT technique (C,D) while further 10 Gy/5#, 2 Gy/# boost was delivered to the breast surgical cavity using 12 MeV electrons (not shown). Composite treatment plan (E,F).*

excision is generally considered first if lesions are localized and surgically resectable with functional preservation and acceptable morbidity.[1] Adjuvant RT has been utilized to reduce the risk of local recurrence. With more recent advancements in radiation delivery techniques, definitive RT use has increased.[7] Optimal dose and fractionation for resected and unresected EHE still remain controversial, and various RT protocols have been described.[7-12]

A case described by Drazin et al[9] delivered adjuvant RT to a total dose of 59.4 Gy in 33 fractions for subtotally

resected recurrent EHE of the mastoid, and the patient was alive with no evidence of recurrence at 8 years.

Scott et al[7] reviewed 14 patients with hemangioendothelioma treated with RT at a single institution. Surgical resection followed by postoperative RT (PORT) was performed in 4 patients while 10 received definitive RT. The median dose for PORT was 62.2 Gy (range 60 to 64.8 Gy). Two patients were treated with 60 Gy in 30 fractions while the other two were treated using a hyperfractionated approach of 1.2 Gy twice daily to a total dose of 64.8 Gy. None of the 4 patients showed recurrent disease over their follow-up periods, ranging 5.1 to 28 years.

Our case presented additional complexity in treatment planning due to the concurrent adjuvant RT aimed for right breast cancer. Phase I was planned with a 2D-tangential technique for the right breast and partial-arc volumetric-modulated arc therapy (VMAT) technique for the mediastinum using 10 MV photons and delivering 50.4 Gy. Phase II utilized 12 MeV electron beams for the breast boost, delivering an additional 10 Gy in 5 fractions. The partial-arc VMAT technique was again used for the mediastinal boost volume, delivering another 9 Gy in 5 fractions. Acceptable coverage of planning target volumes was achieved (**Figure 3**). Mean doses of esophagus, heart and lung were 25.4 Gy, 7.3 Gy (V25 < 10%), and 17 Gy, respectively, achieving their dose constraints. Dose constraints also were met for the spinal cord and bilateral brachial plexuses.

The patient completed adjuvant RT to her right breast and mediastinum with moderate toxicities including skin erythema and desquamation of her right breast and moderate odynophagia. She recovered from these toxicities approximately 1 month after RT. Our patient remained well with no clinical or radiological evidence of recurrence at 12 months after completion of adjuvant RT. She will continue ongoing surveillance for both EHE and breast cancer.

CONCLUSION

In conclusion, we have presented the management of a patient with mediastinal EHE in the presence of concurrent early stage breast cancer. Our patient received adjuvant RT to the mediastinum and right breast concurrently. We have outlined the complex planning for radiation therapy to 2 adjacent anatomical sites. While some evidence suggests the benefit of adjuvant RT to improve local control, heterogeneous dose and fractionation regimens are reported for EHE. Future collaborative studies are needed to further define the role, dose and fractionation of PORT for EHE with active participation in rare cancer databases such as Rare Cancer Australia, European RareCareNet, and the US-based rarediseases.org.

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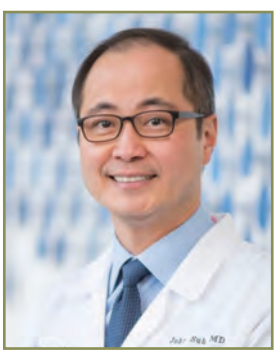

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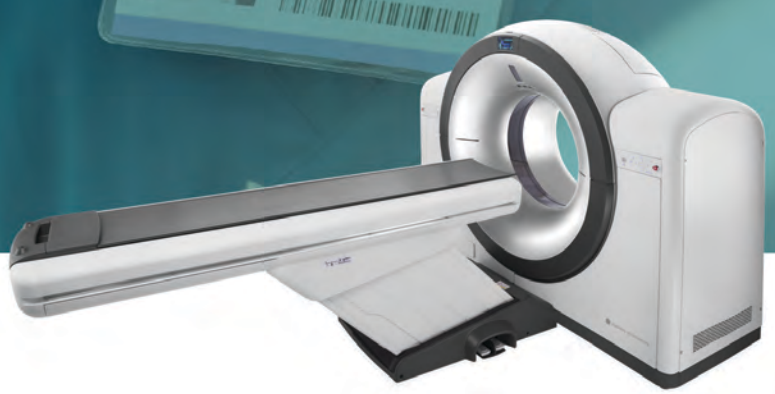

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