APPLIED RADIATION ONCOLOGY™
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Liver cancer turf wars

E Sapir, E ElAlfy, P Novelli, and M Feng, University of Michigan Health System, Ann Arbor, MI

Predicting close local failure after liver resection for hepatocellular carcinoma

ET Fredman, AMS Kumar, G El-Gazzaz, F Aucejo, C Coppa, and M Abdel-Wahab, Cleveland Clinic, Cleveland, OH

Proton therapy for pituitary adenoma

WR Kennedy, R Dagan, RL Rotondo, D Louis, CG Morris, and DJ Indelicato, University of Florida Health Proton Therapy Institute and University of Florida, Gainesville, FL

Radiation Oncology Case
Radiation-induced pathologic complete response of gross nodal disease in recurrent head and neck melanoma

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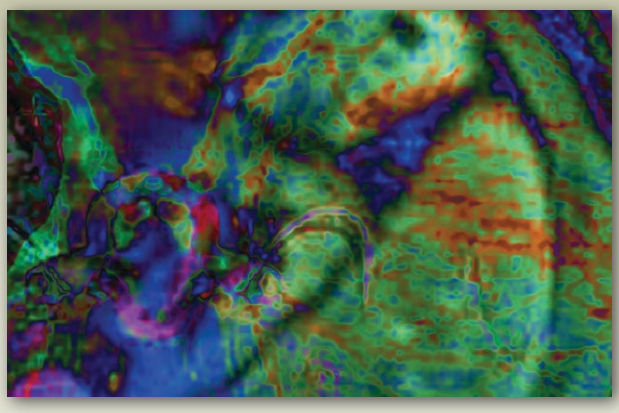
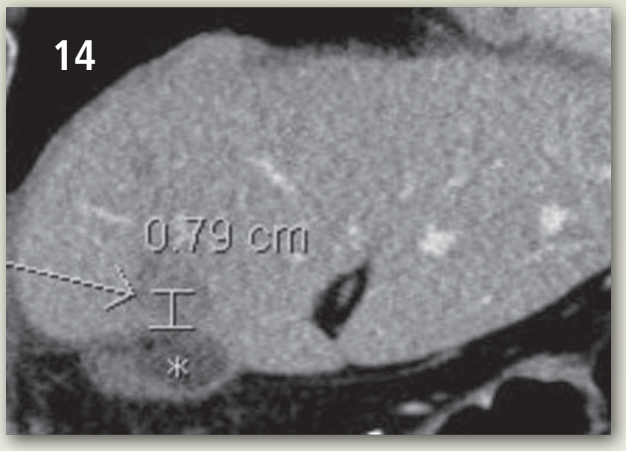
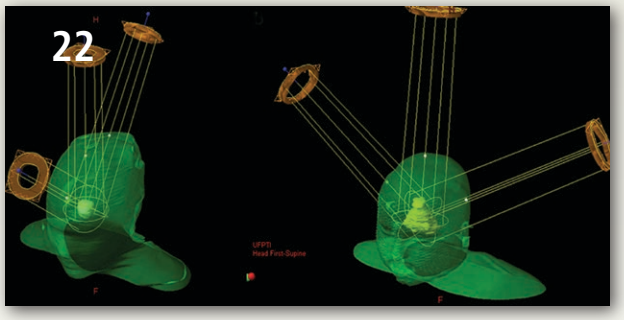
LIVER CANCER FOCUS







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Launched as an eJournal in 2012, Applied Radiation Oncology (ARO) is now available in print, online or on your mobile device. Published quarterly under the editorial guidance of John Suh, MD, Chairman of the Department of Radiation Oncology and Associate Director of the Gamma Knife Center at the Brain Tumor and Neuro-Oncology Center at Cleveland Clinic, each issue presents board--reviewed case presentations and clinical review articles that provide practical, actionable information that radiation oncologists can use to enhance the efficiency and quality of radiotherapy.

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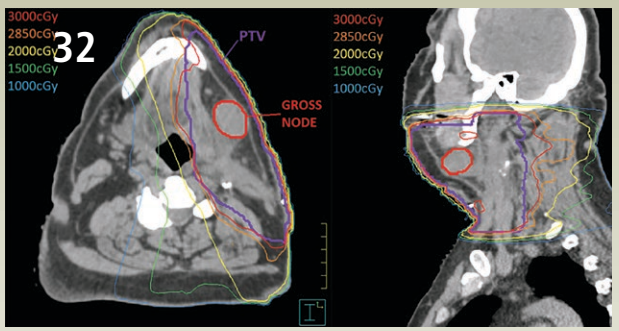
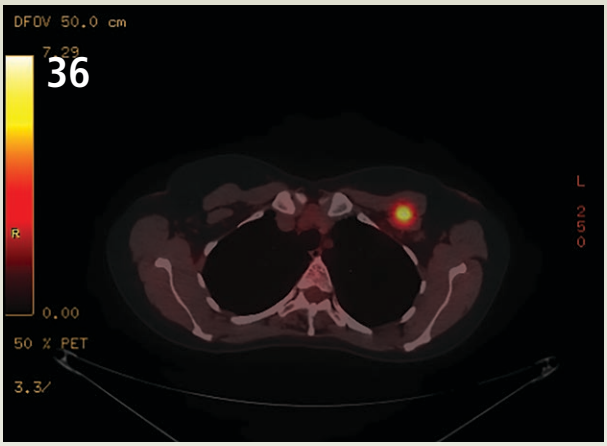
DEPARTMENTS



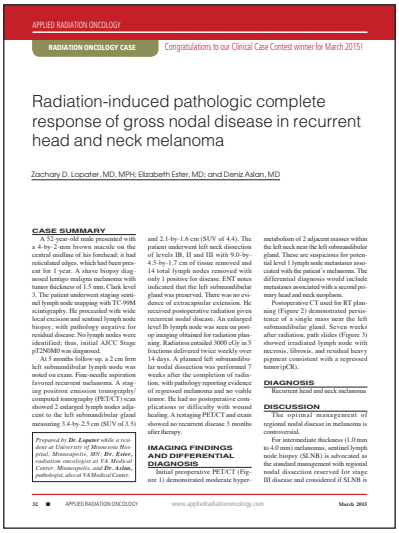


Bonus Online Content

RADIATION ONCOLOGY CASE
Whole-brain radiation therapy in pregnant patients with brain metastases: risks of ionizing radiation exposure to the fetus
Shireen Parsai BS, MS4; Mihir Naik MD; Toufik Djemil PhD, DABR; Samuel Chao MD

RADIATION ONCOLOGY CASE
Postradiation cardiac sarcoma and other secondary cancers more than 25 years after chemotherapy and mantle-field radiation for Hodgkin's lymphoma
Jerry T. Liu, MD; Jessica Niakan, MD; Mary B. Beasley, MD; Paul Stelzer, MD; Robert G. Maki, MD, PhD; Michael Buckstein, MD, PhD

CONTEST OPPORTUNITIES



APPLIED RADIATION ONCOLOGY

RADIATION ONCOLOGY CASE

Congratulations to our Clinical Case Contest winner for March 2015!

Radiation-induced pathologic complete response of gross nodal disease in recurrent head and neck melanoma

Zachary D. Lopater, MD, MPH; Elizabeth Ester, MD; and Deniz Aslan, MD

CASE SUMMARY

A 52-year-old male presented with a 4-by-2-mm brown macule on the central midline of his forehead; it had reticulated edges, which had been present for 1 year. A shave biopsy diagnosed lentigo maligna melanoma with tumor thickness of 1.5 mm, Clark level 3. The patient underwent staging sentinel lymph node mapping with TC-99M scintigraphy. He proceeded with wide local excision and sentinel lymph node biopsy, with pathology negative for residual disease. No lymph nodes were identified; thus, initial AJCC Stage pT2N0M0 was diagnosed.

At 5 months follow-up, a 2 cm firm left submandibular lymph node was noted on exam. Fine-needle aspiration favored recurrent melanoma. A staging positron emission tomography/computed tomography (PET/CT) scan showed 2 enlarged lymph nodes adjacent to the left submandibular gland measuring 3.4-by-2.5 cm (SUV of 3.5) and 2.1-by-1.6 cm (SUV of 4.4). The patient underwent left neck dissection of levels IB, II and III with 9.0-by-4.5-by-1.7 cm of tissue removed and 14 total lymph nodes removed with only 1 positive for disease. ENT notes indicated that the left submandibular gland was preserved. There was no evidence of extracapsular extension. He received postoperative radiation given recurrent nodal disease. An enlarged level Ib lymph node was seen on post-op imaging obtained for radiation planning. Radiation entailed 3000 cGy in 5 fractions delivered twice weekly over 14 days. A planned left submandibular nodal dissection was performed 7 weeks after the completion of radiation, with pathology reporting evidence of regressed melanoma and no viable tumor. He had no postoperative complications or difficulty with wound healing. A restaging PET/CT and exam showed no recurrent disease 3 months after therapy.

Prepared by ***Dr. Lopater*** *while a resident at University of Minnesota Hospital, Minneapolis, MN;* ***Dr. Ester****, radiation oncologist at VA Medical Center, Minneapolis, and* ***Dr. Aslan****, pathologist, also at VA Medical Center.*

IMAGING FINDINGS AND DIFFERENTIAL DIAGNOSIS

Initial preoperative PET/CT (Figure 1) demonstrated moderate hypermetabolism of 2 adjacent masses within the left neck near the left submandibular gland. These are suspicious for potential level I lymph node metastases associated with the patient's melanoma. The differential diagnosis would include metastases associated with a second primary head and neck neoplasm.

Postoperative CT used for RT planning (Figure 2) demonstrated persistence of a single mass near the left submandibular gland. Seven weeks after radiation, path slides (Figure 3) showed irradiated lymph node with necrosis, fibrosis, and residual heavy pigment consistent with a regressed tumor (pCR).

DIAGNOSIS

Recurrent head and neck melanoma

DISCUSSION

The optimal management of regional nodal disease in melanoma is controversial.

For intermediate thickness (1.0 mm to 4.0 mm) melanomas, sentinel lymph node biopsy (SLNB) is advocated as the standard management with regional nodal dissection reserved for stage III disease and considered if SLNB is

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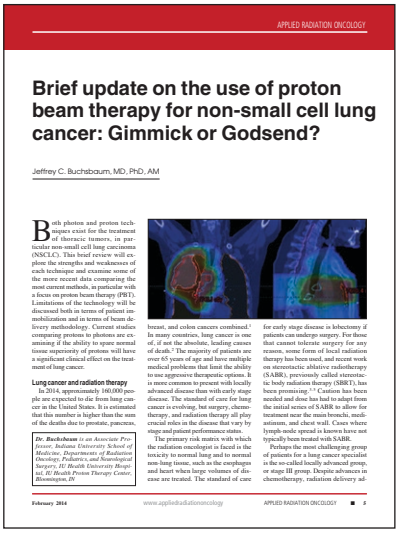
CLINICAL CASE CONTEST

ARO's quarterly Clinical Case Contest is an excellent opportunity to share your thoughts on management of a controversial or uncommon situation. Enter your clinical case for review by an international audience of your peers and the ARO advisory board, and a chance to win a $250 American Express Gift Card. The winning case will be published in next issue of *Applied Radiation Oncology.*

Cases that do not win will undergo the ARO advisory board review process for potential publication.

Visit appliedradationoncology.com/CaseContest for information about how to submit your case.

Deadline for submission is April 30, 2015!



APPLIED RADIATION ONCOLOGY

Brief update on the use of proton beam therapy for non-small cell lung cancer: Gimmick or Godsend?

Jeffrey C. Buchsbaum, MD, PhD, AM

Both photon and proton techniques exist for the treatment of thoracic tumors, in particular non-small cell lung carcinoma (NSCLC). This brief review will explore the strengths and weaknesses of each technique and examine some of the more recent data comparing the most current methods, in particular with a focus on proton beam therapy (PBT). Limitations of the technology will be discussed both in terms of patient immobilization and in terms of beam delivery methodology. Current studies comparing protons to photons are examining if the ability to spare normal tissue superiority of protons will have a significant clinical effect on the treatment of lung cancer.

Lung cancer and radiation therapy

In 2014, approximately 160,000 people are expected to die from lung cancer in the United States. It is estimated that this number is higher than the sum of the deaths due to prostate, pancreas,

breast, and colon cancers combined.[1] In many countries, lung cancer is one of, if not the absolute, leading causes of death.[2] The majority of patients are over 65 years of age and have multiple medical problems that limit the ability to use aggressive therapeutic options. It is more common to present with locally advanced disease than with early stage disease. The standard of care for lung cancer is evolving, but surgery, chemotherapy, and radiation therapy all play crucial roles in the disease that vary by stage and patient performance status.

The primary risk matrix with which the radiation oncologist is faced is the toxicity to normal lung and to normal non-lung tissue, such as the esophagus and heart when large volumes of disease are treated. The standard of care for early stage disease is lobectomy if patients can undergo surgery. For those that cannot tolerate surgery for any reason, some form of local radiation therapy has been used, and recent work on stereotactic ablative radiotherapy (SABR), previously called stereotactic body radiation therapy (SBRT), has been promising.[3,4] Caution has been needed and dose has had to adapt from the initial series of SABR to allow for treatment near the main bronchi, mediastinum, and chest wall. Cases where lymph-node spread is known have not typically been treated with SABR.

Perhaps the most challenging group of patients for a lung cancer specialist is the so-called locally advanced group, or stage III group. Despite advances in chemotherapy, radiation delivery ad-

Dr. Buchsbaum *is an Associate Professor, Indiana University School of Medicine, Departments of Radiation Oncology, Pediatrics, and Neurological Surgery, IU Health University Hospital, IU Health Proton Therapy Center, Bloomington, IN*

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ARTICLE OF THE YEAR CONTEST

All review articles published in ARO in 2015 will be automatically entered into the Article of the Year contest.

The first-place winner will receive a $500 American Express gift card for the best review article published in the ARO journal in March, June, September or December 2015.

The ARO Advisory Board will judge entries based foremost on practical application, but also on originality and presentation. A first-place winner and honorable mention will be announced in December 2015.

Visit appliedradiationoncology.com/author-guidelines for information about how to submit an article.

EDITORIAL

Liver focus and ARO's inaugural print issue

John Suh, MD, Editor-in-Chief

Welcome to the March 2015 issue of *ARO*! This month marks the exciting debut of the journal in print—in addition to running online—as requested by many ARO supporters. Offering each format delivers the best of both worlds: Among the benefits, print media is tangible, easy to use, and familiar. E-journals are readily accessible, easily searchable, simple to share (copy, paste, send), and provide a gateway to more information via links and search engines a click away.

Whatever your reading preference, you'll find an insightful two-part liver cancer focus featured this month. "Liver cancer turf wars" by Eli Sapir, MD, et al., University of Michigan, explores how treatment options for patients with localized HCC who are not candidates for surgery often vary based on institutional expertise. These differences can prompt liver cancer turf wars between experts—even in facilities with multidisciplinary panels. This review better defines the roles for surgery, radiation oncology and interventional radiology.

Second, "Predicting close local failure after liver resection for hepatocellular carcinoma" by Elisha T. Fredman, MD, et al., from Case Western Reserve University, discusses how advances in three-dimensional radiation planning, IGRT, and high-dose radiation therapy have demonstrated the effectiveness of radiation treatment as an adjuvant therapy in preventing intrahepatic HCC recurrence. To help select ideal patients for additional radiotherapy, the authors conducted a systematic radiological analysis of intrahepatic recurrence patterns to better understand where a failure will develop relative to the original surgical bed.

Also featured is "Proton therapy for pituitary adenoma," a retrospective review of patients treated at the University of Florida Proton Therapy Institute. The review describes how the high conformality of proton therapy does not appear to compromise local control or increase early toxicity. The authors provide additional information about the use of protons for pituitary adenomas.

As in every issue, we are pleased to showcase the winning case report from our quarterly Clinical Case Contest. "Radiation-induced pathologic complete response of gross nodal disease in recurrent head and neck melanoma," by Zachary D. Lopater, MD, MPH, et al., University of Minnesota Hospital, details how hypofractionated radiation therapy induced a pathological complete response in recurrent gross nodal disease.

A close runner-up is "Radiation therapy following a positive sentinel lymph node biopsy: A radiation oncologist's dilemma," by Zaker Rana, BS, et al., University of Maryland. This case examines why radiation oncologists and surgeons must be cautious when applying the findings of the ACOSOG Z0011 trial to patients with a positive sentinel lymph node biopsy and poor prognostic factors.

Case reports are an excellent opportunity to share your thoughts on management of a controversial or uncommon situation and allow you to bolster your CV. Please consider submitting your case here, and you may be the next *ARO* winner—online *and* in print.

As always, we welcome your thoughts on how to improve ARO. Please enjoy the inaugural print issue!

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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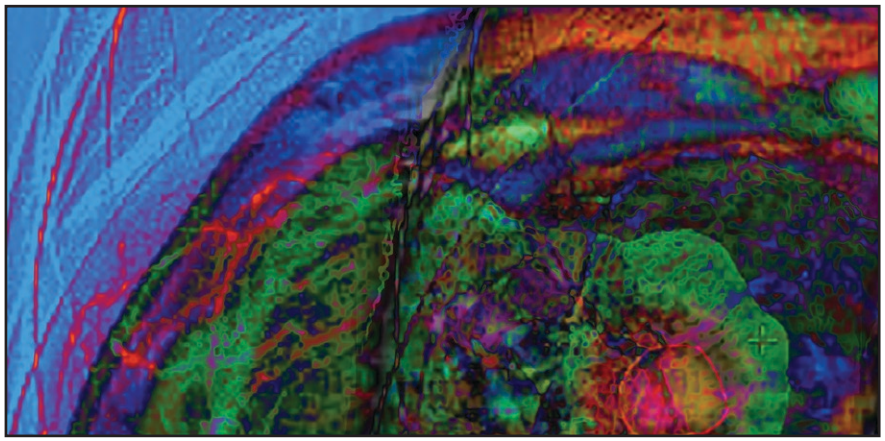
Liver cancer turf wars

Eli Sapir, MD; Eman ElAlfy, MD; Paula Novelli, MD; and Mary Feng, MD

Hepatocellular carcinoma (HCC) is a common diagnosis and problem worldwide: In males it is the 5th most frequent cancer, and in women it is the 7th.[1] The incidence of HCC in the United States continues to rise, and in 2011 it reached 6.2 cases per 100,000.[2] From the 1970s to 2000s, overall survival increased significantly (2 vs. 8 months). As expected, the survival improvement was predominantly noted in patients with localized disease (3 vs. 18 months),[2] reflecting diagnosis at earlier disease stages through screening high-risk populations with cirrhosis and the emerging broad arsenal of effective local and systemic treatment options.

Many patients with underlying cirrhosis have impaired liver function, and the degree of this dysfunction dictates prognosis as well as treatment options. The "best players" with preserved liver function and with early stage disease could benefit the most from liver transplantation, which not only treats the cancer but the underlying liver disease. However, there is a substantial wait time for transplantation and it is not unusual that many patients progress while waiting for the procedure. Another treatment option for patients with localized HCC and preserved liver function is a partial liver resection, which does not require a waiting period. Some advocate this in place of transplant but it is controversial, and is a turf war beyond the scope of this article. Unfortunately, most patients are not suitable for any surgical intervention either due to extensively disseminated intrahepatic HCC, vascular invasion, insufficient liver functional reserve, or other medical contraindications. For this population, treatment options may include localized ablative techniques such as radiofrequency ablation (RFA) and stereotactic body radiation therapy (SBRT); regional transarterial embolization techniques most commonly with chemotherapy or radiation (Yttrium-90); and systemic therapy with sorafenib, as well as combination therapy. The treatment modalities are evolving faster than level I evidence, suggesting challenges in determining the superiority of any one technique over the other. Thus, therapeutic approaches tend to vary based on institutional expertise, causing liver cancer turf wars between experts in different specialities, even in institutions with multidisciplinary panels. This review is aimed at better defining the roles for surgery, radiation oncology and interventional radiology, based on current data.



***Drs. Sapir** and **ElAlfy** are research fellows at the University of Michigan Health System, Ann Arbor, MI. **Dr. Novelli** is assistant professor in the Department of Radiology, Division of Vascular and Interventional Radiology, and **Dr. Feng** is associate professor in the Department of Radiation Oncology.*

Surgery

Liver transplantation

Liver transplantation is an excellent treatment for a highly selective cohort of patients, since in the proper situation

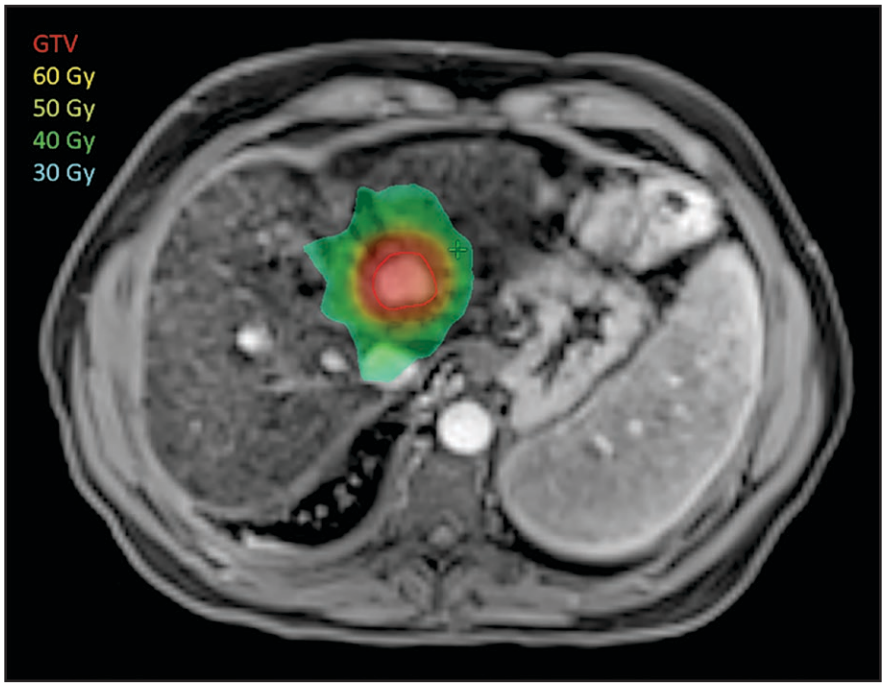


FIGURE 1. *Stereotactic body radiotherapy (SBRT) plan. High doses are delivered to the tumor with sparing of normal tissues*

it can both cure the HCC and cirrhosis simultaneously. For decades, the Milan criteria[3] (a single HCC ≤5 cm or multiple HCC 3 nodules ≤3 cm each with no macrovascular invasion or extrahepatic disease) have been used for optimal patient selection worldwide, with an overall survival rate of 75% and the recurrence-free survival of 83%.[3] Several institutions are stretching this standard practice with expanded transplant criteria or by downstaging patients with encouraging results. However, these potentially expanded criteria are still in flux and need to be validated.[4-10]

Partial hepatectomy

Liver resection is indicated in non-cirrhotic patients or patients with well-compensated cirrhosis and stage I-II disease. With limited perioperative morbidity and mortality, modern surgical techniques can achieve 5-year survival rates of at least 50%.[11] In patients with very early disease (single lesion ≤2-3 cm), partial hepatectomy has yielded outcomes similar to transplantation in several retrospective series.[12,13] Unfortunately, tumor recurrence rates in the remaining liver remain high (up to 80-100%[14,15]) due to the underlying cirrhosis, so patients often need multiple treatment strategies over a lifetime. This high recurrence rate can result in a potential turf war between transplant surgeons and surgical oncologists or hepatobiliary surgeons, which is beyond the scope of this article.

Local ablative treatment options

Radiofrequency ablation

When tumors are localized, focal treatments are preferred to minimize the risk of collateral damage in an already diseased and poorly functioning liver. RFA, performed percutaneously or intraoperatively, is a common treatment for unresectable HCC or medically inoperable patients. Efficacy is best for small tumors, less than 3-4 cm.[16-19] For these patients, local recurrence rates range between 0% and 26%.[20,21] Larger tumors are a bit more of a challenge, requiring several insertions to achieve complete ablation, if possible. RFA is rather convenient, typically a single outpatient treatment. On the other hand, it is an invasive procedure with placement of needle electrodes directly into liver tumors and requires anesthesia. Additionally, based on the tumor location, RFA also carries a small risk of injury to nearby structures including the lung, stomach, bowel, gall bladder and heart. Tumors near the diaphragm are difficult to visualize with ultrasound for targeting, and tumors near large vessels often cannot be fully heated, leading to incomplete treatment.

Radiotherapy

Liver SBRT (Figure 1) is a relatively new technique, which has been refined over the past decade, taking advantage of the explosion of new technologies for treatment planning, targeting and delivery. It is a non-invasive treatment that delivers high doses of precisely targeted radiation to tumors while avoiding nearby organs. Rather than extending over weeks like conventional radiotherapy, SBRT is completed in a few (1-5) treatments.

SBRT has come a long way since the first reports in the early 1990s.[22] In 2008, Tse and colleagues published a phase I study of 31 patients with primary intrahepatic tumors treated with SBRT. Treatment was well-tolerated, with 17% of patients declining from Child-Pugh class A to B at 3 months, and 65% local control at 1 year.[23] The phase II extension of this study to 102 patients recently demonstrated 87% 1-year local control.[24] Numerous retrospective reviews have been published also demonstrating high local control rates.[25-27] Toxicity has been variable, and can include liver failure and GI bleed, highlighting the importance of patient selection, careful treatment planning, dose selection (based on liver function) targeting and delivery, which should not only seek to cover the tumor with high-dose radiation, but also

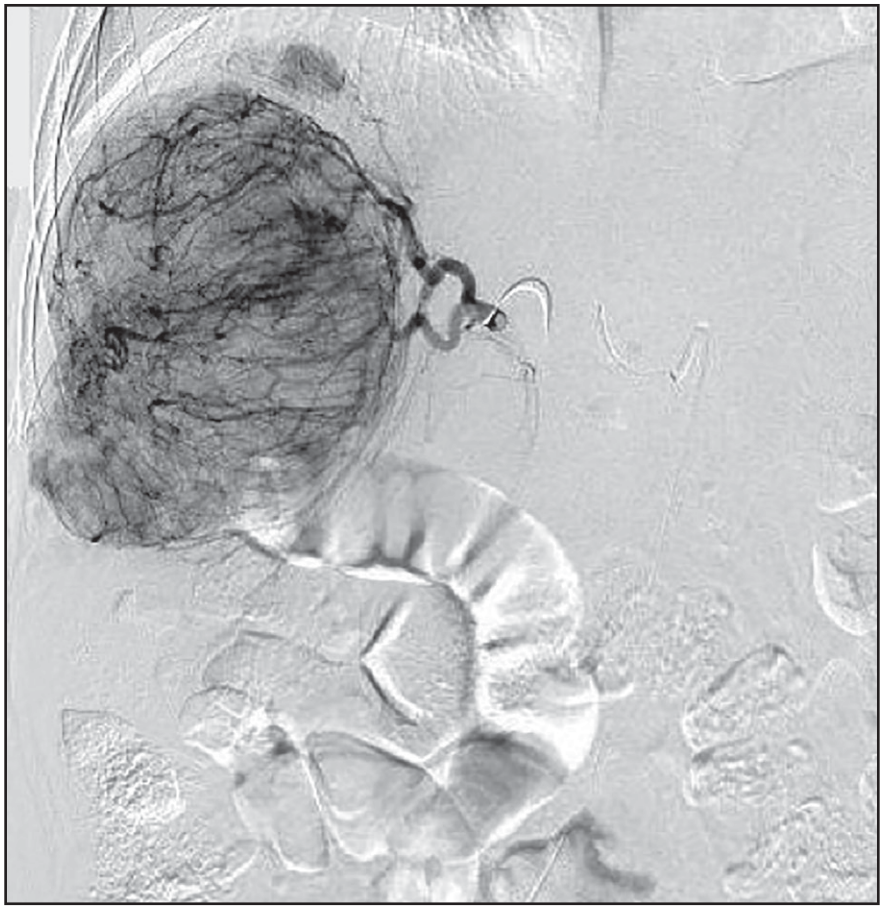


FIGURE 2. *Pre-embolic therapy angiogram. Tumors are filled with contrast.*

prioritize avoiding adjacent normal tissues. Multiple methods have emerged to assess treatment safety, from mean normal liver dose to more complicated normal tissue complication probability models. Whichever method is used, safety is stressed first, as patients with HCC typically also have cirrhosis and tenuous liver function. Dose is attenuated when necessary depending on normal liver volume. Indeed, many would advocate treating only Child-Pugh class A patients, although select B patients can be treated very carefully, preferably in a clinical trial.

In addition to treatment planning, image guidance and treatment delivery must also be meticulous. Rather than relying on external surrogates, which correlate poorly with internal tumor position, alignment is typically performed with either implanted fiducials or injected lipiodol and planar imaging, or cone-beam CT, which allows for simultaneous visualization of the tumor region and adjacent normal tissues, so potential tradeoffs between tumor coverage and normal tissue protection can be assessed. Motion management is an important component of the process. Radiated liver volumes are minimized in patients who can tolerate breath holds. For those who cannot, 4DCT can help ensure full coverage of a moving tumor.

New on the horizon is an interest in treating patients with worse hepatic function, particularly those with aggressive tumors that would otherwise progress more quickly than the patient's liver failure. For these patients, the balance between tumor control and safety is especially difficult, and treatment is generally less aggressive to preserve safety. In a recent trial of Child-Pugh class B-C patients, 1-year local control was 55%, with 58% of patients experiencing a worsening of CP score at 1 month.[28] Rather than decrease treatment intensity for all patients to maintain safety, the University of Michigan is aiming to customize treatment based on *individual* tolerance to therapy, using blood and imaging biomarkers to assess the liver's response to the first 3 treatments, adjusting the last 2 treatments to maintain safety.[29,30] Local control and safety have both been preserved well over 90%, even in CP B patients. Proton therapy also is a promising advance, since the low dose radiation region is dramatically reduced. Still, the potential technical limitations of proton therapy mandate that comparative clinical trials be conducted.[31]

SBRT for HCC is still mainly confined to academic centers, although through clinical trials such as RTOG 1112 discussed below, community centers have the opportunity to become credentialed in planning and delivery. When properly delivered, SBRT is very safe and effective. In a large single-institution review, SBRT had similar local control and less toxicity than RFA. Indeed, for larger tumors, SBRT had better results.[32] Thus, at the very least, SBRT is an excellent alternative treatment when RFA is not possible or would be high-risk. A randomized trial is definitely warranted to directly compare these modalities.

Other ablative therapies

In addition to RFA and SBRT, other ablative therapies are offered in some centers. Percutaneous ethanol injection (PEI) has mostly fallen by the wayside, as multiple randomized trials have demonstrated superior tumor control with RFA.[33-34] A recent meta-analysis suggests that RFA is also superior to cryoablative therapy.[35] Irreversible electroporation is a new technology that

has not been fully tested or compared with existing options, but could potentially be added to the growing arsenal of effective treatments in the future.

Regional ablative treatment options

Transcatheter arterial chemoembolization (TACE)

If local therapies are not available or the patient has too many tumors for safe treatment, regional therapies should be pursued (Figure 2). Response rates are generally not as high as local ablative therapies, but regional therapies can simultaneous treat numerous tumors. The main goals of TACE[36,37] are: 1. Primary treatment of multinodular HCC. 2. Downstaging of large liver tumors for later transplantation or resection. 3. Palliation of pain, bleeding and arteriovenous fistula caused by the tumor. The best—but not exclusive—TACE candidates are patients with relatively preserved liver function, lesions ≤ 5cm without portal trunk thrombosis, and tumor burden occupying less than 70% of the liver. The effectiveness decreases with increasing tumor size. In the series of over 8,500 patients 1-, 3-, 5-, and 7-year survival rates following TACE were 82%, 47%, 26%, and 16%, respectively.[38] Modern Drug Eluting Beads TACE (DEB-TACE) compared to conventional lipidol containing TACE[39] showed higher rates of complete response (27% vs. 22%), objective response (52% vs. 44%), and disease control (63% vs. 52%), although overall survival was similar. For best results, TACE typically must be delivered repeatedly. Post-embolization syndrome consists of mild, transient nausea; fever; and abdominal pain that typically requires overnight hospitalization for observation and pain management. A transient mild decompensation in liver function is common, but acute liver failure is seen in less than 3% of procedures. Gastrointestinal and biliary events are not common. Rare serious complications include liver abscesses and vascular injury from repeated procedures.

Radioembolization (RE)

Radioembolization is a newer treatment option, aiming to combine the embolic effect of particle injection with radiation. Tumor response rates for this microsphere therapy vary between 40% and 90%, and overall disease control rates are as high as 80% in highly selective populations.[40] The response is usually observed in 2-6 months. No randomized controlled trial comparing RE with other modalities has been published yet, but in large prospectively studied cohorts, intermediate stage patients treated by RE reach a median survival of 16-18 months.[41-43] Side effects are similar to TACE, except for substantially less pain and potentially longer lasting fatigue, particularly in older patients.

Bridging and downstaging

Any of the above therapies can be used for bridging and downstaging, allowing successful liver transplantation or resection in selective groups. Long-term survival ranges between 49% to 92% in series describing different neoadjuvant approaches.[44-47] Of note, retrospective series have demonstrated the feasibility of SBRT (35-54 Gy in 3, 50 Gy in 5) as a bridge to transplant[48] to prevent progression beyond Milan Criteria while on the wait list. No intraoperative or long-term complications have been noted.

Systemic treatment

Sorafenib, an oral tyrosine kinase inhibitor, has demonstrated a small survival benefit (10.7 vs. 7.9 months) in patients with unresectable HCC with CP A liver reserve.[49] The vast majority of patients were previously treated with different modalities prior to Sorafenib initiation; but unfortunately, due to lack of available local and regional therapies, many centers prescribe the drug upfront.

Combination therapies

Several rationales are behind combination therapies for HCC. First, regional and local therapies could be combined: Since regional therapies are usually not completely effective, perhaps the combination of a local therapy could improve overall response. Alternatively, local therapy to tumor thrombus in the portal vein may open the door for regional therapies. Second, systemic and local or regional therapies could be combined: Systemic therapy could be adjuvant or suppressive, or in the case of advanced disease, local therapy could be used to prevent progression-related morbidity and mortality.

Multiple randomized controlled trials have evaluated the efficacy of TACE added to RFA, compared with RFA alone. A meta-analysis involving 598 patients suggested that combination therapy had higher overall survival (OR3-year = 2.65, P < 0.001) and recurrence-free survival rate (OR5-year = 2.26, P = 0.0004) compared with RFA alone for study patients.[50] Prospective studies and a meta-analysis also have reported improved survival results when radiotherapy is added to TACE.[51-53] Indeed, RT to portal vein tumor thrombus is effective approximately 35% of the time,[54] which could make patients eligible for regional therapies. The opposite study of whether TACE improves the outcome after RT has not yet been performed.

Any local treatment can cause upregulation of circulating *vascular endothelial growth factor* (VEGF)—thus, the rationale behind combining ablative therapy with antiangigenetic therapy. A meta-analysis with a total of 1,254 patients favored the combination of TACE with sorafenib in terms of significantly improved overall survival (OS) (hazard ratio [HR] = 0.65, P = 0.007), time to progression (TTP) (HR = 0.68, P = 0.003), and overall response rate (ORR) (HR = 1.06, P = 0.021), but did not affect progression-free survival (PFS).[55] The combination therapy was generally well-tolerated but, as expected, had more side effects related to TKI compared with

observation alone—mostly fatigue, diarrhea and skin changes. The addition of sorafenib to RFA and RE for intermediate and advanced stage patients is being explored in randomized controlled trials.

Another important clinical question is whether adding local treatment to systemic treatment in intermediate and advanced HCC could improve overall outcome. This hypothesis is tested in RTOG 1112, an ongoing international phase III study of sorafenib vs. SBRT followed by sorafenib. Another ongoing phase III trial STOP-HCC evaluates the efficacy of RE added to sorafenib.

Conclusion

Whenever suitable, surgical options should be considered as a gold standard. Otherwise, based on the data above, clinicians can propose several treatment options in almost every clinical setting. Unfortunately, Level I evidence to guide decisions is lacking in most situations. Generally, we prefer discussion over argument in the absence of data, but are there certain patients we should strongly advocate for? The most important question that we, as radiation oncologists, should ask ourselves is: Which patients would benefit the most from SBRT—i.e., who should we fight for on the tumor board battlefield? This question answers itself if we consider the main advantages of SBRT: It is highly effective, noninvasive and relatively safe, even in situations and geometries that would be relatively high risk for other treatments. We propose the following scenarios where SBRT could be considered favorably:

If local ablative treatments such as RFA are under consideration, SBRT is preferred if the tumor is >3 cm (likely incomplete RFA) at the liver dome (poor visualization by ultrasound makes RFA difficult), in a close proximity to major vessels (poor heating due to the heat sink leads to incomplete RFA), gallbladder, or gastrointestinal tract (potential for perforation).

When other modalities could pose danger if the patient has certain medical conditions (such as thrombocytopenia or is at high risk for anesthesia), SBRT has a very favorable risk-benefit profile.

SBRT can be considered following TACE or RE with mixed response (e.g., 1-3 growing lesions). SBRT of single lesions following RE failure can be considered if other local ablative treatment modalities are not appropriate.

If portal vein thrombosis is making regional therapy high-risk, SBRT should be strongly considered. Depending on the size and number of tumors, treatment can be directed at all disease. Another option would be SBRT aiming to open the portal vein to make the patient a candidate for additional treatment modalities.

Despite these scenarios, we should keep in mind that SBRT requires appropriate treatment planning, delivery and image-guidance equipment, as well as the expertise of radiation oncologists, physicists, dosimetrists and therapists. RTOG/NRG guidelines and protocols, training workshops, and fellowships aim to help centers develop SBRT programs and bring this treatment option to more patients worldwide.

References

1. Jemal A, Bray F, Center MM, et al. Global cancer statistics. CA *Cancer J Clin.* 2011;61(2):69-90.
2. Njei B, Rotman Y, Ditah I, et al. Emerging trends in hepatocellular carcinoma incidence and mortality. *Hepatology.* 2015;61(1):191-199.
3. Mazzaferro V, Regalia E, Doci R, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *N Engl J Med.* 1996;334(11):693-699.
4. Yao FY, Ferrell L, Bass NM, et al. Liver transplantation for hepatocellular carcinoma: expansion of the tumor size limits does not adversely impact survival. *Hepatology.* 2001;33(6):1394-1403.
5. Onaca N, Davis GL, Goldstein RM, et al. Expanded criteria for liver transplantation in patients with hepatocellular carcinoma: a report from the International Registry of Hepatic Tumors in Liver Transplantation. *Liver Transpl.* 2007;13(3): 391-399.
6. Takada Y, Ito T, Ueda M, et al. Living donor liver transplantation for patients with HCC exceeding the Milan criteria: a proposal of expanded criteria. *Dig Dis.* 2007;25(4):299-302.
7. Soejima Y, Taketomi A, Yoshizumi T, et al. Extended indication for living donor liver transplantation in patients with hepatocellular carcinoma. *Transplantation.* 2007;83(7):893-899.
8. Lee SG, Hwang S, Moon DB, et al. Expanded indication criteria of living donor liver transplantation for hepatocellular carcinoma at one large-volume center. *Liver Transpl.* 2008;14(7):935-945.
9. Silva M, Moya A, Berenguer M, et al. Expanded criteria for liver transplantation in patients with cirrhosis and hepatocellular carcinoma. *Liver Transpl.* 2008;14(10):1449-1460.
10. Mazzaferro V, Llovet JM, Miceli R, et al. Predicting survival after liver transplantation in patients with hepatocellular carcinoma beyond the Milan criteria: a retrospective, exploratory analysis. *Lancet Oncol.* 2009;10(1):35-43.
11. Llovet JM, Schwartz M, Mazzaferro V. Resection and liver transplantation for hepatocellular carcinoma. *Semin Liver Dis.* 2005;25(2):181-200.
12. Adam R, Bhangui P, Vibert E, et al. Resection or transplantation for early hepatocellular carcinoma in a cirrhotic liver: does size define the best oncological strategy? *Ann Surg.* 2012;256(6):883-891.
13. Sapisochin G, Castells L, Dopazo C, et al. Single HCC in cirrhotic patients: liver resection or liver transplantation? Long-term outcome according to an intention-to-treat basis. Ann Surg Oncol. 2013;20(4):1194-1202.
14. Fuster J, García-Valdecasas JC, Grande L, et al. Hepatocellular carcinoma and cirrhosis. Results of surgical treatment in a European series. *Ann Surg.* 1996;223(3):297-302.
15. Sasaki A, Iwashita Y, Shibata K, et al. Improved long-term survival after liver resection for hepatocellular carcinoma in the modern era: retrospective study from HCV-endemic areas. *World J Surg.* 2006;30(8):1567-1578.
16. Tateishi R, Shiina S, Teratani T, et al. Percutaneous radiofrequency ablation for hepatocellular carcinoma. An analysis of 1000 cases. *Cancer.* 2005;103:1201.
17. Sala M, Llovet JM, Vilana R, et al. Initial response to percutaneous ablation predicts survival in patients with hepatocellular carcinoma. *Hepatology.* 2004;40:1352.
18. Livraghi T, Meloni F, Di Stasi M, et al. Sustained complete response and complications rates after radiofrequency ablation of very early hepatocellular carcinoma in cirrhosis: Is resection still the treatment of choice? *Hepatology.* 2008;47:82.
19. Llovet JM, Fuster J, Bruix J. The Barcelona approach: diagnosis, staging, and treatment of hepatocellular carcinoma. *Liver Transpl.* 2004;10(2 Suppl 1):S115-20.
20. Ikeda K, Seki T, Umehara H, et al. Clinicopathologicstudy of small hepatocellular carcinoma with microscopicsatellite nodules to determine the extent of tumor ablationby local therapy. *Int J Oncol.* 2007;31:485-491.
21. Lam VW, Ng KK, Chok KS, et al. Risk factors and prognostic factorsof local recurrence after radiofrequency ablation of hepatocellularcarcinoma. *J Am Coll Surg.* 2008;207:20-29.
22. Blomgren H, Lax I, Näslund I, et al. Stereotactic high dose fraction radiation therapy of extracranial tumors using an accelerator. Clinical experience of the first thirty-one patients. *Acta Oncol.* 1995;34(6):861-870.

23. Tse RV, Hawkins M, Lockwood G, et al. Phase I study of individualized stereotactic body radiotherapy for hepatocellular carcinoma and intrahepatic cholangiocarcinoma. *J Clin Oncol.* 2008;26(4):657-664.
24. Bujold A, Massey CA, Kim JJ, et al. Sequential phase I and II trials of stereotactic body radiotherapy for locally advanced hepatocellular carcinoma. *J Clin Oncol.* 2013;31(13):1631-1639.
25. Liu E, Stenmark MH, Schipper MJ, et al. Stereotactic body radiation therapy for primary and metastatic liver tumors. *Translational Oncology.* 2013;6; 442-446.
26. Choi BO, Choi IB, Jang HS, et al. Stereotactic body radiation therapy with or without transarterial chemoembolization for patients with primary hepatocellular carcinoma: Preliminary analysis. *BMC Cancer.* 2008; 8:351.
27. Van der Pool AE, Méndez Romero A, Wunderink W, et al. Stereotactic body radiation therapy for colorectal liver metastases. *Br J Surg.* 2010; 97:377-382.
28. Culleton S, Jiang H, Haddad CR, et al. Outcomes following definitive stereotactic body radiotherapy for patients with Child-Pugh B or C hepatocellular carcinoma. *Radiother Oncol.* 2014;111(3):412-417.
29. Normolle D, Pan C, Ben-Josef E, et al. Adaptive trial of personalized radiotherapy for intrahepatic cancer. *Per Med.* 2010;7(2):197-204.
30. Feng M, Schipper MJ, Balter JM, et al. A phase 2 trial of individualized adaptive stereotactic body radiation therapy (SBRT) for patients at high risk for liver damage. *Int J Radiat Oncol Biol Phys.* 2013:87(2),S27.
31. Lawrence TS, Feng M. Protons for prostate cancer: the dream versus the reality. *J Natl Cancer Inst.* 2013;105(1):7-8.
32. Liu E SM, Schipper MJ, Caoili EM, Ben-Josef E, Lawrence TS, Feng M. SBRT as an Alternative to RFA for the Treatment of Primary and Metastatic Liver Tumors. *Journal of Clin Oncol 2012;* 30:158.
33. Lencioni RA, Allgaier HP, Cioni D, et al. Small hepatocellular carcinoma in cirrhosis: randomized comparison of radio-frequency thermal ablation versus percutaneous ethanol injection. *Radiology.* 2003;228(1):235-240.
34. Brunello F, Veltri A, Carucci P, et al. Radiofrequency ablation versus ethanol injection for early hepatocellular carcinoma: a randomized controlled trial. *Scand J Gastroenterol.* 2008;43(6):727-735.
35. Huang YZ, Zhou SC, Zhou H, et al. Radiofrequency ablation versus cryosurgery ablation for hepatocellular carcinoma: a meta-analysis. *Hepatogastroenterology.* 2013;60(125):1131-1135.
36. Vogl TJ, Naguib NN, Nour-Eldin NE, et al. Review on transarterial chemoembolization in hepatocellular carcinoma: palliative, combined, neoadjuvant, bridging, and symptomatic indications. *Eur J Radiol.* 2009;72(3):505-516.
37. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. European Association For The Study Of The Liver; European Organisation For Research And Treatment Of Cancer. *J Hepatol.* 2012;56(4):908-943.
38. Takayasu K, Arii S, Ikai I, et al. Prospective cohort study of transarterial chemoembolization for unresectable hepatocellular carcinoma in 8,510 patients. *Gastroenterology.* 2006;131(2): 461-469.
39. Cammà C, Schepis F, Orlando A, et al. Transarterial chemoembolization for unresectable hepatocellular carcinoma: meta-analysis of randomized controlled trials. *Radiology.* 2002;224(1):47-54.
40. Salem R, Lewandowski RJ, Mulcahy MF, et al. Radioembolization for hepatocellular carcinoma using Yttrium-90 microspheres: a comprehensive report of long-term outcomes. *Gastroenterology.* 2010;138(1):52-64.
41. Sangro B, Carpanese L, Cianni R, et al. Survival after yttrium-90 resin microsphere radioembolization of hepatocellular carcinoma across Barcelona clinic liver cancer stages: a European evaluation. *Hepatology.* 2011;54(3):868-878.
42. Mazzaferro V, Sposito C, Bhoori S, et al. Yttrium-90 radioembolization for intermediate-advanced hepatocellular carcinoma: a phase 2 study. *Hepatology.* 2013;57(5):1826-1837.
43. Salem R, Lewandowski RJ, Kulik L, et al. Radioembolization results in longer time-to-progression and reduced toxicity compared with chemoembolization in patients with hepatocellular carcinoma. *Gastroenterology.* 2011;2140(2): 497-507.e2.
44. Lei JY, Yan LN, Wang WT. Transplantation vs resection for hepatocellular carcinoma with compensated liver function after downstaging therapy. *World J Gastroenterol.* 2013; 19:4400-4408.
45. Fan J, Tang ZY, Yu YQ, et al. Improved survival with resection after transcatheter arterial chemoembolization (TACE) for unresectable hepatocellular carcinoma. *Dig Surg.* 1998;15: 674-678.
46. Tang ZY, Zhou XD, Ma ZC, et al. Downstaging followed by resection plays a role in improving prognosis of unresectable hepatocellular carcinoma. *Hepatobiliary Pancreat Dis Int.* 2004;3: 495-498.
47. Yao FY, Kerlan RK, Hirose R, et al. Excellent outcome following down-staging of hepatocellular carcinoma prior to liver transplantation: an intention-to-treat analysis. *Hepatology.* 2008;48 819-827.
48. Katz, AW, Chawla, S, Qu, Z et al. Stereotactic hypofractionated radiation therapy as a bridge to transplantation for hepatocellular carcinoma: Clinical outcome and pathologic correlation. *Int J Radiat Oncol Biol Phys.* 2012;83: 895-900.
49. Llovet JM, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med.* 2008;359(4):378-90.
50. Ni JY, Liu SS, Xu LF, et al. Meta-analysis of radiofrequency ablation in combination with transarterial chemoembolization for hepatocellular carcinoma. *World J Gastroenterol.* 2013;28;19(24):3872-3882.
51. Shim SJ, Seong J, Han KH, et al. Local radiotherapy as a complement to incomplete transcatheter arterial chemoembolization in locally advanced hepatocellular carcinoma. *Liver Int.* 2005; 25:1189-1196.
52. Oh D, Lim do H, Park HC et al. Early three-dimensional conformal radiotherapy for patients with unresectable hepatocellular carcinoma after incomplete transcatheter arterial chemoembolization: a prospective evaluation of efficacy and toxicity. *Am J Clin Oncol.* 2010;33: 370-375.
53. Meng MB, Cui YL, Lu Y, et al. Transcatheter arterial chemoembolization in combination with radiotherapy for unresectable hepatocellular carcinoma: a systematic review and meta-analysis. *Radiother Oncol.* 2009;92(2): 184-194.
54. Xi M, Zhang L, Zhao L, et al. Effectiveness of stereotactic body radiotherapy for hepatocellular carcinoma with portal vein and/or inferior vena cava tumor thrombosis. *PLoS One.* 2013;8(5):e63864.
55. Zhang L, Hu P, Chen X, et al. Transarterial chemoembolization (TACE) plus sorafenib versus TACE for intermediate or advanced stage hepatocellular carcinoma: a meta-analysis. *PLoS One.* 2014;9(6):e100305.

Predicting close local failure after liver resection for hepatocellular carcinoma

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Hepatocellular carcinoma (HCC) is the 5th leading cause of cancer worldwide,[1] and the 3rd most common cause of cancer-related death.[2] In the United States, where risk factors of viral hepatitis and alcoholic cirrhosis are rising, the incidence of new HCC is also expected to increase.[3] The age-adjusted incidence of HCC tripled from 1975-2005,[4] and although overall survival improved, the 5-year survival is 40% to 50%.[5] Partial hepatic resection remains the most common surgical management of HCC. However, even though advances in operative technique and postoperative care have reduced postoperative mortality in immediate hospital deaths to nearly zero,[6] the prognosis remains grim. After surgery, many studies show the 3-year intrahepatic recurrence to be 60% to 70%.[7-10] A proportion of these recurrences is in close proximity to the original surgical margin.[8-10]

Retrospective reviews have consistently identified numerous patient, tumor and treatment-related risk factors that increase the rates of recurrence, including microvascular invasion, satellite nodules and tumor size.[11-15] Other factors, such as α-fetoprotein (AFP) level, cirrhosis, resection type and resection margin, have demonstrated a less consistent correlation with recurrence.

Historically, the use of radiotherapy for HCC has been restricted due to poor radiation tolerance of the liver.[16,17] However, with advances in three-dimensional radiation planning, image-guided radiotherapy (IGRT), and high-dose stereotactic body radiation (SBR), radiotherapy has demonstrated its effectiveness as an adjuvant treatment as well as its utility in preventing intrahepatic HCC recurrence.[18-25]

A systematic radiological analysis of intrahepatic recurrence patterns was done at our institution to better understand where a failure will subsequently develop relative to the original surgical bed. In particular, we investigated factors associated with recurrences found within 2 cm of the original surgical site, a region that could be easily treated with local adjuvant or even intra-operative radiation therapy (IORT). This information can help in future selection of patients likely to benefit from additional radiotherapy.

Materials and methods

Internal Review Board approval from the Cleveland Clinic, Cleveland, Ohio, was obtained to perform a retrospective chart and radiographic review of all patients who underwent non-transplant surgical resection at our institution for primary HCC between September 1996 and May 2012. HCC diagnosis was either by characteristic radiological findings on a triphasic CT scan or through biopsy, according to the updated American Association for the Study of Liver Diseases (AASLD) guidelines.[26] A total of 169 patients had hepatic resection; however, 22 were excluded due to insufficient available data regarding treatment and follow-up, or because they presented with metastatic disease. All patients were closely followed with computed tomography (CT) or magnetic resonance imaging (MRI) for recurrence.

Patient demographic data were recorded, as well as details of pre-existing hepatic disease. Information regarding

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Table 1

Patient characteristics (n = 147)		Value (%)		
		Local Recurrence (n = 19)	Distant Intrahepatic (n = 54)	Non-Recurrence (n = 74)
Age (years)	Mean	64 ± 13.4	61 ± 14.8	66 ± 12.0
	Range	28-82	16-85	31-91
Sex	Male	14 (73.7)	31 (57.4)	48 (64.9)
	Female	5 (26.3)	23 (42.6)	26 (35.1)
HBV antigen positive		3 (15.8)	4 (7.4)	5 (6.8)
HCV antigen positive		5 (26.3)	16 (29.6)	21 (28.4)
Cirrhosis		11 (57.9)	23 (42.6)	30 (40.5)
NAFLD		2 (10.5)	7 (13.0)	9 (12.2)
Child class	A	18 (94.7)	44 (81.5)	64 (86.5)
	B	1 (5.3)	10 (18.5)	10 (13.5)
Liver function tests	Bilirubin >3 (mg/dL)	0 (0)	0 (0)	1 (1.4)
	Elevated ALT (> 3x ULN)	1 (5.3)	10 (18.5)	8 (10.8)
AFP >400 (IU/mL)		9 (47.4)	14 (25.9)	15 (20.3)
Tumor size (cm)	≤5	5 (26.3)	21 (38.9)	34 (45.9)
	5-10	6 (31.6)	16 (29.6)	26 (35.1)
	>10	8 (42.1)	17 (31.5)	14 (18.9)
Tumor number	Single	15 (78.9)	40 (74.1)	58 (78.4)
	Multiple	4 (21.1)	14 (25.9)	16 (21.6)
Grade	1	3 (15.8)	10 (18.5)	13 (17.6)
	2	14 (73.7)	40 (74.1)	56 (75.7)
	3	2 (10.5)	4 (7.4)	5 (6.8)
Time from diagnosis to surgery (days)	Mean	59 ± 59	137 ± 227	122 ± 20
	Median	48	76	48
	Range	8-273	5-1513	12-1252
Type of resection	Hepatectomy	5 (26.3)	10 (18.5)	12 (16.2)
	Extended hepatectomy	2 (10.5)	6 (11.1)	6 (8.1)
	Partial hepatectomy	0 (0)	1 (1.9)	8 (10.8)
	Segmentectomy	8 (42.1)	25 (46.3)	29 (39.2)
	Trisectionectomy	3 (15.8)	3 (5.6)	5 (6.8)
	Wedge	1 (5.3)	9 (16.7)	14 (18.9)
Margin	Positive	4 (21.1)	8 (14.8)	6 (8.1)
	Negative	15 (78.9)	46 (85.2)	68 (91.9)
	<10 mm	14 (73.7)	41 (75.9)	50 (67.6)
	≥10 mm	5 (26.3)	13 (24.1)	24 (32.4)
Vascular Invasion		10 (52.6)	26 (48.1)	24 (32.4)
Tumor Rupture		1 (5.3)	1 (1.9)	1 (1.4)
Time to Recurrence (d)	Mean	507 ± 539	459 ± 335	N/A
	Median	319	365	N/A
	Range	47-2097	52-1583	N/A

* HBV – Hepatitis B virus; HCV – Hepatitis C virus; NAFLD – Non-alcoholic fatty liver disease; ALT – Alanine aminotransferase; ULN – Upper limit of normal; AFP – α-fetoprotein

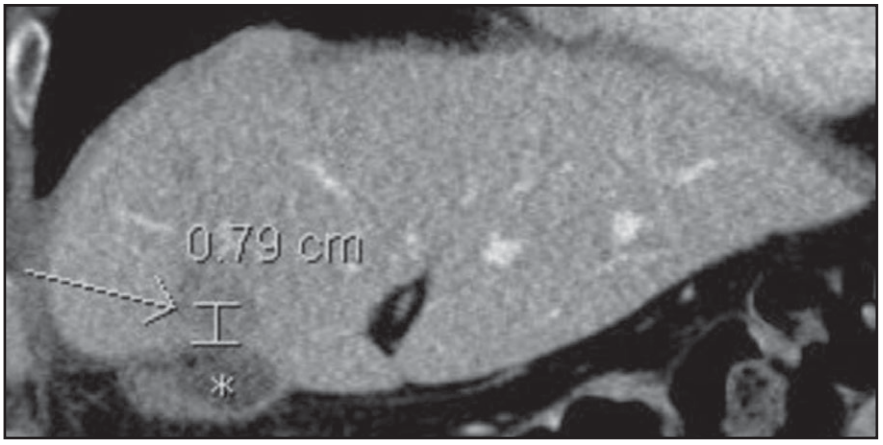

FIGURE 1. *Three-dimensional distance measurement of intrahepatic recurrence. Using either CT or MRI, the three-dimensional distance to intrahepatic recurrence was measured from the closest identifiable resection margin to the center point of the new lesion.*

pre- and postoperative liver function and radiographic detail, method of diagnosis, tumor stage and grade, adjuvant treatment, surgical method and resulting pathology, tumor recurrence, further treatment, and date and cause of death were also gathered (Table 1). Tumors were graded based on the WHO 2010 criteria as outlined in the WHO Classification of Tumors of the Digestive system.[27] Recurrence was defined as new radiographic, or biopsy-proven, evidence of HCC not visualized prior to previous resection. Distance to recurrence from the site of the excised primary lesion was defined as the shortest three-dimensional distance from the closest resection margin to the center of the new lesion(s) (Figure 1). The measurement tool and in some instances, the three-dimensional reconstruction software, were used on the hospital Impax image archiving system (AGFA, Mortsel, Belgium) to determine these distances.

Patients were divided into 1 of 3 groups based on the specific location of intrahepatic recurrence: local recurrence (defined as < 2 cm from surgical margin), non-local intrahepatic recurrence (>2 cm from surgical margin) and concurrent local and intrahepatic recurrence. Risk factors associated with each of the above recurrence patterns were characterized and quantified. A 2-cm radius around a given tumor bed was chosen to model the dose distribution characteristics of IORT.

Assessment of tumor resectability was based on AASLD guidelines.[28,29] Types of resection included all of the following: right and left hepatectomy, extended or partial right and left hepatectomy, right and left trisectionectomy, segmentectomy, and sub-segment wedge resection of the tumor. Extended left hepatectomy included, in addition to Couinaud segments 2-4, an adjacent narrow portion of segments 5 and 8, and extended right hepatectomy included, in addition to segments 5-8, an adjacent narrow portion of segment 4. Partial right and left hepatectomy was defined as a left or right hepatectomy that did not extend to include the entirety of the segment(s) adjacent to the contralateral hemiliver. Resection types were described according to the Liver Resection Guidelines as reported by the International Hepato-Pancreato-Biliary Association.[30] Segmentectomy was defined as resection of an entire Couinaud segment together with its portal vessels, while wedge resection implied removal of the tumor with margin without regard to segmental, sectional or lobar anatomy.

Analysis of patient demographic factors, tumor factors and treatment factors was undertaken. Time from diagnosis to surgery, surgery to recurrence, overall follow-up and overall survival was assessed. Initial diagnosis and recurrence were determined as defined above, and date of death was verified using an online social-security death index. The data was analyzed using logistical regression modeling and Kaplan-Meier survival analysis. A p value of <0.05 was considered statistically significant.

Results

Clinical and surgical data

There were 93 men and 54 women. The mean age of the studied group was 63.7 (range: 16-91) years. Seventy-four patients (50.3%) had histologically proven chronic liver disease: 64 (43.5%) with cirrhosis, 12 (8.0%) with hepatitis B virus (HBV), 42 (29.0%) with hepatitis C virus (HCV), and 18 (12.0%) with non-alcoholic fatty liver disease. The mean AFP level prior to surgery was 3,548.2 (median: 17.8, range: 0.9-88000) ng/mL. A total of 113 (76.9%) patients presented with a solitary lesion on radiological scan. The mean maximum diameter of lesions was 7.3 (range: 0.7-20) cm, and 110 (74.8%) patients had grade II tumors, while 26 (17.7%) and 11 (7.5%) had grades I and III respectively. Upon resection, 103 (72.0%) had a margin >10 mm, and the average margin taken was 6.6 (0-50) mm. Eighteen (12.6%) patients had positive margins, only 3 (0.02%) patients had tumor rupture upon resection, and 62 (42.2%) patients had histologic evidence of vascular invasion. The types of resection performed included right and left hepatectomy, including extended or partial (50 patients, 34.0%); segmentectomy (62 patients, 42.2%); right and left trisectionectomy (11 patients, 7.5%); and local wedge resection (24 patients, 16.3%).

Tumor recurrence

Of the 147 patients, 73 (49.7%) had clinical/radiological evidence of tumor recurrence. Median time to recurrence

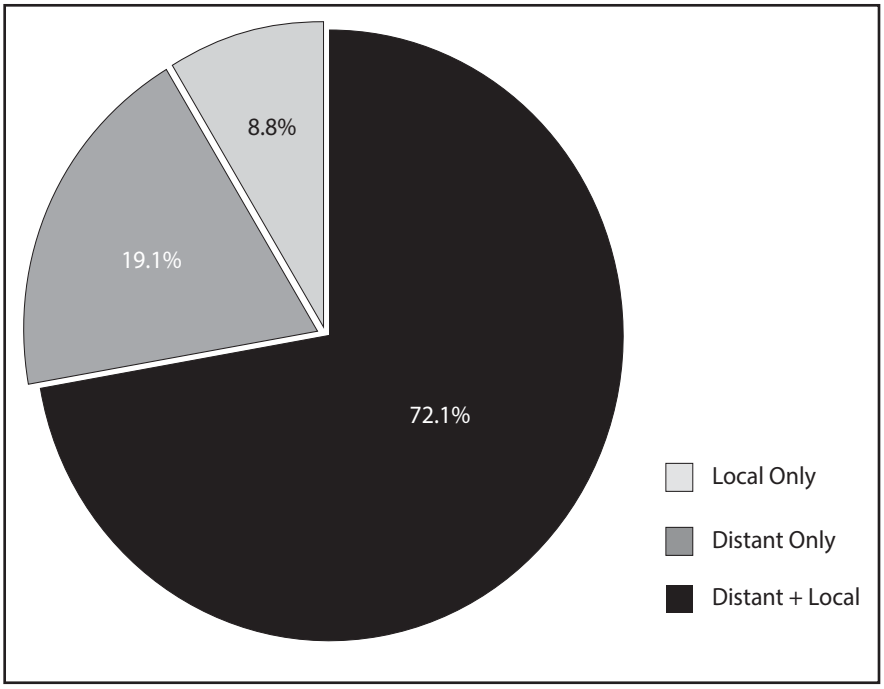

FIGURE 2. *Intrahepatic recurrence patterns 27.9% of intrahepatic recurrences emerged within 2 cm of the original tumor site.*

Table 2. Factors associated with intrahepatic recurrence

	Number	Percent (%)	*P* value
All Recurrence			
Vascular invasion	62/147	42.2	0.01
Local Recurrence			
Single lesion	15/19	79	0.02
	Mean (days)	**Standard Error**	***P* value**
Time from diagnosis to surgery	59 ± 59	14	0.02

was 11.9 (range: 1.6-69.9) months. In 47 (64.4%) of these, the recurrence was confined to the hepatic remnant. Extrahepatic recurrence, in addition to intrahepatic failure, was found in 21 (28.8%) patients, and 5 (6.9 %) patients had exclusively extrahepatic tumors: lung (1 patient), omentum and abdominal wall (1 patient), ovary (1 patient), bi-lateral adrenals (1 patient), femoral head (1 patient). Nineteen (27.9%) of the patients who had intrahepatic recurrence failed within 2 cm of the primary surgical margin.

Local vs. distant intrahepatic recurrence

Among patients who had intrahepatic recurrence, 19 (27.9%) were local failures and 49 (72.1%) had recurrences elsewhere in the liver. Mean tumor size for local recurrence was 8.9 (range: 2.6-14.5) cm and 7.5 (range: 1.5-20) cm for distant intrahepatic recurrence. Of those with local recurrence, 6 (32%) had local failure exclusively, while 13 (68%) had both local and distant intrahepatic recurrence (Figure 2). Tumor rupture correlated with recurrence, but was not statistically significant (p = 0.09). While 48% of margin negative resections had recurrence (n = 60/125) compared with 67% with margin positive resections (n = 12/18), the difference was not statistically significant for recurrence (p = 0.16). Vascular invasion was significant for overall recurrence (p = 0.01), but did not specifically correlate with local or distant recurrence. Median time from diagnosis to surgery did correlate with local recurrence (p = 0.02), with a shorter delay associated with increased likelihood of local failure. The presence of a single lesion prior to initial resection also correlated with recurrence (p = 0.02) (Table 2). Tumor grade, tumor size, segmental location, and the concomitant existence of cirrhosis were not significant correlates.

Discussion

The purpose of this study was to review all patients who had partial hepatic resection for primary HCC between September 1996 and May 2012 to determine the patterns and risk factors for local recurrence. We found that, of the 47.9% of resected patients who had intrahepatic recurrence, 27.9% were within 2 cm of the original surgical margin. Multiple studies have distinguished between intra- and extrahepatic recurrence, and some report the number of recurrences close to the primary surgical margin;[7] however, to our knowledge no studies have identified risk factors specifically for such close local recurrence.

Previous studies differ regarding the exact constellation of risk factors for HCC recurrence. Previous reports have included vascular invasion, cirrhosis and perioperative blood transfusion,[12] tumor size, encapsulation and preoperative AFP,[7] to merely preoperative AFP and close resection margin.[9] In addition, Huang et al. added pathological grade and tumor thrombus,[31] while still others propose 3 or more lesions as predictive of recurrence.[32] Aside from vascular invasion, tumor size and tumor number,[5]

there does not seem to be a clear consensus in the literature regarding what clinical, surgical or pathological factors can be used to predict post-resection HCC recurrence. In our limited patient population, we corroborated vascular invasion as a risk factor for any recurrence. No other risk factors were identified.

It has been suggested that anatomical resection of HCC that includes an entire Couinaud segment with its portal vessels results in a decreased rate of recurrence compared to non-anatomical, or wedge, resection. By removing an entire hepatic segment, there is a chance of including in the resection any local micrometastases or disease extension. Some authors report improved 5-year and disease-free survival using segmentectomy, while others have failed to demonstrate a survival benefit over wedge resection. A large 2012 meta-regression analysis found significant advantages with segmentectomy in 5-year and disease-free survival, but noted that in the retrospective, observational studies analyzed, patients who underwent non-anatomical resection were also more likely to have poorer liver function and reserve.[33] Cucchetti et al. recently reported fewer early recurrences and a survival advantage with anatomical resection, though limited to cases with poorly differentiated tumors and microvascular invasion, 2 known risk factors for tumor recurrence.[34] In our study, there was little difference in outcomes between patients who had anatomical and non-anatomical resections (Table 1). This may support existing data that suggest there is little recurrence and survival advantage to segmentectomy. Since this study, as well as the vast majority of the relevant literature is retrospective in nature, one major potentially confounding factor is the variability in the practical distinction between segmentectomy and wedge resection. Non-anatomical resections can differ from one case to another, as well as between surgeons; therefore, prospective data would better elucidate whether segmentectomy is truly superior to wedge resection, and in which specific clinical scenarios.

The apparent inability to find a consistent set of risk factors may relate to the numerous potential mechanisms by which HCC can recur and spread. At the time of initial diagnosis, there may already have been multifocal hepatic disease, and in patients with cirrhosis of the liver, the tumor may have developed through a multicentric origin.[35] Over time, there could be intrahepatic spread via the portal venous system, and during surgery, there may not have been an adequate margin taken.[9] To try and account for multifocal disease on presentation, intraoperative ultrasound was performed on all patients in this series. In our patients with distant intrahepatic recurrences, 10 were detected more than 2 years post resection. This long interval and the significant distance from the primary surgical site, especially in cases with cirrhosis, suggests that these recurrences may have been a new primary lesion. Although a trend may have suggested this relationship, we did not find a statistically significant correlation between the presence of cirrhosis and distant intrahepatic or multicentric tumor recurrence.

In our series, patients who had a local recurrence were statistically more likely to have had a shorter time interval from diagnosis to surgery and only 1 radiographically apparent lesion at the time of surgery. In patients whose tumor recurred, these two factors conferred a 79% risk of the recurrence emerging within 2 cm of the original tumor. While these 2 factors may decrease the likelihood of recurrence overall, when patients with these characteristics recurred, it was often a close local failure. Vascular invasion correlated significantly with overall recurrence, although not with local or distant recurrence in particular. The lack of significance within this division may be reasonably explained by the small sample size of each group and, therefore, decrease in statistical power. Similarly, tumor rupture correlated with recurrence, as all 3 patients with tumor rupture had both local and distant intrahepatic recurrence, although due to the small sample size, it was not statistically significant. Patients who had local recurrence had a shorter overall survival from the time of resection, as well as from the time of recurrence. However, the wide survival time range and the relatively small sample size limited the ability to find statistical significance in overall survival time.

Nevertheless, these findings suggest that there may be a subset of patients who have a predictable recurrence pattern and associated worse prognosis and, therefore, may benefit from enhanced local control. Historically, a number of pre and post-operative adjuvant therapies have been attempted to minimize local recurrence with mixed results. In 2 prospective randomized trials, neoadjuvant transarterial chemoembolization (TACE) showed no statistically significant improvement over surgery alone, and in some cases, even worse overall survival.[36,37] Postoperative regional chemotherapy has also been studied to reduce local recurrence, and while 2 randomized controlled trials yielded increased overall survival,[38,39] others found little benefit to regional chemotherapy when combined with systemic chemotherapy.[40,41] Studies of the use of oral chemotherapy alone have also shown minimal promise, and use is limited by systemic toxicity.[42,43]

A few small studies have reported the rate of intrahepatic recurrence after radiotherapy alone, or combined with TACE. In a series of 44 patients assessing survival in patients with unresectable HCC treated with radiotherapy, Liu et al. reported a 43.2% rate of intrahepatic recurrence.[20] In another small series of 25 patients, Cheng et al. found that at 2 years, 56% of patients had

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either local or regional intrahepatic tumor recurrence after radiotherapy.[25] Park et al. reported a 47.5% intrahepatic recurrence rate in a survival analysis of 59 patients.[24] In the latter 2 of these studies, many of the patients had also been treated with TACE. No studies, however, specifically detail a pattern of close local intrahepatic failure, at best separating intrahepatic recurrence into general categories of local vs. regional recurrence. As such, there is currently no data on the potential utility of radiation to prevent such close local failure.

In addition to neoadjuvant TACE, chemotherapy and external beam radiotherapy (EBRT), radiofrequency ablation (RFA) combined with resection has shown promise as part of multimodality treatment of HCC. In a recent retrospective study, Prassas et al. found moderate improvement in overall and disease-free survival with an RFA-assisted liver resection method. Of note, they reported no close local recurrences with this technique.[44] Liu compared the efficacy of RFA in HCC vs. metastatic disease, concluding that RFA was beneficial for small, localized tumors.[45] Yi et al. prospectively compared RFA plus TACE with RFA alone and reported a significant survival benefit with combined treatment.[46] While not yet applied to HCC, IORT to reduce local recurrence has shown to be a feasible, beneficial and low-risk treatment option for other cancer types. IORT has resulted in improved survival outcomes and treatment adherence in breast, colon, pancreatic, head and neck, sarcoma and gynecological cancers.[47-55] This technique allows the delivery of an increased and concentrated dose of radiation in a precise, focused manner to specifically target the tumor bed and closely associated at-risk regions. Still other potential, though yet uncorroborated, methods to decrease local recurrence of HCC include segmental resection, earlier liver transplant, and expansion of planned surgical margins by 2 cm.

Conclusion

Based on the analysis of our experience with local and distant-intrahepatic recurrence of HCC after resection, we believe a subgroup of patients, namely those with only 1 radiographically apparent lesion at the time of diagnosis and who underwent resection soon after diagnosis, are more likely to have tumor recurrence within 2 cm of the original surgical bed. Identifying the ideal treatment method by which to substantially reduce the risk of local failure for HCC patients with high-risk features is ongoing. Perhaps, using time from diagnosis to surgery and number of lesions at diagnosis as exclusion criteria, the application of IORT for this subgroup at greater risk for local recurrence can be studied in the future.

References

1. Jemal A, Bray F, Center MM, et al. Global cancer statistics. *CA Cancer J Clin.* 2011;61(2):69-90.
2. Ferlay J, Autier P, Boniol M, et al. Estimates of the cancer incidence and mortality in Europe in 2006. *Ann Oncol.* 2007;18(3):581-592.
3. Sherman M. Hepatocellular carcinoma: Epidemiology, risk factors, and screening. *Semin Liver Dis.* 2005;25(2):143-154.
4. Altekruse SF, McGlynn KA, Reichman ME. Hepatocellular carcinoma incidence, mortality, and survival trends in the United States from 1975 to 2005. *J Clin Oncol.* 2009;27(9):1485-1491.
5. Poon RT, Fan S, Wong J. Risk factors, prevention, and management of postoperative recurrence after resection of hepatocellular carcinoma. *Ann Surg.* 2000;232(1):10-24.
6. Fan ST, Lo CM, Liu CL, et al. Hepatectomy for hepatocellular carcinoma: Toward zero hospital deaths. *Ann Surg.* 1999;229(3):322-330.
7. Llovet JM, Schwartz M, Mazzaferro V. Resection and liver transplantation for hepatocellular carcinoma. *Semin Liver Dis.* 2005;25:181-200.
8. Wu CC, Cheng SB, Ho WM, et al. Liver resection for hepatocellular carcinoma in patients with cirrhosis. *Br J Surg.* 2005;92(3):348-355.
9. Chen MF, Hwang TL, Jeng LB, et al. Postoperative recurrence of hepatocellular carcinoma. Two hundred five consecutive patients who underwent hepatic resection in 15 years. *Arch Surg.* 1994;129(7):738-742.
10. Poon RT, Fan ST, Lo CM, et al. Long-term survival and pattern of recurrence after resection of small hepatocellular carcinoma in patients with preserved liver function: Implications for a strategy of salvage transplantation. *Ann Surg.* 2002;235(3):373-382.
11. Kozyreva ON, Chi D, Clark JW, et al. A multicenter retrospective study on clinical characteristics, treatment patterns, and outcome in elderly patients with hepatocellular carcinoma. *Oncologist.* 2011;16(3):310-318.
12. Chen Z, Ni JL, Liu LY. Analysis of prognostic factors in patients with huge primary liver cancer after surgical resection. *Zhonghua Zhong Liu Za Zhi.* 2011;33(9):710-713.
13. Ji SP, Li Q, Dong H. Therapy and prognostic features of primary clear cell carcinoma of the liver. *World J Gastroenterol.* 2010;16(6):764-769.
14. Ng KK, Poon RT, Lo CM, et al. Analysis of recurrence pattern and its influence on survival outcome after radiofrequency ablation of hepatocellular carcinoma. *J Gastrointest Surg.* 2008;12(1):183-191.
15. Yan K, Chen MH, Yang W, et al. Radiofrequency ablation of hepatocellular carcinoma: Long-term outcome and prognostic factors. *Eur J Radiol.* 2008;67(2):336-347.
16. Ingold JA, Reed GB, Kaplan HS, et al. Radiation hepatitis. *Am J Roentgenol Radium Ther Nucl Med.* 1965;93:200-208.
17. Lawrence TS, Robertson JM, Anscher MS, et al. Hepatic toxicity resulting from cancer treatment. *Int J Radiat Oncol Biol Phys.* 1995;31(5):1237-1248.
18. Thomas E, Chapet O, Kessler ML, et al. Benefit of using biologic parameters (EUD and NTCP) in IMRT optimization for treatment of intrahepatic tumors. *Int J Radiat Oncol Biol Phys.* 2005;62(2):571-578.
19. Zeng ZC, Tang ZY, Yang BH, et al. Radiation therapy for the locoregional lymph node metastases from Hepatocellular carcinoma, Phase I clinical trial. *Hepatogastroenterology.* 2004;51(55):201-207.
20. Liu MT, Li SH, Chu TC, et al. Three-dimensional conformal radiation therapy for unresectable hepatocellular carcinoma patients who had failed with or were unsuited for transcatheter arterial chemoembolization. *Jpn J Clin Oncol.* 2004;34(9):532-539.
21. Herfarth KK, Debus J, Wannenmacher M. Stereotactic radiation therapy of liver metastases: Update of the initial Phase- I/II trial. *Front Radiat Ther Oncol.* 2004;38:100-105.
22. Goitein M. Organ and tumor motion: An overview. *Semin Radiat Oncol.* 2004;14(1):2-9.
23. Seong J, Park HC, Han KH, et al. Clinical results and prognostic factors in radiotherapy for unresectable Hepatocellular carcinoma: A retrospective study of 158 patients. *Int J Radiat Oncol Biol Phys.* 2003;55(2):329-336.
24. Park W, Lim DH, Paik SW, et al. Local radiotherapy for patients with unresectable Hepatocellular carcinoma. *Int J Radiat Oncol Biol Phys.* 2005;61(4):1143-1150.
25. Cheng JC, Chuang VP, Cheng SH, et al. Local radiotherapy with or without transcatheter arterial chemoembolization for patients with unresectable hepatocellular carcinoma. *Int J Radiat Oncol Biol Phys.* 2000;47(2):435-442.
26. Bruix J, Sherman M. American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma: An update. *Hepatol.* 2011;53(3):1020-1022.
27. Bosman FT, Carneiro F, Hruban RH, et al. *WHO classification of tumours of the digestive system* (4th ed). France, Lyon: IARC Press.

28. Bruix J, Sherman M. Practice Guidelines Committee, American Association for the Study of Liver Disease. Management of hepatocellular carcinoma. *Hepatol.* 2005;42(5):1208-1236.
29. de Lope CR, Tremosini S, Forner A, et al. Management of HCC. *J Hepatol.* 2012;56 Suppl 1:75-87.
30. Liver Resection Guidelines. http://www.ihpba.org/92_Liver-resection-Guidlines.html. Accessed July 1, 2013.
31. Huang X, Wei W, Ya N, et al. A mathematical model to predict short-term recurrence and metastasis of primary hepatocellular carcinoma larger than 10cm in diameter. *Hepatogastroenterology.* 2012;60(122). [Epub ahead of print]
32. Chan KM, Chou HS, Wu TJ, et al. Characterization of hepatocellular carcinoma recurrence after liver transplantation: Perioperative prognostic factors, patterns, and outcome. *Asian J Surg.* 2011;34(3):128-134.
33. Cucchetti A, Cescon M, Ercolani G, et al. A comprehensive meta-regression analysis on outcome of anatomic resection versus non-anatomic resection for hepatocellular carcinoma. *Ann Surg Oncol.* 2012;19(12):3697-3705.
34. Cucchetti A, Qiao GL, Cescon M, et al. Anatomic versus nonanatomic resection in cirrhotic patients with early hepatocellular carcinoma. *Surg.* 2014;155(3):512-521.
35. Belli L, Romani F, Belli LS, et al. Reappraisal of surgical treatment of small hepatocellular carcinomas in cirrhosis: Clinicopathological study of resection or transplantation. *Dig Dis Sci.* 1989;34(10):1571-1575.
36. Wu KT, Wang CC, Lu LG, et al. Hepatocellular carcinoma: Clinical study of long-term survival and choice of treatment modalities. *World J Gastroenterol.* 2013;19(23):3649-3657.
37. Zhou WP, Lai EC, Li AJ, et al. A prospective, randomized, controlled trial of preoperative transarterial chemoembolization for resectable large hepatocellular carcinoma. *Ann Surg.* 2009;249(2):195-202.
38. Nagano H, Kobayashi S, Marubashi S, et al. Combined IFN-□ and 5-FU treatment as a postoperative adjuvant following surgery for hepatocellular carcinoma with portal venous tumor thrombus. *Exp Ther Med.* 2013;5(1):3-10.
39. Tanaka S, Shimada M, Shirabe K, et al. A novel intrahepatic arterial chemotherapy after radical resection for advanced hepatocellular carcinoma. *Hepatogastroenterology.* 2005;52(63):862-865.
40. Ikai I, Arii S, Ichida T, et al. Report of the 16th follow-up survey of primary liver cancer. *Hepatol Res.* 2005;32(3):163-172.
41. Ono T, Yamanoi A, Nazmy El Assal O, et al. Adjuvant chemotherapy after resection of hepatocellular carcinoma causes deterioration of long-term prognosis in cirrhotic patients: Meta-analysis of three randomized controlled trials. *Cancer.* 2001;91(12):2378-2385.
42. Hasegawa K, Takayama T, Ijichi M, et al. Uracil-tegafur as an adjuvant for hepatocellular carcinoma: A randomized trial. *Hepatol.* 2006;44(4):891-895.
43. Yamamoto M, Arii S, Sugahara K, et al. Adjuvant oral chemotherapy to prevent recurrence after curative resection for hepatocellular carcinoma. *Br J Surg.* 1996;83(3):336-340.
44. Prassas E, Petrou A, Kontos M, et al. Radiofrequency ablation assisted resection for hepatocellular carcinoma: Morbidity, mortality and long term survival. *J BUON.* 2014;19(1):256-262.
45. Liu J, Qian LX. Therapeutic efficacy comparison of radiofrequency ablation in hepatocellular carcinoma and metastatic liver cancer. *Exp Ther Med.* 2014;7(4):897-900.
46. Yi Y, Zhang Y, Wei Q, et al. Radiofrequency ablation or microwave ablation combined with transcatheter arterial chemoembolization in treatment of hepatocellular carcinoma by comparing with radiofrequency ablation alone. *Chin J Cancer Res.* 2014;26(1):112-118.
47. Fisher ER, Anderson S, Redmond C, et al. Ipsilateral breast tumor recurrence and survival following lumpectomy and irradiation: Pathological findings from NSABP protocol B-06. *Semin Surg Oncol.* 1992;8(3):161-166.
48. Vaidya JS, Joseph DJ, Tobias JS, et al. Targeted intraoperative radiotherapy versus whole breast radiotherapy for breast cancer (TARGIT-A trial): An international, prospective, randomised, non-inferiority phase 3 trial. *Lancet.* 2010;376(9735):91-102.
49. Alektiar KM, Zelefsky MJ, Paty PB, et al. High dose rate intraoperative brachytherapy for recurrent colorectal cancer. *Int J Radiat Oncol Biol Phys.* 2000;48(1):219-226.
50. Kusters M, Holman FA, Martijn H, et al. Patterns of local recurrence in locally advanced rectal cancer after intraoperative radiotherapy containing multimodality treatment. *Radiother Oncol.* 2009;92(2):221-225.
51. Nuyttens JJ, Kolkman-Deurloo IK, Vermaas M, et al. High-dose-rate intraoperative radiotherapy for close or positive margins in patients with locally advanced or recurrent rectal cancer. *Int J Radiat Oncol Biol Phys.* 2004;58(1):106-112.
52. Bachireddy P, Tseng D, Horoschak M, et al. Orthovoltage intraoperative radiation therapy for pancreatic adenocarcinoma. *Radiat Oncol.* 2010;5:105-110.
53. Tran PT, Hara W, Su Z, et al. Intraoperative radiation therapy for locally advanced and recurrent soft-tissue sarcomas in adults. *Int J Radiat Oncol Biol Phys.* 2008;72(4):1146-1153.
54. Zeidan YH, Shiue K, Weed D, et al. Intraoperative radiotherapy for parotid cancer: A single-institution experience. *Int J Radiat Oncol Biol Phys.* 2012;82(5):1831-1836.
55. Tran PT, Su Z, Hara W, et al. Long-term survivors using intraoperative radiotherapy for recurrent gynecologic malignancies. Int J Radiat Oncol Biol Phys. 2007;69(2):504-511.

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Proton therapy for pituitary adenoma

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Pituitary adenomas arise from the adenohypophysis and represent approximately 10% to 15% of all primary brain tumors. Tumor classification is divided by size and functional characteristics.[1] Morbidities owing to tumor size include visual and neurological defects due to proximity to the optic chiasm and cavernous sinuses. Perhaps the most important distinction in classifying pituitary adenomas is functional capacity. Secretory adenomas may cause potentially fatal biochemical imbalances because of overproduction of pituitary hormones like prolactin, growth hormones, adrenocorticotropic hormones and, more infrequently, thyroid-stimulating hormones.[2] Standard treatment for nonfunctioning macroadenomas is transsphenoidal resection, and functioning adenomas can be medically managed when indicated.

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Radiation therapy (RT) is used in the adjuvant setting after a subtotal resection or as a primary treatment for symptomatic primary or recurrent gross disease that is not amenable to surgical excision and cannot be medically managed. External-beam RT (EBRT) results in excellent radiographic disease control rates, ranging from 80% to 98% in nonfunctioning adenomas and 67% to 89% in functioning adenomas.[3] While photon-based RT has consistently produced high tumor control with low toxicity, room remains for improving the therapeutic ratio, especially in younger patients who may be at greatest risk from radiation-induced late effects. Hypopituitarism of 1 or more axes is by far the most common adverse effect, with a 20% 5-year incidence rising to nearly 80% within 15 years of follow-up. Less frequent toxicities include visual and neurological complications, secondary tumors, cerebral vascular accidents, and cerebral necrosis.[4,5]

The advantage of proton therapy over conventional RT is a potential for decreased late effects of radiation attributable to lower doses to adjacent normal tissues. While there is little hope that pituitary function will be spared, additional toxicities may be avoided given the more favorable dose distribution. Dosimetric studies comparing different radiotherapy modalities suggest proton therapy could improve the therapeutic ratio in pituitary adenoma treatment by reducing the dose to the retinas, optic nerves, brainstem, and temporal lobes compared with conventional photon techniques including intensity-modulated radiation therapy (IMRT).[6,7] In addition, proton therapy reduces the dose to the hippocampi, thus lowering radiation exposure to the neural stem cells, which may lessen the neurocognitive impact of radiotherapy.[8] To date, the literature regarding proton therapy for pituitary adenoma is sparse. We have conducted a retrospective review of patients treated at our institution with proton therapy for pituitary adenoma in an effort to contribute to the literature.

Patients and methods

In accordance with an institutional review board-approved protocol and the Health Insurance Portability and Accountability Act (HIPAA), we reviewed the medical records of 17 patients with pituitary adenomas treated between 2007 and 2013 at the University of Florida Proton Therapy Institute in Jacksonville. All patients were treated with curative intent using three-dimensional conformal proton therapy. All patients were radiographically evaluated with computed tomography (CT) and/or magnetic resonance imaging (MRI) before and

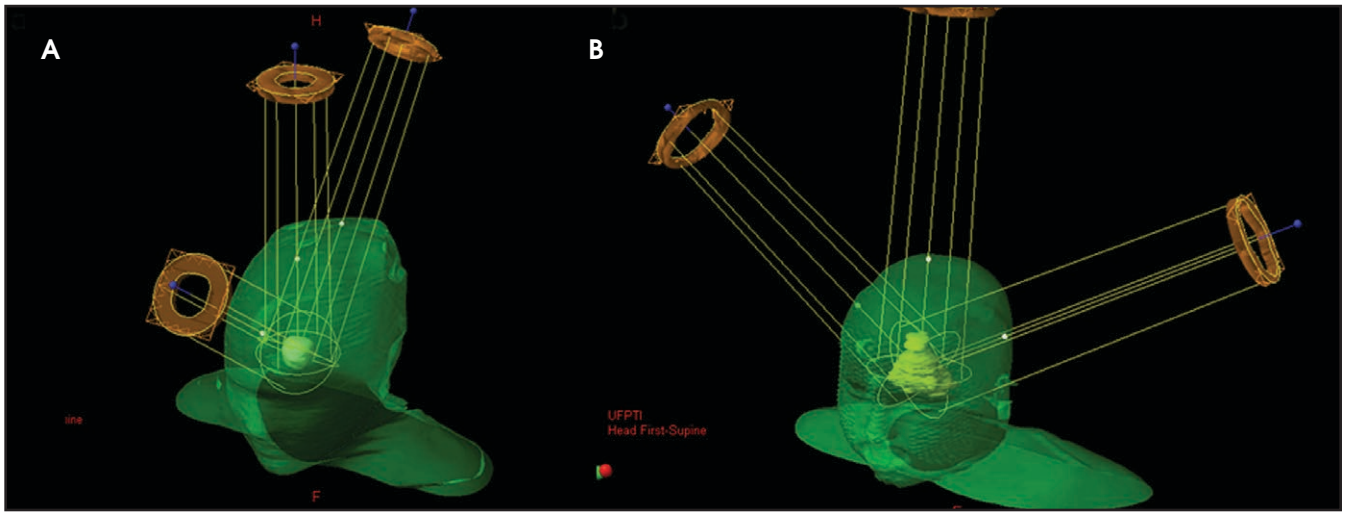

FIGURE 1. *Typical proton therapy beam arrangements and apertures in a (A) "mohawk" configuration and (B) 2-lateral oblique and superior-anterior oblique configuration.*

Table 1. Patient, tumor, and treatment characteristics (N=17)

Characteristic	Number of patients
Sex	
Male	11
Female	6
Age (range)	**62 yrs (10-83 yrs)**
Hormone secretion	
Secreting	4
Non-secreting	13
Surgeries before Radiotherapy	
None	1
1	12
2	4
Timing of Radiotherapy	
Postoperative	11
Salvage	5
No prior surgery	1
Tumor size (range)	**26.5 mm (18-50 mm)**
Extension Beyond Sella	
Cavernous sinus extension	15
Sphenoid sinus extension	7

after treatment. In addition, all patients' pituitary adenoma diagnoses were histologically confirmed prior to RT. Only benign pituitary tumors were included in the study; pituitary carcinomas were excluded from analysis. Patients treated with modalities other than transsphenoidal or transcranial surgical resection, such as stereotactic radiosurgery (SRS), were also excluded from our study.

Follow-up was calculated from the date the patient initiated RT. Length of follow-up ranged from 0.3 to 5.7 years, with a median time of 3.0 years. Patient, tumor, and treatment characteristics are presented in Table 1. All but 1 patient underwent surgery before proton therapy. Of the 16 who received surgery, 15 underwent transsphenoidal resection, and 1 was resected via transcranial approach followed by a second transsphenoidal operation. In total, 5 patients received a second operation before proton therapy. All patients had measurable gross disease at the time of proton therapy so that no patient was classified as undergoing a gross total resection. The predominant reason for the proton therapy referral was locally invasive disease (15 patients had a cavernous sinus invasion). Proton therapy was delivered as adjuvant treatment in 11 patients, salvage therapy for a recurrence in 5 patients, and definitive treatment in 1 patient. For patients undergoing adjuvant therapy, the median interval from surgery to initiation of proton-based irradiation was 114 days (range, 45–283 days).

Radiation treatment

All 17 patients were treated with three-dimensional double-scattered conformal proton therapy (3DCPT) in a continuous course of 5 fractions per week at 1.8 Gy relative biological effectiveness (RBE) per fraction. For each patient, pre- and postoperative treatment planning MRIs were co-registered to the treatment planning CT. Target volumes were defined as both the pre- and postoperative gross

Table 2. Patient endocrine function

Characteristic	Number of patients
Preradiotherapy Endocrinopathy	
Yes	10
No	5
Postradiotherapy Endocrinopathy	
Yes	11
No	4

Table 3. Dosimetric results for serial Organs at Risk

Serial organ-at-risk volume	Maximum dose, Gy(RBE)* 3DCPT	IMRT	P value
Retina – left	2.14 (0 – 13.99)	17.15 (6.29 – 26.44)	0.007†
Retina – right	2.15 (0 – 11.20)	10.70 (4.88 – 22.14)	0.019†
Optic nerve – left	47.60 (45.52 – 52.90)	48.25 (46.46 – 51.51)	0.371
Optic nerve – right	47.36 (45.69 – 51.92)	48.10 (46.26 – 51.89)	0.325
Optic chiasm	47.41 (43.61 – 53.20)	48.19 (46.80 – 52.08)	0.152
Cochlea – left	13.93 (0 – 28.29)	25.23 (7.39 – 38.40)	0.210
Cochlea – right	12.24 (0 – 38.98)	18.35 (7.18 – 35.63)	0.244
Brainstem	46.25 (38.22 – 52.29)	48.17 (46.45 – 51.45)	0.283

*Values are mean (range). Statistical significance is indicated by a dagger (†).
Abbreviations: 3DCPT, 3-dimensional conformal proton therapy; IMRT, intensity-modulated radiotherapy

tumor volumes, with the clinical target volume (CTV) adding a 5-mm margin off the gross tumor volume to account for tumor spread. The planning target volume (PTV) was defined as the CTV with an additional 3-mm margin. Two 3-field beam arrangements were used—either a mohawk (Figure 1A) or a 2-lateral oblique, superior-anterior oblique arrangement (Figure 1B). Beam-shaping apertures were designed based on a customized expansion of the PTV projection in the beam's eye-view of approximately 5 to 7 mm. Customized beam compensators were individually designed to maximize dose conformality and reduce the effects of tissue heterogeneity on the dose distribution. Total dose ranged from 45 to 50.4 Gy (RBE) (median, 45 Gy [RBE]). Plans were normalized such that 99% of the CTV was covered by the prescription, which nearly always meant that 95% of the PTV received 95% of the prescription.

Statistical methods

JMP software (SAS Institute, Cary, NC) was used to compute the Kaplan-Meier product limit estimates for local control, progression-free survival, and cause-specific survival.

Results

Local control

The 3-year radiographic local control rate for both secreting and nonfunctional pituitary adenomas after treatment with proton therapy was 100%, meaning all patients exhibited either stabilization or regression in tumor size. Objective measures of biochemical control were not available for the 4 patients with secreting tumors. Of these, 3 patients reported no signs, symptoms or biochemical evidence that they remained hypersecretory. It was not evident at what time their baseline hypersecretion normalized. The patient with a tumor secreting growth hormones continues to visit her local endocrinologist and reports no endocrine-related symptoms.

Survival

The 3-year overall survival rate was 100%. There was 1 intercurrent death that occurred at 4.98 years after treatment due to cardiovascular disease.

Complications

Several factors potentially lead to adverse neurological events, including surgery, radiation therapy, tumor mass effect, and hormonal secretion. The most commonly observed side effect was hypopituitarism, evident in 11 patients following RT. Table 2 shows the presence of pituitary dysfunction after both surgery and RT. All but 1 of the patients who were hormone-deficient after proton therapy had baseline pituitary dysfunction. In this series, no other major complications, such as cerebrovascular accidents, decline in visual function, ototoxicity, and second malignancies, have been observed as of the most recent follow-up. Objective neurocognitive function was not available for most patients, but all patients who were alive at the time of data collection report no signs or symptoms of significant cognitive deficits.

Dosimetric outcomes

Dosimetric data were reviewed for all 17 proton plans. In addition, 4 IMRT comparison plans were generated, normalized to the same target coverage achieved with the proton plans. Table 3 shows the mean maximum doses to serial organs at risk (OARs) for both the 3DCPT and IMRT plans. Compared to the IMRT plans, the left and right retinae received lower doses with 3DCPT; however, none of the doses delivered to serial OARs with either technique are expected to result in significant normal tissue complications. Nevertheless,

Table 4. Dosimetry for brain, temporal lobe, and hippocampal volumes

Volume	Dose (CGE)* 3DCPT	IMRT	P value
Maximum dose			
Whole brain	48.55 (46.20 – 53.22)	50.42 (48.30 – 53.29)	0.152
Temporal lobe – left	47.87 (45.42 – 53.04)	50.09 (47.48 – 53.15)	0.073
Temporal lobe – right	47.80 (45.17 – 51.89)	48.98 (46.75 – 50.97)	0.325
Hippocampus – left	41.49 (24.78 – 51.51)	46.76 (43.41 – 49.07)	0.089
Hippocampus – right	39.85 (18.94 – 51.69)	43.59 (35.14 – 49.91)	0.371
Mean dose			
Whole brain	5.53 (2.30 – 13.04)	12.76 (8.24 – 16.90)	0.048†
Temporal lobe – left	7.69 (1.75 – 24.12)	16.08 (8.60 – 22.26)	0.020†
Temporal lobe – right	8.41 (1.56 – 18.41)	14.02 (8.46 – 23.13)	0.039†
Hippocampus – left	10.95 (1.44 – 37.66)	26.36 (18.89 – 32.71)	0.032†
Hippocampus – right	10.85 (0.89 – 34.94)	23.28 (17.79 – 31.64)	0.039†

*Values are mean (range). Statistical significance is indicated by a dagger (†).
Abbreviations: 3DCPT, 3-dimensional conformal proton therapy; IMRT, intensity-modulated radiotherapy

these data show that proton therapy did not result in any unacceptable physical dose heterogeneity within serial OARs. Comparison of both maximum and mean doses to the whole brain, temporal lobes, and hippocampi are presented in Table 4. On average, the proton plans produced lower doses to whole brain, temporal lobes and hippocampi. Average dose-volume histograms are shown in Figure 2, demonstrating that most of the benefits of proton therapy were seen from a reduction in the low and moderate doses to these organ-at-risk volumes (ORVs).

Discussion

In the management of pituitary adenomas, surgical resection alone yields control rates that substantially differ by tumor characteristics. A large series by Mortini and colleagues[9] reported control rates of 55.5% in macroadenoma patients, compared to 78.9% for microadenomas. Much poorer outcomes were reported in tumors invading the cavernous sinuses, at 7.4%. While surgical resection is often indicated as a first line of treatment for these tumors, recurrence after surgery alone is 19% vs. 2% in patients receiving surgery and RT.[10] RT is an effective treatment modality either postoperatively when the likelihood of recurrence is high, or definitively when tumors are unresectable and cannot be medically managed.

Long-term outcomes of patients treated with postoperative conventional RT have been well-documented in the scientific literature. In one of the largest and most-cited analyses, Brada et al. reported the outcomes of 411 patients, of which 252 had non-functioning adenomas, 131 had functional adenomas, and the remaining 28 were of unknown secretory status. At 10 years, the progression-free survival rate was 94%, and at 20 years it was 88% for all patients. The only factor affecting prognosis in this study was hormone secretion.[11] In 2008, Chang et al. reported the outcomes of adjuvant RT in 663 patients with non-functioning pituitary adenomas, with progression-free survival rates of 93% at 5 years, 87% at 10 years, and 74% at 20 years. Out of these patients, cavernous sinus involvement was the only significant prognostic factor.[12] Snead and colleagues reviewed the records of 100 patients with pituitary adenomas, 69 of which were nonfunctioning and 31 were functioning. Overall, the 10-year progression-free survival rate was 95% for nonfunctioning and 88% for functioning adenomas. No statistically significant variables influenced prognosis in this study.[2] A 2009 study by Erridge et al. reported the progression-free survival rate of 385 patients treated with RT to be 97% at 10 years, and 96% at 20 years. No identifiable factors affected control rates in this study.[13]

In contrast to conventional RT, the outcomes of patients treated with fractionated proton therapy either definitively or adjuvantly are less well-documented. While several studies have reported outcomes of both conventional and proton-based SRS for treating pituitary adenomas, SRS is best indicated for tumors < 3 cm in diameter and further than 5 mm from the optic chiasm.[4] In the only other series reporting outcomes using fractionated proton therapy to date, Ronson and colleagues analyzed 47 patients treated with fractionated proton therapy. They observed 100% radiographic local control of all 41 patients who had available

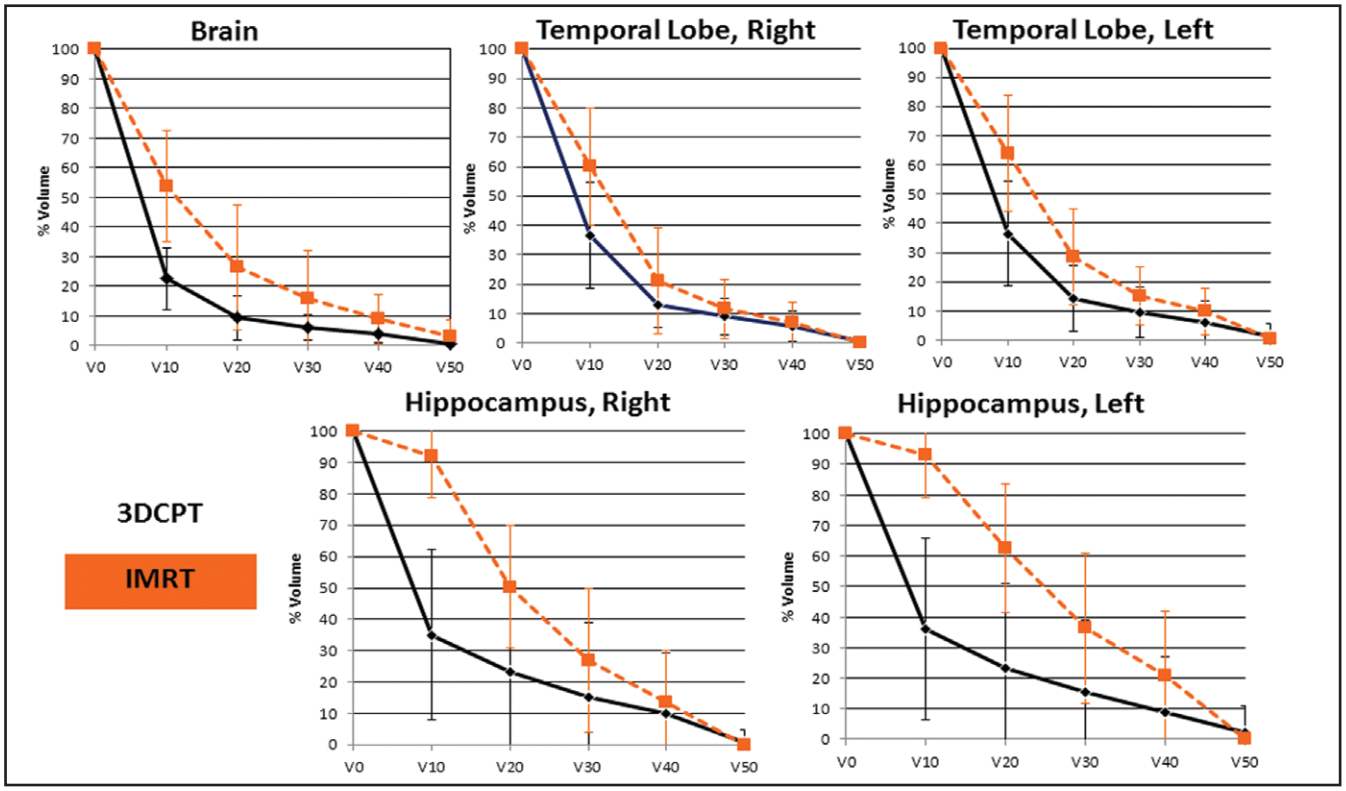

FIGURE 2. *Average dose-volume histograms for the volumes of the organs at risk.*

follow-up, with a median follow-up of 3.9 years.[14] These control rates are consistent with our results (100% at 3 years). A recent review by Loeffler et al. estimates that RT achieves biochemical remission rates of approximately 50% at 10 years, with these rates enhanced by concomitant medical management.[4] Our series reports treatment of 4 patients with functioning tumors—2 with prolactinomas, 1 with a growth hormone-secreting tumor, and 1 with an adrenocorticotropic hormone-secreting tumor. Unfortunately, objective endocrine follow-up was unavailable in these patients. Nevertheless, all 4 patients report no signs, symptoms or other evidence of hypersecretion.

The most common complication of RT, by far, is hypopituitarism of 1 or more hormonal axes. The literature suggests that this toxicity requires many years to develop. With fractionated RT, radiation-associated endocrinopathies is seen in roughly 20% of patients after 5 years of follow-up. Some studies have revealed pituitary decline to reach as high as 80% in patients after 10 years of follow-up data.[4] In our series, only 5 patients had normal pituitary function before RT, while the remainder had existing postoperative pituitary dysfunction. We observed 1 of those 5 patients develop new-onset hypopituitarism associated with RT (Table 2). With our median follow-up of 3.9 years, this rate is consistent with the current literature.

Other documented complications of RT include visual decline, cerebrovascular accidents, ototoxicity, temporal lobe necrosis, and secondary brain tumors. These toxicities are fortunately rare, and often do not manifest until many years after treatment. Perhaps the most documented of these extrapituitary events is injury to the optic pathways, with a 1.5% likelihood at 20 years after RT, and radiation-induced tumors, likely in 1.9% at 20 years.[11,13] Ronson and colleagues reported 1 case of temporal lobe necrosis 19 months after treatment. Several factors may have contributed to this event, but it is noteworthy that this patient received 54 Gy (RBE) in 2 Gy fractions.[14] While, fortunately, we report none of these complications in our series, continued follow-up is required to adequately assess such toxicities, as the incidence of these events slowly rises over time.

The rationale for particle therapy treatment such as fractionated proton therapy stems from a phenomenon known as the Bragg peak, which allows dose escalation to a target volume while sparing adjacent peripheral structures. Proton therapy has garnered particular interest in the treatment of intracranial tumors, especially as the importance of neuroprotection in radiation therapy is becoming increasingly realized. Neural stem cells serve a central role in neuroplasticity, with reserves located primarily in the subventricular zone as well as the subgranular layer of the hippocampal dentate gyrus.[15,16]

Conventional radiation therapies that do not spare these areas have been shown to damage hippocampal neurogenesis, contributing to the neurocognitive decline in patients treated for many intracranial tumors.[17,18] Dosimetric comparisons have established that proton-based modalities have the potential to better spare these structures vs. conventional techniques in treating intracranial tumors.[8,9]

Recent prospective data support these hypotheses; increased doses to the temporal lobes and hippocampi significantly impair patients' performances on standardized neurocognitive tests.[20] Dose-cognitive effect models have also been applied in dosimetric comparisons to estimate the improved preservation of IQ in patients who receive proton therapy.[21] But the relationship between brain irradiation and neurocognition is not entirely agreed upon. Some cross-sectional studies have found no significant differences in cognitive performance between patients with pituitary adenomas receiving surgery plus postoperative conventional RT, and patients receiving surgery alone.[22,23] These studies analyzed patients with median ages between 55 and 61, whereas the Redmond et al. study included only pediatric patients.[20] The patients in our study have a median age of 63 years, yet ages range from 10-83; thus, our findings may be difficult to apply uniformly. In addition, ongoing clinical trials such as RTOG 0933 aim to further assess the potential benefits of hippocampal avoidance and the relationship between radiation dose and cognitive function.

Our dosimetric analysis aimed to assess dosage differences in several serial OARs by comparing the 17 proton treatment plans used in our patients to 4 equivalent IMRT plans generated from our series. Of note, temporal lobe and hippocampal avoidance were objectives in the IMRT planning process. Despite specific goals to avoid these structures in IMRT planning, the whole brain, both temporal lobes, and both hippocampi were spared using 3DCPT. Dose-volume histograms of the 5 aforementioned structures also show significant decreases in the volume receiving up to 10 Gy (RBE; V10) in all 5 structures, as well as the V20 of the whole brain. Reducing doses to structures outside the tumor volume may potentially mitigate the unwanted effects of therapy on surrounding tissues. While we used no objective measures of neurocognitive function during follow-up of our patients, the dosimetric advantages characterized in our series may be of further interest given our growing understanding of RT doses to specific brain structures and cognitive impairment.

Conclusion

Our study demonstrates the feasibility of delivering proton therapy for pituitary adenoma. The high conformality of proton therapy does not appear to compromise local control and there is no increased early toxicity. Given the results of RTOG 0933, the lower dose to the hippocampi and temporal lobes should reduce the neurocognitive impact of radiotherapy. This greatest benefit will likely be in younger patients who are expected to have long-term survival.

References

1. Ezzat S, Asa SL, Couldwell WT, et al. The prevalence of pituitary adenomas: A systematic review. *Cancer.* 2004;101:613-619.
2. Snead FE, Amdur RJ, Morris CG, et al. Long-term outcomes of radiotherapy for pituitary adenomas. *Int J Radiat Oncol Biol Phys.* 2008;71:994-998.
3. Becker G, Kocher M, Kortmann RD, et al. Radiation therapy in the multimodal treatment approach of pituitary adenoma. *Strahlenther Onkol.* 2002;178:173-186.
4. Loeffler JS, Shih HA. Radiation therapy in the management of pituitary adenomas. *J Clin Endocrinol Metab.* 2011;96:1992-2003.
5. Brada M, Ashley S, Ford D, et al. Cerebrovascular mortality in patients with pituitary adenoma. *Clin Endocrinol (Oxf).* 2002;57:713-717.
6. Bolsi A, Fogliata A, Cozzi L. Radiotherapy of small intracranial tumours with different advanced techniques using photon and proton beams: A treatment planning study. *Radiother Oncol.* 2003;68:1-14.
7. Winkfield KM, Niemierko A, Bussiere MR, et al. Modeling intracranial second tumor risk and estimates of clinical toxicity with various radiation therapy techniques for patients with pituitary adenoma. *Technol Cancer Res Treat.* 2011;10:243-251.
8. Boehling NS, Grosshans DR, Bluett JB, et al. Dosimetric comparison of three-dimensional conformal proton radiotherapy, intensity-modulated proton therapy, and intensity-modulated radiotherapy for treatment of pediatric craniopharyngiomas. *Int J Radiat Oncol Biol Phys.* 2012;82:643-652.
9. Mortini P, Losa M, Barzaghi R, et al. Results of transsphenoidal surgery in a large series of patients with pituitary adenoma. *Neurosurg.* 2005;56:1222-1233; discussion 1233.
10. Chun M, Masko GB, Hetelekidis S. Radiotherapy in the treatment of pituitary adenomas. *Int J Radiat Oncol Biol Phys.* 1988;15:305-309.
11. Brada M, Rajan B, Traish D, et al. The long-term efficacy of conservative surgery and radiotherapy in the control of pituitary adenomas. *Clin Endocrinol (Oxf).* 1993;38:571-578.
12. Chang EF, Zada G, Kim S, et al. Long-term recurrence and mortality after surgery and adjuvant radiotherapy for nonfunctional pituitary adenomas. *J Neurosurg.* 2008;108:736-745.
13. Erridge SC, Conkey DS, Stockton D, et al. Radiotherapy for pituitary adenomas: Long-term efficacy and toxicity. *Radiother Oncol.* 2009;93:597-601.
14. Ronson BB, Schulte RW, Han KP, et al. Fractionated proton beam irradiation of pituitary adenomas. *Int J Radiat Oncol Biol Phys.* 2006;64:425-434.
15. Eriksson PS, Perfilieva E, Bjork-Eriksson T, et al. Neurogenesis in the adult human hippocampus. *Nat Med.* 1998;4:1313-1317.
16. Doetsch F, Caille I, Lim DA, et al. Subventricular zone astrocytes are neural stem cells in the adult mammalian brain. Cell. 1999;97:703-716.
17. Monje ML, Vogel H, Masek M, et al. Impaired human hippocampal neurogenesis after treatment for central nervous system malignancies. *Ann Neurol.* 2007;62:515-520.
18. Dietrich J, Monje M, Wefel J, et al. Clinical patterns and biological correlates of cognitive dysfunction associated with cancer therapy. *Oncologist.* 2008;13:1285-1295.
19. Blomstrand M, Brodin NP, Munck Af Rosenschold P, et al. Estimated clinical benefit of protecting neurogenesis in the developing brain during radiation therapy for pediatric medulloblastoma. *Neuro Oncol.* 2012;14:882-889.
20. Redmond KJ, Mahone EM, Terezakis S, et al. Association between radiation dose to neuronal progenitor cell niches and temporal lobes and performance on neuropsychological testing in children: a prospective study. *Neuro Oncol.* 2013;15:360-369.
21. Merchant TE, Hua CH, Shukla H, et al. Proton versus photon radiotherapy for common pediatric brain tumors: comparison of models of dose characteristics and their relationship to cognitive function. *Pediatr Blood Cancer.* 2008;51:110-117.
22. van Beek AP, van den Bergh AC, van den Berg LM, et al. Radiotherapy is not associated with reduced quality of life and cognitive function in patients treated for nonfunctioning pituitary adenoma. *Int J Radiat Oncol Biol Phys.* 2007;68:986-991.
23. Brummelman P, Elderson MF, Dullaart RP, et al. Cognitive functioning in patients treated for nonfunctioning pituitary macroadenoma and the effects of pituitary radiotherapy. *Clin Endocrinol. (Oxf).* 2011;74:481-487.

Safety stance: programs and initiatives to minimize errors in radiation therapy

Mary Beth Massat

Patient safety is at the crux of medicine, from the Hippocratic Oath to government regulations to accreditation programs and beyond. And for good reason: If it's not safe medicine, it's not good medicine. In radiation therapy, patient safety is crucial not only to successfully target cancer, but to limit damage to healthy tissue and prevent potentially devastating human errors. At minimum, maximizing safety requires a team commitment and knowledge of the intricacies of advanced technologies. It also means knowing what field-specific resources to harness, including learning systems, accreditation opportunities and task group initiatives.

But the first step in any safety program is developing a safety culture, says Jennifer L. Johnson, MS, MBA, senior medical physicist in the Department of Radiation Physics, Division of Radiation Oncology, University of Texas MD Anderson Cancer Center in Houston. "Without a safety culture—which is neither a blame culture nor a blame-free culture, but an accountable culture—other efforts may fall short," she says. "Part of that means having active engagement by all members, including physician and administrative leadership."

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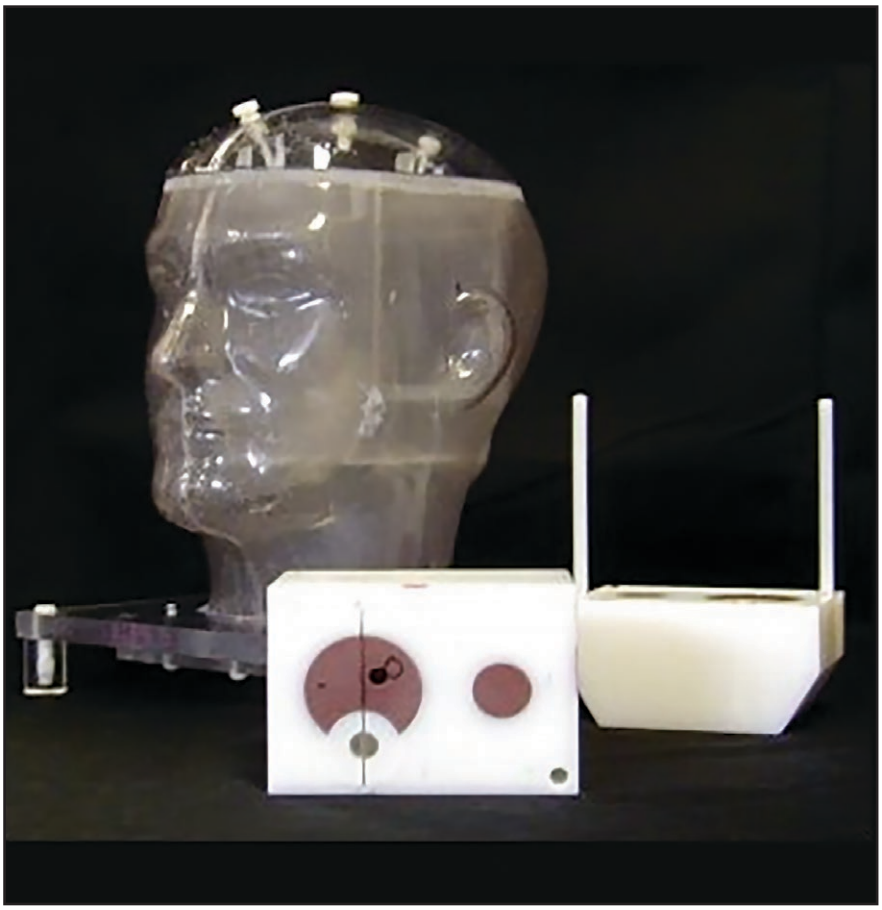
Improving the process also requires communication and feedback mechanisms, Johnson adds. "If people submit information and don't hear of the outcome or see improvements, then you may not get continued involvement. 'Near misses' or 'good catches' are also very useful for learning and improving the process since these…can give clues as to where to focus efforts to prevent actual incidents."

The RO-ILS Treatment

Toward this end, the American Society for Radiation Oncology (ASTRO) and the American Association of Physicists in Medicine (AAPM) launched a patient safety initiative last year called RO-ILS: The Radiation Oncology Incident Learning System. The only medical specialty society-sponsored radiation oncology learning system within a federally recognized patient safety organization (PSO), RO-ILS is a platform that collects and shares information anonymously to identify potential errors, minor deviations, procedural issues or an event that occurred with a machine, explains Bruce G. Haffty, MD, FASTRO, chair of the ASTRO board of directors and professor and chair of the Department of Radiation Oncology, Rutgers, Cancer Institute of New Jersey, Robert Wood Johnson Medical School, New Jersey Medical School.

"The goal of the initiative is to communicate any patient safety issue in a transparent and open way, so if a similar issue occurs in another facility, all members can be informed and take the proper corrective action," he says. "By signing up…facilities are participating in a quality improvement program," Dr. Haffty continues. "While the rate of known errors is quite small, and radiation therapy is extremely safe for



During a 2-week period, institutions use the IROC Houston head and neck phantom to image, plan and treat the phantom to become credentialed for this protocol.

the number of treatments delivered, there is always room for improvement and the sharing of information."

"RO-ILS is an extremely important initiative," adds Bruce R. Thomadsen, PhD, FAAPM, professor of medical physics and biomed engineering at the University of Wisconsin. "We don't know what events take place in radiotherapy because we haven't collected that data. In some cases an individual institution does not have the depth [of experience] to determine how to fix the issue. Collectively, professionals who perform analyses often can provide a deeper analysis and generate a deeper understanding—and hopefully a better solution."

In addition to RO-ILS is the PSO offered through the Center for Assessment of Radiological Sciences (CARS), which Dr. Thomadsen helped spearhead. With a broader mission than ROI-ILS, CARS-PSO centers on education and working with vendors when equipment problems arise. Also of help, 27 states and the District of Columbia have an adverse event or medical error reporting system. Even New York City has in the health code a reporting requirement and list of reportable events, notes Jean M. St. Germain, MS, vice chair, Department of Medical Physics and chief of Radiation Safety Service at Memorial Sloan Kettering Cancer Center (MSKCC).

"Not all states have a reporting system, and it varies from state to state," says St. Germain. "Some of it is voluntary reporting, so there could be some underreporting of events."

Task Group 100

Since its inception, The AAPM has likewise launched numerous other safety-oriented initiatives, including more than 250 task groups that primarily assess quality assurance (QA) and quality control (QC) in healthcare. Over the last 10 years, Task Group 100 has focused on evaluating QA needs in radiation therapy, and has embraced the systems engineering approach to safety, says Dr. Thomadsen. Results and recommendations will be published this year. "The task group is bringing a systematic approach to developing quality and safety at any institution," he says, "including the equipment, people, and organization, and how it all works together."

In most cases, facilities that experienced an event have missed core safety components, says Dr. Thomadsen. Although obvious, the following items bear emphasis for a safe, quality radiation therapy program:

1. Complete training.
2. Resources to carry out procedures.
3. Communication lines across team members.
4. Preventive equipment maintenance.
5. Standardized procedures and policies.

Regarding item 5, Dr. Thomadsen adds that while every patient is different, many similarities span clinicians' work, patient to patient. "Have a standardized approach within the institution for patients who are similar, rather than approach every patient differently," he advises. "If a patient is outside the normal case, then look at that more closely." By streamlining efforts, clinicians can improve safety and bolster efficiency.

St. Germain says the AAPM task group reports remain an important tool for safety officers and medical physicists—or anyone involved in QC and safety of radiation therapy programs. These reports, and ASTRO's book, "Safety is No Accident: A Framework for Quality Radiation Oncology and Care" (part of ASTRO's Target Safely initiative), also provide guidance for equipment maintenance and testing. The key lies in continuing education, she says, which many societies now require. "It's a matter of people availing themselves of the information out there—the task group reports, annual meetings, and maintenance of certification programs," stresses St. Germain.

Safety and self-referral

At the legislative level, ASTRO, the American College of Radiology (ACR), the Radiology Business Management Association (RBMA) and several other societies support H.R. 2914, the Promoting Integrity in Medicare Act, which aims to close the loophole in the federal physician self-referral law that excludes radiation therapy among other healthcare services. While this bill has not been brought to the floor of the House of Representatives for a vote, it received additional support in December from the American Association of Retired Persons (AARP).

"It makes common sense to discourage physicians to make a referral for complex services in which they have a vested financial interest," stresses Dr. Haffty. "The bottom line is to give patients an unbiased, informed choice and encourage the appropriate use of radiation and safety." Dr. Haffty cites a 2013 study in the New England Journal of Medicine that "scientifically and statistically demonstrated the fact that physician self-referral leads to doctors altering practice based on that financial interest." The authors found that nearly all of the 146% increase in IMRT for prostate cancer among urologists with an ownership interest in the treatment was due to self-referral.[1]

IROC and APEx

MD Anderson, in conjunction with AAPM and the National Cancer Institute (NCI), also supports IROC (Imaging and Radiation Oncology Core) Houston QA Center, which provides integrated radiation oncology and diagnostic imaging QC programs in support of NCI's National Clinical Trial Network (NCTN). While the focus of the NCTN is on clinical trials, Johnson says facilities that are implementing new technologies and/or procedures, such as volumetric modulated arc therapy (VMAT), can request QA phantoms and other QA services from the IROC Houston center for an independent peer review before or early in the release to the clinic.

Accreditation is another method for obtaining an independent review of a facility's equipment, personnel, and treatment planning, as well as assessing patient safety, QA and QC activities. The ACR provides accreditation services, and ASTRO is launching the Accreditation Program for Excellence (APEx) this year, which includes self-assessment, processes and policies to improve safety and quality of care. With a four-year accreditation cycle, APEx was created to ensure accountability in radiation therapy practices, and offers transparent, measurable, evidence- and consensus-based standards that emphasize commitment to safety and quality.

"Even though accreditation is not yet mandated by law, it is important, and ASTRO would like to see greater involvement by all the radiation oncology facilities in the U.S., as most have staff who are ASTRO members," says Dr. Haffty. "Accreditation…raises self-awareness and enhances quality."

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New technologies drive need

When implementing a new technology or procedure, the first step is understanding the process, Dr. Thomadsen says. Map it out and examine flow so everyone understands what to expect, he says. At each step, perform a risk assessment, create fault trees, and project the fall-out in case something goes awry. Then, design a quality management program for the procedure with safety barriers that can halt the error before it impacts the patient, he adds. Finally, go through equipment commissioning and walk through the procedure so each team member knows what information to share, and include checks and balances so each member knows how to flag a concern.

As technology changes, so will standards. As mentioned above, information within RO-ILS and accreditation-driven self-assessment will become increasingly important as technologies and techniques evolve. "With new procedures comes a learning curve, and that curve can benefit by sharing information," Dr. Haffty says. "If early adopters share their experience and any events through RO-ILS, then other facilities that follow will have a better understanding of what to expect."

Understanding potential risks before implementing new technology is critical, adds Johnson. Independent validation through an organization such as IROC Houston before treating patients is an important first check. Practices can also participate in peer review processes by ACR, ASTRO and others.

Certainly, when implementing hypofractionated treatment or stereotactic body radiation therapy, the room for error is virtually non-existent, explains St. Germain. "In a typical fractionated treatment over the course of 5 or 6 weeks, subsequent doses can be adjusted to account for any error. With hypofractionated treatment, we can't afford to make any mistakes, so these techniques are physics-driven and require a commitment to quality control, assurance and assessment."

Both Johnson and St. Germain agree that patients being re-treated warrant additional treatment planning and safety considerations as well. They both say the most important aspect for these patients is access to prior treatment records. Whether they can be re-treated safely is a complex paradigm, and the physicians and physicist must consider the person's overall health and physical condition, St. Germain explains.

The most important person

Patient education plays a role as well, although it can be challenging, Johnson adds. "Patients are likely overwhelmed with making decisions and understanding potential consequences. Ongoing communication and education is key, as [is] documenting and addressing their concerns."

"There is a lot of information out there—some of it on websites—and many institutions have patient resources," adds St. Germain. "Make sure the right information gets into the patient's hand."

Reference

1. Mitchell JM. Urologists' use of intensity-modulated radiation therapy for prostate cancer. *N Engl J Med.* 2013; 369:1629-1637.

RADIATION ONCOLOGY CASE

Congratulations to our Clinical Case Contest winner for March 2015!

Radiation-induced pathologic complete response of gross nodal disease in recurrent head and neck melanoma

Zachary D. Lopater, MD, MPH; Elizabeth Ester, MD; and Deniz Aslan, MD

CASE SUMMARY

A 52-year-old male presented with a 4-by-2-mm brown macule on the central midline of his forehead; it had reticulated edges, which had been present for 1 year. A shave biopsy diagnosed lentigo maligna melanoma with tumor thickness of 1.5 mm, Clark level 3. The patient underwent staging sentinel lymph node mapping with TC-99M scintigraphy. He proceeded with wide local excision and sentinel lymph node biopsy, with pathology negative for residual disease. No lymph nodes were identified; thus, initial AJCC Stage pT2N0M0 was diagnosed.

At 5 months follow-up, a 2 cm firm left submandibular lymph node was noted on exam. Fine-needle aspiration favored recurrent melanoma. A staging positron emission tomography/computed tomography (PET/CT) scan showed 2 enlarged lymph nodes adjacent to the left submandibular gland measuring 3.4-by-2.5 cm (SUV of 3.5) and 2.1-by-1.6 cm (SUV of 4.4). The patient underwent left neck dissection of levels IB, II and III with 9.0-by-4.5-by-1.7 cm of tissue removed and 14 total lymph nodes removed with only 1 positive for disease. ENT notes indicated that the left submandibular gland was preserved. There was no evidence of extracapsular extension. He received postoperative radiation given recurrent nodal disease. An enlarged level Ib lymph node was seen on post-op imaging obtained for radiation planning. Radiation entailed 3000 cGy in 5 fractions delivered twice weekly over 14 days. A planned left submandibular nodal dissection was performed 7 weeks after the completion of radiation, with pathology reporting evidence of regressed melanoma and no viable tumor. He had no postoperative complications or difficulty with wound healing. A restaging PET/CT and exam showed no recurrent disease 3 months after therapy.

*Prepared by **Dr. Lopater** while a resident at University of Minnesota Hospital, Minneapolis, MN; **Dr. Ester,** radiation oncologist at VA Medical Center, Minneapolis, and **Dr. Aslan,** pathologist, also at VA Medical Center.*

IMAGING FINDINGS AND DIFFERENTIAL DIAGNOSIS

Initial preoperative PET/CT (Figure 1) demonstrated moderate hypermetabolism of 2 adjacent masses within the left neck near the left submandibular gland. These are suspicious for potential level 1 lymph node metastases associated with the patient's melanoma. The differential diagnosis would include metastases associated with a second primary head and neck neoplasm.

Postoperative CT used for RT planning (Figure 2) demonstrated persistence of a single mass near the left submandibular gland. Seven weeks after radiation, path slides (Figure 3) showed irradiated lymph node with necrosis, fibrosis, and residual heavy pigment consistent with a regressed tumor (pCR).

DIAGNOSIS

Recurrent head and neck melanoma

DISCUSSION

The optimal management of regional nodal disease in melanoma is controversial.

For intermediate thickness (1.0 mm to 4.0 mm) melanomas, sentinel lymph node biopsy (SLNB) is advocated as the standard management with regional nodal dissection reserved for stage III disease and considered if SLNB is

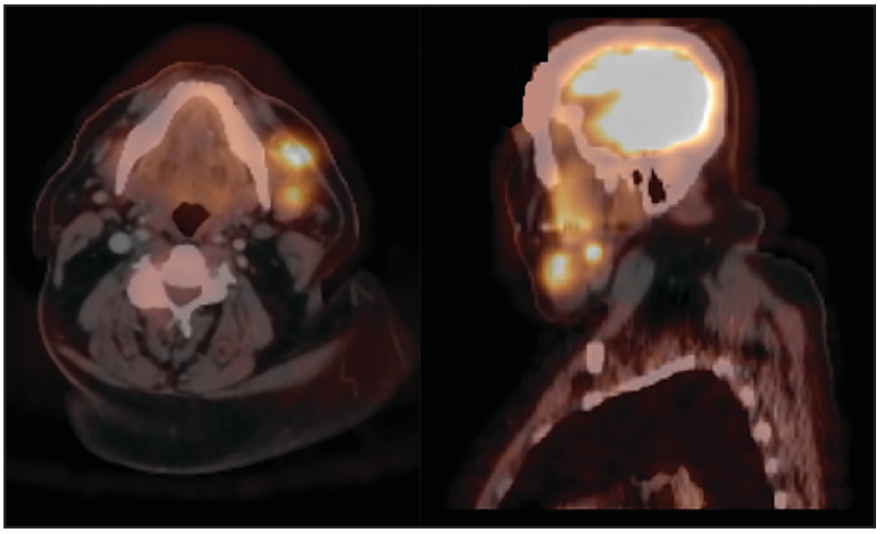

FIGURE 1. *Fused axial and sagittal PET/CT images showing left submandibular nodal recurrent disease. The patient proceeded with left neck dissection of levels IB, II, and III followed by postoperative radiation.*

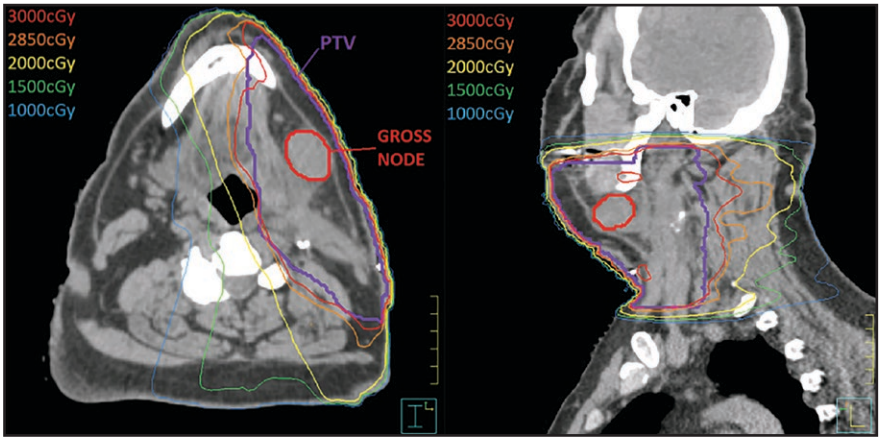

FIGURE 2. *Postoperative axial and sagittal planning CT images with corresponding isodose lines. Radiation was delivered to the operative bed, which was encompassed within the PTV (purple) including a lymph node with gross disease (red). Prescription was 3000 cGy in 5 fractions via IMRT.*

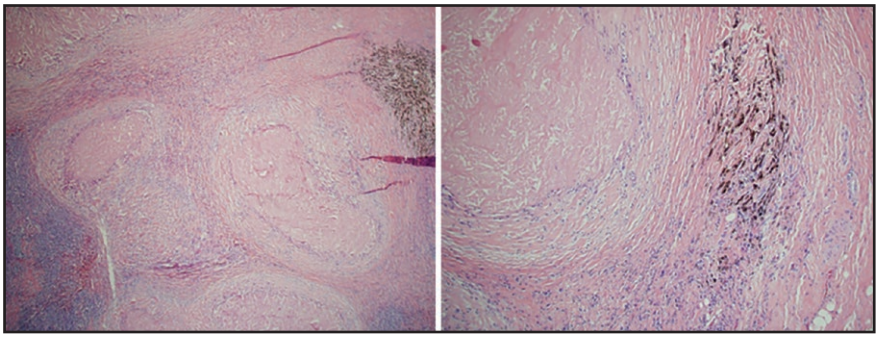

FIGURE 3. *Slides from neck dissection 7 weeks after radiation therapy. Images show irradiated lymph node with necrosis, fibrosis and residual heavy pigment consistent with regressed tumor (pCR). Tissue was also examined with immunostains for SOX-10 and melanocyte cocktail antigens; no viable tumor cells were identified.*

positive.[1,2] Despite the utility of SLNB providing staging information that is helpful for adjuvant treatment decisions, overall survival benefit was not demonstrated in a large randomized study.[3] In the setting of a negative sentinel lymph node, elective dissection is not recommended given no overall survival benefit in 4 early randomized surgical trials.[4-7]

Adjuvant radiation therapy should be considered for patients with possible residual microscopic disease to improve local control.[2] Increased risk of microscopic residual disease is often estimated with the presence of the following pathologic features: primary lesions >4 mm, satellitosis, desmoplastic subtype, presence of 1 or more parotid lymph nodes of any size, lymph nodes ≥ 3 cm, extranodal extension, multiple nodes, recurrent disease, and close or positive margins.[8-14]

A phase III randomized multi-institutional study was conducted by the Trans-Tasman Radiation Oncology Group (TROG), evaluating the benefit of adjuvant radiation vs. observation after therapeutic lymphadenectomy for melanoma.[14] Eligible patients were considered high risk for regional relapse due to large lymph nodes, multiple involved nodes, and/ or extracapsular extension. Eligibility criteria differed depending on nodal site (ie., parotid, cervical, axillary, etc.) for lymph node size and number. Radiation consisted of 48 Gy/20 fractions within 12 weeks following surgery. At a median of 3 years, local control within the nodal basin was improved with radiation, 82% vs. 69% ($p = 0.041$), HR of 0.56. Overall survival and rate of distant metastasis were similar. Toxicity was low for patients treated with neck radiation (3% grade 3 or 4 dermatitis). Sentinel lymph node biopsy was not routinely performed within the study, and patients with recurrent disease were not included.[14]

The ideal radiation fraction size for melanoma remains unknown. Early radiobiological data from Dewey[15] showed that melanoma cells in vitro had broad shoulders on survival curves, which suggested that hypofractionated radiation would induce higher response rates compared to standard fractionation. MD Anderson Cancer Center (MDACC) introduced an adjuvant hypofractionated radiation regimen, 6 Gy x 5 fractions for subclinical disease, and 6 Gy x 6 for gross disease, with promising results from their phase II trial showing 88% locoregional control at a median follow-up of 3 years.[16,17] This regimen was delivered twice weekly over 2.5 weeks, while limiting spinal cord, brain and small bowel to 24 Gy, when treating subclinical disease. However, a randomized clinical study (RTOG 83-05) disputed the laboratory data given no significant difference in response comparing 32 Gy/4 fractions vs. 50 Gy/20 fractions.[18] The University of Florida performed a retrospective comparison of 30 Gy/5 fractions vs. 60 Gy/30 fractions, showing no significant difference in local control, 87% vs. 78% respectively, when treating subclinical disease. Hypofractionation was advocated given the benefit of a shorter treatment time, unless the cosmetic and/or functional outcome could be compromised.[19,20]

Hypofractionated radiotherapy regimens for melanoma of the head and neck have been primarily utilized in the adjuvant setting to reduce local regional relapse rates. This is the first case report we are aware of demonstrating histologic confirmation of a pathological complete response (pCR) for gross cervical nodal disease following hypofractionated radiation. A small (n=12) retrospective study evaluated neoadjuvant radiation in patients with locally advanced axillary, inguinal or popliteal metastatic melanoma.[21] No patients with head and neck disease were included in the study. Forty-eight Gy in 20 fractions was the most common radiation regimen (8/12 patients) with the remaining 4 patients receiving different schedules (30 Gy/6, 32 Gy/8, 36 Gy/9, 50 Gy/20 fractions). Node dissection was performed in 10/12 patients with 9 samples available for histologic response. There were 2 patients (22%) with pCR, 5 with pPR, and 2 with no evidence of treatment response. One year in-field control was 92%. Overall, this treatment strategy was well-tolerated, with 4 patients developing minor wound complications.[21]

MDACC reported excellent regional control for patients who underwent radiation in lieu of completing neck dissection for melanoma of the head and neck. In a retrospective review (n=36), patients underwent excision of the primary cutaneous melanoma and any clinically apparent lymphadenopathy. No formal neck dissections were performed. Hypofractionated radiation (30 Gy in 5 fractions for elective disease) was delivered to the nodal basin with locoregional control rates of 93% at 5 years.[22]

Long-term toxicities associated with hypofractionated radiation appear tolerable. MDACC reported 5-year rates of grade 1 toxicity of 12% (atrophy, loss of subcutaenous fat), and grade 2 toxicity of 10% (functional deficits and/or long-term pain).[23] University of Florida described 2 patients with long-term toxicity after 30 Gy/5 fractions with 1 case of osteoradionecrosis of the external auditory canal and 1 case of plexopathy.[19] Long-term lymphedema risk is low after head and neck radiation, but higher rates have been reported for inguinal node irradiation.[24] Some advocate conventional fractionation for disease near optic structures, spinal cord, or brainstem to prevent long-term sequelae. If using hypofractionated RT, neurologic structures are generally limited to 24 Gy.[17]

Radiation has not demonstrated any survival benefit in treating melanoma given the high rate of distant metastatic recurrences. However, increasingly effective systemic agents such as ipilimumab[25] and vemurafenib (in patients with candidate genetic *BRAF* mutations)[26] have demonstrated overall survival benefits. Better distant disease control and further understanding of the interaction of radiation with the immune system[27] may lead to an expanded role of radiation therapy in melanoma treatment.

CONCLUSION

Current guidelines for head and neck melanoma with localized nodal disease include neck dissection with or without adjuvant radiation depending on pathologic risk factors. Adjuvant radiation offers improvement in local control; however, no effect on overall survival has been demonstrated. The current goal of radiation therapy is to improve locoregional control through prevention of recurrences and the associated morbidity of local progression including pain, ulceration, bleeding, disfigurement, and the need for additional surgery.

In this case, hypofractionated radiation induced a pathological complete response in recurrent gross nodal disease. This case reinforces the efficacy of 30 Gy hypofractionated radiation therapy for localized nodal melanoma. This regimen could be considered for future study in the neoadjuvant setting, or as a potential definitive therapy for inoperable patients.

REFERENCES

1. Wong SL, Balch CM, Hurley P, et al. Sentinel lymph node biopsy for melanoma: American society of clinical oncology and society of surgical oncology joint clinical practice guideline. *J Clin Oncol.* 2012;30(23):2912-2918. doi: JCO.2011.40.3519.
2. Coit DG, Thompson JA, Andtbacka R, et al. Melanoma, version 4.2014. *J Natl Compr Canc Netw.* 2014;12(5):621-629. doi: 12/5/621 [pii].
3. Morton DL, Thompson JF, Cochran AJ, et al. Final trial report of sentinel-node biopsy versus nodal observation in melanoma. *N Engl J Med.* 2014;370(7):599-609.
4. Veronesi U, Adamus J, Bandiera D, et al. Delayed regional lymph node dissection in stage I melanoma of the skin of the lower extremities. *Cancer.* 1982;49(11):2420-2430.

5. Sim, FH, Taylor, WF, Pritchard, DJ, et al. Lymphadenectomy in the management of stage I malignant melanoma: a prospective randomized study. *Mayo Clin Proc.*1986;61(9):697-705.
6. Cascinelli N, Morabito A, Santinami M, et al. Immediate or delayed dissection of regional nodes in patients with melanoma of the trunk: a randomised trial. *The Lancet.* 1998;351(9105):793-796.
7. Balch CM, Soong S, Ross MI, et al. Long-term results of a multi-institutional randomized trial comparing prognostic factors and surgical results for intermediate thickness melanomas (1.0 to 4.0 mm). *Ann of Surg Oncol.* 2000;7(2):87-97.
8. Leon P, Daly JM, Synnestvedt M, et al. The prognostic implications of microscopic satellites in patients with clinical stage I melanoma. *Arch Surg.* 1991;126(12):1461-1468.
9. Calabro A, Singletary SE, Balch CM. Patterns of relapse in 1001 consecutive patients with melanoma nodal metastases. *Arch Surg.* 1989;124(9):1051-1055.
10. Shen P, Wanek LA, Morton DL. Is adjuvant radiotherapy necessary after positive lymph node dissection in head and neck melanomas? *Ann Surg Oncol.* 2000;7(8):554-559.
11. Lee RJ, Gibbs JF, Proulx GM, et al. Nodal basin recurrence following lymph node dissection for melanoma: Implications for adjuvant radiotherapy. *Int J Radiat Oncol Biol Phys.* 2000;46(2):467-474.
12. Vuylsteke RJ, van Leeuwen PA, Statius Muller MG, et al. Clinical outcome of stage I/II melanoma patients after selective sentinel lymph node dissection: long-term follow-up results. *J Clin Oncol.* 2003;21(6):1057-1065.
13. Ballo MT, Ang KK. Radiotherapy for cutaneous malignant melanoma: rationale and indications. *Oncol.* 2004;18(1):99-107.
14. Burmeister BH, Henderson MA, Ainslie J, et al. Adjuvant radiotherapy versus observation alone for patients at risk of lymph-node field relapse after therapeutic lymphadenectomy for melanoma: a randomised trial. *The Lancet Oncol.* 2012;13(6):589-597.
15. Dewey DL. The radiosensitivity of melanoma cells in culture. Br J Radiol. 1971;44(526):816-817.
16. Ang K, Byers R, Peters L, et al. Regional radiotherapy as an alternative or adjuvant to nodal dissection for high risk cutaneous malignant melanoma of the head and neck. *Arch Otolaryngol Head Neck.* 1990;116:169-172.
17. Ang KK, Peters LJ, Weber RS, et al. Postoperative radiotherapy for cutaneous melanoma of the head and neck region. *Int J Radiat Oncol Biol Phys.* 1994;30(4):795-798.
18. Sause W, Cooper J, Rush S, et al. Fraction size in external beam radiation therapy in the treatment of melanoma. *Int J Radiat Oncol Biol Phys.* 1991;20(3):429-432.
19. Chang DT, Amdur RJ, Morris CG, et al. Adjuvant radiotherapy for cutaneous melanoma: Comparing hypofractionation to conventional fractionation. *Int J Radiat Oncol Biol Phys.* 2006;66(4):1051-1055.
20. Mendenhall WM, Shaw C, Amdur RJ, et al. Surgery and adjuvant radiotherapy for cutaneous melanoma considered high-risk for local–regional recurrence. *Am J Otolaryngol.* 2013;34(4):320-322.
21. Foote M, Burmeister B, Dwyer P, et al. An innovative approach for locally advanced stage III cutaneous melanoma: radiotherapy, followed by nodal dissection. *Melanoma Res.* 2012;22(3):257-262. doi: 10.1097/CMR .0b013e3283531335 [doi].
22. Ballo MT, Garden AS, Myers JN, et al. Melanoma metastatic to cervical lymph nodes: Can radiotherapy replace formal dissection after local excision of nodal disease? *Head Neck.* 2005;27(8):718-721.
23. Ballo MT, Bonnen MD, Garden AS, et al. Adjuvant irradiation for cervical lymph node metastases from melanoma. *Cancer.* 2003;97(7):1789-1796.
24. Guadagnolo BA, Zagars GK. Adjuvant radiation therapy for high-risk nodal metastases from cutaneous melanoma. *Lancet Oncol.* 2009;10(4):409-416.
25. Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. *N Engl J Med.* 2010;363(8):711-723.
26. Chapman PB, Hauschild A, Robert C, et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. *N Engl J Med.* 2011;364(26):2507-2516.
27. Barker CA, Postow MA. Combinations of radiation therapy and immunotherapy for melanoma: a review of clinical outcomes. *Int J Radiat Oncol Biol Phys.* 2014;88(5):986-997.

RADIATION ONCOLOGY CASE

Radiation therapy following a positive sentinel lymph node biopsy: A radiation oncologist's dilemma

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CASE SUMMARY

SD, a 40-year-old African-American female, presented with a palpable mass in the left breast. Her work-up led to the diagnosis of an infiltrating ductal carcinoma. The patient underwent a partial mastectomy and sentinel lymph node biopsy, with pathology demonstrating a 2.8 cm high-grade carcinoma that was ER(-), PR(-), HER2(-); 1 of the 2 sampled sentinel lymph nodes demonstrated metastatic disease. Thereafter, she received 4 cycles of dose-dense Adriamycin and Cytoxan, followed by weekly paclitaxel. Following chemotherapy, she received radiotherapy at an outside institution to the intact breast to a total dose of 5040 cGy, followed by a boost of 1400 cGy to the tumor bed for a total dose of 6440 cGy.

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Unfortunately, she palpated a mass below her clavicle, which was biopsied and confirmed recurrent disease 3 years following therapy completion. She was treated with induction chemotherapy and had a good response. She then presented to our cancer center for consideration for further local therapy. The patient underwent a completion axillary lymph node dissection, which demonstrated multiple residual lymph nodes involved with cancer. She was subsequently offered radiation therapy to the axilla and supraclavicular fossa, which included an area of overlap from her prior radiation fields. To minimize risk of late effects from radiation, a hyperfractionated schedule was employed (1 Gy BID to 50 Gy with 6 hours between treatments). The patient is currently free of disease one year following radiation treatement. This case illustrates an important point regarding the adoption of the results of the American College of Surgeons Oncology Group (ACOSOG) Z0011 trial in all patients with involved sentinel lymph nodes.

IMAGING FINDINGS

A PET/CT scan performed at the site of recurrence demonstrated a large palpable high axillary lymph node with a maximum standardized uptake value (SUV) of 8.9 (Figure 1).

DIAGNOSIS

Recurrent invasive ductal carcinoma in the high axilla

DISCUSSION

The results of ACOSOG Z0011 have been widely accepted in the surgical community as the new standard of care for patients who have undergone breast-conserving surgery in the absence of a clinically involved axilla where it is common practice not to undergo a completion dissection. This case illustrates that these nodal failures occur, and it is vital for the practitioner to realize how these failures are a significant challenge to curing and treating patients safely. In managing these marginal failures, the risks of

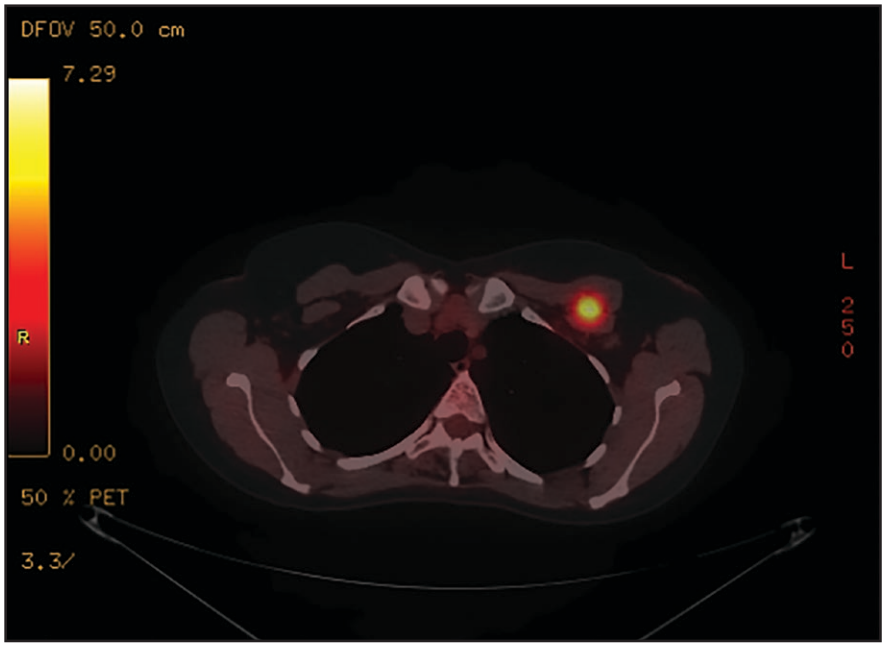

FIGURE 1. *FDG-PET/CT for infiltrating ductal carcinoma with high axillary lymph node recurrence following breast-conservation surgery and chemoradiation.*

recurrence locally and distantly are very high. Nodal failures following definitive treatment for patients with head and neck[1] and gynecologic cancers[2] are rarely curable, mostly because radiation is not typically offered. In breast cancer, nodal failures were salvageable in the pre-chemotherapy era, but will likely be lower when distant metastases are decreased with chemotherapy.[3] When offering radiation therapy after a marginal failure, physicians have to weigh the risks and benefits of therapy for the specific site treated, especially given that irradiated tissue will have a lower tolerance. In this specific case, skin and subcutaneous tissue toxicity, fibrosis in the lymphatic nodal basin, and irradiating a small volume of the brachial plexus, were all considered risk factors. As the risk of recurrence was thought to be substantial, and minimizing overlap using image guidance and intensity-modulated radiotherapy (IMRT) was not going to prevent overlap, hyperfractioned radiotherapy was recommended to minimize late side effects.[4,5]

Taking a step back, reviewing the literature regarding the omission of a lymph node dissection is vital. ACOSOG Z0011 was a prospective randomized cooperative group trial designed to test the benefit of a complete axillary dissection for patients treated with breast-conserving surgery who were planning to receive adjuvant whole-breast irradiation.[6,7] The findings demonstrated similar disease-free results and overall survival, with substantially fewer side effects when the axillary dissection was omitted, which has led physicians to quickly adopt this approach. These results have spurred a significant interest in extrapolation to patients outside the scope of this trial, leading to a change in the standard of surgical practice. This has left radiation oncologists wondering how much of the axilla and other regional lymph node areas should be targeted, especially in light of emerging data on the benefits of treating all regional lymph nodes.[8-10]

In the post-mastectomy setting, the benefit of treating regional nodes is unequivocal. The British Columbia and Danish trials demonstrated that a 75% reduction in local regional recurrences translated into a survival advantage when the first generation of modern chemotherapy was used.[11-13] It must be emphasized that these trials entailed irradiation of the chest wall, entire axilla, supraclavicular fossa, and the internal mammary lymph node chain. These studies support the benefit of adding radiation therapy in post-mastectomy patients with any positive lymph nodes. Nevertheless, many clinicians believe that 1) radiotherapy for patients with 1 to 3 positive lymph nodes is not necessary and, 2) the target need not include the axilla or internal mammary lymph nodes.[14] Why does this controversy persist?

To derive a benefit from radiotherapy, the risk of recurrence must be > 15%. The largest experience in the U.S. literature reported the results from 4 prospective trials that omitted radiotherapy, in which the locoregional recurrence rate was 12.9% at 10 years.[15] In contention with this data, the re-analysis of the British Columbia and Danish trials demonstrated a similar absolute survival benefit (9%) of regional nodal irradiation in both patients who have 1 to 3 positive nodes, and those with 4 or more positive nodes.[16] This latter data is supported by the recent Early Breast Cancer Trialists' Collaborative Group meta-analysis, which demonstrates a significant reduction in breast cancer mortality at 20 years ($p = 0.01$).[17] Of note, the majority of data includes patients who had irradiation of the axilla or internal mammary lymph nodes. These trials are certainly based on older data, and patient populations with potentially more advanced disease when compared to Z0011, but there are logical reasons to believe they offer meaningful information for treating today's breast cancer patient.

The first issue to highlight is the patient population included in these

Table 1. Population characteristics between trials

	Z0011 (n = 813)	MA 20 (n = 1832)	EORTC (n = 4004)
Tumor size > 2 cm	30.7%	47.5%	39.5%
Tumor size < 2 cm	69.3%	52.5%	60.5%
ER -	17.3%	25.5%	16%
Node negative	4.4%	10%	44.4%
Node positive (1-3)	88.9%	85%	43.1%
Node positive ≥4	6.7%	5%	12.5%
Median axillary lymph nodes resected in dissection	17	12	n/a
Adjuvant chemotherapy	69.4%	91%	85%
Adjuvant hormonal therapy	57.3%	76.5%	59.7%
Age	55 (median)	55 (mean)	54 (median)
Grade 3 toxicities	28%	42%	n/a
Median follow-up (years)	6.3	5.2	10.9
Sentinel node biopsy	100%	39%	7.1%

recent trials. Those enrolled on Z0011 primarily had good prognostic factors: 67% were older than 50 years, 70% had T1 tumors, 80% were ER+ or PR+, 71% had grade 1 or 2 tumors, 62% had no lymphovascular space invasion, 71% had only 1 positive node, 44% had micrometastases, and the mean tumor size was 1.6 cm. These details are important to consider when extrapolating the results of the study to patients with poor prognostic factors. In the case described above, the patient was young, with a large high-grade tumor that demonstrated no overexpression of ER, PR or HER2/neu (not reported in Z0011). All of these features increase the risk of local and regional recurrence and, therefore, must factor into decision-making.[18]

Fundamentally, the Z0011 study asked a question pertaining to the extent of surgery; it did not directly address the role of radiation therapy. Let's shift our attention to the 2 large cooperative group studies that have recently demonstrated similar paradigm-shifting results, specifically for radiation therapy field design for a similar patient population.

The first study is the NCIC Clinical Trials Group MA.20, which was initiated to test the benefit of the addition of irradiation to the axilla, supraclavicular fossa, and the internal mammary lymph nodes, to breast-conserving surgery and axillary dissection followed by standard whole-breast radiotherapy.[10] This trial included more than twice as many patients as Z0011, and a very similar patient population with regard to nodal involvement (see Table 1). What is different is that the MA.20 study included slightly more patients with poor prognostic features, such as: high-grade histology (42% vs. 28%), ER- (25.5% vs. 17.3%), and tumors > 2 cm (47.5% vs. 30.7%). As a result, more of the MA.20 patients received chemotherapy (91% vs. 69.4%). The results of this trial demonstrated a marginal improvement in locoregional control as a result of the addition of comprehensive nodal irradiation (94.8% vs. 96.8%). More importantly, there was a substantial improvement in disease-free survival (87% vs. 92.4%), which translated to a 2% increase in overall survival. There was an increase in morbidity related to the larger radiation volumes: Grade 2 and higher pneumonitis increased from 0.2% to 1.3% (p = 0.01), and lymphedema increased from 4.1% to 7.3% (p = 0.004).

The discrepancy between locoregional control and disease-free survival may be attributed to the inability to detect a nodal recurrence by physical exam, especially in the dissected axilla and internal mammary chain. The case presented illustrates this point, since this large lymph node was missed on clinical exam.

A second explanation for the lack of an overwhelming benefit in locoregional control may be due to the way in which patients were categorized. Overall, this disease appears to be a

harbinger of distant metastases, and by the time a regional recurrence is noted, distant disease may already be present. Such patients may not have been designated as having a locoregional recurrence, as it is common practice in many trials to record only the first site of recurrence, thereby categorizing such patients in the distant failure group.

The second study examining the role of comprehensive nodal irradiation is the EORTC 22922/10925 trial. This study was designed to determine whether there is an overall survival benefit of adding radiation therapy to the internal mammary and medial supraclavicular lymph nodes to standard chest wall or whole-breast irradiation. Patients eligible for the trial were required to have one of the following adverse prognostic factors: positive axillary lymph nodes or central/medial tumor location in the absence of axillary lymph node involvement. In contrast to Z0011, this trial incorporated patients who underwent a mastectomy as well as a large cohort of patients who were lower risk, including 44% of patients who were node negative (see Table 1). This study accrued 4004 patients from 1996 to 2004. With a median follow-up of 10.9 years, the addition of nodal irradiation was found to reduce the regional recurrence rate from 4.2% to 2.7%. Similar to the MA.20 study, there was a more impressive improvement in distant metastases-free survival with a hazard ratio of 0.86 ($p = 0.029$), which translated to an increase in overall survival at 10 years from 80.7% to 82.3% (hazard ratio 0.87 with $p = 0.0496$). The EORTC data implies that lower risk patients may also substantially benefit, as a subset analysis stratified by nodal stage suggests those with node negative disease may benefit the most: hazard ratio for N0 is 0.79, in contrast to 0.89 for pN1, 0.85 for pN2, and 1.00 for pN3.

As we move forward with the results of these trials, the question now becomes: "What is the optimal target volume for radiation oncologists when treating patients who have node positive disease?" All 3 randomized post-mastectomy RT trials demonstrated a benefit when the whole axilla, supraclavicular fossa, and the internal mammary chain were included; however, there is controversy over what target volumes should be covered. Most experts believe the greatest benefit is in covering the chest wall and the supraclavicular fossa and, therefore, purposely exclude the axilla and internal mammary lymph chain due to the potential increased morbidity. For example, the American College of Radiology appropriateness criteria for post-mastectomy radiotherapy recommends radiotherapy to the chest wall, and does not make any specific recommendations regarding the regional lymph nodes.[14] In the NCCN guidelines (NCCN guidelines for invasive breast cancer version 3), the nodal region targeted includes the paraclavicular nodes and the axilla, while only including the internal mammary chain if it is clinically involved or biopsy-proven. Based on the data presented, the regional lymph nodes seem to have a substantial impact on outcomes. The MA.20 study mandated irradiation of the chest wall in both treatment arms, and there was a clear benefit in breast cancer mortality with the addition of regional nodal areas in the RT field. In Z0011, the axilla was treated in both arms and there was no detriment in breast cancer mortality no matter what fields were treated,[19] suggesting the internal mammary lymph nodes and medial supraclavicular lymph nodes have a major impact in improving breast cancer mortality.

CONCLUSION

Radiation oncologists and surgeons must exercise caution when applying the findings of the Z0011 trial to patients with a positive sentinel lymph node biopsy and poor prognostic factors. Additionally, translating the treatment used in Z0011 to early stage patients may not be appropriate. The survival benefit in the setting of minimal added morbidity demonstrated in MA.20 and EORTC suggests that we may be undertreating certain patients. Patient SD was technically a candidate for the Z0011 trial, but because of her age and triple-negative status, it may have been better to initially treat her more aggressively as per the MA.20 protocol. It is extremely important to consider patient and tumor characteristics when applying the adjuvant radiation treatment approaches used in the Z0011 trial to a broad patient population without considering the potential survival benefit of regional node irradiation (RNI).

At our institution, treatment volumes are based on the risk of additional lymph node involvement, individual patient characteristics, dose to surrounding structures and the patients' life expectancy. Prior to the results of MA.20 and EORTC 22922/10925, we used the Memorial Sloan Kettering Cancer Center (MSKCC)[20] and MD Anderson Hospital (MDAH)[21] risk nomograms. If a patient had a > 15% risk of finding additional non-sentinel lymph nodes, then levels 1 and 2 were treated. If a patient had a > 15% chance of finding 4 or more lymph nodes, then level 3 and the supraclavicular field were treated.[22] Currently, we prescribe comprehensive nodal irradiation for all macroscopically node positive patients and strongly consider it for younger patients with high grade ER/PR negative and HER2/neu positive tumors or those with a lesion in a medial/central location. Omission of radiation to the internal mammary lymph nodes, or consideration of proton therapy is explored when the heart V30 > 5%, V10 > 30% if IMRT is used, or when the mean heart dose is > 10 Gy. If a woman has a cardiac risk factor such as history of ischemic heart disease, diabetes, smoking, or high BMI, a lower mean heart dose (< 10 Gy) is pursued. Women with

multiple cardiac risk factors require an even lower mean heart dose and are judged on a case-by-case basis for internal mammary lymph node omission or consideration for proton therapy. This approach provides excellent locoregional control with acceptable morbidity, and will help prevent recurrences seen in the case of patient SD.

REFERENCES

1. Mabanta SR, Mendenhall WM, Stringer SP, Cassisi NJ. Salvage treatment for neck recurrence after irradiation alone for head and neck squamous cell carcinoma with clinically positive neck nodes. *Head & Neck.* 1999;21:591-594.
2. Creutzberg CL, van Putten WL, Koper PC, et al. Surgery and postoperative radiotherapy versus surgery alone for patients with stage-1 endometrial carcinoma: Multicentre randomised trial. Portec study group. Post operative radiation therapy in endometrial carcinoma. *Lancet.* 2000;355:1404-1411.
3. Marks LB, Prosnitz LR. Reducing local therapy in patients responding to preoperative systemic therapy: Are we outsmarting ourselves? *J Clin Oncol.* 2014;32:491-493.
4. Eric J, Hall AJR. *Radiobiology for the radiologist.* Philadelphia, PA: Lippincott Williams & Wilkins; 2011.
5. Bhandare N, Monroe AT, Morris CG. Does altered fractionation influence the risk of radiation-induced optic neuropathy? *Int J Radiat Oncol Biol Phys.* 2005;62:1070-1077.
6. Giuliano AE, Hunt KK, Ballman KV, et al. Axillary dissection vs no axillary dissection in women with invasive breast cancer and sentinel node metastasis: a randomized clinical trial. *JAMA.* 2011;305:569-575.
7. Giuliano AE, McCall L, Beitsch P, et al. Locoregional recurrence after sentinel lymph node dissection with or without axillary dissection in patients with sentinel lymph node metastases: The American College of Surgeons Oncology Group z0011 randomized trial. *Ann Surg.* 2010;252:426-432; discussion 432-423.
8. Haffty BG, Hunt KK, Harris JR, et al. Positive sentinel nodes without axillary dissection: Implications for the radiation oncologist. *J Clin Oncol.* 2011;29:4479-4481.
9. Poortmans P, Kirkove C, Budach V, et al. Irradiation of the internal mammary and medial supraclavicular lymph nodes in stage i to iii breast cancer: 10 year results of the EORTC radiation oncology and breast cancer groups phase iii trial 22922/10925. *EJC.* 2013;47(Suppl 2).
10. Whelan T, Olivotto I, Ackerman I, et al. Ncic-ctg ma.20. An intergroup trial of regional nodal irradiation in early breast cancer. *J Clin Oncol.* 2011;29.
11. Overgaard M, Hansen PS, Overgaard J, et al. Postoperative radiotherapy in high-risk premenopausal women with breast cancer who receive adjuvant chemotherapy. Danish breast cancer cooperative group 82b trial. *N Engl J Med.* 1997;337:949-955.
12. Overgaard M, Jensen MB, Overgaard J, et al. Postoperative radiotherapy in high-risk postmenopausal breast-cancer patients given adjuvant tamoxifen: Danish breast cancer cooperative group dbcg 82c randomised trial. *Lancet.* 1999;353:1641-1648.
13. Ragaz J, Olivotto IA, Spinelli JJ, et al. Locoregional radiation therapy in patients with high-risk breast cancer receiving adjuvant chemotherapy: 20-year results of the british columbia randomized trial. *J Natl Cancer Inst.* 2005;97:116-126.
14. Taylor ME, Haffty BG, Rabinovitch R, et al. Acr appropriateness criteria on postmastectomy radiotherapy expert panel on radiation oncology-breast. *Int J Radiat Oncol Biol Phys.* 2009;73:997-1002.
15. Recht A, Gray R, Davidson NE, et al. Locoregional failure 10 years after mastectomy and adjuvant chemotherapy with or without tamoxifen without irradiation: Experience of the eastern cooperative oncology group. *J Clin Oncol.* 1999;17:1689-1700.
16. Buchholz TA, Woodward WA, Duan Z, et al. Radiation use and long-term survival in breast cancer patients with t1, t2 primary tumors and one to three positive axillary lymph nodes. *Int J Radiat Oncol Biol Phys.* 2008;71:1022-1027.
17. EBCTCG: McGale, P, Taylor, C, Correa, C, et al. Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials. *Lancet.* 2014;383:2127-2135.
18. Miles RC, Gullerud RE, Lohse CM, et al. Local recurrence after breast-conserving surgery: multivariable analysis of risk factors and the impact of young age. *Ann Surg Oncol.* 2012;19:1153-1159.
19. Jagsi R, Chadha M, Moni J, et al. Radiation field design in the acosog z0011 (alliance) trial. *J Clin Oncol.* 2014;10:32(32):3600-3606.
20. Van Zee, KJ, Manasseh, DM, Bevilacqua, JL, et al. A nomogram for predicting the likelihood of additional nodal metastases in breast cancer patients with a positive sentinel node biopsy. *Ann Surg Oncol.* 2003;10:1140-1151.
21. Mittendorf, EA, Hunt, KK, Boughey, JC, et al. Incorporation of sentinel lymph node metastasis size into a nomogram predicting nonsentinel lymph node involvement in breast cancer patients with a positive sentinel lymph node. *Ann Surg.* 2012;255:109-115.
22. Katz, A, Smith, BL, Golshan, M, et al. Nomogram for the prediction of having four or more involved nodes for sentinel lymph node-positive breast cancer. *J Clin Oncol.* 2008;26:2093-2098.

RADIATION ONCOLOGY CASE

Whole-brain radiation therapy in pregnant patients with brain metastases: Risks of ionizing radiation exposure to the fetus

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CASE SUMMARY

A 38-year-old, right-handed female with a 15 pack-year smoking history presented at 11 weeks gestation with a 3-day history of "heaviness" and numbness in her right leg, especially posterior to her knee. Her previous obstetrical history was significant for 1 pregnancy, which was electively aborted. Initially, a presumed diagnosis of lumbar plexopathy was made. Three days later, she presented with a seizure described as whole-body rigidity with her left arm bent upwards at the elbow and right arm extended, in a fencing position, accompanied by tongue biting and left facial droop lasting approximately 5 minutes. During her hospital stay, imaging studies were obtained, revealing a lung mass, followed by bronchoscopy with fine-needle aspiration, with pathology revealing a diagnosis of non-small cell lung carcinoma (NSCLC).

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IMAGING FINDINGS

MRI without contrast of the brain revealed a 1.7 x 1.3-cm nodular focus of heterogeneous high T2 signal with apparent internal cystic foci along the paramedian aspect of the falx in the left parietal lobe, a second smaller lesion in the left frontal lobe with a round focus of high T2 signal measuring 0.9 cm, and several small (< 5 mm) foci of abnormal fluid attenuated inversion recovery (FLAIR) signal seen along the posterior aspect of the right insula and right frontal pole.

CT scan of the chest without contrast revealed a 1.4 × 1.3-cm lobulated nodule in the medial and anterior aspect of the lingula compatible with a primary bronchogenic neoplasm and left hilar adenopathy.

MRI of the abdomen and pelvis was unremarkable for mass or lymphadenopathy.

DIAGNOSIS

The diagnosis of stage IV (M1b) moderately differentiated non-small cell lung carcinoma favor adenocarcinoma was made. No molecular diagnostics (e.g., EGFR, ALK, ROS-1) were available.

DISCUSSION

This case report presents a pregnant female seeking treatment for her newly diagnosed lung adenocarcinoma with brain metastases. The physician engaged in thoughtful discussion regarding the gravity of her diagnosis and the need for treatment, outlining various options including surgery, stereotactic radiosurgery (SRS), and whole-brain radiation (WBRT). Surgery was not considered as the patient had multiple brain metastases. A discussion was held on the benefit of SRS vs. WBRT. Given that SRS is associated with a higher risk of distant brain failure lending to a higher likelihood of retreatment during her pregnancy and the contraindication to administering gadolinium contrast, which further complicated accurate determination of the number of lesions and treatment targeting with SRS, WBRT alone was presented as the safest and most conservative management. The patient was also presented with the option of terminating her pregnancy to allow

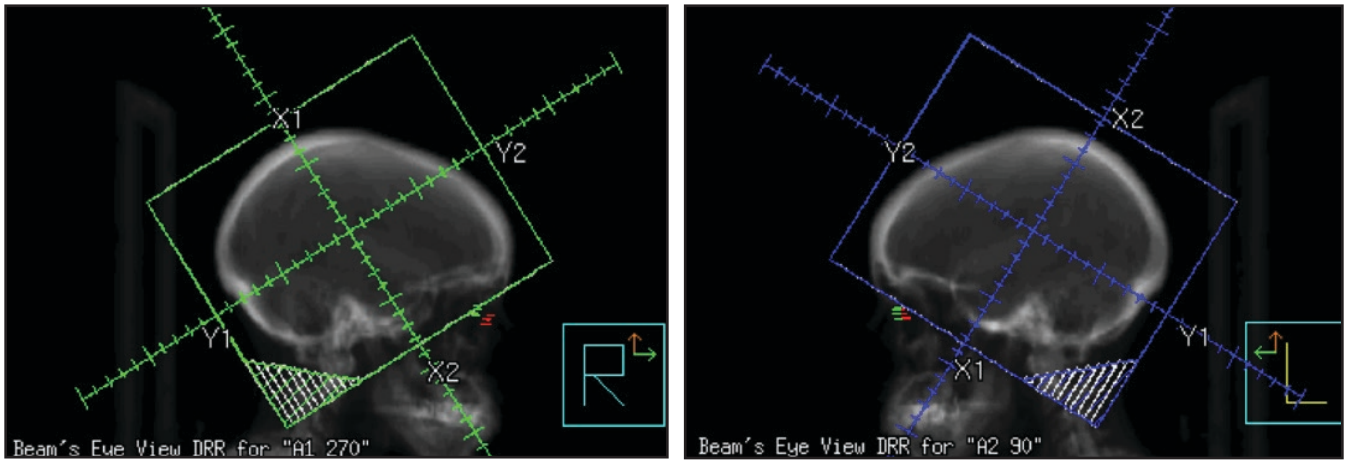

FIGURE 1. *(A) Right lateral beam arrangement. (B) Left lateral beam arrangement.*

FIGURE 2. Representation of abdominal shielding set-up during WBRT.

for more accurate staging, although termination was not a prerequisite to WBRT and subsequent systemic therapy. The patient expressed her desire for continuing her pregnancy unless doing so would jeopardize her life. The risks and benefits of WBRT were described in detail, including potential harms to the patient's fetus. These included but were not limited to risks of mental retardation, organ malformations, and subsequent secondary malignancy in the child.[1,2] Literature was referenced regarding case reports of healthy babies following head radiation. Magne et al highlighted a case of WBRT for a brain metastasis secondary to NSCLC, which exemplified the importance of discussing risks vs. benefits of therapy and respecting the patient's desires regarding her pregnancy.[3] In Magne's case, the patient was faced twice with making the decision of accepting radiation therapy while pregnant or terminating the pregnancy. In the first instance she chose to terminate her pregnancy and sought radiation, while in the second she continued her pregnancy while receiving radiation therapy. Our patient continued her pregnancy and underwent WBRT at 14 weeks gestation to 3,750 cGy in 15 fractions with opposed lateral fields using 6MV photons. Figure 1 illustrates the fields used.

Report Number 50 of American Association of Physicists in Medicine (AAPM) Task Group 36 presents data and techniques to minimize radiation dose delivered to the fetus for radiation treatment delivered during pregnancy.[1] In radiotherapy photon treatments, the dose outside the geometrical field size is caused by photons originating from either external scatter, which results from head leakage and scattering off high-Z materials used for the collimation system and beam modifiers, or internal scatter. Sneed et al has reported that 0.04% to 0.09% of the target dose is received by the fetus when implementing opposed lateral fields and bicoronal wedged arc fields to treat intracranial tumors.[4] Compared to external scatter, internal scatter is a lesser contributor of the dose received by the fetus. Sneed et al reported internal scatter contributes to 13% to 20%

Table 1. TLD measurements with abdominal shielding on 3rd treatment day

Location	Dose on fraction #3 (cGy)	Percent of fraction dose (%)	Percent standard deviation (%)
Mid abdomen	0.16	0.064	5.89
Waist	0.12	0.048	5.23
Under table at level of abdomen	0.19	0.076	5.4

Table 2. TLD measurements with abdominal shielding on 6th treatment day

Location	Dose on fraction #3 (cGy)	Percent of fraction dose (%)	Percent standard deviation (%)
Mid abdomen	0.18	0.07	2.93
Waist	0.12	0.05	5.67
Under table at level of abdomen	0.18	0.07	4.51

Table 3. Summary of reported cases of pregnant patients treated with brain radiotherapy

RT Technique	Prescribed Dose	Fetal dose (cGy)	Shielding	Gestational Age	Delivery	Reference
3DCRT	45 Gy to pituitary adenoma	2.0 ± 0.08 cGy	Absent	6-7 weeks		5
GK radiosurgery	25 Gy to single brain metastasis from melanoma	0.15-0.31		25 weeks		6
WBRT	30 Gy single brain metastasis from NSCLC	0.3	Present	24 weeks	Healthy boy at age 3 years	3
Opposed lateral beams	68 Gy to atypical ependymoma	6	Absent	~30 weeks	Healthy girl at age 2.5 years	4
Bicoronal 110° arcs	78.2 Gy to anaplastic astrocytoma	3.0	Absent	~29 weeks	Healthy girl at age 1.5 years	4
IMRT	60 Gy to glioblastoma	1.6	Present	27 weeks delivered at	Healthy baby 35 weeks	7

of total fetal dose. This is consistent with the AAPM's report, which states that at distances > 30 cm from the field edge, external scatter from head leakage becomes the greatest contributor of fetal dose. Internal scatter remains an unavoidable contributor to the peripheral dose, however dose to the fetus originating from head leakage can be minimized by implementing shielding during treatment.[1] In this case, a 2-inch thick lead plate, representing 3.4 half-value layers, was positioned above the patient's abdomen as illustrated in Figure 2. Other considerations include using the smallest radiation field, minimizing the use of secondary blocking, and maximizing the use of the primary block in the inferior aspect of the field, which all together minimizes external scatter. Also, the lowest energy was used to minimize neutron contamination seen with higher-beam energies.

To approximate the dose delivered to the fetus, thermoluminescent dosimeter (TLD) measurements were obtained during radiation delivery with the

abdominal shield in place. Nine TLDs were positioned, 3 each at the level of the midabdomen, waist, and under the table at the level of the abdomen. The average of the 3 TLD readings at each level was recorded for a given fraction. This data is summarized in Tables 1 and 2. AAPM Task Group 36 reported a small change in peripheral dose with depth ranging from 2 to 15 cm; therefore, average TLD measurements were used to extrapolate an estimated dose delivered to the fetus.[1] The estimated fetal dose of 2.4 cGy (0.064% of target dose) is in keeping with previously reported data. Other reports of brain irradiation during pregnancy are summarized in Table 2, all of which remain below the generally accepted threshold of 10 cGy, above which fetal harm is associated.[1]

Upon completing radiation therapy, the patient met with her treating medical oncologist to consider systemic therapy. After discussing the risks and benefits of treatment she decided to accept adjuvant chemotherapy consisting of cisplatin and gemcitabine at 23 weeks gestation. The FDA has classified cisplatin and gemcitabine as pregnancy category D, yet reports have suggested that cisplatin and gemcitabine can be given without acute fetal toxicity, although no long-term follow-up exists for these children.[8,9]

The patient had a spontaneous rupture of membranes at 37 6/7 weeks gestation and vaginally delivered a healthy baby girl without complications. At last follow-up, marking 5 years following initial WBRT, the patient's child had met all developmental milestones consistent with a healthy 5-year-old child. After initial therapy, the patient progressed to develop subsequent brain metastases, which were treated with Gamma Knife radiosurgery. The patient had no neurological sequelae from her disease.

CONCLUSION

In conclusion, we highlight a case of a 14-week pregnant female with newly diagnosed metastatic lung adenocarcinoma with brain metastases who was treated with WBRT and is now 5 years post therapy with a healthy 5-year-old girl. Our estimated cumulative fetal dose of 2.4 cGy delivered during treatment is consistent with data previously reported. We describe how with careful shielding, attempts can be made to reduce fetal dose to as low as is reasonably achievable. While a thorough discussion of the risks and benefits of any radiation exposure during pregnancy is vital prior to undergoing therapy, in our experience WBRT to a pregnant woman can be performed using techniques to minimize unnecessary radiation exposure to the fetus.

REFERENCES

1. Stovall M, Blackwell CR, Cundiff J, et al. Fetal dose from radiotherapy with photon beams: report of AAPM Radiation Therapy Committee Task Group No. 36. *Medical physics.* Jan 1995;22(1):63-82.

2. Wakeford R. Childhood leukaemia following medical diagnostic exposure to ionizing radiation in utero or after birth. *Radiation protection dosimetry.* 2008;132(2):166-174.

3. Magne N, Marcie S, Pignol JP, Casagrande F, Lagrange JL. Radiotherapy for a solitary brain metastasis during pregnancy: a method for reducing fetal dose. *The British journal of radiology.* Jul 2001;74(883):638-641.

4. Sneed PK, Albright NW, Wara WM, Prados MD, Wilson CB. Fetal dose estimates for radiotherapy of brain tumors during pregnancy. *Int J Radiat Oncol Biol Phys.* Jun 15 1995;32(3):823-830.

5. Sharma DS, Jalali R, Tambe CM, Animesh, Deshpande DD. Effect of tertiary multileaf collimator (MLC) on foetal dose during three-dimensional conformal radiation therapy (3DCRT) of a brain tumour during pregnancy. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology.* Jan 2004;70(1):49-54.

6. Yu C, Jozsef G, Apuzzo ML, MacPherson DM, Petrovich Z. Fetal radiation doses for model C gamma knife radiosurgery. *Neurosurgery.* Mar 2003;52(3):687-693; discussion 693.

7. Horowitz DP, Wang TJ, Wuu CS, et al. Fetal radiation monitoring and dose minimization during intensity modulated radiation therapy for glioblastoma in pregnancy. *Journal of neuro-oncology.* Aug 6 2014.

8. Wiesweg M, Aydin S, Koeninger A, et al. Administration of Gemcitabine for Metastatic Adenocarcinoma during Pregnancy: A Case Report and Review of the Literature. *AJP reports.* May 2014;4(1):17-22.

9. Dawood R, Instone M, Kehoe S. Neo-adjuvant chemotherapy for cervical cancer in pregnancy: a case report and literature review. *European journal of obstetrics, gynecology, and reproductive biology.* Dec 2013;171(2):205-208.

Postradiation cardiac sarcoma and other secondary cancers more than 25 years after chemotherapy and mantle-field radiation for Hodgkin's lymphoma

Jerry T. Liu, MD; Jessica Niakan, MD; Mary B. Beasley, MD; Paul Stelzer, MD; Robert G. Maki, MD, PhD; and Michael Buckstein, MD, PhD

CASE SUMMARY

In July 2013, a 48-year-old Caucasian female presented to the emergency department with rapid-onset fatigue, shortness of breath and palpitations. Her medical history was remarkable for early stage Hodgkin's lymphoma (HL) diagnosed at age 19 (1984) for which she underwent doxorubicin, bleomycin, vinblastine and dacarbazine chemotherapy, then mantle-field radiation to 40 Gy (port films unavailable) with a complete response. During the late-1990s, she was diagnosed with hypothyroidism and a prolactinoma, both managed medically. She had regular surveillance of the breasts and thyroid. In early 2012, she was diagnosed with a Stage IA T1aN0M0 invasive tubular carcinoma in the upper outer quadrant of the right breast. After consideration of risks from re-irradiation as part of breast conservation therapy, she opted for bilateral mastectomy with flap reconstruction. In July, 2012, surveillance ultrasound of the thyroid revealed the growth of a nodule. Fine-needle aspirate was suspicious and she underwent total thyroidectomy, revealing a T1a follicular papillary microcarcinoma.

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IMAGING FINDINGS

As part of her workup, chest computed tomography and angiography (CTA) was performed, and demonstrated a 6.7 cm mass filling the right ventricle (RV). Cardiac magnetic resonance imaging confirmed this mass, which seemed adherent to endocardial surface and tricuspid leaflets (Figure 1). Echocardiography showed severe RV inflow obstruction and dysfunction.

DIFFERENTIAL DIAGNOSIS

Primary sarcoma, metastasis, myxoma, papillary fibroelastoma, lipoma, paraganglioma

DISCUSSION

The patient underwent radical resection of the tumor, tricuspid bioprosthesis replacement with pacemaker implantation, and was placed on the cardiac transplant list. Pathology revealed undifferentiated pleomorphic sarcoma (Figure 2). Postoperative imaging showed residual tumor along the RV wall. She was started on liposomal doxorubicin but developed an anaphylactic reaction.

In August 2013, the patient developed profound shortness of breath with chest pain and fatigue. Echocardiography confirmed interval mass growth with near-complete RV obstruction. Extensive multidisciplinary discussion yielded recommendations for palliative radiation for a bridge to heart transplant. Combined modality therapy was not advocated due to her fragile clinical status. After a single 300 cGy fraction of radiation, however, she developed progressive multi-organ failure. She decided to pursue comfort care measures, and radiation was discontinued. She was transferred to hospice care and died shortly after.

In the early decades of combined modality therapy for HL, large radiation fields (eg., mantle field, Figure 3)

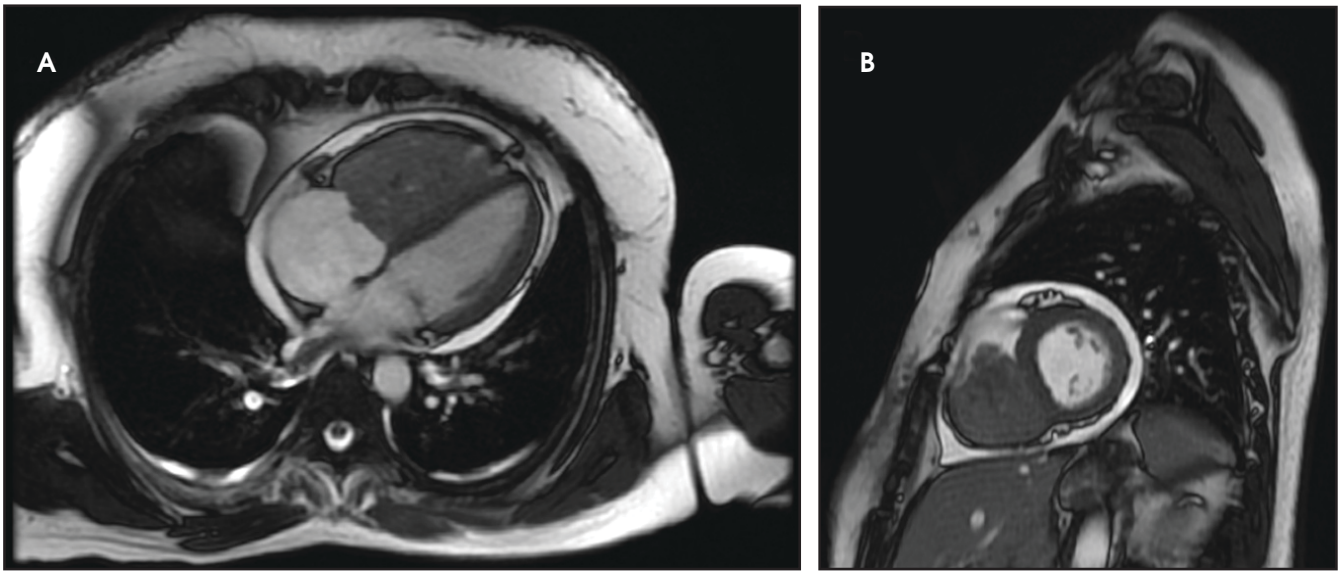

FIGURE 1. *Cardiac magnetic resonance imaging (A, B) showing a large 7 cm right ventricle mass.*

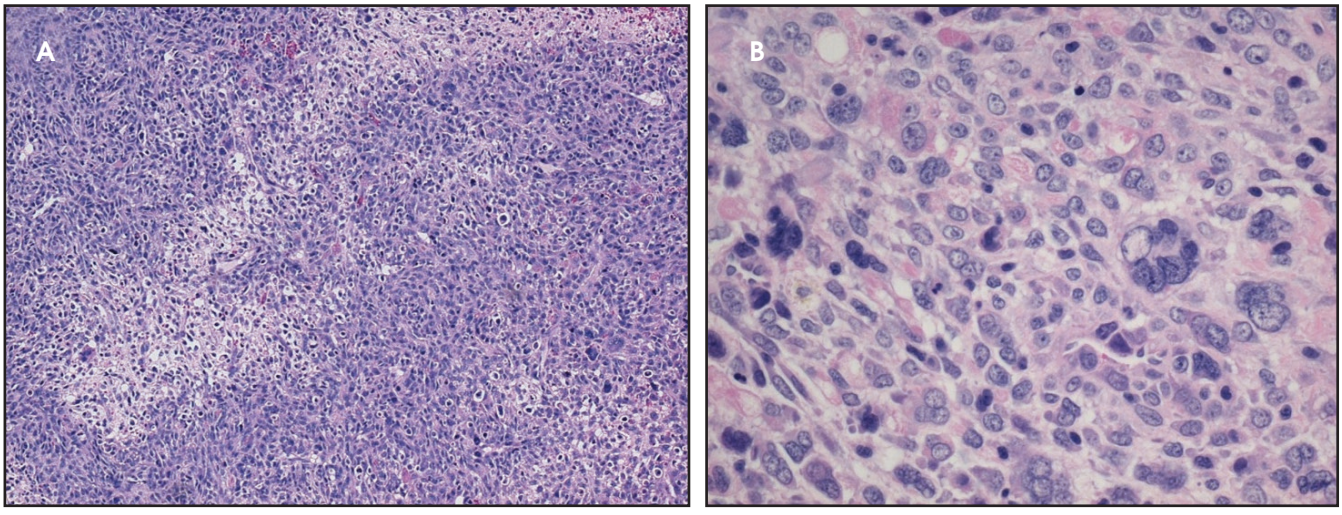

FIGURE 2. *Pathologic features of right ventricle undifferentiated pleomorphic sarcoma on lower (A) and higher (B) power microscopic imaging of hematoxylin and eosin stained sections: hypercellular, vaguely fascicular growth pattern with bizarre and spindled cells.*

were routinely used to cover all at-risk nodal stations. The combined effects of large-field radiation and chemotherapy have resulted in considerable long-term risk for secondary cancers (SC), with over 20% risk for developing a solid tumor at 25 years after HL diagnosis.[1,2] The risks are highest for survivors of younger age-at-diagnosis and older attained-age.[3]

The majority (≥ 75%) of SC after radiation for HL develop within or adjacent to previously irradiated fields with increasing risks of development associated with increased dose, especially ≥ 35 Gy.[4,5] Over 20% of these tumors are lung cancers, > 10% are breast cancer, with thyroid cancers (2%) and sarcomas (1.3%) occurring more rarely.[1]

Postradiation sarcomas are defined by a history of radiation exposure, no prior sarcoma, and histologic features distinct from any previously treated primary. These tumors have significantly worse prognosis than sporadic sarcomas regardless of histologic type.[6] Postradiation cardiac sarcomas (PCS) are exceedingly rare and have yet to be reported in HL survivors.

For sporadic cardiac sarcomas (SCS), complete resection is the only curative treatment, with reported median survival of up to 23.5 months after definitive resection,[7] but many cases are unresectable due to extensive myocardial involvement. Multimodality therapy (palliative debulking surgery, anthracycline-based chemotherapy, and/or

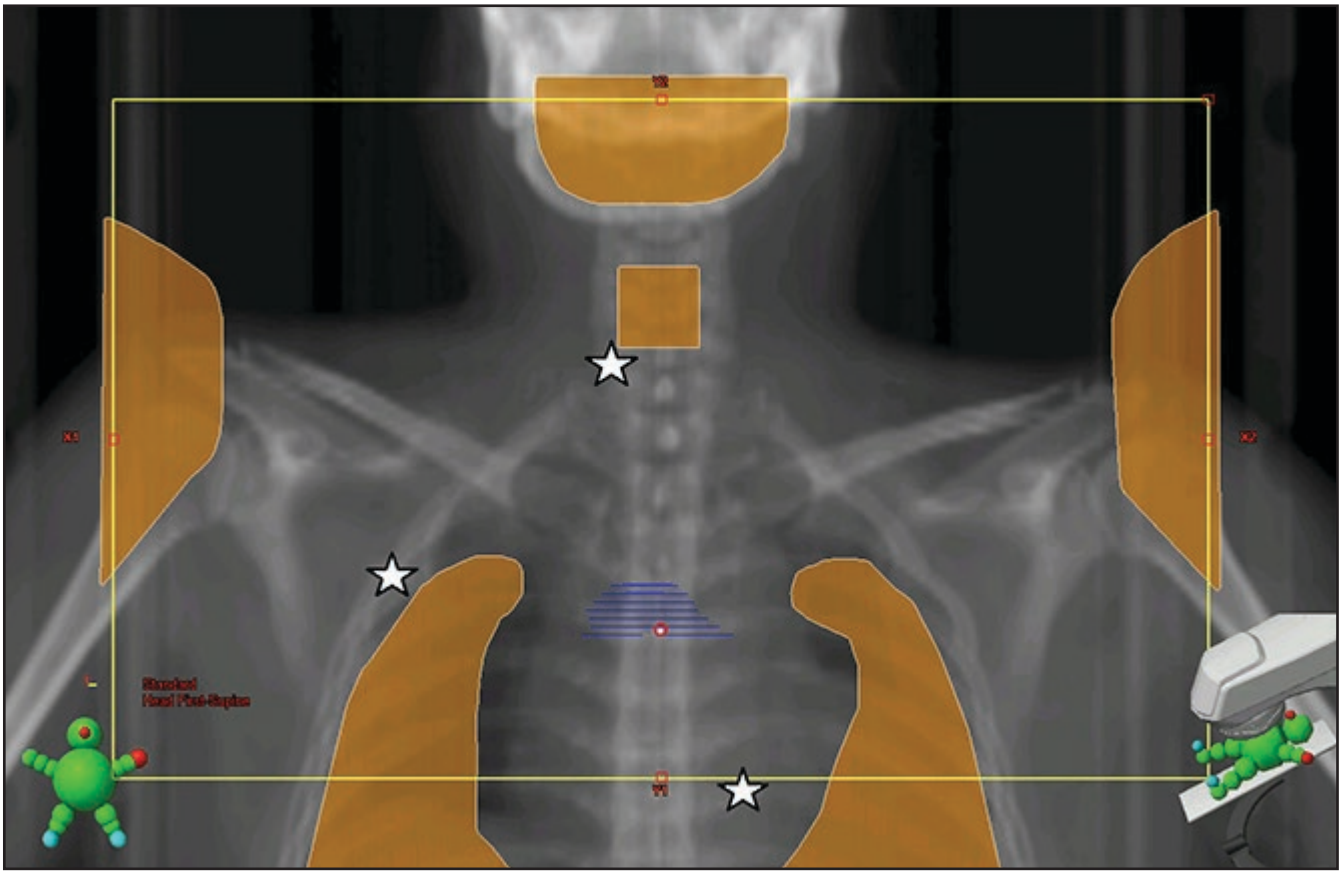

FIGURE 3. *Example of a mantle field. Coverage includes the bilateral cervical necks, bilateral axillae and the mediastinum. Stars indicate sites of secondary tumors (thyroid, right upper outer breast, cardiac) in patient case.*

radiation) has been advocated in cases of unresectable and recurrent tumors, although the value of this treatment approach is unknown due to the paucity of data.[8] There is limited evidence for orthotopic cardiac transplantation in otherwise unresectable SCS, providing survival of up to 3 years in selected patients.[9] Due to the scarcity of PCS cases, management strategies are extrapolated from evidence for SCS.

CONCLUSION

We report a 48-year-old woman with history of HL at age 18, treated with chemotherapy and mantle-field radiation to 40 Gy, who subsequently developed early stage breast cancer, thyroid cancer, and ultimately died of a cardiac sarcoma. The mantle field used to treat this patient to 40 Gy would have covered her thyroid, upper outer quadrants of bilateral breasts, and heart, likely contributing to each of her secondary malignancies. This case reflects the importance of early screening and management of radiation-induced secondary malignancies in long-term HL survivors and is, to our knowledge, the first reported case of cardiac sarcoma following mantle-field radiation.

REFERENCES

1. Dores GM, Metayer C, Curtis RE, et al. Second malignant neoplasms among long-term survivors of Hodgkin's disease: a population-based evaluation over 25 years. *J Clin Oncol*. 2002;20(16):3484-3494.
2. Mudie NY, Swerdlow AJ, Higgins CD, et al. Risk of second malignancy after non-Hodgkin's lymphoma: a British Cohort Study. *J Clin Oncol*. 2006;24(10):1568-1574.
3. Hodgson DC, Gilbert ES, Dores GM, et al. Long-term solid cancer risk among 5-year survivors of Hodgkin's lymphoma. *J Clin Oncol*. 2007;25(12):1489-97.
4. Constine LS, Tarbell N, Hudson MM et al. Subsequent malignancies in children treated for Hodgkin's disease: associations with gender and radiation dose. *Int J Radiat Oncol Biol Phys*. 2008;72(1):24-33.
5. Nyandoto P, Muhonen T, and Joensuu H. Second cancer among long-term survivors from Hodgkin's disease. *Int J Radiat Oncol Biol Phys*. 1998;42(2):373-378.
6. Gladdy RA, Qin LX, Moraco N et al. Do radiation-associated soft tissue sarcomas have the same prognosis as sporadic soft tissue sarcomas? *J Clin Oncol*. 2010;28(12):2064-2069.
7. Bakaeen FG, Jaroszewski DE, Rice DC, et al. Outcomes after surgical resection of cardiac sarcoma in the multimodality treatment era. *J Thorac Cardiovasc Surg*. 2009; 137(6):1454-1460.
8. Butany J, Nair V, Naseemuddin A, et al. Cardiac tumours: diagnosis and management. *Lancet Oncol*. 2005;6(4):219-228.

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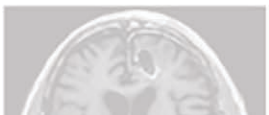

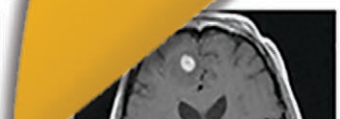

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