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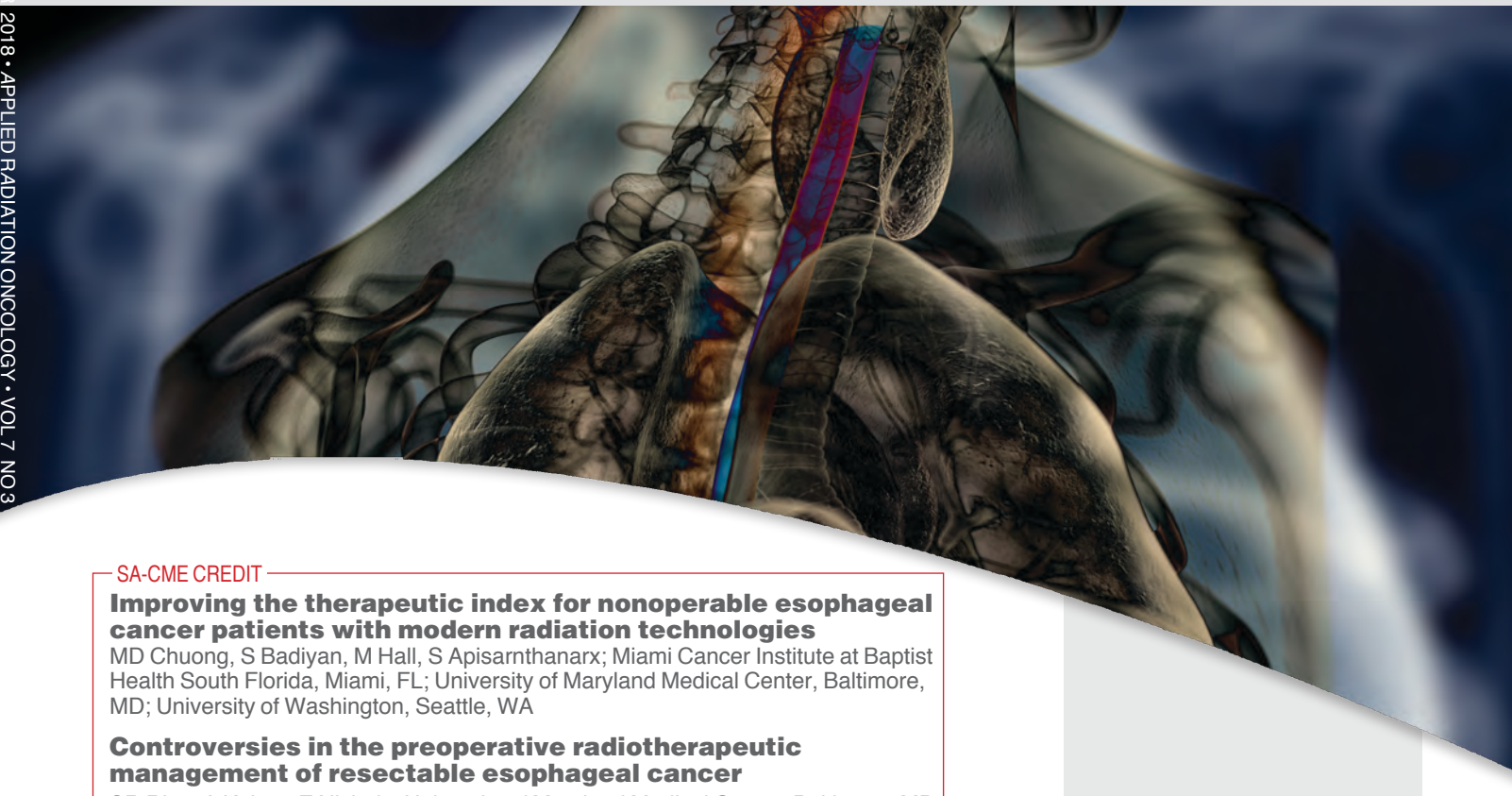

SA-CME CREDIT

Improving the therapeutic index for nonoperable esophageal cancer patients with modern radiation technologies
MD Chuong, S Badiyan, M Hall, S Apisarnthanarx; Miami Cancer Institute at Baptist Health South Florida, Miami, FL; University of Maryland Medical Center, Baltimore, MD; University of Washington, Seattle, WA

Controversies in the preoperative radiotherapeutic management of resectable esophageal cancer
SR Rice, A Kaiser, E Nichols; University of Maryland Medical Center, Baltimore, MD

Surgical salvage of oropharyngeal cancer with local-regional recurrence after primary radiation therapy
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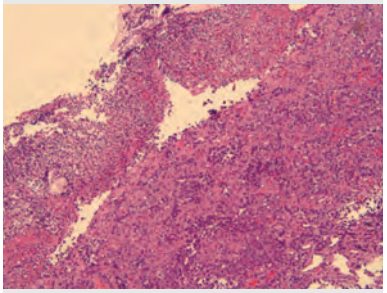
Postprostatectomy radiation therapy for biochemically recurrent prostate cancer
M Schloss, S Peddada, A Bakhshi, A Phelps, A Velayati, JB Adkison; Alabama College of Osteopathic Medicine, Dothan, AL; Southeast Alabama Medical Center, Dothan, AL



Radiation Oncology Case
Long-term cure of stage IVB esophageal adenocarcinoma

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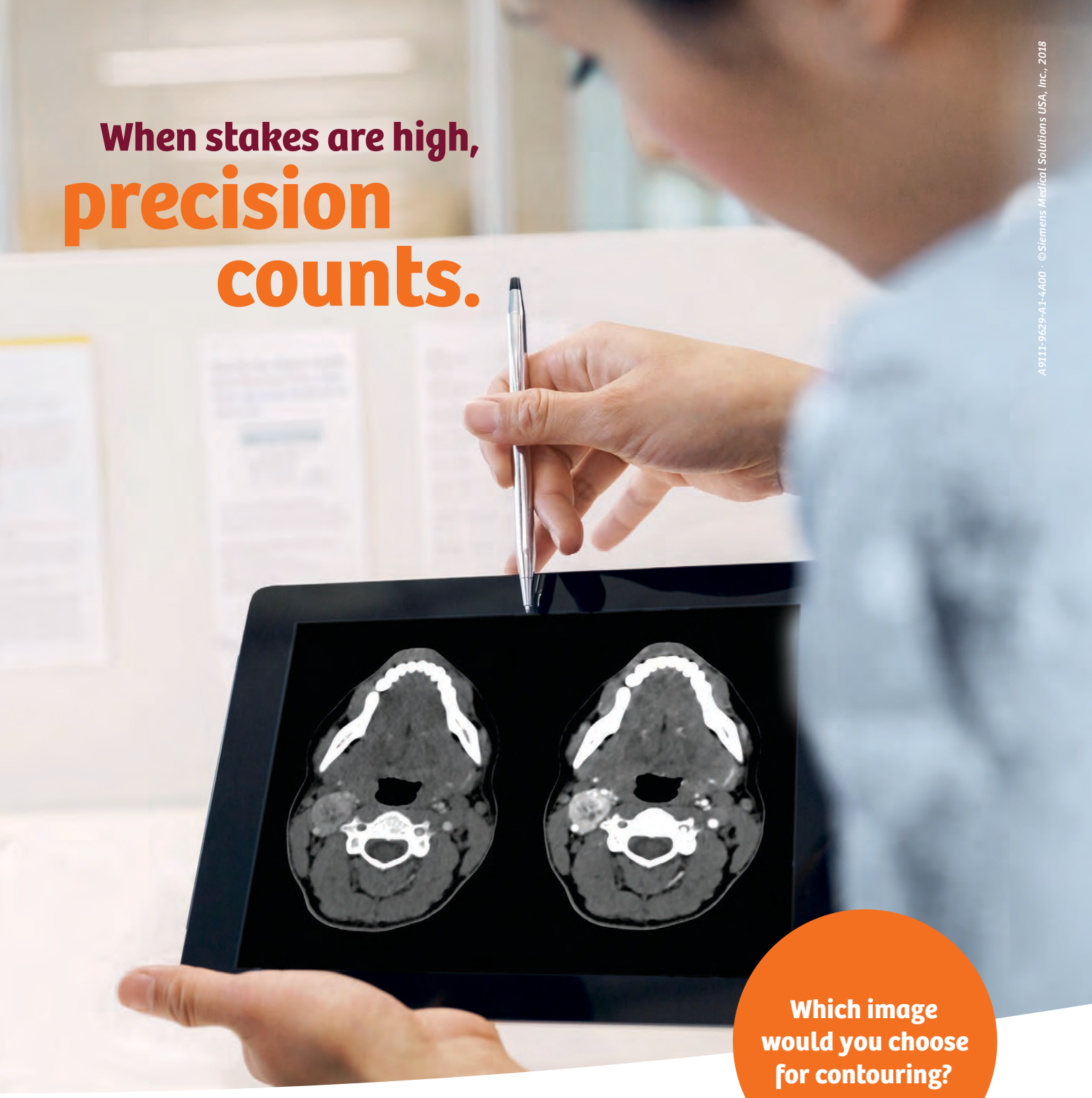

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FOCUS: ESOPHAGEAL CANCER

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EDITORIAL

Advances in radiation therapy for esophageal cancer

John Suh, MD, FASTRO
Editor-in-Chief

Welcome to the September issue of *Applied Radiation Oncology!* As part of this month's focus on esophageal cancer (EC), we are pleased to offer an array of articles examining important updates in what remains a leading cause of cancer death worldwide.

In *Improving the therapeutic index for nonoperable esophageal cancer patients with modern radiation technologies,* the authors provide an excellent summary of the timely issues surrounding the protons vs. photons question in the context of definitive conformal radiation therapy treatment for EC.

A second review, *Controversies in the preoperative radiotherapeutic management of resectable esophageal cancer,* is a well-written and concise summary of data driving the management of resectable esophageal carcinoma. In examining the role of trimodality therapy for locally advanced EC, the authors analyze controversies surrounding optimal total neoadjuvant radiation therapy (RT) dose, and describe the impact of RT technologies on overall survival and toxicity.

Both reviews offer complimentary SA-CME credits, with details on pages 7 and 15. Additional topics, which also provide complimentary SA-CME, are listed at *www.appliedradiology.org/SAM.*

Along with our Technology Trends article on EC, which is featured in our digital edition this month, we are pleased to offer *Long-term cure of stage IVB esophageal adenocarcinoma: Integrating local therapy modalities to maximum treatment effect in patients responsive to systemic therapy.* This case is an informative and uplifting report of a patient with an unexpectedly good outcome achieved through aggressive, nonstandard local therapy.

Two well-written research articles are offered as well, a paper on salvage RT for biochemically recurrent prostate cancer, and a retrospective analysis of the University of Florida experience of oropharyngeal cancer patients who underwent salvage surgery due to a local or locoregional recurrence—one of the larger series with excellent documentation of patient outcomes.

Additional issue highlights include a poignant editorial on the vital need for resident self-care in radiation oncology, which is a very important topic given the high rates of burnout among physicians, and a detailed and timely review of concerns and initiatives regarding undergraduate medical education in radiation oncology.

In other news, I would like to recognize two ARO board members who were among those selected for ASTRO Fellow status earlier this year: Jeffrey Buchsbaum, MD, PhD, AM, of the National Cancer Institute, and Robert Price, PhD, DABR, of Fox Chase Cancer Center. At the upcoming ASTRO conference in San Antonio, please be sure to congratulate them and the 33 others who have earned this esteemed designation.

Speaking of ASTRO, we greatly look forward to connecting with you at the annual meeting October 21-24, and learning about the latest research, technological advances, and practice-changing updates to continually improve and refine the care we offer our patients.

Please enjoy the issue, and hope to see you in San Antonio!

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

RESIDENT VOICE

To hurt and to heal: A cry for better resident self-care

Lauren Colbert, MD, MSCR

***Dr. Colbert** is a PGY5 radiation oncology resident at MD Anderson Cancer Center in Houston, TX.*

"Please," I begged my chief resident during intern year. "I need to switch my next rotation. I. Cannot. Watch. Another. Person. Die."

I did my transitional year internship at a large cancer hospital, where we were responsible for caring for incredibly sick inpatient oncology patients. After a particularly long stretch of inpatient service, I had a sense that a piece of my heart was being ripped out each time I faced another tragic situation, and a growing feeling there wasn't much heart left. I was scheduled to rotate on the palliative care service next. Not usually one to ask for help, I went to my chief residents and asked for pathology, radiology, or any other rotation that would take me away from patients for a month. In that moment, a wise attending explained to me that the moment I stopped feeling that way when a patient passed was the moment I wasn't doing my patients justice. She made me a deal: Do two weeks on the service and re-evaluate. "Trust me," she said.

Two weeks later I realized she was right. On this service, we took time to reflect on the deaths and pain we witnessed. One morning a hospital therapist brought in a guitar and performed music therapy with us. Another morning, we reflected on poetry. Each day, in some form, we talked not only to our patients—and about our patients—but about our feelings in caring for those patients. It seemed a little corny, but not only did it feel better, we were better doctors.

As I moved on and began a radiation oncology residency, the acute pain of actively dying patients was more distant, but the minute daily traumas still added up. The 30-year-old with aggressive inflammatory breast cancer and two kids my daughters' ages. The 9-year-old who came to her pediatrician for nausea and was diagnosed with disseminated glioblastoma. The 60-year-old schizophrenic, homeless man with the excruciatingly painful basal cell carcinoma devouring his face because he had no family, no resources and no idea how to get medical help sooner.

One particularly painful time on the pediatric radiation oncology service, I spent a day with a 7-year-old boy in his last days of an agonizing and drawn out battle with multiply recurrent leukemia. All he and his mother wanted was for

continued on page 6

continued from page 5

him to make it to his birthday party in three days at his favorite park, which seemed highly unlikely. "How do you do this every day?" I asked my attending. She responded with a sad smile and a half-joke. I went back to the resident room, feeling overwhelmed and, needing some feedback, I settled for a sarcastic comment from an older resident before we both went back to working. Humor, sarcasm, work—all ways we've learned to drown the tough emotions this job brings.

Oncologists have one of the highest risks of compassion fatigue,[1] even higher than other cancer center staff,[2] and compassion fatigue is linked to increased risk of depression, burnout and work-family conflict.[3] Studies also show that medical residents are already at higher risk for depression, burnout, and suicidal ideation vs. their age-matched peers.[4] In fact, suicide is the leading cause of death among male residents, and second leading cause of death among female residents.[4] I'm not aware of any specific studies in radiation oncology residents, but I can only imagine what this means for us. We are trained to have compassion for our patients. To listen. To ask open-ended questions. To let someone know if we are worried about their mental health.

Residents, with a new academic year recently underway, I ask you to extend those same courtesies to your resident colleagues: Listen. Take care of each other. Check in with a co-resident. Talk about what's tough. Reach out if you're worried about a colleague or yourself. Take care of yourself and your colleagues, so we can all take better care of our patients and our families. Hopefully, the references and resources below will help. Program directors and chairs, make it easier to do so. Let's brainstorm ways to combat compassion fatigue and burnout in our educational programs so we can learn better – it's time.

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Resources

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National Suicide Prevention Lifeline: 1-800-273-8255

SA–CME Information

IMPROVING THE THERAPEUTIC INDEX FOR NONOPERABLE ESOPHAGEAL CANCER PATIENTS WITH MODERN RADIATION TECHNOLOGIES

Description

Although there is general awareness that modern radiation technologies both reduce normal organ dose while permitting safe dose escalation in nonoperable EC patients, there is lack of consensus about how these technologies should be routinely employed in the clinic. There clearly is need for well-designed clinical trials to guide clinical decision making in this regard, several of which are being planned (NCT01102088) or already underway (NCT01512589). This course examines how contemporary radiation technologies can improve the therapeutic index, including both reduced cardiopulmonary and hematologic toxicity and higher tumor control, for nonoperable esophageal cancer patients receiving definitive chemoradiation.

Learning Objectives

After completing this activity, participants will be able to:

1. Learn and use advanced radiation technologies to improve normal tissue sparing, especially the lungs and heart.
2. Adopt modern radiation techniques to permit safe tumor dose escalation.

Authors

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As part of this CME activity, the reader should reflect on how it will impact his or her personal practice and discuss its content with colleagues.

SA-CME (see page 7)

Improving the therapeutic index for nonoperable esophageal cancer patients with modern radiation technologies

Michael D. Chuong, MD; Shahed Badiyan, MD; Matthew Hall, MD, MBA; Smith Apisarnthanarx, MD

Esophageal cancer (EC) is one of the leading causes of cancer-related death worldwide.[1] Approximately 50% of newly diagnosed EC patients are not surgical candidates due to extensive locoregional disease, distant metastasis, and/or being medically unfit. Definitive chemoradiation (CRT) became a standard of care many years ago for nonsurgical patients based on results of the Radiation Therapy Oncology Group (RTOG) 85-01 randomized trial that demonstrated superior overall survival (OS) with 50 Gy plus 4 cycles of 5-fluorouracil (5-FU) and cisplatin compared with 64 Gy alone; 5-year survival was 26% vs. 0%, respectively.[2] There is also an apparent benefit of concurrent chemotherapy in elderly EC patients.[3,4] The standard radiation dose in nonoperable EC patients has not changed for decades ever since the Intergroup (INT) 0123 trial reported no survival benefit in escalating dose from 50.4 Gy in 28 fractions to 64.8 Gy in 36 fractions, both given with 4 cycles of 5-FU and cisplatin.[5]

It is important to recognize that these seminal trials were conducted many years ago using 2-dimensional (2D) x-ray radiation therapy (RT) prior to dramatic improvements in technology. Whereas generous treatment ports were used in the 2D treatment era, the development of 3-dimensional conformal radiation therapy (3DCRT) and intensity-modulated radiation therapy (IMRT) has enabled highly conformal treatment delivery and the lowering of normal tissue dose.[6-8] As opposed to x-rays, which exponentially deposit dose in tissue along the beam path resulting in exit dose in surrounding normal tissues (eg, heart and lungs), protons deposit more efficiently as they lose the majority of their energy near the end of their beam range as they come to rest. This results in a sharp rise in absorbed dose called the "Bragg peak" followed by a sharp dose falloff. Proton beam therapy (PBT) represents another step in the evolutionary ladder of radiation technology.[9] Lastly, present-day treatment planning techniques including heterogeneity corrections, high-quality image guidance including cone-beam computed tomography (CT), and the use of tighter margins have also contributed to reducing dose outside of the target volume.[10,11]

Herein we review how contemporary radiation technologies provide opportunities for potential improvements in the therapeutic index, including both reduced toxicity and higher tumor

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Disclosure: Dr. Badiyan has received speakers' bureau honoraria from Varian, Palo Alto, CA, and Drs. Chuong and Hall have received speakers' bureau honoraria from Accuray, Sunnyvale, CA. The authors have no other conflicts of interest to disclose. None of the authors received outside funding for the production of this original manuscript and no part of this article has been previously published elsewhere.

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control, for nonoperable EC patients receiving definitive CRT.

Reducing Cardiopulmonary Toxicity

Delivering RT to the esophagus is challenging due to its central location within the chest, surrounded by multiple critical structures, notably the lungs and heart. There is heightened awareness, particularly from outcomes of breast and lung cancer patients, that increasing heart and lung dose, even in the low dose range, can significantly increase the risk of cardiopulmonary toxicity (CPT).[12-14] As such, efforts have focused on evaluating whether modern radiation technologies can spare both of these critical organs, and whether any dosimetric differences are clinically meaningful.

Intensity-Modulated Radiation Therapy

IMRT delivers improved conformality and reduced normal organ dose compared to less sophisticated techniques for EC patients as demonstrated by multiple treatment planning studies.[15,16] A recently published analysis of 7 dosimetric studies demonstrated dramatic lung and heart sparing with IMRT vs. 3DCRT; for example, IMRT resulted in significantly lower average irradiated volume of the heart among patients treated to at least 50 Gy (mean difference: 4.78 cc [95% CI: 0.88-8.68], P = .02).[17]

The ability of IMRT to minimize dose outside of the target volume appears to be clinically meaningful. A study published from the phase II/III SCOPE1 (Study of Chemoradiotherapy in OesoPhageal cancer with Erbitux) trial found that higher OS was strongly associated with a higher conformality index and that plan quality was strongly related to receiving IMRT (vs. 3DCRT).[18] Freilich et al reported reduced grade 3 or higher toxicity (OR 0.51; P = 0.05), defined as any hospitalization, feeding tube, or > 20% weight loss, with IMRT vs. 3DCRT.[19] An analysis of 676 patients treated at MD Anderson Cancer Center (MDACC) reported significantly improved OS (HR 0.72, p < .001) with IMRT compared with 3DCRT. Although there was no difference in cancer-related or pulmonary-related death, patients receiving 3DCRT had a significantly greater risk of cardiac death (5-year estimate, 11.7% (3DCRT) vs. 5.4% (IMRT), Gray's test, P = 0.0029).[20] Lastly, an analysis of two large cancer center registries including over 2500 elderly patients further supports the advantage of IMRT; on propensity score inverse probability of treatment weighting multivariate analysis, IMRT was associated with less all-cause, other-cause, and cardiovascular mortality compared to 3DCRT.[21]

Despite these retrospective data suggesting a large and significant benefit of IMRT, a small randomized trial from China of 60 patients reported significant improvements in complete response rate and reduction in lung V20 and V30 in patients receiving IMRT, but did not report improvements in OS.[22] However, comprehensive evaluation of cardiac-related mortality was not performed.

Collectively, these largely retrospective data suggest that IMRT should be considered over 3DCRT because of reduced CPT and potentially improved OS. There is a need to confirm these benefits in a prospective manner.

Proton Beam Therapy

The published literature has demonstrated benefits of PBT compared to x-ray therapy in sparing critical thoracic organs. Zhang et al compared passive scattering PBT with fixed-field IMRT plans prescribed to 50.4 Gy for 15 distal esophageal cancer patients.[23] Compared to IMRT plans, PBT plans had improved lung sparing at low-to-moderate doses from V5-V20, as well as mean lung dose. Lung sparing was the greatest at the lowest dose levels; PBT reduced V5 lung dose relatively by 36% to 70% depending on the beam arrangements. Heart V40 was more modestly reduced (up to 22% relatively) with PBT. Shiraishi et al published a detailed analysis of dose delivered to cardiac substructures in EC patients, concluding that PBT could deliver markedly reduced dose to many, but not all, of these substructures compared to x-ray techniques.[24]

PBT delivered with pencil-beam scanning (PBS) offers increased dose conformality compared to passive scattering technique. A study from MDACC demonstrated significant lung and heart sparing in the low-to-moderate range with various PBS-PBT beam arrangements compared to IMRT.[25] PBS-PBT delivered with a single posterior field (SPF) with volumetric rescanning has been proposed to minimize normal organ dose.[26] Zeng et al from University of Washington demonstrated that when compared to anterior-posterior/posterio-anterior (AP/PA) beams, the SPF approach significantly spared more heart by approximately 50%, and when compared to PA/left posterior oblique (PA/LPO) beams, the SPF approach significantly spared more lungs by approximately 40%.

Although dosimetric superiority does not always translate into clinically significant differences, the published literature demonstrates reductions in CPT with PBT (**Table 1**). Wang et al reviewed 444 patients treated with preoperative PBT (n = 72), IMRT (n = 164), and 3DCRT (n = 208) with concurrent chemotherapy.[27] Pre-treatment lung capacity and radiation modality were found to be independent predictors of pulmonary complications. PBT-treated patients had the lowest rate of postoperative pulmonary complications (14%) compared to those who received IMRT (24%) or 3DCRT (30%). However, only the PBT and 3DCRT differences were statistically significantly different, leaving up for debate whether there are

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Table 1. Clinical Studies Focused on Cardiopulmonary Toxicity Reporting

Institution (Year)	*n*	Median f/u (yrs)	Esophageal location	Histology	Stage	Intent	PBT technique, beams	Dose	Chemo	CPT
MDACC (2013)[27]	All 444, PBT 72, IMRT 164, 3DCRT 208	NR	Upper 1% Mid 6% Lower 93%	SCC 9% AC 89%	I-IVa	Preop	DS, PA/LT LAT	Median 50.4 Gy/GyE	Concurrent 5-FU/taxane- or platinum-based	Pulm PBT 14% IMRT 24% **3DCRT 30%**
Tsukuba (2015)[28]	All 44, PBT 25, Photons 19	PBT 2 Photons 1.7	Cervical 23% Thoracic 77%	SCC100%	0-IIIC	Def	DS, AP/PA or AP/LPO or RAO/LAO for cervical	Median 60 Gy/GyE	Concurrent 5-FU/cis	Cardiac G2+ PBT 4% Photons 52% Pulm G2+ PBT 0% Photons 18%
Multi-institutions* (2013)[29]	All 580, PBT 111, IMRT 255, 3DCRT 214	NR	Upper/mid 7% Lower/GEJ 93%	SCC 7% AC 93%	I/II 36% III/IV 64%	Preop	DS, PA/LPO	50.4 Gy/GyE	Concurrent, NR	Cardiac PBT 12% IMRT 12% **3DCRT 27%** Pulm PBT 16% IMRT 24% **3DCRT: 40%** LOS PBT 9 days IMRT 12 days 3DCRT 13 days

Key: n = patient number, f/u = follow-up, yrs = years, CPT = cardiopulmonary toxicities, MDACC = MD Anderson Cancer Center, NR = not reported, SCCa = squamous cell carcinoma, AC = adenocarcinoma, preop = preoperative, DS = double scattering, PA = posterior-anterior, LT LAT = left lateral, 5-FU = 5-fluorouracil, pulm = pulmonary, def = definitive, RAO = right anterior oblique, LAO = left anterior oblique, LOS = length of hospital stay. *MDACC, Mayo Clinic, University of Maryland. Bold represents statistically significant difference.

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meaningful differences between PBT and IMRT. The authors concluded that the lung sparing from PBT was likely responsible for the decrease in pulmonary complications since mean lung dose was found to correlate with pulmonary complications. No differences in cardiac complications were observed. Investigators from the University of Tsukuba also reported reduced pulmonary toxicity among PBT vs. x-ray patients, although they found reduced cardiac toxicity with PBT, in contrast to the MDACC study.[28]

To further evaluate their findings of decreased CPT with PBT, MDACC pooled their data with two other academic institutions and analyzed a total of 580 lower esophageal/GEJ cancer patients (111 PBT, 255 IMRT, 214 3DCRT).[29] The type of radiation modality was associated with CPT on multivariate analysis. Specifically, PBT patients had significantly less pulmonary toxicity compared with 3DCRT patients (16% vs. 40%) although there was no statistically significant difference compared to IMRT patients (24%). As opposed to the initial MDACC study, this pooled analysis reported fewer cardiac complications in PBT patients when compared to 3DCRT patients (12% vs. 27%), although there was no difference when compared to IMRT patients (12%).

Reducing Hematologic Toxicity

There is increasing interest in studying the effects of radiation modality on hematologic toxicity (HT). While most of the body's bone marrow (BM) is in the pelvis, approximately 35% of the active BM resides in the thoracic vertebrae (TV).[30] The risk of developing ≥ grade 2 HT such as leukopenia and neutropenia has been associated with BM irradiation in both pelvic and thoracic RT patients.[31-34]

In a dosimetric planning study, IMRT and PBT were recently reported by a group from the United Kingdom as superior to 3DCRT in overall BM sparing.[35] PBT, however, was the only modality to provide significant sparing in the very loswest dose range (ie, bone V10). Warren et al performed a study including 12 patients with mid-esophageal tumors and compared the BM (TV, sternum, scapulae, ribs, clavicles) and TV (T1-T12) doses among 3DCRT, volumetric-modulated arc therapy (VMAT) IMRT, simultaneous integrated boost (SIB)-VMAT, PBS-PBT, and TV-sparing (TVS) VMAT plans.[35] Only the PBS plan showed clinically significant sparing of the bone V10, V20 and mean dose compared to all techniques. However, the PBS plans showed no dosimetric advantage over the TVS-VMAT plans for any TV dose-volume metrics. While the clinical relevance of these results remains unclear, this study provides evidence that PBT can substantially reduce HT, depending on the bone OAR being spared.

Radiation-induced adverse effects on the immune system include severe lymphopenia and impaired recruitment of tumor-infiltrating lymphocytes (TILs), which have been correlated with unfavorable clinical outcomes.[36-39] Because lymphocytes are exquisitely radiosensitive to low dose (ie, V5-V15), a priority should be to minimize radiation exposure especially to large volumes of the blood and, therefore, lymphocytes that circulate through the heart and lungs at any given time.[40,41] The importance of this was supported by a retrospective analysis of 711 non-small cell lung cancer patients who received definitive RT and found an association between lung V5, lymphocyte nadir, and survival.[42] Shiraishi et al compared the risk of radiation-induced grade 4 lymphopenia between PBT and IMRT patients with EC (n = 136 in each group) using propensity matching based on key clinical characteristics.[40] PBT patients had markedly less frequent grade 4 lymphopenia compared to IMRT patients (17.6% vs. 40.4%; $p < 0.0001$). On multivariate analysis, PBT was found to be an independent predictor for grade 4 lymphopenia (OR 0.29; 95% confidence interval, 0.16 to 0.52; $p < 0.0001$). However, grade 4 lymphopenia was not found to be an independent predictor for poorer OS.

Dose Escalation

Rationale for Dose Escalation

Local control (LC) is poor for EC patients treated with definitive CRT.[2,5] Adenocarcinomas and squamous cell carcinomas both recur in the original gross tumor volume in about 40% of patients.[43] Radiation dose escalation for such patients remains controversial based on the results of the aforementioned INT trial in which patients in the high dose arm had worse OS.[5] However, 7 of the 11 deaths during RT occurred prior to delivery of 50.4 Gy, making it impossible for dose escalation to be responsible for the higher mortality rate. Also, with longer follow-up, there was a significantly higher number of deaths not attributable to EC in the high dose arm compared with the standard dose arm (13 vs. 3; $P < 0.01$). Hence, the results of this trial cannot be used to conclude that radiation dose escalation does not offer clinical benefit, largely because of the technological limitations of the era in which it was conducted. For now, we can only speculate whether the results of this trial would have differed if modern techniques were used.[44]

The era of 3D planning has seen increasing interest in exploring whether dose escalation specifically to gross disease offers therapeutic benefit in nonoperable EC patients. This strategy is based on studies showing that at least 75% of local recurrences after definitive CRT prescribed to 50.4 Gy occur within the gross tumor volume (GTV) and not within electively treated regions, suggesting that selective delivery of higher dose to gross disease may improve outcomes.[45,46]

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Intensity-Modulated Radiation Therapy

IMRT can selectively increase dose to the GTV while reducing dose to normal organs.[6,47]A potential benefit of IMRT delivered with SIB is that fraction sizes > 2 Gy prescribed to the GTV may have a radiobiological advantage in counteracting accelerated repopulation and more effectively eliminating cancer stem cells.[48] Early results from a Chinese phase 2 trial that prescribed concurrent chemotherapy plus 63 Gy to the GTV and 50.4 Gy to the PTV, all in 28 fractions using IMRT-SIB, were encouraging; locoregional control at 3 years was 67.5% and no grade 4-5 toxicity occurred.[49] Investigators from MDACC subsequently published outcomes of a phase 1/2 trial that employed IMRT-SIB over 28 fractions with 63 Gy being the maximum tolerated dose.[50] After a median follow-up of 13.3 months, 11 (29%) patients experienced local recurrence and the rate of acute esophagitis was similar to historical control. When compared to 97 similar nonoperable EC patients who received a total of 50.4 Gy, there was significantly improved LC in patients who received a boost. This trial included patients mostly treated with IMRT, but a minority received PBT.

Several ongoing trials are evaluating the role of dose escalation based on tumor response to initial therapy as determined by PET/CT. A phase 1 trial from China (NCT03113214) is evaluating PET/CT-directed hyperfractionated radiation dose escalation and concurrent carboplatin/paclitaxel with total doses ranging from 57.2 to 93.2 Gy prescribed to residual tumor after an initial 50 Gy. The SCOPE2 phase 2/3 trial (NCT02741856) uses PET/CT response after initial cisplatin/capecitabine to 50 Gy in 25 fractions vs 60 Gy in 25 fractions.

Proton Beam Therapy

The University of Tsukuba was the first institution to publish clinical outcomes using PBT for esophageal cancer in 1994, which was given in a dose-escalated fashion.[51] Koyama et al treated 15 patients with superficial and advanced esophageal cancer (93% SCC) using definitive hypofractionated passive scattering PBT alone to 80.4 gray equivalent (GyE) with a single AP field either as a boost after 3DCRT or as a single full PBT course. OS at 5 years was 27% with 67% LC for advanced tumors. Over the next several years the same institution updated their clinical experience with hypofractionated passive scattering PBT in a series of publications.[52-54] A hypofractionated regimen and single AP or AP/PA beam approach were employed primarily due to resource allocation and technology limitations. For locally advanced tumors, 5-year LC was 29% to 43% and 5-year OS was 13% to21% in these series.

There is continued interest in esophageal dose escalation with PBT. Two ongoing trials from University of Florida and University of Pennsylvania are investigating the potential toxicity reduction and safety of PBT escalation in both unresectable and resectable esophageal cancer. A phase 2 trial from University of Florida (NCT03234842) is treating patients to 59.4 GyE with concurrent carboplatin/paclitaxel and PBT. Patients who decline or are not able to receive PBT will be treated on a comparator x-ray cohort. The primary endpoint of this study is to assess the differences in lung function as defined by reduction in diffusing capacity of the lung for carbon monoxide (DLCO) between PBT and x-rays. A phase 1 study from University of Pennsylvania (NCT02213497) is systematically investigating the safety of simultaneous integrated boost dose escalation with PBT in the preoperative setting with 5 dose levels starting at 53.75 GyE and escalating to 62.50 GyE in 25 fractions. Dose-limiting toxicity occurring prior to surgery will be the primary endpoint to inform on a recommended phase 2 dose.

Brachytherapy

Dose escalation using intraluminal brachytherapy as a boost in EC patients treated with curative intent is not commonly used, although it may benefit select patients. A phase 2 RTOG trial of 49 EC patients, nearly all with SCC who received chemoradiation to 50 Gy followed by a brachytherapy boost, demonstrated no difference in survival or local control compared to the historical control.[55] Furthermore, a high incidence of life-threatening toxicity (24%) or treatment-related death (10%) occurred. A Japanese randomized trial that included patients with SCC of the esophagus who after 60 Gy received a boost with external beam vs. brachytherapy demonstrated no difference in overall survival.[56] However, those with tumors < 5 cm in length had more than twice the cancer-specific survival (64 vs. 31.5%; p = 0.025).

In conclusion, dose escalation using a brachytherapy boost should not be recommended for all EC patients, although it could be reasonable for a subset with limited disease, as endorsed by published guidelines from the American Brachytherapy Society.[57]

Patient Selection for Dose Escalation

These data suggest that radiation dose escalation may be effective using both x-rays and protons, although all patients may not benefit from higher doses. Variable responses to definitive CRT are well documented, with some patients achieving a complete response while others have persistent disease after 50 to 50.4 Gy. For instance, Ishikawa and colleagues observed more local recurrences (38%) in patients with residual disease seen on endoscopy after 50 GyE who were then dose escalated to 64 to 70 GyE compared with those with no residual disease who were prescribed 60 GyE (5%).[58] We are gaining a better understanding of treatment response predictors that include, but are not limited

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to, tumor stage,[59] imaging parameters,[60] and intrinsic tumor radiosensitivity,[61] although robust clinical decision-making tools are lacking to identify patients for whom radiation dose escalation could be considered. This is clearly an area in need of further study.

Conclusion

Although there is general awareness that modern radiation technologies reduce normal organ dose while permitting safe dose escalation in nonoperable EC patients, consensus is lacking about how these technologies should be routinely employed in the clinic. Well-designed clinical trials are clearly needed to guide clinical decision making in this regard, several of which are being planned (NCT01102088) or underway (NCT01512589).

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SA–CME Information

CONTROVERSIES IN THE PREOPERATIVE RADIOTHERAPEUTIC MANAGEMENT OF RESECTABLE ESOPHAGEAL CANCER

Description

This review examines the role of trimodality therapy in the management of esophageal cancer, focusing on controversies surrounding the optimal total neoadjuvant RT dose employed. Current and past technologies for radiation treatment delivery and their impact on overall survival and toxicity are discussed. The authors also detail the data driving the management of resectable esophageal carcinoma, reviewing studies comparing neoadjuvant CRT followed by surgery to definitive CRT, neoadjuvant CRT followed by surgery to surgery alone, and controversies in radiation dose and planning considerations for preoperative resectable esophageal cancer.

Learning Objectives

After completing this activity, participants will be able to:

1. Apply data comparing trimodality therapy to definitive chemoradiation for esophageal cancer.
2. Apply data comparing trimodality therapy to surgical resection only in esophageal cancer.
3. Understand advances in radiation therapy that have the potential to improve outcomes.

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SA-CME (see page 15)

Controversies in the preoperative radiotherapeutic management of resectable esophageal cancer

Stephanie R. Rice, MD; Adeel Kaiser, MD; Elizabeth Nichols, MD

Esophageal cancer remains the 7th leading cause of cancer death in the United States with annual incidence and mortality of 17,290 and 15,580 individuals, respectively.[1] Several strategies have been employed over the years to improve outcomes. Initial studies comparing surgery to radiation therapy (RT) showed high operative mortality in surgical patients, and poor survival in both the surgical and radiation-alone patients.[2] In the 1990s, improvements in survival were made with the addition of concurrent chemotherapy to RT,[3,4] with no patients alive at 3 years in the RT-alone arm. The 2- and 5-year overall survival rates in definitive chemoradiation (CRT) were 35% to 40%, and 20%, respectively, with local failure rates of 45% to 55%.[5-7] To improve these outcomes, the use of surgical resection after chemoradiation was investigated.[8-13]

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In this review, we examine the role of trimodality therapy in the management of locally advanced esophageal cancer, focusing on controversies surrounding the optimal total neoadjuvant RT dose employed. We will additionally review the current and past technologies for radiation treatment delivery, and their impact on overall survival and toxicity in this patient cohort.

A Review of Prior Phase III Concurrent Chemoradiation Trials

Studies Comparing Neoadjuvant CRT Followed by Surgery to Definitive CRT

Two randomized trials have compared the use of definitive CRT to neoadjuvant CRT followed by surgical resection. The German Esophageal Study Group performed a phase III trial comparing definitive CRT to preoperative CRT followed by resection in locally advanced squamous cell carcinoma of the esophagus. Patients were randomized to induction chemotherapy (5-FU, leucovorin, etoposide and cisplatin) followed by CRT (40 Gy) and surgical resection or induction chemotherapy (5-FU, leucovorin, etoposide and cisplatin) followed by CRT (at least 65 Gy) without surgical resection.[5] At a median follow-up of 6 years, overall survival was equivalent between the arms, with improvements in local progression-free survival in the surgery group ($p = 0.003$), but at the cost of a 9% higher risk of treatment-related mortality ($p = 0.03$). The FFCD 9102 trial randomized 444 patients with resectable esophageal cancer (majority squamous histology) to induction CRT consisting of either 46 Gy in 23 fractions with concurrent cisplatin and 5-FU or split course 30 Gy in 10 fractions RT given over 4 weeks (5 days on, 10 days off, 5 days on).[7] Responders proceeded to surgical resection while nonresponders completed chemoradiation to a total dose of either 66 Gy in 33 fractions (standard fractionation) or 45 Gy in 15 fractions (for the hypofractionated arm). At 4 years median follow-up, there was no difference in overall survival between the groups (2-year OS of 39.8% vs. 33.6%, $p = 0.03$). However, improved local control was observed in the surgery arm at 66.4% compared with 57.0% in the definitive CRT arm, but with higher acute, 3-month mortality in the surgical group (9.3% vs. 0.8%).

A meta-analysis of 7 studies and 1,114 patients compared surgical with

Table 1. Phase III Randomized Controlled Trials Comparing Definitive CRT to Neoadjuvant CRT + Surgery

Reference #	AC/SCC	Chemo	RT Dose (Gy)/ Fractions	Surgery	No. of Patients	pCR	Median Survival (mo)	3-year Survival (%)	P-value
9	100/0	Cis, 5-FU	40/15	Post Alone	58 55	25	16 11	32 6	**0.01**
8	0/100	Cis	37/10 (split course)	Post Alone	143 139	26	19 19	38 37	0.78
10	75/25	Cis, 5-FU, Vincristine	45 (bid)	Post Alone	50 50	28	17 18	30 16	0.15
11	60/40	Cis, 5-FU	35/15	Post Alone	128 128	16	22 19	36 33	0.57
12	75/25	Cis, 5-FU	50.4/28	Post Alone	30 26	40	53 21	65 20	**0.002**
13	75/25	Carbo, Taxol	41.4/23	Post Alone	363	29	49 26	53 48	**0.003**

Key: AC = adenocarcinoma, SCC = squamous cell carcinoma, Cis = cisplatin, 5-FU = 5 fluorouracil, carbo = carboplatin, taxol = paclitaxel, pCR = pathologic complete response, post = following chemoradiation, alone = no chemoradiation

nonsurgical management of esophageal cancer.[14] When comparing definitive CRT to neoadjuvant CRT followed by surgery, there was no difference in long-term recurrence or mortality (HR = 0.88). The impact of cancer histology could not be adequately assessed since most trials were limited to squamous cell carcinoma (SCC) only. The evidence in these studies was considered low or very low based on trial size and design and, therefore, strong conclusions cannot be derived from this data. Future work is needed in this arena.

Studies Comparing Neoadjuvant CRT Followed by Surgery to Surgery Alone

Multiple studies have evaluated the outcomes of neoadjuvant chemoradiation followed by surgical resection with surgical resection alone **(Table 1)**.[8-13] Walsh et al evaluated outcomes of esophageal adenocarcinoma (AC) patients treated with 40 Gy in 15 fractions of RT combined with cisplatin and 5-fluorouracil (5-FU) chemotherapy followed by surgical resection compared with surgical resection alone. Three-year survival improved from 6% in the surgery alone arm to 32% in the trimodality arm (p = 0.01), and pathologic complete response (pCR) at time of surgical resection was 25%.[9] Similarly, the European Organization for Research and Treatment of Cancer (EORTC) trial[8] randomized SCC patients to surgery alone or neoadjuvant CRT consisting of two 1-week courses of RT, separated by a 2-week break, to a total dose of 37 Gy in 10 fractions with concurrent cisplatin. A pCR rate of 26% was noted, with equivalent 3-year overall survival near 36%. Urba et al compared concurrent cisplatin, 5-FU and vincristine with 45 Gy radiation given twice-daily (BID) to surgery alone in a study population of 100 patients with mostly AC histology (3:1 AC to SCC ratio in both arms). Trial results demonstrated a pCR rate of 28% and a numerical, but not statistically significant, improvement in survival (3-year OS of 30 months vs. 16 months in the neoadjuvant CRT vs. surgery arms, p = 0.15). The Trans Tasman Radiation Oncology Group (TROG) randomized trial compared cisplatin, 5-FU and 35 Gy in 15 fractions followed by surgical resection with surgical resection alone in a study population of SCC and AC patients. No survival difference was observed (3-year survival of 36 months vs. 33 months in neoadjuvant CRT vs. surgery, p = 0.57), with pCR rates of 16%.[11]

In the Cancer and Leukemia Group B (CALGB) trial, 56 patients were randomized to either surgery alone or surgery following neoadjuvant CRT with 50.4 Gy in 28 fractions plus cisplatin and 5-FU.[12] The trial showed a significant improvement in overall survival (5-year OS of 39% vs. 16%, p = 0.002).

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The ChemoRadiotherapy for Oesophageal Cancer Followed by Surgery Study (CROSS) trial randomized 368 patients with resectable esophageal cancer (75% AC) to a new better tolerated CRT regimen of carboplatin and paclitaxel combined with 41.4 Gy in 23 fractions followed by surgical resection to surgical resection alone.[13] These impressive results included a 5-year OS of 47% vs. 34% in the neoadjuvant CRT vs. surgery alone arms (p = 0.003). Neoadjuvant treatment resulted in an overall pCR rate of 29% (49% for SCC, 23% for AC, p = 0.008), and an increased rate of R0 resection (92% vs. 69%, p < 0.001). These improvements were achieved without an increase in acute complication rates, which remained below 5% in both study arms.

Finally, a meta-analysis of trials from 2007 suggested a 13% absolute difference in survival at 2 years (HR 0.81) with the addition of neoadjuvant CRT to surgery, thus confirming the benefit of preoperative CRT.[15]

Controversies in Radiation Dose and Planning Considerations for Preoperative Resectable Esophageal Cancer

The studies shown in **Table 1** vary widely with total dose and fractionation schemes ranging from daily 2 Gy fractions to hypofractionated split courses of radiation with 2-week breaks to BID regimens. Total doses of radiation have ranged from 30 Gy to as high as 50.4 Gy in patients who were eligible to undergo surgical resection. The debate of dose-escalation has been tested in a randomized clinical trial6 in the setting of definitive chemoradiation, and the question remains unanswered at this point in time. Although improved local control is noted in higher dose fractionations,[6,16,17] translation into an overall survival benefit remains to be seen in this population. The results of the Intergroup (INT) 0123[6] trial did not demonstrate a survival benefit to dose-escalation to 64.8 Gy compared with 50.4 Gy, but the results of this have been debated as the majority (7/11) of deaths on the high-dose arm of the trial occurred before reaching 50.4 Gy. Therefore, the INT 0123 study does not preclude the possibility of a benefit with dose escalation.

In surgical candidates, questions have centered on the appropriate dose of radiation offering optimal tumor response yet minimizing postsurgical complications to enhance the therapeutic ratio. In light of the CROSS trial,[13] lower doses of 41.4 Gy are acceptable in the neoadjuvant CRT setting in patients who are certain to undergo surgical resection. However, in patients unable to complete surgical resection, or for whose surgery candidacy is equivocal, 41.4 Gy may not be an appropriate dose if these patients are ultimately transitioned to definitive chemoradiation. In such circumstances, a preoperative dose of 50.4 Gy with concurrent chemoradiation may be preferable to ensure that an adequate dose of radiation is administered in case surgical resection cannot be completed.

Results from the CROSS trial allude to the increased likelihood of perioperative pulmonary complications from esophagectomy after neoadjuvant treatment. Wang et al evaluated 110 patients with esophageal cancer treated with trimodality therapy who underwent concurrent chemoradiation with cisplatin, 5-FU and 41.4 to 50.4 Gy followed by surgical resection.[18] The primary endpoint of pulmonary complications included pneumonia or acute respiratory distress syndrome (ARDS) within 30 days after surgery. Multivariate analysis showed that the volume of lung spared from doses ≥ 5 Gy (V5) was a significant independent factor associated with postoperative pulmonary complications (p = 0.005). Other studies have indicated that a V10 > 40% resulted in a 35% risk of pneumonia or ARDS.[19] Additionally, pericarditis has been noted in up to 27% of patients undergoing chemoradiation for esophageal carcinoma, with highest risk noted among patients who received lung V30 > 46% (risk 73% vs. 13% if the V30 is above or below 46%) and mean dose > 26.1 Gy (risk 73% vs. 13% at doses above and below 26.1 Gy).[20] Most recently at the 2018 Gastrointestinal American society of Clinical Oncology (GI ASCO) conference, a study from Memorial Sloan Kettering Cancer Center and the University of Colorado found that that the median overall survival with trimodality therapy dropped from 44 months to 24 months for those who had a total lung V20 ≥ 20%.[21] These data illustrate the importance of minimizing lung dose in patients who may proceed to surgical resection, and suggest a possible benefit for patients with radiation modalities that may limit lung dose, such as proton beam therapy (PBT).

Similar to the heterogeneity of doses delivered in preoperative CRT trials, contouring practice varies widely. Matzinger et al reported on the EORTC-ROC guidelines for cancers of the gastroesophageal junction (GEJ) in 2009,[22] which differ from the more recent U.S. guidelines by Wu et al designed for integration into intensity-modulated radiation therapy (IMRT) delivery.[23] Significant variation of practice with respect to contouring elective nodes exists in the available trials. Moreover, tumors of the most common GEJ location show variation in motion with respect to breathing and heartbeat[24] as well as gastric filling.[25] At this time, there is no consensus on how best to account for such motion, and studies vary widely.

Many studies discussed in this review employed 3DCRT techniques. With 3DCRT, the esophageal cancer is initially treated using an anterior posterior (AP)/ posterior anterior (PA) field arrangement followed by a cone-down volume with oblique fields angled off the spinal cord. While this approach can

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minimize dose to the spinal cord, radiation exposure to the heart and lungs remains substantial. This tradeoff has sparked considerable research to improve radiation dose distributions using alternative methods such as IMRT or PBT. Chen et al evaluated helical tomotherapy's ability to spare heart and lung dose compared with 3DCRT in 6 patients with mid-distal esophageal carcinoma receiving 50 Gy to gross disease.[26] Dose-volume histogram (DVH) analysis showed significant sparing of the heart and lung with significantly reduced V30 and V45 in both organs. In a propensity score analysis comparing 3DCRT with IMRT, despite imbalances in the arms favoring 3DCRT (IMRT patients had lower FEV1, poorer performance status, and were less likely to undergo induction chemotherapy) there was an overall survival benefit to patients receiving IMRT compared with 3DCRT (Med OS for IMRT 43 months vs. 25 months for 3DCRT).[27] The largest retrospective analysis of nonmetastatic esophageal cancer patients (n = 587) undergoing 50.4 Gy IMRT with concurrent chemoradiation either preoperatively or definitively showed a 3-year OS of 51.8% with very low grade 3 toxicity (1.4% radiation pneumonitis, 13% grade 3 esophagitis).[28] A meta-analysis of 5 studies comparing IMRT and 3DCRT treatment of esophageal carcinoma concluded that IMRT can improve overall survival in patients, but did not decrease radiation pneumonitis or radiation esophagitis compared with 3DCRT.[29]

PBT can further reduce normal tissue radiation exposure beyond the capabilities of IMRT and could further reduce cardiopulmonary toxicity in locally advanced esophageal cancer patients, especially those who undergo trimodality therapy. More recently, a dosimetric study of 10 patients planned to a total dose of 50.4 Gy with 3DCRT, IMRT, and PBT showed benefit of PBT and IMRT over 3DCRT. MD Anderson Cancer Center (MDACC) reported on 62 patients treated with passive scatter PBT and concurrent chemotherapy to a median dose of 50.4 cobalt gray equivalent (CGE) and noted a 28% pCR and 50% near CR rate at the time of surgical resection with decreased local recurrence in the preoperative group compared with the definitive RT group, although OS did not differ between the 2 groups.[30] A comprehensive review of PBT for esophageal cancer can be found in the accompanying article by Chuong et al.[31]

Conclusions and Future Directions

In this article we have reviewed the data driving the management of resectable esophageal carcinoma. Preoperative doses of 41.4 to 50.4 Gy are commonly used with concurrent chemotherapy, with surgical resection to follow 4 to 6 weeks after completion of chemoradiation. To minimize postoperative complications including pulmonary and cardiac toxicity, studies involving modern RT approaches including IMRT and PBT are warranted. Several prospective, advanced modality trials are underway: Loma Linda University (NCT01684904), The Mayo Clinic (NCT02452021), University of Pennsylvania (NCT02213497), and MDACC (NCT01512589). The MDACC study will compare protons and IMRT, while the remainder focus on proton therapy alone. Prospective data from these trials will help clarify future directions in managing resectable locally advanced esophageal carcinoma.

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Undergraduate medical education and radiation oncology: Current concerns and effective initiatives

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While radiation oncology (RO) has become an increasingly popular and competitive specialty over the past decade, the proportion of medical graduates entering RO residencies may be leveling off, or even declining.[1] At the same time, cancer remains one of the leading causes of death in the United States and worldwide,[2] fueling the demand for oncologists, including radiation oncologists. Thus, there is a critical role for the integration of RO teaching in medical school education, with the goal of continuing to attract students to the specialty. However, the majority of medical schools lack formal teaching of this discipline, and many students receive little exposure to the field.[3] The question of how to improve integration of RO into medical education remains up for debate. This article will examine limitations to, and the various methods of, implementing radiation oncology education in medical school curricula.

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Concerns, Challenges in Radiation Oncology Medical School Education

While oncology is a common choice of specialty for medical graduates, oncology education at many medical schools remains relatively fragmented and underemphasized compared with other fields.[4-6] The multidisciplinary nature of oncology and its span across different organ systems makes its integration into medical school curricula complex and sometimes disjointed. As a result, there is significant variability between schools in the way oncology and its subspecialties, including RO, are taught,[5] and students may lack confidence in their overall knowledge regarding cancer care despite having learned about its various components.[7] Moreover, students have reported less confidence with oncologic treatment compared to the basic science and diagnosis of cancer,[4,6] indicating a need for greater emphasis on multidisciplinary clinical management in cancer education during medical school.

Compared with other oncologic subspecialties, less is taught about radiation oncology in medical school;[8] thus, many students receive little meaningful exposure to this smaller and more specialized field. The inadequacies in radiation oncology education during medical school have been well described.[8] For example, a 2016 survey analysis of 105 medical students at two U.S. medical schools found that while medical students report increased comfort from MS1 to MS4 with medical and surgical oncology, the same trend was not found in radiation oncology.[7] Moreover, upper-year medical students were found to have the least experience in RO and survivorship care compared with other aspects of oncology.[7] Another analysis of students at a single institution who participated in an oncology education initiative found that while the majority of students considered oncology and RO to be important topics in medical education, most reported that the clinical years provided insufficient exposure to these topics.[9] While misconceptions about radiation oncology have been shown to decrease with increased level of training, from MS1 to MS4, medical students still have misguided notions about different aspects of RO, including those about RO as a profession, the appropriateness of radiation therapy in clinical contexts, and radiation toxicity.[10] Many schools lack requirements to participate in nonsurgical oncology rotations during the clinical curriculum, while others do not require any oncology-focused clerkship.[4,6] As a result, the majority of students who

participate in RO electives are those who plan to apply for an RO residency, and most students entering other fields have little exposure.[4,9]

Several factors are thought to contribute to the lack of RO education in medical curricula. One noteworthy contributor is likely an imbalance in the types of specialists providing the majority of oncology education.[6] Some evidence suggests that a large portion of oncology teaching during the preclinical years is by medical oncologists, pathologists, and PhDs, while most teaching during the clinical years is provided by surgical and medical oncologists. Radiation oncologists, in contrast, have been shown to be significantly less involved in medical education during both the preclinical and clinical years compared with other oncologic subspecialists.[6,11] Moreover, being a particularly small and specialized field, RO is often considered a "niche" specialty and, thus, is given less importance and time compared with other more general disciplines in already jam-packed medical school curricula.[9] The smaller number of radiation oncologists compared with medical and surgical oncologists is likely a contributing factor as well.

It is important to note that issues of diversity and inclusion render exposure to radiation oncology critical in regard to subsets of the medical provider population under-represented in the field. Specifically, reports have shown that radiation oncology lacks diversity in its representation of women and certain minority groups at all levels of training.[12,13] Female representation in academic radiation oncology specifically may lag behind other oncologic subspecialties, with the number of female trainees declining in recent years.[14] Moreover, while representation of women and under-represented minorities (URMs) in medical school has improved over the past several years, their representation in RO has only slightly increased over time.[15] Several factors are thought to contribute to this trend, including inadequate and/or late exposure to radiation oncology as well as fewer female and URM role models in the field, owing to the lack of representation of these two groups in RO.[14,16] Therefore, greater exposure to RO during medical school is needed to help create an RO provider population that accurately represents its patient population. Initiatives to ensure that under-represented groups in particular have access to meaningful exposure to and experience in radiation oncology can help bridge this disparity. The American Society for Radiation Oncology (ASTRO), for example, offers a Minority Summer Fellowship Award, which aims to provide URM students with early research and clinical experiences in RO and mentorship opportunities with members of ASTRO's Committee on Health Equity, Diversity and Inclusion.[17] Additionally, early exposure through electives and student interest groups, particularly at medical schools with a greater percentage of URM students, as well as greater effort to provide mentorship to female and URM students potentially interested in RO, can help address this problem.[16]

There are several methods of integrating radiation oncology teaching into medical school curricula, not only in terms of teaching format but also with regard to timing in the curriculum and subject matter covered. The principles of radiation oncology can be taught during the preclinical years (M1-M2) of medical school, through different learning formats including lectures and workshops. Radiation oncology can also be introduced during the clinical year (M3) through optional or mandatory clerkships with or without didactic components. Subject matter covered in preclinical teachings and clinical RO electives can include radiobiology, medical physics, treatment planning, patient treatment process, and patient follow-up. Students can also gain informal exposure to radiation oncology through research—either during the summer after M1 or through a year-long research experience in RO, typically after M3—and other extracurricular activities. These options for exposing medical students to the field of radiation oncology will be explored throughout this article.

Radiation Oncology and the Clinical Clerkship

One of the most established and effective methods for introducing medical students to radiation oncology is through a clerkship during the clinical year. Interventions to improve exposure to RO during the core clerkships have been described in the literature, with RO elective rotations significantly improving knowledge and understanding in several aspects of the specialty and found to be highly useful by participants.[18] Different models of the RO clerkship exist—including those with didactics, those lacking a didactic component, and those integrated into mandatory pre-existing clerkships—with varying degrees of efficacy, as will be discussed.

The structure of the clinical clerkship in RO is critical to its effectiveness. While clinical clerkships can serve as a valuable method of increasing student understanding of RO, many clerkship structures have had limitations—namely, a lack of a formal didactic curriculum to accompany clinical activities.[7,19] A 2012 survey analysis of 35 MS4s applying for radiation oncology residency found that of the 97 clerkship experiences evaluated, only 23% included hands-on didactic sessions and only 35% included lectures specifically for MS4s, while 52% (50) had no formal lecture, case discussion, or hands-on didactic session.[7] At the same time, the participants ranked didactic hands-on sessions in contouring/planning and lectures on treatment planning, radiobiology, physics, and evidence-based medicine to be among the educational activities of most importance in a

radiation oncology clerkship curriculum. Similarly, a survey analysis including responses from 70 applicants to a single radiation oncology residency program between 2012 and 2013 found that only 27% of applicants had completed at least one clerkship with an appropriate-level didactic component.[19] Given that little is taught about radiation therapy during the preclinical years of medical school and that it remains one of the lesser-known specialties, the need for a structured didactic curriculum to provide foundational information during RO clinical rotations is significant. Moreover, participation in radiation oncology clerkships that include a formal didactic component has been significantly correlated with greater confidence in preparation for RO residency.[19] Thus, recent research has focused on improving the quality and structure of education and, in particular, that of didactics, during these clinical clerkships.

Radiation oncology clinical clerkship models that include didactic components are more effective and can teach medical students aspects of RO that might otherwise be difficult to learn without a formal lecture component, such as medical physics and radiobiology. Programs that have introduced didactics into their RO rotations have shown success. For example, Golden et al reported on a formal didactic curriculum designed in 2012 to accompany a 4-week radiation oncology clerkship.[20] While the curriculum began as a bi-institutional intervention, it has now grown into a multi-institutional cooperative. It consists of a series of three 1-hour lectures on topics including the foundations and history of radiation oncology; radiobiology and radiation physics; and simulation, treatment planning, and emergencies in radiation.[21] Additionally, the course includes a 1-hour hands-on dosimetry workshop in which students use a guide to delineate a target, select beams, and optimize beam parameters. The pilot curriculum was a success, rated as extremely useful along all curriculum components by the 18 participating students. Moreover, students reported that the clerkship curriculum helped them feel more confident in their choice of specialty and more prepared for RO residency. Consequently, the curriculum was expanded to 11 institutions as a research cooperative in 2013 with 94 participating students, again with similarly successful results based on qualitative student feedback.[21] Moreover, the benefits of this didactic clerkship curriculum have been demonstrated in comparison to radiation oncology clerkships lacking structured curricula through a survey analysis, which found participation in a clerkship curriculum site to be significantly correlated with higher confidence in future ability as an RO resident.[22] In addition, the didactic curriculum has demonstrated the ability to produce lasting objective improvements in knowledge about radiation oncology in participants through pre- and post-test assessments.[23] The radiation oncology clerkship developed at Jefferson Medical College in 2010 includes two small-group standardized didactic sessions per week on various topics within radiation, inpatient and outpatient consults, as well as case-based presentations by the students. Participating students also observe simulation, treatment planning, dosimetry, and radiation therapy technologists. The rotation has been found to significantly improve objective knowledge in RO and was well-rated in usefulness by participating students.[11]

Other interventions to improve radiation oncology education during the clinical years have been explored, including those that introduce students to the specialty outside of a standard radiation oncology clerkship. For example, Singh et al have reported on the efficacy of a multidisciplinary oncology education initiative integrated into the required radiology clerkship at Boston University School of Medicine.[9] The initiative included didactics on cancer diagnosis and management, and concepts in radiation oncology, as well as optional student participation in RO consultations and treatment planning sessions. Most students found that the radiology rotation was an appropriate time to learn about oncology and radiation oncology and reported that the experience motivated them to learn further about oncology and RO. Thirty-two percent of the students also decided to pursue advanced on-site training in RO after this educational initiative. Moreover, the fact that most students reported knowing little to nothing about radiation therapy before the course highlights the value of incorporating RO teaching into a required clerkship or other mandatory curricular component so that all students have a baseline level of exposure. The initiative has also been shown to significantly improve medical students' knowledge about RO, including treatment, brachytherapy, and side effects, through pre- and post-test examinations, indicating the efficacy and feasibility of integrating radiation oncology teaching into a pre-existing clerkship.[24,25] Such a model may provide the greatest benefit by ensuring that all students, regardless of professional interests, are exposed to some degree to this lesser known specialty.

Although substantial progress has and continues to be made in improving the structure of radiation oncology clinical clerkships, shortcomings remain. For example, evidence suggests significant grade inflation in RO clerkships compared with other clinical rotations. In an analysis of applicants to a single radiation oncology residency program in 2011 and 2012, 80% of the 167 who participated in a graded radiation clerkship received the highest possible grade. Moreover, compared to clerkship grades in medicine, surgery, pediatrics, and obstetrics/gynecology, grades in radiation oncology were significantly higher ($p < 0.001$), resulting in more challenging evaluation of applicants and missed opportunities for meaningful feedback. Additionally, the timing of didactic components within RO clerkships may be improved

to ensure an adequate foundation of knowledge before students progress through the clerkship.[21]

RO clinical clerkships can provide students with valuable clinical experience in treatment planning, dosimetry, and patient care, as well as a greater understanding of radiation fundamentals including medical physics and radiobiology through didactic components. However, a major disadvantage of using this model exclusively to provide RO education in medical school is providing students with late exposure to the specialty. Early integration of RO teaching during medical school, such as in the preclinical curriculum, can overcome this challenge, as will be discussed in the next section.

Preclinical Exposure to Radiation Oncology

In addition to clinical clerkships, radiation oncology can be integrated into the preclinical curriculum through lectures, workshops, and other methods of instruction. Importantly, students could benefit from early introduction to RO to better inform their career path and shape their trajectory throughout medical school. Since RO residency programs desire significant research experience, particularly within the field, exposure to the specialty during the preclinical years may benefit students by providing them with more time to engage in RO-specific research as well as other RO and oncology-oriented activities.

The oncology unit may provide an opportune time for introducing medical students to RO in the preclinical curriculum. Formal discussion of RO at this point may better prepare students for RO clerkships and rotations in the later part of medical school and can help inform students' decisions to participate in such clerkships. Given its multidisciplinary and inter-disciplinary nature, there are different methods to integrate oncology teaching during the preclinical years. For example,oncology teaching can be interspersed throughout system-based modules or taught as a single block.[26] Agarwal et al found success with a dedicated core oncology block during MS2.[27] The course was led by a radiation oncologist course director, and students reported that it helped them understand cancer therapy and prepared them for oncology-focused clinical electives, including electives in RO. Many believe the block format provides more cohesive and comprehensive education in oncology compared with the integrated method. Moreover, introduction to the principles of radiation oncology—including radiation therapy fundamentals, treatment planning, radiobiology, and radiation physics—may be integrated seamlessly during this dedicated core oncology block structure, and can provide context to subsequent lectures on site-specific treatments for the remainder of the preclinical curriculum. However, both approaches along with others are utilized, and there is currently no standard for how to structure oncology curricula during the preclinical years.[5,26]

Moreover, medical school curricula have evolved to include several innovative learning formats beyond standard didactics. There has been a shift toward greater implementation of small group, workshop, team-based, case-based, and experiential learning methods over traditional lectures, with a greater emphasis on the learner rather than teacher.[5] Thus, several methods can be utilized to incorporate radiation oncology teachings into the preclinical curriculum. Duke University School of Medicine, for example, developed an onco-anatomy course in 2005 open to medical students through the department of radiation oncology.[28] The course focuses on providing anatomy teaching relevant to RO, including the correlation between anatomic tumor location and symptoms, anatomical treatment considerations, and anatomic assessment of tumor spread. The course utilized different learning methods including case-based presentations, didactics, and cadaver demonstrations, and received favorable reviews by participants. Similarly, an onco-anatomy elective supervised by the radiation oncology department was developed at University of Rochester for MS1s and MS2s, with an emphasis on radiologic anatomy on computed tomography (CT) and magnetic resonance imaging (MRI).[29] The elective used several learning formats—including group discussions, small group sessions, anatomy reviews, and didactic lectures—providing students with a more nuanced and comprehensive understanding of anatomy relevant to radiation oncology. Employing multiple learning formats in the teaching of radiation oncology can actively engage students and help these learners obtain and synthesize information more dynamically and comprehensively.

Beyond Curriculum Exposure and Implications for Residency

Several opportunities extend beyond those in the standard medical school curriculum for students to gain meaningful experience in radiation oncology, including research, health policy engagements, and dual-degree programs. Moreover, the expectation for students applying to radiation residency programs is that they have engaged in some, if not several, of these other opportunities. Research experience is particularly important in RO, with radiation residency applicants having a significantly higher mean number of publications, posters, and research experiences compared with applicants to other specialties.[30] Effective mentorship is a critical contributor to research productivity, and its value in supporting the development of successful radiation oncology applicants has been documented.[31] In addition to research opportunities with radiation oncologists at one's own institution, several national research programs provide medical students with research experience in radiation, many of which students participate in during the summer after MS.[30]

Year-long programs can provide a more in-depth experience with greater opportunity to produce and publish meaningful research in the field of RO. Moreover, there are opportunities for students to engage in health policy work relevant to the practice of radiation oncology. Dual degrees also provide students the opportunity to study oncology, or RO more specifically, through a variety of disciplinary lenses, and several students matching into RO have pursued a second degree.[30]

Conclusion

Radiation oncology is poorly integrated into the curricula at many medical schools. Thus, students may fail to gain adequate exposure to the field. Cancer remains one of the leading causes of death, making the continued attraction of future radiation oncologists critical. Implementation of RO education into medical school curricula can take several forms, including introduction during both the clinical and preclinical years. Moreover, RO teaching can be integrated into existing components of medical curricula, such as established clerkships and through multi- and cross-disciplinary education initiatives. Ongoing evaluation of the current methods used to teach radiation oncology in medical school is needed to inform future educational interventions.

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Surgical salvage of oropharyngeal cancer with local-regional recurrence after primary radiation therapy

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Abstract

Objective(s): In patients with local or regional recurrence of squamous cell carcinoma of the oropharynx after primary treatment with radiation therapy (+/- concurrent chemotherapy), the chance that salvage surgery will be successful is the critical issue for determining when to recommend salvage surgery and how intensely to follow patients after initial radiation therapy.

Methods: We reviewed the medical records of 137 consecutively treated patients with recurrence in the primary site and/or neck following primary radiation therapy with curative intent at our institution. Overall survival was assessed using the Kaplan-Meier product limit method. The log-rank test statistic was used to detect any statistically significant differences between strata of selected explanatory variables.

Results: The salvage success rate was 12% and the salvage surgery success rate was 37%. Only 3% of patients with neck-alone recurrences were salvaged vs. 18% with recurrences limited to the primary site. Symptoms led to the detection of the initial recurrence in 84% of cases.

Conclusions: While our series suggests that recurrent head and neck cancer patients have a low success rate with salvage therapy, this series represents a heterogeneous patient population with a variety of treatment paradigms. Due to the complexity of this patient population, a multidisciplinary approach to care is recommended with decisions made on a patient-specific basis with incorporation of the newest treatment modalities.

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For a patient with newly diagnosed recurrence of oropharynx cancer after primary radiation therapy (+/- chemotherapy), the success rate of surgical salvage is important only if that patient is eligible for the procedure. Existing series focus on the technical aspects of a good surgical outcome, but while this is critical for the patients taken to the operating suite, it is only one element in the decision of the multidisciplinary tumor board in assigning a care recommendation. Almost monthly, our head-and-neck oncology group struggles with whether to recommend salvage surgery to a patient with squamous cell carcinoma of the oropharynx that has recurred in the primary site and/or neck following radiation therapy (RT). A separate debate is the frequency and intensity of follow-up of our oropharyngeal cancer patients after primary RT. The answers to both questions hinge on the chance that salvage surgery will be successful in this setting.

Most publications on salvage surgery focus on patients treated primarily with surgery, pool patients with a diverse range of primary sites, or report only on the patients who underwent a salvage attempt. The purpose of this paper is to contribute to the literature by reporting

overall and attempted salvage success rates in a well-defined group of oropharyngeal cancer patients with long-term follow-up after primary RT (+/- chemotherapy), at our institution.

Methods and Materials

This study was approved by our institutional review board. The purpose of the study was to evaluate surgical salvage success rates in patients with local and/or regional recurrence following primary RT (+/- chemotherapy), for squamous cell carcinoma of the oropharynx. We included patients with an unknown primary and level 2 adenopathy who were presumed to have occult cancer in the tongue base after comprehensive unknown primary workup, as described in a prior publication from our group.[1]

Patients were retrospectively staged T0-4, N0-3 using the criteria described in the 7th edition of the American Joint Committee on Cancer's staging manual.[2] We limited the analysis to patients who started primary RT after January 1, 1985, because this defines the era in which high-quality cross-sectional imaging was routinely done as part of the workup for head-and-neck cancer patients at our institution. The end date for study accrual was the start of primary RT before December 31, 2005, to ensure that all patients had at least 5 years of follow-up after local and/or regional recurrence. During the study's timeframe, most patients did not have the tumor tested for p16 or human papilloma virus (HPV) status and the only salvage approach undertaken with curative intent was surgery.

Our initial review yielded 143 eligible patients with local and/or regional recurrence, but 6 patients were excluded because we were unable to obtain reliable information regarding recurrence location and the cancer outcome. Thus, our study population is 137 patients.

Demographics

The 137-patient study population was 82% male (113 patients) and 82% white (112 patients), with age at the time of RT ranging from 44 to 78 years (median, 60 years). Subsite distribution within the oropharynx was as follows: tonsil, 58 patients; base of tongue, 35 patients; posterior pharyngeal wall, 21 patients; soft palate, 16 patients; vallecula, 1 patient; and unknown (T0), 6 patients.

Initial Treatment

Initial treatment for all 137 cases included RT delivered with curative intent in our department. The fractionation schedule was 1.2 Gy twice a day in 82% of cases (112/137) and 2.0 Gy once a day to gross disease in the remaining 18%. The total prescription dose to areas of gross disease was 62 to 84.4 Gy with a median of 74.4 Gy. Electively treated areas received at least 50 Gy.

Chemotherapy was delivered in addition to RT in 20% of patients (28/137). The indication for chemotherapy was large-volume adenopathy and/or a T4 primary. In all cases the chemotherapy was delivered only during the course of RT. The chemotherapy regimen was as follows: weekly cisplatin (13 patients), 30 mg/m^2; cisplatin and fluorouracil (5FU; 9 patients), 20 mg/m^2/day and 1000 mg/m^2/day x 4 days twice during RT; carboplatin (3 patients), 60 mg/m^2 × 5 days twice during RT; and weekly carboplatin and taxol (3 patients), area under the curve (AUC) 1.5 and 45 mg/m^2, respectively.

A planned neck dissection for residual adenopathy on computed tomography (CT) scan done 4 to 6 weeks after RT was performed in 41% of patients (n = 56). Of these 56 patients, 7 (13%) had a pathologically positive neck dissection specimen.

Follow-up After Primary RT

The follow-up schedule following primary RT (+/- chemotherapy) was clinical examination by a radiation oncologist and/or head-and-neck surgeon every 3 months for the first 2 years, every 6 months during years 3 to 5, and then annually until death or loss of follow-up. Computed tomography (CT) scanning in asymptomatic patients was not done routinely.

Study Endpoints

Successful salvage was defined as the absence of a second recurrence of oropharyngeal cancer during the follow-up period at any site, except for the rare situation in which a patient developed a distant metastasis alone more than 2 years after salvage surgery, with no evidence of local or regional recurrence. Our rationale for coding late distant metastasis-alone cases as successful salvages is that the patient benefited from the salvage procedure for a substantial period. Patients who died of surgical complications or intercurrent disease without recurrent cancer within 1 year of salvage surgery were coded as salvage failures since the surgery and its attendant morbidity did not benefit the patient.

Our primary study endpoint was the salvage success rate (successful salvages/137). Our secondary endpoints were the salvage attempt rate (attempted salvages/137), salvage surgery success rate (successful salvages/attempted salvages), and survival following initial local and/or regional recurrence. For the actuarial survival plot, an event was defined as death from any cause.

Statistics

All statistical analyses were performed using SAS and JMP software (SAS Institute, Cary, North Carolina). Overall survival was assessed using the Kaplan-Meier product limit method. The log-rank test statistic was used to detect any statistically significant differences between strata of selected explanatory variables.

Table 1. Salvage Success Rates

Site of recurrence	No. of patients	Procedure success) (successful/attempted)	Salvage success (successful/all LR recurrences)
Primary site alone	85	50% (15/30)	18%* (15/85)
Neck alone	36	10% (1/10)	3%* (1/36)
Primary and neck	16	0% (0/3)	0% (0/16)
Total	137	37% (16/43)	12% (16/137)

Key: LR = local-regional. *p = 0.02

Table 2. Salvage Success Rate by Initial T Stage

Initial T stage	Local recurrence alone*	Surgical salvage attempted	Salvage success rate
T0	2	2	100% (2/2)
T1	4	3	25% (1/4)
T2	23	11	22% (5/23)
T3	33	11	18% (6/33)
T4	23	3	4% (1/23†)

*Includes 85 patients with a recurrence only at the primary site (no neck or distant recurrence). Two stage T0 patients recurred in the tongue base. †T4N2b base of tongue: no evidence of cancer 8 years after composite resection. Log-rank comparison: *p = 0.0842

Table 3. Salvage Success Rate by Initial N Stage

Initial N stage	Neck alone* recurrence	Surgical salvage attempted	Salvage success rate
N0	3	0	0/3†
N1	1	1	1/1‡
N2 A, B, or C	22	6	0/22
N3	10	3	0/10

*36 patients recurred in the neck alone (no local or distant recurrence). †All 3 recurrences in N0 necks were in areas that received > 50 Gy. ‡T2N1 soft palate: Recurrence 6 months after radiation therapy in a previously positive level 2 node that received 70 Gy. The recurrence was an incidental (asymptomatic) finding on computed tomography. Log-rank comparison: *p = 0.9999

Results

Follow-up

All but 3 patients were followed until their death. The remaining 3 are alive without cancer over 5 years following their last cancer treatment. Living-patient follow-up after the date of initial local and/or regional recurrence ranged from 0.4 to 23 years with a median of 3.4 years.

Salvage Success Rates

Table 1 summarizes the salvage success rates. The overall salvage success rate was 12% (16/137), the overall salvage attempt rate was 31% (43/137), and the overall salvage surgery success rate was 37% (16/43).

Salvage surgery was not attempted in 94 patients for the following reasons: unresectable local/regional recurrence (53 patients), distant metastases at the time of detection of local/regional recurrence (18 patients), patient refused (14 patients), medically inoperable (7 patients), and unknown reason (2 patients).

The 43 patients for whom salvage was attempted underwent one of the following operations: wide local excision with or without neck dissection without reconstruction (23 patients), composite resection with or without flap reconstruction (10 patients), laryngectomy with neck dissection (1 patient), or neck dissection alone (9 patients).

The 27 patients for whom the salvage attempt was not successful included 3 patients who died of fatal complications from salvage surgery within 3 months of the procedure and 1 patient who died 6 months after salvage surgery from a problem that appeared to be unrelated to the salvage surgery or cancer. The remaining 23 patients developed recurrent cancer above

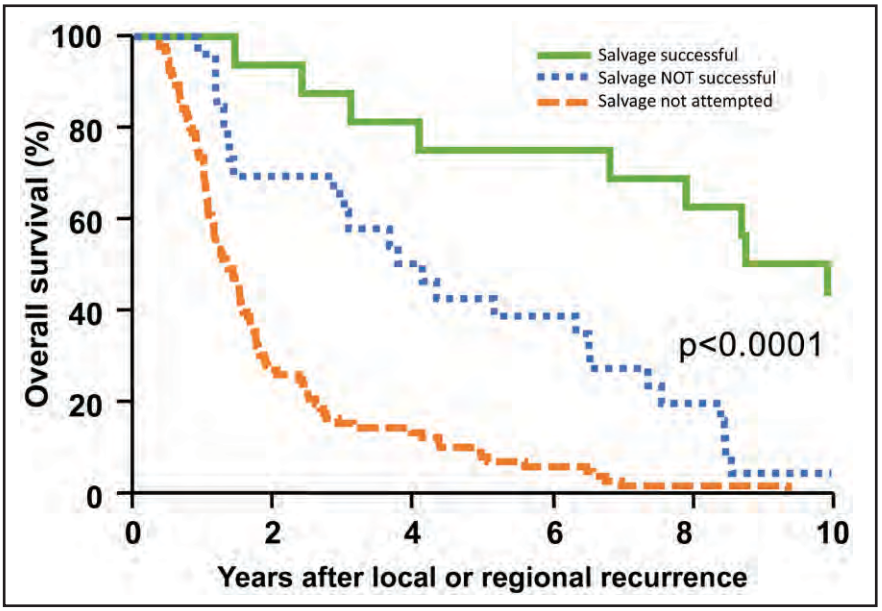

***FIGURE 1**. Actuarial plot of overall survival following the initial local and/or regional recurrence by salvage status. Comparison p value: p < 0.0001.*

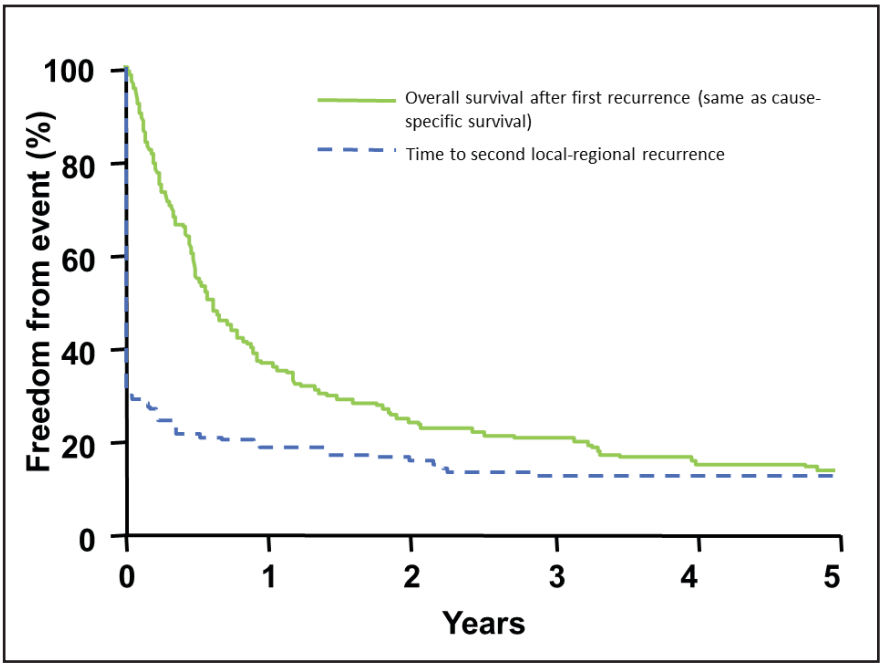

***FIGURE 2.** Actuarial plot of local-regional recurrence and overall survival following the initial local and/or regional recurrence, where patients in whom no salvage was attempted were assigned re-recurrent status at time 0. There were no distant recurrences following the first recurrence.*

the clavicles within 2 years of the attempted salvage surgery.

Three patients who did not undergo salvage surgery were treated with re-irradiation with palliative intent. These patients died within a year of re-irradiation of progressive cancer.

Tables 2 and 3 show the rate of successful salvage by T and N stage at the time of RT. Not shown in these tables is an evaluation of the possible influence of planned neck dissection or the use of chemotherapy. Understanding the limitations of a subgroup analysis in this setting, there was no clear indication that these factors were important determinants of salvage success in our study population. These tables also do not address positive surgical margins at the time of salvage surgery, which were found to be statistically associated with salvage failure (p = 0.0022).

As there was only 1 successful salvage in the 36 patients with a neck-alone recurrence, it is not possible to identify a factor that predicts neck salvage success. The successful salvage was in a patient who had not undergone a planned neck dissection: 1/81 vs. 0/56.

The time interval between RT and the first detection of a local and/or regional recurrence in the total study population averaged 10 months (range, 1 to 78 months). The average time intervals in each salvage subgroup were as follows: no salvage attempt, 9 months (range, 1 to 75 months); unsuccessful salvage, 17 months (range, 4 to 78 months); and successful salvage, 9 months (range, 3 to 27 months). The difference between these detection intervals was statistically significant (p = 0.0176). A time to recurrence of greater or less than 12 months, however, was not significantly associated on univariate analysis with successful salvage (p = 0.7374).

Figure 1 is an actuarial plot of overall survival following the initial local and/or regional recurrence by salvage status. **Figure 2** provides the plot of outcome following the first recurrence, with patients in whom no salvage surgery was attempted shown as local-regional recurrence events at time 0.

Symptoms of Recurrence

Table 4 shows data evaluating how frequently symptoms led to the detection of a local and/or regional recurrence. The most common symptom was pain at the site of recurrence, occurring

Table 4. Symptoms Related to Recurrence

Site of recurrence	Symptomatic	Asymptomatic*	Unknown
Primary site only	75	6	4
Neck only	27	9	--
Primary and neck	13	2	1
Total	84% (115/137)	12% (17/137)	--

*Asymptomatic recurrences were incidental findings on computed tomography in all but 3 patients whose neck nodes were palpated on physical examination.

Table 5. Surgical Salvage Success Rate from Series That Report Results for Oropharynx Primary Sites Treated with Primary Radiation Therapy

Series	Local +/- neck recurrence	Surgical salvage attempted	Salvage procedure success rate	Surgical salvage success rate
Current Study	137	43	37%	Overall, 12% Primary alone, 18%, Neck alone, 3% Both, 0%
White et al, 2013[3] Multi-institutional	Not reported	128	60%	Not reported
Mabanta et al, 1999[4] University of Florida, Gainesville, FL	Neck alone, 51	11	9%	2%
Regueiro et al, 1995[5] Clinica Puerta de Hierro, Madrid, Spain	21	5	0	0
Gehanno et al, 1993[6] Claude Bernard Hosp., Paris, France	Not reported	50	22%	Not reported
Viani et al, 1991[7] Clatterbridge/Liverpool, UK	Primary site, 79 Neck alone, 75	45 65	24% 18%	14% 16%
Wong et al, 1989[8] MD Anderson Cancer Center Houston, TX	37	18	28%	14%
Zafereo et al, 2009[9] MD Anderson Cancer Center Houston, TX	168	39	33%	8%

in nearly all cases; also reported were a new mass, ulceration, dysphagia, otalgia, trismus, nasal congestion, and dysphonia. Not shown in this table is the rate of successful surgical salvage based on symptom status. Of the symptomatic patients, 13% (15/115) were successfully salvaged and all successes were in patients with recurrences only at the primary site. Of the asymptomatic patients, 6% (1/17) were successfully salvaged with the only success being a neck-only recurrence detected by surveillance CT scan. There were no successful salvages in the 5 patients whose symptom status was unknown.

Discussion

Our Results Compared to Prior Publications

Table 5 summarizes the main publications that report overall rates of surgical salvage success for oropharyngeal cancer patients following primary RT.[3-9] Not included in this table

are series that focus on patients whose primary treatment was a surgical procedure or who combine patients treated with primary surgery and RT without separating the results[10-12] or those that pool results from a wide range of primary sites.[13-16] Our series provides the longest published follow-up in the literature regarding an entire population of patients with recurrence after primary RT for squamous cell carcinoma of the oropharynx. Most series focus only on patients offered surgery, but these data ignore outcomes for those who are not surgical salvage candidates, suggesting an unfairly optimistic prognosis after recurrence. The success rate of the procedure only matters to those who are eligible. The most important endpoint is found in the last column, Surgical Salvage Success Rate, which uses "total patients with local and/or regional recurrence" in the denominator of the calculation. Our finding that only 12% of patients were successfully salvaged is sobering, and this figure is very close to what other series have reported.

We were discouraged to confirm our prior study showing that successful salvage is rare with neck-alone recurrences.[4] Our value of 3% is lower than the 16% from Viani and colleagues,[7] but given the heterogeneity of this patient population, both of these studies support the conclusion that the chance of successful salvage is especially low in patients with recurrence confined to the neck, as shown by imaging studies.

We did not have specific criteria for selecting patients for salvage surgery, but we believe our series reflects the culture of most tertiary-care head-and-neck oncology groups. No other publication, to our knowledge, describes prospective guidelines for attempting salvage surgery. This reality likely explains the range of salvage attempt and surgery success rates among the published series.

Our salvage surgery success rate of 37% is slightly higher than most other series except for the outlier result of 60% from White and colleagues, which pools the results from multiple institutions and is almost exclusively limited to patients whose local recurrence appeared to have a good chance of cure with transoral robotic surgery.[3] It is therefore likely that patient selection bias explains the relatively high surgery success rate in our analysis.

Subgroup Analyses

We attempted to evaluate the influence of major factors likely to affect the chance of successful salvage. The value of these analyses is limited by small numbers within each subgroup and the inability to control for confounding factors. Given these limitations, we found that salvage of a primary-site-alone recurrence was inversely related to initial T stage, but even with an initial stage of T4, the chance of successful salvage is not 0.

With only 1 successful salvage in patients with a neck recurrence, it is not possible for our data to determine whether secondary factors, such as initial N stage or extent of neck recurrence, influence the salvage success rate.

No series, including ours, evaluates salvage rate by p16 or HPV status. Our guess is that knowing HPV status would not change the main findings in our study because the number of successful salvages was so low and because it is likely that recurrence after RT identifies a poor prognosis subtype of HPV-associated cancer.

Symptoms Related to Recurrence

In our study, the great majority (84%) of recurrences were symptomatic at the time of detection—meaning that the patient had reported symptoms related to recurrence as a source of specific concern to the physician. Most published series do not report how frequently recurrences were symptomatic, so it is difficult to compare our results to other groups for our specific study population. Follow-up guidelines related to oropharyngeal cancer from the National Comprehensive Cancer Center Network (NCCN) state in a footnote that "Most recurrences are reported by the patient."[17]

Overall Survival After Recurrence

The overall survival results in **Figure 1** support the value of attempting surgical salvage when it is likely to be successful because the great majority of patients who are successfully salvaged live many years after the salvage surgery (5-year survival approximates 75%). Another finding is that, when patients are not successfully salvaged, a substantial percentage of patients live for years with palliative management (often including chemotherapy and additional RT). We interpret the difference between the "salvage not successful" and "salvage not attempted" curves to be the result of patient selection vs. unsuccessful surgery.

Follow-up Schedule as a Result of Findings

The finding that the great majority of local-regional recurrences are symptomatic, combined with a low rate of successful salvage, questions the value of following asymptomatic patients frequently when the purpose of follow-up is recurrence detection. It is possible that more rigorous follow-up programs would detect recurrences earlier such that the salvage success rate would be higher, but our data do not inform this question. As a result of our findings, most of the physicians in our program are lengthening the follow-up interval to fit with the management of treatment-related toxicity. Our usual follow-up program is now clinical examination with CT of the neck and chest every 4 months in the first year, every 6 months for the next 2 years, and annually thereafter.

Conclusions

While our series suggests that recurrent head and neck cancer patients have a low success rate with salvage therapy, this series represents a heterogeneous patient population with a variety of treatment paradigms. Due to the complexity of this patient population, a multidisciplinary approach to care is recommended with decisions made on a patient-specific basis with incorporation of the newest treatment modalities.

Based on our finding, we are highly selective in the patients for whom we recommend a major salvage surgery and we explain the basic results of this study as part of the consent process when a salvage procedure is being offered. We do not have bright-line selection criteria. The main influence of our study has been to make it so that we do not offer salvage surgery in patients with cardiovascular problems that put them at high risk for major head and neck surgery or in patients with neck disease around the carotid that puts them at high risk for a vascular complication from complete tumor resection.

The finding that the great majority of local-regional recurrences are symptomatic, combined with a low rate of successful salvage, questions the value of following asymptomatic patients frequently when the purpose of follow-up is recurrence detection. It is possible that more rigorous follow-up programs would detect recurrences earlier such that the salvage success rate would be higher, but our data do not inform this question. As a result of our findings, most of the physicians in our program are lengthening the follow-up interval to fit with the management of treatment-related toxicity. Our usual follow-up program is now clinical examination with CT of the neck and chest every 4 months in the first year, every 6 months for the next 2 years, and then annually thereafter.

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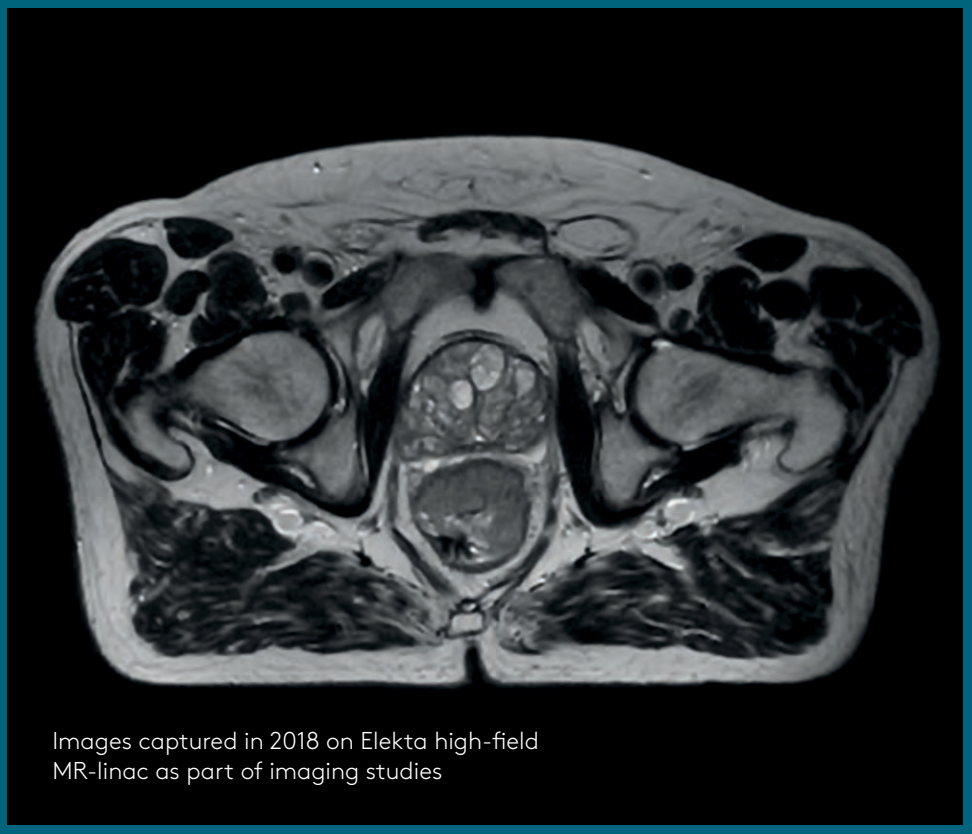

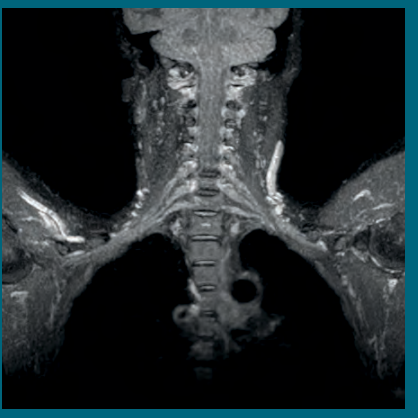

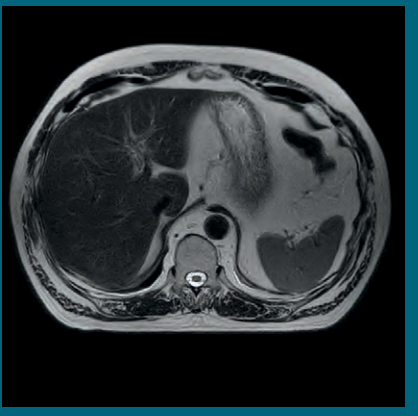

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Postprostatectomy radiation therapy for biochemically recurrent prostate cancer

Michael Schloss, MS-III; Suneal Peddada, MS-IV; Arman Bakhshi, MS-III; Angela Phelps,BS; Arash Velayati, MD; Jarrod B. Adkison, MD

Abstract

Objective: This series retrospectively reviewed the treatment strategy of salvage radiation therapy for patients for whom prostate-specific antigen (PSA) has already demonstrated failure after a period of observation following prostatectomy.

Methods and Materials: At our institution, 102 patients were treated with salvage radiation therapy, 19 of whom had a Gleason score ≤ 6, 52 of whom had Gleason 7, and 31 of whom had Gleason ≥ 8 prostate cancers. Median follow-up after radiation therapy was 51 months. The median PSA prior to salvage radiation therapy was 0.33, and the median time from prostatectomy to radiation therapy was 24.6 months. Positive margins were identified in 52 patients, and perineural invasion was positive in 83. The median dose delivered was 64.8 Gy.

Results: The 5-year actuarial freedom from biochemical failure rates for National Comprehensive Cancer Network (NCCN) low-, intermediate-, and high-risk groups were 100%, 77%, and 62%, respectively (p = 0.2449). The 5-year actuarial freedom from biochemical failure rates for a Gleason score ≤ 6, Gleason 7, and Gleason ≥ 8 patients were 87%, 72%, and 49%, respectively (p = 0.0187). Patients with pre-radiation therapy PSA ≤ 0.5 had better 5-year biochemical control relative to patients with higher pre-radiation therapy PSA, 76% vs. 51% (p = 0.0211). Few interval biochemical failures are observed after the 5-year point of follow-up. The 5-year overall survival for the entire cohort is 92%, with prostate-cancer-specific survival of 96%.

Conclusions: Salvage radiation therapy demonstrated durable PSA control and few failures at 5 years post-radiation. Initiation of salvage radiation therapy for PSA ≤ 0.5 demonstrated improved biochemical control, supporting the adoption of early referral to radiation oncology once post-prostatectomy biochemical failure is identified.

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Approximately one-third of affected men choose to undergo radical prostatectomy as definitive therapy for prostate cancer,[1] and roughly 15% to 35% of these men will experience biochemical recurrence of prostate cancer within 10 years, which is denoted by an increase in serum prostate-specific antigen (PSA).[2-4] It is generally accepted that salvage radiation therapy (SRT), defined as the initiation of radiation therapy upon the identification of biochemical recurrence, offers the best prognosis for patients without distant metastases. Adjuvant radiation therapy (ART), another treatment technique commonly used for patients exhibiting adverse pathological features (APF) at the time of surgical prostate resection, employs radiation therapy as an immediate adjunct to surgical resection. The use of adjuvant vs. salvage radiation therapy is the subject of ongoing randomized trials. Current guidelines recommend that patients exhibiting adverse pathology indicating a high risk

of recurrence should be offered ART.[5] Although ART has been shown to be effective in certain patients, risks may outweigh benefits in others. Therefore, employing ART as the standard of care would expose some patients to unnecessary doses of radiation.[6]

Our series reviews the common treatment strategy of salvage radiation therapy for patients in whom serum PSA values have demonstrated biochemical recurrence after a period of observation following prostatectomy. Salvage radiation therapy represents a curative treatment option for patients who exhibit biochemical failure following prostate resection.[7] The primary goal of this study was to explore our institutional experience and use it to determine if initiating SRT before a specific serum PSA marker value led to better patient outcomes in our cohort. Currently, no official consensus definitively declares the optimal serum PSA cutoff value at which SRT should be initiated. Here we present a retrospective analysis of 102 consecutive patients treated with postprostatectomy salvage radiation therapy.

Materials and Methods

Participants

Between March 2003 and June 2014, 102 patients underwent salvage radiation therapy at a community hospital after biochemical recurrence of localized prostatic adenocarcinoma following radical prostatectomy. All patients were treated with curative intent by multiple physicians following the same departmental protocol. National Comprehensive Cancer Network (NCCN) risk stratification was used to predict the probability of postprostatectomy biochemical failure. Four patients were classified as low risk, 37 as intermediate risk, and 61 as high risk based on PSA values and histopathological features. Face-to-face follow-up with PSA testing and digital rectal exam after radical prostatectomy took place in the office setting and varied based on physician preference. Identifying patient information was stripped by the cancer registrar. The study was reviewed and approved by the institutional review board.

Inclusion and Exclusion

Patients included in the study underwent radical prostatectomy for prostatic adenocarcinoma, developed subsequent biochemical PSA failure and were treated with SRT at our facility. Ultrasensitive PSA assays were used to detect increased serum PSA values indicating biochemical recurrence before deciding whether to initiate SRT. Subjects were chosen based on site (prostate), histology (Gleason score and tumor node metastasis [TNM] staging), surgical resection (prostatectomy), recurrence (biochemical failure) and postrecurrence treatment (radiation). Exclusion criteria were stage T4 cancer, any radiation not done at our facility, any patient who underwent chemotherapy, and any patient with a secondary active cancer other than prostatic adenocarcinoma. Patients with a history of a secondary cancer type that was either inactive or in a period of follow-up after radiation therapy were not excluded from the study.

Treatment

Patients were staged with a bone scan and computed tomography (CT) of the abdomen and pelvis to ensure no distant metastatic disease prior to treatment. The prostate fossa clinical target volume (CTV) was defined to include the posterior bladder and residual seminal vesicles superiorly down to the vesicourethral anastomosis inferiorly, including the urogenital diaphragm. The contents anterior to the rectum and posterior to the pubic symphysis were targeted with a margin for setup uncertainty of 0.7 to 1 cm in all directions, except posteriorly where the margin was 0.5 to 0.7 cm. The elective treatment of the pelvic lymph node basins was left to the discretion of the treating physician, and 73 patients had elective nodal radiation followed by a boost to the prostatic fossa. Three-dimensional conformal radiation therapy (3DCRT) was delivered for 10 patients and intensity-modulated radiation therapy (IMRT) was delivered for 92 patients. The dose delivered to each patient was within a range of 58 Gy to 75 Gy, with a median dose of 64.8 Gy. Fourteen patients received adjuvant androgen deprivation therapy (ADT) with a gonadotropin-releasing hormone (GnRH) agonist and/or anti-androgen agent upon completing salvage radiation therapy, while 88 did not. Optimal treatment strategy with ADT was determined according to physician preference.

Outcomes

Five-year actuarial freedom from biochemical failure was the primary outcome evaluated in this study. Secondary outcomes were overall patient survival and prostate-cancer-specific survival. Biochemical progression indicating failure was defined as and recorded at a serum PSA value of 0.1 ng/mL or more following the initial SRT, a continued rise in serum PSA despite continued SRT, the initiation of systemic therapy after the completion of SRT, or clinical progression.

Statistical Analysis

Actuarial freedom from biochemical progression was calculated using the Kaplan-Meier method for the entire cohort and with respect to prognostic variables. Estimated survival curves for patient subgroups were compared by utilizing the log-rank test to calculate statistical significance, which was evaluated at the conventional significance level of 0.05 for all considerations. Statistical analyses were performed using MedCalc statistical software (MedCalc Software, Belgium).

Table 1. Clinical Characteristics of 102 Patients Undergoing Salvage Radiation Therapy for PSA Recurrence after Radical Prostatectomy

Variable	No. of Patients
Gleason score	
≤ 6	19 (19%)
7	52 (51%)
8-10	31 (30%)
Surgery type	
da Vinci Robotic Assist	69 (68%)
Open Retropubic	33 (32%)
Margin status	
Postitive	52 (51%)
Negative	50 (49%)
Perineural invasion	
Positive	83 (86%)
Negative	8 (8%)
Unspecified	11 (11%)

Variable	Median
Age at surgery	61 years
Pre-operative PSA	5.81 ng/ml
Post-operatvie PSA doubling time	12 months
Time from surgery to radiotherapy	12.6 months
Pre-radiotherapy	0.33 ng/ml
Radiotherapy dose	64.8 Gy
Duration of biochemical control after radiotherapy*	41 months
Duration of follow-up after radiotheraphy	51 months

*Biochemical progression was defined as and recorded at a serum PSA value increase of 0.1 ng/ml or more following the initiation of salvage radiotherapy; a continued rise in serum PSA despite salvage radiotherapy, the intitiation of systemic therapy after the completion of salvage radiotherapy of clinical progression.

Results

Specific patient characteristics are detailed in **Table 1**. The average and median age at the time of surgery was 61 years, with a standard deviation of ± 7. Median pre-operative PSA was 5.81 ng/mL. Only 19% of patients received a surgical Gleason score of ≤ 6, 51% were given a score of 7, and 30% scored ≥ 8. Pathologic stage was T2 in 48% of patients, T3a in 23%, and T3b in 24%. Perineural invasion was identified in 81% of patients and positive surgical margins were identified in 51%. Lymph node sampling was performed in 46 patients, and only 1 patient had pathological evidence of nodal involvement. Lymph node sampling was not predictive for negative surgical margins. Patients treated with open prostatectomy had a positive surgical margin rate of 52% and an overall high-grade disease rate of 21%, while patients treated with da Vinci robotic-assisted prostatectomy had a positive margin rate of 49% and overall high-grade disease rate of 34%. Median postoperative PSA doubling time (PSADT) was 12 months and the median interval from prostatectomy to the initiation of radiation therapy following biochemical recurrence was 12.6 months. Median PSA for the cohort before the initiation of salvage radiation therapy was 0.33 ng/mL.

Twenty-three men in the cohort eventually experienced biochemical progression during the observational period following radiation treatment. The median age of these men was 62. As seen in **Figure 1**, 5-year actuarial freedom from biochemical failure rates for NCCN low, intermediate, and high-risk groups were 100%, 77%, and 62%, respectively (p = 0.2449). Statistical analysis using the log-rank test demonstrated a particularly significant association among groups in remission at 5 years based on Gleason scoring criteria. Five-year actuarial freedom from biochemical failure rates for patients with a Gleason score of ≤ 6, Gleason 7, and Gleason 8-10 were at 87%, 72%, and 49%, respectively (p = 0.0187), as illustrated in **Figure 2**.

Patients with pre-radiation therapy PSA ≤ 0.5 ng/mL had better 5-year biochemical control relative to patients with higher pre-radiation therapy PSA values—76% vs. 51% (p = 0.0211)—as shown in **Figure 3**. Pathological margin status did not predict for biochemical control after salvage radiation across the different Gleason grades. For Gleason ≤ 6, positive margin patients vs. negative was 84% vs. 89% controlled (p = 0.8484). For Gleason 7, positive margin patients vs. negative was 71% vs. 74% controlled (p = 0.9803). For Gleason 8-10, positive margin patients vs. negative was 37% vs. 66% controlled (p = 0.4515). Pathologic T stage did not reach statistical significance (p = 0.1932), although 5-year biochemical control rates were 82% for stage T2 tumors, 67% for stage T3a tumors, and 55% for stage T3b tumors.

Subset analysis was performed to exclude the 14 patients who received ADT immediately following salvage radiation therapy. Of the 88 patients who did not receive ADT, 5-year actuarial freedom from biochemical failure rates for Gleason score ≤ 6, Gleason 7, and

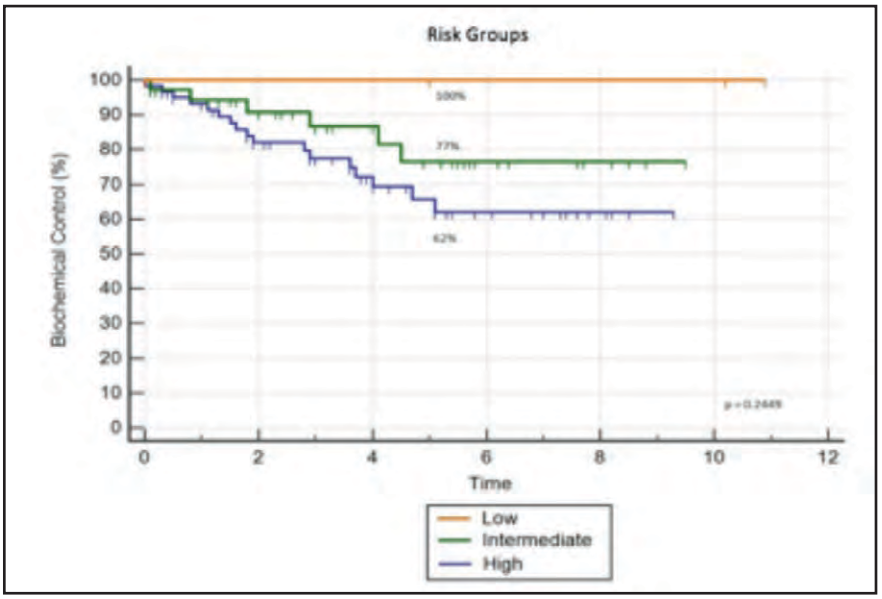

FIGURE 1. *Five-year actuarial freedom from biochemical failure rates for National Comprehensive Cancer Network (NCCN) low-, intermediate-, and high-risk groups.*

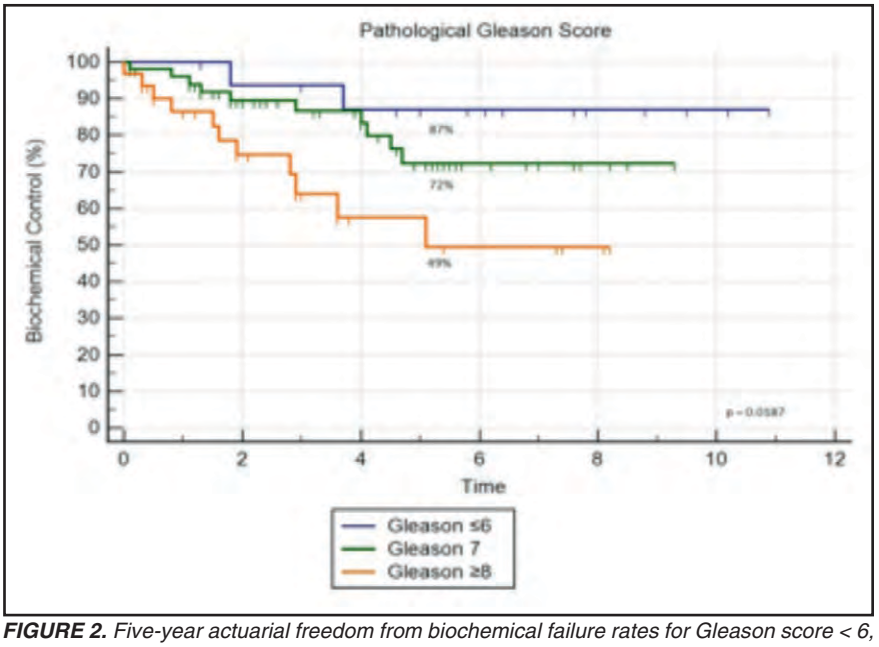

FIGURE 2. *Five-year actuarial freedom from biochemical failure rates for Gleason score < 6, Gleason 7, and Gleason 8-10 patients.*

Gleason ≥ 8 patients were 86%, 77%, and 50%, respectively (p = 0.0347). Interestingly, withholding patients who received ADT from the analysis increased the 5-year biochemical control rate in patients with pre-radiation therapy PSA ≤ 0.5 ng/mL from 76% to 87%. Patients who received adjuvant ADT did exhibit both higher mean and median pre-radiation therapy PSA values of 1.8 ng/mL and 0.38 ng/mL, respectively, vs. a mean of 1.02 ng/mL and median of 0.33 ng/mL for the entire group.

Nine patients in the group of 102 died throughout the follow-up period and 4 of those deaths were documented as prostate cancer specific. All 4 of these patients were being treated for metastatic disease at the time. Of the 5 additional patients who died, none had experienced biochemical recurrence of localized prostate cancer following salvage radiation therapy. Five-year overall survival for the entire cohort is 92%, with prostate-cancer-specific survival of 96%. Very few interval biochemical failures are observed after the 5-year point of follow-up, as seen in the Kaplan-Meier curves, indicating durable disease control after 5 years.

Discussion

This consecutive case analysis demonstrates that salvage radiation therapy remains a curative option for patients in whom it may be undesirable to initiate adjuvant radiation. Because many patients treated with surgical prostate resection will never develop biochemical failure, avoidance of ART prevents such patients from receiving unnecessary treatment with radiation. D'Amico et al studied 1638 men who underwent radical prostatectomy and found no increased risk of all-cause mortality between groups treated with ART vs. SRT.[8] Furthermore, a 16-year, 890-patient study of men staged with pT3N0 prostate cancer following surgical resection identified no significant difference in 5-year biochemical recurrence and survival rates amongst groups treated with either ART or SRT administered at PSA ≤ 0.5 ng/mL after a period of initial observation.[9] This result contrasts with SWOG-S8794, which revealed that ART in men exhibiting evidence of extra-prostatic invasion on pathological sections (T3N0M0) produced a significant reduction in metastatic disease incidence with improved survival benefit.[10] Interpretation of SWOG-S8794 has notably shaped the current school of thought regarding post-prostatectomy follow-up and treatment, characterized by a cautious approach to men exhibiting

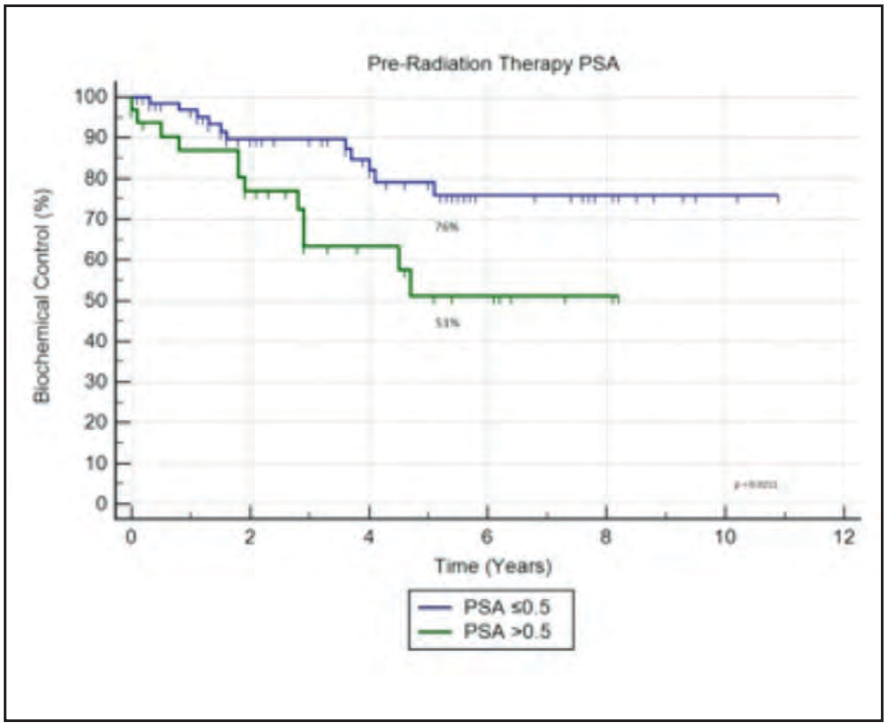

FIGURE 3. *Patients with preradiation therapy prostate-specific antigen (PSA) < 0.5 had significantly better 5-year biochemical control relative to patients with higher PSA values.*

APF with heavy consideration of ART in this subset. A recent meta-analysis of 2629 patients suggested clinicians recommend ART to all patients displaying APF, citing increased overall and disease-free survival at 3 and 5 years.[11] Radiotherapy–Adjuvant Versus Early Salvage (RAVES) is an ongoing phase III randomized, controlled clinical trial slated to run through 2021 that will further investigate the application of ART vs. SRT in patients undergoing surgical prostate resection.[12] For now, multiple analyses of ART vs. SRT continue to support dissenting conclusions. Clinicians should continue to proceed with caution when treating patients displaying APF until additional studies clarify the opposing findings between these divergent treatment arms.

SRT also represents a therapeutic option for patients when ADT is undesired. Indeed, a vital point to consider is that 88 of the 102 patients reviewed in our series did not undergo ADT. A study of 635 patients with biochemical recurrence after prostatectomy at Johns Hopkins previously demonstrated that adjuvant use of ADT during salvage radiation therapy did not significantly improve outcomes.[13] The freedom from biochemical failure and high survival rate of the entire cohort in our series seems to support those findings. RTOG-9601, a double-blind, placebo-controlled trial, found that 24 months of daily bicalutamide led to significantly improved overall patient survival with decreased rates of secondary metastases in patients undergoing SRT.[14] However, patients with higher PSA levels prior to treatment exhibited the greatest overall survival benefit. Interestingly, in both RTOG-9601 and our institutional analysis, patients exhibited marginally improved outcomes with lower pre-treatment PSA values when receiving SRT alone in comparison to those receiving ADT in addition to SRT. Siddiqui et al found that patients who received adjuvant ADT within 90 days of surgery showed mildly improved rates of 10-year progression-free (95% vs. 90%) and cancer-specific survival (98% vs. 95%), but those who received adjuvant ADT following biochemical recurrence at PSA values between 0.4 ng/mL and 1.0 ng/mL exhibited adverse rates of 10-year progression-free survival (75% treated vs. 80% untreated) and cancer-specific survival (86% treated vs. 91% untreated).[15] It is possible that with biochemical recurrence identified at lower serum PSA values prior to SRT, the additional use of ADT with certain agents can be disadvantageous. GETUG-AFU 16, another randomized, controlled multicenter trial, observed significantly improved 5-year biochemical control for patients treated with SRT plus goserelin, a GnRH agonist, when compared to SRT alone (80% vs. 62%), a consistent theme among all measured pre-trial PSA value patient subsets.[16] Radiotherapy and Androgen Deprivation in Combination with Local Surgery (RADICALS), an incomplete large-scale phase III randomized, controlled clinical trial, aims to assess the various roles of ART, SRT and ADT.[17] Hopefully, data gathered from RADICALS will help shed light on the indefinite role of ADT in the setting of SRT, in addition to several other dominant debates concerning existing postprostatectomy patient care.

Multivariate analysis of GETUG-AFU 16 determined that PSADT, surgical margin status, seminal vesicle status and pre-radiation therapy serum PSA values accorded no predictive value for detecting future biochemical failures.[16] Among these 4 factors, we found that a pre-radiation therapy PSA marker value of 0.5 ng/mL or less was a significant factor in gauging the likelihood of 5-year biochemical control ($p = 0.0211$). Briganti et al revealed that patients with less favorable histopathological features following prostate resection had a significantly amplified probability of experiencing biochemical failure when pre-radiation therapy PSA cutoff values were mildly increased.[18] Our findings also seem to suggest that prognostication

of the optimal timing at when to begin SRT is not independent of factors such as TNM staging and Gleason grading. Gleason scores demonstrated positive predictive significance against 5-year freedom from biochemical recurrence ($p = 0.0187$). However, postsurgical margin status offered little prognostic value across differing Gleason grades in our cohort. TNM staging did not show statistical significance ($p = 0.1932$), although our data displayed decreased rates of 5-year biochemical control with worsening stage, as expected.

The foremost goal of our analysis was to determine whether a specific PSA threshold existed at which initiating SRT before said threshold demonstrated superior outcomes in our cohort. A salient improvement in 5-year biochemical control was observed in patients treated with SRT before serum PSA surpassed 0.5 ng/mL compared with patients treated at a pre-radiation therapy PSA value > 0.5 ng/mL. One analysis of 10 retrospective studies and a second multi-institutional retrospective analysis also found that patients treated with SRT at pre-radiation therapy PSA values < 0.5 ng/mL had improved rates of freedom from biochemical failure and that decreasingly lower pre-radiation therapy PSA values among this subset of patients correlated with increasingly improved outcomes.[19,20] Other reports have established that SRT employed at PSA ≤ 0.2 ng/mL significantly improves rates of long-term biochemical control and overall patient survival.[21,22] A comparison of men with pre-radiation therapy PSA values of ≤ 0.5 ng/mL vs. those with values > 0.5 ng/mL showed the most dramatic difference in 5-year freedom from biochemical failure at 76% vs. 51% ($p = 0.0211$). Our data supports the rapid initiation of salvage therapy upon identification of biochemical failure. Such a dramatic improvement in biochemical control at the threshold of 0.5 ng/mL suggests that it could be an important target for those encountering such patients in clinical practice.

Conclusions

Salvage postprostatectomy radiation therapy represents a curative treatment option for patients with biochemical recurrence and no evidence of metastases following prostatectomy. The therapeutic advantages of adjuvant radiation therapy and androgen deprivation therapy in the setting of biochemical recurrence are relatively undefined, with prospective studies of this quandary well on the horizon. Adjuvant radiation therapy should continue to be offered to patients exhibiting adverse pathological features for now. Regarding histopathological prognostication, Gleason grading seems to offer the most precision when ascertaining the likelihood of future biochemical recurrence. Initiation of radiation as soon as biochemical failure is identified appears to offer greater success with salvage, particularly when radiation is initiated with PSA ≤ 0.5 ng/mL. Biochemical control appears very durable past the 5-year point, with few late recurrences.

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RADIATION ONCOLOGY CASE

Long-term cure of stage IVB esophageal adenocarcinoma: Integrating local therapy modalities to maximum treatment effect in patients responsive to systemic therapy

Ethan Y. Song, BA; Nainesh Parikh, MD, MBA; Jessica M. Frakes, MD; Louis B. Harrison, MD; Sarah E. Hoffe, MD

CASE SUMMARY

The incidence of esophageal adenocarcinoma is increasing in the United States.[1] Treatment for localized disease is based on the endoscopic stage, with chemoradiation prior to surgical resection as the standard of care.[2] In this case report, we describe the long-term curative outcome of a patient with metastatic adenocarcinoma of the gastroesophageal junction (GEJ) treated with sequential therapies due to an excellent treatment response.

A 72-year-old man with a history of chronic obstructive airway disease, diverticulosis, and hypertension presented to his primary care physician with mild dysphagia and acute hematemesis, which prompted endoscopic evaluation. Esophagogastroduodenoscopy (EGD) in April of 2007 showed an ulcerating mass at the GEJ, biopsy positive for adenocarcinoma, with endoscopic ultrasound stage T3N1. Site-specific institutional pathology review showed fragments of invasive, poorly to moderately differentiated adenocarcinoma without signet ring cells arising in Barrett's mucosa (**Figure 1**). Immunohistochemical stain was negative for *Helicobacter pylori*. Staging computed tomography (CT) of the chest, abdomen and pelvis did not show evidence of metastatic disease.

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The patient was seen in a multispecialty evaluation with medical/surgical/radiation oncology and was recommended to undergo neoadjuvant chemoradiation prior to resection. The patient underwent radiation oncology simulation and a treatment planning positron emission tomography/CT (PET/CT) scan in the treatment position. Unexpectedly, the PET/CT scan showed a hypermetabolic left supraclavicular node and a left level 1L node (**Figure 2**). Ultrasound-guided fine-needle aspiration (FNA) of the left supraclavicular node was positive for adenocarcinoma, confirming metastasis (**Figure 3**). According to the 6th edition of the American Joint Committee on Cancer (AJCC) staging system, which was in place in 2007, involvement of a cervical lymph node station for a distal esophageal primary tumor represented metastatic disease classified as M1b, stage IVB.[3] Indeed, the only regional nodes for GEJ primary tumors were lower esophageal (below the azygous vein), diaphragmatic, pericardial, left

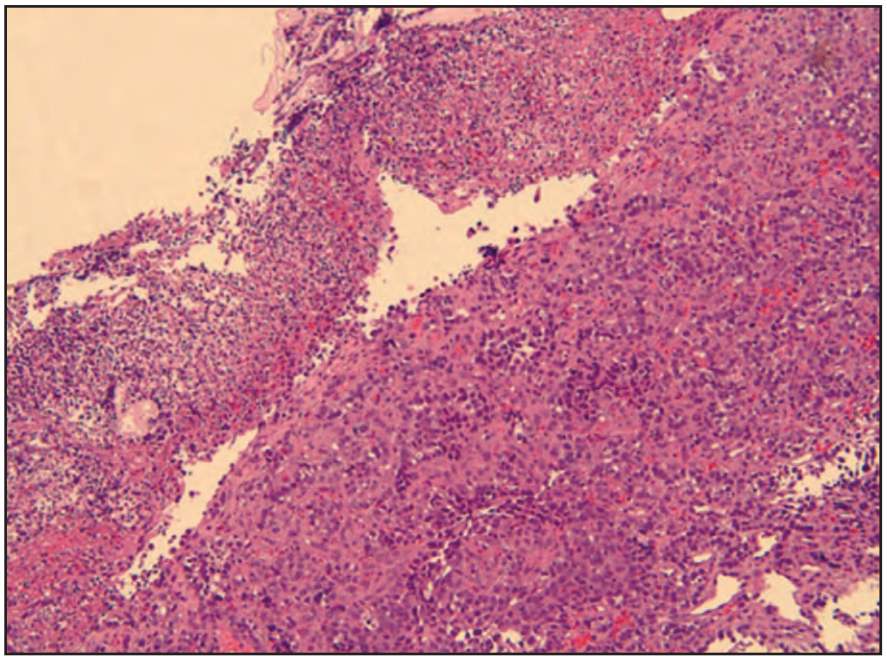

FIGURE 1. *Pathology at the GEJ revealed poorly to moderately differentiated adenocarcinoma without signet ring cells.*

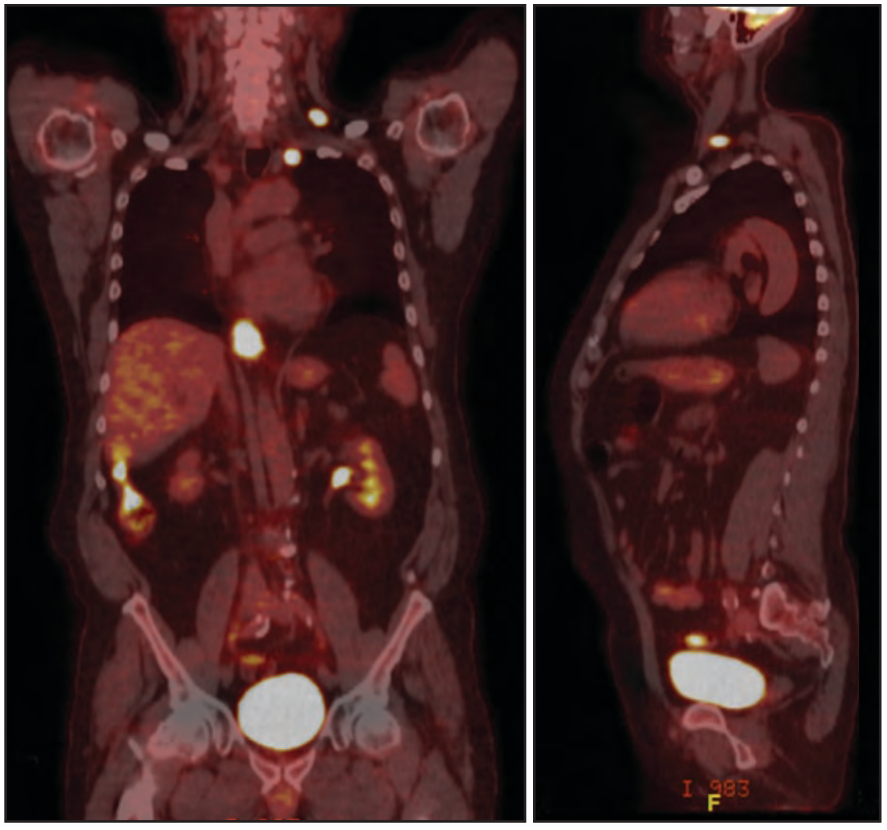

FIGURE 2. *PET/CT images showing a hypermetabolic left level 1L node and left supraclavicular node.*

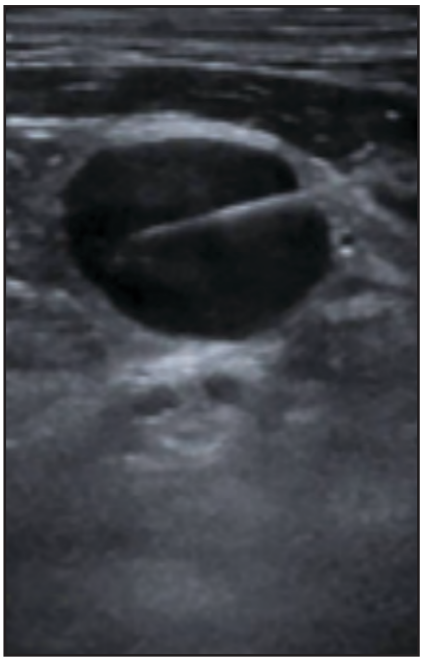

FIGURE 3. *Fine-needle aspiration (FNA) of the left supraclavicular lymph node confirming metastasis of primary esophageal adenocarcinoma.*

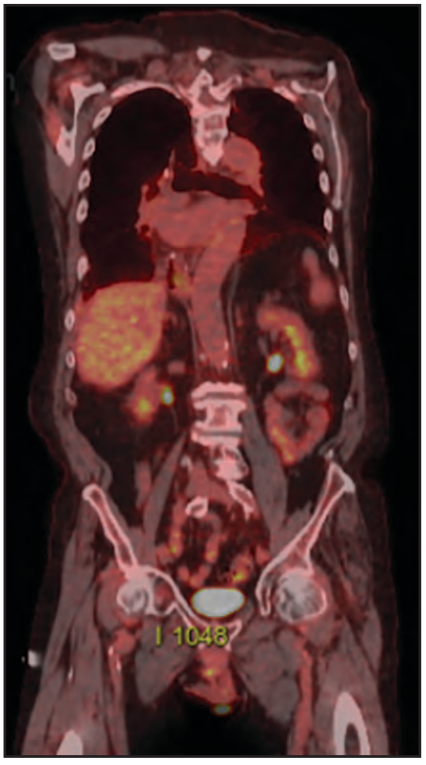

FIGURE 4. *The patient's imaging in November 2017 showed no evidence of disease.*

gastric, and celiac nodes. Standard-of-care treatment for these patients consisted of systemic therapy alone with palliative intent.

Although standard treatment was systemic therapy alone, the patient responded so well to cisplatin and irinotecan after 4 cycles that he proceeded to chemoradiation of both the esophageal primary and neck, completing therapy in October 2007. He received a dose of 50.4 Gy to both sites and treatment was delivered with concurrent capecitabine.

He continued to do well for the next 4 years, with resolution of his neck disease but persistent esophageal disease for which he received endoscopic mucosal resection, cryoablation and further chemotherapy with carboplatin and paclitaxel in conjunction with trastuzumab antibody therapy. Due to his prior excellent treatment response and stable disease, he was presented again to the tumor board for surgical consideration. By June 2011, the tumor board recommendation after localized GEJ disease only without further systemic progression was surgery, so the patient underwent an Ivor Lewis esophagectomy. Pathology showed a 1.2 cm poorly differentiated adenocarcinoma with tumor midpoint at the GEJ with 15 negative lymph nodes, pathologic stage T3N0.

It has now been 11 years since the diagnosis of stage IVB esophageal cancer and the patient remains without any clinical or imaging evidence of disease (**Figure 4**).

IMAGING FINDINGS

Initial staging CT of the chest, abdomen and pelvis did not show any evidence of metastatic disease. However, PET/CT demonstrated increased F-18 fluorodeoxyglucose (FDG) uptake in a left supraclavicular node and left level 1L node. Repeat PET/CT staging after chemoradiation showed resolution of hypermetabolic left supraclavicular and left superior mediastinal lymph nodes as well as a marked reduction in primary tumor size. The patient's subsequent imaging studies after esophagectomy, including a PET/CT in November 2017, were negative for disease.

DIAGNOSIS

Final pathology from the ultrasound-guided FNA of the left supraclavicular node was positive for adenocarcinoma, confirming metastasis of the distal esophageal primary tumor, thus placing the final diagnosis as M1b, Stage IVB (AJCC 6th edition).

DISCUSSION

After a CT scan of the chest/abdomen/pelvis determined no metastases, initial staging was confirmed by endoscopic ultrasound (EUS) and PET/CT scans. The most distinct role of FDG PET is to detect distant metastasis, as it is shown to be more accurate than CT scans.[4] In the classification system of metastasis by the AJCC 6th edition at the time the patient was treated, distant metastasis was divided into M1a and M1b based on the primary tumor location in the esophagus and whether the lymph nodes were considered regional.[3] In the case study, the primary tumor location was GEJ with the M1b classification by virtue of a distant left supraclavicular biopsy-proven lymph node.

There have been several important changes in the AJCC esophageal cancer staging guidelines since this patient completed treatment. The 7th and most recent 8th edition of AJCC staging guidelines have eliminated the M1a and M1b subcategories for esophageal cancer. Distant metastases are simply designated as M0, no distant metastasis, or M1, distant metastasis.[5] Additionally, changes leading up to the 8th edition include redefining cancers originating in the GEJ. While the 6th AJCC edition did not provide definitive anatomic details regarding the GEJ as the primary site, the 8th edition defined adenocarcinomas with epicenters no more than 2 cm into the gastric cardia as esophageal cancer, and those extending further as stomach cancer.[6] Additionally, the new 8th edition of the AJCC staging system now classifies the patient's 1L node as regional but the supraclavicular node would still be metastatic. These findings have implications for radiation therapy contouring delineation for esophageal cancer,[7] emphasizing the importance of the primary tumor location and extension into the stomach as well as the extent of regional vs. nonregional lymph node involvement.

Recent data suggests there may be an expanded role of local therapies in patients who have a favorable clinical response. In a study reported by Kaya et al, 101 patients at MD Anderson Cancer Center received consolidation local therapy for metastatic esophageal cancer with a 20% 5-year survival rate.[8] The majority of these patients (n = 71) had proximal tumors and 30 patients had distal tumors. Overall survival was highly associated with location, with a median survival of 22.8 months for proximal tumors vs. 41.5 months for more distal tumors (p = .03). This data suggests that further study of stage IV patients may be indicated to optimally select patients for this approach.

Over the past several decades, clinical guidelines have increasingly become an integral part of oncology practice. As outlined by the Institute of Medicine, clinical guidelines are "systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstance."[9] Clinical guidelines established upon evidence-based medicine improve the consistency of care and the quality of clinical decisions.[10] In certain

instances, however, there can be potential benefits to developing a treatment strategy tailored to a specific patient. This case exemplifies the opportunity and impact of a personalized approach to cancer care—one that deviates from established clinical pathways. Despite the initial metastatic diagnosis, the patient's excellent treatment response gave pause to the standard clinical treatment plan, which led to the consideration of curative surgery. By evaluating the full context of the patient's disease and response, an individualized approach produced an unexpected cure.

CONCLUSION

The role of multimodality local therapy inclusion for stage IV esophageal patients, particularly with distal tumor location, may be appropriate based on treatment response. Individualized variations to standardized treatment guidelines may apply to patients who have an excellent response to therapy, highlighting the potential for long-term cure.

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RADIATION ONCOLOGY CASE

Spinal leptomeningeal metastasis of sinonasal undifferentiated carcinoma

Yue Meng, BA; Keith Brunckhorst, MD; Christopher G. Filippi, MD; David J. Langer, MD; Anuj Goenka, MD; Sewit Teckie, MD

CASE SUMMARY

Sinonasal undifferentiated carcinoma (SNUC) is a rare malignancy arising from epithelial tissues in the nasal cavity or paranasal sinuses. Less than 300 cases have been reported in the literature worldwide.[1] The U.S. incidence of SNUC is 0.02 per 100,000, with male predominance. SNUC is a clinically distinct entity from other sinonasal tumors with neuroendocrine features. Five- and 10-year overall survival rates are 35% and 31%, respectively, and median survival is 22 months.[2] Although the survival rate of SNUC has improved with advances in surgery and radiation, it remains challenging to manage. Patients with SNUC present with nonspecific symptoms including epistaxis, visual disturbances, nasal obstruction, headache, and facial pain, contributing to the delay in diagnosis and poor prognosis of the disease.[3] Imaging studies often demonstrate extensive local invasive growth involving nasal cavity and ethmoid sinuses, with frequent spread into the orbit, calvarium, and anterior cranial fossa.[4]

Despite the proximity of the sinonasal tumor to the central nervous system (CNS), distant metastases and involvement of the spine or the cerebrospinal fluid (CSF) are infrequently reported. Isolated leptomeningeal recurrence in particular is virtually nonexistent. In patients with localized disease at diagnosis, only 1 case each of spinal involvement[5] and leptomeningeal carcinomatosis[6] as isolated delayed recurrences of SNUC have been reported. In a retrospective study of 23 patients treated for SNUC with radiation therapy (RT) with a median follow-up of 5 years, 5 patients ultimately developed distant metastases simultaneously with leptomeningeal recurrence.[7] The general incidence of leptomeningeal metastasis in cancers is rising and is thought to be due to (1) prolonged survival from improved supportive care and systemic therapy, (2) poor CNS penetration of targeted therapies, and (3) improved diagnostic imaging techniques.[8,9] Here, we present a case of leptomeningeal disease as the isolated recurrence in a patient treated for a locally advanced SNUC, with implications for post-treatment monitoring and management of leptomeningeal recurrence.

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PATIENT HISTORY

A 34-year-old African-American man presented to medical attention with progressive decreased sense of smell and bilateral vision deterioration for 2 to 3 months, and bifrontal headaches for 1 week. Imaging studies including computed tomography (CT) and magnetic resonance imaging (MRI) showed a mass involving the

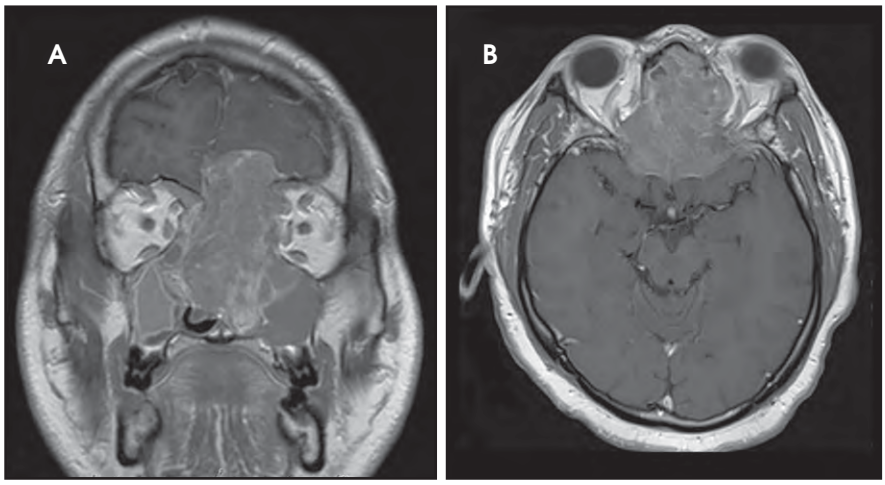

FIGURE 1. *Coronal (A) and axial (B) T1-weighted facial magnetic resonance (MR) images demonstrate a large mass lesion involving nasal cavity with intracranial extension superiorly and extensive involvement of the sphenoid sinuses and orbits bilaterally.*

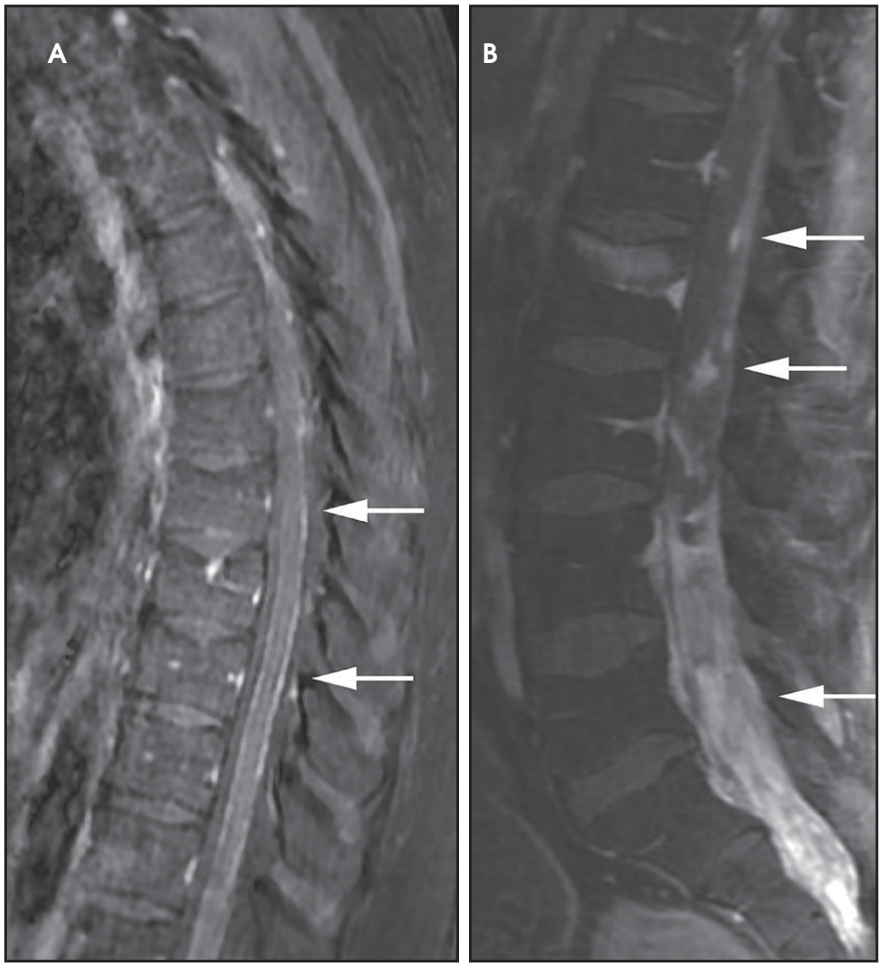

FIGURE 2. *Sagittal T1-weighted postcontrast MR images with fat suppression of the thoracic (A) and lumbar (B) spine demonstrate marked leptomeningeal carcinomatosis (arrows) with involvement of multiple bilateral foraminal and intrathecal nerve roots.*

nasal cavity with extension through the skull base into the anterior cranial fossa. There was involvement of the orbits medially with compression on the optic nerves, left more than right (**Figure 1**). Radiologic stage was T4bN0M0.

OPERATION, PATHOLOGICAL FINDINGS, AND ADJUVANT THERAPY

Intravenous steroids were started. The patient's vision quickly declined further and he underwent emergent subtotal resection of the tumor using anterior craniofacial approach and decompression of the orbits and optic nerves. Dural disease was also removed. Pathology confirmed sinonasal undifferentiated carcinoma originating in the left nasal cavity and involving brain tissue, without lymphovascular or perineural invasion. Postoperatively, the patient's left-sided vision improved and right-sided vision remained poor. Postoperative MRI of the head demonstrated residual tumor involving the lesser wing of the sphenoid bone bilaterally, the basisphenoid, left pterygopalatine fossa, nasopharynx and inferior turbinate. Two weeks after resection, the patient developed right visual loss due to optic nerve encasement and purulence within the epidural space, and a transnasal endoscopic drainage of an epidural abscess was performed.

One month after the initial subtotal resection, the patient began adjuvant RT to the tumor, paranasal sinuses, and neck using simultaneous integrated boost intensity-modulated radiation therapy (IMRT) to a total dose of 7020 cGy in 39 fractions with 5 cycles of concurrent weekly cisplatin and paclitaxel. The patient's course of treatment was complicated by weight loss and several CSF infections requiring neurosurgical intervention. After treatment, his right-sided vision improved. Follow-up MRI of the head did not

show any residual or recurrent disease. He then received 3 cycles of adjuvant cisplatin/etoposide over the course of 2 months. One month after completing adjuvant chemotherapy, the patient developed a nasal encephalocele, bilateral maxillary sinusitis, and frontal lobe radiation necrosis resulting in herniation of the left frontal lobe into the nasal cavity, for which maxillary antrostomy, nasal endoscopy with resection of nasal encephalocele, and reconstruction of the anterior skull base were performed. The patient then missed several follow-up appointments and planned imaging studies. MRI of the brain performed over 1 year after RT demonstrated stable appearance to the sinonasal bed with no evidence of disease, but did show worsening necrosis in the frontal and temporal lobes. He was treated with hyperbaric oxygen for radionecrosis.

INITIAL PRESENTATION OF LEPTOMENINGEAL CARCINOMATOSIS

Nine months after completing adjuvant chemotherapy, and 7 months following his final surgical reconstructive procedure, the patient began to develop lower back pain. The patient eventually developed significant difficulty walking, lower extremity neuropathic pain and numbness, constipation, and urinary retention. In the emergency department, he was nonambulatory and was diagnosed with cauda equina syndrome. MRI of the thoracic and lumbar spine demonstrated diffuse metastases in the spinal fluid of the thoracic, lumbar, and sacral regions, with particularly bulky involvement of the lumbar and sacral spinal canal (**Figure 2**). MRI of the cervical spine could not be completed due to patient intolerance. MRI of the brain demonstrated parenchymal volume loss and radiation necrosis, with decreasing cerebral edema.

TREATMENT FOR LEPTOMENINGEAL DISEASE

After considering treatment options and discussing his case in a multidisciplinary neuro-oncology tumor board, the patient began treatment with palliative RT in a staged manner. The patient first received treatments to the most symptomatic site, the lumbar and sacral canals, encompassing levels T12 to S4. Due to his poor performance status, he was treated to a dose of 2000 cGy in 5 fractions over 7 days. Treatment technique was 3-dimensional (3D) conformal with 6MV photons. After the second radiation fraction, the patient developed lethargy, tonic-clonic seizure and was found to have hydrocephalus. Levetiracetam was started and a surgical ventriculoperitoneal shunt was placed. The patient was then able to complete treatment.

RT to T12-S4 appeared to relieve some pain for the patient, and he continued to improve until he developed 2 episodes of status epilepticus for which he was intubated. Continuous audiovisual electroencephalograms (EEGs) demonstrated subclinical seizure-like activity suggestive of underlying skull defect and diffuse cerebral dysfunction, which was consistent with his history of bifrontal radiation necrosis. For his seizures, the patient was treated with a higher dose of levetiracetam and lacosamide, later titrated to phenytoin.

Other than an episode of laryngeal edema and spasm following extubation, the remainder of the patient's hospital course was unremarkable. He completed palliative RT to the T5 to T11 thoracic spine (2000 cGy in 5 fractions) over 5 days. Upon completion of radiation, which improved his pain, he was discharged from the hospital on anti-epileptics and a prednisone taper. He had been an inpatient for 39 days. He could not ambulate independently and was discharged in a wheelchair.

POST-HOSPITAL COURSE

The patient was discharged to a rehabilitation facility for several weeks. He was able to stand and transfer from his wheelchair and could walk a few steps with a walker, but did not regain the ability to walk unassisted. One month after RT to the thoracic spine, the patient began to experience bilateral shoulder and neck pain, right finger numbness, worsening numbness and neuropathic pain in both feet extending up the calves, as well as persistent and intractable hiccups. MRI of the total spine showed marked leptomeningeal disease of the cervical spine, and progression of leptomeningeal disease in the thoracolumbar spine.

The patient was referred to a radiation oncologist closer to his home so he could receive outpatient RT to the spinal levels C2 to T4 (1620 cGy in 9 fractions). Dose was reduced due to spinal cord dose delivered during prior head-and-neck RT.

The patient succumbed to disease progression 3-and-a-half months after completing initial palliative spine treatment, and 1 week after completing RT to the cervical spine.

DISCUSSION

Despite efforts to intensify treatment, a diagnosis of SNUC carries a poor prognosis with high post-treatment locoregional recurrence rates. Curative-intent treatment of SNUC typically involves multiple modalities that include surgery, radiation therapy, and chemotherapy.[7,10] Patients treated with modern RT, such as intensity-modulated radiation therapy (IMRT) and/or stereotactic radiosurgery (SRS), with radiation doses > 60 Gy showed both better rates of local control[11] and improved survival.[1]

SNUC is known to metastasize regionally to the cervical lymph nodes and distantly to the lung, bone, liver, and brain.[12,13] However, metastasis and involvement of the leptomeningeal system are rarely reported. Leptomeningeal carcinomatosis is a late event in the progression of solid tumors. Treatment options for leptomeningeal disease include RT, intrathecal chemotherapy, and systemic chemotherapy. RT can achieve rapid symptom control and restore CSF flow in 30% to 50% of patients with CSF circulation obstruction.[14] Our treatment strategy focused on palliative RT due to the diffuse and plaque-like nature of the leptomeningeal disease, which precludes adequate penetration of intrathecal and systemic chemotherapy. Despite the initial palliation achieved from RT, the patient developed recurrence in the previously treated spinal levels, which ultimately led to his death.

Systemic therapy has a limited role in metastatic SNUC. Therefore, next-generation sequencing was performed on this patient's tumor to identify an actionable genetic alteration that could be treated with biologically tailored therapy. We identified amplifications of ERBB2 and KRAS, and thus planned to use cetuximab following RT. Unfortunately, the patient's poor functional status prevented him from receiving systemic therapy. Little data exists regarding the role of genomic findings on pathogenesis and metastasis of SNUC. Further research is required to identify the optimal systemic agents for SNUC.

In conclusion, this case report presents a rare case of leptomeningeal carcinomatosis that developed as the only recurrence in a patient with SNUC where local control of the primary lesion was achieved with a combination of surgery, radiation, and chemotherapy. We hope to draw attention to the rare and highly lethal occurrence of leptomeningeal disease in SNUC. We suggest that patients diagnosed with SNUC undergo regular close surveillance for evidence of metastasis. It may be helpful to alert patients to the possibility of CNS involvement to prevent delay in seeking treatment once symptoms occur. Lastly, while a multimodality treatment approach is accepted as standard of care in treating primary SNUC, there remains a need to discover more effective treatments of advanced or metastatic disease.

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Trends, trials and developments in radiation therapy for esophageal cancer

Mary Beth Massat

Although only 1% of cancers diagnosed in the United States are esophageal cancer, patients with this disease often face a poor prognosis. According to the American Cancer Society, approximately 20% of patients survive more than 5 years after diagnosis.[1]

Of the 2 major types of esophagus cancer—squamous cell and adenocarcinoma—the former has historically accounted for 75% of esophageal cancers in the United States, with incidence rates for esophageal adenocarcinoma on the rise. One study reports average annual percentage increases of 6.1% in men and 5.9% in women.[2]

Outside of the United States, esophageal cancer is more prevalent, with the highest incidence rates in Asia and Africa. The World Cancer Research Fund International reports that about 81% of esophageal cancer cases occur in less developed countries.[3]

"In the U.S. where new technology is quickly adopted, esophageal cancer is not very common, so we have a limitation in conducting trials—accruing patients and collecting data," says Michael Rutenberg, MD, PhD, assistant professor in the Department of Radiation Oncology at the University of Florida Proton Therapy Institute. This presents a troubling dichotomy: Advanced technology that could benefit most esophageal cancer patients is not available where incidence rates are highest.

"Landmark studies for esophageal cancer only come every few decades, so there are no landmark studies to support novel technology such as proton therapy," Dr. Rutenberg says. "When we moved from the 3D conformal radiotherapy [3DCRT] era to the [intensity-modulated radiation therapy] IMRT era, the best support for the new technology came not from prospective trials, but from large retrospective cohort comparisons."

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Surgery vs. Radiation

One 1992 landmark study by Herskovic et al, however, changed the role of using radiation therapy (RT) for treating esophageal cancer.[4] "Prior to this study, it was believed that the only curative therapy for esophageal cancer was surgery," says Michael G. Haddock, MD, professor of radiation oncology, Mayo Clinic College of Medicine, and a consultant and chair of the Clinical Practice Committee, Department of Radiation Oncology. At that time, RT was a 2-dimensional treatment—anterior-posterior/posterior-anterior (AP/PA) with lateral and oblique fields that gave adequate dose to the tumor but high doses to the heart and lungs. Today, radiation therapy is indicated for patients with locally advanced esophageal cancer that has penetrated the muscular lining or when regional lymph nodes are involved. It may also be indicated for palliative care in metastatic cancer cases. For many patients, treatment involves a trimodality approach of chemotherapy, radiation, and surgery.

Yet, in cases of locally advanced esophageal cancer, the issue remains when, or if, the patient should undergo surgery. "It is a question of whether there is a pathological complete response to radiation and chemotherapy," Dr. Haddock explains, noting that only about 25 percent of patients who undergo radiation and chemotherapy without surgery are cured. "There is no reliable test to definitively indicate complete response short of surgical resection. We can put off surgery until there is progression of the disease, but then complications increase."

While local control improves with the addition of resection, survival is

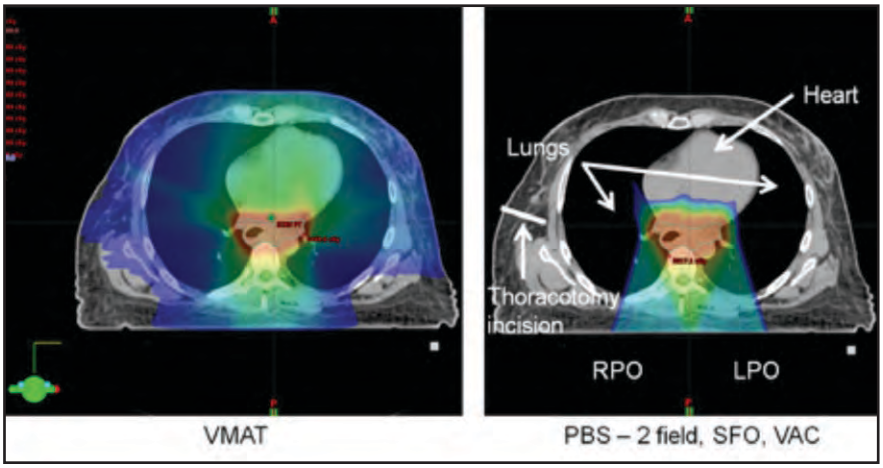

FIGURE 1. *A 5-Gy dose cloud for a volumetric-modulated arc therapy (VMAT) plan vs. a pencil-beam scanning (PBS) proton plan. Images courtesy of Dr. Michael Haddock, Mayo Clinic*

less certain, says Dr. Haddock. Additionally, some patients with early stage disease show excellent survival following radiation and chemotherapy without resection.

While surgery remains under debate, confusion regarding use of preoperative radiation has been lifted, says Dr. Rutenberg. "The CROSS [ChemoRadiotherapy for Oesophageal cancer followed by Surgery Study] Trial is perhaps the most important study for esophageal cancer treatment in the last 10-plus years," he says. "While it doesn't support any single type of equipment or technology, it solidly ended the debate on the importance of pre-operative radiation in the management of esophageal cancers."

Motion Issues and Organ Sparing

The standard of care also involves accounting for motion. At MD Anderson Cancer Center, Stephen G. Chun, MD, assistant professor, Department of Radiation Oncology, Division of Radiation Oncology, uses a 4-dimensional (4D) respiratory-gated scan to account for motion in treatment planning. He also uses deep-inspiration breath holds when appropriate.

As technology has evolved, so have treatments. RT for esophageal cancer migrated to more advanced techniques such as 3DCRT followed by IMRT. In 2017, a large single-institution cohort study conducted at MD Anderson Cancer Center on the long-term outcomes of treatment with IMRT for esophageal cancer found that IMRT improved organ-sparing effects, demonstrating excellent toxicity and survival outcomes compared with 3DCRT. The authors concluded that IMRT should be considered for photon-based treatments.[5]

"With IMRT, there is the ability to achieve dramatically better sparing of radiation doses to the heart and lungs compared with 3D techniques," says Dr. Chun. "With volumetric arc IMRT [VMAT], we are able to get very good plans with substantially shorter treatments than static beam arrangements."

Whether a site uses IMRT or VMAT largely depends on the treatment plan. Dr. Rutenberg often starts with a VMAT plan for esophageal cancers; however, he also evaluates an IMRT plan and selects what's best for individual patients. "We can now focus on the nuances of radiation therapy and perhaps focus on quality of life and reduction in complications," he says. "However, what we do in radiation therapy is contingent on systemic disease control to help improve long-term patient outcomes."

The key consideration in any radiation plan is avoiding critical structures, adds Dr. Haddock. "Recent studies suggest that the outcomes for cancers in the mediastinum are tied to heart and lung dose," he says. "Lower doses to the heart and lung are associated with increased survival, suggesting that the techniques that spare the heart and lung are beneficial."

Proton Therapy

As for the role of proton therapy for treating esophageal cancer, MD Anderson was the first institution to prospectively compare proton therapy with IMRT for stage III or locally advanced esophageal cancer. A 2012 study found few severe toxicities with encouraging pathologic response and clinical outcomes at 20-month follow-up with proton therapy.[6]

"Proton therapy has the ability to further reduce dose to heart and lungs, and that might provide additional benefit for patients," notes Dr. Chun, who has enrolled patients in the randomized phase II trial (open as of press time) comparing IMRT and protons for esophageal cancer,

Both Drs. Haddock and Rutenberg also agree that proton therapy shows promise in treating esophageal cancer and, in particular, sparing the heart and lung (**Figure 1**). "Protons will have a really important role in future treatments," says Dr. Rutenberg, noting that the University of Florida Proton Therapy Institute has treated roughly 20 esophageal cancer patients with protons. While patient volumes are limited due to lack of third-party payor reimbursement for proton therapy, this could change as results from clinical trials emerge. For instance, a 3-site study by the Mayo Clinic, MD Anderson and the University of Maryland that retrospectively compared 3D conformal therapy, IMRT and proton therapy found decreased pulmonary, cardiac and wound complications in patients treated with advanced techniques.[7] Additionally, a randomized study comparing IMRT to

proton therapy is expected to open for enrollment through the NRG Oncology cooperative group later this year, notes Dr. Haddock.

"Of all the disease sites where protons might benefit patients by sparing the heart and lungs, esophageal cancer is on the top of that list," he says.

Related Issues and Considerations

Several additional hot-button issues surround RT for esophageal cancer, including treating cancers in the lower esophagus, known as the gastroesophageal junction. The European standard of care is perioperative chemotherapy—chemotherapy before and after surgery—while the U.S. standard is chemoradiation before surgery.

"These 2 treatment paradigms haven't been compared head to head for esophageal cancer," Dr. Chun explains. "Although the CRITICS [ChemoRadiotherapy after Induction Chemotherapy in Cancer of the Stomach] trial in Europe compared perioperative chemotherapy against adjuvant chemoradiotherapy after surgery, this was mostly for gastric cancer. This is an area that could potentially be studied further in esophageal cancer."

In the CRITICS trial, the authors reported that overall survival was not improved with postoperative chemoradiotherapy compared with postoperative chemotherapy when patients received adequate preoperative chemotherapy and surgery. They suggest that future studies evaluate preoperative treatments.[8]

Oligometastatic disease, an intermediate state of metastasis between localized disease and widespread metastasis, is another concern. The disease was first proposed in 1995 by University of Chicago Medicine physicians Samuel Hellman, MD, FASCO, and Ralph R. Weichselbaum, MD. They hypothesized that some patients in this intermediate state could respond to a curative therapeutic strategy by treating limited metastatic sites with surgery or radiation. They confirmed their hypothesis in a study on oligometastatic colorectal cancer published in May 2018.[9]

Genetics may also factor in to esophageal cancer treatment, as a small percentage of patients with esophageal cancer have the HER-2 gene receptor, the same gene found in some aggressive forms of breast cancer, says Dr. Chun, "We can potentially use a genetic test for the HER-2 receptor, especially in patients with metastatic disease, and if positive, they could be targeted with Herceptin or other treatment drugs," he adds.

While outcomes are not great for locally advanced esophageal cancers, some studies are examining immunotherapy and checkpoint inhibitors in combination with radiation therapy with promising response rates, says Dr. Chun.

"I'm hopeful that immunotherapy can be incorporated if it is shown to improve patient outcomes to move the ball forward for this increasingly common cancer," he says.

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