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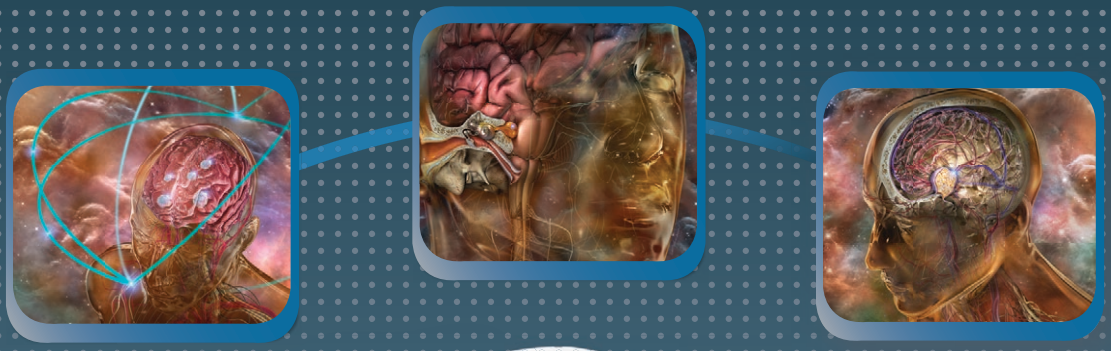

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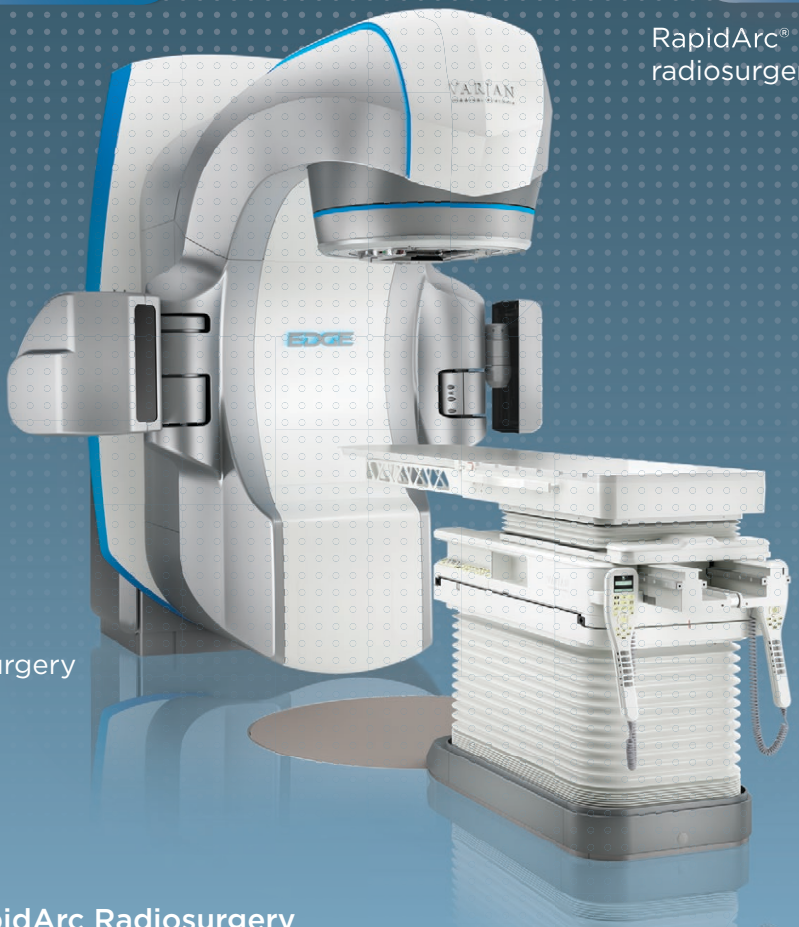

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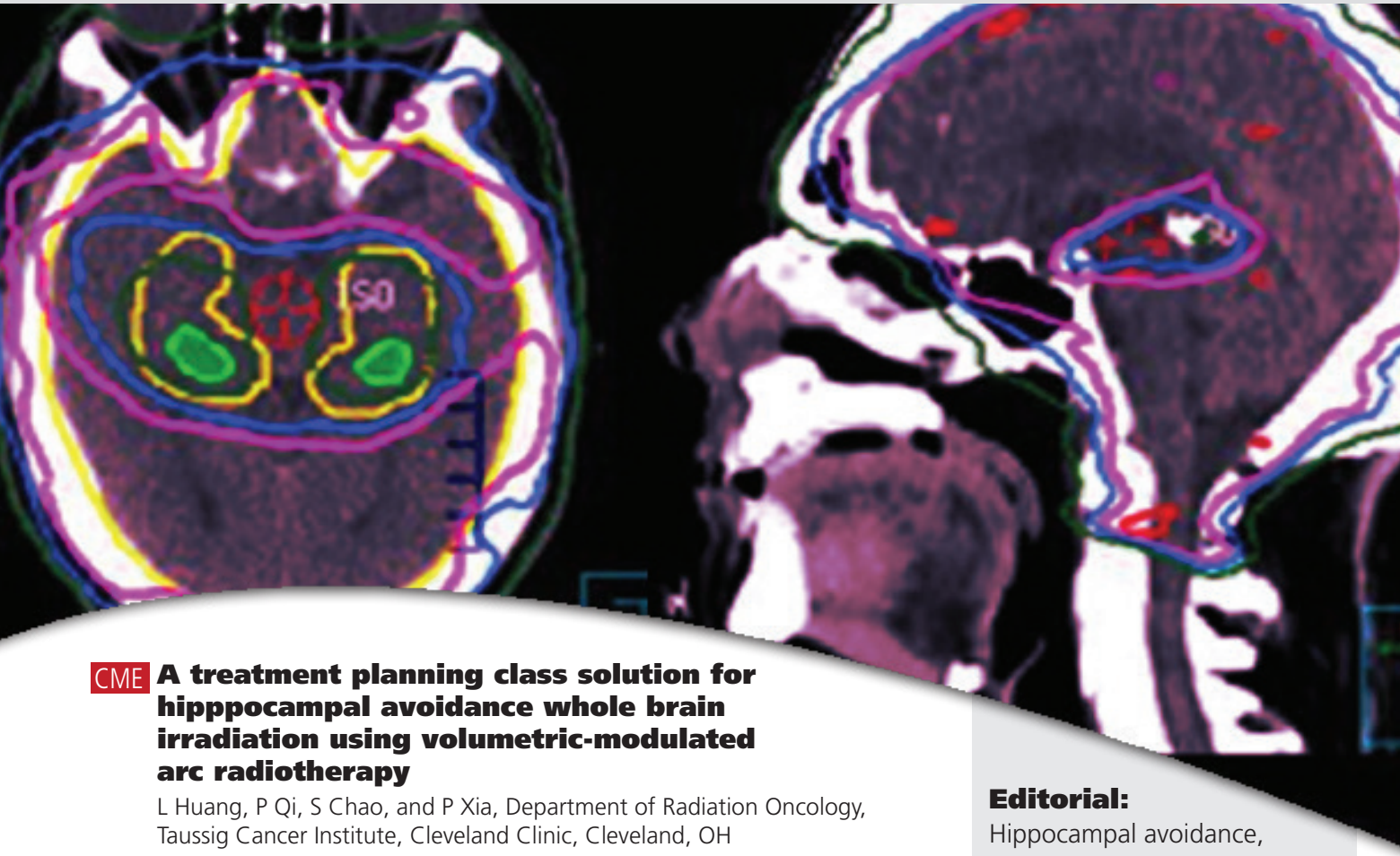


CME **A treatment planning class solution for hipppocampal avoidance whole brain irradiation using volumetric-modulated arc radiotherapy**

L Huang, P Qi, S Chao, and P Xia, Department of Radiation Oncology, Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH

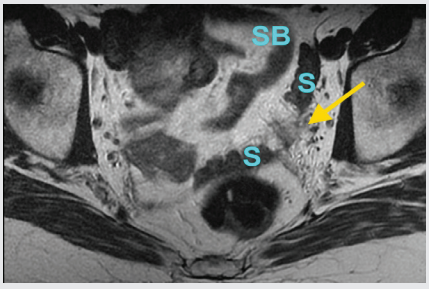
CME **Stereotactic body radiation therapy for early-stage primary liver cancer**

R Schulz, C Huntzinger, Varian Medical Systems, Palo Alto, CA; KE Rosenzweig, S Blacksburg, Icahn School of Medicine at Mount Sinai, New York, NY

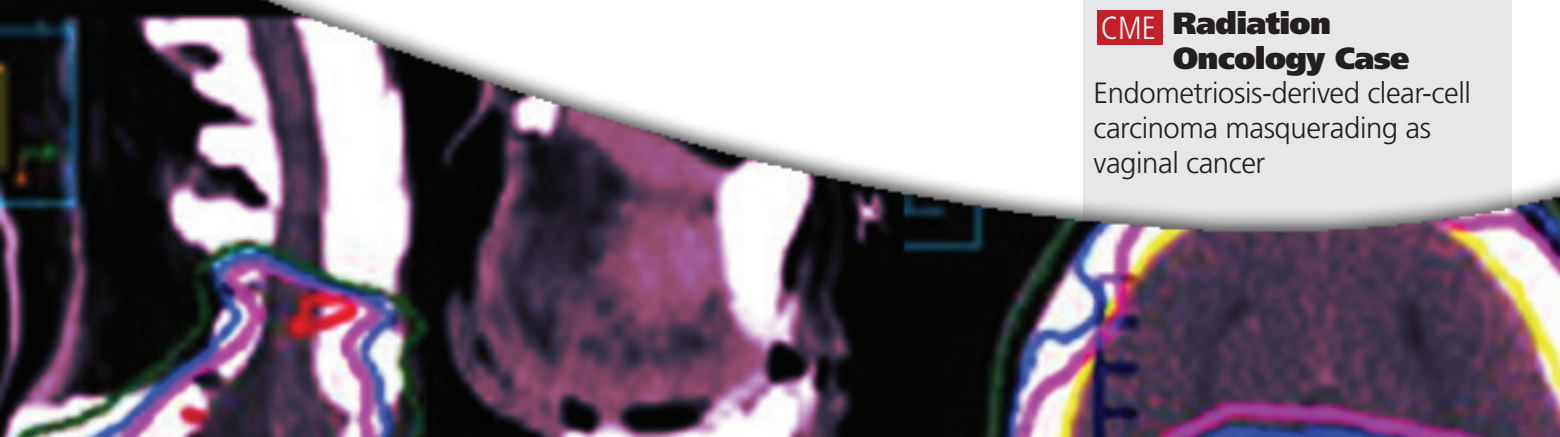
Technology Trends: Expediting the treatment planning process

Cristen Bolan

Editorial:
Hippocampal avoidance, hepatocellular carcinoma and hemangiopericytoma



CME **Radiation Oncology Case**
Endometriosis-derived clear-cell carcinoma masquerading as vaginal cancer



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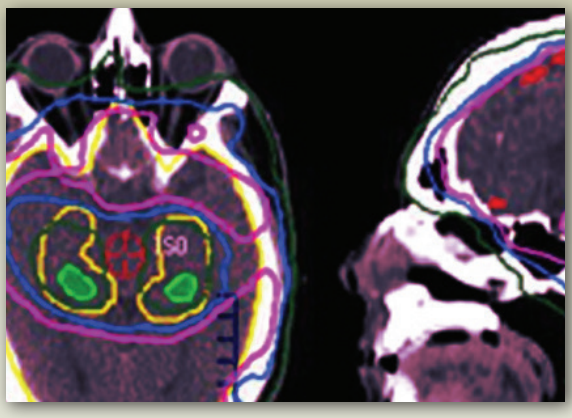

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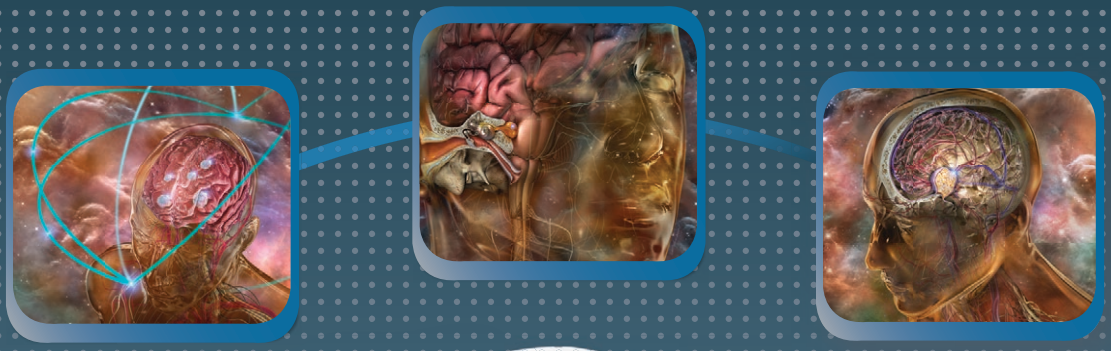

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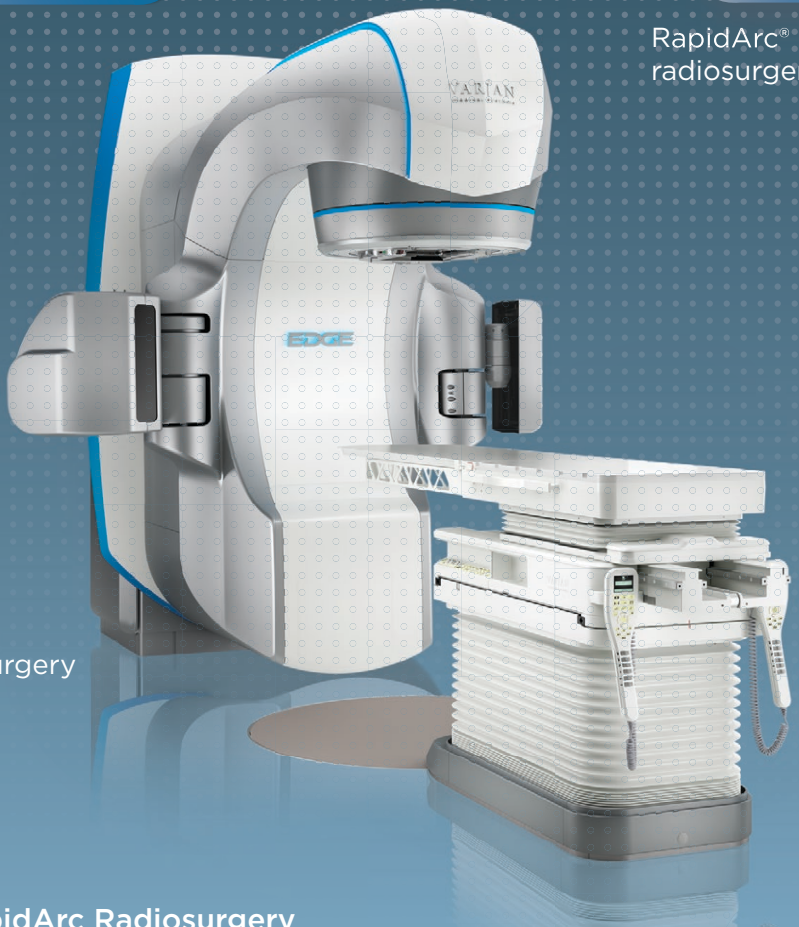

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RADIATION ONCOLOGY CASE

CME SEE PAGE 6 FOR DETAILS

Congratulations to our Clinical Case Contest winner for December 2013, M Crystal Yu, MD. As the winner, Dr. Yu's case received the most votes from our online community and was selected by our Advisory Board as the best prepared and most interesting case submitted during September, October, and November 2013. Dr. Yu will receive an American Express gift card valued at $250.

Endometriosis-derived clear-cell carcinoma masquerading as vaginal cancer

M Crystal Yu, MD, Malolan S. Rajagopalan, MD, Thomas Krivak, MD, Paniti Sukumvanich, MD, and Sushil Beriwal, MD

CASE SUMMARY

The patient is a 47-year-old woman who presented with a 1.5-cm vaginal mass. Seven years ago, she underwent a total abdominal hysterectomy and bilateral salphingo-oophorectomy for endometriosis.

IMAGING FINDINGS

A vaginal lesion was biopsied and the final pathology was interpreted as a vaginal carcinoma that was predominantly clear-cell type arising in a background of endometriosis. However, a magnetic resonance imaging (MRI) scan revealed a 2.5 × 2.1-cm mass arising from the left adnexal region with extension to the vagina (Figure 1) that was intensely FDG-avid, suggestive of endometriosis-associated ovarian cancer (EAOC). The patient was treated with concurrent chemoradiation with

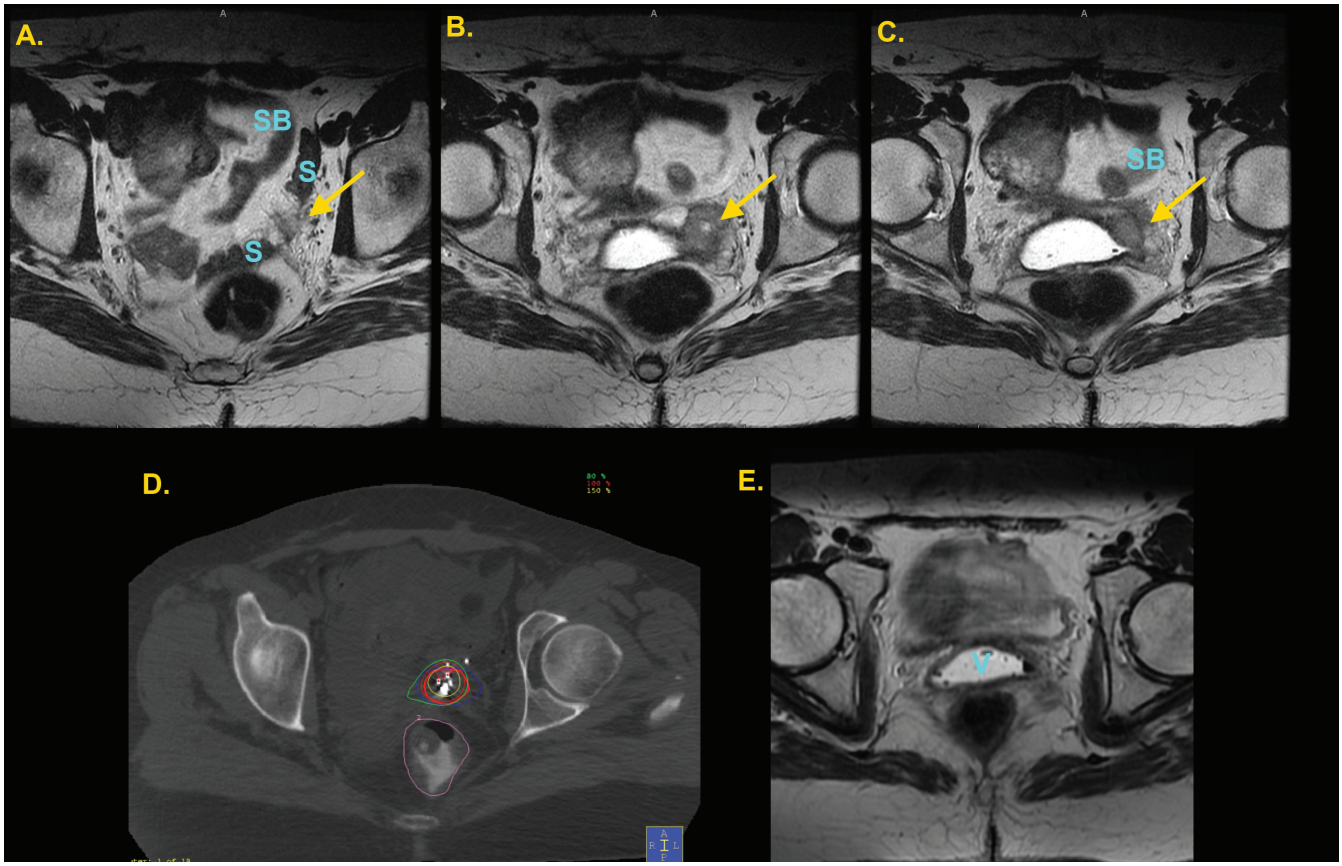

FIGURE 1. *The images (A-C) are sequential pretreatment MRI slices from superior to inferior, demonstrating the mass (arrow) in the left adnexa abutting the sigmoid colon superiorly and extension into the vagina inferiorly. Image D is the treatment planning CT scan for the HDR brachytherapy component of her care. Image E is the follow-up MRI demonstrating a complete clinical response (SB = small bowel, S = sigmoid colon, V = vagina).*

external beam radiation therapy (EBRT) to a dose of 50.4 Gy and radiosensitizing weekly cisplatin (40mg/m2). Upon completion of this, interstitial brachytherapy needles were placed under laparoscopic guidance as the adnexal mass was adherent to sigmoid colon (Figure 1). The patient was treated with image-guided high-dose rate (HDR) brachytherapy to a dose of 25 Gy in 5 fractions for an equivalent dose in 2 Gy fractions (EQD2) of 80.8 Gy. The patient is currently undergoing therapy with carboplatin and paclitaxel for a planned 6 cycles.

DIAGNOSIS

Endometriosis-associated clear-cell carcinoma arising in the adnexal region and presenting as vaginal cancer

DISCUSSION

Since its first description by Sampson, endometriosis has been considered a premalignant lesion with documented degeneration into clear-cell or papillary adenocarcinoma.[1] This is an unusual case of endometriosis-associated clear-cell carcinoma arising in the adnexal region and presenting as vaginal cancer. This case was uniquely treated with chemoradiation and interstitial brachytherapy with complete metabolic and clinical response.

Endometriosis-associated ovarian carcinoma (EAOC) is a well-reported phenomenon. Even though it may present as a vaginal mass,[2,3,4] in our patients, positron emission tomography/computed tomography (PET/CT) and pelvic MRI confirmed that the disease originated in the adnexa with extension into the vagina. Ours is the first case report utilizing laparoscopic-assisted HDR brachytherapy. Due to the lateral location of disease in the paravaginal tissue and pelvic sidewall, laparoscopic assistance was necessary to dissect and manipulate the small bowel so that the interstitial needles could be safely placed. HDR brachytherapy was delivered using an image-guided technique that enabled the conformal delivery of radiation to the target while minimizing dose to the critical structures.

CONCLUSION

While the role of adjuvant chemotherapy in the treatment of endometriosis-associated clear-cell carcinoma arising in the adnexal region and presenting as vaginal cancer still remains to be defined, this patient has achieved a complete clinical response to therapy.

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*Prepared by **Dr. Yu** and **Dr. Sukumvanich** while at the division of Gynecology Oncology, Department of Obstetrics and Gynecology, Magee Women's Hospital, University of Pittsburgh Medical Center, Pittsburgh, PA, and **Dr. Rajagopalan** and **Dr. Beriwal** while at the division of Radiation Oncology, Magee Women's Hospital, University of Pittsburgh Medical Center, Pittsburgh, PA.*

CME Information

Activity description

In this issue of *Applied Radiation Oncology,* our faculty has assembled a number of articles and cases that provide practical insight to radiation oncology professionals on topics, including new techniques in treatment planning for hippocampal avoidance whole brain irradiation, the use of SBRT for early-stage primary liver cancer, cases in which intracranial stereotactic radiosurgery is preferable to conventional radiotherapy, and the use of chemoradiation and interstitial brachytherapy to treat endometriosis.

Learning objectives

After reviewing this activity, participants will:

- Gain an awareness of using SBRT as a treatment for early-stage primary liver cancer.
- Identify risks of SBRT and less likely candidates for SBRT for HCC.
- Understand the planning and delivery method of VMAT.
- Appreciate the importance of using MRI to define critical structures in the brain.
- Understand the role of intracranial stereotactic radiosurgery in cases warranting greater conformation and daily dose.
- Comprehend the use of chemoradiation and interstitial brachytherapy to treat endometriosis.

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Principal faculty and their credentials

Kenneth E. Rosenzweig, MD, Professor, Chair of Radiation Oncology, Icahn School of Medicine at Mount Sinai, New York, NY.

Ping Xia, PhD, Department of Radiation Oncology, Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH.

M. Crystal Yu, MD, Division of Gynecology Oncology, Magee Women's Hospital, University of Pittsburgh Medical Center, Pittsburgh, PA.

Luis Moreno Sánchez, MD, Radiation Oncology-Radiosurgery Department, Clinica Abreu, Santo Domingo, Dominican Republic.

Target audience

Radiation oncologists, surgical oncologists, radiologists, and oncological imaging physicians.

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The cost of CME credits is $50 per issue. As a special offer, you can purchase all the CME credits in every issue through the end of 2013, including our October 2012 issue for the discounted price of just $95. That's just $95 for 15 CME credits.

Estimated time for completion:	2 hours
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Disclosures

Author Ping Xia, PhD, Department of Radiation Oncology, Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH, has received a research grant from Philips Healthcare.

Authors Raymond Schulz, MSc, and Calvin Huntzinger, MSc, are employees of Varian Medical Systems, Palo Alto, CA.

No other authors, or any individuals at IAME or *Applied Radiation Oncology* who had control over the content of this program, have any relationships with commercial supporters.

EDITORIAL

John Suh, MD, Editor-in-Chief

Hippocampal avoidance whole-brain radiotherapy (WBRT) actually reduced cognitive loss in patients for up to 6 months after treatment when compared to historic controls.

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.*

Hippocampal avoidance, hepatocellular carcinoma and hemangiopericytoma

Welcome to the 4th-quarter edition of *Applied Radiation Oncology* 2013! On behalf of the advisory board and publisher, we appreciate your continued support of this e-journal.

This year's ASTRO meeting in Atlanta was a success. One of the plenary studies presented at the American Society for Radiation Oncology's (ASTRO) 55th Annual Meeting found hippocampal avoidance whole-brain radiotherapy (WBRT) actually reduced cognitive loss in patients for up to 6 months after treatment when compared to historic controls. This phase II RTOG study (0933) uses sophisticated treatment planning and delivery to minimize dose to the hippocampus, which has been show to influence memory. In this issue, Dr. Xia and colleagues evaluate techniques used in radiation treatment planning for developing WBRT plans with hippocampal avoidance in their article, *Treatment planning for hippocampus sparing of whole-brain radiation*. By combining treatment planning CT with thin-slice MRI scans and careful delineation of the hippocampus and other critical normal tissues, this article also describes how radiation apertures were designed by computer optimization, while the radiation the gantry rotates around the patient.

Hepatocellular carcinoma (HCC) is not only one of the leading causes of cancer globally, but it is also the third leading cause of cancer mortality after lung and stomach cancer, given its poor survival rate. The need for better management of the disease is increasingly urgent in the United States, where the death rate is rising, primarily due to an increase in hepatitis C and obesity-induced nonalcoholic steatohepatitis. As a result, it is critical that radiation oncologists be current on the most effective treatments, such as stereotactic body radiation therapy (SBRT). In their article, *SBRT for early-stage primary liver cancer*, authors Raymond Schulz and Cal Huntzinger present cases in which refined SBRT techniques allow for safer administration of higher doses of radiation, while minimizing the potential of radiation-induced liver disease.

In the clinical case, *Hemangiopericytoma of the intra- and suprasellar regions,* a female patient presents with hemangiopericytoma, a rare vascular tumor arising from pericytes of Zimmerman, associated with the capillary walls. Dr. Moreno Sánchez and colleagues discuss how intracranial hemangiopericytoma with complete surgical tumor resection was combined with adjuvant radiation therapy and postoperative stereotactic radiosurgery.

Dr. Yu presents a clinical case, *Endometriosis-derived clear-cell carcinoma masquerading as vaginal cancer,* a patient presents with an unusual case of endometriosis-associated clear-cell carcinoma arising in the adnexal region and presenting as vaginal cancer. This case was uniquely treated with chemoradiation and interstitial brachytherapy with complete metabolic and clinical response.

We welcome new article submissions; please visit our website for details. We also encourage you to participate in our monthly clinical case review contest. The winning case of the month will be published in a future issue of *Applied Radiation Oncology*, and the author will receive an American Express Gift Card in the amount of $250.

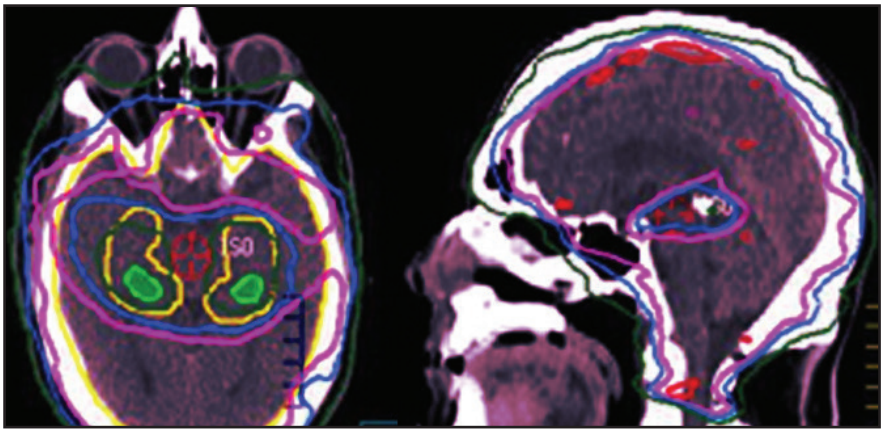
CME SEE PAGE 6 FOR DETAILS

A treatment planning class solution for hipppocampal avoidance whole brain irradiation using volumetric-modulated arc radiotherapy

Long Huang, PhD, Peng Qi, PhD, Sam Chao, MD, and Ping Xia, PhD

Whole brain radiotherapy (WBRT) remains the primary treatment option for patients with multiple brain metastases.[1] Although the conventional method of using opposed lateral beams for WBRT can achieve uniform dose distribution over the whole brain, the high radiation dose to the hippocampus may result in neurocognitive function (NCF) decline.[2,3] Using intensity modulated radiotherapy (IMRT), a phase II Radiation Therapy Oncology Group (RTOG) trial (0933), was designed to study clinical feasibility in hippocampal sparing during WBRT.

Several groups have reported technical feasibilities in implementing HA-WBRT. Gutiérrez et al evaluated hippocampus avoidance (HA) WBRT (HA-WBRT) using tomotherapy with a simultaneous integrated boost to brain metastases, while achieving homogeneous dose distribution in the whole brain (equivalent to conventional WBRT) and sparing the hippocampal regions.[4] Using a volumetric arc therapy (VMAT) technique, Hsu et al reported a planning study of HA-WBRT, while simultaneously boosting one to 3 brain metastases to 63 and 70.8 Gy.[5] The mean delivery time of these VMAT plans was 3.6 minutes. Using the same VMAT method, Awad et al reported their clinical experience on 30 patients with median whole brain dose of 31 Gy and a boost dose to the brain metastases of 51 Gy.[6] They reported that the treatment was clinically feasible and tolerable. The mean time to delivery was about 3.43 minutes compared to 1.3 minutes for the conventional whole brain treatment. Nevelsky et al evaluated the feasibility of HA-WBRT using the Elekta Infinity linear accelerator and Monaco treatment planning system with a nine-field configuration and step-and-shoot delivery method.[7] They achieved planning goals defined by the RTOG 0933 protocol. In this study, we reported our planning and delivery experience of VMAT for HA-WBRT under a mixed vendor environment, using the Pinnacle treatment planning system v9.0 by Philips Healthcare, while delivering treatment on Elekta Synergy and Novalis-TX linear accelerators.



Dr. Huang, Dr. Qi, Dr. Chao, *and* ***Dr. Xia*** *are at the Department of Radiation Oncology, Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH.*

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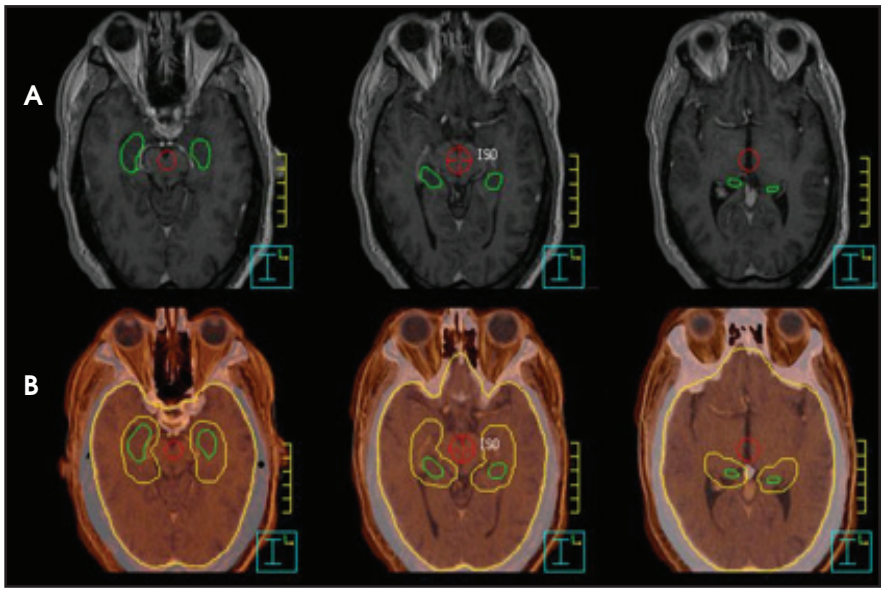

FIGURE 1. *(A) The contours of the hippocampus are shown in T1-weighted contrast-enhanced MP-RAGE MR images (grayscale); (B) the contours of PTV (the outer yellow line), hippocampus avoidance (inner yellow line), and hippocampus (green line) are shown in the fused MR (thermal)/CT images for a selected patient.*

Planning

Ten patients, who received WBRT for brain metastases at our institution, were randomly selected in this study. The computed tomography (CT) images with 2-mm slice thickness were acquired on a Philips Brilliance Big Bore 16-slice CT simulator, and then exported to the Pinnacle treatment planning system. To facilitate contouring, magnetic resonance imaging (MRI) scans (axial T2-weighted and T1-weighted contrast enhanced MP-RAGE) with 1.5-mm slice thickness were imported and registered with the planning CT images in Pinnacle. Following the guidelines in the RTOG 0933 protocol, a radiation oncologist contoured clinical target volume (CTV), hippocampus, and other organs-at-risk (OAR), such as the lenses, eyes, optic nerves, and brainstem based on MR/CT

Table 1. Compliance criteria and critical structure constraints for HA-WBRT from RTOG 0933

Organ	Per Protocol	Variation Acceptable	Deviation Unacceptable
PTV	D2% ≤ 37.5 Gy D98% ≥ 25 Gy	D2% >37.5 Gy, ≤ 40 Gy D98% ≥ 25 Gy	V30 < 90% D2% > 40 Gy
Hippocampus	D100% ≤ 9 Gy Maximum dose ≤ 16 Gy	D100% ≤ 10 Gy Maximum dose ≤ 17 Gy	D100% > 10 Gy Maximum dose > 17 Gy
Optic Nerves and Chiasm	Maximum dose ≤ 37.5 Gy	Maximum dose ≤ 37.5 Gy	Maximum dose > 37.5 Gy

Table 2. Summary of objective settings for the progressive HA-WBRT VMAT planning

	Optimization 1		Optimization 2		Optimization 3	
Structure	**Inverse planning constraints**	**Weight**	**Inverse planning constraints**	**Weight**	**Inverse planning constraints**	**Weight**
PTV	Uniform dose: 30 Gy	50	Uniform dose: 30 Gy	50	Uniform dose: 30 Gy	50
	Min DVH: ≥ 26 Gy, 100%	40	Min DVH: ≥ 25 Gy, 100%	30	Min DVH: ≥ 25 Gy, 100%	30
	Max dose: 35 Gy	40	Max dose: 35 Gy	30	Max dose: 35 Gy	50
Hippocampus	Max dose: 12 Gy	0	Max dose: 12 Gy	5	Max dose: 12 Gy	10
	Max DVH: 10 Gy to ≤ 20%	0	Max DVH: 10 Gy to ≤ 20%	5	Max DVH: 10 Gy to ≤ 20%	10
Lens	Max dose: 5 Gy	0	Max dose: 5 Gy	5	Max dose: 5 Gy	5
Chiasm	Max dose: 30 Gy	0	Max dose: 30 Gy	1	Max dose: 30 Gy	1
Optic nerves	Max dose: 30 Gy	0	Max dose: 30 Gy	1	Max dose: 30 Gy	1

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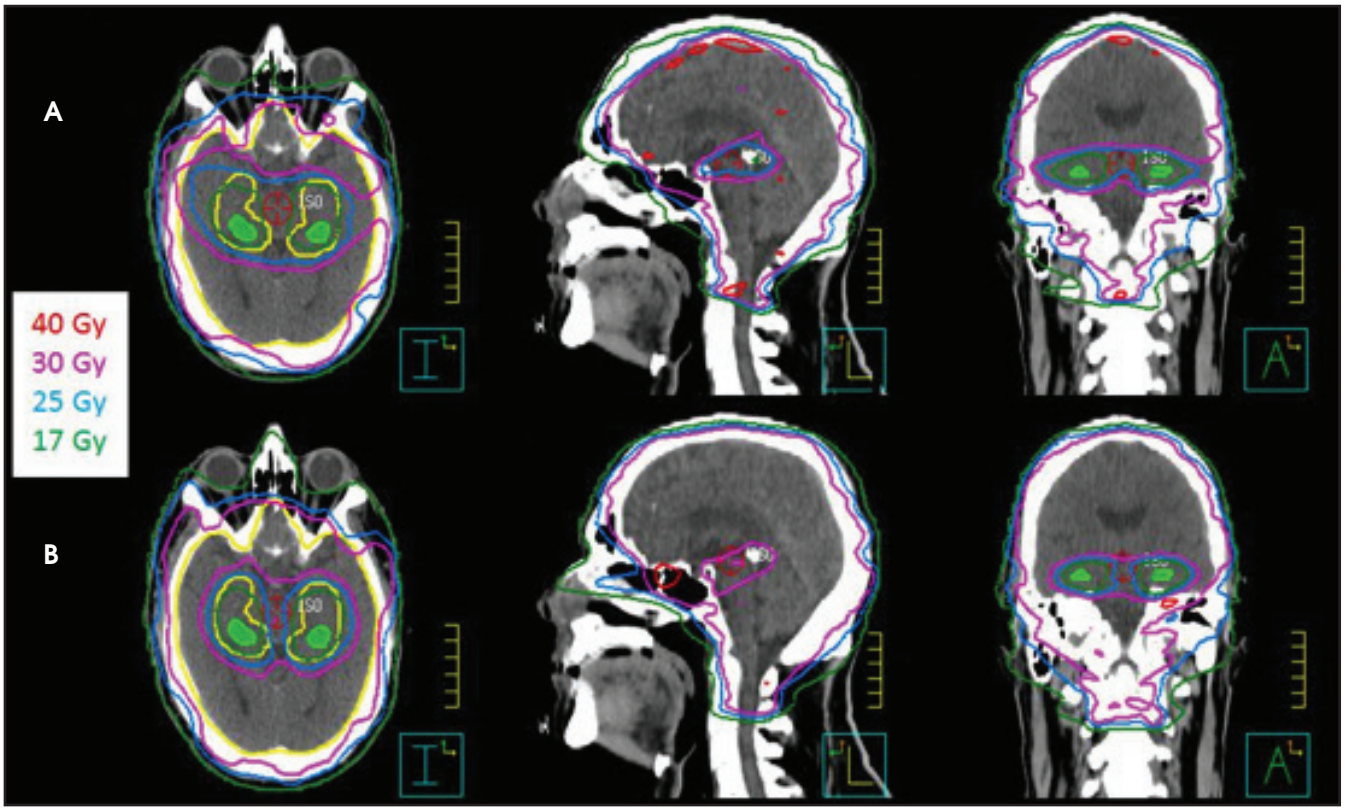

FIGURE 2. *Selected isodose line distributions of 2 VMAT plans (A) for Synergy-S and (B) for Novalis-TX displayed on an axial, sagittal, and coronal images.*

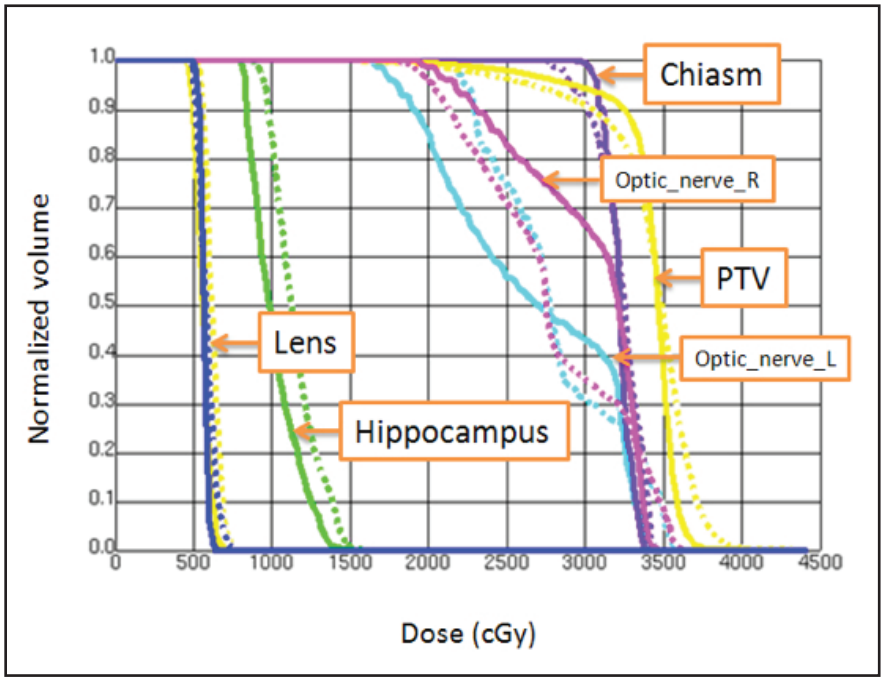

FIGURE 3. *The dose volume histograms (DVHs) from 2 VMAT plans for a HA-WBRT case, with the solid and dashed lines representing a Novalis-TX and Synergy-S VMAT plan, respectively. The plots of the PTV, hippocampus, optic nerves, optic chiasm, and lenses are labeled.*

images (Figure 1). The planning target volume (OTV) was constructed as the CTV (whole brain), excluding the hippocampal avoidance, which was generated with a 5-mm uniform expansion from the contoured hippocampus.

For each patient, 2 VMAT plans were created in Pinnacle for a Novalis-TX and an Elekta Synergy-S system. The Novalis-TX linear accelerator is equipped with 60 leaf pairs of high-definition (HD) multileaf collimator (MLC). With HD-MLC, 32 inner leaf pairs and 28 outer leaf pairs have a respective projection leaf width of 2.5 mm and 5.0 mm at the isocenter plane. The Synergy-S system is equipped with a MLC consisting of 40 leaf pairs of a 4.0-mm projection leaf width at the isocenter plane. All VMAT plans were generated using SmartArc optimization with 2 arcs: a 358° arc (from 181° to 179°) and another 200° (from 100° to 260°) arc. To minimize the dosimetric effect of the tongue-and-

SEE PAGE 6 FOR DETAILS CME

groove in the MLC, the collimator angle of 2 arcs was set to 30° or 45°. Other important optimization parameters were: the maximum iterations of 30, the convolution-dose iterations at 15, the final gantry spacing of 4°, and the maximum delivery time of 90 seconds. The maximum dose rate on each system was set to 400 MU/min. The planning acceptance criteria were to achieve the planning goals recommended by the RTOG 0933 protocol (Table 1).

Because the optimization used in the Pinnacle is a gradient search method, it is likely the optimized solution could be trapped in a local minimum, especially for VMAT plans involved with a concave-shaped target, such as the PTV in the HA-WBRT case. Therefore, the final plan quality from the Pinnacle has a large variation, heavily depending on how the planning objectives were added to guide the computer optimization. A typical set of planning objectives cannot be directly applied and multiple manual tunings of the planning objectives are required. To expedite the planning process, we developed a progressive approach of how to manually adjust the planning objectives for each OARs and the PTV. An example of the planning objectives for this progressive method is listed in Table 2. As shown in Table 2, we started the planning objectives with only PTV coverage in the first optimization. After this optimization, the VMAT plan achieved a uniform dose distribution with excellent dose coverage to the entire brain (or the PTV), but no sparing of the hippocampus avoidance or other OARs. Without resetting the beams after the first optimization, we manually increased the weighting factors to the hippocampus avoidance and other OARs, as shown in Table 2. Because of the nature of the gradient search method, after the second optimization, the dose coverage to the majority of the PTV was maintained while the doses to the hippocampus and other OARs were successfully decreased. However, the maximum dose in the PTV was increased and the percent volume of the PTV receiving the prescription dose was also decreased. To recover PTV dose coverage, the weighting factors in both PTV and hippocampus avoidance were manually adjusted as shown in optimization 3 in Table 2. Such adjustments may continue several times until the VMAT plan meets the plan acceptance criteria in Table 1.

Results

All VMAT plans achieved the plan acceptance criteria (dose compliance) per RTOG 0933 protocol or with acceptable variances. Figures 1 and 2 show an example of dose distributions and dose volume histograms from 2 VMAT plans (Novalis-TX and Synergy-S) for the same patient. With ≥ 90% of the PTV receiving 30 Gy, the average volume of the PTV receiving 25 Gy (37.5 Gy) was 96.9 ± 1.0% (0.7 ± 0.9%) and 96.2 ± 0.7% (1.8 ± 0.9%) for the Novalis-TX and Synergy-S VMAT plans, respectively. For the hippocampus, D100% and the maximum dose were 7.9 ± 0.5 Gy and 15.3 ± 1.3 Gy for the Novalis-TX plans; D100% and the maximum dose were 8.3 ± 0.3 Gy and 15.4 ± 1.0 Gy for the Synergy-S plans. The total MUs for Novalis-TX and Synergy-S machine was 889 ± 109 and 1,157 ± 127, respectively. We noticed that the VMAT plans for Novalis-TX had improved the plan quality compared to the VMAT plans with the Synergy-S plan, partly due to the smaller leaf width for the Novalis-TX linear accelerator.

Conclusion

We developed a planning class solution for hippocampus avoidance of whole brain radiation using planning and delivery systems with mixed vendors. Following the RTOG 0933 protocol and our planning class solution, the treatment plan for the hippocampus avoidance of the whole brain radiation can be completed within 2 to 4 hours after completion of all contours.

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Stereotactic body radiation therapy (SBRT) for early-stage primary liver cancer (HCC)

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Hepatocellular carcinoma (HCC) is the sixth leading cause of cancer globally (fifth in men and eighth in women) with 750,000 new cases per year.[1] Its global prognosis is very poor with only a 7% 5-year survival.[1] Because of such a poor survival rate, at 696,000 deaths, it is currently the third leading cause of cancer mortality after lung and stomach cancer. Within 5 years, global HCC mortality is expected to be second only to lung cancer.[1]

In the United States (U.S.), while primary HCC is small at ~20,000 cases, it is one of the few U.S.-based cancers whose death rate is rising, primarily due an increase in hepatitis C and obesity induced nonalcoholic steatohepatitis (NASH).[3] U.S. 5-year survival rates have improved only marginally in the past 40 years, from 4% in the early 70s to 14% currently,[2] second only to pancreatic cancer, which has a 6% survival rate.

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Eighty percent of HCC cases arise in developing countries and over 55% of all HCC cases are found in mainland China.[1] Asia has a high incidence of chronic viral hepatitis infection (hepatitis B or C), which contributes to the high rate of HCC. Liver cirrhosis, a late-term effect of hepatitis infection, results in a 10-fold risk in HCC, hence the high Asian risk factor.[1] Like lung cancer, HCC is a silent disease whose effects typically do not show up until late stage presentation. Early-stage diagnosis gives a poor 5-year survival of 26%, whereas late-stage diagnosis gives a miserable 2% survival.[2]

Invasive therapies

Invasive therapies that can improve on the 5-year survival of HCC include resection and transplantation. Their improvement in 5-year survival rates range from 30% to 50% and 60% to 70%, respectively. These surgical techniques, first developed in 1949 and 1967, are unfortunately eligible to < 30% of HCC patients due to multiple factors, including tumor size and location within the liver, vascular invasion, and poor liver function.[4] Further, in several large key Asian societies, transplantation is neither culturally acceptable nor clinically practical.[5] Some less invasive treatments include: percutaneous ethanol injection[6] (PEI), transarterial chemo embolization[7] (TACE) radiofrequency ablation[8] (RFA) and yttrium-90 brachytherapy,[9] but these are either only palliative or suffer from many of the same eligibility contraindications as surgery.

Treatment challenges

Treating the liver for HCC using any technique is a challenge for two reasons. Firstly, it is two diseases in one: a chronic viral liver disease and a malignancy resulting from that chronic liver destruction. Secondarily, the heterogeneity (etiology and prognosis) of those different diseases affects treatment and survival.

Tumor stage and underlying liver function are both major determinants of the treatment selection as well as prognosis in HCC patients, thus allowing no

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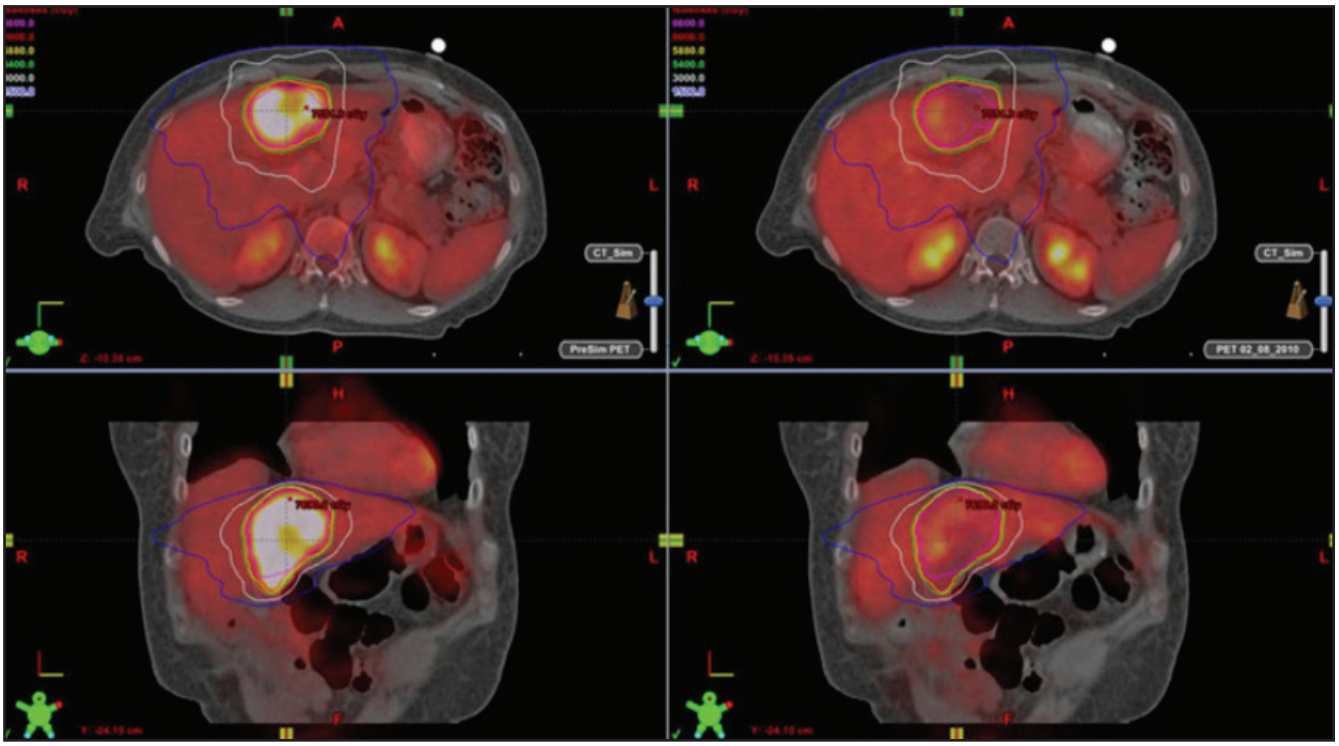

FIGURE 1. *Pre (left) and post (right) SBRT treatment axial (top) and coronal (bottom) images of a large hepatocellular lesion treated on a Novalis Tx with RapidArc and HD120 MLC. The dose was 60 Gy over 5 sessions. The 30-day PET negative images on the right reveal no radiographic evidence of disease. This patient appears to have complete metabolic response after more than 2 years. Image courtesy of Percy Lee, MD, UCLA, Los Angeles, CA.*

more than a 20% chance for potentially curative therapies.[9]The accurate assessment of disease differential, disease extent, and liver function significantly impacts the choice and targeting of treatment. Key to the safe treatment of liver disease is the preservation of liver function.[9]

Lessons learned from surgery provide a model for treating with radiation. In surgery, assessment is done using a variety of metrics to assess liver function and being cognizant of liver volume treated. Assessment metrics include: Child-Pugh (CP) score[10]—a liver function classification system, A to C, scoring severity of disease, CT perfusion, Model for End-Stage Liver Disease (MELD) and Barcelona Clinic Liver Cancer (BCLC) staging.[11] In liver surgery for HCC, preservation of function dictates resections of no more than 0.5% of body weight and 45% of liver volume (~450cc) and resections are only performed when a variety of liver function measures, such as a CP score of no worse than class A, are met. The relationship between CP liver function and BCLC staging is nicely detailed in a recent review paper from Korea.[12]

SBRT for HCC: Early efforts and rationale

The liver was first a target for radiation therapy as early as 1924. The use of conventional external beam radiation therapy (RT) as a curative technique, was hampered by early evidence of radiation's severe toxicity to the diseased liver defined as radiation-induced liver disease (RILD).[10,13] RILD manifests in long-term migration of Child-Pugh score from A to B to C, resulting in likely liver failure with the later scores. A decline in liver function is more likely in patients with higher baseline CP scores and in those with advanced disease requiring larger volumes of irradiated liver.[14]

Thus all forms of RT for HCC have been slower to evolve due to the liver's low tolerance to RT, further reduced in the cirrhotic liver. This is especially true where high doses of radiation are distributed throughout the liver as is the case with non image-guided, non-IMRT treatments. Palliative liver radiation has recently been shown to improve quality of life in patients with active symptoms from HCC or liver metastases.[15]

Liver SBRT, the precise delivery of potent doses of radiation in a small number of fractions to the liver, was first performed by Blomgren & Lax in 1995 in 1 to 3 fractions of 20 to 45 Gy.[16] SBRT is the non-CNS extracranial extension of

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Table 1. Recent Studies on Treatment of Early-Stage Hepatocellular Carcinoma

Author & Center (Year)	Patients Treated (initial CP score)	Gross Tumor Volume (cc) (range)	Dose Range (range & med) (fx per tmt)	Median Follow-up (months) (range)	Local Control (% at yr)
Sanuki[25] Tokai U (Aug 13)	185 (A=158, B=27)	7.6 cc [1.5 – 65]	35 – 44 Gy [in 5 fx]	25 mo [3-80]	99, 93, 81 at 1, 2, 3 yr
Andolino[24] Indiana Univ (Nov 11)	60 (A=36, B=24)	29 cc [2 – 112]	24 – 48 Gy [40 Gy med] [in 3 or 4 fx]	27 mo [1-24]	90 at 2 yr
Louis[23] Liege Univ (Oct 10)	25 (A=22, B=3)	45 cc (18-100)	45 Gy [in 3 fx]	12.7 mo [1-24]	95 at 1 & 2 yr
Kwon[22] Catholic U (Sept 10)	42 (A=38, B=4)	15.4 cc (3-82)	30 – 39 Gy [33 Gy med] [in 3 or 4 fx]	27.8 mo [8.4-49.1]	72 & 68 at 1 & 2 yr
Seo[21] KCCH (Sept 10)	38 (A=34, B=4)	40.5 cc (11-464)	33 – 57 Gy [in 3 or 4 fx]	15 mo (3-47)	79 & 66 at 1 & 2 yr
Cardenes[18] Indiana U (Mar 10)	17 (A=6, B=11)	34 cc (8-95)	36 – 48 Gy [in 3 or 5 fx]	18 mo	100 at 1 yr
Tse[19] PMH (Feb 08)	31 (A=31, B=0)	173 cc (9-1913)	24 – 54 Gy [36 Gy med] [in 6 Fx]	17.6 mo (10.8-39.2)	65 at 1 yr

RILD = Radiation Induced Liver Disease; NR = Not Reported; K-M=Kaplan-Meier; OR=Overall Response; CR=Complete Response; PR=Partial Response; SD=Stable Disease; PFS=Progression Free Survival

* These seven studies represent single institution peer review papers on SBRT for HCC where there were at least 15 (17 to 185) consecutive HCC patients being studied.

* Survival values are based on Kaplan – Meyer probability graphs reporting on the percentage of patients alive after a specific time period, reported as %-alive after y-years.

* Child Pugh (CP) classifies (A, B, or C) severity of pre-treatment liver disease by scoring (1, 2, or 3), five liver health criteria; more points yields poorer status [≤6=A, 7-9=B, ≥10=C]

Toxicity: Radiation Induced Liver Disease (RILD) is a dose limiting complication of conventional liver radiation, because the entire liver gets radiated.

These SBRT studies show that by employing focused stereotactic treatments, high doses of radiation can be safely and effectively delivered with excellent RILD results.

Only one of the 7 studies reported any significant RILD after 3 months and that was in 3/17 patients, or 18% .

Most studies reported 0% late term toxicity of greater than Grade 2. Only two studies reported any post treatment CP progression (A>B and/or B>C).

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(HCC) with Stereotactic Body Radiation Therapy (SBRT

Overall Survival K-M (% at yr)	Toxicity > Grade 2 (% late)	RILD (% of patients)	Child-Pugh[10,11] [change (decline) in CP score]	NOTES
95, 83 & 70 at 1, 2 & 3 yr	13%	10.3%	NR	• TACE performed in 111 patients prior to SBRT. • 19 (10.3%) had a decline in CP score by 2 points. • Grade 5 failures were observed in 1% (CP-B only).
67 at 2 yr	15%	NR	A>B: 7/36 B>C: 5/24	• CP-A patients had a 1-yr 93% LC and 93% OS. • CP-B patients had a 1-yr OS of 70%. • 23 patients proceeded to transplant.
79, 52 at 1 & 2 yr	8%	0%	NR	• Median DFS was 15.8 mo. CP-A patients had an actuarial survival of 86% vs 33% for CP-B patients. • OR=85%, CR=28%, PR=28%, SD=14% for 14 evaluable patients.
93, 77 & 59 at 1, 2 & 3 yr	2%	2%	NR	• Salvage SBRT for patients who failed repeat TACE. • OR=71.9%, CR=59.6%, PR=26.2%
69, 61 & 42 at 1, 2 & 3 yr	3%	0%	NR	• All tumors < 8cm Ø; LR= 63%; CR=2.6% • PR=60.5%; SD= 28.9%; 7.9%=PD • 2 yr PFS=66.4%
75 & 60 at 1 & 2 yr	23%	18%	NR	• OR=75%; 6 patients proceeded to transplant; 10 patients alive at 24 mo. med FU • No RILD was found in CP-A patients, but 27% (3/11)of CP-B patients had RILD
48 at 1 yr	29%	0%	A>B: 5/31	• Dose escalation study. • Median survival 11.7 mo OR=49%. • No RILD but 16% had a decline in CP score

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stereotactic radiosurgery (SRS), which neurosurgeons have been using for ablation of tumors in the brain and spine for >30 and >10 years, respectively. For primary CNS tumors, the intent is primarily curative. With very high dose rates per session, SRS and SBRT treatments require precision with tight margins to the tumor and minimum dose to surrounding organs at risk and normal tissues and employ an overwhelmingly ablative radiobiological mechanism. This is in contrast to conventional RT treatments where cells are allowed to repopulate and precision requirements are an order of magnitude less stringent.

The advantage of refined SBRT techniques is that they allow for a safer administration of higher levels of dose while minimizing the potential of RILD.[17] The past decade has seen a small number of single institution SBRT liver trials every couple of years on various platforms (Figure 1). Klein pointed out that there has been a doubling to 600 publications, on the use of radiation to treat liver tumors, in the 5-year period "2005-2010," over the prior 5-year period.[11] Furthermore, over 75% of all SBRT for HCC studies have published in the last 6 years, and over 66% published in the past 3 years.[18-36]

Refinements in SBRT HCC treatments have led to substantially improved results over both RT and those early SBRT treatments, which had some grade 5 toxicities. Liver toxicity with modern SBRT techniques is low because of precise stereotactic targeting and that ablative dose volumes are substantially reduced. Liver toxicity is uncommon in SBRT treatments where the effective volume irradiated is < 30% of total liver volume and where > 800 cc gets < 18 Gy as shown by a recent Korean paper.[18]

SBRT for HCC: Recent studies

A number of centers have recently reported on SBRT-based HCC treatment and several are summarized in Table 1.

• A Toronto group reported on a phase I liver cancer dose-escalation trial, which included 31 HCC patients with an average gross tumor volume (GTV) of 173 cc [9 to 1913 cc].[19,35] With a median dose 36 Gy (24 to 54 Gy) in 6 fractions, they achieved a 12-month local control (LC) rate of 65%. For patients with portal vein thrombosis (PVT), median survival was 11.6 months, which improved to 17.2 months for patients with no PVT. Overall survival (OS) was 48% at 1-year and 16% (5/31) of patients had a poorer level of liver function measured by a decline to in CP score. No patients had RILD and this study set the stage for other SBRT studies, as previously RILD was considered a treatment limiting toxicity of conventional radiation treatments.

• A group from Indiana reported on 17 patients with 1 to 3 targets (25 HCC total).[20] They had a dose escalation trial delivering 36 to 48 Gy in fractionation schedules from 5x8 Gy to 3x16 Gy. Their tumors (cumulative diameter ≤ 6 cm) were much smaller with an average GTV of 34 cc. With a mean follow up of 18 months, they achieved 100% LC at 1-year and an OS of 75% and 60% at 1 and 2 years respectively. Three patients had grade 3 to 4 toxicity. RILD was not observed in any CP-A patients, but was observed in 27% of CP-B patients.

• One Korean group documented a prospective registry of 38 patients with tumors < 10 cc treated in 33 to 57 Gy in 3 to 4 fractions.[21] One- and 2-year LC was 79 and 66% and 1-, 2- and 3-year OS was 68%, 61% and 41%, respectively. Only one grade-3 skin toxicity was reported. For those 26 patients who received a dose of > 42 Gy, a 2-year OS was reached.

• Another Korean group[22] documented 42 HCC patients with a median GTV of 15.4 cc, treated with a median dose of 33 Gy (30 to 39 Gy) in 3 fractions. With a median follow up of 27.8 months, they achieved a LC of 72 and 67.5% at 1 and 2 years respectively and OS of 92.9, 77.3 and 58.6% at 1, 2 and 3 years respectively. Consistent with other SBRT studies, they had very low toxicity (< 2 %) and low incidence of radiation induced liver disease RILD (2%).

• A Belgian group[23] reported on 25 HCC patients treated with a median dose of 45 Gy in 3 sessions. The treatment was well tolerated overall, and there were no grade 4 toxicities. Overall, actuarial survival was 79% and 52% at 1 and 2 years with a mean overall follow up of 12.7 months. CP-B patients had a 33% actuarial survival versus CP-A patients at 86%. No RILD was observed and excellent response to treatment was observed with overall response of 85% in 14 evaluable patients.

• In the largest North American study to date, a paper[24] from the Indiana group[20] reported on 60 patients treated with an average GTV of 29 cc. 36 CP-A patients were treated with 30 to 48 Gy in 3 fractions. With a median follow- up of 27 months, they achieved a 1-year LC of 93% and a 1-, 2- and 3-year OS of 93%, 77% and 70%, respectively. . 19% had a decline in CP score and 2 patients had grade 5 toxicities. The same paper further reports on 24 patients with CP-B scores treated with 24 to 48 Gy in 3 fractions whose 1-, 2- and 3-year OS were reduced to 70%, 50% and 50%, respectively. Of the 60 patients, 23 went on to othotopic liver transplant (OLT).

• Several even larger studies have more recently been reported from across Asia.[25-27] The largest single study to date is from Japan.[25] In this study, 221 patients with 237 single small HCC lesions were treated from 2005 to 2012. Of these, 185 met a variety of clinical criteria and were evaluable in this study. Patients were treated with either 35 Gy (48 pts) or 40 Gy (137 pts) depending on the CP scores and other factors. The 3-year local control and overall survival rates were 91% and 70% respectively. Ten local recurrences were observed at a median of 21 months. The dosing

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schemes provided equivalent results, acute toxicities (> grade 2) were observed in only 13% of patients and the procedure was deemed to provide excellent and safe outcomes.

Functional imaging techniques may be able to prospectively predict SBRT tumor control. A group from Taiwan retrospectively assessed 31 HCC patients (41 tumors) who had ^{18}F-FDG PET prior to SBRT.[28] They determined that a T_{SUVmax} (maximum standardized uptake value of the tumor) cutoff value of 3.2 was a good prognostic indicator of tumor control for patients treated with SBRT. They concluded that ^{18}F-FDG PET may help in patient selection and dose adjustment for HCC candidates for SBRT.

Definitive liver surgery (transplantation or resection) is considered the only curative option for HCC.[31] SBRT as a bridge to transplant, where the patient is a candidate for OLT, is more common in North America, with a number of centers taking that approach.[24,32-34] A pilot study from the Toronto group was the first paper in the surgical literature.[32] They reported on 5 of 10 patients treated with SBRT who successfully underwent OLT and are cancer free. A group from New York[33] treated 27 HCC patients with SBRT. Seventeen of these had OLT allowing for explants tissue analysis and evaluation. Thirty-seven percent had complete or partial response on imaging, and 93% were stable or had at least partial response. Of 22 pathologically evaluated lesions, 37% had total or partial response to SBRT. More recently, a group from Texas[34] reported on the long-term outcomes of SBRT as a bridge to transplantation with a median follow-up of 62 months from the time of SBRT. Ten patients with 11 HCCs were treated and transplanted. All 10 are alive and free of disease with a 5-year overall survival and disease free survival of 100%. Surgical candidates who fail, or are unsuitable for other treatments, and have a high risk of for disease progression, which would lead to being delisted, could be well served with SBRT as a bridge to transplant.

Conclusion

In summary, small HCC tumors appear to be good candidates for SBRT, though larger (over 1000 cc) tumors have been successfully treated as well.[19,29,30] Risk adaptation and individualization must be used to avoid serious toxicities seen in early treatments. Table 1 shows 7 recent studies, with at least 15 patients, having excellent outcomes for HCC. With one exception, Grade 3 or higher toxicities were 15% or less. The most recent 6 studies have a minimum 2-year survival of over 50% with an average 2-year survival of 75%. Three-year survival is as high as 70% for the CP-A subset of patients.[24,25] Due to the variability of utilization of SBRT in the course of HCC treatment at centers, overall survival from the conclusion of radiation is not always the ideal metric to judge the success of the treatment. Normal tissues will limit doses that can be safely delivered. Treatment beam modulation and image-guidance technologies, which can reduce PTV will aid in successful HCC treatment and OAR avoidance. With the development of modern sophisticated radiotherapy machines, increasing use of SBRT for HCC is expected. Combination therapies are expected to be of additional help. These results provide a strong argument for randomly controlled phase I/II trials.[35] An NCI funded, phase III trial RTOG 1112: Sorafenib versus SBRT followed by Sorafenib, whose goal is to determine if SBRT can help extend HCC survival especially for later stage disease,[14,35] opened in January 2013. Treatments with some of the latest radiosurgery devices now allow for precise delivery of the high doses required by SBRT with beam-on times of under 5 minutes as described in the paper by Mancosu.[36]

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Expediting the treatment planning process

Cristen Bolan, MS

Radiation treatments today can be delivered in a matter of minutes, yet treatment planning continues to be the cog in the wheel slowing down therapy. Within the last year, however, new developments in treatment planning solutions, such as autocontouring and predictive modeling, are streamlining the more time-consuming steps to expedite the overall process.

Key challenges

There are two key challenges in treatment planning—speed and accuracy.

It can take several hours to precisely contour and calculate a dose plan for complicated cases.

"Speed of treatment planning is currently a problem and even the best dosimetrists have a problem with consistency. Historically, treatment planning has been really more of an art than a science; dosimetrists need years of planning experience to gain an intuition of what is possible to provide to individual patients in terms of delivered doses," said Sasha Mutic, PhD, director, Clinical Medical Physics, professor, Radiation Oncology, Mallinckrodt Institute of Radiology at Washington University School of Medicine, St. Louis, MO.

Although dosimetrists strive to optimize the dose plan while minimizing damage to surrounding structures, unknowingly, they may fall short of reaching this goal.

"Commonly, planners try different parameter values to drive the optimizer in the direction they want, and stop when they feel they have done as well as they could. Some plans approach the 'optimal frontier,' but many approved plans are far from optimal," said Kevin L. Moore, PhD, DABR, Assistant Professor, Department of Radiation Oncology, University of California, San Diego, CA. "When you don't know what the absolute best plan is for the patient, you can waste a lot of time, or stop before you've spared the organs at risk as much as possible."

Because contouring variability is a major source of uncertainty in radiotherapy treatment planning, it has become a focus of research, with emphasis on both planning target volumes (PTV) and organs at risk (OAR) for many anatomical sites.[1-5]

Recently, a number of innovations in treatment planning technology have provided new approaches to overcoming obstacles related to speed and accuracy, with the potential to advance the science by leaps and bounds.

Making trade-offs

In radiation therapy, clinicians have to make trade offs between target coverage and organ sparing, and between speed and accuracy.

Speed is often sacrificed for accuracy. Depending on the complexity of the anatomical site being treated, planning for intensity-modulated radiation therapy (IMRT) can range from a couple of hours to a couple of days, says Michele Verst, MS, chief medical physicist, Union Hospital's HUX Cancer Center, Terre Haute, IN.

"There are two challenges in the treatment planning process that go hand in hand—one is developing the most accurate plan from a dosimetric standpoint as far as dose calculation and how it affects what's truly being delivered to the patient," said Dr. Verst.

A significant advancement in accuracy came with the implementation of Monte Carlo calculations into a planning system. "The Monte Carlo algorithm at this point is the most accurate way to predict how the dose is being delivered inside the patient," indicated

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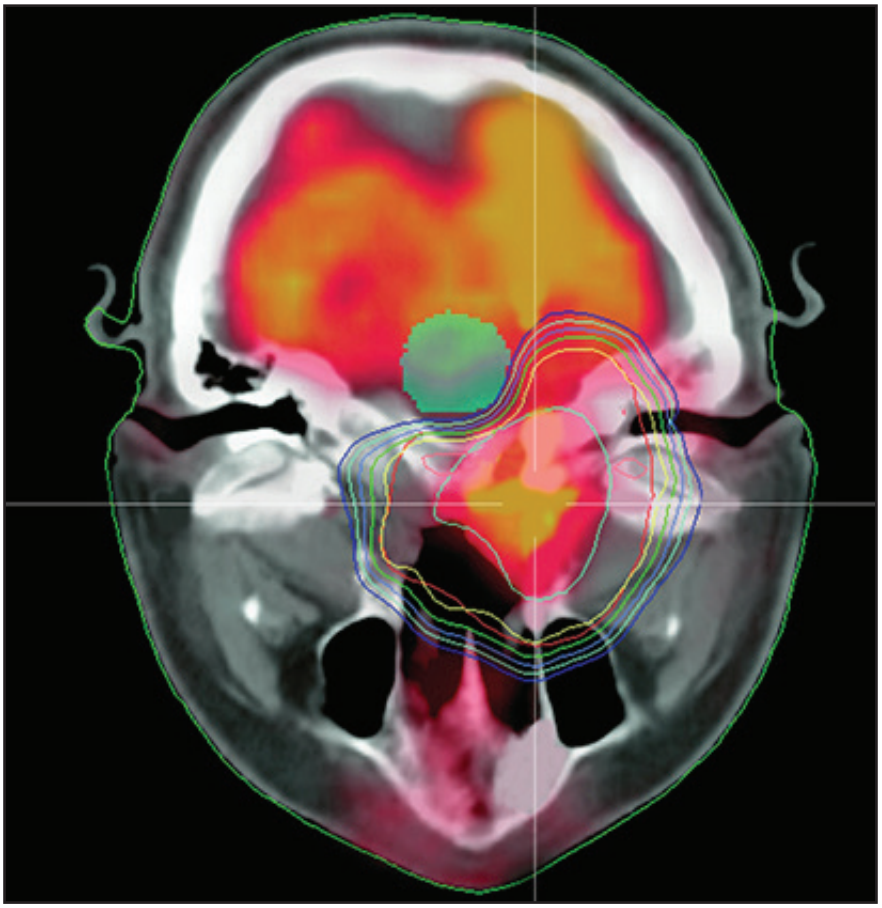

FIGURE 1. *A blended CT and PET image, showing a cross section of the head in the nasal cavity area. This image was co-registered using Eclipse™ treatment planning software. The white cross hairs come together at the tumor site. The lines around the tumor are part of an IMRT treatment plan, and show that the highest radiation dose is being in concentrated right in the tumor, with the dose falling off rapidly as you move away from the tumor. This plan was designed for maximum preservation of the brain stem, which in this case is avoided altogether.*

Dr. Verst. "As a trade off, to get that accuracy, it requires a lot of time. It is very time consuming to make those calculations with that type of precision."

The HUX Cancer Center is a pilot site for the recently FDA 510(k)-cleared version Monaco 5 treatment planning system by ELEKTA. As a pilot site, Dr. Verst compared the legacy system to the new version of Monaco. "We can do the same or better quality plan with Monaco in just 2 to 3 iterations compared to 8 or 10 iterations," she said. "What Monaco has been able to do is merge the best of both worlds. It solves two different challenges: one is getting an accurate view of what's going on inside the patient, and two, giving you a good plan within a reasonable amount of time."

Monaco 5 supports a full spectrum of radiotherapy techniques, including volumetric-modulated arc therapy (VMAT), IMRT, and 3-dimentional (3D) conformal radiation therapy. It also is equipped for stereotactic radiosurgery (SRS) and stereotactic radiotherapy (SRT).

"The software has gone from using standard constraints for your prescription or your dose limitations for your OARs toward more of a biological model with Monaco. For example, the serial and parallel functions are combined along with some other maximum constraints to give you the flexibility to use how the structures function physiologically," indicated Dr. Verst. "You can set it so the maximum part of the structure can get no more than 2400 cGy. But we can say a third of the liver can get a certain amount of dose, while the remaining two-thirds gets another dose. It helps you to tailor the plan specific to the site, allowing you to do dose painting on your target volume."

Additionally, the Segment Shape Optimization feature on Monaco generates an 'ideal plan' with the dose and constraints the user selects. "It allows you to use the strengths of a particular linac to give you the best possible option for delivering the ideal plan that you would like to give. That's one really nice tool," said Dr. Verst.

Optimized contouring

Contouring is a labor-intensive and time-consuming step in the treatment planning process and tends to be highly variable. Some of the quality control tools include RTOG contouring protocols, which are based on a consensus reached among cooperative groups and disease site committees, and are designed to provide treatment guidelines that include quality criteria for a specific type of treatment.

Another quality control measure is computer-assisted auto-contouring algorithms, such as automated atlas-based segmentation. These assist the dosimetrist in overcoming the limitations of manual contouring.[6] Auto-contouring is a well-established technology in treatment planning systems. The Pinnacle$_3$ treatment planning system by Philips Healthcare saves planning time and improves consistency by automating the contouring process. In its latest iteration, Pinnacle$_3$ 9.6, the Dynamic Planning feature provides a fast assessment

to determine the need to re-plan and dynamically tracks the impact of patient changes to treatment plans. The fullAccess feature accelerates the plan review by providing the ability to review and annotate images or plans remotely.

Predictive models

Taking a step beyond autocontouring is knowledge-based treated planning. These algorithms contour anatomical images by using a mathematical model that predicts dose-volume histograms (DVHs) from a patient's anatomy. This predictive model helps determine what the DVHs for each organ of interest should look like.

"Our approach is designed to make use of a database of treatment plans for previously treated patients. Using mathematical techniques, you can analyze IMRT dose distributions designed for patients, and correlate the different dose distributions to the differences in patient anatomy. Ultimately, this work helps you develop a mathematical model that predicts DVHs from a patient's anatomy," explained Dr. Moore, who worked on developing this model while at Mallinckrodt Institute of Radiology.

"Up to this point, there has never been a quantitative way to predict what the DVH should look like in a particular patient treatment based on past data from optimized treatment plans," said Dr. Moore. "It determines, for example, if the current patient has a large target or small OAR, and what the new plan DVHs should look like. As targets or organs grow or shrink, the model can predict how the DVHs change in response. If the OAR moves away from the target, the model will predict that the amount of dose reaching the organ will diminish."

According to Dr. Moore, what contributes to variability in IMRT treatment plan quality is human error, such as estimating the DVH or omission of important data. The predictive model automates the process to make it more reproducible.

The clinical implications could dramatically reduce side-effects, indicates Dr. Mutic, who worked with Dr. Moore on the development of the knowledge-based treated planning solution.

"Predictive models will eliminate variability and help standardize the outcomes and complications across facilities," said Dr. Mutic. "Currently, patients are not being treated the same or delivered the same amount of dose. Ensuring patients receive consistent dose will drive the quality of treatments that will lead to more consistent outcomes."

A case in point is the treatment of head-and-neck cancer, for which there could be dramatic improvements in parotid gland sparing. "There is a very wide gulf between the doses that are called for in treating head-and-neck tumors, versus the doses that the parotid gland can tolerate. Researchers have observed a huge amount of variability from patient to patient in terms of how well dose to the parotid glands was effectively minimized,[7]" said Dr. Moore.

"When we compared plans created with and without the use of a predictive tool, the differences between them were incredibly dramatic. We saw much less variability plan to plan after we had the predictive model, and the average deviations from the predictions were much smaller. The number of patients whose planned doses exceeded tolerance levels was categorically reduced," he said.

The key connecting step with the predictive model is that the data with the predictions is automatically input directly into an IMRT optimizer that is designed to make use of them.

"Instead of having humans punch in numbers based on the average patient or a clinician's intuition, they can work with precise expected values and use them to guide the optimization," said Dr. Moore.

For the patient, reduced variability among treatment plans means less damage from dose distributed to surrounding healthy structures.

Similarly, Varian Medical Systems (Varian) offers a knowledge-based solution that uses predictive modeling for treatment plans. Varian has recently received FDA 510(k) clearance for its RapidPlan software, which is designed to provide standard-of-care models to use as a baseline for developing new IMRT treatment plans. Clinicians can select their best treatment plans to include in a training set that can be used to create new and improved practice models in the future. In doing so, sites can customize RapidPlan to reflect their own practices. The models can also be shared among colleagues within a care network to create a practice standard.

RapidPlan is a comprehensive tool within Varian's Eclipse treatment planning system that may be used to plan external beam radiotherapy, including intensity-modulated radiotherapy (IMRT), image-guided radiotherapy (IGRT), RapidArc radiotherapy, stereotactic body radiotherapy (SBRT), and stereotactic ablative radiotherapy (SABR) (Figure 1). The solution is integrated with Varian's Eclipse treatment planning software.

Flatten the learning curve

Key to knowledge-based technology is that it is a learning system that will allow inter-institutional collaboration and benchmarking.

"Clinics will be able to 'train' their own models. The technology gives local institutions the power to develop their own stereotactic liver radiotherapy model, for example. The automated planning component of it will be based on exactly what clinicians want to do at a local institution," explained Dr. Moore.

RapidPlan is also a learning system. Clinicians can take their best treatment plans and add them to the system for use in creating new, improved practice models for the future. The models can be

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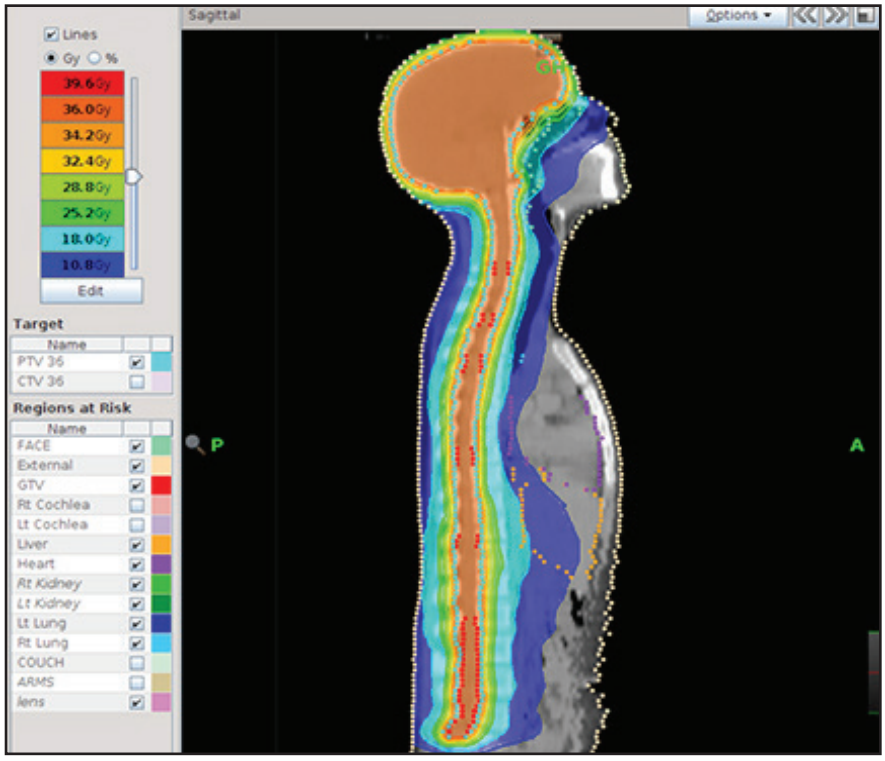

FIGURE 2. *Craniospinal plan developed on TomoTherapy VoLO treatment planning system.*

shared among colleagues within a care network to create a practice standard.

Collaboration among institutions will be greatly facilitated with a knowledge-based solution so widely available. Users will be able to share data without needing approval from the Institutional Review Board or expending valuable time planning benchmark cases.

"Institutions can base models on the RTOG protocols, or share them with others," Dr. Moore said. "You have a means to compare your output to other institutions or gold standard datasets, for example, coming out of a national clinical trial or a large academic institution that provides its own models. Everyone can make use of that—you flatten out the learning curve."

The sharing of data helps clinicians become familiar with newer techniques. Dr. Moore points out that many radiation oncologists are reluctant to move into linear accelerator-based SRS, for example, because the constraints and fractionations are unfamiliar. "This could be a technology that allows them to immediately benchmark their first 10 plans against exemplary work done at established academic institutions," he noted. "There is tremendous potential in terms of what this technology could do for the field in terms of sharing data."

Leveling the playing field

When making the choice, most clinicians would put accuracy before speed. Historically, TomoTherapy's TPS has been considered one of the most conformal treatment planning systems. A recent study found the overall treatment plan quality using TomoTherapy was better than the other TPS technology combinations.[8] Yet it was not faster when compared to Varian's Eclipse, ELEKTA's Monaco or Pinnacle[3] by Philips Healthcare.

Recently, however, the TomoTherapy system got an overhaul that has given it an edge not just in accuracy but also in speed. In October of 2012, Accuray Inc. launched its new TomoTherapy H Series, including the TomoHDA System, designed with faster planning, faster delivery, and increased quality. Some of the key features of the TomoHDA system include TomoEDGE Dynamic Jaws technology, designed to provide added flexibility in treatment delivery by sharpening dose fall off and accuracy. TomoEDGE Dynamic Jaws technology combined with VoLO Planning, a graphics processing unit (GPU)-based treatment planning solution, enables high-speed parallel processing for both dose calculation and optimization (Figure 2). VoLO leverages advanced graphics processing technology and a new calculation algorithm to significantly reduce treatment-planning times and add flexibility in developing even the most complex radiation therapy plans.

The Tulsa Cancer Institute, a large site that treats anal, rectal and gynecological diseases, as well as lung, brain, head and neck and the spine, has 2 TomoTherapy units on site. According to Matthew West, PhD, chief physicist at the Tulsa Cancer Institute, efficiencies are gained in the overall workflow.

"When you look at the efficiencies, the system is very simple. Unlike a conventional accelerator, there are no ancillary components or special modes for special types of treatments, so whether you're planning a prostate, a brain, breast or stereotactic case, you plan it and treat them the same. So the efficiencies come in terms of ease of workflow and safety," said Dr. West. "The treatment data isn't transferred from one computer to another, but is verified by physics prior to treatment. Ultimately, this attention to patient setup and image guidance allows clinicians to reduce treatment margins and minimize dose to critical structures."

The introduction of the VoLO treatment planning system has significantly accelerated the overall process. "The

VoLO part has sped up the time it takes to turn around a treatment plan. Previously, on the older system without VoLO, it could take between 30 minutes and up to 4 hours depending on how complicated it is. Now, on the system with VoLO, it only takes 2 minutes before we start planning," indicated Dr. West.

Similarly at Cancer Healthcare Associates in Miami, FL, Martin Keisch, MD, president and medical director, appreciates how VoLO cuts time-consuming steps in the process, such as record and verify.

"What appealed to me about TomoTherapy is the treatment planning system and the treatment delivery software is on a unified platform. So you don't have the record and verify software between the treatment planning system and treatment delivery, and the process is shortened by an hour or 2," said Dr. Keisch. "Once I complete the plan, the second I close out, the plan is already on the treatment workstation and ready to pull up."

A critical step in treatment planning is meeting predefined goals and establishing an end point. As Keisch explains, the speed with which VoLO meets initial set goals can be as fast as 5 to 10 minutes. This allows for additional time to continue setting more stringent criteria, such as lower dose to critical structures, or evening out doses distributed to the tumor or the target.

Another step that VoLO eliminates is predetermining an angle for the TomoTherapy system because it looks at all angles continuously. "That intermediate step no longer exists, and that's what really makes it fly," said Keisch.

The VoLO TPS provides a protocol library that allows users to customize and adjust anatomical structures, in addition to a library of constraints for the normal tissues and library of goals for the target volumes.

"When you load the plans it prompts you to pull in all of those criteria, plus the jaw size, the pitch, and the fineness of dose calculation matrix," indicated Keisch. "Now for a prostate, I can literally get a good plan in 5 minutes of calculation time. With the head and neck, I can get a good calculation in 10 minutes."

Patients treated on TomoTherapy often receive a boost on Accuray's CyberKnife Robotic Radiosurgery System, a noninvasive alternative to surgery for the treatment of both cancerous and noncancerous tumors. CyberKnife's Multiplan treatment planning solution will soon support integrating treatment plans across the 2 platforms.

"You will be able to import plans from TomoTherapy into Cyberknife and adjust the plans to do a boost on Cyberknife. It is common to boost a tumor to a higher dose to treat lymph nodes," explained Scott MacDonald, medical dosimetrist, Accuray Inc.

"You can also create a contouring library in the Templates feature on the existing Multiplan system. There is also the Sequential Optimization algorithm, which is based on RTOG recommendations and automatically calculates how to avoid critical structures," added MacDonald.

While treatment plan integration has not yet been released, CyberKnife's Multiplan currently includes AutoSegmentation, which automatically generates contours for intracranial and male pelvic anatomy using both model-based and atlas-based delineation methods.

"Autosegmenting for most commonly used applications helps speed up throughput," said MacDonald. "It gives you flexibility on complex plans by autocontouring multiple objects—10 contours within a few minutes."

On the current Multiplan platform, the QuickPlan feature automates the entire planning process, including setting planning parameters and dose calculations. While Sequential Optimization develops tailored treatment plans specific to clinical objectives for each patient, the system also uses Monte Carlo Dose Calculation, often considered the gold standard for dose calculation, to rapidly develop plans. Finally, the 4D treatment optimization tool takes into account the movement of the target and the movement and deformation of the surrounding healthy tissue and critical structures.

Art to science

In striking a balance between optimizing dose and limiting side effects, dosimetrists have historically relied in part on intuition. Yet, as new technologies continue to streamline treatment planning, the process is becoming less of an art and more of a science.

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Hemangiopericytoma of the intra- and suprasellar regions

Luis Moreno Sánchez, MD, Frankie Viñals, MD, Enrique Mendoza, MD, Nathalie González Cazaño, MD, and Mario Ruiz MD,

CASE SUMMARY

A 72-year-old woman with a one-month history of blurred vision, diplopia, left ptosis, dizziness and limited walking ability was referred by her neurosurgeon to the Radiation Oncology-Radiosurgery Department of Clínica Abreu. A cranial magnetic resonance imaging (MRI) scan revealed a sellar mass, and the patient underwent a right frontal craniotomy in July 2007. The surgical pathology revealed an intra- and suprasellar hemangiopericytoma.

One year later, the patient underwent a second right frontal craniotomy because of local recurrence. Posteriorly, the patient received adjuvant 3-dimensional radiotherapy, receiving a total dose of 50.4 Gy with conventional fractionation of 1.8 Gy/day, using photons of 18 Mv. Approximately 3 years later, a follow-up cranial MRI reported a proliferative sellar process with extension to the suprasellar region, the left cavernous sinus, and the sphenoid sinus, measuring 27 mm × 25 mm.

Prepared by ***Dr. Moreno, Dr. Viñals, Dr. Mendoza, Dr. González****, and* ***Dr. Ruiz*** *while at the Clinica Abreu, Department of Oncology-Radiosurgery, Santo Domingo, Dominican Republic*

An MRI scan of the brain in August 2011 revealed the same proliferative sellar lesion, measuring 34 mm × 26 mm × 39 mm, with suprasellar extension, obliterating the suprachiasmatic cistern, exerting discrete mass effect on the optic chiasm and gently contacting the left rectus gyrus, as well as invading the left cavernous sinus, sphenoid sinus, and clivus, and obliterating the prepontine cistern. A CT angiography performed at this time showed left carotid compromise surrounded by the lesion.

The patient underwent a third surgery, but this time with a transnasal approach. A postsurgical MRI scan showed an intra- and suprasellar expansive lesion with slight increase of volume in the described lesion, compared with previous studies (Figure 1). Before treatment planning, visual campimetry revealed a bilateral hemianopsia. After immobilizing the patient with a thermoplastic Byte Block mask, we performed brain MRI and CT scans with and without contrast, with subsequent image fusion and planning in the Helios Eclipse® system.

The patient underwent stereotactic radiosurgery in a Clinac 21 iX linear accelerator (Varian), setting the target with one isocenter and 9 fields, with 27 Gy prescribed in 5 sessions with a dose-per-fraction of 5.4 Gy/day. This was radiobiologically equivalent to one treatment session at 16 Gy using an α / β of 10 (Figure 2). The patient tolerated the treatment without complications, and 3 months' post-treatment demonstrated significant improvement on her left eyelid movement. At 6 months, an MRI scan showed appreciable tumor volume decrease compared with previous studies; at 1 year post-treatment, a cranial MRI demonstrated a 70% decrease in tumor volume compared to pretreatment lesion volume (Figure 3). At 14 months, our patient completely recovered her left eyelid mobility and experienced significant improvement in visual acuity and stability of walking ability.

DIAGNOSIS

Hemangiopericytoma of the intra- and suprasellar regions

DISCUSSION

Hemangiopericytoma (HPC) is a rare vascular tumor that arises from the

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Table 1. Chronological history of the case

Date	Event
July 2007	1st surgery (right frontal craniotomy)
July 2008	2nd surgery (local recurrence)
November 2008	3D radiation therapies (pituitary) 50.4 Gy
January 2011	2 local recurrences
October 2011	3 surgeries (transnasal approach)
January 2012	Stereotactic radiosurgery: 27 Gy in 5 fractions ≈16 Gy in 1 fraction
March 2013	14 months follow up, significant decrease in tumor volume (>70%), clinical improvement, free of disease progression.

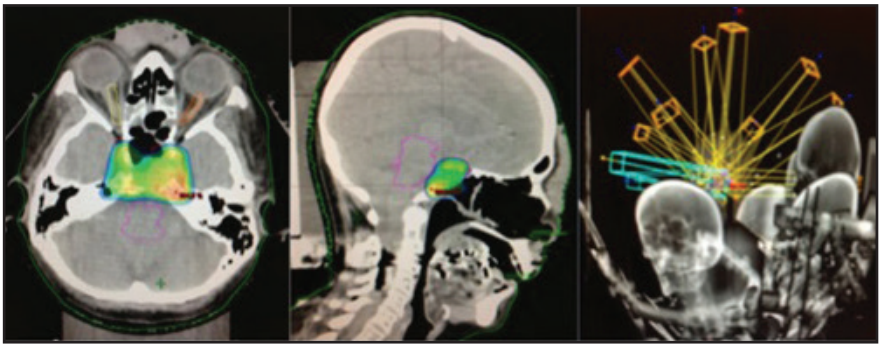

FIGURE 1. *Cranial MRI before stereotactic radiosurgery.*

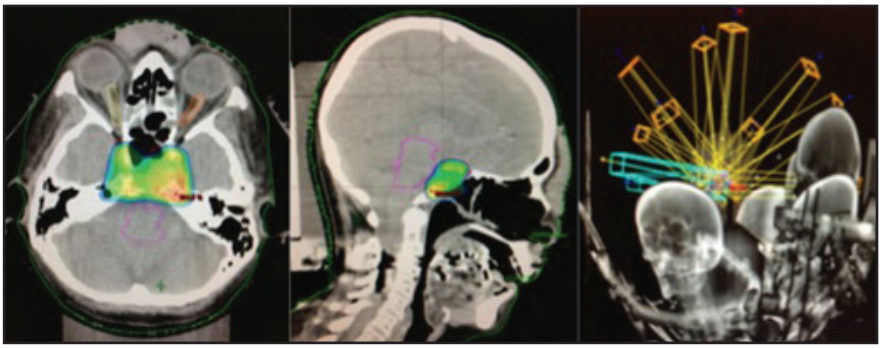

FIGURE 2. *Stereotactic radiosurgery planning.*

pericytes of Zimmerman, is associated with the capillary walls, and can appear anywhere in the body. HPC's appearance in the central nervous system (CNS) is rare, accounting for only 0.4% of primary CNS tumors; only about 137 cases are reported in the literature. Hemangiopericytomas of the sellar and parasellar regions are extremely rare and represent only 1% of all primary intracranial hemangiopericytomas, with only 6 cases reported worldwide. Although initially it was believed that HPC was a variant of meningioma (angioblastic meningioma) it has been recognized as a distinct entity with different clinical, immunohistochemical and ultrastructural characteristics.

Historically, hemangiopericytomas have been wrongfully grouped with other neoplasms. In 1938, Cushing and Eisenhard rated the HPC as one of 3 variants of angioblastic meningioma. In 1942, Stout and Murray first described hemangiopericytoma as a malignant, separated neoplasm of capillary pericytes

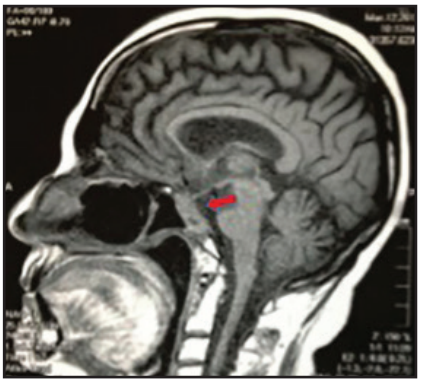

FIGURE 3. *Cranial MRI after stereotactic radiosurgery.*

with different pathologic features, and Begg and Garret in 1954 reported the first case of intracranial HPC.

It is well known and accepted that hemangiopericytomas and meningiomas originate from multipotential precursor cells, the difference being that hemangiopericytomas originate from pericytes, not from arachnoid cells. Ultrastructurally, the presence of a basement membrane and the absence of desmosomal attachments distinguish hemangiopericytomas from meningiomas, so definitive diagnosis is based on histopathological, ultrastructural, and immunohistochemical differences.[4,6] Meningiomas have tumor markers such as keratin and epithelial membrane antigen, whereas hemangiopericytomas, being of mesodermal origin, do not.[6]

The term "meningeal hemangiopericytoma" is commonly used because most hemangiopericytomas arise from the meninges (where pericytes also exist), but they may also occur in the brain parenchyma in a pure form, without the meningeal component. HPC is usually seen in adults, and compared with meningioma, it occurs more often in young men (mean age at diagnosis is 43 years), exhibits faster growth and tends to recur and metastasize, commonly outside the CNS in such areas as the bone, liver and lung. Recurrence depends on the extent of resection, tumor volume, and histopathological aggressiveness.[6]

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In the literature, recurrence rates at 5, 10, and 15 years are 65%, 76%, and 87%, respectively, with an overall survival rate of approximately 43% at 15 years.[1,5,12] Hemangiopericytomas located in the sellar, suprasellar, and parasellar regions are extremely rare; only 6 cases are reported in the literature.[4,12] They can mimic pituitary adenomas, with similar symptoms. In all reported cases patients have shown decreased visual acuity; 4 were diagnosed with bilateral hemianopsia, as was our patient.

Although hemangiopericytomas are more common in men, sellar lesions are more common in women.[4,12] These neoplasms usually present as discrete masses, but they may invade adjacent structures, such as in our case, where the lesion extended into the left cavernous sinus, sphenoid sinus, clivus, and even the left carotid artery. Indeed, the biologically aggressive behavior of these tumors is another factor that can limit treatment.

Radiation therapy is used in almost all intracranial hemangiopericytomas, especially unresectable hemangiopericytomas. Ecker and colleagues reported 38 HPCs treated with RT with or without SRS and concluded that SRS in recurrent disease contributed to improved survival.[1,10] In 1993, Coffey and colleagues published the first preliminary report of SRS for HPC, with a total of 11 lesions treated in 5 patients who had undergone previous surgical resection. Of the 11 tumors, 9 shrank or remained stable at an average of 14.8 months.[1] In a recent series of 20 patients, a higher dose of 14 Gy was significantly associated with improved progression-free survival (average of 79.4 months at dose >14 Gy vs. 45.2 months at dose <14 Gy).[1]

At this writing, our patient is experiencing progression-free survival of 14 months and showing no evidence of extracranial metastases

CONCLUSION

Hemangiopericytoma is an aggressive vascular tumor that tends to recur and metastasize, even after total resection.They are extremenly rare in the sellar and parasellar regions and they can often mimic pituitary adenomas.

Postoperative radiotherapy is mandatory, even when complete tumor removal is achieved, especially when the tumor extends to adjacent structures, significantly reducing local recurrence. Stereotactic radiosurgery is of great value for recurrences in the central nervous system, even in previously irradiated patients or after tumor multiple resections.

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