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SA-CME CREDIT

Multimodality management of colorectal liver oligometastasis
SR Campbell, EH Balagamwala, NM Woody, KL Stephans, Cleveland Clinic, OH

Proton therapy for colorectal cancer
SA Alex, Baylor College of Medicine, Houston, TX; ED Brooks, EB Holliday, MD Anderson Cancer Center, Houston, TX

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MB Massat

Radiation Oncology Case
Substituting SBRT boost for brachytherapy using Mayo protocol for peri-hilar cholangiocarcinoma

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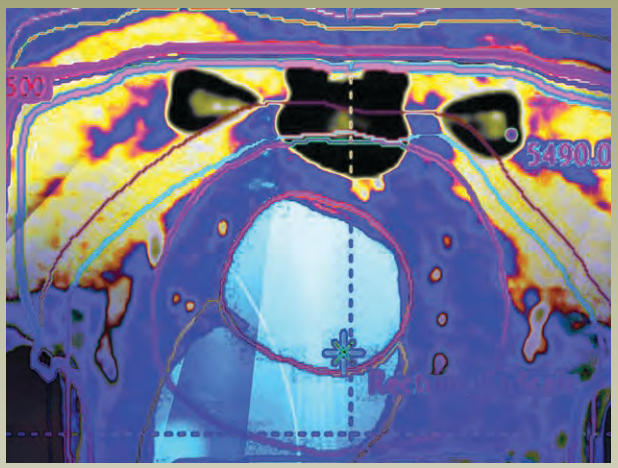

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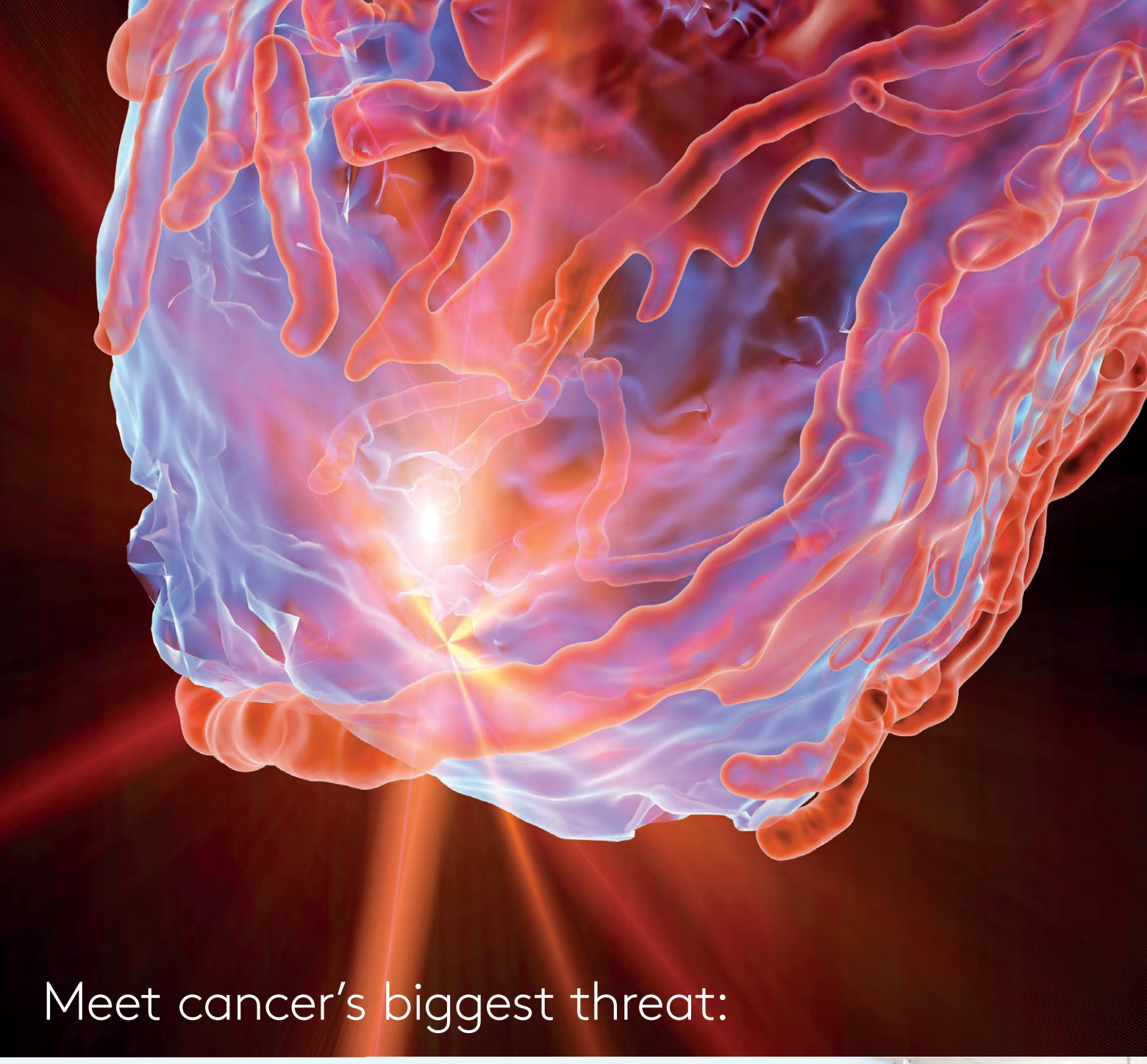

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EDITORIAL

Colorectal cancer: Pathways to optimized care

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

Welcome to the September issue of *ARO!* This month's focus centers on colorectal cancer, the third leading cause of cancer-related deaths in the US for men and women and the second most common cause when genders are combined. Fortunately, the death rate overall has been receding for decades thanks to screening efforts and improved treatments. But among those younger than 55, deaths from colorectal cancer have steadily increased 1% per year from 2007-2016.[1]

In the SA-CME review article, *Proton therapy for colorectal cancer,* authors examine clinical and dosimetric data and describe how this radiation therapy technique has the potential to improve treatment by lowering toxicity in locally advanced rectal cancer. This well-written and comprehensive update further explores the rationale for protons, as well as outcomes, limitations, and exciting future directions.

Since 25% of patients with colorectal cancer are metastatic at diagnosis, with liver the most common site, we are pleased to also feature another SA-CME article, *Multimodality management of colorectal liver oligometastases*. This detailed review describes modern treatment approaches for low-volume liver metastases that may complement multi-agent systemic therapy, as well as indications for focal therapies. At the end of the article, a compelling case of a patient with stage IVA rectal cancer who demonstrated a complete response following stereotactic body radiation therapy (SBRT) is discussed.

An additional case report, *Substituting SBRT boost for brachytherapy using Mayo protocol for peri-hilar cholangiocarcinoma,* offers an interesting and important example for patients who cannot undergo brachytherapy for this bile duct cancer due to anatomical constraints or for centers lacking access or expertise to brachytherapy.

Rounding out the theme is the Technology Trends article, *IMRT, VMAT and image guidance: Changing the landscape of colorectal cancer treatment*. Experts discuss the shift from 3-dimensional conformal RT (3DCRT) to intensity-modulated radiation therapy (IMRT) in colorectal cancer, along with personalized care, reimbursement and recent trials.

We are also pleased to provide an SA-CME review on chemoradiation treatment for glioblastoma multiforme, a research paper exploring radiation dose and overall survival in ependymoma, a case report that helps expand the literature on the abscopal effect with malignant melanoma, and the Resident Voice editorial that shares intriguing journeys to and wise advice for a career in radiation oncology.

We hope you enjoy this issue and look forward to seeing you at the ASTRO 2019 conference in Chicago this month to further your education, network, and growth in radiation oncology. Safe travels to the Windy City, and best wishes for a terrific meeting!

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

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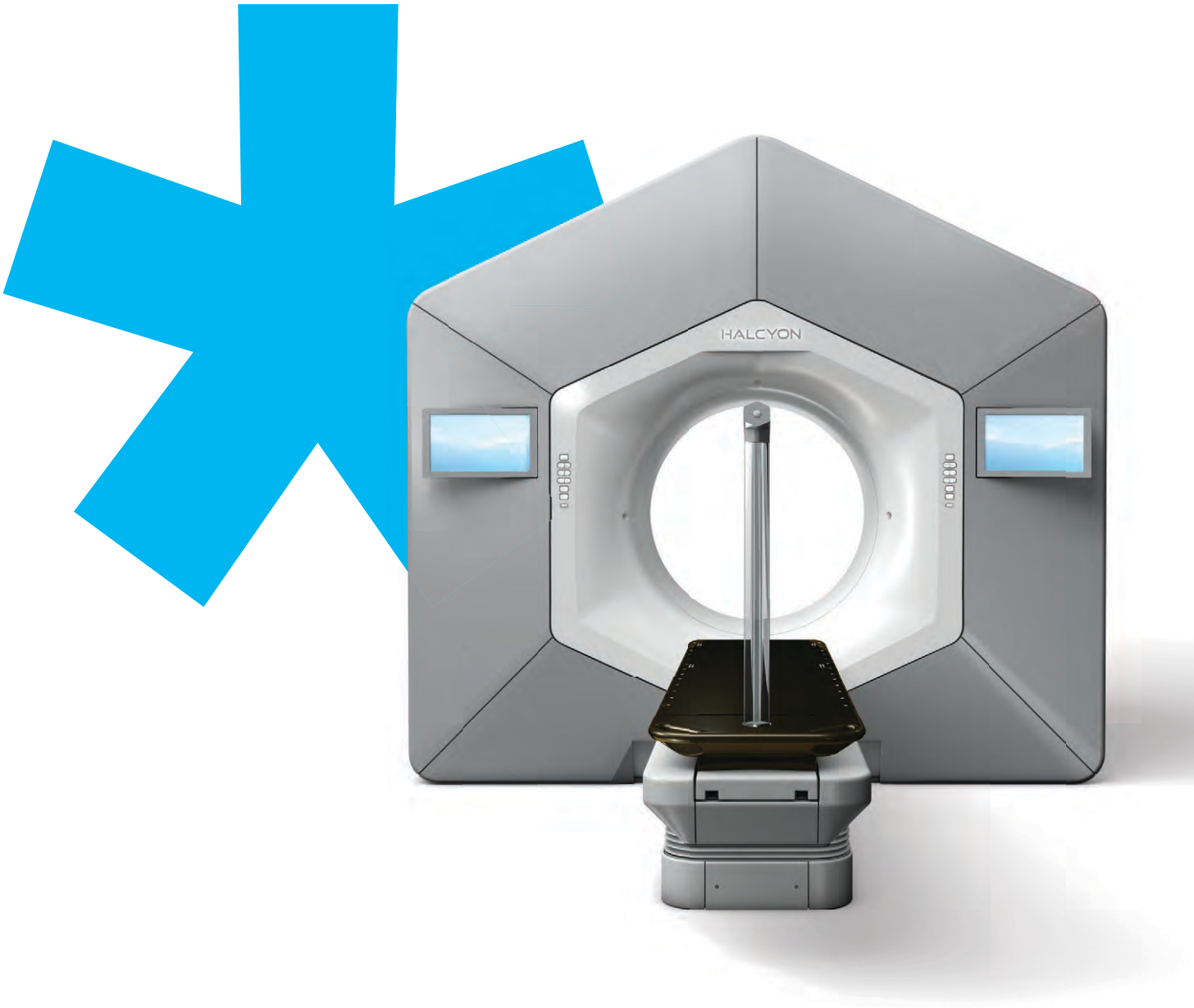

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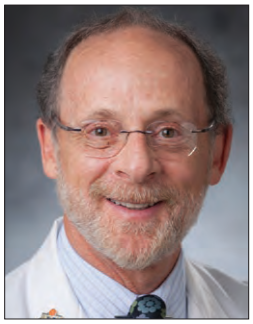
RESIDENT VOICE

Journeys to radiation oncology

Anna M. Laucis, MD, MPhil

Anna M. Laucis, MD, MPhil



David Brizel, MD

Caitlin Schonewolf, MD

Radiation oncology is an amazing field with opportunities to foster meaningful patient relationships and professional collaborations. I have had the privilege to learn from many incredible mentors and was curious about their paths to radiation oncology. David Brizel, MD, a Leonard Prosnitz professor of radiation oncology at Duke University, and Caitlin Schonewolf, MD, assistant professor of radiation oncology at the University of Michigan, graciously took time to reflect on their journeys to this awesome specialty.

AL: What led you to consider a career in radiation oncology?

DB: This question really starts with Question 0, which is how did I find out about the field? My father is a retired radiation oncologist, so as a kid I have various memories of going to the radiation center at the University of Louisville with my father and seeing the equipment. The machines were massive. I didn't know what a tumor was but knew these were machines that my dad used to treat patients. One of them was one of the first isocentric cobalt machines, and it needed a trap door to open when it rotated to the PA (posterioanterior) position so it wouldn't slam into the floor. That was really cool to see. The other machine was a betatron. The betatron was massive and suspended from the ceiling. It was a fixed unit and patients were positioned by moving them on their stretchers beneath the treatment cone. That machine was totally impressive.

As I grew older, I knew he used radiation to treat cancer. It wasn't foreign to me. I knew it was out there as a career possibility. Nevertheless, in medical school, my dad didn't push me toward any particular specialty. I loved surgery, absolutely loved surgery, and I also liked oncology. So for some time, I thought about being a surgical oncologist.

Then toward the end of my third year, I was home for spring break. It was near the end of my vacation, in March/April of 1982. My father was involved in a symposium on the management of early stage breast cancer. Lumpectomy plus radiation therapy (RT) was a relatively new and controversial treatment. David Kinney from Memorial Sloan Kettering was advocating mastectomy and debating Jay Harris from Harvard, who was advocating lumpectomy plus RT. I went to the debate, was introduced to Jay Harris, and was invited to do a 4th-year rotation at the Joint Center for Radiation Therapy. So I went. I met many of the luminaries in our field, several of whom have gone on to win the ASTRO Gold Medal.

While at Harvard, I was impressed with the evidence-based approach of the program. I remember cases being presented and analyzed in an intellectually rigorous

Dr. Laucis *is a resident physician in the Department of Radiation Oncology, University of Michigan, Ann Arbor.*

way with emphasis on the Socratic method. The focus was on "What are the issues" and "What are the data?" It was the first time in medical school that I had experienced this type of competitive challenge. I subsequently chose to go into radiation oncology. I liked seeing patients and there were plentiful opportunities for integrating them into research. I liked that it taught me how to think, to develop a set of tools to solve problems.

CS: I always had an interest in oncology, but I didn't consider radiation oncology until the end of my second year of medical school when I was paired with a radiation oncologist for our patient-centered medicine course. His rapport with patients, compassion, and depth of knowledge exemplified the type of doctor I wanted to become. I worked closely with him, not only to learn the mandatory H&P (history and physical) skills through the course, but also to explore radiation oncology. I enjoyed the clinic, learning about the technology and interacting with each part of the radiation team (therapy, physics, dosimetry, etc). I also enjoyed the translational research projects I was involved with in the lab, seeing the connection between radiation biology and the clinic. Through these interactions, I realized that radiation oncology was the right fit for me.

AL: What do you like the most about being a radiation oncologist?

DB: I like that it's a field that has evolved throughout my career. It's never the same job two days in a row. It provides the ability to be intellectually and emotionally fulfilling. The clinical and research challenges provide numerous opportunities to meaningfully improve patients' lives.

CS: The part I love most about being a radiation oncologist is the relationship I am able to have with my patients. Our field is unique in that we see patients for consultation and then at least once a week during treatment, which can be several weeks long. This allows an intense doctor-patient relationship to form. I think there is great satisfaction in developing a close relationship with patients and being able to have an impact on the patient, whether it is to cure or to help alleviate symptoms with radiation treatment.

AL: What advice do you have for students considering a career in radiation oncology?

DB: At your medical school, if there is an opportunity to spend time in the radiation oncology department during core clerkships, then do a rotation. Approach the program director and ask about opportunities to shadow. If there is time in medical school for blocked research, find a way to do research in radiation biology or other radiation sciences. It is also important to spend time gaining exposure to the oncologic disciplines. Radiation oncology also requires an understanding of both medical and surgical oncology. It is a hands-on field like surgery that requires an in-depth knowledge of anatomy. It's not just the knowledge but also the meticulous attention to technique that matters. We also understand and exploit cancer biology, which has traditionally and mistakenly been considered in the purview of medical oncology. Acquiring an understanding of the roles of the different oncologic disciplines can help with deciding whether radiation oncology aligns most with your interests.

CS: Radiation oncology is a wonderful field of medicine that brings together technology, imaging, and human connection through cancer care. If you are considering a career in radiation oncology, I would encourage you to get involved in all aspects of radiation treatment in the clinic and through research to make sure it's a good fit for you. When you come across a physician who exemplifies the type of doctor you want to be, work closely with that person to develop a good mentoring relationship and help guide your career path in radiation oncology.

SA–CME Information

MULTIMODALITY MANAGEMENT OF COLORECTAL LIVER OLIGOMETASTASIS

Description

Authors examine modern treatment approaches to limited liver metastases from colorectal cancer, discussing the intent and sequencing of treatment, chemotherapy, surgical resection, radiofrequency ablation/cryoablation, chemoembolization, radioembolization, external-beam radiation therapy, stereotactic body radiation therapy (SBRT), and proton therapy and the indication for each modality. The review also describes circumstances in which SBRT is preferred over other liver-directed therapies.

Learning Objectives

After completing this activity, participants will be able to:

1. Apply the most common indications for transarterial radioembolization in the treatment of colorectal liver metastases.
2. Apply the most common indications for SBRT in the treatment of colorectal liver metastases.
3. Adopt appropriate normal tissue dose constraints for safe liver SBRT treatment plans.

Authors

Shauna R. Campbell, DO, *is a resident physician,* ***Ehsan H. Balagamwala, MD,*** *is an attending physician,* ***Neil M. Woody, MD, MS****, is a staff physician, and* ***Kevin L. Stephans, MD,*** *is a staff physician, Department of Radiation Oncology, Cleveland Clinic.*

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SA-CME (see page 8)

Multimodality management of colorectal liver oligometastases

Shauna R. Campbell, DO; Ehsan H. Balagamwala, MD; Neil M. Woody, MD, MS; Kevin L. Stephans, MD

Colorectal cancer (CRC) represents the second-leading cause of cancer-related mortality in the United States.[1] Due to drainage of the majority of intestinal mesentery through the hepatic portal venous system, metastases to the liver are the most common site of spread of CRC. While many patients present with widespread or extra-hepatic metastases, a subset of patients with limited liver metastases (LM) have been reported to experience high rates of long-term survival, and even cure, after liver resection.[2-5] In a series of patients with CRC from the British Columbia Cancer Agency, 46% of those with metastatic disease presented with liver-only metastases, 38% of these had 1-3 sites of disease, and resected patients had the highest rates of survival.[6] Patients with limited metastatic disease in which long-term control or even cure may be achievable are regarded as oligometastatic. The definition of oligometastatic is continually evolving, but typically refers to patients with 1-3, or 1-5 metastases.[7] While larger-scale randomized trials are ongoing, exploratory studies have suggested the potential for improved survival with local therapy directed at oligometastatic CRC.[8,9] Herein we review the treatment options for patients with oligometastatic CRC LM.

Treatment

Intent and Sequencing

A critical first step in managing patients with oligometastatic CRC is to define the intent of treatment: determining those patients who may have a chance for long-term control or cure and those whose quality of life would best be served by palliation. Either approach requires a multidisciplinary approach to sequence management of the primary tumor, metastases, and chemotherapy. Considerations include age, comorbidities, performance status, presence of symptoms from the primary tumor, extent and distribution of disease, and resectability of metastatic lesions. If the primary tumor is symptomatic, it is typically addressed first to limit risk of complications. Patients with asymptomatic primary tumor and limited LM may undergo simultaneous resection followed by adjuvant chemotherapy. Patients with asymptomatic primary tumor and extensive LM require systemic therapy first. Multi-agent fluorouracil (5-FU) based chemotherapy is first line; however, oxaliplatin (FOLFOX) and irinotecan (FOLFIRI) regimens may increase the risk of steatohepatitis and noncirrhotic portal hypertension when given preoperatively.[10,11] A randomized trial of perioperative chemotherapy vs surgery alone demonstrated increased perioperative complications in the chemotherapy group (25% vs 16%, p = 0.04); however, there was no difference in operative mortality, and perioperative chemotherapy was associated with a sustained benefit in progression-free survival (PFS) (median 20.9 months vs 12.5 months for eligible patients, p = 0.035).[12] Although there is no proven impact on overall survival (OS), many centers favor neoadjuvant chemotherapy as an assessment of biologic

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behavior and *in vivo* chemosensitivity, improving surgical selection and PFS. While randomized trials do not demonstrate an OS benefit to adjuvant chemotherapy after hepatic resection, patients with LM are likely to have unresected micrometastatic disease. Therefore, society guidelines, including the National Comprehensive Cancer Network, suggest 6 months of FOLFOX-based chemotherapy.[13]

Chemotherapy

While there is no universally accepted first-line chemotherapy regimen, the 5-FU-based multi-agent regimens (FOLFOX and FOLFIRI) achieve the most promising response rates in chemotherapy-naive patients.[14] The administration of these regimens depends on patient tolerability and frequently require dose reductions and/or early discontinuation secondary to toxicity.

The addition of bevacizumab to 5-FU-based multi-agent chemotherapy demonstrates modest improvement in OS and PFS across all clinically relevant subgroups, albeit at the cost of a 10% absolute increase in grade ≥ 3 toxicity.[15] Cetuximab or panitumumab may be added for patients with left-sided tumors that are RAS and BRAF wild-type, but should not be combined with bevacizumab. CRC is not generally sensitive to immunotherapy; however, patients with mutations in DNA mismatch repair genes (< 5% of all metastatic CRCs) have exhibited high response rates to pembrolizumab and nivolimab with or without ipilimumab.[16]

For patients who do not progress, the optimal duration of first-line chemotherapy is not established. Several randomized trials have compared pre-defined regimens vs maintenance chemotherapy, and none have demonstrated a clear difference in survival. These trials are heterogeneous, varying in the re-introduction of active agents at time of progression, which limits the ability to reach definitive conclusions.[17-20] Importantly, the data clearly demonstrate that 5-FU, irinotecan, and oxaliplatin are the most active chemotherapy agents and should be given to all patients, whether it be concurrently or sequentially, and with or without maintenance. These regimens appear to have lower rates of cross-resistance, and patients offered all available agents during their disease course appear to have improved outcomes.[21]

The genetic profile of CRC is an important characteristic established at diagnosis, but there can be a discordance of genetic expression between the primary tumor and metastatic sites. In a novel gene expression analysis of both primary and metastatic CRC, investigators demonstrated that molecular signals that stratify for outcome in primary CRC were of limited prognostic utility in the subset of patients with resected CRC LM. Based on surgical pathology, investigators identified molecular signals risk stratifying patients into low-, intermediate-, and high-risk groups with relative 10-year OS rates of 94%, 45%, and 19%, respectively.[22] Similarly, in a broader group of patients with CRC metastases to multiple sites, a multigene radiation sensitivity index score (RSI) suggested slightly greater radiation resistance in metastatic sites compared to CRC primary tumors, with the highest median resistance scores found in ovary, abdominal, and liver metastases.[23] Molecular risk profiling of both primary and metastatic sites, in combination with other known prognostic features, likely reflects the future of individualized therapy.

To summarize the current systemic therapy guidelines, a 5-FU-based, multi-agent therapy remains the backbone of treatment for patients with metastatic CRC, regardless of the mutational status or metastatic burden. Newly diagnosed patients should be started on FOLFOX or FOLFIRI, with the addition of a monoclonal antibody based on mutational status. Given low rates of cross-resistance, patients should be offered second-line chemotherapy at progression. For the small percentage of patients with DNA mismatch repair mutations, treatment with immunotherapy is the preferred second-line treatment after progression on standard first-line therapy.

Surgical Resection

Surgical resection is the standard of care for low-volume CRC LM. Surgery has the largest body of evidence demonstrating long-term survival, although only 20% to 30% of metastatic patients are resectable at diagnosis.[2-5] A limited group of patients, unresectable at presentation, may become surgical candidates following a favorable response to chemotherapy. This is known as down-staging, and patients who undergo resection after down-staging have similar outcomes to patients who are resectable at diagnosis.[24] In select cases, surgical resection for bilateral liver involvement can be achieved with partial right and left hepatectomies. During surgical planning, if the expected liver remnant is not expected to be of sufficient volume, portal vein embolization may be performed. Embolization should prompt hypertrophy of the perfused liver and, if the remaining liver grows to an adequate volume, resection is feasible.[25]

Overall, for the high-performing patient with low-volume CRC LM, the standard of care is surgical resection of LM. This can be preceded by chemotherapy and/or portal vein embolization in cases appropriate for down-staging. For most patients who are not surgical candidates, other liver-directed therapies have emerged.

Radiofrequency and Cryoablation

For unresectable CRC LM, minimally invasive ablation techniques for LM treatment include radiofrequency ablation (RFA), microwave ablation, and cryoablation. The prospective EORTC 4004 phase II trial randomized 119

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Table 1. Indications for Focal Therapies in Unresectable CRC LM

Table 1	SBRT	TACE[50] and ^{90}Y	RFA[51-55]
Indications	- small to medium size well-defined tumor - tumor abutting vasculature - portal vein involvement - tumor in dome of liver - not accessible by other modalities	- higher burden of disease involving segment or lobe - limited portal vein involvement (^{90}Y)	- small (≤ 3 cm) well-defined tumor - peripheral location accessible via percutaneous or surgical approach
Contraindications (not limited to)	- decompensated liver failure - diffuse disease - adjacent stomach or bowel limiting dose required for local control	- decompensated liver failure - > 50% liver replacement by tumor - inability to undergo arteriography - inability to isolate arterial blood supply - > 20% lung shunt - reflux to unaffected gastrointestinal organs - main portal vein thrombosis - unmanageable coagulopathy	- decompensated liver failure - diffuse disease - < 1 cm from bile duct - intrahepatic bile duct dilation - anterior exophytic tumor - major vessel invasion - unmanageable coagulopathy

Key: CRC LM = colorectal cancer liver metastases, SBRT = stereotactic body radiation therapy, TACE = transarterial chemoembolization, RFA = radiofrequency ablation

patients with unresectable CRC LM (< 10 LM and no extrahepatic disease) to systemic therapy alone (FOLFOX and bevacizumab) vs systemic therapy and RFA (+/- resection).[9] The majority (73.3%) of patients had ≤ 5 metastases. After a median follow-up of 9.7 years, 10% of patients were alive in the systemic therapy arm and 35% in the combined modality arm. The combined modality arm demonstrated improved OS (HR 0.58, p = 0.01), median OS (45.6 months vs 40.5 months), and PFS (16.8 months vs 9.9 months, p = 0.005) compared to systemic therapy alone. Local progression occurred in 11 out of 170 RFA-treated lesions (6.5%), although the median tumor size was not reported. Postoperative complications included infection (13.3%), fever (16.7%), and hospitalization > 24 hours (13.3%). This study lends strong support to aggressive local control via ablation in CRC patients with limited LM. Contraindications to RFA are discussed in **Table 1**.

Ablation techniques should be considered when the number of peripheral LM is limited and preferably ≤ 3 cm. Tumors abutting or involving a bile duct should not be treated with ablation due to a high risk of biliary complications. Ablation technique selection is often institution and expertise dependent, but there are considerations for each. In thermal ablation, microwave is a newer technology than RFA, tends to be faster, can treat a larger area, and is less sensitive to the "heat sink" effect. This means microwave ablation will be more effective than RFA for larger tumors or those abutting vasculature. Cryoablation is more time intensive than thermal techniques, but visualization of the "ice ball" during freezing permits close monitoring of the ablation zone, which is not possible with RFA or microwave ablation.

Chemoembolization and Radioembolization

LM receive most of their blood supply from the hepatic artery. Transarterial chemoembolization (TACE) delivers a high local concentration of chemotherapy while reducing blood supply to LM via direct embolization of the hepatic artery. Transarterial radioembolization (TARE) delivers radioactive microspheres filled with yttrium 90 (^{90}Y). In both techniques, normal tissue is relatively spared because of preserved portal vein blood supply. A randomized trial compared FOLFIRI to FOLFIRI with TACE in 74 patients who had progressed on second- or third-line chemotherapy. The addition of TACE improved response, OS, and increased time to extra-hepatic progression compared with FOLFIRI.[26] As one would not expect a systemic effect after TACE, explaining improved extra-hepatic control is challenging. It is unclear if this suggests a benefit to treating local disease, or potentially reflects an imbalance in this small randomized trial given unexpected differences in extra-hepatic progression.

Multiple randomized trials have demonstrated the safety and efficacy of ^{90}Y with systemic therapy in patients with LM. A phase III trial compared 5-FU alone vs ^{90}Y with 5-FU in unresectable, chemotherapy-refractory, liver-only metastases. Time to liver progression was improved (2.1 months vs 5.5 months, p = 0.003), but there was no difference in OS.[27]

Subsequently, 3 randomized phase III trials evaluated the addition of ^{90}Y to first-line chemotherapy for patients with liver-only or liver-dominant metastatic CRC. These studies, known as FOXFIRE, SIRFLOX, and FOXFIRE-Global, were published in a combined analysis of 1103 patients

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Table 2. Liver SBRT Series

Table 2	Number of Patients and LM	Radiation Dose	Local Control	Acute Toxicity
Hoyer et al[32] (Phase II)	44 pts UNK LM	45 Gy in 3 fx	2 yr 79%	2 grade 2 GI ulceration 1 grade 3 GI ulceration 1 grade 5 hepatic failure
Rusthoven et al[33] (Phase I-II)	47 pts 63 LM	36-60 Gy in 3 fx	2 yr 92%	1 grade 3 soft tissue necrosis
Mendez Romero et al[34] (Phase II)	17 pts (14 CRC) 34 LM	30-37.5 Gy in 3 fx	1 yr 100% 2 yr 86%	3 grade 3 ↑GGT 1 grade 3 asthenia
Scorsetti et al[35] (Phase II)	61 pts (30 CRC) 76 LM	75 Gy in 3 fx	1 yr 94% 3 yr 78% 5 yr 78%	1 grade 3 chest wall pain
Mahadevan et al[36] (RR)	427 pts 568 LM	12-60 Gy in 1-5 fx Median 45 Gy in 3 fx	2 yr 77%	Not available
Hong et al[37] (Phase II)	89 pts (34 CRC) 143 LM	30-50 GyE in 5 fx	1 yr 71.9% 3 yr 61.2%	No grade ≥ 3
McPartlin et al[38] (Phase I/II)	60 pts 93 LM	22.7-62.1 Gy in 6 fx	1 yr 50% 2 yr 32% 4 yr 26%	1 grade 3 nausea
Sufficool et al[39] (Phase II - BR001 liver subset)	41 pts (21 CRC) 80 LM	30-50 Gy in 3-5 fx	6 m 92% 1 yr 75%	No grade ≥ 3
Joo et al[40] (RR)	70 CRC pts 103 LM	30-60 Gy in 3-5 fx	1 yr 93% 2 yr 73% 3 yr 68%	No grade ≥ 3

Key: SBRT = stereotactic body radiation therapy, Pts = patients, Fx = fractions, Yr = year, M = month, GI = gastrointestinal, GGT = gamma-glutamyl transferase

that randomized patients to FOLFOX alone vs a single dose of ^{90}Y during cycle 1 or 2 of FOLFOX. Median OS was not significantly different (23.9 months vs 23.4 months, p = 0.61), and there was no difference in OS for the prespecified analysis of patients with liver-only metastases.[28] A post-hoc analysis of the SIRFLOX and FOXFIRE-Global trials evaluated right-sided vs left-sided primary tumors with the knowledge that right-sided primary tumors are a poor prognostic factor. Of the 739 patients in these 2 trials, 179 patients (24.2%) had right-sided primary tumors and improvement in median OS (17.1 months vs 22 months, p = 0.008) with the addition of ^{90}Y to FOLFOX. For patients with liver-only metastases, PFS improved for both right-sided (9.6 months vs 13.2 months, p = 0.001) and left-sided primary tumors (12.5 months vs 15.3 months, p = 0.015). The addition of ^{90}Y to first-line systemic therapy does not improve OS in an unselected group of patients with CRC LM, but future studies may reveal a benefit in a subgroup of patients.

TACE and TARE should be considered in patients with liver-dominant metastatic disease who progress on first- or second-line therapy or have residual LM after a favorable response to systemic therapy. They are preferred over ablation and SBRT when there are multiple LM in a lobe of the liver that can be treated simultaneously. The efficacy of TACE and TARE are similar, but TARE is more likely to promote liver remnant hypertrophy and should be favored if future resection is planned.[29,30] TACE is associated with an increased incidence of post-embolization syndrome and hospitalization, and carries a high risk of hepatic decompensation when portal vein invasion is present. TARE can be used with limited portal vein thrombus as long as the portal vein invasion does not involve the main trunk; otherwise, SBRT is preferred.[30]

SA-CME (see page 8)

Table 3. Liver SBRT Dose Constraints

Table 3[42,46]	3 Fraction	5 Fraction
Liver: noncirrhotic	≥ 700 cm^3 of uninvolved liver < 15 Gy	≥ 700 cm^3 < 21 Gy
Liver: cirrhotic		
Child Pugh A	≥ 700 cm^3 < 15 Gy and mean liver dose < 15 Gy in 3 or 5 fractions	
Child Pugh B	≥ 700 cm^3 < 15 Gy, ≥ 500 cm^3 < 7 Gy, and mean liver dose < 10 Gy in 5 fractions	
Central liver	V33.8 < 21 cm^3 V32 < 24 cm^3 Mean dose < 19 Gy	V26 < 40 cm^3 V21 < 37 cm^3
Duodenum	D 1 cm^3 < 30 Gy	D 1 cm^3 < 35 Gy
Small Bowel	D 2 cm^3 < 24.5 Gy D 5 cm^3 < 21 Gy	D 2 cm^3 < 30 Gy D 5 cm^3 < 25 Gy

External-beam Radiation, Stereotactic Body Radiation Therapy, and Protons

The use of external-beam radiation for LM was historically limited by intolerance of the liver to high doses of radiation and subsequent risk of radiation-induced liver disease (RILD). As treatment delivery, image guidance, and motion management techniques have advanced, we can now deliver ablative doses of radiation while sparing normal liver.

For patients with CRC LM, stereotactic body radiation therapy (SBRT) has proven effective with reliable dosimetry and high rates of local control (LC), as outlined in **Table 2**. Low rates of toxicity have been reported, with the incidence of RILD from SBRT rarely described in noncirrhotic patients.[31]

A consensus SBRT dose for CRC LM does not exist; however, it is reported that higher BED (biologically equivalent dose) correlates with improved LC. In a retrospective multi-institutional series of 427 patients with 568 LM treated with SBRT, BED_{10}≥100 Gy demonstrated improved 2-year LC of 77.2% vs 59.6% for BED_{10}<100 Gy. OS was also improved with higher dose (27 months vs 15 months, p < 0.0001).[36] Dose prescription varies significantly throughout published trials, but the lack of RILD suggests greater liver tolerance than previously proposed, and an opportunity for further dose escalation in noncirrhotic patients.

Tumor volume has been established as a driving factor, albeit variable, in the LC of lesions treated with SBRT, with lesions > 40 cm^3 demonstrating decreased LC and OS.[36] Most phase I and II studies required lesions < 6 cm for inclusion. Hong et al published the first series of LM treated with proton SBRT, and included larger tumors.[37] For tumors ≥ 6 cm, they report LC of 73.9% and 65.2% at 1 and 3 years, respectively, challenging the theory that SBRT is not effective for large tumors. Furthermore, they also demonstrated the strongest predictor for inferior LC was not lesion size but mutational status. Tumors with a KRAS mutation demonstrated significantly decreased LC of 42.9% compared with 72.1% in tumors without the mutation (p = 0.02). The same has been reported in the ^{90}Y literature suggesting this as a marker of radiation resistance.[41] Presence of a TP53 mutation was also associated with decreased LC of 46.2% vs 70.5% for wild type (p = 0.08), and tumors with both mutations had a 1-year LC of 20% vs 69.2% for all others (p = 0.001).[37]

In addition to following established SBRT constraints,[42,43] (**Table 3**) many centers extrapolate from surgical literature estimating a minimum necessary residual volume of liver of 700 cm^3, and spare this volume below an ablative dose-level. While this is a frequently applied estimate, the minimum required functional reserve likely varies based on many factors (age, BMI, liver size and health). Additional models for liver constraints use mean dose, effective volume of radiated liver (V_{eff}),[44] and functional imaging to spare more critical portions of a functioning liver.[45] We recommend evaluating multiple toxicity models to balance the risk-benefit ratio for each patient. Although not uniformly agreed upon, dose constraints to the central liver are used to limit toxicity such as biliary stricture. The central liver is most commonly delineated as an expansion of the portal vein, and toxicity is more common in the treatment of primary biliary malignancy, such as cholangiocarcinoma. This suggests that in addition to radiation dose, disruption of normal biliary tree architecture likely contributes to the risk of central liver toxicity.[46] The importance of dose constraints to the duodenum and small bowel come from the toxicity seen following the early pancreas SBRT experience and the increased incidence of ulceration, hemorrhage, and perforation.

Generally, the experience of liver SBRT has been in heavily pretreated patients, who often have received prior liver-directed therapy and multiple lines of chemotherapy. Comparative analyses of SBRT with other liver-directed therapies are scarce, but those available demonstrate that SBRT patients commonly have less favorable characteristics, but equal or superior control rates. Jackson et al compared a cohort of SBRT patients with RFA and found a higher local failure risk with RFA for tumors ≥ 2 cm.[47] Franzese et al performed a propensity-score-based comparison of SBRT with microwave ablation and showed a reduced risk of local relapse with SBRT (adjusted HR 0.31; p = 0.005).[48] Shen et al also

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completed a propensity-score-based comparison of SBRT with TACE, for hepatocellular carcinoma lesions 3-8 cm, and found that SBRT demonstrated superior LC and OS, and was especially effective for recurrent cases.[49] The favorable outcomes of SBRT are likely attributable to the high reliability of SBRT dosimetry, image guidance, and delivery of the planned treatment.

Conclusion

Oligometastatic CRC LM comprises a heterogeneous group of patients who require individual consideration when assessing treatment decisions. Multi-agent systemic therapy remains the backbone of treatment, but there are several options for complementary liver-directed therapy. LM location, size, and baseline hepatic function are the most important considerations when selecting optimal liver-directed therapy.

Surgical resection remains the standard of care, but the development of nonsurgical liver-directed therapies have been vital for the 70% of patients unresectable at diagnosis. Thermal and cryoablation techniques are best suited for LM ≤ 3 cm, of limited number, and in the periphery of the liver. SBRT is effective for small to medium LM and portal vein thrombosis, but should be carefully considered if multiple lesions require treatment. TACE or TARE is best for patients with higher volume LM in which treatment of a hepatic segment or lobe will address multiple LM synchronously. **Table 1** summarizes indications and contraindications that can aid treatment selection based on individual patient and tumor factors.

Patients will commonly require more than 1 liver-directed therapy, and critical evaluation of disease response and toxicity to prior therapy should be considered. Given the complex clinical decision making and lack of definitive randomized evidence for CRC LM, multidisciplinary care by physicians specializing in the treatment of LM is imperative.

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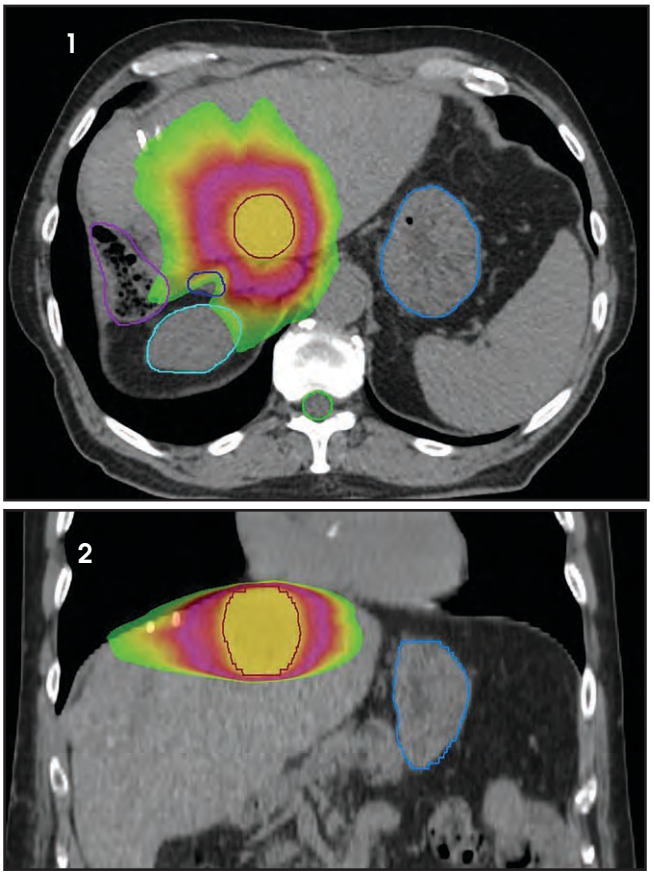
Case Example

A 63-year-old man was diagnosed with cT2N1bM1a, stage IVA, adenocarcinoma (KRAS mutated) of the rectum with multiple liver metastases. The patient was initiated on chemotherapy with FOLFOX, and bevacizumab was added on cycle 2. After 3 cycles of chemotherapy the patient was treated with ^{90}Y to the right liver, the dominant site of liver metastases. Following 4 additional cycles of chemotherapy, computed tomography (CT) imaging of the chest, abdomen, and pelvis demonstrated a favorable response to therapy with a reduction in size of the primary rectal mass, near resolution of regional lymph nodes, and significant volume reduction of liver metastases. The patient's CEA had decreased from 1205 ng/mL to 13 ng/mL during this time and he was continued on chemotherapy for 3 cycles (bevacizumab held the last cycle in anticipation of possible surgery). Follow-up imaging demonstrated a continued response to chemotherapy, so the patient was taken for surgical resection of the primary tumor via laparoscopic transanal total mesorectal excision. Surgical pathology demonstrated 0.5 cm of invasive moderately differentiated adenocarcinoma with a partial response to treatment. There was a microscopic focus of residual disease in only 1 of 27 lymph nodes, final pathologic staging ypT1N1a(mic). Six weeks following surgery the patient was restarted on FOLFOX with bevacizumab for an additional 2 cycles. Repeat imaging demonstrated residual but stable disease in the right liver, and no other evidence of metastatic disease. Following multidisciplinary tumor board discussion, the patient was then taken for right hepatectomy. Surgical pathology revealed no evidence of viable carcinoma and hepatic parenchyma with histologic features consistent with treatment effect. At this time, 15 months following diagnosis, the patient demonstrated no evidence of disease and CEA was within normal limits at 1.5 ng/mL. Following right hepatectomy, the patient received 2 additional cycles of FOLFOX and then transitioned to surveillance follow-up every 3 months. Nine months following systemic therapy, imaging demonstrated a solitary liver metastasis and there was a slight rise in CEA to 4.0 ng/mL. Following multidisciplinary tumor board discussion, it was determined that SBRT was the best treatment option given the patient's single site of disease.

The patient received 54 Gy in 3 fractions to the 3.6-cm-x-2.7-cm segment II lesion. Treatment was delivered over 8 days (minimum 40-hour interfraction interval) with volumetric arc therapy (VMAT) using 10 MV flattening filter-free photons. The patient was treated at 80% maximum inhalation breath-hold utilizing Automatic Breathing Control (ABC) (Elekta, Stockholm, Sweden). Daily image guidance was performed with ABC-gated cone-beam CT.



FIGURES 1 and 2 *illustrate the highly conformal stereotactic body radiation therapy (SBRT) treatment plan with sharp dose fall-off near the critical structures (bile duct and bowel). An internal target volume (ITV-not shown) was generated by combining the gross tumor volume (GTV) from 3 separate breath-hold scans. The ITV was expanded by 5 mm uniformly to create a PTV, which is delineated by the red outline. The prescription dose of 54 Gy is represented by the yellow color wash, 27 Gy by the magenta color wash, and 15 Gy by the lime green color wash. Delineated organs at risk include the stomach in light blue, bile duct in dark blue, right kidney in teal, large bowel in purple, and spinal cord in lime green.*

The patient tolerated SBRT well with toxicity isolated to grade 2 diarrhea 2 weeks following SBRT. Follow-up CEA decreased to 1.8 ng/mL 1 month after SBRT and imaging 14 months after SBRT demonstrates a complete response in the segment II lesion, and no other hepatic metastases.

versus chemotherapy alone in patients with liver metastases from colorectal cancer (FOXFIRE, SIRFLOX, and FOXFIRE-Global): a combined analysis of three multicentre, randomised, phase 3 trials. *Lancet Oncol.* 2017;18(9):1159-1171.
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SA–CME Information

PROTON THERAPY FOR COLORECTAL CANCER

Description

Based on current standards, colon cancer is treated with surgical resection and chemotherapy, and rectal cancer is treated with preoperative radiotherapy. This review of the literature suggests the potential for improved local control and reduced toxicity when treating colorectal cancer with proton therapy compared to the current treatment paradigms. Additionally, surgery and ablative techniques have traditionally been used to treat metastatic colorectal cancer. This review discusses how proton therapy could offer an alternative approach to reduce toxicity and act in lieu of surgery in the metastatic setting.

Learning Objectives

After completing this activity, participants will be able to:

1. Evaluate dosimetric data and case reports supporting use of proton therapy for treatment of colorectal cancer.
2. Analyze role of proton therapy for treatment of oligometastatic colorectal cancer.

Authors

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Proton therapy for colorectal cancer

Saira E. Alex, BS; Eric D. Brooks, MD; Emma B. Holliday, MD

Ever since the first proton beam therapy (PBT) treatment in 1954 at University of California, Berkley, the use of PBT worldwide has rapidly increased.[1] Due to the depth-dose characteristics of protons that allow for steep fall-off just distal to the tumor target, PBT can reduce unnecessary radiation dose to nearby normal tissues and allow for safer dose escalation in select clinical scenarios. Superior normal tissue avoidance can lead to reductions in acute and late toxicities, safe dose escalation can lead to improved local control, and the combination of both factors has the potential to impact overall survival (OS).

Early data have suggested that PBT led to improved clinical outcomes in the treatment of various pediatric cancers, ocular melanomas, sarcomas of the paravertebral region, and brain tumors when compared with traditional photon-based radiation.[2] Historically, fewer studies evaluated the utility of PBT in the treatment of gastrointestinal (GI) malignancies; however, retrospective studies in the setting of gastroesophageal cancer and pancreatic cancer show that preoperative PBT may reduce postoperative complications and definitive PBT may improve outcomes for those with unresectable disease.[3-6] Even fewer studies have evaluated the role of PBT in the primary or neoadjuvant treatment of colorectal cancer (CRC), but there have been published clinical outcomes in the treatment of recurrent disease as well as liver metastases. The aim of this review is to discuss the existing dosimetric and clinical data for PBT in the treatment of patients with CRC.

The Role of Radiation

Although colorectal cancer is often discussed as a single entity, colon and rectal cancer are drastically different in their clinical management. While colon cancer is treated with surgical resection and adjuvant chemotherapy for high-risk patients, radiation therapy is a standard component of preoperative treatment of rectal cancer given the higher risk of local recurrence in the pelvis (National Comprehensive Cancer Network).[7] Preoperative long-course chemoradiation or short-course radiation therapy are standard-of-care strategies for improving local-regional control in stage II and III rectal cancer. Preoperative radiation therapy reduces the risk of local recurrence,[8] which can be extremely morbid and difficult to salvage. However, radiation therapy is not without potential long-term risks, which include anastomotic leak, fistula formation, bowel adhesions/narrowing predisposing to obstruction, bladder scarring, erectile dysfunction, dyspareunia, pelvic insufficiency fracture and secondary malignancy.[9] As such, recent efforts have been made to reduce toxicity while maintaining excellent control and survival rates. One strategy has been to omit radiation therapy in patients with more favorable disease characteristics on advanced magnetic resonance imaging (MRI) who may not need it.[10] A recently completed trial evaluated omitting preoperative radiation after a good clinical response to induction chemotherapy (NCT01515787). Another strategy involves delivering radiation therapy in a more conformal way. RTOG 0822 evaluated preoperative intensity-modulated radiation therapy (IMRT) and failed to show decreased toxicity when compared to historic controls treated with a 3-dimensional (3D) conformal technique.[11] This trial was difficult to evaluate, however, as concurrent oxaliplatin was used with the IMRT.

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In the era of neoadjuvant therapy and total mesorectal excision, although local control rates for locally advanced rectal cancer are > 90%, distant metastases occur in approximately 30% of patients.[8] Additionally, 25% of all patients with colorectal cancer are metastatic at diagnosis, with the liver being the most common site.[12] For patients with oligometastatic disease, multimodality, definitive treatment can yield long-term survivorship.[13] Resection of liver metastases in combination with more effective chemotherapy has increased the median survival to 20 months and the 10-year OS to 20% to 25%.[14] However, as many patients are not surgical candidates, interest is growing in the use of radiation therapy or other ablative modalities in the treatment of liver metastases. Using advanced radiation techniques to achieve dose escalation is of particular interest because of studies showing a correlation between higher biologically effective dose (BED) and prolonged survival.[15,16]

Finally, for a small subset of patients, local recurrence of rectal cancer presents a unique clinical challenge. While surgical salvage is preferred, this approach can be morbid and technically challenging. As most recurrences arise within a previously irradiated field, preoperative or definitive reirradiation options are limited. Hyperfractionated, accelerated schedules have been shown to be safe,[17] although more conformal techniques such as stereotactic body radiation (SBRT) or particle therapy may further improve the therapeutic ratio for these patients.

The Rationale for Protons

PBT is a nuanced radiation therapy technique that has the potential to greatly reduce toxicity in the settings of locally advanced rectal cancer as well as oligometastatic colorectal cancer. Due to the favorable physical properties of the proton beam, the unnecessary exposure of normal tissue to radiation can be reduced. The proton is a positively charged particle given energy via acceleration in a cyclotron (or synchrotron), which then enters the patient's body at a brisk speed, depositing very little dose. The dose absorbed by the body increases as the proton slows down at greater depth until the absorbed dose rises to an abrupt peak called the Bragg peak. The proton beam can be programmed such that the Bragg peak occurs exactly within the tumor site. After the Bragg peak, there is a steep dose fall-off, which eliminates unnecessary dose distal to the intended tumor target.[18]

These physical properties offer potential acute and late toxicity advantages in the treatment of localized rectal cancer where sparing of the small bowel, femoral heads, bladder, genitalia, and other abdominal and pelvic structures is desired. In the metastatic colorectal cancer setting, PBT has the potential to spare healthy, nontarget liver and lung tissue from radiation allowing for dose escalation while respecting normal tissue dose constraints. This is particularly important when treating large or multiple liver metastases as the risk for radiation-induced liver disease (RILD) may be greater with photon-based techniques.

Dosimetric Data

Treatment planning studies have nicely illustrated the ability of PBT to reduce unnecessary dose to normal tissues adjacent to the tumor targets, and these dosimetric benefits are thought to translate to acute and late toxicity reduction. For localized rectal cancer, several dosimetric analyses have compared PBT to photon radiation for pelvic radiation. In these studies, PBT was significantly superior in reducing V5Gy, V10Gy, V15Gy, and V20Gy to bone marrow; V10Gy and V20Gy to small bowel; and V40Gy to the bladder.[19-23] Others have found better conformality indices with protons and sparing of male genitalia with proton compared to photon therapy.[20] There is also some suggestion that proton dosimetry may be particularly better for larger tumors.[2]

This evidence suggests that long-term toxicity risk may be significantly reduced for patients undergoing pelvic radiation for locally advanced rectal cancer. In particular, bone marrow sparing can be highly advantageous as patients often undergo myelosuppressive chemotherapy. Being able to preserve marrow progenitors enables better tolerance to curative intent treatment, and the bone marrow is one organ where low doses matter. Lower V10 to the pelvic bone marrow has been associated with lower rates of significant cytopenia for patients being treated with pelvic radiation for anal cancer.[24] Preserving bone marrow function is particularly important for patients with locally advanced or metastatic rectal cancer who inevitably require long courses of cytotoxic systemic therapy.

Treatment planning studies have also shown dosimetric advantages of PBT over photon therapy in the oligometastatic setting as well. Radiation is playing an increasing role in the treatment of inoperable liver metastases. However, the low-dose bath to the rest of the liver can place the patient at risk for liver dysfunction and injury. Recent dosimetric analyses show that PBT can reduce the mean liver dose by more than half, from 20Gy to 9Gy, and reduce the V15Gy to the liver. This ability to achieve established dose constraints more easily allows for the delivery of the full intended ablative prescription dose for optimal tumor control, 90% for PBT vs only 20% with photon therapy.[25] As such, for these patients PBT may offer a toxicity and control benefit over photon therapy. Overall, dosimetric data for PBT are encouraging, although clinical outcomes are needed to ensure dosimetric benefits translate to meaningful reductions in toxicity and/or gains in tumor control.

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Clinical Outcomes

In general, published clinical outcomes for the use of PBT in the treatment of CRC are sparse. In the localized rectal cancer setting, most of the clinical data produced to date come from the salvage or reirradiation setting. In 2014, Berman published a study on 7 patients with locally recurrent rectal cancer who received reirradiation with PBT, to an average total cumulative dose of 109.8 gray relative biological effectiveness (Gy [RBE]).[26] Three patients experienced acute grade 3 toxicity, and 3 patients experienced late grade 4 toxicity at a median follow-up of 19.4 months. Out of the 7 patients, 4 were alive at the time of analysis. When compared to photon plans, PBT reduced small bowel and femur dose. The study concluded that PBT is clinically feasible and showed dosimetric improvements over IMRT when treating locally recurrent rectal cancer. In 2018, Ogi et al published a retrospective study on 23 patients who received PBT (up to 70 Gy [RBE]) for salvage reirradiation of locally recurrent rectal cancer.[27] Of these 23 patients, the grade 3 toxicity at 2.25 years after salvage was only 13% with an in-field local control rate that was moderate at 57%. In 2019, Kawamura et al published a report on 4 patients who received PBT after debulking surgery for locally recurring rectal cancer.[28] One patient died of lung metastasis after 2 years, 2 died of lymph node metastasis after 11 and 31 months, and one is alive without recurrence after 43 months. Thus, reirradiation with protons in the recurrent setting is largely considered feasible. Overall, however, the long-term outcomes for protons in this setting are sparse and there are no direct published comparisons to patients having received photon-based radiation. Furthermore, there are currently no published reports evaluating the use of PBT in the upfront treatment of locally advanced rectal cancer.

Compared with localized CRC, much more data have been published describing the use of PBT in the treatment of oligometastatic liver disease, including some prospective trials. One report discussed 5 patients with bilateral liver metastases treated with PBT.[29] These patients were planned to undergo a staged resection to allow liver hypertrophy and functional reserve between hepatectomies, but they did not have adequate hypertrophy to undergo the second stage of the operation. Using PBT, however, where the bulk of the normal liver can be spared, these investigators were able to treat all remaining disease to a BED of > 89.6 Gy (RBE) to the tumor and achieve tumor control in 4 out of 5 patients. Although this series was small, 40% of patients were without evidence of disease following treatment without any major toxicity. As such, proton therapy appears to be a feasible alternative for select patients with high burdens of liver disease who decline or are not amenable to surgery or may be combined with surgery or other ablative techniques in a multimodality approach. Hong et al recently published a single-arm phase II study on 89 patients who had received 30 to 50 gray-equivalent (GyE) proton-based stereotactic body radiation therapy (SBRT) to liver metastases, the majority of which were from CRC.[30] One-year local control was 71.9%, and 3-year local control was 61.2%. Grade 3 to 5 toxicity was not observed in these patients, and the patients had a median survival time of 18.1 months. Lastly, in 2019, Kang et al published a phase I study on the maximum tolerated dose of proton SBRT for liver metastases on 9 patients with liver lesions < 5 cm, and with no lesions within 2 cm of the GI tract. Patients did not experience dose-limiting toxicity, and dose escalation was possible without reaching maximum tolerated dose. In one patient, within 90 days of treatment, a grade 1 skin hyperpigmentation was noted. Two patients had local recurrence, and patients were treated with proton SBRT again. Recently, a consensus report emerged regarding the advantages and scenarios of PBT in treating CRC liver metastases, which will be valuable to the radiation therapy community as they consider PBT going forward.[31]

Future Directions

Currently, one ongoing clinical trial is evaluating PBT with concurrent chemotherapy for previously irradiated recurrent rectal cancer, and 2 ongoing clinical trials are exploring PBT for metastatic CRC—all led by Korean centers. A single-arm prospective study aims to treat previously irradiated, locally recurrent rectal cancer with 70.4 Gy (RBE) delivered in 16 fractions to the gross tumor volume and 44.8 Gy (RBE) in 16 fractions with the clinical target volume with concurrent capecitabine and with or without resection and spacer insertion. (A spacer is an injected degradable hydrogel that pushes structures such as the rectum in the case of re-irradiation away from normal tissues to reduce toxicity and is being explored in both the genitourinary and GI radiation therapy settings [NCT03098108].) In a phase II study of treating CRC lung metastasis, the prescription dose given is 72 Gy (RBE) in 15 fractions. The main aim is to evaluate the 3-year local control rate. Three-year survival rate and 3-year disease free survival rates are also being assessed to evaluate whether PBT offers better survival outcomes when compared to surgery (NCT03566355). In a phase II study of treating liver metastasis of colorectal adenocarcinoma, the main aim is to evaluate the 2-year local control rate. Similar to the first trial, the same regimen of 72 Gy (RBE) in 15 fractions is being used, and 5-year survival rates and 5-year disease free survival rates are listed as secondary endpoints to evaluate whether PBT offers better survival outcomes when compared with surgery, as PBT is a noninvasive procedure

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(NCT03577665). However, there is still an urgent need for more clinical trials to demonstrate whether PBT has an impact on overall survival of patients with CRC. There is a similar need for clinical trials comparing PBT to photon therapy to evaluate toxicity levels, dose escalations, and local control rates. An ongoing cooperative group trial randomizing PBT with photon-based radiation for hepatocellular carcinoma may set the stage for such phase III trials for CRC in the future (NCT03186898).

Limitations of PBT for CRC

As the radiation community seeks to leverage advanced technologies to find novel solutions for challenging clinical scenarios, it is important to recognize some of the currently limiting factors. Protons have thus far shown the largest benefit in the treatment of tumors requiring high doses delivered to tumor targets directly adjacent to radiosensitive critical structures. Notable examples include chordoma and chondrosarcoma.[32] Additionally, protons can achieve less integral body dose by minimizing low radiation dose in the beam path, which makes it potentially advantageous in reducing the risk of long-term side effects such as secondary malignancy, and neurocognitive and endocrine toxicities in the pediatric population.[33] Not much enthusiasm exists for the use of PBT in the neoadjuvant treatment of locally advanced, resectable rectal cancer partially because the tumor arises from within, rather than adjacent to, a radiosensitive luminal GI organ. Additionally, the need to treat the entire mesorectum and adjacent nodal basins necessitates a large clinical target volume that expressly overlaps with pelvic organs such as the bladder, bowel and bones. While the treatment planning studies described above show significant dose reduction, bowel and bladder toxicity is mostly due to high-dose exposure within the target area rather than low-dose scatter to adjacent normal tissues. Bone marrow is a potential exception and is one example where low dose matters. Young patients at higher risk for secondary malignancies and patients who have received prior radiation to the intended field are two other potential exceptions.

Additionally, some physical and biological properties of PBT are incompletely understood. Even though linear energy transfer (LET) and RBE are known to drastically rise at the very distal edge of the spread-out Bragg peak, conventional treatment planning systems implement standard RBE corrections uniformly across the beam. This means the RBE can be 2 to 3 times higher than prescribed and has grave potential implications should the beam's edge end just adjacent to a critical organ. This has been well described in the pediatric central nervous system literature.[34] The location of CRC targets in and around organs that have considerable inter- and intrafractional variability of positioning due to the presence of bowel contents and gas further add to this uncertainty. The stopping power of protons varies widely between tissue and air, and the presence of rectal gas can increase the range of the proton beam leading to undercoverage of the target and/or overdoing nearly critical structures.[35]

There are ongoing innovations to help improve PBT delivery. Currently, spot sizes, the size of the proton beamlets used to treat, are being reduced. With further reduction, more precise sculpting of proton dose delivery will be enabled. Additionally, new techniques such as dual-energy CT (DECT) can reduce the stopping power uncertainty with protons by as much as 50%.[36-41] Reducing this uncertainty will help to further reduce dose and spare normal tissue. Also, more experience with beam angling to optimize treatment positioning will help to perfect treatment planning. Improvements in robust optimization and evaluation will allow for better confidence in PBT treatment, and there is work ongoing to explore LET- or RBE-based optimization strategies.[42-44] Finally, advances in motion management for CRC tumors at sites such as the lung and liver where breathing can cause the tumor to move are being developed to minimize the interplay effect and ensure tumor coverage and organ at risk sparing during spot painting.[45-46]

Conclusion

With the increased use of PBT to treat various malignancies, there is renewed interest in its application in the treatment of CRC due to the location of disease and the desire to reduce toxicity from a multimodality treatment approach. In the setting of localized rectal cancer, PBT spares bone marrow, small bowel, femoral heads, and abdominopelvic structures from unnecessary radiation exposure, which may allow patients to tolerate chemotherapy or other treatment modalities. In the setting of oligometastatic disease, PBT can preserve organ function and allow for dose escalation, which has been shown to correlate with control. Numerous small series have been published but are primarily limited to cases of reirradiation or salvage in the localized rectal cancer setting. More robust data show the promise of PBT in the treatment of CRC liver metastasis. However, large, randomized clinical trials are needed to validate the efficacy and safety of PBT in treatment of CRC, particularly in the upfront setting with resectable disease.

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SA–CME Information

CHEMORADIATION TREATMENT OF GLIOBLASTOMA MULTIFORME: TREATMENT GUIDELINES AND CONSIDERATIONS

Description

Authors review the North American and European guidelines for chemoradiation of GBM created as a result of the new 2016 WHO classification system, focusing specifically on age, performance status, molecular markers, and disease recurrence. They also discuss factors such as socioeconomic and insurance status that impact radiation treatment compliance and GBM outcomes.

Learning Objectives

After completing this activity, participants will be able to:

1. Learn about radiation treatment indications for glioblastoma and the factors impacting treatment recommendations.
2. Apply radiation volume determinations and varying radiation schedules based on patient age, performance status, and methylation status.
3. Expand arsenal of adjuvant treatment modalities to include tumor-treating fields (TTFields), proton beam therapy (PBT), and dendritic cell vaccines.
4. Define social determinants of health and socioeconomic status.
5. Adopt a better understanding of the impact of social determinants of health on radiation treatment and glioblastoma outcomes.

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Chemoradiation treatment of glioblastoma multiforme: Treatment guidelines and considerations

Krissia Margarita Rivera Perla, ScB; Ollin Gomez Venegas, BA; Steven A. Toms, MD, MPH

Glioblastoma (GBM) is the most common primary malignant neoplasm of the brain, with an incidence of 3.19 per 100,000 persons in the US.[1] Standard of care includes maximal surgical resection and radiation therapy (RT) with concomitant temozolomide (TMZ) chemotherapy. The median 3-year survival rate for a newly diagnosed patient with this aggressive cancer remains a dismal 10.1%.[2] Nevertheless, recent advancements in the use of alternating electric field therapy, also known as tumor-treating fields (TTFields), and dendritic cell vaccines are beginning to challenge the status quo with initial results yielding a median overall survival of 20.9 months.[3,4] Moreover, molecular characterization of primary brain tumors has had a substantial impact on the stratification of central nervous system (CNS) neoplasms. This includes a more nuanced characterization of GBM molecular markers, thus leading to the creation of an integrated diagnosis.[5] In this review, we highlight the North American and European guidelines for chemoradiation of GBM created as a result of the new 2016 World Health Organization (WHO) classification system. Specifically, we focus on the factors of age, performance status, molecular markers, and disease recurrence as the main components for the clinical application of the guidelines. Furthermore, we highlight factors, such as socioeconomic and insurance status, that impact radiation treatment compliance and GBM outcomes.

Standard of Care

Therapy for GBM is divided into multiple strata of treatment modalities including surgery, radiation and chemotherapy. Tumor molecular markers may be used as a guiding prognostic factor to optimize a personalized treatment plan.[6,7] These molecular features confer a survival advantage in GBM, as they predict a favorable treatment response. Markers screened for after a histologic diagnosis of GBM may include: O^6-methylguanine DNA methyltransferase (MGMT) promoter methylation status and isocitrate dehydrogenase (IDH) mutation.[7] In this article, however, we will focus on MGMT promoter methylation status. Furthermore, tumor resectability, Karnofsky Performance Score (KPS), and patient age are important components of the clinical-care decision-making process (**Table 1**).[8]

Patients Age < 70

For patients age < 70 years and a KPS ≥ 60, guidelines recommend maximal surgical resection followed by adjuvant therapy.[7-11] The type of adjuvant treatment is dictated by postresection KPS and MGMT promoter status. For patients < 70, postresection KPS ≥ 60, and methylated MGMT promoter status, guidelines recommend standard brain RT, concurrent plus adjuvant temozolomide (TMZ), and TTFields.[7] Recommendations remain the same for patients with the same age and KPS bracket but an unmethylated/indeterminate MGMT promoter.[7] However, standard brain RT alone is an option for this second group. According to the American Society for Radiation Oncology (ASTRO) guidelines, standard brain RT entails partial-brain RT of 60 Gy in 2-Gy fractions (30 total fractions) delivered throughout 6 weeks.[8] Similarly, the European Association for Neuro-Oncology (EANO) guidelines recommend focal

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Table 1. Overview of Adjuvant Treatment According to Age, KPS, and Recurrence

	KPS 60 ± methylated MGMT promotor status	KPS < 60
Patients < 70 years	Standard brain RT + concurrent & adjuvant TMZ ± alternating electric fields therapy	Hypofractionated brain RT ± concurrent & adjuvant TMZ or TMZ alone or Palliative care
Patients > 70 years	Standard brain RT + concurrent & adjuvant TMZ ± alternating electric fields therapy or Hypofractionated brain RT ± concurrent & adjuvant TMZ or Hypofractionated brain RT alone or TMZ alone (unmethylated only)	Hypofractionated brain RT ± concurrent & adjuvant TMZ or TMZ alone or Palliative care
Recurrent Glioblastoma	Palliative care or Consider systemic chemotherapy or Consider reirradiation	

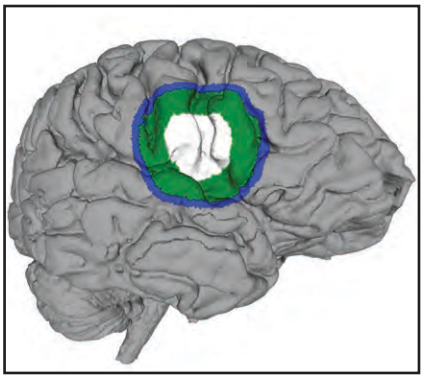

FIGURE 1. *Computer-generated rendition of targeted partial-brain radiation therapy of a right hemispheric glioblastoma (surface only). White represents gross tumor volume (GTV); surgical bed. Green shows clinical target volume (CTV); GTV + 1 to 2.5 cm margin. Blue is the planning target volume (PTV); CTV + 0.3 to 0.5 cm margin. Note: For illustration purposes only; dimensions not drawn completely to scale.*

RT of 50-60 Gy in 1.8-2.0 Gy fractions following surgical resection or biopsy in patients < 70 years of age and a KPS ≥ 70. Gross total resection has been shown to improve outcomes and is therefore recommended for clinically eligible patients.[6] Both ASTRO and EANO guidelines recommend targeted delivery of radiation against whole-brain therapy to minimize toxicity to structures such as the optic nerves, optic chiasm, retinas, brainstem, pituitary, cochlea, hippocampus and other sensitive structures.[6-8]

Determining the tumor volumes is an important consideration when conducting partial-brain RT in GBM patients (**Figure 1**). The gross tumor volume (GTV) includes the surgical bed and any area of postsurgical or postbiopsy T1 MRI enhancement. The clinical target volume (CTV) is defined as the GTV and any residual T2W or fluid-attenuated inversion recovery (FLAIR) signal abnormalities plus an additional margin of 1 to 2.5 cm. Finally, the planning target volume (PTV) of 0.3 cm to 0.5 cm is added onto the CTV to account for daily setup error.[6] Radiation may be administered using 1- or 2-phase radiation target volume strategies. The 1-phase target volume approach encompasses the CTV and margin without targeting edema.[8] In contrast, the 2-phase target volume method includes the CTV, margin, and edema measured using hyperintense T2 and FLAIR MRI regions as a guide. This is subsequently narrowed down to target only the gross residual tumor and resection cavity in the second phase.[8]

In addition to surgery and radiation, chemotherapeutic agents are the mainstay of treatment. Concurrent and adjuvant TMZ is recommended as its addition to radiation in the treatment of newly diagnosed GBM has been shown to provide a survival benefit.[12,13] A study by Ballhausen et al demonstrated improved survival with daily concurrent TMZ administration (15.7 months) during radiation treatment compared to TMZ administration for 5 out of 7 days (12.6 months).[14] Currently, the Radiation Therapy Oncology Group (RTOG) / NRG, National Comprehensive Cancer Network (NCCN), EANO, and the Medical Oncology Spanish Society (SEOM) guidelines recommend 75mg/m^2 daily concurrent TMZ throughout radiation treatment followed by maintenance therapy of 150-200mg/m^2 for 5 days every 4 weeks for 6 cycles.[6]

Finally, the inclusion of TTFields as part of the treatment plan is improving the overall survival of patients with GBM. This noninvasive antimitotic therapy consists of low intensity, 200 kHz frequency, and alternating electrical currents delivered via 2 transducer arrays on a shaved scalp (**Figure 2**). The device is worn ≥ 18 hours/day on the same days as administrations of TMZ.[3] When used at a monthly compliance of > 90% TTFields have resulted in a statistically significant improvement in the median overall survival to 24.9 months.[15] TTFields, however, are an option only for patients with supratentorial disease.[7]

Patients Age > 70

For patients > 70 years old, performance status and MGMT status are important considerations when choosing the treatment regimen with the utmost benefit in survival and quality of life. Treatment remains controversial and attempts are underway to understand the role of TMZ and hypofractionated RT in the elderly, especially in those

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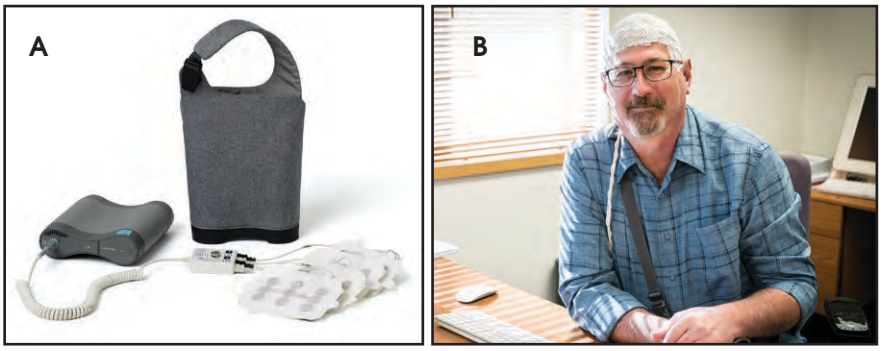

FIGURE 2. *(A) Optune Device, an FDA-approved medical device for delivering alternating electric field therapy via 4 transducers. (B) Patient with transducers placed on scalp. ©2019 Novocure. All rights reserved.*

with unmethylated MGMT promoters and those with poor performance status.[16] Nonetheless, there is surmounting evidence that RT in those >70 improves survival when compared to supportive care alone with similar quality of life and cognitive evaluations between groups.[17] In addition, hypofractionated RT has been shown to reduce steroid utilization and decrease early RT termination when compared with standard-length RT.[18]

According to EANO guidelines, treatment decisions should be based on MGMT status for patients >70 who are not eligible for radiation with concurrent or maintenance TMZ. Patients with MGMT methylation status are recommended to receive TMZ alone for 5 consecutive days every 28 days. Patients with non-MGMT/indeterminate methylation status should undergo hypofractionated RT of 40 Gy in 15 fractions using a similar T2W abnormality plus a 2-cm margin for planning tumor volumes.[6] ASTRO guidelines recommend a similar radiation schedule (40 Gy in 2.66 fractions) in addition to TMZ in elderly patients with good to reasonable performance status.[8] In contrast, SEOM recommends treatment with TMZ alone for patients with poor performance status and MGMT methylation.[19] In addition, the Nordic randomized phase III clinical trial found similar median survival when comparing TMZ alone to hypofractionated RT (34 Gy in 10 fractions) in patients > 60 years.[20] Results from Perry et al on elderly patients with GBM, however, have led to the consideration of short-course RT (40 Gy in 15 fractions) plus TMZ as standard of care.[21] CTV determinations for patients > 70 receiving hypofractionated RT should be made as described above for patients < 70 years old.[6]

In elderly patients with GBM, a KPS > 70, and MGMT promotor methylation, a study by Palmer et al reported that 49% of physicians surveyed recommended a standard course of radiation and chemotherapy while 39% recommended a short course of radiation and chemotherapy.[22] In elderly patients with KPS > 70 and non-MGMT methylation status, 51% of physicians recommended a short course of radiation alone. In patients with KPS < 50, 57% of physicians recommended supportive care. Although more studies are needed to elucidate optimal treatments in elderly patients with GBM, evidence suggests improved outcomes with use of hypofractionated RT and TMZ. A clinical trial by Perry et al showed improved median overall survival and median progression-free survival in elderly patients age > 65 who received hypofractionated RT (40 Gy in 15 fractions) and TMZ compared with those who received hypofractionated RT alone.[21]

Finally, despite advantages seen in patients < 70 years, and calls from the medical community and several medical governing bodies worldwide, the EANO and ASTRO have yet to include the use of TTFields in this patient cohort. However, 1 randomized clinical trial demonstrated a survival benefit in patients > 70 with a good performance status (KPS ≥ 70).[3]

Recurrent Glioblastoma

Unfortunately, most patients experience GBM recurrence despite maximal surgical resection, radiation and chemotherapy. Typically, recurrence of GBM occurs locally, most commonly within approximately 2 cm of the surgical resection cavity.[23,24] One study found a median progression-free survival of 7 months after local tumor recurrence.[24] The median overall survival rate after diagnosis of recurrence is still an estimated 22-44 weeks.[25] Nonetheless, maximal safe surgical resection can be done in clinically eligible patients; however, no consensus exists regarding maximal safe resection or dosage or type of chemoradiation therapy for tumor recurrence; the treatment plan remains the choice of the physician and patient.[23,24] To date, Scoccianti et al provides the most comprehensive effort to create a treatment protocol for recurrent GBM combining various approaches used in the US and Europe.[26] The results of their retrospective analysis suggest that radiation-only therapy as a salvage treatment has the likelihood of a relatively good outcome.[26] Patients are stratified according to the CTV of the recurrent neoplasm. Moreover, to minimize neurotoxicity patients should be treated using different fractionation and differentiated total dose in 2 Gy fractions. If the CTV is < 12.5 ml, then < 65 Gy with radiosurgery should be administered; if > 12.5 ml and < 35 ml, then <50 Gy with hypofractionated stereotactic RT should be administered; and if > 35 ml and < 50 ml, then < 36 Gy with conventionally fractionated RT should be administered.[26] Furthermore, newer technologies such as proton beam therapy may be a promising mo-

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dality given its role in many skull base tumors and pediatric cancers; however, it has not yet established itself in the treatment of GBM. More research will be required to determine whether protons and other heavy particles offer an advantage in GBM dosimetry.[27]

In the US, several options are available to the patient. First, if the postresection KPS > 60, systemic chemotherapy can be considered. Recommended regimens include TMZ, bevacizumab, lomustine/carmustine, procarbazine, and/or vincristine. If there has been a long time between stopping TMZ and tumor progression, it is reasonable to restart the patient on TMZ—especially if the tumor is MGMT methylated.[28] Similarly, lomustine/carmustine is a reasonable second-line therapy for a tumor that is MGMT methylated.[29] Next, although bevacizumab has not demonstrated improved overall survival in recurrent GBM, it is still FDA-approved based on improved performance status.[30,31] Furthermore, evidence from the EF-11 randomized phase III clinical trial indicates the equivalence of chemotherapy and TTFields in treatment of recurrent GBM. TTFields were found comparable to chemotherapy in median survival and progression-free survival with improved quality of life seen in the TTFields cohort.[32]

Radiation Treatment and Social Determinants of Health

In recent years, social determinants of health—the circumstances in which people are born, grow up, live, work and age, and the systems put in place to deal with illness—have increasingly become a topic of research in the treatment of GBM.[33] One influential factor driving this exploration is the ever-rising cost of US healthcare, especially in neuro-oncology. As the use of TMZ, trial-combined chemotherapy (such as TMZ and bevacizumab), and TTFields has increased, so has the overall cost of the treatment course for newly diagnosed GBM. A recently published analysis evaluating the direct medical costs of GBM found that the mean total cumulative costs per patient from 3 months prediagnosis to 12 months, and to 5 years post diagnosis were $201,749 and $268,031, respectively.[34] Broken down further, the average per-patient per-month post-GBM diagnosis was $7,394.[34] Given these substantial costs, there is little surprise that the standard-of-care treatment course can be deemed cost-prohibitive. Rhome et al found that compliance with chemotherapy treatment was associated with male gender, white race, younger age (< 50 years), higher performance status (> 70), insurance status, higher income/education, and receipt of treatment at an academic center.[35] This can have an overwhelming negative effect on overall patient survival, especially when compliance with treatment such as TTFields is closely linked with overall rates of survival.[15]

Unfortunately, supporting evidence in this matter is only beginning to be discovered, despite the use of surgery, chemotherapy, and radiation in the treatment of GBM for more than 20 years. For example, a recent national survey of NCCN panel members showed that neither sexual orientation nor gender identity, which are part of social determinants of health, were thought to be relevant to the focus of the NCCN guidelines.[36] Moreover, 77% responded that their panels currently do not address LGBTQ issues, with no plans to address them in the future.[36]

Furthermore, socioeconomic status, which encompasses education, income, and occupation, has been shown to impact time to radiation treatment.[37] One study by Pollom et al showed that in patients who underwent gross total tumor resection, those who received radiation within 15 to 21 days had a statistically significant improved survival with a trend in improved survival in those receiving treatment within 22 to 35 days.[36] The study found that patients who had Medicaid, government insurance, were uninsured, or lived in metropolitan areas were less likely to receive radiation within 35 days compared to patients from higher income areas. Other studies have shown the impact of insurance on radiation treatment. A study by Brown et al demonstrated a significant association between insurance type and odds of receiving radiation treatment. Patients with Medicare had the highest odds of receiving radiation, Medicaid patients had lower odds, and uninsured patients had the lowest odds.[38] Lastly, a study by Chandra et al showed that uninsured patients had significantly lower rates of radiation and TMZ treatment.[39]

Conclusion

In this review, we provide a simple overview of the current state of radiation use for treatment of GBM. Some of the most important prognostic factors and guiding principles are based on age, performance status, and tumor molecular markers. Conventionally fractionated stereotactic RT for patients < 70 years old yields the best results for progression-free survival. Hypofractionated stereotactic RT for patients > 70 years old can also be considered for improved progression-free survival. Recent studies have elucidated the benefit of newer treatment modalities such as TTFields and their significant benefit in progression-free and overall survival. Lastly, recent literature has demonstrated the impact of socioeconomic status and insurance status on radiation treatment after GBM surgical resection.

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Effect of radiation dose escalation on overall survival in ependymoma: A National Cancer Database analysis

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Abstract

Objective: Although adjuvant radiation therapy is the standard of care in treatment of localized grade II/III ependymoma, the appropriate dose to which to treat remains controversial. Excellent local control has been demonstrated after treatment to 5940 cGy, but there is no randomized evidence evaluating the effect of dose escalation on overall survival (OS). To address this question, we utilized the National Cancer Database (NCDB) to evaluate the effect of radiation dose escalation on OS in patients with localized ependymoma.

Materials and Methods: Patients > 2 years of age with localized World Health Organization (WHO) grade II and III ependymoma treated from 2010 to 2015 were identified from the NCDB and dichotomized into cohorts receiving 5400 cGy and ≥ 5940 cGy. OS was compared using the Kaplan-Meier estimator and multivariable Cox proportional hazards analysis.

Results: A total of 548 patients met study criteria. Of these, 196 (36%) received 5400 cGy and 352 (64%) received ≥ 5940 cGy. Gross total resection was performed in 105 cases (54%) and 238 patients (43%) were ≤ 18 years of age. On multivariable survival analysis, there was no difference in OS between patients receiving 5400 cGy and those receiving ≥ 5940 cGy (hazard ratio [HR] = 0.74, 95% conformity index [CI]: 0.39-1.40, $p = 0.36$).

Conclusions: In this assessment of the NCDB, dose-escalated radiation of ≥ 5940 cGy was not associated with improved OS among patients with localized high-grade ependymoma. Further prospective study of the role of dose escalation in localized ependymoma is warranted.

Ependymoma is a rare primary malignancy of the central nervous system (CNS), which has an annual incidence of approximately 2-4 new cases per million with a peak age of approximately 5 years in children and 55 years in adults.[1-3] The current standard of care for management of World Health Organization (WHO) grade II/III ependymoma includes maximal feasible resection followed by radiation therapy. While treatment to a dose of 5400 cGy is generally standard, progression-free survival (PFS) is only about 40% at 5 years.[4-6] Therefore, dose escalation is an active area of interest in ependymoma management. A recent phase II study using dose-escalated radiation to 5940 cGy reported excellent local control, further supporting the potential benefits of higher doses.[7]

The benefits of dose escalation may be limited by late toxicities associated with radiation therapy to the CNS.[8-10] In particular, risk of radiation necrosis may be correlated with increasing dose and volume delivered to the brainstem.[11-13] Currently, there is no randomized evidence that evaluates the effect of dose escalation above 5400 cGy on overall survival (OS) in localized

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ependymoma. Therefore, we sought to evaluate the effect of radiation dose escalation on OS in patients with localized ependymoma utilizing the National Cancer Data Base (NCDB).

Materials and Methods

Data Source

The study population was identified from the NCDB, a national cancer registry sponsored by the American College of Surgeons and American Cancer Society that draws upon hospital registry data from Commission on Cancer-accredited facilities in the United States.[14,15] Data are collected prospectively from cancer registries with nationally standardized data-coding definitions.[16]

Study Population

Inclusion criteria (**Figure 1**) consisted of patients >2 years of age at diagnosis with localized supratentorial or infratentorial WHO grade II and III ependymoma treated with surgical resection and adjuvant external-beam radiation therapy from 2010 to 2015. Dates were restricted to this time period to account for changes in practice based on a phase II dose-escalation study published in 2009.[7] In addition, information regarding extent of resection was not available for intracranial tumors prior to 2010. Patients < 2 years old were excluded given that this group is often treated to lower dose due to concern for CNS toxicity.[7] Those who received < 5400 cGy or > 6800 cGy were excluded as such doses may fall outside of the conventional dose range for treatment of ependymomas.[17] Patients who received radiation to extracranial sites, had unknown dose data, or were not known to have received radiation therapy were also excluded.

Patient Cohorts and Variables

The overall cohort was divided into 1) a standard dose cohort that received 5400 cGy and 2) a dose escalated radiation cohort that received ≥ 5940 cGy. Covariates analyzed included gender, age, race, insurance status, treatment facility geographic location, distance to facility, education levels, income (median income in patients' zip codes), Charlson-Deyo comorbidity score, tumor location (cerebrum, ventricle, cerebellum, brainstem, brain not otherwise specified), tumor size and grade, extent of surgical resection, receipt of chemotherapy, and year of diagnosis.

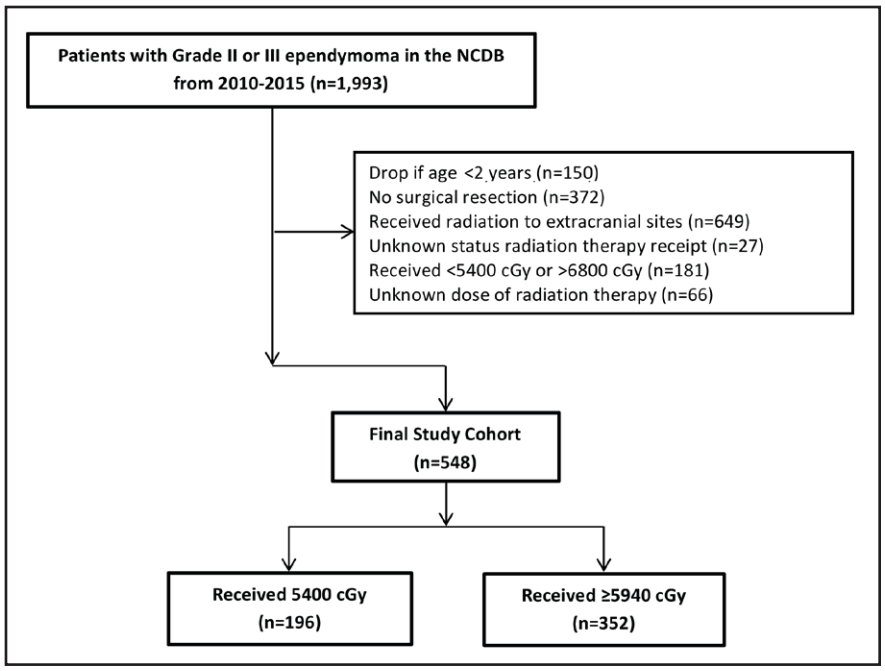

FIGURE 1. *Consolidated standards of reporting trials (CONSORT) diagram. NCDB = National Cancer Data Base*

Aims/Endpoints

The primary endpoint was OS in patients treated to doses ≥ 5940 cGy compared to those treated with 5400 cGy. OS was defined as the time from diagnosis until death or last follow-up. As a secondary aim, we evaluated factors associated with receipt of dose-escalated radiation therapy.

Statistical Analysis

Baseline demographic and clinical characteristics between cohorts were compared using the chi-squared test for categorical variables and rank-sum tests for continuous variables. A multivariable logistic regression model was constructed using all baseline covariates reaching a univariable analysis threshold significance of $p < 0.1$ to assess the independent effect of each covariate on the likelihood of being treated with dose-escalated radiation therapy.

The Kaplan-Meier estimator and log-rank tests were used to assess OS between study cohorts. A Cox proportional hazards model was constructed using all variables achieving a threshold significance of $p < 0.1$ on univariable analysis to assess the independent effect of radiation dose on hazard of death. Patients diagnosed in 2015 were excluded from survival analysis due to insufficient follow-up data.

To more robustly account for baseline differences between study cohorts, a matched cohort of 338 patients (all 169 patients who received 5400 cGy matched with 169 patients who received ≥ 5940 cGy) was identified using 1-to-1 nearest neighbor propensity score-matching without replacement.[18] Propensity scores were derived

Table 1. Baseline Characteristics, Study Cohorts

	Pts receiving 5400 cGy (%)		Pts receiving ≥ 5940 cGy (%)		Total (%)		p (χ2)
Total no.	**196**	**36**	**352**	**64**	**548**	**100**	
Sex							0.31
Male	114	58	189	54	303	55	
Female	82	42	163	46	245	45	
Age (years)							< 0.001
≤ 18	48	24	190	54	238	43	
> 18	148	76	162	46	310	57	
Race							0.61
Non-Hispanic White	134	68	221	63	355	65	
Non-Hispanic Black	21	11	42	12	63	11	
Hispanic	27	14	60	17	87	16	
Other	14	7	29	8	43	8	
County Size							0.84
Metropolitan	168	86	302	86	470	86	
Urban	21	11	34	10	55	10	
Rural	2	1	7	2	9	2	
Unknown	5	3	9	3	14	3	
Distance to Treatment							0.22
Median (IQR)	16	8	17	5	16	3	
Insurance Status							0.04
Commercial Insurance	108	55	210	60	318	58	
Medicare	23	12	19	5	42	8	
Medicaid	39	20	89	25	128	23	
Uninsured	13	7	16	5	29	5	
Other/Unknown	13	7	18	5	31	6	
Education							0.99
≥ 21%	41	21	72	20	113	21	
13%-20.9%	45	23	80	23	125	23	
7%-12.9%	61	31	108	31	169	31	
< 7%	49	25	92	26	141	26	
Income ($)							0.64
< 38,000	35	18	66	19	101	18	
38,000-47,999	37	19	75	21	112	20	
48,000-62,999	47	24	85	24	132	24	
> 63,000	76	39	126	36	202	37	
Unknown	1	1	0	0	1	0	

Key: PTs = patients, IQR = interquartile range, NOS = not otherwise specified

using multivariable logistic regression methods and denoted the probability of any patient receiving 5400 cGy. An absolute standardized difference of < 0.1 was accepted as a measure of adequate balance between matched covariates.[19] Cox survival analysis was then repeated in the matched cohort to assess the robustness of the traditional multivariable analysis.

A two-tailed *p*-value < 0.05 was considered statistically significant. All statistical analyses were performed using Stata SE, version 14.0 (College Station, Texas).

Results

Patient Characteristics

A total of 548 patients met study inclusion criteria (**Table 1**). Of these, 196 (36%) were treated with standard dose radiation therapy and 352 (64%) were treated with dose-escalated radiation. Most patients were >18 years old (n = 310, 57%) and the median age of the cohort was 24 years (interquartile range [IQR], 8-24). Most patients had tumors in the cerebrum (n = 165, 30%), brainstem (n = 127, 23%), or unspecified location (n = 139, 25%). Tumors were most commonly > 4 cm (n = 265, 48%) and grade 3 (n = 258, 47%). Most patients underwent gross total resection (n = 312, 57%) and did not receive chemotherapy (n = 433, 79%).

Table 1. Baseline Characteristics, Study Cohorts (continued)

	Pts receiving 5400 cGy (%)		Pts receiving ≥ 5940 cGy (%)		Total (%)		p (χ2)
Charlson/Deyo Comorbidity Score							0.017
0	166	85	310	88	476	87	
1	23	12	23	7	46	8	
2	7	4	9	3	16	3	
3	0	0	10	3	10	2	
Location of Tumor							< 0.001
Cerebrum	24	12	141	40	165	30	
Ventricle	40	20	37	11	77	14	
Cerebellum	23	12	17	5	40	7	
Brainstem	68	35	59	17	127	23	
Brain NOS	41	21	98	28	139	25	
Size (cm)							< 0.001
≤ 4	92	47	90	26	182	33	
> 4	72	37	193	55	265	48	
Unknown	32	16	69	20	101	18	
Grade							< 0.001
2	134	68	117	33	251	46	
3	39	20	219	62	258	47	
Unknown	23	12	16	5	39	7	
Type of Surgery							0.38
Subtotal	60	31	89	25	149	27	
Gross total	105	54	207	59	312	57	
Biopsy	31	16	56	16	87	16	
Receipt of Chemo							< 0.001
No	176	90	257	73	433	79	
Yes	18	9	83	24	101	18	
Unknown	2	1	12	3	14	3	
Year of Diagnosis							0.54
2010	31	16	64	18	95	17	
2011	30	15	58	16	88	16	
2012	39	20	64	18	103	19	
2013	38	19	63	18	101	18	
2014	31	16	40	11	71	13	
2015	27	14	63	18	90	16	

Key: PTs = patients, IQR = interquartile range, NOS = not otherwise specified

Factors Associated with Receipt of Dose-escalated Radiation Therapy

On multivariable analysis, grade III disease was associated with receipt of dose-escalated radiation therapy (odds ratio [OR] 3.55, 95% conformity index [CI] 2.16-5.83, $p < 0.001$) (**Table 2**). Factors that predicted for a decreased likelihood of dose-escalated radiation therapy included age >18 years (OR = 0.36, 95% CI 0.22-0.59, $p < 0.001$), and tumor location outside of the cerebrum. Notably, extent of resection was not associated with dose-escalated radiation therapy.

Overall Survival

The median follow-up time for the entire cohort was 36.1 months (IQR, 24.4-51.8 months). The median 5-year OS was 79.6% for the standard dose cohort and 74.9% for the dose-escalated cohort ($p = 0.86$, **Figure 2**). No significant differences in OS were observed after propensity matching ($p = 0.86$, **Figure 3**). On univariable analysis, gross total resection (GTR) was associated with improved survival compared to biopsy alone (OR = 0.53, 95% CI 0.31-0.93, p = 0.026). On multivariable analysis, there was no difference between treatment with dose-escalated as compared to standard dose radiation therapy in the overall cohort (hazard ratio [HR] = 0.74, 95% [conformity index] CI 0.39-1.40, $p = 0.36$) or after propensity score matching (HR = 0.83, 95% CI 0.44-1.57,

Table 2. Factors Associated with Receipt of ≥ 5940 cGy

	— Multivariable —	
	OR [95% CI]	*p*
Age (years)		
≤ 18	-	-
> 18	0.36 [0.22, 0.59]	< 0.001
Charlson/Deyo Comorbidity Score		
0	-	-
1	0.92 [0.44, 1.90]	< 0.001
2	1.02 [0.31, 3.37]	0.15
3	0.89 [0.34, 3.92]	0.18
Location of Tumor		
Cerebrum	-	-
Ventricle	0.30 [0.14, 0.63]	0.001
Cerebellum	0.24 [0.09, 0.57]	0.001
Brainstem	0.24 [0.12, 0.47]	< 0.001
Brain NOS	0.50 [0.26, 0.97]	0.042
Grade		
2	-	-
3	3.55 [2.16, 5.83]	< 0.001
Unknown	0.56 [0.26, 1.22]	0.15
Tumor size		
≤ 4 cm	-	-
> 4 cm	1.55 [0.96, 2.50]	0.08
Unknown	1.81 [0.98, 3.31]	0.06
Receipt of Chemo		
No	-	-
Yes	1.32 [0.70, 2.50]	0.41
Unknown	3.43 [0.57, 20.5]	0.18

Key: CI = conformity index, NOS = not otherwise specified

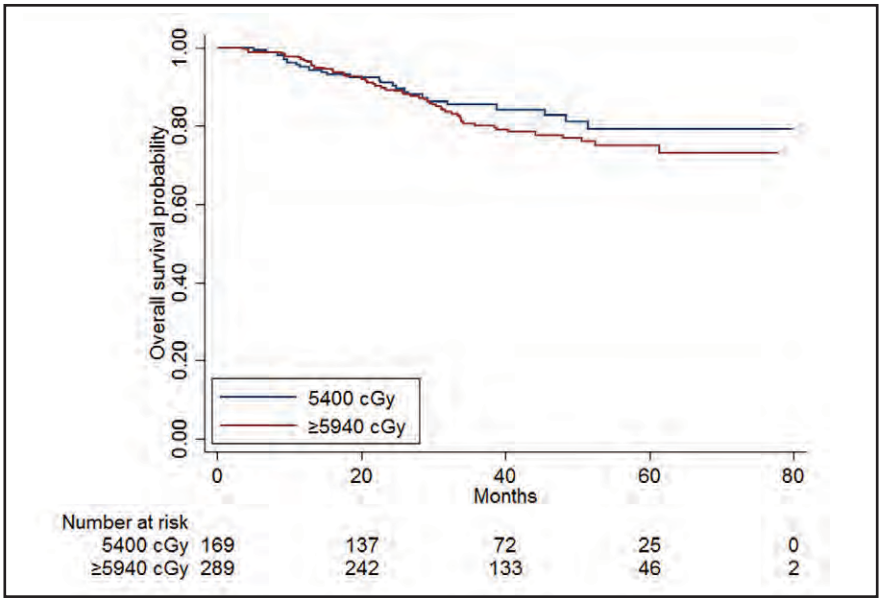

FIGURE 2. *Overall survival after receipt of 5400 cGy compared to ≥ 5940 cGy (log-rank p = 0.86).*

p = 0.57). GTR was not associated with OS (HR = 0.61, 95% CI 0.34-1.11, *p* = 0.11) (**Table 3**). Grade III disease was significantly associated with decreased OS (HR = 2.41, 95% CI 1.25-4.62, *p* = 0.008) (**Figure 4**, *p* = 0.005)

Discussion

In this analysis of 548 patients with localized WHO grade II or III ependymoma identified from a national cancer registry, we found no difference in OS after receipt of dose-escalated radiation therapy.

Radiation therapy has been shown to improve OS and PFS in patients with localized ependymoma.[20] While there have been no randomized comparisons of radiation dose, dose response has been observed in select retrospective studies. In an initial report from the Children's Hospital of Philadelphia, local control was 32% for patients who received > 4500 cGy as compared to 0% for those who received lower doses.[19] A subsequent study from the same institution demonstrated improved PFS after receipt of ≥ 5400 cGy.[4] However, even after receipt of postoperative radiation therapy, patients remain at risk of local failure. In a recent study, patients who received radiation had a 58% risk of isolated local recurrence.[5]

Dose escalation has been evaluated in numerous studies in order to improve local control and survival outcomes. On the Pediatric Oncology Group protocol 9132, the potential benefits of dose escalation were evaluated using a hyperfractionated regimen of 6960 cGy (120 cGy twice daily). Patients had a 5-year event-free survival (EFS) of 52%, which compared favorably to historical controls.[22] On an Italian Association of Pediatric Hematology Oncology (AEIOP) protocol, patients without residual disease were treated to 7040 cGy (110 cGy twice daily).[23] Those with residual disease were treated with systemic therapy followed by the

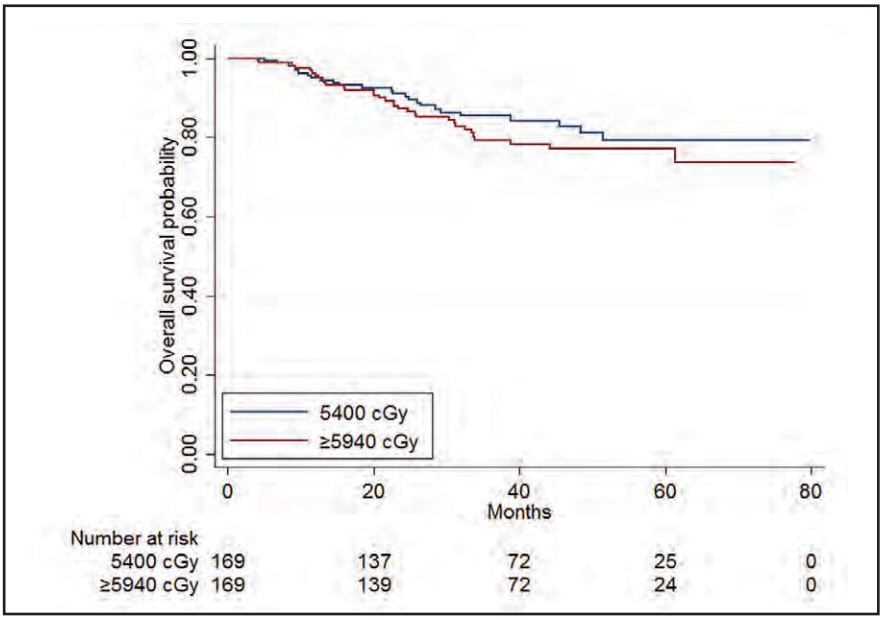

FIGURE 3. *Propensity score matched overall survival after receipt of 5400 cGy compared to ≥ 5940 cGy (log-rank p = 0.86)*

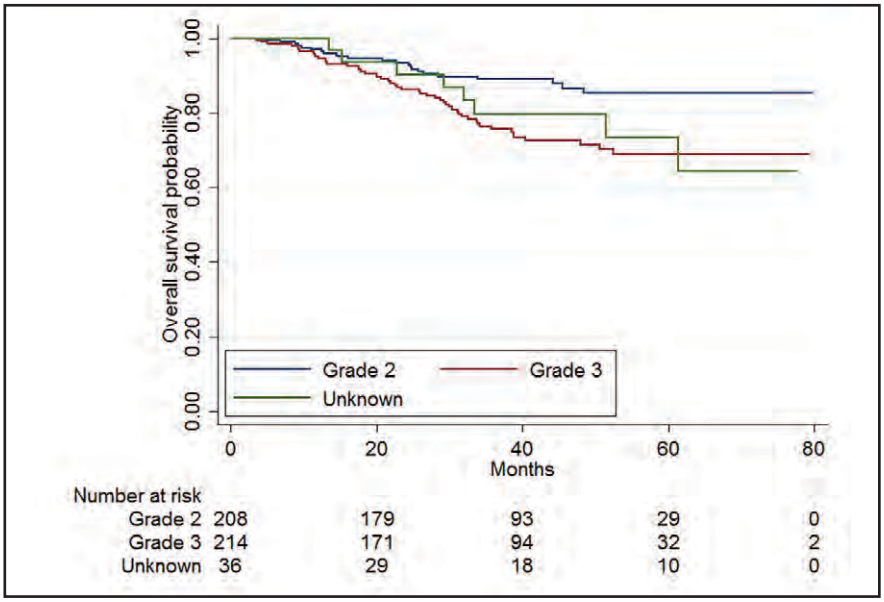

FIGURE 4. *Overall survival by grade (log rank p = 0.005).*

same radiation therapy. The 5-year PFS was 56% (95% CI 41-70%), 65% for those without residual disease (95% CI 49-82%) and 35% for those with residual disease (95% CI 10-61%). A subsequent AEIOP protocol attempted to improve results for patients with residual disease.[17] Patients who underwent gross total resection received adjuvant radiation to 5940 cGy using standard fractionation while those with residual disease after surgery received chemotherapy followed by 5940 cGy to the resection cavity and an 800 cGy boost in 2 fractions of 400 cGy each to any residual disease. For the whole series, 5-year EFS and OS were 65.4% (95% CI 57.7-74.0%) and 81.1% (95% CI 74.6%-88.2%). The 5-year probability of local relapse was 20.7% (95% CI 14.8-29.1%).

Dose escalation to 5940 cGy using standard fractionation was also evaluated in a phase II study from St. Jude's utilizing conformal radiation therapy.[7] Given concern for toxicity, patients < 18 months after gross total resection were treated to 5400 cGy. The estimated 7-year local control and OS were 83.7% (95% CI 73.9-93.5%) and 81.0% (95% CI 71.0-91.0%), respectively. Based on these impressive results, dose-escalated radiation therapy to 5940 cGy has become a common treatment regimen and has been adopted in an ongoing national pediatric ependymoma protocol for patients ≥ 18 months in age, or < 18 months with subtotal resection.[24]

Increased radiation dose, however, may result in several late side effects of CNS radiation which can be debilitating or fatal. Pediatric patients may experience a decline in intelligence quotient which has been associated with total dose and dose per fraction.[25-26] Radiation damage to critical structures can also result in endocrine and sensory changes.[27-31] Radiation necrosis is of significant concern given proximity of many infratentorial tumors to the brainstem and has been reported in 2.5% of patients with ependymoma treated with dose-escalated radiation therapy.[7] This risk has been correlated with dose and volume, especially the maximal dose and dose to 50% and 10% of the brainstem.[11,12] In general, the entire brainstem may be treated to 5400 cGy using conventionally fractionated photon therapy without significant risk of permanent neurologic deficits. Smaller volumes may be irradiated to maximum doses of 5900 cGy and risk significantly increases with maximal dose > 6400 cGy.[13] Given concern for increased risk of brainstem necrosis using proton radiation, more stringent brainstem constraints have been proposed.[11]

Other factors associated with OS in pediatric and adult ependymoma include

Table 3. Factors Associated with Overall Survival

	— Multivariable —		— Propensity Score Matched Cohort —	
	HR [95% CI]	p	HR [95% CI]	p
Dose				
5400 cGy	-	-	-	-
≥ 5900 cGy	0.74 [0.39, 1.40]	0.36	0.83 [0.44, 1.57]	0.57
Age (years)				
≤ 18	-	-		
> 18	1.64 [0.94, 2.87]	0.08		
Race				
White	-	-		
Black	0.60 [0.26, 1.36]	0.22		
Hispanic	0.59 [0.24, 1.42]	0.24		
Other	0.31 [0.09, 1.05]	0.06		
Insurance Status				
Commercial Insurance	-	-		
Medicare	2.56 [1.28, 5.11]	0.008		
Medicaid	1.30 [0.70, 2.43]	0.40		
Uninsured	2.10 [0.92, 4.79]	0.078		
Other/Unknown	2.61 [0.92, 7.36]	0.070		
Charlson/Deyo Comorbidity Score				
0	-	-		
1	1.21 [0.52, 2.81]	0.66		
2	0.33 [0.04, 2.70]	0.30		
3	2.80 [1.02, 7.66]	0.045		
Location of Tumor				
Cerebrum	-	-		
Ventricle	0.38 [0.14, 1.07]	0.07		
Cerebellum	0.77 [0.26, 2.26]	0.63		
Brainstem	0.90 [0.42, 1.95]	0.79		
Brain NOS	1.38 [0.74, 2.55]	0.31		
Grade				
2	-	-		
3	2.41 [1.25, 4.62]	0.008		
Unknown	1.59 [0.68, 3.72]	0.28		
Extent of Resection				
Biopsy only	-	-		
Subtotal resection	1.00 [0.50, 1.99]	0.99		
Gross total resection	0.61 [0.34, 1.11]	0.11		
Receipt of Chemo				
No	-	-		
Yes	1.56 [0.91, 2.70]	0.11		
Unknown	0.62 [0.08, 4.75]	0.65		

Key: CI = conformity index, NOS = not otherwise specified

greater extent of resection, low-grade disease, and supratentorial location.[4,5,7] In this series, grade III disease was associated with decreased OS and increased likelihood of receiving dose-escalated radiation therapy. In multiple studies, GTR compared to subtotal resection has been associated with significantly improved OS.[5,7] While GTR was associated with OS in univariable analysis, no association with extent of resection and OS was observed on multivariable analysis.

Several shortcomings limit the generalizability of the current study. First, there is inherent selection bias that cannot be controlled in the setting of a retrospective, observational study. In particular, bias toward treating patients with higher grade disease with dose-escalated radiation may have influenced outcomes seen on this study. Factors such as extent of resection, tumor location, and histopathologic grade are determined by the treating facility and not subject to central review, which may alter baseline patient characteristics given the relatively subjective nature of these features. Genetic information, which may affect the overall prognosis, was not available for inclusion in this analysis.

In addition, given the available data within the NCDB, no assessment of other treatment-related outcomes including local control, PFS, or toxicity could be made. While there are risks of dose-escalated radiation therapy, toxicities from local failure and salvage therapies may justify use of higher dose radiation even in the absence of an OS benefit. Furthermore, the limited follow-up of this study may not be enough to observe a meaningful difference in OS. Finally, although the NCDB captures a large volume of cancer cases, there is a lack of participation of many large independent children's hospitals, which may bias results. This lack of pediatric cases is evident in our data where the majority of patients are ≥ 18 years, which is not representative of the epidemiology of this disease.

In conclusion, we show no OS benefit to dose-escalated radiation therapy in a population of pediatric and adult patients with localized, high-grade ependymoma identified from the NCDB. Given possible toxicities associated with dose-escalated radiation in the CNS, additional study to determine which patients may benefit from dose-escalated therapy is warranted.

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IMRT, VMAT and image guidance: Changing the landscape of colorectal cancer treatment

Mary Beth Massat

Surgery has long been a primary treatment for colorectal cancer. While it remains a fundamental pillar of curative therapy, it doesn't come without potential consequences for a patient's quality of life. For example, if the cancer is in the lower part of the rectum close to or involving the anus, an abdominal perineal resection (APR) is performed, resulting in removal of the anus and a permanent colostomy.[1]

Radiation therapy (RT), frequently in combination with chemotherapy, is often used as a neoadjuvant therapy prior to surgery, especially in rectal cancers (**Figure 1**). Although historically 3-dimensional conformal RT (3DCRT) has been used, intensity-modulated radiation therapy (IMRT) is now utilized more often when RT is included in a patient's treatment. However, not all insurance plans in the US cover the cost of IMRT in colorectal cancer.

"Reimbursement is an issue. It is so frustrating that it often comes down to this because I want to do what is best for my patients and minimize the risk of toxicity associated with the treatment," says Karyn A. Goodman, MD, MS, professor of radiation oncology and the David F. and Margaret Turley Grohne Chair in Clinical Cancer Research at the University of Colorado Denver School of Medicine. Dr. Goodman is also co-chair of the National Cancer Institute's Gastrointestinal Cancer Steering Committee.

"If there was no cost difference in reimbursement between IMRT and 3D conformal, we would do all plans as IMRT," Dr. Goodman says. (**Figure 2** compares a dose volume histogram of a 3DCRT plan with an IMRT plan.) Her dosimetrist also prefers IMRT and, in most cases, VMAT (volumetric-modulated arc therapy) plans for rectal cancers. "They just feel more comfortable with IMRT than a plan that has 3 fields, uses wedges, etc."

Dr. Goodman believes the RTOG 0822 clinical trial, which compared the gastrointestinal toxicity in patients treated with IMRT combined with 5-FU and oxaliplatin to a historical control group of patients treated with 3DCRT with 5-FU and oxaliplatin, has made it difficult to justify the benefit of IMRT.[2] Unfortunately, the oxaliplatin, a chemotherapy drug found to have more GI toxicity when combined with 5-FU and RT, probably contributed more to the GI toxicity than the radiation so the GI toxicity rates were not different in the IMRT group vs the 3DCRT group.[3,4]

"Typically, GI toxicity is much lower in our clinic than what the RTOG 0822 trial was studying. Unfortunately, the use of IMRT couldn't make up for the added toxicity of oxaliplatin," Dr. Goodman says. "An ideal study would be a randomized prospective study; however, that likely will not be funded."

Instead, she says, the best way to overcome the RTOG 0822 trial results is for radiation oncologists to continue publishing their studies regarding toxicity when using IMRT in rectal cancer patients. She is also hopeful that the new recommendations from the Centers for Medicare & Medicaid Services (CMS) that may tie reimbursement to the type of cancer, not the type of RT

***Ms. Massat** is a freelance healthcare writer based in Crystal Lake, IL.*

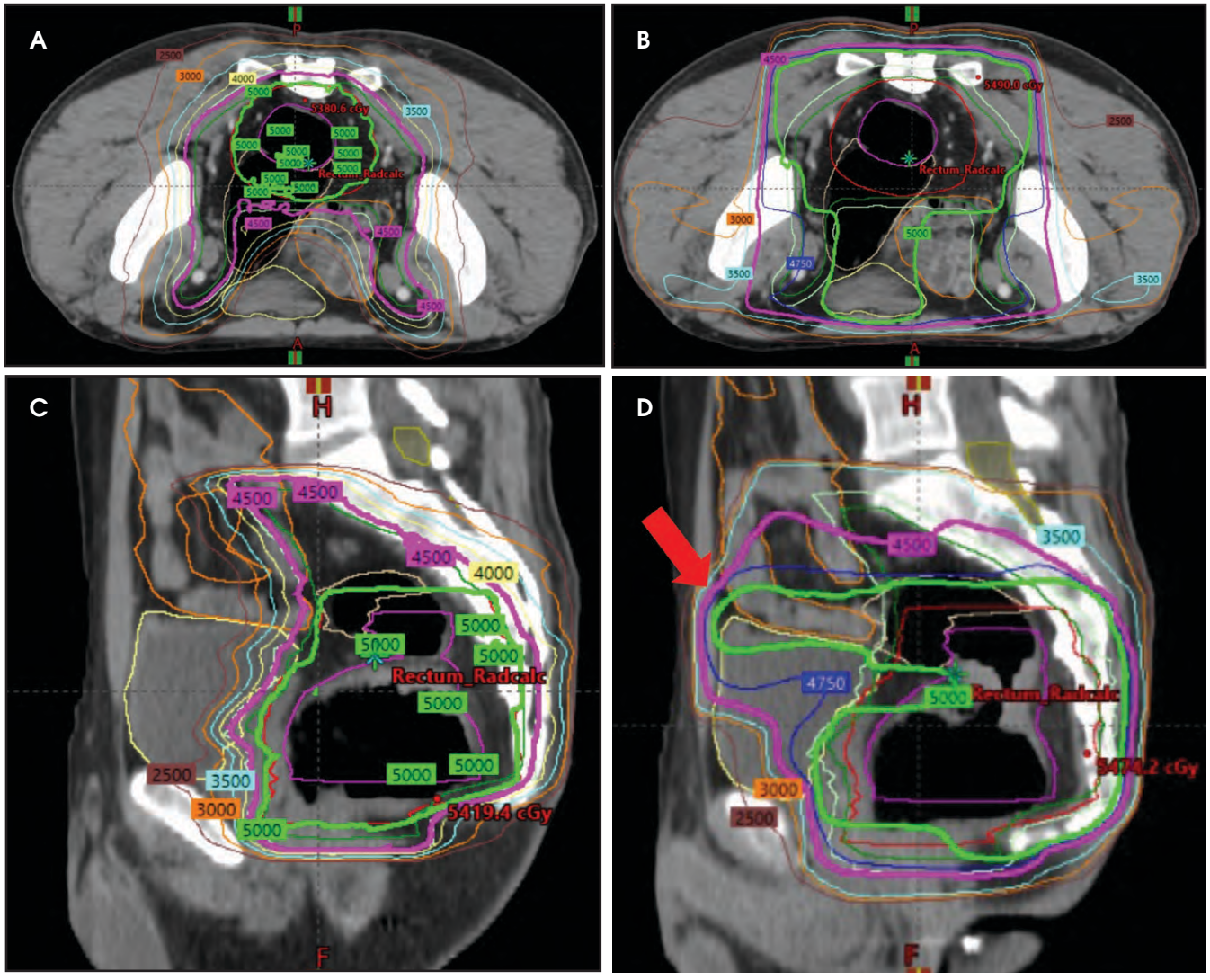


FIGURE 1. *A 34-year-old man with rectal adenocarcinoma with seminal vesical involvement who underwent neoadjuvant chemotherapy with FOLFOX and was referred for preoperative chemoradiation. Due to the seminal vesical involvement, the external iliac nodes were included. The pelvic radiation therapy field with the isodose lines are shown comparing an intensity-modulated radiotherapy (IMRT) plan in axial (A) and sagittal planes (C) and the 3D conformal radiation therapy plan in axial (B) and sagittal (D) planes. The dose to the primary tumor is shown in green and the elective nodal dose is in pink. The IMRT plan allows for improved sparing of normal tissue, including the bowel and bladder, which are receiving more of the prescription dose using the 3DCRT plan (red arrows). Images courtesy of Dr. Karyn A. Goodman, University of Colorado Denver School of Medicine.*

used, may alleviate this issue altogether.

Dr. Goodman was co-author of a study that examined toxicity profiles and outcomes among rectal cancer patients treated with either IMRT or 3DCRT prior to surgery to identify predictive clinical factors tied to increased toxicity.[5] The study reported that more patients suffered from grade 2 diarrhea in the 3DCRT group, which also had greater odds of a higher diarrhea score than IMRT. Additionally, the 3DCRT group had higher grade 2 genitourinary toxicity (13 percent) vs the IMRT group (6 percent), which also had a trend toward decreased grade 2 proctitis (22 percent for the IMRT group vs 32 percent for the 3DCRT group).[5]

Location Matters

At Memorial Sloan Kettering Cancer Center (MSKCC), RT is primarily used for rectal cancers. According to Marsha Reyngold, MD, PhD, 3DCRT is the most commonly used technique, although IMRT is used for specific clinical situations depending on the location of the primary tumor.

"The small bowel is the sensitive organ that we want to avoid," Dr. Reyngold explains. "There are various positioning techniques, such as a belly board, that we can use to avoid the small bowel with 3D conformal."

IMRT is typically employed at MSKCC when a significant volume of

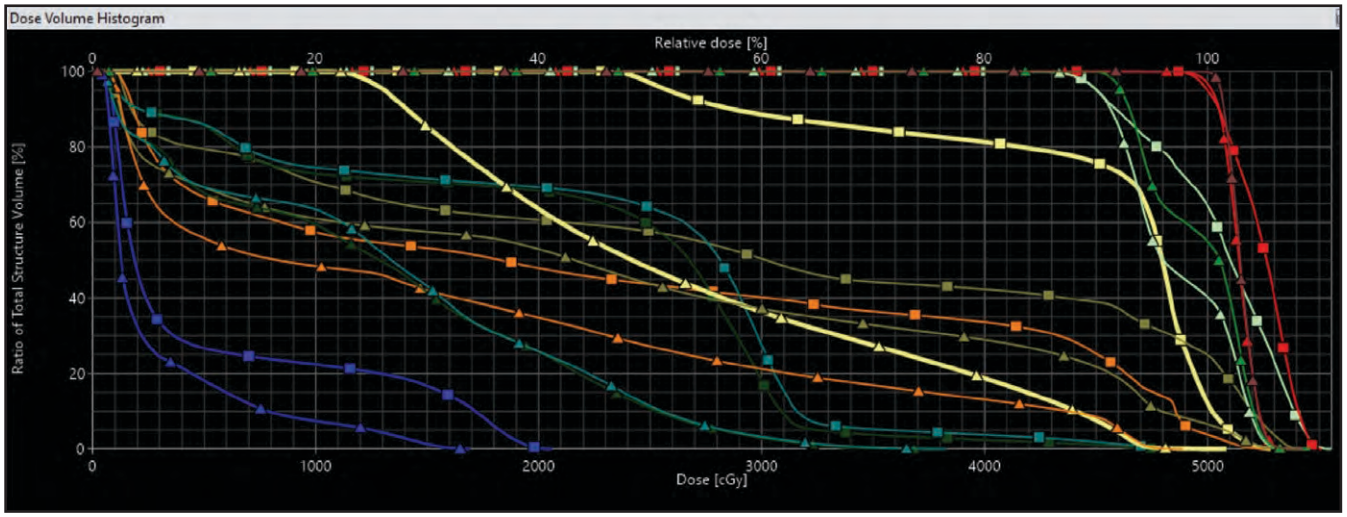


FIGURE 2. *A comparison of the dose volume histogram of the 3DCRT plan (squares) and the IMRT plan (triangles) for the bladder (yellow lines), large bowel (tan lines), small bowel (orange lines), right and left femoral heads (teal and green lines) and external genitalia (blue lines). The IMRT plan decreases the doses to the normal tissues so the triangle lines are consistently lower than the square lines. Image courtesy of Dr. Karyn A. Goodman, University of Colorado Denver School of Medicine.*

"If there was no cost difference in reimbursement between IMRT and 3D conformal, we would do all plans as IMRT."

Karyn A. Goodman, MD, MS
University of Colorado
Denver School of Medicine

the patient's small bowel is inside their pelvis or if they have already undergone prior surgery for pelvic disease (benign or malignant), resulting in a fixed small bowel. If the rectal cancer involves the prostate, bladder, uterus or vagina, then the treatment area is larger and IMRT may be more beneficial as it allows for more bowel sparing. Also, IMRT is very useful in treating tumors that are low in the rectum where avoidance of the genitalia is key to preventing sexual dysfunction, Dr. Reyngold explains.

A recent article co-authored by Dr. Reyngold and Dr. Goodman analyzed the use of IMRT for locally advanced rectal cancer at National Comprehensive Cancer Network (NCCN) centers. Using the NCCN Colorectal Cancer Outcomes Database, the authors looked at trends in the use of IMRT between 2005 and 2011, patient factors in selecting IMRT and acute toxicity of IMRT and 3DCRT. While increased use of IMRT was reported, it was not uniform across the 9 NCCN sites included in the analysis. Furthermore, a key predictor of the use of IMRT in the cohort was RT dose and not having undergone surgery. Patients receiving more than 5040 cGy had triple the likelihood of receiving IMRT. Also, not undergoing surgery as part of treatment was also a predictor of receiving IMRT vs 3DCRT.[6]

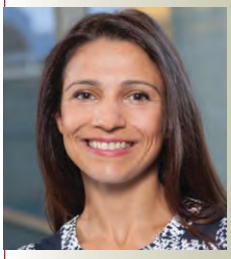
"As a field, we need to also look at long-term toxicity, including sexual dysfunction or the risk of hip and bone fractures," adds Dr. Reyngold. "We don't have very good data, and while we believe [toxicity] is low, it is not zero," she said, noting that use of IMRT may reduce long-term toxicity.

"While we use 3D conformal at MSKCC for the majority of patients, IMRT is not inferior, it is just less cost effective at this time," she adds. "IMRT may be superior to 3D conformal for a larger group of patients than we currently know, but more work needs to be done to identify what that group may be."

The Importance of Imaging

In addition to using standard linac-based IMRT plans, the University of California San Francisco (UCSF) Medical Center often uses VMAT integrated with image-guided radiation therapy (IGRT) to deliver precision radiation therapy.

"VMAT allows for a more rapid plan to be delivered that is more efficient



"As a field, we need to look at long-term toxicity, including sexual dysfunction or the risk of hip and bone fractures. We don't have very good data, and while we believe [toxicity] is low, it is not zero."

Marsha Reyngold, MD, PhD
Memorial Sloan Kettering Cancer Center

and highly conformal," says Mekhail Anwar, MD, PhD, assistant professor of radiation oncology at UCSF. Advances in treating rectal cancer have improved to the point where select patients with metastatic disease can be approached with curative intent. Dr. Anwar will also use stereotactic body radiation therapy (SBRT) in patients with metastases in the liver, bone or lung. Given the high doses used, image-guidance is an essential component in treatment planning for patients with colorectal cancers at UCSF.

"We capture cone-beam CTs to ensure we are aligning the patient precisely but also to look at internal changes, such as the bladder filling or bowel gas, that may impact dose to the internal organs," Dr. Anwar explains. He can visualize unexpected changes prior to treatment, especially if the small bowel falls into the beam or if the bladder is not in the same condition—empty or full—as the simulation and plan. "Our goal is to deliver precise and safe treatments."

Additionally, some cancers in the pelvis experience dramatic shrinkage while on therapy. This can be seen in advanced anal cancers, which are radiosensitive and can experience significant changes in size during treatment.

Although the decision to use IMRT or 3DCRT is guided by insurance, when IMRT is reimbursed Dr. Anwar and his colleagues typically use a VMAT plan.

Motivated by the challenges his patients face and tapping his PhD in electrical engineering, Dr. Anwar also conducts research on cancer imaging using microfabricated sensors and integrated circuits to evaluate patient response to treatment and increase personalized therapy.

IMRT and IGRT are complementary technologies that enable Dr. Anwar to deliver a high dose to the primary tumor as well as a meaningful yet lower dose to the surrounding areas at risk, using smaller margins on the volumes than a standard plan.

"IMRT and VMAT require more attention to detail as opposed to treating a large target area with a uniform dose," Dr. Anwar explains. "These techniques involve more contouring precision and knowledge of the patient's anatomy. We fuse not only our planning CT but also other clinical information, such as MRI and PET [positron emission tomography], to best interpret what areas are at risk for tumor development and to better understand patterns of spread."

Dr. Goodman will also use VMAT at the University of Colorado because it delivers a good conformal dose and leads to more areas of low dose in the patient compared to a static IMRT plan.

"With static IMRT fields, we have a higher dose delivered from each field, but there are areas of the body with no entry dose and areas with less dose," Dr. Goodman explains. "One area where we need to refine the planning technique with VMAT is in anal cancer or very low rectal cancer, which requires that we treat lymph nodes in the groin, and can increase the skin toxicity."

She has noted that special attention must be given to sculpt around the genitalia.

Nonoperative Management

While an emerging trend is to avoid surgery in treating low rectal cancers, more clinical evidence is needed. There is growing interest as to whether resection of low-grade tumors—particularly in elderly patients or when the tumor is low or in the anus—can be treated only with RT, chemotherapy or other targeted agents.

"Part of this emerging paradigm is to look at dose escalation and radiosensitizing systemic agents," says Dr. Anwar. "Both strategies are focused on delivering the maximal dose to the tumor while preserving the surrounding tissue. It is widely accepted that a permanent colostomy bag is not the most optimal outcome, although it is better than cancer returning. For, now the most concerted efforts are in determining who the right patient is for this approach."

Dr. Reyngold was also a co-author of a study that investigated the relationship between a pathologic complete response to neoadjuvant therapy in locally advanced rectal cancer and the distance to the anal verge. Using clinical data from MSKCC, the authors reported "a bimodal association between the distance to the anal verge and pathologic complete response with low tumors (<4 cm) and higher tumors (8-10 cm and >10 cm) less likely to have a complete pathologic response."[7]

"As we move to personalized therapy, daily imaging will be a big contributor for assessing response. We can look more in depth at the response as it is actually happening."

Mekhail Anwar, MD, PhD
University of California—San Francisco

"We want to identify patients with a complete response to chemo and chemoradiation who have a tumor that is close to the anal verge," Dr. Reyngold explains. "Surgery in these patients means their sphincter will be removed, and that is a quality-of-life issue for them. If we can avoid surgery, we are giving something back to the patient.

"In the analysis, we found that distance was a factor that strongly correlated to response," Dr. Reyngold adds.

The excitement surrounding nonoperative management of colorectal cancers is also supported by surgeons, says Dr. Goodman.

"Fifteen years ago, it was unheard of for a colorectal cancer patient to not have surgery. However, we know that in upwards of 25 percent of the cases, the patient has a pathological response after chemoradiation," she adds. "In these patients, the prospect of avoiding surgery and still curing them is exciting."

Dr. Goodman is studying options such as induction chemotherapy followed by chemoradiation and new combinations of targeted agents with chemoradiation to increase the rate of pathological response with chemo and RT.

"We can see over a 35 percent response rate where there is no cancer left," Dr. Goodman explains. "We are using MRI and endoscopy to help identify these patients and make this decision prior to surgery."

The idea is to do more focal dose painting with IMRT and then utilize a novel agent, such as a PARP inhibitor that prevents DNA damage by RT, or with a DNA-PK inhibitor that is radiosensitive and enhances the effect of RT, potentially improving the patient's response to therapy.

"We are looking to move the field to enhance radiation in the pre-op setting to improve outcomes in select groups of patients and allow for nonoperative management," Dr. Goodman adds.

The growing use of MRI and MR-based linear accelerators may also help assess response and personalize patient care in colorectal cancer. "We can now obtain a good anatomic look at the tumor using an onboard MRI in an MR-based linac," says Dr. Anwar.

Dr. Anwar is also examining treatment of anal cancer in challenging populations, such as HIV-positive patients who may be more vulnerable to toxicities, as well as quantifying changes in patients, such as skin reaction and blood counts, before the toxicity of treatment leads to difficult side effects.

Integrating multiparametric MRI and molecular PET imaging with machine learning may also help radiation oncologists identify subtle changes, he adds. Genetic-based biomarkers will hopefully guide clinicians on which patients will respond to radiation with chemotherapy or radiation with a targeted therapy or immunotherapy, although development of better biomarkers are greatly needed.

"As we move to personalized therapy, daily imaging will be a big contributor for assessing response," adds Dr. Anwar. "We can look more in depth at the response as it is actually happening to determine if we are on the right track and who is responding and may not need surgery."

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Substituting stereotactic body radiation therapy boost for brachytherapy using Mayo protocol for peri-hilar cholangiocarcinoma

James Broughman, MD; Sarah Sittenfeld, MD; Kristine Bauer-Nilsen, MD; Kevin Stephans, MD

CASE SUMMARY

This is a 56-year-old man with history of primary sclerosing cholangitis (PSC) who was found to have an elevated CA 19-9 of 126 units/mL. Endoscopic retrograde cholangiopancreatography (ERCP) revealed atypical cells suspicious for adenocarcinoma, and fluorescent in situ hybridization (FISH) demonstrated a gain of 1q21 and deletion of 9p21. MRI revealed a dominant stricture of the right hepatic duct without a discrete mass, and a few mildly prominent peri-portal lymph nodes. A clinical diagnosis of peri-hilar cholangiocarcinoma was made based on the combination of a dominant stricture and FISH findings.[1] The peri-portal lymph node was sampled by endoscopic ultrasound revealing benign lymphocytes, and was presumed to be reactive secondary to PSC. His lesion was determined to be unresectable given bilateral intrahepatic duct involvement. Following multidisciplinary discussion, neoadjuvant chemoradiation followed by orthotopic liver transplant was recommended. The patient received external-beam radiation therapy (EBRT) (45 Gy in 30 fractions delivered twice daily [BID]) with concurrent capecitabine. He was subsequently scheduled for intrabiliary high-dose rate (HDR) brachytherapy; however, due to a long-standing PSC-related stricture and subsequent severe atrophy of the right liver, the right intra-hepatic duct could not be traversed by percutaneous transhepatic cholangiography. Thus, a stereotactic body radiation therapy (SBRT) boost (30 Gy in 3 fractions) was utilized to approximate the planned brachytherapy dose (**Figure 1**). One week following completion of the SBRT boost he underwent exploratory laparotomy to verify the absence of extra-hepatic disease, and was subsequently listed for transplant. He resumed capecitabine and ultimately underwent planned living donor total liver transplant 3 months after completing chemoradiation. Pathology revealed moderately differentiated adenocarcinoma involving the common hepatic duct and extending proximally to the confluence of the left and right hepatic ducts with invasion into adjacent liver parenchyma. The volume of residual disease was unable to be assessed as the tumor could not be differentiated grossly from extensive scarring. Surgical margins were negative for malignancy (though positive for high-grade dysplasia), and 0 of 3 lymph nodes were involved.

Dr. Broughman, Dr. Sittenfeld, *and* ***Dr. Bauer-Nilsen*** *are radiation oncology residents, and* ***Dr. Stephans*** *is an attending radiation oncologist, Department of Radiation Oncology, Cleveland Clinic.* *Disclosure: The authors have no conflicts of interest to disclose. None of the authors received outside funding for the production of this original manuscript and no part of this article has been previously published elsewhere.*

IMAGING FINDINGS

Magnetic resonance cholangiopancreatography (MRCP) demonstrated a stricture of the right hepatic duct without a discrete mass.

DIAGNOSIS

Peri-hilar cholangiocarcinoma (CCA)

DISCUSSION

Cholangiocarcinoma is a rare neoplasm arising from the epithelial cells of the bile ducts. Approximately 95% of cholangiocarcinomas involve the extra-hepatic bile ducts and, of those, 60% to 70% arise from the peri-hilar region. Patients with primary sclerosing cholangitis have a lifetime risk of CCA of 10% to 15%.[2]

The primary means of achieving a cure is a negative-margin resection, although this can be achieved in < 30% of patients due to bilateral liver parenchymal involvement, vascular invasion, or poor hepatic functional reserve. Thus, the search for better treatment alternatives has led to transplantation, which provides wide surgical margins and addresses underlying liver dysfunction.

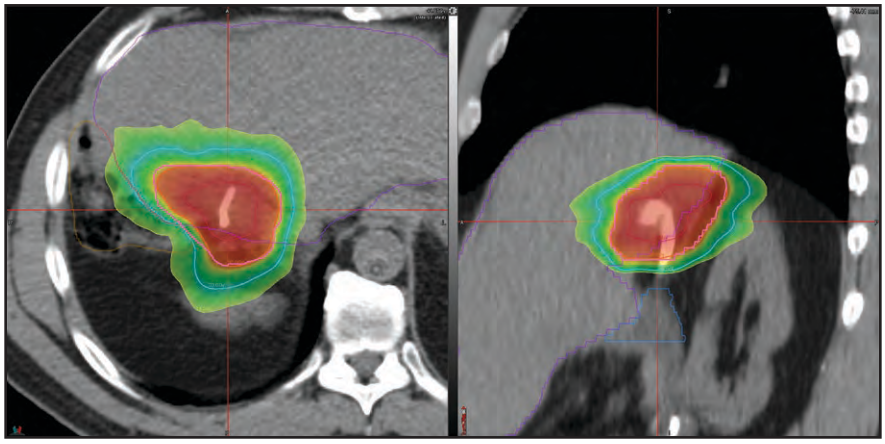

FIGURE 1. *An SBRT boost (30 Gy at 10 Gy per fraction) was delivered to the PTV (pink contour). Isodose lines including 37.5 Gy (red line), 30 Gy (orange line), 20 Gy (blue line), and 15 Gy (green line) are shown. Organs at risk including liver (purple contour), duodenum (blue contour), and large bowel (brown contour) were delineated. Key: SBRT = stereotactic body radiation therapy, PTV = planning target volume*

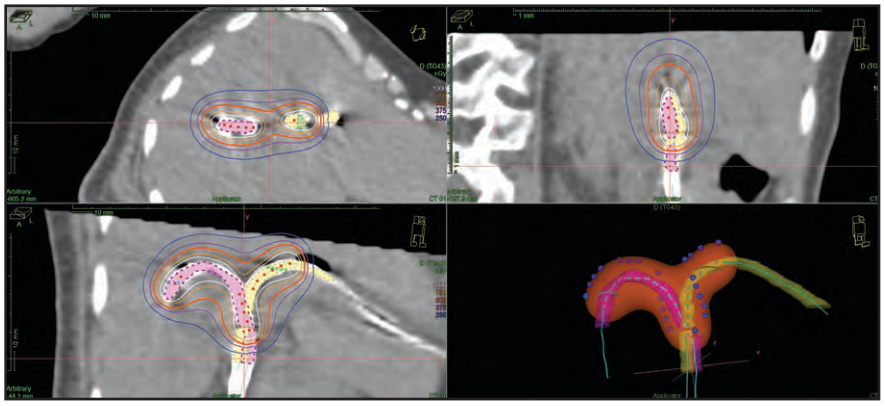

FIGURE 2. *Sample intra-biliary brachytherapy plan utilizing 5 Gy per fraction over 3 fractions prescribed to 1 cm depth given BID. The 5 Gy prescription isodose line is shown in orange. Note that the 10 Gy isodose line shown in white extends just beyond the catheter tubing. In selecting our SBRT prescription dose of 10 Gy per fraction, we sought to approximate the brachytherapy surface dose. Key: BID = twice daily, SBRT = stereotactic body radiation therapy*

Early experiences with transplantation alone were disappointing with 5-year overall survival < 30%.[3] To improve outcomes, the University of Nebraska pioneered neoadjuvant chemoradiation followed by liver transplantation.[4] This approach was later adopted by the Mayo Clinic utilizing neoadjuvant chemoradiation followed by transplant in carefully selected patients with early stage cholangiocarcinoma that is either unresectable or in the setting of primary sclerosing cholangitis. Outcomes were encouraging with 5-year survival rates of 71%,[5] with a subsequent series verifying reproducibility of these outcomes in a multi-institutional setting.[6] Given these excellent outcomes, some have even advocated for this approach in resectable patients, although this would be a resource-intensive approach overall.[7]

On this neoadjuvant protocol, patients are treated initially with EBRT (45 Gy at 1.5 Gy/fraction BID with concurrent 5-fluorouracil-based chemotherapy to an initial volume including the primary tumor plus margin and first echelon lymph nodes. At 2 to 3 weeks after completion of EBRT, an intraluminal brachytherapy boost (20-30 Gy initially utilizing low-dose-rate radium sources prescribed to 1 cm over the course of 1-2 insertions) was delivered to encompass the tumor and a 1.5- to 2-cm margin above and below the radiographic extent of disease. Currently, most institutions substitute high-dose rate brachytherapy with a variety of fractionation schedules to approximate the original low-dose rate prescription. Our practice is to utilize 5 Gy per fraction over 3 fractions prescribed to 1 cm depth given BID. After brachytherapy, patients undergo exploratory laparotomy to confirm lack of extra-hepatic disease and, after recovery, resume oral capecitabine until transplantation.

Intraluminal brachytherapy is an important component in the treatment of cholangiocarcinoma. The advantage of intraluminal brachytherapy over EBRT is the ability to deliver high doses to the tumor, while maximally sparing normal tissue due to rapid dose fall-off. Brachytherapy has a very different dose distribution than EBRT with extremely high doses at the surface, and rapid fall-off based on the inverse square of the distance from the source. In selecting our SBRT prescription dose of 10 Gy per fraction, we sought to approximate the brachytherapy surface dose, which is an estimate of the dose to a small biliary tumor after downsizing from EBRT. Admittedly this is not precise and varies depending on catheter orientation and the thickness of the tubing used. As noted in **Figure 2**, the 10 Gy line lies for the most part just beyond the surface of the HDR tubing. Given the significant heterogeneity of brachytherapy (small portions of the bile duct surface appear to receive significantly > 10 Gy per fraction) we did not emphasize uniformity of SBRT

dosing in our treatment plan. While SBRT can achieve relatively rapid dose fall-off, it is certainly not as rapid as that achieved by brachytherapy and, as such, the volume of the 10 Gy dose using SBRT is significantly higher in our plan than it would have been with brachytherapy. We presumed that this would be safe given that the toxicity of a serial structure such as the bile duct should be driven more by point doses and hot spots leading to risk of stricture rather than volume. Some parameters for central biliary dose and toxicity have been reported and, of note, cholangiocarcinoma patients are at highest risk given direct tumor involvement of the bile ducts;[8] however, these are not uniformly consistent across reports. Acute toxicity to the ducts appeared modest in the published neoadjuvant series[5,6] noted above, albeit with prophylactic stenting for most patients and subsequent transplant to prevent further late toxicity. Furthermore, a single retrospective series reported primary SBRT for the full course of treatment in 12 patients with peri-hilar cholangiocarcinoma (50-60 Gy in 3-5 fractions) prior to transplant, with 6 of those patients reaching transplant with an acceptable 1-year survival rate of 83% at the time of publication.[9]

SBRT has potential advantages including greater generalizability, minimal invasiveness, and greater simplicity compared to percutaneous transhepatic cholangiography (PTHC) placement and intraluminal brachytherapy. However, given the limited body of data using SBRT prior to transplant for peri-hilar cholangiocarcinoma, our preference remains to use conventional EBRT and a brachytherapy boost as described in the Mayo and multi-institutional series when feasible.

CONCLUSION

Peri-hilar cholangiocarcinoma portends a poor prognosis. Traditionally, resection has offered the highest chance of cure, although unfortunately most patients are unresectable due to frequent involvement of both bile ducts due to tumor location. Neoadjuvant chemoradiation with brachytherapy boost followed by liver transplantation has led to promising survival outcomes in early published experiences, perhaps even surpassing surgery alone. For patients in whom brachytherapy boost is not feasible, SBRT may provide a safe and effective alternative.

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RADIATION ONCOLOGY CASE

Abscopal effect of radiation therapy in monotherapy in a patient with malignant melanoma

Catarina Martins Silva, MD; Carlos Fardilha, MD; Diana Freitas, MD; Graça Fonseca, MD; Manuel Louro, MD; Paulo Costa, MD

INTRODUCTION

There is increasing interest in the systemic effect that radiation therapy may provide, namely the abscopal effect—the ability of locally administered radiation therapy to trigger antitumor effects at a distance in nonirradiated metastatic lesions.[1] However, the abscopal effect caused by conventional radiation therapy alone has been sparsely reported.

In this work we discuss a representative case of this effect, with the objective of adding to the minimal literature on this subject.

CASE SUMMARY

We report a case of malignant metastatic melanoma in a 93-year-old woman, who is completely independent in activities of daily living. In October 2015, the patient was diagnosed with malignant melanoma in the fifth toe of the right foot with a 2.8-mm Breslow depth. Cervical, thoracic, abdominal and pelvic computed tomography (CT) scans taken in November 2015 did not demonstrate metastatic disease.

In February 2016, lymphoscintigraphy showed drainage of the radiopharmaceutical into the right inguinal region and subsequent accumulation of the radiopharmaceutical into several ganglia of this region. The 2 most proximal ganglia of the lesion (sentinel) received a dermal marking with the aid of a surgical probe. The patient underwent amputation of the toe and excision of the sentinel node in the ipsilateral inguinal region in the same month.

In March 2017, clinical progression of the disease was noted, with the patient noting pain in the right lower limb. Examination revealed a nodal conglomerate in the right inguinal region of about 4 cm, painful to palpation. There were also 5 cutaneous lesions (**Figure 1**), hard to palpation, in the region of the anterior and inner face of the right leg, with about 3 months of evolution, macroscopically compatible with in-transit metastases.

In the same month, the patient underwent hypofractionated palliative radiation therapy to the right inguinal regions with volumetric-modulated arc therapy. She was treated to a dose of 36 Gy in 3 fractions with 6 MV photons on alternate days (**Figure 2**). The patient did not have any other systemic therapy, such as chemotherapy or immunotherapy. One month following radiation therapy there was regression not only of the lesions within the irradiated field, which presented only as a soft patch in the inguinal region with no pain to palpation, but also in nonirradiated areas, showing only a slight alteration in epidermal pigmentation, with no significant hardened lesions on the right lower limb (**Figure 3**).

The patient underwent treatment without relevant side effects, and her

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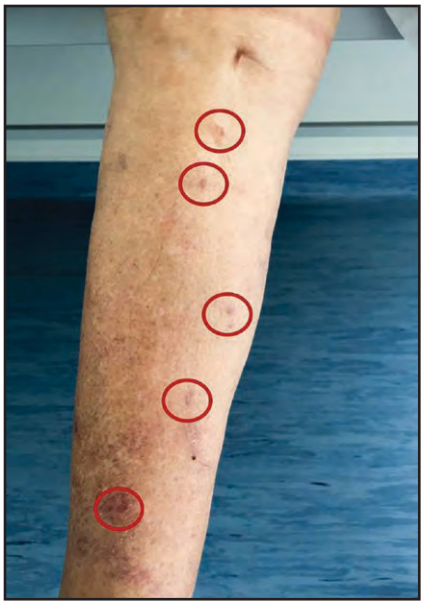

FIGURE 1. *Cutaneous sporotrichosis lesions in the region of the anterior and inner face of the right leg.*

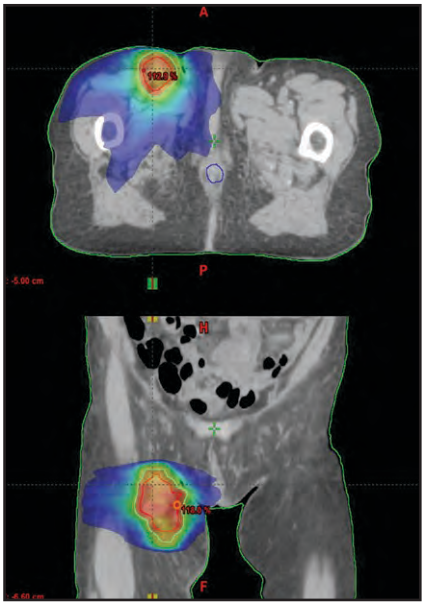

FIGURE 2. *Treatment plan of the right inguinal region treated with isodose curves.*

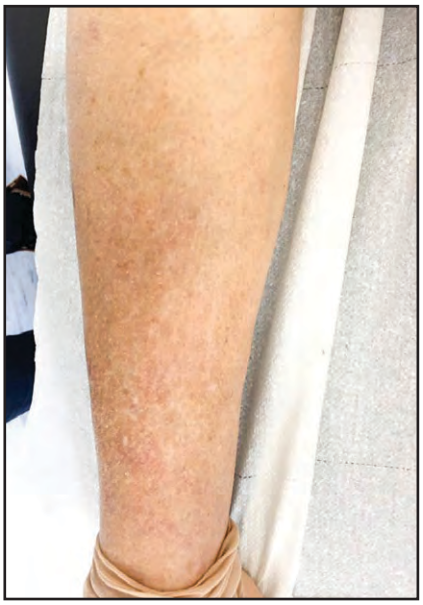

FIGURE 3. *Anterior and inner face of the right leg without the cutaneous sporotrichosis lesions after inguinal level radiation therapy.*

overall status improved. The follow-up lasted a year and 2 months after the radiation therapy treatment, during which the patient did not present any treatment side effects. After then, we lost access to follow-up information since the patient moved to a different city.

DISCUSSION

Radiation therapy has been considered valuable for the control and eradication of local foci in several malignant tumors. However, there is increasing interest in the systemic effect it may produce, namely the abscopal effect.

The clinical evaluation of the abscopal effect changes the paradigm of treatment for radiation oncologists, whose main objective is to eradicate local disease, maximizing the direct death of the tumor cells, while minimizing damage to nearby normal tissue.

This concept was first reported by RH Mole in 1953,[1] and has been elucidated in the recent work of several researchers such as Formenti and Demaria, who have shown that this process is probably mediated by the immune system, as ionizing radiation therapy exerts direct cytotoxic effects on tumor cells but also has the potential to enhance tumor immunogenicity by reprogramming the tumor microenvironment and eliciting antitumor T-cell responses. Radiation therapy can induce direct tumor cell death and generate inflammatory signals, such as production and release of the cytokines and chemokines into the tumor microenvironment. This causes chemoattraction and infiltration of dendritic cells—essential antigen presenting cells—and effector T cells to the tumor site. Subsequently, these properties increase the anticancer immunological response and may be responsible for the indirect anticancer effects of radiation therapy on cancers outside of the radiation field, also known as the abscopal effect.[2-5]

A recent review of clinical cases reporting an abscopal effect after radiation therapy treatment has shown that most reported cases have occurred in immunogenic tumors, such as renal cell carcinoma, melanoma, lymphoma and hepatocellular carcinoma.[6-8]

We found 2 other case reports of the abscopal effect in melanoma where the patient was only treated with radiation therapy. The first is about a 28-year-old man with a primary cutaneous melanoma lesion on his right knee.[9] He also had a lymphangiogram showing abnormal inguinal, iliac and para-aortic nodes up to the level of the second lumbar vertebra. The patient was treated with fast neutrons with a dose of 14.40 Gy in 12 fractions over 35 days only to the palpable right inguinal region, with the uppermost border of the radiation field being at the level of the inferior border of the right sacroiliac joint. A repeat lymphangiogram 3 months after the radiation therapy treatment showed a remarkable regression not only on the inguinal nodes, but also on the iliac and para-aortic nodes. Nine months after treatment was started, the lymphangiogram was normal.

The second case report is about a 71-year-old man with an ulcerated malignant melanoma without lymph node involvement, which was resected.[10] A year later pulmonary and mediastinal recurrence was detected. The patient refused systemic treatment. Four months later he reported pain in the right temporal region where a subcutaneous node was detected. The biopsy confirmed a melanoma metastasis. He then received local radiation therapy to the right temporal region with a dose of 30 Gy in 10 fractions, with disappearance of the palpable lesion and pain relief. During the follow-up after radiation therapy, there was a significant reduction in the size of the mediastinal nodes and disappearance of pulmonary nodules.

The total dose and fractionation of the radiation therapy treatment in these case reports are considerably different from our case, reinforcing how variable and uncharted the abscopal effect is.

This effect can be stimulated if we combine immunotherapy with radiation therapy, as reported in some published clinical cases. However, the ideal conditions and appropriate concomitant therapy are not yet known.[11,12]

The abscopal effect mediated by radiation therapy alone is rare and not extensively investigated. By documenting and understanding the abscopal effect of radiation therapy, we present a potential approach to help maximize local and systemic disease control in select cases.

CONCLUSION

Considering these results and the rarity of the abscopal effect with radiation therapy alone, this case report should encourage subsequent study and investigation.

Many questions remain and require clarification depending on the type of tumor and its microenvironment. Treatment timing, the total dose and fractionation of treatment (dose per fraction and number of fractions), the size of the irradiation field, and patient selection are among aspects to consider in future studies.

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