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GUEST EDITORIAL

What's Wrong with Dr. Oz?
by Steven J. Dell, MD 332

Televised Medical Talk Shows: What They Recommend and the Evidence to Support Their Recommendations 334

MEDICAL | LEGAL



Tax Resolution and Bankruptcy for Professionals
by Raymond S. Kreienkamp & Stefanie A. Ravenhill 337



To Roth or Not to Roth, That is the Question
by Michael T. Carpenter, JD & Robert L. Hehmeyer, JD 340

PRESIDENT'S FORUM

Protecting Our Profession Through Telemedicine
by **John O. Stanley, MD** 344

Washington University in St. Louis School of Medicine

DEAN'S REPORT

Discoveries the Forefront of BioMedical Research
by **Larry J. Shapiro, MD** 351

SITEMAN CANCER CENTER

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SCIENCE OF MEDICINE WASHINGTON UNIVERSITY RADIATION ONCOLOGY

New Developments in Radiation Oncology
by Jeff M. Michalski, MD, MBA 354

Proton Therapy:p An Update on the S. Lee Kling Proton Therapy Center at Barnes-Jewish Hospital and Washington University
by Jeffrey Bradley, MD, FACR, Beth Bottani, CMD & Eric Klein, PhD 355

World's First Application of MR-Guidance for Radiotherapy
by Jeffrey Olsen, MD, Olga Green, PhD & Rojano Kashani, PhD 358

Lung Stereotactic Body Radiation Therapy
by Sana Rehman, MD, Michael C. Roach, MD, Jeffrey D. Bradley, MD & Cliff G. Robinson, MD 361

Intracavitary Brachytherapy for Gynecologic Malignancies: Applications and Innovations
by Ashley A. Weiner, MD, PhD & Julie K. Schwarz MD, PhD 366

Imaging Advances in Stereotactic Radiosurgery
by Christina I. Tsien, MD, Robert E. Drzymala, PhD & **Keith Rich, MD** 373

Accelerated Partial Breast Irradiation: A Safe, Effective, and Convenient Early Breast Cancer Treatment Option
by Maria A. Thomas, MD, PhD, Laura L. Ochoa, PhD, Theresa M. Zygmunt, RN, Melissa Matesa, RN, Michael B. Altman, PhD, Jose L. Garcia-Ramirez, MS, Jacqueline Esthappan, PhD & Imran Zoberi, MD 379

ADDITIONAL SCIENTIFIC

The Evolution of Axillary Staging in Breast Cancer
by Roshni Rao MD, FACS 385

Blood Conservation Strategies and Liver Transplantation Transfusion-Free Techniques Derived from Jehovah's Witness Surgical Cohorts
by Mansi Sheth, BS, Sujit Kulkarni, MD, Kiran Dhanireddy, MD, Alexander Perez, Randy Henderson & Rick Selby, MD 389

FROM YOUR ASSOCIATION

Missouri Physicians Share Medical Expertise with the Country of Georgia through A Call to Serve International (ACTS-I)
by **Milamari A. Cunningham, MD, Elizabeth James, MD** & **Ted Groshong, MD**; in collaboration with **Patricia J. Blair, MD** & Giorgi Tsilosani, MD, ACTS Georgia President 346

Missouri Medicine In the News 348
Statement of Ownership 349
Correspondence 350

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What's Wrong With Dr. Oz?

Oscar Zoroaster Phadrig Isaac Norman Henkle Emmanuel Ambroise Diggs* IS the Wizard of Oz

by Steven J. Dell, MD

On April 15, 2015, ten prominent physicians sent a letter to Columbia University calling Doctor Oz's faculty position there unacceptable and citing his "egregious lack of integrity."

I want to introduce you to a physician. After training at some of the country's top institutions, he has risen to the level of full professor and vice chair of his department at an Ivy League university. Triple board certified, he has authored hundreds of peer-reviewed articles and been awarded several patents. He clearly understands the scientific method and the importance of basic science and clinical research. He has dedicated years of his life to the pursuit of scientific truth. His name is Mehmet Oz, MD

Dubbed "America's doctor" by Oprah Winfrey, Oz is well known as the star of his own television show, which provides information on healthy lifestyles. In 2008, *Time* magazine included him on its list of the "100 Most Influential People."[1]

To say that Oz is a controversial figure in medicine is an understatement. He is a tireless promoter of so-called alternative and complementary medicine. In March 2011, Oz excitedly stated on his show that homeopathy could ease people's aches and pains without the use of prescription medication. His guest, Russ Greenfield, MD, explained how homeopathy works, even in extremely dilute concentrations, when not a single molecule of the original drug remains: "The essence of the medication—oh, let's say the spirit of the medication—is imbibed and it sends a message to the body to heal itself."[2] Oz stated, during the same show, that his family uses homeopathic treatments.

In March 2012, on a show titled "Medium vs. Medicine," Oz had as a guest a psychic who claimed she could communicate with the dead. In fact, Oz has devoted several shows to psychics and those who claim to speak to spirits. Describing his own reading from television psychic John Edwards, Oz stated, "Let me tell you, it changed my life!" and "I've learned in my career that there are times when science just hasn't caught up with things, and I think this may be one of them."[3]

During another show, Oz interviewed Dr. Mosaraf Ali, the miracle healer to Sylvester Stallone, Prince Charles of England, and others, regarding his use of iridology. According to this widely debunked, bizarre belief, each part of the iris corresponds to a specific area of the body, and a person's state of health can be diagnosed by examining particular regions of the iris.[4] After expressing his amazement at Dr. Ali's diagnostic abilities, Oz stated, "I want to applaud Doctor Mosaraf Ali because these are ancient traditions and they have been around for centuries so who am I to dismiss them?"[5]

Who? Oz is a trained clinician and scientist, someone who can read a scientific article with a critical eye. He is someone who can filter out the noise of the placebo effect or discern the simple carnival tricks of a charlatan. The problem is that most people in his audience cannot.



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Many believe he is doing great harm by preventing or delaying proper diagnosis, providing false hope, and encouraging people to waste money on useless treatments.

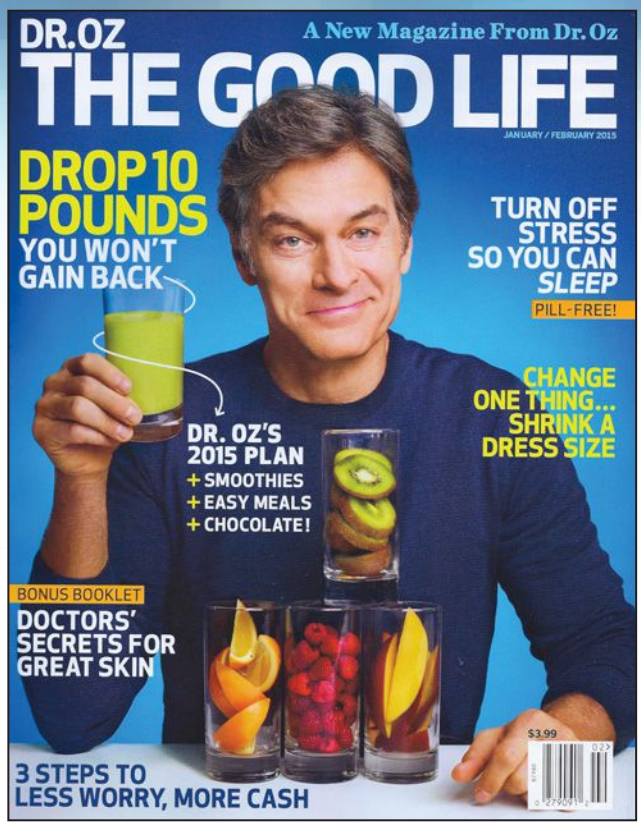
Some observers of this spectacle have had enough. In 2013, *Forbes* magazine published a list of Oz's "Five Wackiest Medical Beliefs."[2]

In an influential 2013 article for *The New Yorker,* Michael Specter asked rhetorically, "Is the most trusted doctor in America doing more harm than good?"[6]

In 2014, a Senate subcommittee grilled Oz regarding his unfounded claims about miraculous dietary supplements.[7] Missouri Senator Claire McCaskill, demonstrating some Show Me State bluntness, scolded Oz: "I don't know why you need to say this stuff, because you know it's not true. Why—when you have this amazing megaphone and this amazing ability to communicate—would you cheapen your show by saying things like that?"[7] On April 15, 2015, ten prominent physicians sent a letter to Columbia University calling Oz's faculty position there unacceptable and citing his "egregious lack of integrity."[8]

Although the scientific community has turned against Oz, the unfortunate reality is that he is perceived as a scientific authority by millions of people who receive their relationship advice from Dr. Phil and, presumably, their time-travelling advice from Dr. Who.

Simply put, Oz is an entertainer. Many believe he is doing great harm by preventing or delaying proper diagnosis, providing false hope, and encouraging people to waste money on useless treatments. As far as I am concerned, the wackier he gets, the easier it is to logically debunk his claims.



Hearst Magazines introduced the bi-monthly Dr. Oz The Good Life in January 2014.
Source: Hearst Magazines

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*Editor's Note

Oscar Zoroaster Phadrig Isaac Norman Henkle Emmannuel Ambroise Diggs is the full name of "The Wizard of Oz" or "The Great and Powerful Oz" from the fictional novel by L. Frank Baum. **MM**

Televised Medical Talk Shows: What They Recommend and the Evidence to Support Their Recommendations

A Prospective Observational Study

Source: BMJ 2014; 349 doi: http://dx.doi.org/10.1136/bmj.g7346 (Published 17 December 2014) Cite this as: BMJ 2014;349:g7346
Read full study at http://www.bmj.com/content/349/bmj.g7346.full.pdf+html

Abstract

Objective

To determine the quality of health recommendations and claims made on popular medical talk shows.

Design

Prospective observational study.

Setting

Mainstream television media.

Sources

Internationally syndicated medical television talk shows that air daily (The Dr Oz Show and The Doctors).

Interventions

Investigators randomly selected 40 episodes of each of The Dr Oz Show and The Doctors from early 2013 and identified and evaluated all recommendations made on each program. A group of experienced evidence reviewers independently searched for, and evaluated as a team, evidence to support 80 randomly selected recommendations from each show.

Main Outcomes Measures

Percentage of recommendations that are supported by evidence as determined by a team of experienced evidence reviewers. Secondary outcomes included topics discussed, the number of recommendations made on the shows, and the types and details of recommendations that were made.

Results

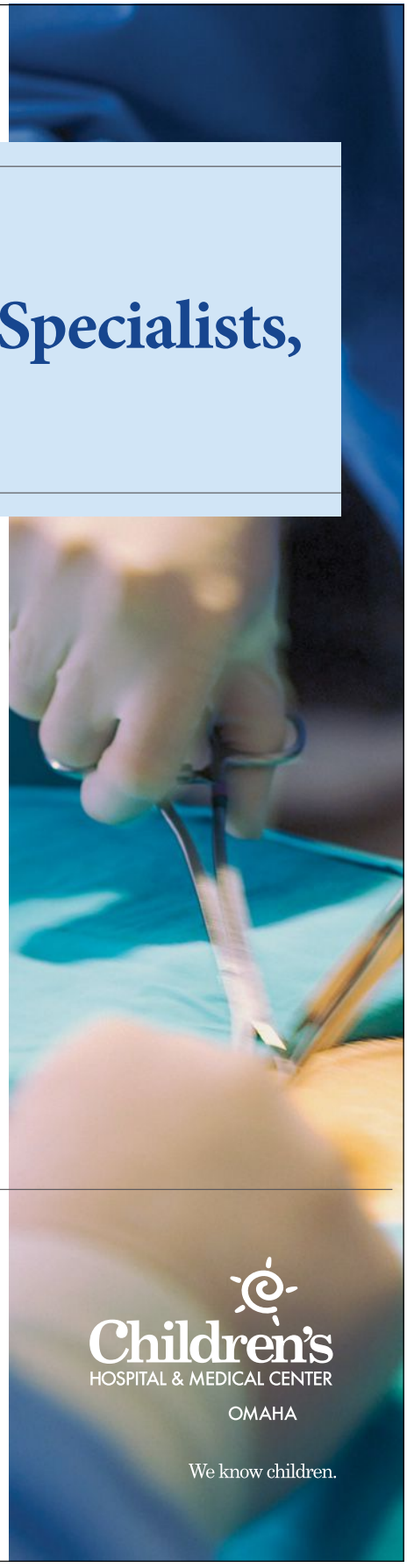
We could find at least a case study or better evidence to support 54% (95% confidence interval 47% to 62%) of the 160 recommendations (80 from each show). For recommendations in The Dr Oz Show, evidence supported 46%, contradicted 15%, and was not found for 39%. For recommendations in The Doctors, evidence supported 63%, contradicted 14%, and was not found for 24%. Believable or somewhat believable evidence supported 33% of the recommendations on The Dr Oz Show and 53% on The Doctors. On average, The Dr Oz Show had 12 recommendations per episode and The Doctors 11. The most common recommendation category on The Dr Oz Show was dietary advice (39%) and on The Doctors was to consult a healthcare provider (18%). A specific benefit was described for 43% and 41% of the recommendations made on the shows respectively. The magnitude of benefit was described for 17% of the recommendations on The Dr Oz Show and 11% on The Doctors. Disclosure of potential conflicts of interest accompanied 0.4% of recommendations.

Conclusions

Recommendations made on medical talk shows often lack adequate information on specific benefits or the magnitude of the effects of these benefits. Approximately half of the recommendations have either no evidence or are contradicted by the best available evidence. Potential conflicts of interest are rarely addressed. The public should be skeptical about recommendations made on medical talk shows.

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Tax Resolution and Bankruptcy for Professionals

by Raymond S. Kreienkamp & Stefanie A. Ravenhill

Introduction

Shrinking insurance reimbursements, changing regulations, and the rising costs of practice are forcing more and more physicians into financial difficulties.[1] Adding to the issues of decreasing revenues and increasing costs of practice is the necessity of paying off student loan debt. Faced with these pressures, physicians may be tempted to keep their practice afloat and fund practice operations by incurring loans or misusing funds designated for payment of tax liabilities. Consequently, physicians' need for tax resolution and bankruptcy protection have become more prevalent in recent years.

Tax Resolution Procedures

Most individuals are subject to both federal and state income taxes. Some individuals may also be subject to a local taxing regime. For example, taxpayers who work or reside in St. Louis or Kansas City are subject to an earnings tax for which they may need to file an earnings tax return and pay the related taxes.

Our tax system works on voluntary compliance. An individual is required to self-report his or her income and related deductions on his or her income tax return. If an individual fails to file an income tax return, the IRS has the authority to file a return on behalf of the individual.[2] Those returns are generally not taxpayer favorable because the government includes on the return the income and gain information reported to the taxpayer and does not include deductions or credits to which the taxpayer may avail himself or herself or use filing positions that may reduce the tax liability.

The laws and regulations enforced by the tax enforcement arm of federal and state governments present numerous procedural hurdles over which one must jump in order to have his or her tax issues resolved. The first step in any dealings with a government tax department is to promptly engage the services of a competent tax professional. The IRS has received increased scrutiny and consequent Congressional pressure in recent years to resolve tax issues more quickly, and reports in the news suggest that the manner in which the IRS may be addressing these issues is not favorable to taxpayers and imposes increased diligence on taxpayers to promptly respond.[3]

The commencement of an audit by a taxing authority generally starts with the receipt of a letter from the government. Taxpayers who receive telephone calls notifying them of tax issues should be aware they are almost certainly receiving a telephone call from a scam artist. The governmental letters typically have short response periods, often 30 days or less. It is imperative to respond within the time period stated to preserve administrative remedies for resolving the issues being raised. Delay only adds to the cost of answering the questioning by the governmental authority and could have serious adverse consequences if the deadline is not met.

At the conclusion of a federal audit, the IRS may propose an adjustment with which the taxpayer does not agree. Taxpayers may attempt to resolve their disagreement with the IRS through the appeals process, which must be specifically requested in writing by taxpayers. "Appeals" is a separate branch of the IRS whose objective is to resolve tax issues between the IRS and taxpayers.[4] If a taxpayer cannot resolve his or her tax issue at Appeals, the taxpayer will then need to use the court system. Determining the court in which to bring one's contest against the IRS requires the analysis and assistance of an attorney experienced in this area of the law.



Sometimes a taxpayer may address his or her failure to file tax returns or timely pay taxes by participating in a voluntary disclosure or tax amnesty program. These programs are more prevalent at the state level than at the federal level. On April 27, 2015, the Missouri governor signed legislation authorizing a state tax amnesty program.[5] The program applies to taxes administered by the Missouri Department of Revenue and only applies to taxpayers who (i) apply for amnesty from September 1, 2015, to November 30, 2015, (ii) file a tax return for each taxable period for which amnesty is requested, and (iii) pay the entire balance of their taxes by November 30, 2015. The amnesty program relieves a taxpayer from having to pay penalties, additions to tax, and interest with respect to unpaid taxes and taxes due.[6] Taxpayers who may qualify for the tax amnesty program should seek the assistance of a knowledgeable tax professional to ensure they comply with the amnesty program requirements.

In addition to individual income tax, some business taxes impose personal liability on an individual. For example, if a medical practice uses taxes withheld from the paychecks of employees to fund the expenses of the medical practice instead of depositing those funds with the taxing authority, the physician may be personally liable for those taxes.[7]

Once the amount of taxes owed to the taxing authority has been determined (whether by agreement of the taxpayer, failure to contest, or court judgment), several payment options exist. Of course, the government's initial position is that full payment of the assessed tax is immediately required. Depending upon the taxpayer's circumstances, a taxpayer may be able to enter into an agreement with the authority to pay the liability in installments or enter into an Offer in Compromise whereby the authority agrees to reduce the amount of taxes owed by the taxpayer in order to make sure that the authority collects at least some taxes.

Finally, it is important to remember that some states, including Missouri, protect property held in the joint names of husband and wife from the creditors of one spouse. However, the United States Supreme Court has held that those laws do not necessarily apply to federal tax liens.[8] Accordingly, taxpayers cannot assume that, because they hold property jointly with their spouse, they will be able to avoid tax collection activities against one of the spouses.

Discharging Tax Debts in Bankruptcy

The goal of bankruptcy is to provide the debtor with a fresh start. The filing of a bankruptcy petition gives rise to an automatic stay, which stops creditors from continuing to try to collect their debts from the debtor.[9] Nevertheless, filing for bankruptcy should not be taken lightly as it can have serious implications for one's finances for many years.[10] Further, not all taxes are dischargeable in bankruptcy. A professional familiar with bankruptcy and taxes should analyze whether the particular taxes with which an individual is struggling ultimately must be paid even if the individual files for bankruptcy.

Several categories of taxes are not dischargeable. First, taxes due within three years before the bankruptcy petition is filed and trust fund taxes (e.g., employment taxes withheld from employees) are not dischargeable.[11] Due to the three year time limit, the appropriate time to file the bankruptcy petition may require professional analysis to make sure the filing is soon enough to protect from creditor collection actions but late enough to avoid having a large tax liability within the previous three years that can't be discharged. Further, tax professionals can advise business owners on techniques to limit personal liability if an employer is able to pay some, but not all, of the employment taxes.

Second, taxes attributable to returns that are not filed and taxes attributable to tax returns that are filed late and within two years before the bankruptcy petition are not dischargeable.[12] These rules are another reason it is extremely important to have a professional analyze the timing of the filing of the bankruptcy petition. If the governmental authority files the return for the taxpayer or the taxpayer files a return after the governmental authority issues a deficiency assessment, courts disagree over whether the tax is dischargeable in bankruptcy. To be certain, a debtor should make sure that he or she has filed all tax returns before considering filing for bankruptcy protection.

Finally, a taxpayer will not be granted a discharge if the taxpayer files a fraudulent return or willfully attempts to evade or defeat the tax.[13] This could include an excessive lifestyle which avoids or prevents earlier payment of an otherwise non-fraudulent tax. In one case, an individual's taxes were not discharged when the IRS submitted evidence that, after the taxpayer incurred significant tax liabilities, he concealed accounts, attended numerous golfing junkets throughout the United States, went on vacations to

Europe and the Caribbean, and spent over $25,000 annually to maintain his country club memberships.[14]

Taxpayers in bankruptcy may owe tax penalties in addition to taxes. Whether a tax penalty is dischargeable depends upon the type of penalty and the tax year to which the penalty applies. For example, one court found that a "failure to file" penalty was dischargeable where the return's due date occurred before the beginning of the three-year period prior to the bankruptcy filing.[15] An individual with significant tax penalties will need a professional to determine the impact of bankruptcy on the dischargeability of those penalties.

Most importantly, however, is that bankruptcy will generally not discharge a liability that is omitted from the schedules that are part of the bankruptcy filing.[16] This limitation applies to taxes as it does to any other liability. It is of utmost importance that the debtor fully discloses all of his or her financial issues to his or her bankruptcy attorney to allow the attorney to provide adequate representation.

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- Ophthalmology
- Optometry
- Oral & Maxillofacial Surgery
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- Otolaryngology
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AA/EOE

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Conclusion: Consult Your Tax Professional

As Albert Einstein is quoted to have said, "The hardest thing in the world to understand is the income tax." Tax issues can be resolved, and sometimes bankruptcy is a tool in that arsenal. Taxpayers need to elicit the early support of knowledgeable tax professionals to avoid losing alternatives for early and efficient resolution of their tax liability.

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MM





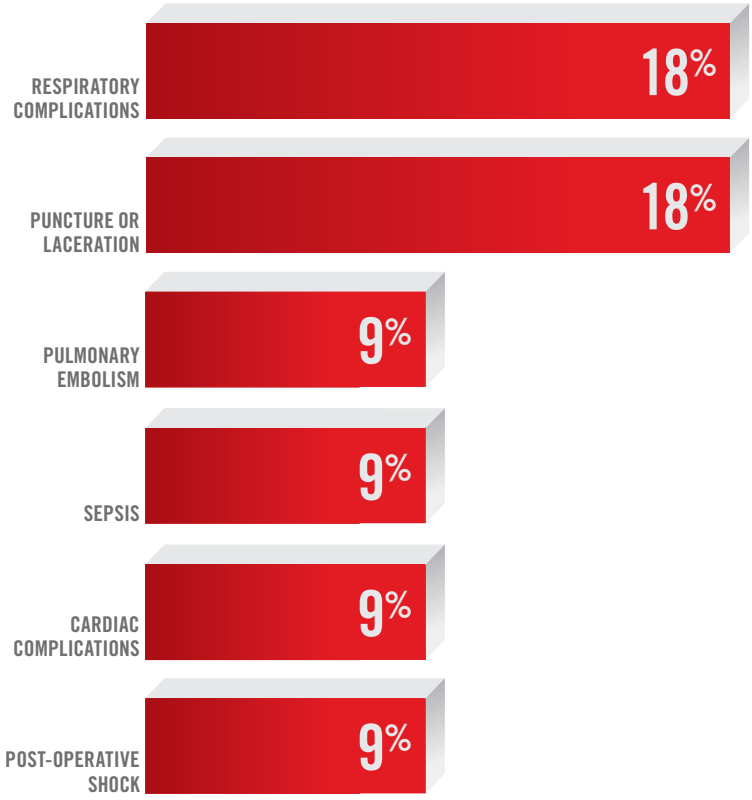
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To Roth or Not to Roth, That is the Question

by Michael T. Carpenter, JD & Robert L. Hehmeyer, JD

Learn some factors to consider and planning ideas for Roth Individual Retirement Accounts



Income tax season is well behind us, and taxpayers are now redirecting their efforts to closing the 2015 tax year. A question often asked by our clients is whether to utilize a Roth Individual Retirement Account (IRA). The answer, as you might expect, is often complex and may differ from person to person. The purpose of this article is to shed some light on the topic of Roth IRAs, and to outline factors that should be considered as you analyze whether a Roth IRA is appropriate for you. Also included are a few planning ideas that may be of benefit.

Background

Individual Retirement Accounts (IRAs) have been around since the mid-1970s. Traditional IRAs came to life as part of The Employee Retirement Income Security Act of 1974 (ERISA), and were designed to promote a tax-advantaged way for Americans to save for their retirement years. At a basic level, the benefit was that a taxpayer would be able to deduct his or her IRA contribution on the current year tax return, with the money inside the account growing tax-deferred over his or her lifetime. Federal and state taxes would not be due until the funds were withdrawn from the account, generally at retirement.





Michael T. Carpenter, JD, CPA, CFP®, and Robert L. Hehmeyer, JD, CFP®, are Moneta Group Professional Consultants, Family Planner CFOs.
Visit: www.monetagroup.com Contact: mcarpenter@monetagroup.com

Utilizing Roth IRAs presents a tremendous opportunity to transfer wealth to future generations in a tax-efficient manner.

As part of the Taxpayer Relief Act of 1997, Senator William Roth of Delaware added a new wrinkle, introducing the Roth IRA. While there are a number of distinctions between a Traditional IRA and a Roth IRA, two fundamental differences are (1) Roth contributions are made on an "after-tax" basis (no upfront income tax deduction), and (2) withdrawals are typically income tax-free (versus withdrawals from a Traditional IRA which are fully taxable at ordinary income rates).

For 2015, individual taxpayers can make an annual contribution of $5,500 to a Roth IRA ($6,500 for those ages 50 or greater), subject to certain income limitations. Under the current rules, phase-outs for eligibility to make a Roth IRA contribution begin for single individuals when Modified Adjusted Gross Income (MAGI) exceeds $116,000. For joint-filers the limitation begins at $183,000. Once singles reach a MAGI of $131,000 and joint-filers reach $193,000, contributions are completely phased out. (Note that one must have wages or earned income to be eligible to contribute to a Roth IRA, meaning income other than interest, dividends, and capital gains.)

In addition to making annual *contributions* to a Roth IRA, investors can also *convert* their Traditional IRAs to Roth IRAs in order to cause future distributions to be tax-free income. When an individual converts from Traditional to Roth, there typically is a tax liability at the point of conversion since no taxes have been paid on the Traditional account to that point. It's not surprising that Uncle Sam and your state taxing authority want their tax money, so if you are considering conversion, be ready to pay-up! Note, years ago there was an income limitation preventing individuals with higher income from converting Traditional IRA monies to Roth IRAs. However, as of 2010, the Internal Revenue Service (IRS) lifted the income cap restriction relating to *conversions*. Many who were prohibited from even considering such an idea in the past now have the option.

Factors to Consider

Ultimately, the question most individuals ask is, "What's the right answer for me?"

The reality is that there isn't a right or wrong answer. Instead, the goal is to ascertain the *best* answer given the facts and circumstances. In order to find the answer that fits you best, consider the following general guidelines:

- If your age is less than 40, conversion probably makes sense, because there should be enough time over the remainder of your life for compounded investment growth to easily exceed the "cost" of paying the tax now on the converted amount.
- If your age is between 40 and 50, it is not obvious whether conversion makes sense.
- If your age is greater than 50, it likely doesn't make sense to convert because there is not enough time to allow the Roth IRA growth to exceed the tax cost today.
- Notwithstanding the two previous bullets, no matter your age, if you believe you will never need to draw on Roth IRA assets, it likely makes sense to convert – your heirs will be able to then withdraw after your death income tax-free.



As mentioned, an individual should review the specific facts and circumstances of their situation to determine if conversion makes sense. Some of the arguments and considerations that have surfaced in recent conversations with clients include the following:

- How does my current tax rate compare to what I expect it to be in the future?
    - If tax rates increase significantly in the future, money being withdrawn from a Roth IRA won't be impacted (no lifestyle infringement because of an income tax rate increase), whereas Traditional IRA withdrawals will be impacted.
    - If tax rates decrease in the future, not converting may be beneficial. Our experience is that many individuals tend to fall in *lower* tax brackets later in life frequently as a result of increased deductions from medical expenses.
- Roth conversions are not an all-or-nothing proposition – you can do a partial conversion up to the point where you enter the next tax bracket.
- If you are in a low tax bracket, and do not have enough earned income to utilize all of your itemized deductions, a partial conversion may be appropriate.
- Considering a conversion after a severe market drop (like 2008) is prudent since the amount includible in income would be lower. (Wouldn't it be nice to capture any future market recovery in a tax-free manner, not just tax-deferred?)
- Utilizing Roth IRAs (tax-free withdrawals) in conjunction with Traditional IRAs (taxable withdrawals) and personal savings can create "tax diversification."
- Given that Roth IRAs are not subject to the IRS' Required Minimum Distribution (RMD) requirements at age 70 ½ like Traditional IRAs, it's possible that a Roth account can continue to grow tax-free for a much longer period of time.
- Heirs of a Roth IRA, as opposed to a Traditional IRA, receive greater value since they receive tax-free distributions over their lifetimes.
- Roth *contributions* are accessible immediately, both tax and penalty-free. Roth *conversion* amounts are accessible both tax and penalty-free five years after conversion (even if not age 59 ½).
- If you don't qualify for making a Roth contribution today, because your income is too high, you could still make a "non-deductible" IRA contribution, then immediately convert those dollars to Roth (in effect it's like making a Roth IRA contribution even though you're not eligible).
    - Caveat: All Traditional IRA monies (tax-deferred and not tax-deferred) are viewed as one IRA for purposes of calculating the conversion amount includible as income. In other words, an individual cannot "cherry-pick" the non-deductible monies for conversion. For this reason, it is frequently advisable to only convert non-deductible IRA assets if there are no other "deductible" IRA assets in the individual's name.
- Investors who convert to a Roth IRA are able to re-characterize the assets back to a Traditional IRA, effectively allowing the investor to *negate* the conversion. This is useful when circumstances change substantially from the time of conversion.
    - Re-characterization must occur prior to the due date of the tax return for the year the conversion was made (October 15th if extended). This would allow for a "look back" if the converted assets decline substantially in value after conversion.
- Conversion is appropriate for those who have non-IRA assets to pay the tax due on conversion. That is because IRA assets used to pay the tax are subject to the 10% early withdrawal penalty unless the IRA owner is at least 59 ½ when the conversion occurs, or qualifies for an exception to the penalty.

Estate Planning Considerations

Utilizing Roth IRAs presents a tremendous opportunity to transfer wealth to future generations in a tax-efficient manner. This opportunity is particularly attractive for older individuals or those who have accumulated more assets than they anticipate expending during their lifetime. When heirs inherit a Roth IRA, the converted Roth assets could continue to grow tax-free *over the beneficiaries' lives*. Further, while they would be forced to take out some minimal amount each year, the distributions would be income tax-free. Because there is generally a long investment horizon over the Roth IRA owner's life, and the lives of the heirs, the tax-free growth is likely to overcome the "cost" of paying income taxes at conversion, even if at high tax rates.

Conclusion

As with many financial decisions, there are a number of variables to consider when deciding whether to convert a Traditional IRA to a Roth IRA. And each individual will place varying degrees of emphasis on the different variables. At the very least, this article should create a general framework for guiding that decision. If the benefits outlined here resonate with you, we recommend contacting your financial advisor or CPA for additional information. **MM**

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Protecting Our Profession Through Telemedicine

by John O. Stanley, MD

It is important to remember that telemedicine is not a separate medical specialty, but instead is a method of providing better access and improved care to patients.

Telemedicine is the use of telecommunication and information technologies to allow health care providers to extend care to patients who are unable, for a variety of reasons, to visit them in person. Practitioners can use a variety of tools such as computers, smart phones, and two-way radios to communicate with patients. Telemedicine was initially adopted by hospitals as a way to extend care to patients in remote rural areas. However, advances in communication technology have allowed telemedicine to spread rapidly, and it is now being used by an increasing number of hospitals, along with specialty departments, home health agencies, and some private physician's offices.

Though some physicians might be hesitant to add aspects of telemedicine to their practices, I believe that, as a profession, we need to be adaptable. As communication technology continues to advance, a certain amount of telemedicine is going to be inevitable in our practices, whether we are primary care physicians or specialists. If we embrace these changes, and advocate for legislation that will be beneficial to physicians who choose to work in telemedicine, we can avoid encroachment by non-physicians, and keep the care of our patients under our own roofs, even as we care for them remotely.

It is important to remember that telemedicine is not a separate medical specialty, but instead is a method of providing better access and improved care to patients. Primary care physicians and specialists alike can utilize live interactive videos with patients, and also can use store and forward transmission of diagnostic images and/or vital signs, as well as lab results, for later review. Remote patient monitoring is made possible with devices placed in a patient's home that are used to collect and send data to a home health agency or remote diagnostic facility. Patients can receive consumer health information or participate in online discussion groups via the internet, and online medical education can be provided to targeted groups in remote locations.

Basic Benefits of Telemedicine

Improved Access to Patients in Distant Locations

Physicians who adopt telemedicine technology will be able to expand their reaches beyond the physical boundaries of their practice areas, and can thereby serve many more patients. This could be a key strategy to alleviate the projected physician shortage, by increasing each physician's capacity to reach patients. In keeping with the Patient Centered Medical Home model, it makes sense to reach out to distant patients, rather than see them utilize walk-in clinics at pharmacies & grocery stores, with the resulting fragmentation of care.

Cost Effectiveness

Telemedicine can reduce the cost of health care and improve efficiency. In an urgent care situation, a telemedicine encounter with a patient can offer an alternative to a walk-in clinic or an emergency room visit. A recent study showed that 80% of patients who sought care in an emergency room did so because they lacked access to a primary care provider. A hospital emergency room is a terribly expensive place for a patient to receive non-emergent care; a telemedicine encounter is a far less costly alternative. Less stressful, too.

Improved Quality, in Certain Situations

While not all illnesses can be adequately treated via telemedicine, in many cases telemedicine can improve timeliness of care, in a non-stressful environment.

Patient Demand

Patients generally like to have the option of telemedicine, particularly when it reduces travel time, or allows the patients to avoid missing work or having to rearrange child care.

Increased Patient Engagement

Telemedicine allows patients to increase their level of engagement in a variety of ways, and studies show that patient engagement is tied to lower health care costs, and improved overall health.

Problems Facing Telemedicine

Investment in Equipment and Training

The need for investment in equipment and technical training. Training physicians and nurses on new systems takes time, and equipment is expensive.

Reduced Care Continuity

Depending on what care model is used, a patient might receive care from more than one physician.

Fewer In-Person Consultations

The "hands-on" benefit, which is a huge component of what many of us do, is lost without the in-person exam, and this can also lead to erosion of the doctor-patient relationship. In addition, face-to-face consultations between primary care physicians and specialists can diminish personal relationships among doctors.

Technical Limitations

There is always the risk of equipment failure, power failure, or communication difficulties similar to those we are experiencing with our electronic medical records. Patient confidentiality is also a concern whenever records are being transmitted electronically.

Restrictive Health Care Laws and Unfair Reimbursement Policies

There is potential for undue restriction on the practice of telemedicine in some states, and insurance companies could resist payment parity.

Conclusion

The emerging practice of telemedicine is receiving a fair amount of legislative attention. As of February, 2015, thirty-six states had introduced bills related to telemedicine. Many states are discussing payment parity laws, whereby insurers reimburse physicians for services delivered by a telemedicine mode at the same rate as if they were delivered in person. Missouri is among the 21 states to have such a parity law. Some states are creating more restrictive licensing requirements, including requiring in-person visits before or after a telemedicine encounter, or requiring the presence of a care facilitator during each encounter. I think it should be up to each provider to establish policies for treating his or her patients via telemedicine. Requiring in-person visits might not be practical or beneficial in all cases, and might unduly restrict some patients' access to care. Missouri law requires an initial in-person visit before a telemedicine visit. Again, I believe that this type of rule is unnecessary and is an impediment to access.

As physicians, we tend to be resistant to change, and are skeptical about new ideas regarding the practice of medicine until we see evidence to support those ideas. With telemedicine, there is already evidence demonstrating that it is effective, is safe when common-sense guidelines are followed, and is cost-efficient. We need to be proactive and attentive as legislation is proposed that will guide the adoption and progress of telemedicine. Lobbyists for many groups, including an array of "want-to-be" doctors, will be walking the halls of congress, trying to increase their access to patient care via telemedicine. It's up to us to protect our profession by embracing the technology and asserting our role as the ultimate head of the patient care team. **MM**



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Missouri Physicians Share Medical Expertise with the Country of Georgia through A Call to Serve International (ACTS-I)

by Milamari A. Cunningham, MD, ACTS-I Grant Coordinator, Elizabeth James, MD, ACTS-I Vice President & Ted Groshong, MD, ACTS-I Board Member; In collaboration with Patricia J. Blair, MD, ACTS-I President & Giorgi Tsilosani, MD, ACTS Georgia President.

This year, Boone County Medical Society (BCMS) and "A Call To Serve - International," (ACTS-I), celebrated 20 years of collaboration with the Georgian Medical Association (GMA), recognizing John Cowden, MD, as the 2015 Doctor of the Year. He is the ACTS program director for the corneal transplant program in Georgia with Dr. Merab Dvali. The Gift of Sight program has given 143 Georgians eyesight through Lions Eye Research Bank donated corneas hand carried by ACTS delegates to Georgia.



Dr. Guram Amiridze, GMA toasts ohn Cowden, MD, BCMS Doctor of the Year at BCMS 2015 Gala, after the ACTS slideshow including his work in Georgia.

The late Beverly Murrell, MD, coordinated the Lions eyeglass distribution in Georgia providing over a hundred thousand pairs of eyeglasses.

The ACTS/Lions Ron James Georgian Diabetic Children's Camp celebrated the camp's twentieth annual session in August 2015. ACTS is currently using a rented school campus. They hosted 50 diabetic campers ranging from 6 to 17 years of age, 17 diabetic alumni counselors as well as medical personnel. This camp was created as an education camp for Type 1 diabetics teaching patients how to self-manage their chronic disease and survive into adulthood. They learn how to balance insulin dosage with daily activities including exercise and food intake (timing, quantity and quality). After age 17, campers are eligible to continue as camp counselors and senior staff overseeing sports activities, arts and crafts, the Brain Ring (a trivial pursuit game developed by campers involving Georgian-related items), and games that teach children how to assess the food choices they deal with at home. Over 80 diabetic camp alumni who are over 30-years-old are living productive lives and having families long past the 10-year expected survival rate in Soviet times.

Each year Missouri Lions Clubs and private donors sponsor the camp. Every camper costs $500 per session. Each year Lions gather enough deer hides from Missouri hunters to sponsor at least one camper. Missouri Lions Clubs also donate funding and supplies for hygiene kits for campers annually.

ACTS is actively seeking a permanent site for this Georgian diabetic camp. The Lions Clubs International Foundation and Missouri Lions have funded a permanent dining hall facility when the site is secured.

The ACTS/Rotary "Breathing Life into Georgian Babies" project blends the efforts of Missouri Rotarians with the skills of BCMS physicians. They are providing hand-held neonatal resuscitation kits to be used in delivery



Ted Groshong, MD, Rotarian and Past President of BCMS, holds the Georgian dagger given to him by the GMA.

rooms. They taught a culturally appropriate version of the American Academy of Pediatrics Neonatal Resuscitation Program as part of a train-the-trainer course on their June 2015 trip to the Kvemo Kartli District of Georgia. Patricia Blair, MD, ACTS-I President, who is familiar and experienced in training Georgian physicians, and John Pardalos, MD, Medical Director of the Neonatal Intensive Care Unit at University of Missouri, head up this delegation working with Georgian physicians to reduce neonatal mortality and stillbirths in rural Georgia.

The Georgian physician ethics program is a ground-breaking development in this post-Soviet era. The 2011 reference book "Rules of Physician's Professional Conduct" was written by a working group of Georgian medical specialty association leaders: Drs. Givi Javashvili, Georgian Society for Bioethics and Healthcare Legal Affairs Studies; Guram Kiknadze, Georgian Association of Family Doctors; Irina Karosanidze and Tamar Gabunia, Georgian Union of Family Medicine Professionals; Revaz Tataradze GMA and Giorgi Tsilosani ACTS Georgia President. ACTS/GMA is seeking sponsors for regional ethics seminars. The goal is to create the ethical foundation for Georgian physicians code of conduct to provide modern ethical patient care.

Since 1995, 16 MSMA physicians have traveled to Georgia to share their medical expertise and resources with the Georgian medical community. ACTS-I provides a vital service by facilitating the charitable coordination of Missouri civic organizations like Lions and Rotary with MSMA physicians to improve Georgian health by working with Georgian physicians.

"People helping people to build a free and peaceful world" is the ACTS-I Motto.

Photos reprinted with permission by Boone County Medical Society

MM



MSMA Members in the News



Congratulations, Jason Anast, MD, MSMA member since 2013, on providing urology care to patients at Ray County Memorial Hospital!



Thank you for joining MSMA as a new member, Muhammad Asif, MD, and congratulations on your new practice at Building Blocks Pediatrics in Warrensburg.



The first "gentle" Ceasarean section at Texas County Memorial Hospital took place in July by Christopher Baldwin, MD, MSMA member since 2011.



Past MSMA President and candidate for AMA President-Elect for 2016 David Barbe, MD, of Mountain Grove, has been honored with the prestigious Missouri Award.



Amber Brown-Keebler, MD, hosted a Summer Reading Program at Mound City Public Library and showed children how a doctor can be a hero to sick patients. She read to them, presented her doctor's bag, and provided play bags with first aid items so the children could practice emergency techniques. Thanks for your support of the kids, and organized medicine, as a new MSMA member, Dr. Brown-Keebler!



MSMA member since 1984, Nancy Bunge, MD, has joined Arthur Center Community Health, bringing skilled and compassionate care to the children of Mexico.



Jeffrey Carter, MD, of St. Louis, just began his term as President of the Missouri Board of Registration for the Healing Arts for 2015-2016. He has been an MSMA member since 2002 and also served as President of the Board in 2012-2013.



Windsor's William Dailey, MD, earned his Master's Degree in Medical Informatics and has been an MSMA member for five years.



Congratulations, Rafael Figueroa, MD, on joining Parkland Health Center in Farmington, MO. MSMA appreciates your membership this year!



Robb Hicks, MD, of Creve Coeur, MSMA member since 1992, presented a lecture and experiential workshop on "Relapse Prevention" at the Missouri Department of Mental Health's Spring Training Institute.



Want to know how to keep your beach body? Well, Bhargav Kanani, MD can tell you how! This MSMA member since 2001 presented to his community on September 24 in Ste. Genevieve on diet trends, calorie intake, carbohydrates, fats and protein needs.



Serenity HospiceCare in Farmington has announced that David F. Kapp, MD, FAAFP, has joined its team as assistant medical director. Dr. Kapp has been an MSMA member since 1984.

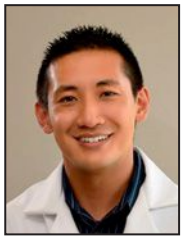


For the 10th year, Tim Long, MD, MSMA member since 1981, has presented the Long Leadership Award to high school graduates in Washington. Pictured here with Dr. Long are two of three recipients of $2,500 scholarships, Eric Hasenjaeger and Jodi Glosemeyer.

MSMA wishes to commend MSMA Member Rob Martin, MD, for volunteering to provide athletic physicals to 411 students in West Plains. Thank you for your service to the community and for being an MSMA member since 1991.

Alan Mead, MD, MSMA member since 2001, has joined Lake Regional Health System's Board of Directors. Congratulations, Dr. Mead!





One of MSMA's newest and youngest members, Christopher Paynter, DO, is now caring for patients in both the Versailles and Tipton clinics with SSM Health Medical Group.



H. Andrew Pickett, MD, MSMA member since 2005, has officially joined the team at Excelsior Springs Hospital Physician Clinics after having privileges there and providing care in Excelsior Springs for the past 32 years.

Congratulations, James Rushford, MD, new MSMA member, on the groundbreaking of your new orthopaedic clinic in West Plains.



Sonja Williams, MD, recently attended the ribbon cutting for the Women's Functional Health & Hormone Center in Osage Beach where she is practicing. MSMA is pleased to have her as a new member.



MSMA is cheering on Mike Williamson, MD, member since 2011, as he cares for patients all across the northwest part of the state. He is a former star-athlete from Chillicothe who now provides orthopedic and sports medicine to the same, CHS Hornet football team, with which he once played.



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The Good and the Bad

The article by Arthur Gale, MD, "The Good and the Bad," from the July/August 2015 *Missouri Medicine*, was clear, well researched and well balanced.

It traced the history of Medicare, and current payment plans of insurance companies. The federal bureaucracy and insurance companies rule the day. Shortcomings will be blamed on the doctors.

As stated in the article, the non-partisan Congressional Budget Office predicts that the Medicare Trust Fund will run out of money in 2030 or in 15 years.

As usual America seems to only change through crisis. As the Chinese proverb says "From chaos comes order."

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Washington University in St. Louis
SCHOOL OF MEDICINE

Discoveries the Forefront of BioMedical Research

by Larry J. Shapiro, MD

Our students are a continual source of amazement and promise. Among them are dedicated and compassionate future physicians, brilliant scientists in the making, and energetic community volunteers.

Later this year will mark the end of my 12-year tenure as Executive Vice Chancellor for Medical Affairs and Dean of Washington University School of Medicine in St. Louis. Filling this role has been the greatest honor and privilege of my career. As I prepare to step aside for our school's new Dean, David H. Perlmutter, MD – a familiar face to those who knew him when he served on the Department of Pediatrics' faculty a few years ago — I find myself reflecting on the advances I've been fortunate enough to witness while at this wonderful institution.

Nearly a decade ago, the University launched a strategic planning process that identified four themes: improving human health; preparing future leaders; inspiring and growing innovation and entrepreneurship; and enhancing quality of life. While our work toward these goals remains ongoing, I can say with great confidence that the talented and dedicated faculty, staff and students at the School of Medicine have welcome and embraced these challenges.

The school remains at the forefront of biomedical research — despite hurdles presented by cuts in federal research funding. Over the past 12 years, the school has ranked fourth among all medical schools in National Institutes of Health (NIH) funding. Such support has been key to the advances in research our scientists have made and aim to make.

In that time, the first sequencing of a cancer genome in a human occurred here, a critical step toward understanding the genetic underpinnings of cancer. Further, our scientists have contributed significantly to understanding the root causes of Alzheimer's, and they've become leaders in stroke care and research to improve stroke diagnosis and treatment.

And, as noted in this issue of *Missouri Medicine*, the school is a leader in Radiation Oncology — and across the spectrum of cancer research and treatment. The National Cancer Institute (NCI) recently awarded Siteman Cancer Center at Barnes-Jewish Hospital and Washington University School of Medicine an "exceptional" rating. This rating — NCI's highest — was based on a rigorous review of the research programs at Siteman, including genomics, cancer imaging, cancer prevention and disparities, immunology and immunotherapy, and early-phase clinical trials.

Among the work reviewed: vaccines against breast cancer and melanoma, now in clinical trials; high-tech goggles that help surgeons see cancer cells during surgery; and community-based research to understand and eliminate cancer disparities in our region.



Larry J. Shapiro, MD, a Pediatrician and MSMA member since 2006, is the Executive Vice Chancellor for Medical Affairs and Dean of the Washington University School of Medicine.
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Regarding the School of Medicine's Department of Radiation Oncology specifically, it is a national leader in developing and delivering cutting-edge treatments for cancer patients. Among its newest and most innovative such treatments is proton therapy, which targets tumors more precisely than other forms of radiation, making it ideal for treating pediatric cancer patients and adults with tumors in sensitive locations, such as the brain. At Washington University Medical Center, the S. Lee Kling Center for Proton Therapy is well into its second year of operation.



Cancer Goggles in Use
High-tech glasses developed at the School of Medicine help breast surgeon Julie Margenthaler, MD, MSMA member since 1988, visualize cancer cells in a patient. The cancer cells glow blue when viewed through the eyewear, wearable technology used during surgery for the first time in February 2014, at the Alvin J. Siteman Cancer Center at Barnes-Jewish Hospital and Washington University School of Medicine.
Photo credit: Robert Boston

Research Initiatives

The venture of which I am most proud is BioMed 21, the University's research initiative to translate basic research findings into advances in medical treatment. BioMed 21, which includes faculty from the Schools of Medicine, Engineering, and Arts & Sciences, brings together basic scientists and clinical researchers from different disciplines to tackle important questions in medicine. As with most of the research on the Medical Campus, BioMed21 efforts are funded by the NIH.

Among other achievements involving the School of Medicine was the launch of the Institute for Public Health (IPH), a universitywide initiative that addresses health issues affecting our region and beyond. Gun violence, cognitive decline as we age, the influence of diet on disease are just a few of the areas IPH explores and seeks to change for the better.

The School of Medicine also recently celebrated the dedication of the McDonnell Genome Institute, which was established with a gift from longtime philanthropists and civic leaders James S. and Elizabeth H. McDonnell. Their gift is funding innovative research to understand the genetic origins of cancer and other diseases, with the aim of developing more effective diagnosis and treatment for patients.

Most recently, the school announced a partnership with a campus neighbor, the St. Louis College of Pharmacy. The collaboration is the Center for Clinical Pharmacology, an effort that will have the two institutions working together to find better, safer, and more effective ways to use prescription medications to improve health.

And I would be remiss if I did not mention the CORTEX innovation district, a collaboration of Washington University, Saint Louis University, BJC Healthcare, the University of Missouri-St. Louis, and the Missouri Botanical Garden. CORTEX's goal is to develop a 187-acre Central West End area into one of the nation's leading research districts and biomedical powerhouses. The entrepreneurial efforts alone that it has drawn are exceptionally encouraging and have some referring to St. Louis as the next Silicon Valley.

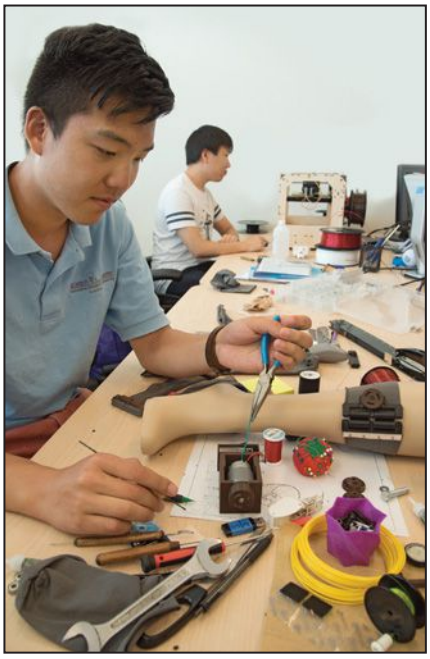
In regard to our faculty practice, Washington University Physicians has experienced significant growth in recent years. Last year, it earned $874 million in revenue, and it has gained 8 to 10 percent annual growth in the last decade. Among the most recent additions involving our faculty physicians is the St. Louis Children's Specialty Care Center in west St. Louis County. The center, which is co-owned and operated by the university and SLCH, opened its doors this summer.

Shaping the Future

Meanwhile, the School of Medicine has remained true to its mission of shaping the finest physicians. The school is at the top nationwide in student selectivity, a measure of medical student undergraduate grade-point averages and MCAT scores. And it consistently has remained a top 10 medical school, according to annual rankings by *U.S. News & World Report*.

Our students are a continual source of amazement and promise. Among them are dedicated and compassionate future physicians, brilliant scientists in the making, energetic community volunteers — and students who still manage to write plays, perform in musical ensembles, and inspire a love for science in high school students who otherwise might never consider a career in science or medicine.

Their numbers also include entrepreneurs that we encourage, mentor and oftentimes celebrate for bold ideas they turn into realities. MD/PhD student Avik Som, MSMA member since 2011, founded IDEA Labs, a bioengineering





Howard Hughes Fellows
Four students at the WU-SOM are among 68 students nationwide selected for the Howard Hughes Medical Institute's Medical Research Fellows Program. They are (from left) Kow Essuman, Julia Wagner, Amy Xu, MSMA member since 2012, and Jessie Ge. The annual initiative is designed to develop the next generation of physician-scientists by giving students a full year of mentored research training with some of the nation's top biomedical scientists.
Photo credit: Robert Boston

IDEA Laboratories
WU students Brett Gao (left) a biochemisty and economics major, and Kenny Kim, a biomedical engineering major, work to make compression stockings that are easier for patients to put on. MD/PhD student Avik Som, MSMA member since 2011, founded IDEA Labs, which sparks entrepreneurial innovations designed to improve medical care. Problems posed to the group are solicited through its website and in partnership with the St. Louis Metropolitan Medical Society.
Photo credit: Robert Boston

design and entrepreneurship incubator at the University in which students, faculty, staff and outside entrepreneurs team up to tackle unmet needs in health care delivery and clinical medicine. Problems posed to the group are solicited through its website and in partnership with the St. Louis Metropolitan Medical Society.

IDEA Labs (its name stands for Innovation, Design & Engineering in Action) was founded in 2013, but as of this year it has led to 31 prototypes, 16 provisional patents, nine national competition winners and finalists, and 17 startups. Further, its teams have raised $2 million in outside investments. To label what these entrepreneurs do as inspiring is an understatement.

It's difficult to step down from my position as Dean. But it is because of these students and the faculty and staff who help shape them that I know the School of Medicine will continue to thrive in terms of the research and future leaders in medicine it sparks, and the comprehensive, continually improving patient care we provide.

Our challenges will continue, of course. Our leaders recognize their responsibility to join in the chorus of national voices in urging legislators to restore — and grow — NIH research funding. There are far too many important discoveries within reach to simply adjust or settle for less.

As health providers and fellow citizens of the state of Missouri, we all need to work toward solutions to help the state's nearly 300,000 low-income people who don't have health insurance. Missouri has the opportunity to make significant strides in improving the health and well-being for a large number of vulnerable individuals if we take advantage of the tools made available to us through the Affordable Care Act. The decision to expand health insurance coverage, including Medicaid, has implications for the health care industry, small businesses and local economies, but most importantly for low-income individuals, most of whom are working but at risk of falling deeper into poverty if they get sick.

And on a more personal level, we need to continue to build a more diverse workforce and student body at the School of Medicine and in other medical institutions if we are to best serve not only the St. Louis region and our state but our society as a whole.

I plan to step down, but I don't plan to walk away. Though I have not yet decided what my role at the School of Medicine will be, there are many initiatives at the University that I care deeply about and want to help advance.

As always, we invite you to share any suggestions you might have on how the school can better serve the state of Missouri and more effectively work in partnership with our state's fine medical institutions and physicians.

If you would like to learn more about our school's initiatives in research, patient care, and education, please visit our website at http://medicine.wustl.edu.

Photography Credit

The photo of Dr. Shapiro was taken at the School of Medicine in Ellen S. Clark Hope Plaza by Tim Parker. **MM**

New Developments in Radiation Oncology

by Jeff M. Michalski, MD, MBA

We are honored that *Missouri Medicine* has given us this fantastic opportunity to publish some of the exciting and new developments that we have in our Department of Radiation Oncology at the Washington University School of Medicine and the Siteman Cancer Center. In this issue we illustrate unique technologies that our physicians utilize to provide exceptional care to our patients. Some of these technologies have been available for many years but the personal skill set of our experienced physicians and recent modifications in techniques make them available to a growing number of patients. For example, brachytherapy is the use of implanted radioactive sources in or around a malignant tumor. This treatment has been available to treat gynecological, breast, and prostate cancers for decades. Recent imaging and technical enhancements now make this treatment more effective with fewer risks than in the past. Drs. Weiner and Schwarz highlight the use of brachytherapy in cervical and endometrial cancer and how we have integrated MRI imaging into our practice to individualize treatment to women with these gynecologic cancers. Likewise, Dr. Thomas describes the growing role of brachytherapy in breast cancer. In appropriately selected women this treatment has reduced the overall course of radiation therapy from six weeks to one with excellent tumor control and cosmetic results.

Increasingly, we are using sophisticated imaging systems to plan and monitor our treatments for a variety of cancers. Dr. Tsien describes the role of functional MRI imaging to improve targeting of radiation therapy to patients with brain tumors. She is also leading clinical studies to assess early responses to treatment using unique MRI sequences and imaging techniques.

Finally, two exciting technological developments have been launched at the Siteman Cancer Center and Barnes Jewish Hospital over the past two years. The Mevion S250 Proton Therapy system is the first of its kind in the world. While proton therapy has been used to treat cancers for decades, the extremely high cost of these facilities has limited access to this technology for most patients. The system at our center utilizes superconducting magnets to reduce the size and cost of the facility to one fourth that of other centers in the U.S. This treatment is now available to patients in Missouri, Illinois and beyond. The other innovative introduction of a first of its kind technology is the ViewRay MRIdian system. This system integrates real time magnetic resonance imaging with simultaneous radiation delivery. Today we can see where treatment is going while the beam is on. Never before have radiation oncologists been able to see a tumor while it is being irradiated. This is like taking the blindfold off of a surgeon in the operating room. The ability to see while we treat is opening up the possibility of personally adapting radiation treatments to a patient's unique anatomy and organ motion. We are conducting trials with these new systems to demonstrate their value to our patients. Clinical trials remain a focus of our department as we continue to contribute to the improvement in outcomes for patients with cancer. **MM**



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SITEMAN CANCER CENTER

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Proton Therapy

An Update on the S. Lee Kling Proton Therapy Center at Barnes-Jewish Hospital and Washington University

by Jeffrey Bradley, MD, FACR, Beth Bottani, CMD & Eric Klein, PhD

The Alvin J. Siteman Comprehensive Cancer Center opened a first-of-its-kind proton beam radiation therapy (PBT) center in December 2013. The S. Lee Kling Proton Therapy Center is jointly operated by Washington University School of Medicine and Barnes-Jewish Hospital to bring the latest technology to patients in the Midwestern region of the United States (U.S.). The Kling Proton Therapy Center is the 14th proton therapy center to open in the U.S. and is designed and developed by Mevion Medical, Inc. This PBT unit is the first of several smaller, less expensive proton therapy facilities that are scheduled to be installed worldwide. The unique first-of-its-kind features of this unit are; first single-room proton facility worldwide, first gantry-mounted cyclotron, and first proton unit to use a six-degree robotic couch. The rotating gantry function allows the proton beam to enter the room from 190 degrees. The robotic couch allows the patient to be positioned while small adjustments can be made in six dimensions (three translational, three rotational) so that the proton beam can precisely reach the tumor from any angle. The treatment room is shown in Picture 1.



Picture 1
This picture of the proton treatment room at Barnes-Jewish Hospital shows the inner gantry with applicator, where the protons enter the room, and the six-degree robotic couch.

PBT is a useful tool to treat many types of cancer in adults and children. The main advantage to PBT is the ability to precisely localize radiation dose to the tumor, while minimizing dose to adjacent normal tissue. An advantage of PBT compared to x-rays is that protons have a charge and mass. Protons travel a finite distance in tissue, depending on the beam energy (and other factors) and do not have an exit dose deposition beyond the tumor. The scientific term for this feature is called the Bragg peak (see Figure 1), named after physicist William Henry Bragg's discovery in 1903. A composite of Bragg peaks deposited at various depths delivers a spread-out-Bragg-peak (SBP). Compared to x-rays, protons have a lower entrance dose (to skin) and do not have an exit dose beyond the tumor target. The major advantage to PBT is a reduction in side effects, enabled by the ability to spare adjacent normal tissues.

Cancers commonly treated with protons include tumors in locations near critical structures, such as those near the brain, eye, base of skull, spinal cord, major nerve trunks, bowel, and heart. Protons are particularly useful in pediatric patients due to the desire to reduce radiation dose to developing brain or bone, which can lead to long-term

cognitive, hormonal, and growth disturbances. In adults, protons can reduce dose to normal brain and the optic structures in patients with brain tumors. In the chest, protons can reduce dose to normal lung and heart. In the abdomen in pelvis, the goals are to reduce dose to bowel, kidneys, liver, and bladder.

A classic example of the advantage for PBT over x-rays is shown in Figure 2. This image shows the radiation dosimetric plan of a pediatric patient receiving craniospinal radiation following resection of a medulloblastoma brain tumor. Patients with medulloblastoma are at risk for tumor recurrence throughout the craniospinal axis by seeding of the cerebrospinal fluid. In this case, PBT was used to treat both the brain and spinal canal. The advantage for protons is that there is no exit dose and the patient received no dose to the heart, lungs, or bowel.

Another example of a plan comparison between protons and x-rays is shown in Figure 3. This is a middle-aged patient who was treated with PBT for a base of skull chondrosarcoma. The patient was initially recommended to have a primary resection which would have included a left orbital exenteration. He sought out other options which included PBT. The proton beam plan is on the left, and the x-ray plan is on the right. The red shaded area is the tumor target. The colored lines represent the radiation isodoses. The PBT plan spared the adjacent brain, left and right eyes, and optic nerves for this patient. This happened to be our very first patient!

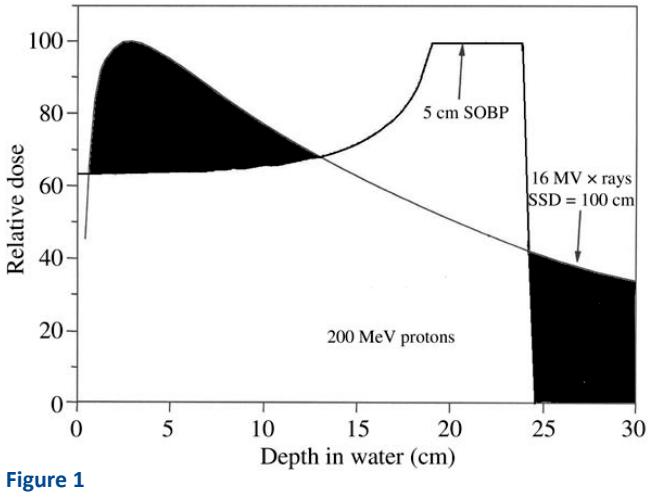


Figure 1
Depth-dose curve for x-rays and for protons. As x-rays enter tissue, they have a quick buildup just below the skin surface and deposit radiation dose from entrance through exit. As protons enter the skin surface, they deposit a lower skin dose and build up to deposit most of their dose at the end of their depth range. Protons have no exit dose, which is a major advantage compared to x-rays.

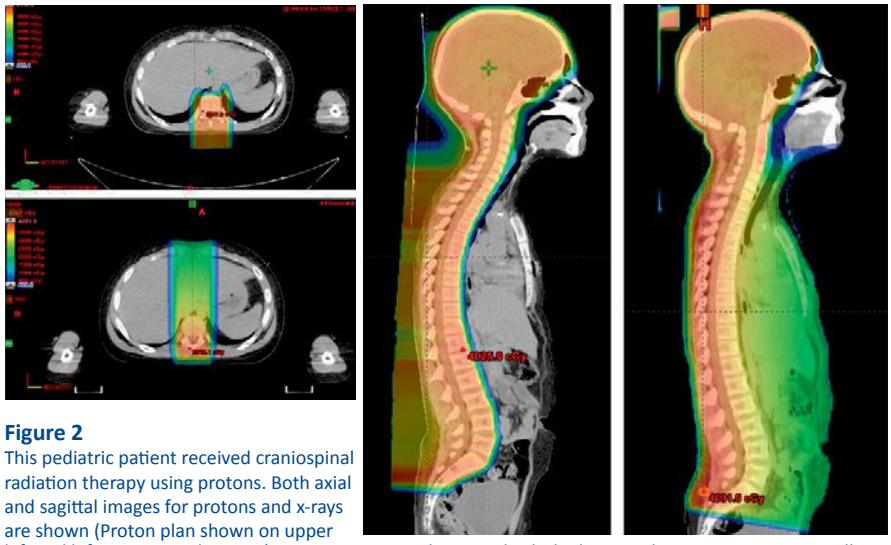


Figure 2
This pediatric patient received craniospinal radiation therapy using protons. Both axial and sagittal images for protons and x-rays are shown (Proton plan shown on upper left and leftmost sagittal images). Protons were used to treat both the brain and spine, encompassing all tissues bathed in cerebrospinal fluid for the proton plan compared to the x-ray plan. Note that there is no exit dose within the thorax or abdomen, sparing heart, lungs and bowel from unnecessary radiation.

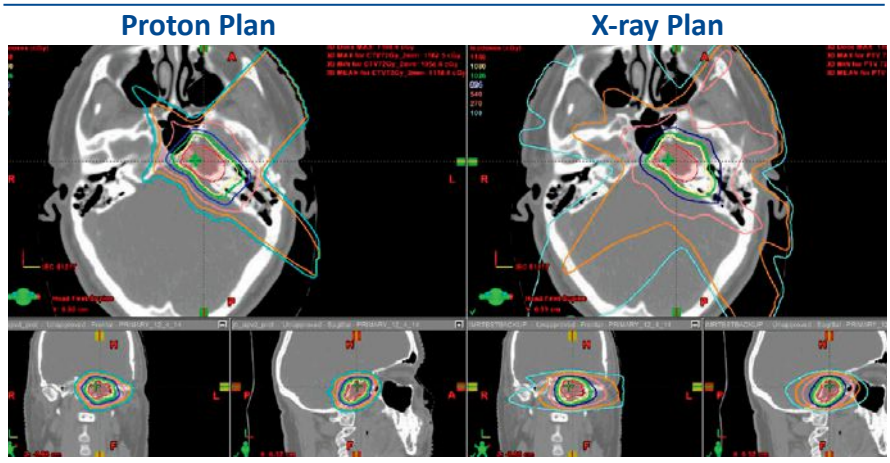


Figure 3
This figure shows a dosimetric plan comparison for PBT versus x-rays. The red shaded area represents the tumor volume of a chondrosarcoma located in the base of skull. The yellow line in both images represents the prescription dose. The other colored lines represent successive decreasing radiation doses that irradiate normal tissues. In this example, the proton beam plan (left) is more conformal to the shape of the tumor and is able to avoid radiation dose to the eyes and brain compared to the x-ray plan.

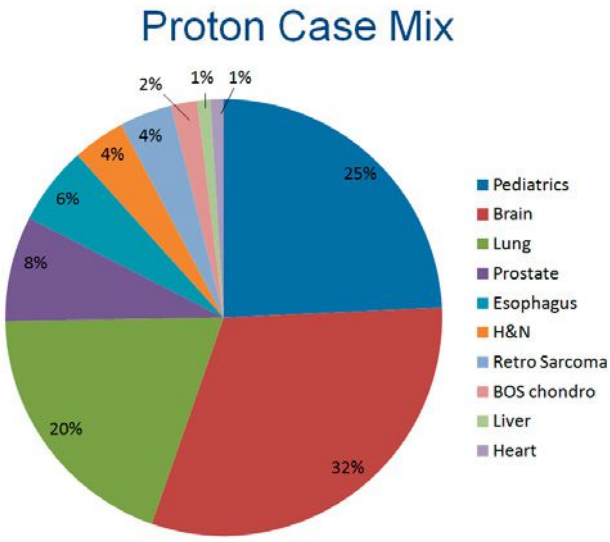


Figure 4
This figure shows the proton case mix at the Siteman Cancer Center for the first year of operation, 2014.

The Kling Proton Therapy Center opened in December 2013. We treated 110 patients during the first year. An example of the types of cancers treated are shown in Figure 4. Approximately 32% of patients have had brain tumors. About 25% of our patients have been children, referred through St. Louis Children's Hospital and other regional pediatric oncologists. Another 20% have been patients with lung cancer. Our relationship with St. Louis Children's Hospital is an important one. We have dedicated pediatric oncologists, a pediatric radiation oncologist, pediatric nursing and child-life specialists. Our dedicated staff provide care to our families on a personal level. During the first year of operation, our pediatric patients have come from a six state region to travel here for this specialized treatment.

An important component of offering PBT is participation in prospective clinical trials. Many insurers cover PBT for classic proton therapy cases, such as for pediatrics, tumors in the brain, base of skull, brain, eye, and spine. However for other types of cancers such as prostate and lung, insurers consider protons still unproven and encourage participation in clinical trials or prospective registries. Each of the following studies are collecting scientific information evaluating the value of PBT. The Siteman Cancer Center houses an open prospective registry for every patient who wishes to participate. This registry will be open to many other proton centers that are planning to open in coming years. Pediatric patients are offered participation in a national pediatric patient registry operated through the Francis Burr Proton Center at Harvard University. We also have dedicated prospective clinical trials that are currently accruing patients with lung, brain, esophagus, and prostate cancers. RTOG 1308 is a phase III randomized trial funded through the National Cancer Institute (NCI) comparing x-rays to protons for patients with unresectable Stage III non-small cell lung cancer. NRG BR001 is an NCI-sponsored phase III randomized clinical trial comparing dose-intensified intensity modulated radiation therapy (IMRT with x-rays) compared to dose-intensified proton beam therapy for patients with glioblastoma multiforme brain tumors. Furthermore, men with low or intermediate-risk prostate cancer may participate in the NCI-sponsored trial entitled Prostate Advanced Radiation Technologies Investigating Quality of Life (PARTiQOL). This randomized trial compares patient-reported quality of life scores for bowel function for patients treated with IMRT versus PBT at participating centers. Due to ongoing interest in evaluating the efficacy and toxicity associated with PBT, other multi-institutional studies are being planned.

Disclosure

J. B. has received a clinical trial grant from ViewRay, Inc. E.K. has received travel reimbursement to scientific meetings from Mevion. **MM**



Jeffrey Bradley, MD, FACR, (right), Professor of Radiation Oncology, the S. Kling Endowed Chair of Radiation Oncology, Director, Proton Center, and Chief, Thoracic Service and Eric Klein, PhD, FAAPM, FASTRO, Professor of Radiation Oncology, are both at Washington University School of Medicine in St. Louis. Beth Bottani, CMD, Proton Therapy Manager is at Barnes-Jewish Hospital. *Contact: jbradley@radonc.wustl.edu*

SITEMAN CANCER CENTER

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World's First Application of MR-Guidance for Radiotherapy

by Jeffrey Olsen, MD, Olga Green, PhD & Rojano Kashani, PhD

It is hoped that the increased precision of this new technology may allow increased tumor dose, reduced complication risk, and tolerance of more potent systemic therapies concurrent with radiotherapy.



Jeffrey Olsen, MD, (above), Assistant Professor of Radiation Oncology and Clinical Clerkship Director; Olga Green, PhD, Lead Authorized Medical Physicist, ViewRay MR-IGRT; Rojano Kashani, PhD, Instructor Radiation Oncology; all are at Washington University School of Medicine in St. Louis.
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Abstract

Radiotherapy localization is the process by which patient treatments are aligned on a daily basis. Localization has historically been accomplished using 2-dimensional x-ray images, or cone-beam CT-imaging which permits excellent visualization of bony anatomy, but suboptimal soft-tissue imaging. The Department of Radiation Oncology at Washington University recently implemented the world's first MR-Image Guided Radiation Therapy program (MR-IGRT), which utilizes a 0.35T MR scanner integrated with three ^{60}Co heads for treatment delivery. A high-resolution volumetric MR image is acquired for each patient at the time of daily treatment setup, which allows localization based on soft-tissue anatomy, and modification to the treatment plan when required while the patient is on the treatment table. Herein, we review principles of radiotherapy localization, describe implementation of the world's first MR-IGRT program, and present future directions where MR-IGRT may be applied for patient treatments.

Introduction

Modern radiotherapy delivery requires accurate and reproducible patient localization for each treatment. Although 2-dimensional "port films" were historically used to confirm patient setup, the improved conformality of modern treatment delivery requires greater setup precision to confirm patient positioning each day. On-board imaging technologies such as cone

Figure 2
The MRIdian (Viewray, Cleveland, OH) MR-IGRT system as installed at Washington University.



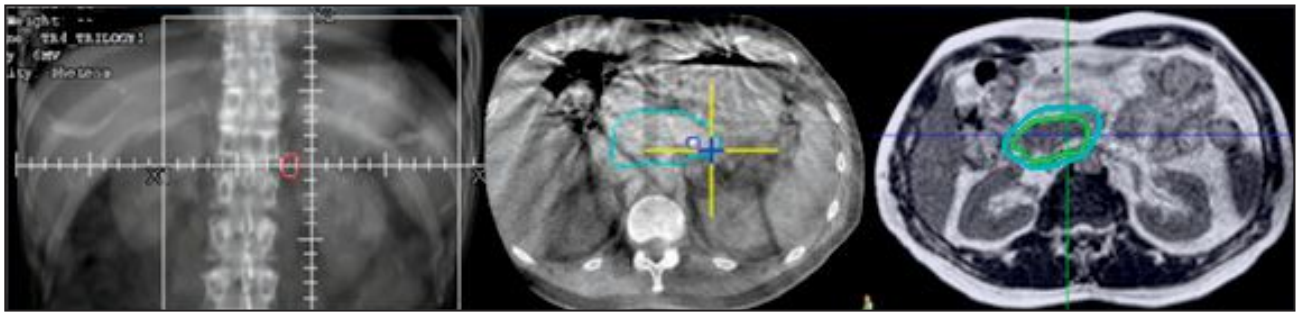


Figure 1
Pancreatic cancer localization performed using 2-dimensional kv-imaging (left), cone-beam CT (middle), and MR-IGRT (right). MR-IGRT allows visualization of the pancreas and critical adjacent structures including small bowel and kidneys.

beam computed tomography (CBCT) offer improved daily setup precision compared to port-films, although soft-tissue visualization is often limited. Implanted fiducial markers are often required as a surrogate for localization based on soft tissue anatomy, but provide limited information regarding changes in patient anatomy and the location of normal tissues. Magnetic resonance imaging (MRI) provides a potential method to improve treatment localization due to superior identification of soft-tissue anatomy compared to CBCT. Figure 1 illustrates a comparison among treatment localization techniques for a patient being treated with radiotherapy for pancreatic adenocarcinoma. Compared to 2-dimensional localization based on bony anatomy (left), CBCT (middle) offers limited visualization of the target (light blue) and implanted fiducial marker (dark blue), but lacks detailed soft tissue visualization of tumor and adjacent bowel. MRI (right) allows improved visualization of the tumor (green), and normal structures including bowel, liver, and kidneys. Although MRI had not previously been used for radiotherapy localization, incorporation of MRI as a component of the localization process may also facilitate treatment adaptations, allowing changes to a radiation plan based on variability in patient anatomy. Table I illustrates a comparison between the previous standard of care for image-guided radiotherapy (IGRT) and MR-IGRT for radiotherapy localization, tracking, and treatment adaptation parameters. The implementation of and initial clinical experience with MR-IGRT at Washington University is described here.

	Standard of Care	MR-IGRT
Treatment Localization	Bony or surface anatomy Implanted fiducial markers	Tumor
Tracking/gating	Fluoroscopy External surface anatomy Spirometry	Tumor Critical structures (e.g. bowel)
Adaptation	Based on gross anatomic change (e.g. weight loss)	Based on changes observed in target or critical structures on MRI

Table 1
Comparison of localization, tracking, and adaptive radiotherapy parameters between previous standard of care and MR-IGRT.

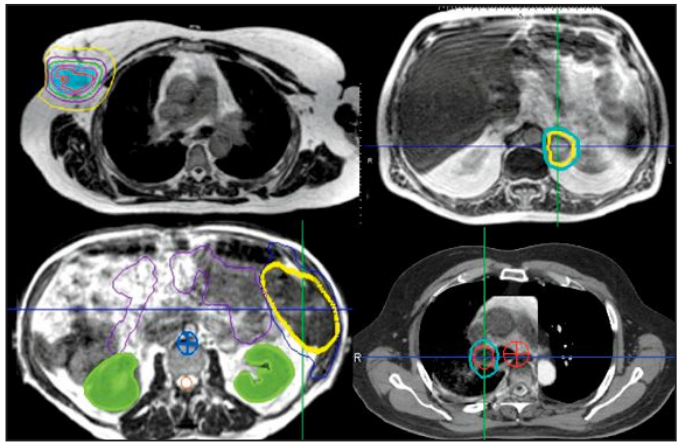


Figure 3
Examples of MR-IGRT localization for accelerated partial breast irradiation based on tumor cavity anatomy (upper left), stereotactic bodyradiation therapy (SBRT) for medically inoperable pheochromocytoma based on tumor anatomy (upper left), preoperative chemoradiotherapy for locally advanced colon cancer based on tumor anatomy (lower left), and SBRT for ablation of oligometastatic soft tissue sarcoma based on tumor anatomy (lower right).

Implementation of MR-IGRT at Washington University

Technical parameters of the MR-IGRT system implemented at Washington University (MRIdian, Viewray, Inc, Cleveland OH) have been previously described[1] In brief, the system consists of three components:

(1) The MRI, a split gradient 0.35T whole body unit with a 50-cm diameter spherical imaging field of view (FOV).

(2) The radiotherapy delivery system, utilizing 3 ^{60}Co heads that provides a maximum dose rate of 550 cGy/min at isocenter with simultaneous delivery from 3 gantry angles that are 120° apart. Gating is a radiotherapy technique that allows administration of treatment only during specific phases of the respiratory cycle, to minimize radiation dose to normal tissues

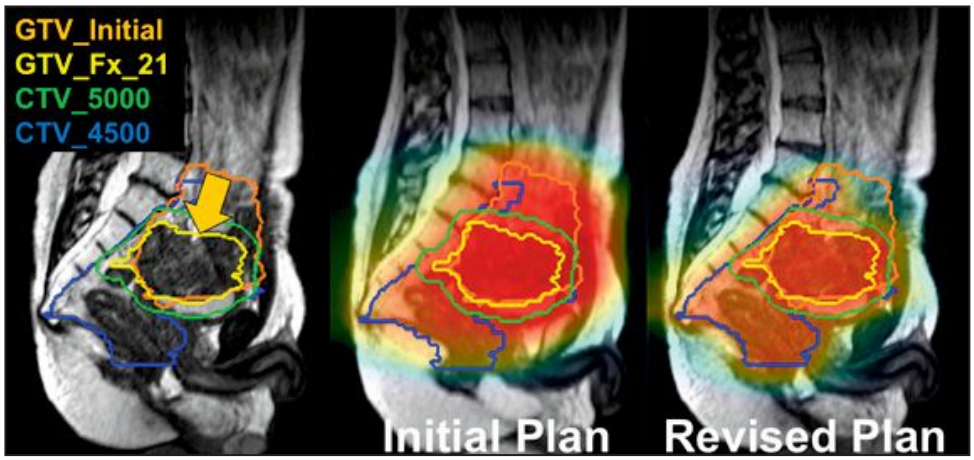


Figure 4
Adaptive radiotherapy technique in a patient undergoing neoadjuvant chemoradiotherapy for a locally advanced sigmoid cancer. Compared to the initial tumor volume (orange), a response was observed during chemoradiotherapy resulting in a smaller tumor volume (yellow). Compared to the initial radiotherapy plan (middle), the adaptive plan (right) allows significantly improved sparing of bowel in the area previously occupied by tumor.

based on respiratory motion. During MR-IGRT, cine MR images may be used for tumor or normal tissue tracking, and for treatment gating.

(3) The treatment planning system (TPS) which may be used for adaptive radiotherapy (ART) utilizes a Monte Carlo based dose calculation algorithm for both conformal and intensity modulated radiation therapy (IMRT) planning. The speed of the TPS allows plans to be reoptimized based on changing patient and tumor anatomy observed on daily MRI localization.

System installation commenced in 2012, with completion of the commissioning process and the first clinical patient treatment in January, 2014. Figure 2 shows the MR-IGRT system as installed in the Department of Radiation Oncology at Washington University.

Initial Clinical Experience with MR-IGRT

Approximately 100 patients were treated during the first year of clinical operation, including application of MR-IGRT for treatment of breast, esophageal, lung, gastric, pancreatic, colorectal, and prostate malignancies. Figure 3 illustrates localization images for patients undergoing accelerated partial breast irradiation based on lumpectomy cavity anatomy, stereotactic body radiation therapy (SBRT) for medically inoperable pheochromocytoma based on tumor anatomy, preoperative chemoradiotherapy for locally advanced colon cancer based on tumor anatomy, and SBRT for solitary metastatic soft tissue sarcoma in a paratracheal lymph node based on tumor anatomy.

In September 2014, the first application of on-table ART was performed. The selected patient was undergoing preoperative chemoradiotherapy with concurrent 5-FU for a locally advanced sigmoid colon cancer with bladder invasion. Neoadjuvant treatment was chosen due to concern for tumor abutment of the pelvic sidewall inferiorly that was felt to be at high risk of positive margin at resection. During MR-IGRT localization, the patient was noted to have a substantial clinical response. Due to tumor regression, small bowel was noted to occupy the cephalad aspect of the radiotherapy field which previously had been occupied by tumor. The patient's tumor and anatomy were re-contoured and re-planned on the treatment table due to this change in anatomy, and continued to receive MR-IGRT with the amended plan until scheduled completion. He subsequently underwent negative margin resection and is without evidence of recurrence. Figure 4 illustrates the observed change in patient anatomy during treatment, and the resulting adaptive radiotherapy plan.

Future Directions

Improved localization and treatment adaptation due to changing tumor and critical structure anatomy has the potential to improve the therapeutic ratio for patients undergoing radiotherapy treatment. Clinical trials are required to demonstrate benefit of this new technology. Since the initial implementation of MR-IGRT, the Department of Radiation Oncology has initiated several clinical trials to evaluate the ideal setting for application of MR-IGRT. Trials are underway for patients with lung, pancreatic, and oligometastatic malignancies. It is hoped that the increased precision of this new technology may allow increased tumor dose, reduced complication risk, and tolerance of more potent systemic therapies concurrent with radiotherapy.

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Lung Stereotactic Body Radiation Therapy

by Sana Rehman, MD, Michael C. Roach, MD, Jeffrey D. Bradley, MD & Cliff G. Robinson, MD

Lung stereotactic body radiation therapy offers a safe and effective method of treating thoracic tumors using high doses of radiation in less than five treatments. It is most often used in early stage non-small cell lung cancer but it has an expanding role in other types of malignant thoracic diseases as well.



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Abstract

Lung stereotactic body radiation therapy (SBRT) is a novel and effective modality for treatment of early stage non-small cell lung cancer (NSCLC), with expanding indications in locally advanced and metastatic disease. Herein, we will review current treatment recommendations for early stage NSCLC, detail treatment planning of SBRT, and discuss future directions.

Introduction

Stereotactic body radiotherapy (SBRT) is a specialized delivery of external beam radiation therapy. It is defined by the American Society for Therapeutic Radiology and Oncology (ASTRO) and American College of Radiology (ACR) as a "method used to very precisely deliver a high dose of radiation to an extracranial target within the body, using either a single dose or a small number of fractions".[1] The technology delivers a high dose of radiation to a target with a rapid dose fall-off, maximizing dose to the tumor while minimizing dose to normal structures. While this strategy has a long history of successful use in intracranial lesions for more than 30 years, the ability to deliver similar treatments outside the brain is a more recent development. The first reports of extracranial stereotactic radiotherapy treatments were published in the 1990s. A seminal study from Sweden reported the results of their first 31 patients treated in a stereotactic body frame to extracranial sites of disease, including five patients treated to metastases in the lungs, with local control of 80%.[2] Lately, its use in treating thoracic tumors has seen a particularly rapid expansion in use as technology and understanding of the biology associated with such treatments has improved.

Background and Clinical Uses

Lung cancer is the most common cause of cancer death in the United States, with an estimated 159,260 deaths in 2014.[3] In Missouri each year, there will be an estimated 5,370 new cases and 3,950 deaths of cancer of the lung and bronchus.[4] Currently, 15% of non-small cell lung cancer (NSCLC) cases are diagnosed as early stage.[5] As CT-based screening for lung cancer in high risk patients increases, the percentage of lung cancers diagnosed as early stage may increase up to 33%.[6] This increase in the incidence of early stage NSCLC, coupled with the parallel increase in proportion of older (>65 years) adults [7] that may not tolerate aggressive surgical therapy, necessitates alternative treatment strategies.

For appropriate surgical candidates, the standard treatment for early stage NSCLC is surgical resection, often consisting of lobectomy, yielding five-year overall survival (OS) rates of up to 70%.[8] If a patient does not have the pulmonary reserve to tolerate a lobectomy, a sublobar resection such as a wedge resection or segmentectomy may also be offered for select patients, though older randomized data suggests this has inferior outcomes to lobectomy.[9] However, patients may be deemed inoperable due to pulmonary or cardiac comorbidities, advanced age, poor functional status, or patient refusal, among other reasons. In these situations, definitive doses of radiation can be used for tumor control. Historically, patients were treated to 60 to 70 Gray (Gy) in 30-35 daily fractions of 1.8-2.0 Gy per fraction, yielding five-year OS rates of only 5-10% with 50-70% of patients failing locally.[10, 11] Older studies also treated patients to larger volumes, including the primary tumor as well as elective nodal coverage, which could include the ipsilateral and contralateral mediastinum, ipsilateral and contralateral hila, and/or supraclavicular lymph node areas. The large treatment volume is one source of increased toxicity in this patient population. As radiation advanced from two-dimensional (2D) technique to three dimensional (3D) conformal radiotherapy, radiation was able to be delivered more precisely, and five-year OS improved from 10% for the 2D patients to 36% for patients treated with 3D radiation.[12] However, outcomes were still worse when compared to surgical treatment of early stage NSCLC.

More recently, SBRT has been used increasingly for treatment of early stage NSCLC. SBRT uses higher doses of radiation per fraction, often delivered in five fractions or fewer, and targets a volume using 3D localization. Since the target is more precisely localized, higher doses per fraction can be safely delivered while minimizing dose delivered to normal tissue. The outcomes for early stage NSCLC in medically inoperable patients treated with SBRT have been promising. After completing a phase I dose escalation trial, a phase II trial from Indiana evaluated SBRT for T1-2N0 NSCLC in 70 patients and found a three-year local control rate of 88% and three-year OS of 43%.[13] While this OS is lower than historical surgical controls, this patient population treated with SBRT also has more medical comorbidities that contribute to lower OS. In the multi-institutional phase II trial RTOG 0236, which excluded centrally located tumors within 2 centimeters of the proximal bronchial tree, three-year local control was 91% and three-year overall survival was 56%.[14] These early promising results led to an expanded role of lung SBRT.

The advantage of delivering a higher dose per fraction is based on an increased cytotoxic effect which can translate to an increased probability of tumor control. However,

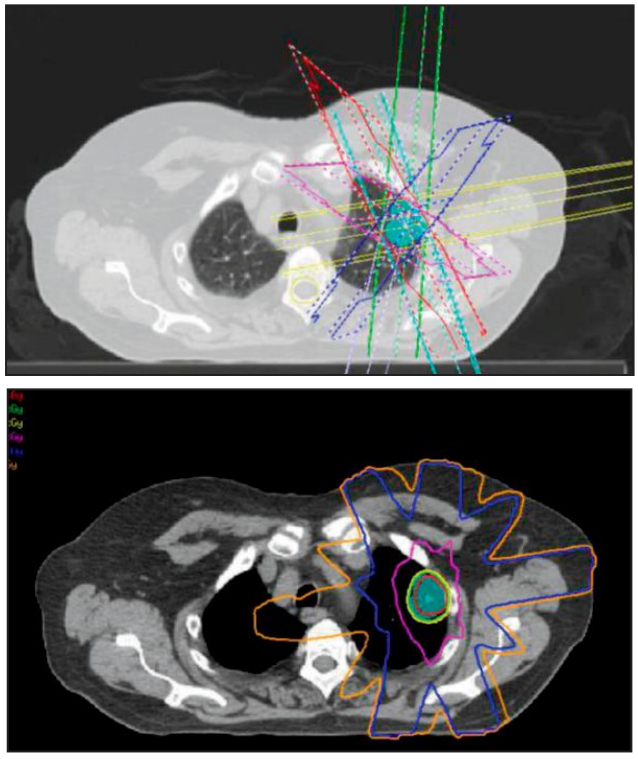


Figure 1
A Top) A left upper lobe lesion (shown in cyan colorwash) being treated to 5400 centigray (cGy) total in three fractions. The various beam angles to target the lesion are shown.
B Bottom) The dosimetric coverage of the lesion. The 100% isodose line (5400 cGy) covers the tumor. There is a rapid dose fall-off to the 50% isodose line (2700 cGy).

the location of the tumor and proximity to critical normal structures plays a role in determining the ideal dose that can be delivered safely. In a phase II trial where all patients received 60 to 66 Gy total in 3 fractions, two-year freedom from severe toxicity for peripheral tumors was 83% compared to 54% for centrally located tumors.[15] Doses used at Washington University most commonly are 54 Gy in 3 fractions for peripheral thoracic tumors and 50-55 Gy total in 5 fractions for centrally located thoracic tumors.

At our institution, there is a phase I/II trial exploring SBRT dose escalation of central tumors. The phase I dose escalation level portion of the trial began at 9 Gy for 5 fractions for a total dose of 45 Gy and was escalated to 10 Gy x 5 fractions, 11 Gy x 5 fractions, and 12 Gy x 5 fractions. There were no local failures in the 50 Gy, 55 Gy, or 60 Gy cohorts. It was determined to proceed to the phase II portion of the trial using 55 Gy.[16] As these data mature, further tumor control and toxicity profile will be available for centrally located tumors. Currently there is a national phase I/II trial, Radiation Therapy Oncology Group (RTOG 0813), that also looks to evaluate optimal dosing for early stage, centrally located NSCLC.

For more peripheral tumors, a higher dose can be delivered; however, the ideal dose for these tumors has yet to be determined. There is a wide range of acceptable doses that provide excellent tumor control while minimizing normal tissue toxicities. RTOG 0915 was a phase II trial that compared 34 Gy in one fraction to 48 Gy total in 4 fractions; both arms had similar rates of adverse events and local control.[17] From RTOG 0236, 60 Gy in 3 fractions was delivered safely to peripheral lung tumors. At our institution, it is common practice to treat peripherally located tumors to 54 Gy in 3 fractions.

Treatment Planning

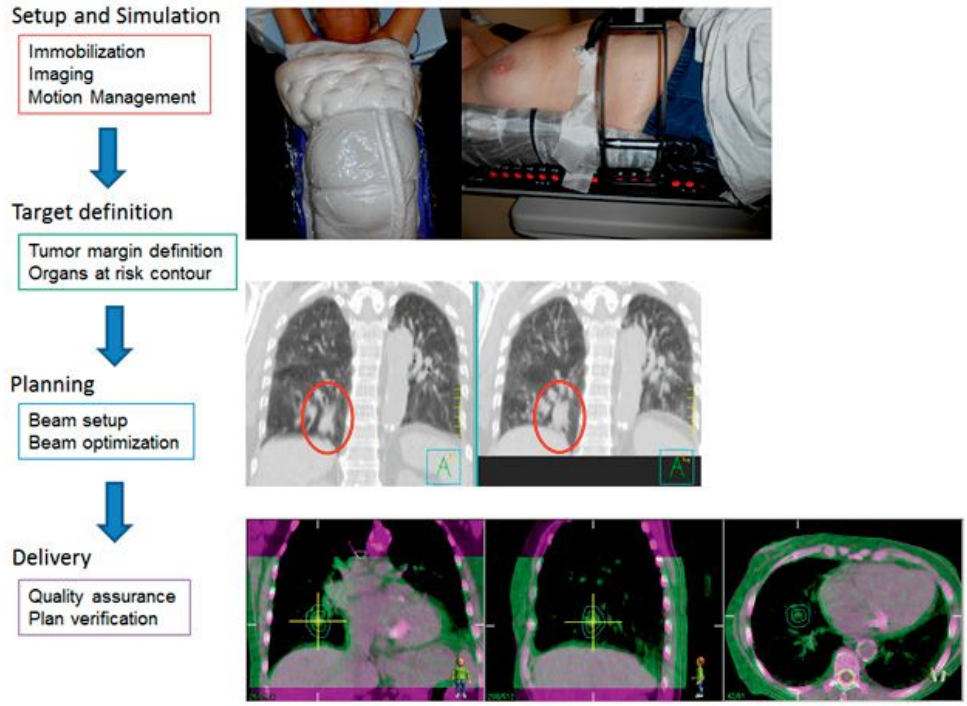
Prior to planning a patient for SBRT, the patient undergoes a computed tomography (CT) simulation within our radiation oncology department. This simulation includes a free breathing scan and a four-dimensional CT (4DCT) scan. The 4DCT acquires images throughout the breathing cycle, allowing an assessment of tumor motion. Patients are placed in a body frame to facilitate patient immobilization. As the target lies within the lung parenchyma, there is often significant tumor motion secondary to the respiratory cycle. It is important to monitor these motion changes in order to adequately cover the tumor. Images from the CT simulation are then used to define the gross target volume (GTV) and assess tumor motion. Generally, 1 centimeter or less of motion in any direction is considered acceptable. One method of decreasing tumor motion is to apply abdominal compression. Tumor motion can also be monitored using respiratory gating or patient breath holding. An additional margin is added to account for set-up inaccuracies called the planning target volume (PTV). After the tumor is contoured and the final target volume determined (i.e., the PTV), a plan is generated utilizing beams from various directions to cover the target adequately (Figure 1). On the day of each treatment, the patient is immobilized identically to the simulation session. Set-up is verified, which includes in-room imaging with a CT scanner built into the radiation treatment machine. Treatment is then delivered as planned with images reviewed prior to delivery of radiation (See Figure 2)

Toxicity

While delivering high doses of radiation per fraction has been shown to provide good local control, there are toxicities associated with the treatment from damage to

Figure 2
The Process of Stereotactic Body Radiation Therapy

A) Two types of immobilization devices are shown. In the left panel, the patient is immobilized with BodyFIX. It utilizes vacuum technology to create a mold of the patient's body contour. In the right panel, the patient is immobilized with a custom fitted foam frame with a paddle on the patient's abdomen to minimize tumor motion with the respiratory cycle.
B) During simulation, a four-dimensional or respiratory CT scan is obtained. It allows for visualization of structures throughout the respiratory cycle. The scan on the left is during the exhale portion of respiration when the tumor motion is typically minimal. The right panel shows the maximum intensity projection (MIP) images. MIP is a surrogate for where the tumor is moving during respiration. The red oval encircles the tumor; the tumor appears fuller and larger on the MIP images.
C) Prior to delivering each fraction, a cone beam CT (CBCT) is performed on the treatment machine. The purple shade CT is the scan from the simulation. The green shade scan is from the CBCT prior to treatment. Depending on the location of the tumor, the CBCT can be matched to the simulation CT by bony landmarks or soft tissue to ensure the tumor is lining up properly prior to delivery of treatment.



nearby normal tissue. While overall toxicity rates after SBRT are exceptionally low, the most common adverse events include chest wall pain and radiation pneumonitis. In the RTOG 0236 phase II trial, which included 55 evaluable patients, 24% of patients developed a moderately severe adverse event and 4% of patients developed a severe adverse event.[14] The majority of moderately severe adverse events were related to the pulmonary or upper respiratory tract or musculoskeletal or soft tissue. Severe adverse events included hypocalcemia and decrease in pulmonary functions.

Specifically regarding chest wall toxicity, in an analysis from our institution, Creach et al. reported 16% of patients developed CW pain at a median time of 12.6 months after completion of SBRT. Dosimetric factors predictive for developing chest wall pain included chest wall volume receiving ≥30 Gy (V30), while clinical factors predictive included high BMI and connective tissue disease [(18)]. This chest wall pain can be treated with anti-inflammatories and narcotic medications, similar to how chest wall toxicity from a surgical resection would be treated.

Radiation-induced pneumonitis (RP) is another reported toxicity. It consists of inflammation of the lung parenchyma which is often asymptomatic or easily treatable; however, rare cases may be fatal. On RTOG 0236, the rate of grade 1-3 RP was 16%. When grade 1 (asymptomatic but radiograhically diagnosed) RP was excluded, the rate of symptomatic radiation pneumonitis was less than 10%. There was no severe pneumonitis.[19] At Washington University, our overall rate of symptomatic RP in a recent analysis of 321 patients was only 5%.[20]

With careful planning and awareness of normal structures at risk, lung SBRT can be safely delivered and risk of acute and long term side effects can be minimized.

Expanding Role of SBRT

SBRT is an accepted therapy for early stage NSCLC, but it also has expanding roles such as for patients who present with multiple primary lung nodules. It is often difficult to ascertain if these patients have multiple primary lung cancers or intrapulmonary metastases. Those treated with SBRT for multiple lung cancers at presentation are classified as undergoing synchronous treatment. Alternatively, patients may relapse in the future with a new lung lesion which may represent a recurrence or a new primary and are again treated with SBRT (metachronous treatment). Data from our institution reveal two-year OS for synchronous and metachronous tumors was 50% and 61%, respectively.[21] However, patients with centralized tumors did worse than those with peripheral tumors in this cohort, supporting the need for optimized strategies for this patient population.

Lung SBRT has also gained popularity in patients with limited number and sites of metastatic disease (i.e. oligometastases), where potential for long term disease control is possible. Singh et al. reported results of 34 patients treated with SBRT for oligometastatic cancer to the lung.[22] Patients were treated with doses ranging from 40 to 60 Gy total in 5 fractions. Patients included in the study had up to five lung metastases, local control of primary tumor, and no other sites of active metastatic disease. As with primary lung cancer, a high rate of local control of the metastases was achieved (one- and three-year local control of 93% and 80%, respectively). Our institutional experience in SBRT for oligometastases has shown one- and two-year local control rates of 93% and 77%, respectively (unpublished data). This data lends support to the role of lung SBRT in the setting of oligometastatic disease with an emphasis on carefully selecting patients that would benefit from this treatment modality. At our institution, this is becoming more common practice.

As the overall United States patient population ages and is often frail, patients more commonly present without the capability of safely undergoing biopsy to confirm malignancy. Particularly in Missouri, the differential diagnosis for a newly diagnosed pulmonary nodule includes fungal infection from histoplasmosis or blastomycosis. However, with the proper selection criteria, this patient population can be safely treated even without a histopathologic diagnosis for a presumed early stage NSCLC. The diagnosis of NSCLC is favored when patients have growing, positron emission tomography (PET) avid nodules with an appropriate clinical history. At Washington University, 22% of patients have been treated with lung SBRT without a pathologic diagnosis based on clinical grounds alone. Our recently updated institutional data shows equivalent local control and OS between patients with and without a biopsy, confirming our practice to treat carefully selected patients without a pathologic diagnosis.[23]

Future Directions

Lung SBRT has had an expanding role in the treatment of medically inoperable lung cancer. However, there may also be a role for lung SBRT in patients with medically operable disease. RTOG 0618 was a phase II trial that studied the outcomes of SBRT for operable early stage lung cancer patients. Preliminary results showed a two-year primary tumor failure rate of 8% and local failure (including primary tumor and lobar failure) rate of 19%. Two year OS was 84%. The authors concluded that SBRT provided a high rate of tumor control with survival comparable to historic surgical series.[24]

While lung SBRT is most often used for early stage lung

cancer, it can also be used in the setting of a boost for more advanced disease. Currently, there is a phase I/II alternative radiation fractionation trial for locally advanced NSCLC open at our institution. Patients are treated with standard 2 Gy per fraction to 44 Gy with concurrent carboplatin and paclitaxel. The residual gross disease then receives a SBRT dose (using a dose escalation schema). The trial is exploring delivery of a higher total effective dose with this alternative radiation fractionation schema.

As the role of lung SBRT expands in the setting of oligometastases, this has also become an important area of research, and we co-developed and recently opened a phase I trial (NRG BR001) exploring the safety and efficacy of SBRT for ≤4 oligometastases in patients with breast, prostate, and lung cancer. Once the results are available, this study will provide more information about the safety of treating multiple sites of metastatic disease.

As technology continues to evolve, new ways of delivering SBRT will continue to improve. At our institution, we have started to treat patients on the ViewRay™ system, the world's first MRI-guided radiation therapy machine. Using image guidance with MRI can help guide radiation treatments and evaluate tumor motion, and possibly reduce margins as well as adapting treatment if tumor location or size changes. We will wait for our clinical data to mature as we continue to use this new technology.

Conclusion

Lung SBRT offers a safe and effective method of treating thoracic tumors using high doses of radiation in less than five treatments. It is most often used in early stage NSCLC, but it has an expanding role in other types of malignant thoracic diseases as well. Tremendous progress has been made in our understanding of the technology and clinical effects of lung SBRT, and with continuing research, there is potential to continue to expand its clinical indications.

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Intracavitary Brachytherapy for Gynecologic Malignancies: Applications and Innovations

by Ashley A. Weiner, MD, PhD & Julie K. Schwarz MD, PhD

New advances in imaging techniques, 3-dimensional adaptive treatment planning, and dose-volume reporting are adding precision and versatility to this powerful treatment tool in the curative treatment for cervical and endometrial cancers.



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Abstract

While surgical management is a common approach for gynecologic malignancies; often disease is locally advanced such that surgery is precluded or surgical pathology reveals disease extent that mandates adjuvant treatment. Gynecologic brachytherapy is an important tool for both definitive and adjuvant treatment of cervical and endometrial cancers. Brachytherapy enables high radiation doses to a target with rapid fall-off to protect adjacent normal structures. This paper aims to detail the usage of brachytherapy in gynecologic cancers with a focus on advances in technique.

Introduction

Of the 810,320 malignancies expected to be diagnosed in females in the United States in 2014, gynecologic malignancies are estimated to total 94,990 cases. Over half of these diagnoses will be cancers of the uterine corpus. Table 1 shows the expected distribution of gynecologic malignancies among the various subsites including uterine cervix, uterine corpus, ovary, vulva and vagina.[1] In Missouri in 2014, the estimated number of new diagnoses of uterine cancer is 1,090, while there are expected to be 240 new cases of cervical cancer.[1] Cervical cancer incidence rates have declined in the past several decades and have now stabilized among women younger than 50, and continue to decline in women age 50 and older. Uterine cancer incidence rates continue to increase among women both over and under age 50.

The primary presenting symptom of both cervical and uterine cancer is abnormal vaginal bleeding. The majority of patients are treated by surgical approaches, typically via hysterectomy. However, some patients have risk factors found on surgical pathology that predict for increased risk of recurrence, warranting further adjuvant treatment with radiation and/or chemotherapy. Additionally, particularly in locally advanced malignancies, a definitive management approach with chemotherapy and radiation is recommended. Brachytherapy is a

particularly attractive approach for radiation treatment of the gynecologic malignancies by the principles of source proximity to treatment target as well as an ability to generate rapid dose fall-off to protect surrounding organs at risk. It should be emphasized that brachytherapy is part of the standard of care for the treatment of locally advanced cervical cancers. In fact, recent studies have emphasized the importance of brachytherapy in the primary management of this disease.[2]

History and Physics of Gynecologic Brachytherapy

The first report of the use of gynecologic intracavitary brachytherapy was in 1903 by Margaret Cleaves, MD, in an effort to treat a patient with a locally advanced cervical squamous cell carcinoma with bladder and rectal invasion and extension to the introitus. After standard treatment with UV light and intracavitary x-rays, Dr. Cleaves elected to attempt application of radium bromide acquired from a local chemistry lab in attempt for deeper penetration of the tissues. After application for 10 minutes on day 1, and 5 minutes on day 2, an intense reaction of the mucous membranes was noted. However, several days later the tissues had healed without bleeding, odor, and discharge with a grossly normal appearance.[3]

The term brachytherapy is derived from the Greek brakhus, meaning "short." In this radiation therapy technique, sealed radioactive sources are placed near or in direct contact with target tissues. Brachytherapy sources are typically unstable gamma-emitting radioisotopes, classically radium (which is no longer in clinical use) as well as isotopes of cesium or iridium. Brachytherapy source physics allows a high dose concentration immediately surrounding the radioactive source, with rapid dose fall-off within adjacent tissues. There are a variety of different delivery methods for brachytherapy including intracavitary, in which the applicator is placed within an existing body cavity and interstitial, in which sources are placed directly into tissue. Of the gynecologic subsites, cervical and endometrial cancers are most amenable to treatment via intracavitary brachytherapy, while the vagina and vulvar subsites are more suited for interstitial brachytherapy.

An additional variable in brachytherapy is the concept of dose rate. Traditionally, treatments were low-dose rate (LDR) and occurred over a period of 40-60 hours. The patient is nonambulatory during the duration of treatment, and as such the treatments would require inpatient hospitalization with regional or even general anesthesia. The clinical usage of high-dose rate (HDR) brachytherapy has dramatically increased, significantly decreasing treatment times. As a result, these treatments can occur on an outpatient basis with patient preparation, implantation procedure, imaging and treatment being completed within a few hours. Patient risks such as prolonged immobilization and hospitalization are therefore minimized and as such the treatments are more convenient and potentially more cost-effective. Additionally, there are opportunities to perform adaptive treatment planning and dosimetry with each fraction. From a radiation biology perspective, HDR has been proposed to be superior if adequate time is allotted between fractions for normal tissue to repair sublethal damage between fractions.[4]

A final modern improvement in gynecologic brachytherapy has arisen from the development of computer-controlled remote afterloading devices for brachytherapy. These devices allow automated loading of the radioactive source while the patient is within the shielded treatment room. This eliminates radiation exposure to health care workers in contrast to manual application or manual afterloading of radioactive sources in which the operator must manually place the radioisotope.

	Diagnoses	Deaths
All sites	810,320	275,710
All Gynecologic sites	94,990	28,790
Uterine cervix	12,360	4,020
Uterine corpus	52,630	8,590
Ovary	21,980	14,270
Vulva	4,850	1,030
Vagina	3,170	880

Table 1
Data from American Cancer Society. Cancer Facts and Figures 2014. Available at www.cancer .org

Cervical Cancer

The widespread use of the Papanicolaou screening has greatly reduced the incidence of cervical cancer

in the United States; however worldwide this disease remains quite prevalent. Treatment of cervical cancer largely depends on the stage at diagnosis, which is determined by a clinical stage established by the International Federation of Gynecology and Obstetrics (FIGO). FIGO staging depends on the physical examination with tumor size, extension past the cervix into the vagina or parametria, involvement of pelvic sidewall or hydronephrosis being the factors that upstage a tumor. Radiographic studies such as CT, MRI or PET do not determine a patient's tumor stage; however these modalities are used to make treatment management decisions. An early stage microinvasive cervical cancer may be treated with simple or radical hysterectomy. However, with increase in tumor size, the likelihood of a recommendation of post-operative radiation increases based on operative pathology. For example, in one study by the Gynecologic Oncology Group (GOG), patients with stage IB cervical cancer treated with radical hysterectomy and pelvic lymphadenectomy with at least two risk factors (>1/3 stromal invasion, lymphovascular space invasion, or large clinical tumor) were randomized to pelvic irradiation vs observation. Pelvic radiation was found to decrease cancer recurrence by 50% in this set of patients, although a risk of increase in treatment-related toxicities was noted.[55] Additionally, in a subsequent GOG study, patients with pathologically positive parametria, pelvic lymph nodes or positive surgical margins after surgery were randomized to pelvic radiation vs. pelvic radiation with cisplatin-based chemotherapy.[6] The combination of chemotherapy with radiation increased both progression-free survival and overall survival with increased risk of grade severe toxicity. An Italian study randomizing patients with bulky cervical cancer to primary RT vs radical hysterectomy showed no difference in five-year overall survival or progression-free survival.[7] Greater than 50% of patients in the surgery arm warranted post-operative radiation based on surgical pathology findings. Complications and toxicities were significantly increased in the surgical arm.

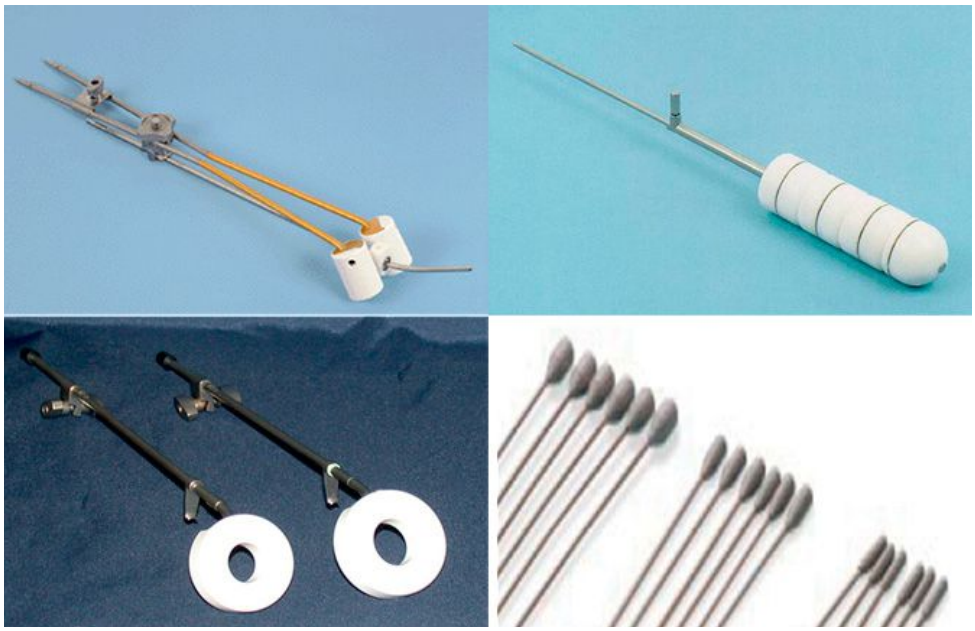


Figure 1
Applicators used in gynecologic intracavitary brachytherapy. A: Tandem and ovoids, used in definitive treatment of cervical cancer. B: Vaginal cylinder, used in post-hysterectomy treatment of endometrial cancer to decrease vaginal cuff recurrence. C: Vaginal Ring, which can be used in conjunction with an intrauterine tandem for definitive cervix treatment or used alone for palliation of cervical tumor bleeding. D: Simon-Heyman capsules which are used with tandem and ovoids for early-stage medically inoperable endometrial cancer.

Due to the high likelihood of need for postoperative radiation for patients with a bulky cervical cancer and the increased toxicities with this treatment, definitive chemoradiation is the treatment of choice for cervical cancers greater than 4 cm and those with extension past the cervix. PET has been shown to be more sensitive for detection of nodal metastases than CT scan[8] and as such, a pre-treatment PET should be performed to guide treatment volumes. Presence of lymph node metastasis and degree of PET uptake within lymph nodes are prognostic factors in patients with advanced cervical cancer.[9, 10] Typical treatment for a locally advanced cervical cancer involves external beam radiation to the pelvic lymph node regions to a dose of 50 Gy over five to six weeks. Cisplatin-based chemotherapy is typically administered

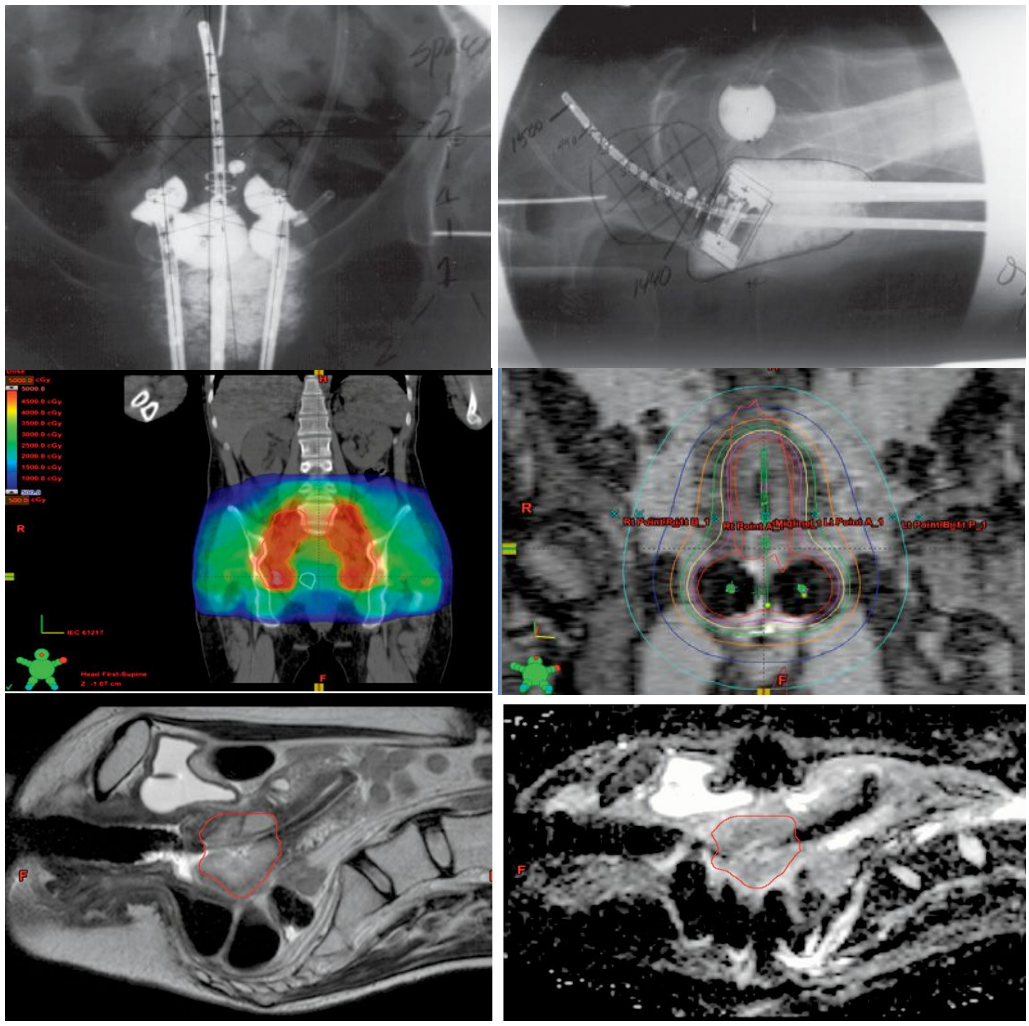


Figure 2
A and B: Posterior and lateral views of a tandem and ovoid implant. C. Coronal representations of an radiation plan delivering 45 Gy to the pelvic lymph nodes (red contour), and 20 Gy to the metabolically active primary cervical tumor (white contour) in a patient with FIGO stage IIb squamous cell carcinoma with pelvic lymph node involvement. D: Coronal isodose lines for a tandem and ovoid implant. The prescription isodose line is seen in green (650 cGy).E and F: Corresponding T2-weighted sagittal brachytherapy planning image with primary tumor in red (left), and corresponding diffusion-weighted sequence (right).

concurrently with radiation, as randomized studies have shown improved overall survival, and progression-free survival in comparison with other regimen.[11,12] Treatment breaks can decrease the acute toxicities of radiation, though they can decrease efficacy of treatment by accelerated repopulation of tumor clones. In cervical cancer, each additional day of treatment beyond 55 days has been shown decrease overall survival by 1%.[13]

Brachytherapy is an integral component of definitive treatment of locally advanced cervical cancer by providing high radiation dose to the primary cervical tumor while allowing relative sparing of the bladder and rectum. In a Surveillance, Epidemiology and End Results (SEER) analysis, Han et al. have demonstrated a dramatic decline in the use of brachytherapy in the definitive treatment of cervical cancer from 1988 – 2009. In this study, the use of brachytherapy was associated with significantly higher cause-specific survival and overall survival.[2] Tanderup et al. detail the risks of attempting to utilize new external-beam radiation techniques (intensity modulated or stereotactic body radiotherapy) in lieu of brachytherapy; these risks include decreased local control and increased toxicities.[14] These findings suggest that inclusion of brachytherapy in treatment planning for locally advanced cervical cancer is paramount for treatment success.

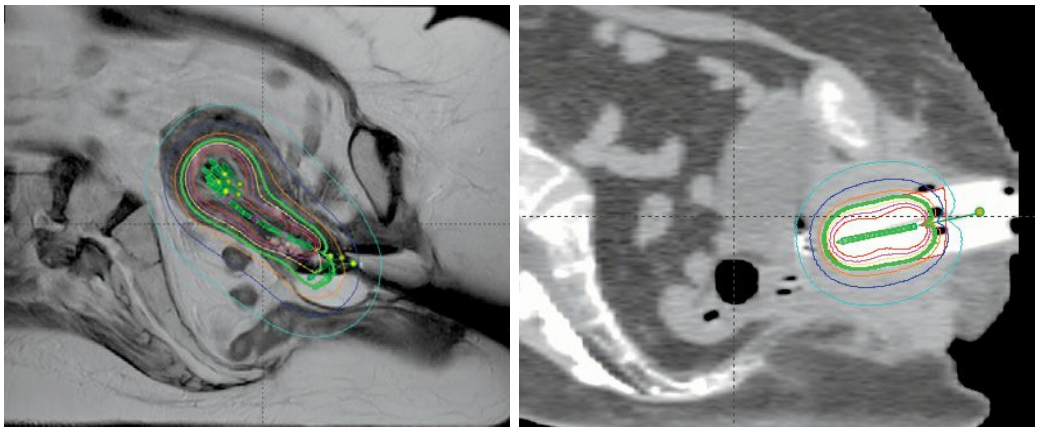


Figure 3

A: Sagittal plane representative isodose lines for a tandem, ovoid and Simon-Heyman capsule brachytherapy. The prescription isodose line for a single brachytherapy treatment (375 cGy) is shown in green, while the 188cGy (dark blue) and 113 cGy (light blue) lines can also be seen. The isodose line in the center of the implant (red) is 750 cGy.

B: Sagittal plane representative isodose lines for a vaginal cylinder brachytherapy fraction. The prescription isodose line for a single brachytherapy fraction (400 cGy) is shown in green, while the 200cGy (dark blue) and 120 cGy (light blue) lines can also be seen. The isodose line in the center of the implant (red) is 800 cGy.

The components of brachytherapy for cervical cancer include an intrauterine applicator, called a tandem which is used in conjunction with intravaginal components such as vaginal ovoids (seen in conjunction with a tandem in Figure 1A), or a vaginal ring. Varieties of tandem lengths and curvatures, as well as different ovoid diameters are available and are selected based on patient anatomy. Intravenous conscious sedation is utilized prior to implantation of the applicators. Gauze or vaginal balloons are used as packing anterior and posterior to the ovoids to decrease bladder and rectum dose. Timing of brachytherapy with external beam radiation is institution-dependent; at our institution, weekly HDR brachytherapy treatments are administered concurrently with external beam treatments. The patient does not receive an external beam radiation treatment on the day of brachytherapy. In an analysis of patterns of radiation therapy practice in the treatment of intact cervical cancer, Eifel et al. have estimated that only 8% of radiation therapy facilities in the United States treat more than three patients per year with intact cervical cancer.[1515] Patients receiving their treatments at low volume centers are less likely to receive brachytherapy, likely receive a lower dose, and require a longer average time to complete treatment – all factors that are detrimental to the efficacy of treatment.

In brachytherapy treatments, the geometry of the implant is critical for optimizing dose to the tumor target. Traditional implant evaluation was via pelvic x-rays (Figure 2A and 2B), with radiation prescribed to Point "A" which is 2 cm lateral to the center of the uterine canal and 2 cm superior to the lateral fornices of the vagina. This point is to approximate where the uterine vessels cross the ureter and the dose represents the normal tissue tolerance to prevent necrosis. More modern 3D treatment planning, in which an MRI is performed immediately following each implantation and prior to each treatment fractions allows customized treatments based on implant geometry. A variety of HDR dose prescriptions are acceptable based on guidelines by the American Brachytherapy Society, consisting of four to six HDR treatments which, in conjunction with pelvic external beam treatment will yield an equivalent dose of 85 Gy to point A.[16] External beam radiation treatment is performed in conjunction with tandem and ovoid brachytherapy, and in the external beam plan the pelvic lymph node regions receive 45 Gy while the metabolically active cervical tumor receives 20 Gy, shown in Figure 2C. Figure 2D depicts the planned isodose lines for a tandem and ovoid brachytherapy fraction. A composite plan is created with the external beam treatment plan and the brachytherapy fractions to assess total overall dose. In the Figure 2E and F, T2-weighted and diffusion-weighted sagittal MRI sequences of a brachytherapy implant are seen with the cervical tumor target for that fraction contoured

in red. Adjacent normal structures (bladder, rectum and sigmoid colon) are contoured to generate radiation dose information for the organs at risk in addition to the tumor target. MRI-guided brachytherapy in conjunction with PET-CT guided intensity-modulated external beam radiation for definitive cervical cancer treatment is currently being actively investigated to determine optimal radiation distribution that correlates with tumor control. Recently, Dyk et al. have shown the dosimetric parameters D100 (minimum dose covering 100% of the cervical target), D90, and Dmean of the gross tumor volume (GTV) as defined by MRI are associated with improved local tumor control.[17]

In addition to serving as a component of definitive treatment for locally advanced cervical cancer, brachytherapy plays a role in palliation of bleeding from cervical tumors. Two treatments of 500 cGy via a vaginal ring (Figure 1C) have been demonstrated to reduce the need for additional transfusion in 93% of patients without acute or long-term grade 3-5 toxicity.[18] The dose conformality of these treatments minimizes dose to the rectum, bladder or Point A and, as such, the definitive treatment planning is not jeopardized or limited. Patients who present with symptomatic bleeding from a cervical tumor may undergo vaginal ring brachytherapy with improvement in symptoms prior to initiation of definitive treatment.

Endometrial Cancer

Endometrial cancer, the most common gynecologic malignancy, is typically diagnosed at an early stage after presentation with post-menopausal bleeding. Initial management generally includes total hysterectomy, bilateral salpingo-oophorectomy, pelvic and para-aortic lymph node sampling and peritoneal cytology. FIGO staging of endometrial cancer is based on surgical pathology. In FIGO stage I patients, where involvement is limited to the endometrium or myometrium, stratification by adverse risk factors including age, lymphovascular space invasion, and depth of myometrial invasion is used to make adjuvant therapy recommendations. Randomized trials for low-intermediate risk endometrial cancer have demonstrated that the majority of recurrences in this group are limited to the vaginal cuff.[19, 20] A subsequent trial randomized patients with high-intermediate risk endometrial cancer to pelvic external beam radiation versus vaginal cuff brachytherapy showing no difference in vaginal cuff relapse between the two groups.[21] While the risk of pelvic nodal relapse was greater in the brachytherapy alone group, there was no overall survival difference between the two groups. Importantly, there was less acute toxicity after brachytherapy, and quality of life analysis showed significantly worse bowel symptoms and social functioning in patients who received external beam radiation.[21, 22]

Post-operative vaginal cuff HDR brachytherapy is performed via implantation of a vaginal cylinder (Figure 2B) for treatment of the upper vagina, with a target of the vaginal submucosal lymphatics with administration in three to six doses per American Brachytherapy Society guidelines.[23] After implantation of the vaginal cylinder, CT images are obtained to verify implant position and to perform dosimetric analysis for each fraction (Figure 3B). Unlike tandem and ovoid brachytherapy, sedation is often not necessary for vaginal cuff treatments.

In contrast, stage I endometrial cancer in a medically inoperable patient may be treated with definitive brachytherapy. In these treatments, tandem and ovoid applicators are used similarly to definitive cervical cancer treatment. Radiation dose to the uterine serosa is achieved by the addition of Simon-Heyman capsules (Figure 3A), which are inserted through the dilated cervical os prior to placement of the intrauterine tandem. This technique is particularly useful in newly diagnosed endometrial cancer patients who cannot undergo surgery due to medical co-morbidities including obesity.

Endometrial cancer patients with extrauterine disease, such as a FIGO stage III patient with positive pelvic or para-aortic lymph nodes receive external beam radiation to the pelvis (and para-aortic region if involved) in addition to vaginal cuff brachytherapy. Chemotherapy may be given either prior to or concurrently with radiation depending on patient and pathologic factors.

Vulvar and Vaginal Cancers

Early-stage vulvar and vaginal cancers may be treated with surgical resection, though advanced or bulky tumors warrant a definitive approach of chemotherapy and radiation. These sites are generally

not amenable for intracavitary brachytherapy, and in order to safely deliver high radiation doses to the tumor target, interstitial brachytherapy may be a component of treatment planning. In interstitial HDR brachytherapy, catheters are inserted directly into the tumor target while the patient is under conscious sedation. Catheter arrangement is determined by patient anatomy and tumor geometry. After catheter placement, treatment planning is done via a post-procedure CT. The catheters remain in place for four days during which the patient receives two brachytherapy fractions daily at six-hour intervals. Due to the complexity of both the implantation procedure and treatment planning, patients who are candidates for vaginal or vulvar brachytherapy warrant referral to a tertiary care center specializing in these techniques.

Conclusions

Brachytherapy is one of the cornerstones of treatment for gynecologic malignancies due to the ability to deliver high target doses while minimizing normal tissue toxicity due to rapid dose fall-off. New advances in imaging techniques, 3D adaptive treatment planning, and dose-volume reporting are adding precision and versatility to this powerful treatment tool in the curative treatment for cervical and endometrial cancers.

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Disclosure

None reported.

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Imaging Advances in Stereotactic Radiosurgery

by Christina I. Tsien, MD, Robert E. Drzymala, PhD & Keith Rich, MD

Novel functional MRI imaging provides the ability to analyze tumor tissue properties including chemical composition, vasculature and perfusion, water mobility, permeability, hypoxia, and tumor proliferation. These imaging modalities have the potential to improve radiosurgery planning and post-treatment monitoring.



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Abstract

Novel functional and metabolic MRI imaging provides the ability to analyze tumor tissue properties including tumor vasculature, vascular permeability, tumor cellularity, hypoxia, and tumor proliferation. Stereotactic radiosurgery involves the delivery of a very precise, focal dose of radiation to a target. Recent advances in MR imaging have the potential to improve accuracy for target volume delineation and to potentially improve outcome. Novel MR imaging techniques may also be used in subsequent post-treatment follow-up to distinguish between tumor recurrences versus non-neoplastic treatment-related changes. In this paper, we address multiparametric MR imaging and cerebral angiography as tools to reduce toxicity.

Introduction

Gamma Knife stereotactic radiosurgery (SRS) involves the delivery of a very precise, focal dose of radiation (RT) to a target. The accurate delineation of the treatment volume is critical to ensure maximal dose to the target as well as optimal sparing of the normal surrounding tissue. Conventional imaging reflects only anatomic rather than functional properties of the tumor. In contrast, metabolic and functional imaging provides in vivo measures of tumor and normal tissue properties. Although Gamma Knife SRS treatment has been established for many years, recent advances in modern imaging combined with improved radiotherapy techniques can provide better target delineation; reduce normal tissue toxicity as well as provide better assessment of treatment response. The role of conventional imaging in defining target volumes for SRS management of both malignant and benign CNS tumors as well as novel MR and PET imaging techniques that seek to improve upon these target definitions will be described.

Imaging and Treatment Planning Considerations

Conventional contrast enhanced CT scanning provides anatomic information as well as electron density information, with a geometric accuracy to support stereotactic targeting and to calculate RT dose. Contrast-enhanced T1-weighted and T2-weighted MRI provides superior soft tissue contrast relative to CT and has been used routinely in target volume definition in stereotactic radiosurgery treatment. The goal of SRS is not only to give maximal dose to the target, but also to prevent damage to the surrounding

normal tissue. Gamma-knife SRS has been used to treat a variety of malignant and benign tumors at the Washington University and Siteman Cancer Center Program. (See Table 1)

Tumor size and proximity to critical structures need to be taken into consideration during treatment planning. Tumor size determines the feasibility of radiosurgery. Increasing tumor size is potentially associated with a higher risk of complications. Results from the Radiation Therapy Oncology Group (RTOG) 9005 trial showed significantly higher CNS toxicity in patients with larger tumor diameters.[1] Compared to tumors 2cm or less in diameter, tumors 2.1-3 cm had a 7.3 times higher risk of developing toxicity, and tumors 3.1-4 cm had an odds ratio of 16. In general, radiosurgery is not recommended for tumors more than 4 cm in size.

Critical neuro-anatomic structures are important to consider during SRS planning. Relative contraindications for SRS include close proximity or involvement of the optic tract including optic nerves and chiasm. The optic apparatus dose is usually limited to 10 Gy to lower the risk of optic neuropathy.[2,3] In contrast, the remaining cranial nerves have higher dose tolerances.[4,5]

Table 1
Washington University – Gamma Knife SRS Program

Tumor Type	No. of Cases Treated
Brain Metastases	1681
Trigeminal Neuralgia	585
AVM	265
Vestibular Schwannoma	324
Meningioma	395
Pituitary	240

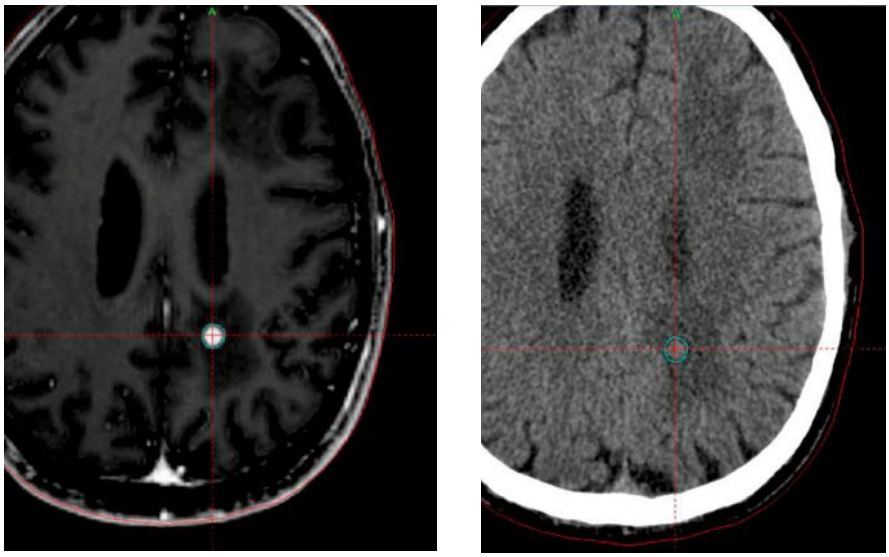


Figure 1
Image registration of MR and CT for left parietal brain metastases for SRS treatment planning.

Physiologic MR Imaging

Physiologic MR imaging can provide additional information not obtainable by morphological imaging, and in some instances they can serve as a surrogate marker for specific biologic processes. These newer imaging modalities are now routinely available and will continue to play an increasingly important role in precisely defining target volumes at risk as well as accurate normal tissue delineation.[6-8]

Assessing tumor response after SRS can be difficult due to occurrence of early imaging changes that mimic tumor progression, characterized by areas of contrast enhancement and edema on T1-weighted imaging. (See Figure 1.) New areas of contrast enhancement in the region of a tumor previously treated with SRS can represent either recurrent or progressive tumor, or treatment-related inflammatory or necrotic changes. Mechanisms that may contribute to radiation-induced neurotoxicity include vascular injury, glial and white matter changes, and immunological mechanisms. Post-treatment conventional imaging features are often nonspecific, and often the underlying processes of radiation injury cause a temporary increase in contrast enhancement on MRI, (termed "pseudo-progression), making the differentiation between true progression and radiation effects often extremely difficult. Novel imaging provides additional metabolic information that can potentially improve our ability to reliably differentiate between tumor growth and radiation effects from SRS.

Dynamic susceptibility contrast (DSC) T2*-weighted MR imaging obtained during intravenous injection of Gd-DTPA allows estimations of cerebral (tumor) blood volume, bolus transit time and flow.[6] Relative cerebral (tumor) blood volume (CBV), mean transit time (MTT) and their ratio for cerebral (tumor) blood flow (CBF) can be measured in the imaged volume by mathematical de-convolution of the arterial input function (from a cerebral

artery), and the tissue response signal.[5,9,10] MR perfusion provides evidence of tumor viability and is also sensitive to tumor vascular properties and transport kinetics following therapy.[9]

MR dynamic contrast enhanced MR imaging provides a method for assessing vascular permeability. Dynamic MR image acquisition is obtained over several minutes during intravenous injection of a bolus of Gd-GTPA using T1 weighted imaging. A voxel by voxel CBV map can be estimated by integrating the area under the first pass of the dynamic contrast uptake curve. Estimations of CBF and vascular permeability in tissue require the application of pharmacokinetic models with an artery input function and therefore much more complex than CBV estimation. Several studies have shown a correlation between vascular permeability and the histological grade of a tumor.[10,11] It has been also shown to be important in the assessment of tumor growth as well as treatment effects from anti-angiogenic agents and radiation.[12]

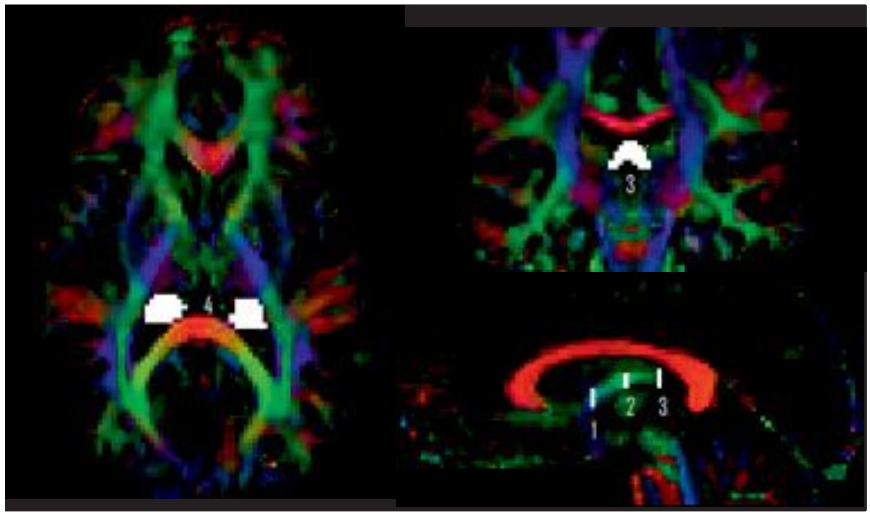


Figure 2
MR Diffusion Tensor imaging and tractography obtained to delineate normal tissues at risk.

Diffusion MRI measures the mobility of water (the direction and magnitude of diffusion) within tissues at the cellular level and therefore can detect microenvironment changes in tumor tissue. These changes can include cell swelling, necrotic/apoptotic cell death after therapy, or extracellular water space changes as a result of edema, as well as differences in cell membrane permeability. [13] In addition, there may be changes in the cell membrane permeability between intracellular and extracellular space. Regional alterations in the tumor following successful therapy such as cytolytic death, lead to transient increases in regional diffusion. This may be an important early indicator of treatment response.

Diffusion tensor imaging (DTI) is a diffusion technique that allows visualization of white matter architecture, and has been increasingly investigated as an imaging biomarker for detecting physiological changes prior to any detectable changes on imaging. (See Figure 2.) Surgical series have demonstrated its importance by reducing the risk of permanent toxicity when operating on brain tumors near critical structures. Similar incorporation of DTI imaging in SRS treatment may be valuable in providing normal tissue avoidance in the treatment planning of lesions located near eloquent regions. DTI tractography has been evaluated in treatment planning to delineate areas at risk.[14] A recent study showed that functional structures of the brain as well as white matter fiber pathways could receive high RT doses (i.e. greater than 50% of the maximum dose) depending on their distance from the treated lesion if these structures were not identified during the treatment planning process. Incorporation of DTI tractography data decreased doses to critical structures including the optic tract and pyramidal tracts.[15]

Imaging Consideration in the SRS Treatment of Brain Metastases

Due to the lack of survival benefit with the addition of whole brain radiotherapy, there has been a shift with a significant increase in the use of stereotactic radiosurgery in patients with a limited number of brain metastases and with controlled systemic disease.[16] Target volume definition is typically defined using conventional thin-cut CT or MR imaging with contrast enhancement.

SRS is frequently used as adjuvant treatment after surgical resection, achieving local control rates of approximately 80% at one year.[17] In planning treatment in the adjuvant setting, one also needs to take into consideration changes in the size of the surgical cavity when delineating the target volume. In a study by Atalar et al[18] on 68 lesions, the post-resection cavity volume was smaller than the pre-resection tumor volume by a median percent volume change of 29%.[18] The authors found that the greatest volume change occurred immediately after

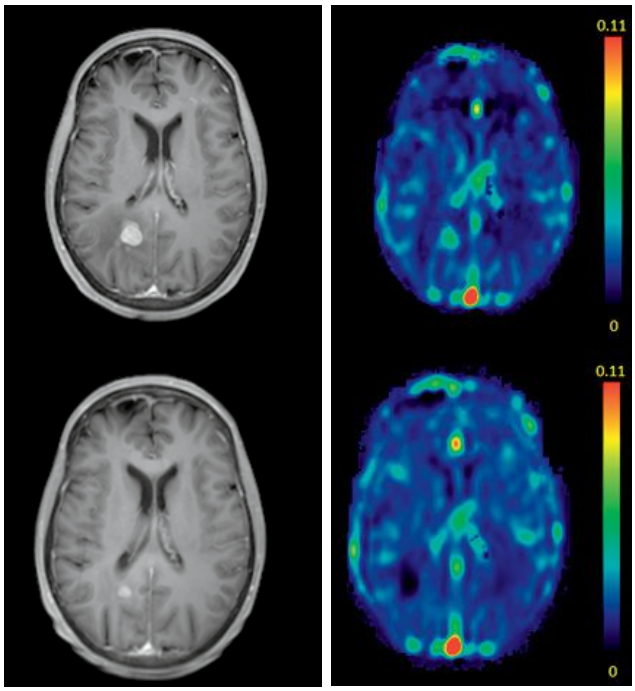


Figure 3
T1- weighted images on the right as well as the perfusion maps are shown on the left. Pre-RT (top rows) scans and 1 month scans (bottom row) are shown. Qualitatively, there are significant decreases noted in both tumor volume and no blood flow noted 1 month following treatment suggesting excellent response to SRS treatment.

surgery during postoperative days 0-3, with no significant change occurring up to 33 days after surgery. Thus, there may not be a benefit to waiting an extended period of time beyond an initial one to two weeks after surgery to proceed with SRS.

Imaging Considerations in the SRS Treatment of Benign Lesions

Acoustic Neuroma (Vestibular Schwannomas)

Acoustic neuromas are benign neoplasms derived from Schwann cells of the myelin sheath that show predilection for sensory nerves. Most lesions arise from CN VIII, and secondly CN V. Acoustic neuromas account for approximately 5-8% of intracranial tumors and 80-90% of cerebellopontine angle tumors. Retrospective data have shown excellent tumor control rates with stereotactic radiosurgery.[19] A University of Pittsburgh series[20] with 216 patients treated with Gamma knife with a marginal tumor dose of 12-13 Gy showed a 10-year resection-free control rate of 98.3%. The 10-year Robertson-Gardner serviceable and any testable hearing preservation rate was 45% and 85%. Unchanged facial nerve function was seen in 100% of patients, and unchanged trigeminal nerve function was seen in 95%.

Following SRS treatment, acoustic neuromas may temporarily expand in size initially and then stabilize, and thus a longer period of follow-up is required before determining disease progression. A retrospective study involving 87 patients showed that peak tumor volume expansion was observed at 8.6 months after SRS.[21] At 5 years follow-up, the mean reduction in tumor volume was 31%. However, there were still 10% of tumors that remained larger than their initial volume. Therefore, follow-up recommendations include post-treatment MR imaging to establish a baseline and at 24 months, followed by yearly imaging. No salvage therapy should be initiated before 3 years unless there is significant clinical deterioration.

Trigeminal Neuralgia

Trigeminal neuralgia is due to pathology of cranial nerve V that results in severe episodes of lancinating pain in one or more of its three divisions. Although benign, trigeminal neuralgia can greatly impact quality of life. Common treatment options include anti-epileptic and antidepressant medications, microvascular surgical decompression, ablation, and SRS. Clinical data shows good efficacy of SRS in pain control.[22] In a prospective clinical trial, 100 patients were treated with Gamma Knife radiosurgery to a median dose of 85 Gy, with a minimum follow-up of 12 months.[23] 83% of the patients were pain-free at last follow-up, of which 70% had stopped taking medications during the study. Post-treatment complications of facial paresthesia were seen in 6%, and hypesthesia in 4%. (See Figure 3.)

MRI imaging is required for radiosurgery planning, however studies have shown limited use in predicting effective treatment outcome. The post-treatment imaging characteristics of trigeminal neuralgia was assessed by Massager et al, who reported that at 6 months post-treatment, contrast enhancement on T1-weighted MRI was seen in 83% of trigeminal nerve roots. However, there was no correlation between the occurrence of focal enhancement of the nerve root and pain outcome, or development of trigeminal dysfunction.[24]

Arteriovenous Malformations (AVM)

AVMs are abnormal communications between arteries and veins, usually associated with high blood flow that results in blood vessel remodeling. The incidence of AVMs is approximately 0.01-0.1%, and

presenting symptoms include hemorrhage, seizure, and headaches. The annual risk of bleeding is 2-3% (2-6% if there is a prior history of bleed, and 1-3% if no prior bleed). Current treatment options include surgery, with operability depending on AVM location, embolization, and SRS.

Clinical data show obliteration rates of 60-90% after SRS.[25,26] In one study, 351 patients were treated to a median dose of 20 Gy, and the rate of obliteration was 73% by angiography, 86% by MR alone, and 75% overall.[27] A persistent out-of-field nidus was seen in 18% of previously embolized and 5% of non-embolized pts. Data on larger AVMs show decreasing obliteration and higher complication rates with increasing volume.

Cerebral Angiography

Cerebral angiography is the gold standard in the initial diagnosis and evaluation of AVMs, as part of radiosurgery treatment planning, and post-treatment residual AVM monitoring. It is a dynamic, real-time study that shows not only the presence or absence of an AVM but also the vascular transit time. It is also an essentially artifact free modality that provides superior spatial resolution without overlap of adjacent vascular structures as would be seen on CT or MRI. AVM visualization requires rapid injection of contrast medium and filming. Upon visualization of the AVM, markedly dilated veins are usually the prominent feature. The AVM nidus and the feeding arteries and draining veins can be clearly differentiated. The potential complications of the invasive procedure include stroke, arterial dissection, and reactions to the contrast agent.

AVM Radiosurgery Treatment Planning

The primary goal of AVM radiosurgery is to develop a plan with a target volume that conforms closely to the surface of the AVM nidus while maintaining a steep dose gradient to minimize the radiation dose to the surrounding brain.

More recently, tractography has been used in the AVM setting to identify with better accuracy areas at risk in the brain that can cause patient morbidity if compromised.[28] A prospective study by Koga et al integrated tractography in 71 AVM radiosurgery treatments where the tumor was less than 1cm from fiber tracts including the pyramidal tract, optic tract, and the accurate fasciculus. Morbidity as a result of treatment was minimized, with only 1 patient experiencing permanent and 1 experiencing transient pyramidal tract dysfunction[29]

Following radiosurgery, MR perfusion imaging has been utilized to study AVM transnidal flow and perinidal perfusion disturbances. After treatment, starting at 6 months follow-up, the ratio of rCBV and rCBF of the AVM nidus to normal brain gradually decreased to 1.0. Decrease was seen in the hemispheric perfusion ratios, reflecting reversal toward normal perfusion. Currently, the standard for post-treatment follow-up of AVMs is MRI every year with cerebral angiography for confirmation of obliteration of the nidus. An angiographic cure requires that no nidus or shunting is identified on imaging study.

Pituitary Adenoma

Gamma knife radiosurgery also plays an important role in the management of pituitary adenomas. SRS can provide local control for those patients with substantial residual tumor following maximal safe resection, or for those patients that develop progression or recurrence following surgical resection. Additionally, SRS can also lead to endocrine remission for those patients that progress following both surgical and medical management. Delayed hypo-pituitarism is the most common long-term complication. However, this occurs in a minority of patients.[30]

Meningioma

Recent surgical advances provide safe and more complete resections. However, SRS continues to be an important mainstay in the management of meningioma. Long-term data suggest single fraction SRS can provide tumor control equivalent to a Simpson grade 1 resection for small to medium sized meningiomas.[31] Location and tumor volume are important factors in determining the appropriateness of single fraction SRS treatment.[32] Recent advances in meningioma biology and genetics also provide a potential role for targeted therapy.[33]

Conclusion

Novel functional MRI imaging provides the ability to analyze tumor tissue properties including chemical composition, vasculature and perfusion, water mobility, permeability, hypoxia, and tumor proliferation. These imaging modalities have the potential to improve radiosurgery planning and post-treatment monitoring, including evaluation of differences in treatment efficacy between patients and heterogeneity of response within tumors. Developing reliable biologic maps which can be correlated to the treatment planning CT scan would permit us to reduce toxicity by avoidance of critical

structures leading to treatment toxicity and differentially directing higher radiation doses to areas of greater tumor burden or functional radio-resistance to improve the therapeutic ratio.

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Disclosure

None reported.

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Accelerated Partial Breast Irradiation: A Safe, Effective, and Convenient Early Breast Cancer Treatment Option

by Maria A. Thomas, MD, PhD, Laura L. Ochoa, PhD, Theresa M. Zygmunt, RN, Melissa Matesa, RN, Michael B. Altman, PhD, Jose L. Garcia-Ramirez, MS, Jacqueline Esthappan, PhD & Imran Zoberi, MD

All women with early stage breast cancer and their caregivers should be aware of this treatment option.



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Abstract

Accelerated partial breast irradiation (APBI) is an excellent treatment option for many women with early stage breast cancer. Patient selection criteria include age over 40, status post lumpectomy, breast cancer (invasive or *in situ* disease) measuring <3 cm, negative margins (at least 2 mm), negative lymph nodes, and no lymphovascular space invasion. APBI is effective, well tolerated, and convenient. Women with early stage breast cancer and their caregivers should be aware of this potential treatment option.

Introduction

For women with early stage breast cancer, breast-conserving therapy (BCT, which is lumpectomy plus breast radiation therapy) is an important treatment option which allows women the opportunity to preserve their breast. Randomized trials and meta-analyses have demonstrated comparable outcomes between mastectomy and BCT.[1-2] The addition of radiation to lumpectomy reduces the risk of ipsilateral breast tumor recurrence (IBTR)[1-3] and improves overall survival.[2-3] In these trials demonstrating the benefits of adjuvant radiation, whole breast radiation was utilized. A typical course of whole breast radiation is delivered over five to six weeks. While whole breast radiation is generally well-tolerated, it carries risk of late effects such as radiation pneumonitis, cardiotoxicity, and secondary malignancy.

Accelerated partial breast irradiation (APBI) has been evaluated as an alternative to whole breast radiation for appropriately selected women with early stage breast cancer. With APBI, radiation is delivered only to the breast tissue immediately adjacent to the initial tumor site, typically a 1-2 cm margin of breast tissue surrounding the surgical cavity. The rationale for this approach is that most recurrences occur near the initial tumor location. The appeal of this approach is reduced radiation exposure to the remainder of the breast, as well as other normal tissues such as the lungs, heart, ribs, and musculature of the chest and shoulder. For a comparison of the radiation delivered with whole breast radiation and APBI, see Figure 1.

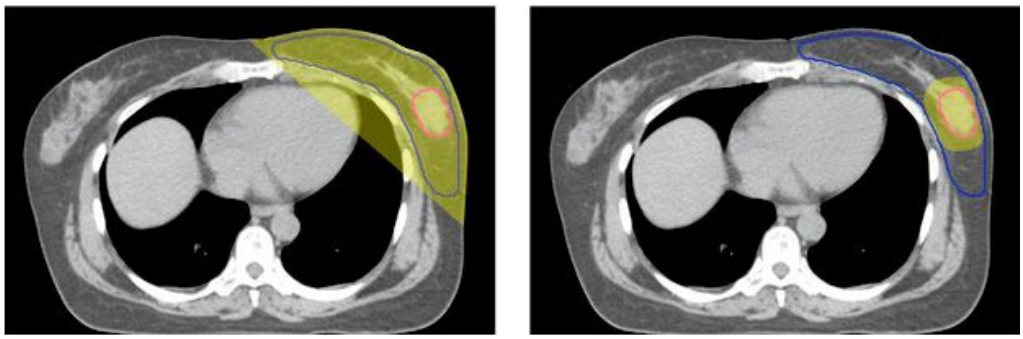


Figure 1
Comparison of radiation dose delivered with whole breast radiation (left panel) and with APBI, accelerated partial breast irradiation, (right panel). For both panels, the blue contour outlines the breast tissue and the pink contour outlines the surgical cavity. The yellow colorwash depicts the distribution of radiation dose.

Additionally, APBI is a more convenient option, which is completed in one week (five treatment days).

APBI can be delivered with a number of techniques. The technique that has been studied with the longest follow up is interstitial brachytherapy, in which multiple catheters are inserted in the breast. A Phase III randomized trial was conducted in Europe, in which women were randomized to whole breast radiation or APBI.[4] With a median follow up of 10.2 years, there was no difference in local recurrence, disease-free survival, or overall survival. Rates of excellent/good cosmetic outcome were higher with APBI (81%) than with whole breast radiation (63%). Accrual to a Phase III randomized trial in the United States, NSABP B-39, has been completed and the results of this study are pending.[5]



Figure 2
Partial breast brachytherapy SAVI applicators. There are 4 sizes of SAVI applicators, and the appropriate applicator is selected at the time of applicator placement based on the size of the surgical cavity. Image courtesy of Cianna Medical, with permission.

Alternative techniques have been developed which utilize a single-entry brachytherapy applicator for delivery of APBI. The MammoSite™ applicator (Hologic, Inc.) was the first in this category, and favorable treatment outcomes from the MammoSite Breast Brachytherapy Registry Trial have been reported.[6] The final analysis of the MammoSite Registry included 1,449 women. With a median follow up of 63.1 months, the five-year rate of IBTR was 3.8%. Excellent/good cosmetic result was achieved in 91% of patients at 60 months. Other applicators exist as well, including the SAVI™ (strut-adjusted volume implant; Cianna Medical),[7] which is a single entry applicator with multiple channels (see Figure 2). Multiple channels for brachytherapy delivery allow more flexibility in dose distribution and the ability to avoid dose to the skin, chest wall, and ribs, when these structures are in close proximity to the surgical cavity (for example cases, see Figure 3).

External beam radiation therapy (EBRT) has been evaluated as a method of APBI delivery. However, given the uncertainties of patient setup and movement during and between treatments, a larger margin of breast tissue must be targeted in order to adequately treat the area at risk. A recent randomized trial found a higher rate of adverse cosmesis with EBRT APBI than with whole breast radiation.[8] Currently, at our institution, brachytherapy is the preferred approach for APBI, and this article will focus on this technique.

	Washington University	ASBS	ABS	ASTRO
Patient Age	≥ 40	≥ 45 (invasive) ≥ 50 (DCIS)	≥ 50	≥ 60
Tumor Types	Invasive carcinoma DCIS	Invasive carcinoma DCIS	Invasive carcinoma DCIS	Invasive carcinoma
Tumor Size	≤ 3 cm	≤ 3 cm	≤ 3 cm	≤ 2 cm
Margin Status	Negative	Negative	Negative	Negative
Lymph Nodes	Negative	Negative	Negative	Negative
LVSI	Negative	Not addressed	Negative	Negative

Table 1
APBI patient selection criteria, per Washington University criteria and the consensus statements from the American Society of Breast Surgeons (ASBS), American Brachytherapy Society (ABS), and American Society for Radiation Oncology (ASTRO). The ASTRO consensus statement describes three categories of suitability for APBI: suitable, cautionary, and unsuitable. Characteristics for the "suitable" category are listed above.

Who is a Good Candidate for APBI?

Many women with early stage breast cancer may be candidates for APBI. There are three consensus statements which describe the appropriate candidates for APBI: American Society of Breast Surgeons (ASBS),[9] American Brachytherapy Society (ABS),[10] and American Society of Radiation Oncology (ASTRO).[11] Of these, the ASBS and ABS consensus statements have been recently updated. Our institutional criteria at Washington University were developed prior to the publication of the consensus statements, but are generally in agreement with the ABS and ASBS consensus statements. The selection criteria from the ABS, ASBS, and ASTRO consensus statements, as well as our institutional criteria, are summarized in Table 1.

APBI patient selection criteria include both clinical factors and technical factors. In terms of clinical factors, it is important to note that this is only an option for women who have had a partial mastectomy (lumpectomy). Patients over the age of 40, with less than 3 cm of invasive cancer or ductal carcinoma in situ (DCIS) are eligible. In addition, there should be negative margins. Currently, for the purposes of APBI, this is defined as greater than or equal to 2 mm. There should not be lymphovascular space invasion (LVSI). Lymph nodes should be assessed surgically (typically by sentinel lymph node biopsy), and should be pathologically node negative. Finally, APBI is used only when surgery is performed up front, and not in cases where neoadjuvant systemic therapy (chemotherapy or endocrine therapy) has been given prior to surgery.

In terms of technical factors, the resection cavity must be of appropriate size and shape to accommodate the brachytherapy applicator. Currently at our institution, we primarily use the SAVI applicator due to its ability to modulate dose away from adjacent structures. There are four different sizes of SAVI applicators, and most cavities will be amenable to one of

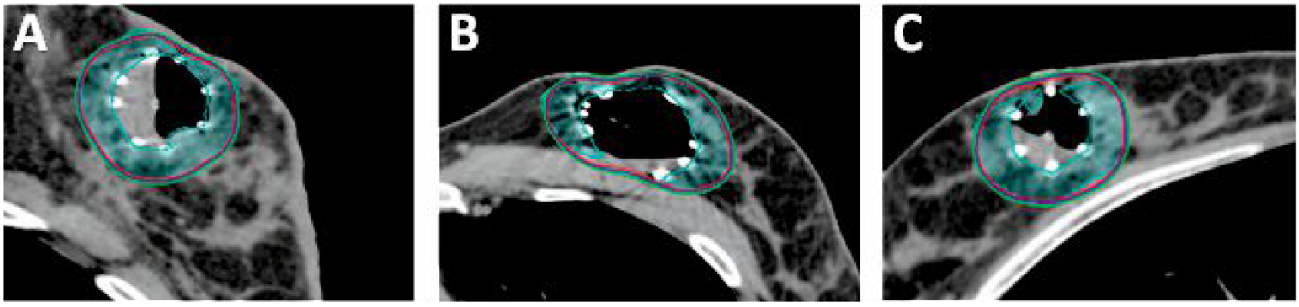


Figure 3
APBI cases demonstrating ability to sculpt radiation dose using the SAVI applicator in challenging anatomic situations. Shown here are three examples of lumpectomy cavities that are located in close proximity to the skin surface, chest wall, and/or ribs. In each case, the SAVI applicator has been placed in the cavity and the radiation target area has been defined (shown in cyan colorwash). Custom treatment plans for each patient have been generated that follow specific constraints for target coverage and normal tissue sparing. The radiation dose is displayed with 100% prescription dose (red), 95% dose (blue) and 90% dose (green). As displayed in these examples, prescription dose has been sculpted away from the skin (Panels A, B, and C), chest wall (Panels B and C), and ribs (Panel C).



Figure 4
Overview of the partial breast brachytherapy process using the SAVI applicator. Step 1 shows the SAVI applicator in collapsed state prior to placement. Step 2 shows applicator placement, which is performed with ultrasound guidance. Step 3 shows the radiation delivery to the breast tissue. Step 4 shows removal of the applicator. Image courtesy of Cianna Medical, with permission.

these. The cavity is assessed with ultrasound or CT at the time of consultation. Generally, APBI is appropriate when the target breast tissue (cavity plus a margin) is less than one-third of the total volume of breast tissue. In terms of timing, two to three weeks after surgery is optimal for applicator placement, but up to six weeks is acceptable. If APBI is being considered for a patient, she would be seen in consultation by a radiation oncologist prior to or shortly after surgery. The other timing consideration is coordination with chemotherapy. For those who will be receiving adjuvant chemotherapy, APBI is delivered first, and chemotherapy afterwards. It is generally recommended that chemotherapy is not initiated until four weeks after completion of APBI.

What is the Process for Treatment with APBI?

The process begins with consultation with a radiation oncologist, ideally one who specializes in APBI treatment and has the ability to deliver APBI with brachytherapy at his/her institution. At the time of consultation, it is determined whether the patient is a good candidate for APBI, using the criteria described above. An important part of this assessment is an ultrasound or CT scan of the surgical cavity. If the patient is found to be a good candidate for APBI, all treatment options are discussed. Often the options might include both whole breast radiation and APBI. The outcomes, side effects during treatment, long-term side effects, and logistics of both courses of radiation are discussed. Due to the favorable side effects and shorter treatment course with APBI, many patients choose APBI when presented with both treatment options. However, this is always an individual decision.

An overview of the process of SAVI applicator placement and brachytherapy treatment delivery is shown in Figure 4. The applicator placement is a 20 minute outpatient procedure that is performed with local anesthetic. Once the skin is numb, a small (1 cm) incision is made in the breast, separate from the surgical incision. Using ultrasound guidance, the cavity is entered and its volume is assessed with a balloon. Using the cavity measurements, the appropriate SAVI applicator size is chosen and this applicator is placed into the surgical cavity. The applicator diameter is small when inserted into the breast, but once it is in proper position in the cavity, it is expanded to fill the surgical cavity. After applicator placement, a CT simulation is performed. At this time, the applicator position within the cavity and the symmetry of applicator expansion are assessed. The length of each channel of the applicator is precisely

measured. A dressing is applied to the breast, and the patient is discharged home. In total, the procedure day typically requires two to three hours for: pre-medication, applicator placement, CT simulation, and catheter measurements.

Later that day, treatment planning begins. This is a highly specialized process which involves dosimetrists, medical physicists, and physicians with training and experience in APBI brachytherapy planning. Each channel of the SAVI applicator is carefully identified, the target breast tissue is defined, and organ avoidance structures, such as the skin, ribs, lung, and heart are delineated. The treatment plan is customized for each patient, and involves optimization of the treatment plan until the target breast tissue is covered and normal tissues are spared. Specific dose constraints are given to the dosimetrists describing optimal plan parameters, in terms of coverage of the target breast tissue and sparing of normal tissues. The treatment plan is reviewed, modified as necessary, and then approved by both a medical physicist and physician.

Treatment generally begins one to three days after applicator placement. APBI is delivered twice daily, on five business days, over the course of one week, for a total of 10 treatments (fractions). Prior to each treatment, several quality checks are performed. Applicator position, symmetry, and expansion are verified with CT (first fraction) or x-ray films (each subsequent fraction). Additionally, the applicator position is confirmed using reference marks placed on the patient's skin. The exact duration of each treatment delivery is calibrated according to the current HDR brachytherapy source activity. Prior to each treatment delivery, each channel of the SAVI applicator is connected to a long channel called a transfer guide tube, which is connected to the HDR unit. Within the HDR unit, there is a long wire with a radioactive source at its tip, stored in a shielded compartment. During treatment delivery, the source wire travels into each channel of the SAVI applicator and pauses for a specified period of time (ranging from $<$ 1 second, up to several seconds) at each prescribed point along each channel. After treatment delivery, the source wire returns to its position inside the HDR unit, the long transfer guide tubes are disconnected from the SAVI applicator, and the patient is released.

Although the SAVI applicator remains in the patient during the treatment course, there is no residual radioactivity in the patient after the treatment sessions. Therefore, there are no restrictions regarding being around young children or pregnant women. This treatment delivery process is repeated for each fraction. Treatments are given twice daily, typically in early morning and mid-afternoon. After the final treatment fraction is delivered, the applicator is collapsed and removed from the breast. A sterile dressing is applied to the breast and specific post-treatment care instructions are given. Patients typically return at approximately one week after completion of radiation for the first follow up visit and skin check. Patients are seen for breast exams, mammograms, and monitoring for any side effects of treatment, in accordance with standard breast cancer follow up guidelines.

What are the Side Effects of APBI?

One of the advantages of APBI is the favorable side effect profile, and reduced radiation exposure to healthy breast tissue and adjacent organs. Side effects are often minimal, but can be categorized as related to applicator placement, acute radiation side effects, and late radiation side effects.

As with any minor procedure involving an incision in the skin, there is potential for pain, bleeding, and infection related to placement of the applicator in the breast. These risks are minimized with standard precautions. Although pain medication is provided to be used as needed, most patients do not require pain medicine after applicator placement and report little to no pain in the breast. The risk of infection is reduced with a course of prophylactic antibiotics and standard aseptic techniques at the time of applicator placement.

Acute radiation side effects with APBI are generally mild in nature. There may be some faint pink or red skin changes on the skin surface near the surgical cavity which may develop during or in the few weeks following treatment. This area of skin may subsequently become slightly hyperpigmented and dry, which can be alleviated with moisturizer. Less commonly, the skin irritation after APBI can result in peeling, blistering, and tender skin, which is more common with whole breast radiation.

Late radiation side effects after APBI are fairly uncommon, but can include fibrosis, focal skin pigmentation changes, telangiectasias, fat necrosis, or adverse breast cosmesis. Although rates of late toxicities vary somewhat among reported series, the

approximate risk of breast infection is 3-11%,[12-15] risk of symptomatic seroma is 3-13%,[12,13,16] risk of telangiectasias is 2-13%,[12,16] and risk of symptomatic fat necrosis is 1-12%.[12,14,16,17,18] Rates of late toxicities were all quite low (less than 3%) with the SAVI applicator at five years follow up.[16] Excellent or good cosmetic results at five years after treatment are seen in most (88-94%) patients.[12,13,15,16] One study demonstrated lower rates of toxicity and better cosmetic outcomes in patients treated at high volume centers,[13] showing the value of receiving treatment at a facility with expertise in APBI delivery.

Summary

In summary, accelerated partial breast irradiation (APBI) is an excellent treatment option for many women with early stage breast cancer. Patient selection criteria generally include women over the age of 40, status post lumpectomy, with breast cancer (invasive disease or DCIS) measuring <3 cm, excised with negative margins, negative lymph nodes, no LVSI, and with a surgical cavity amenable to partial breast applicator placement. APBI is an effective, well tolerated, and convenient treatment option. The most common acute side effect is mild, transient skin irritation, and the most common late side effect is mild fibrosis in the treated area of the breast. Generally, patients who receive APBI are very pleased with their treatment. All women with early stage breast cancer and their caregivers should be aware of this treatment option.

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Disclosures

None reported. **MM**

The Evolution of Axillary Staging in Breast Cancer

by Roshni Rao MD, FACS

Approaches towards less invasive sentinel node evaluation utilizing enhanced magnetic resonance imaging, ultrasound guided percutaneous sentinel node excision, and intra-operative assessment without removal are being explored.



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Abstract

Breast cancer treatment has a long, fascinating history. Multimodality therapy utilizes surgery, systemic therapy and radiation. The role of surgical axillary staging in breast cancer continues to evolve. Secondary to randomized, controlled trials, sentinel lymph node biopsy is the standard for surgical staging in patients with a clinically negative axilla. Traditionally, when sentinel nodes revealed metastases, a complete axillary lymph node dissection was performed. Recently however, the value of complete axillary dissection is being challenged.

Introduction

There has been a long-standing interest in breast cancer treatment, from the "fire-drill" of the ancient Egyptians,[1, 2] to today's precise surgical excisions,[3-6] dramatic changes have occurred in the operative management of breast cancer.[7] Initial treatments included non-standardized combinations of excisions, fulguration and poultices, and reported three-year survival rates of 5 – 29%.[1, 7] In the United States, Sir William Halsted incited a revolution in breast cancer treatment. He postulated an organized progression from local disease to regional nodal metastases and then the subsequent development of systemic disease. In 1907, he demonstrated that radical removal of the entire breast, pectoralis muscles, and all regional lymph nodes increased three-year survival to over 40% when compared to no operation.[8] The Halsted radical mastectomy remained the standard for the next 75 years. The second revolution came in the 1970s, when Dr. Bernard Fisher postulated that breast cancer was a systemic disease at inception, and thus required systemic therapies. Recently, advances in breast cancer treatment have been guided by results from randomized prospective clinical trials assessing recurrence and survival. From these trials, we have learned that in terms of survival, a simple mastectomy that preserves the chest wall muscles is equivalent to a Halsted radical mastectomy and that a lumpectomy followed by adjuvant radiation therapy (breast conserving therapy) is just as good as total mastectomy.[9, 10] Through these large scale studies and due to advances in adjuvant systemic therapies and population screening, five-year breast cancer survival rates in the United States have now reached 90%.[11]

Axillary Lymph Node Dissection

Surgical treatment of the axilla has also undergone an evolution. Since the 1800s, a complete axillary dissection was performed in most patients diagnosed with breast cancer. This operation provided staging information and was utilized to achieve regional disease control.[7] The

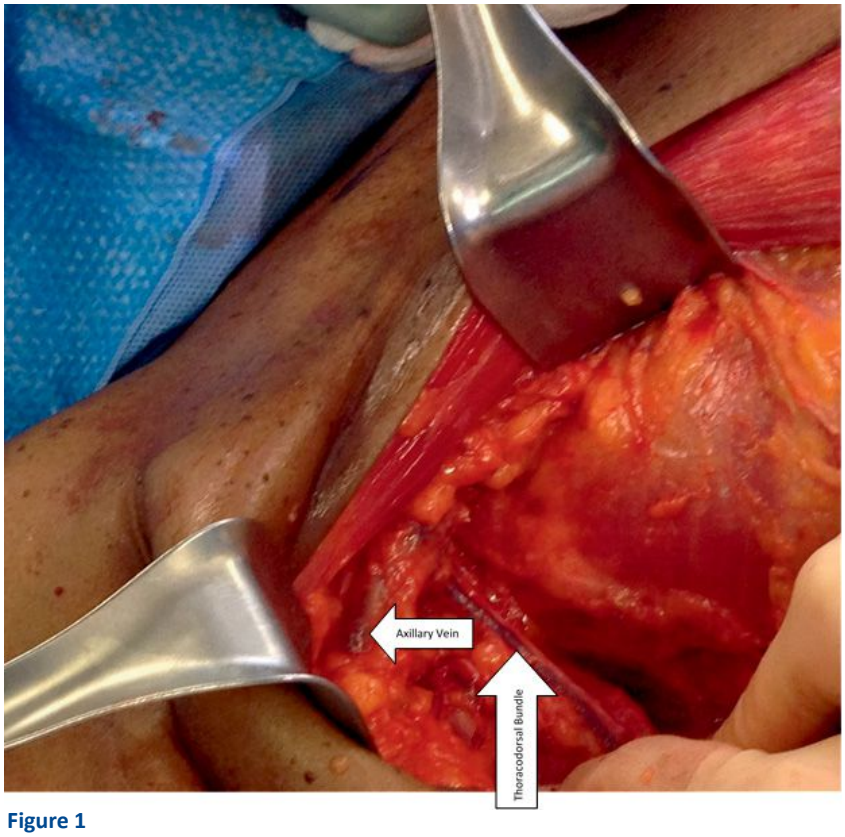


Figure 1
Completed Axillary Lymph Node Dissection



Figure 2
Sentinel Node ***In-Situ***

presence of metastatic disease in the lymph nodes required more aggressive systemic therapies, and potentially axillary/chest wall radiation to improve survival and reduce the risk of local recurrence.[12] Pathologic analysis of the lymph nodes could only be performed with the surgical removal of these nodes. Axillary lymph node dissection involves removal of all tissue between the anatomic landmarks of the axillary vein (superiorly), the thoracodorsal bundle (laterally) and the chest wall (medially), 10-40 lymph nodes are typically removed en bloc (See Figure 1). With more extensive surgery, however, there is an increased risk of complications such as lymphedema, limited shoulder motion, and neuropathic pain.[13] A need to minimize these complications, and the growing numbers of patients without nodal metastases at presentation,[14] due to improvements in breast cancer screening,[15] led to an interest in the sentinel lymph node biopsy technique.

Sentinel Node Biopsy

Sentinel lymph node biopsy was first described in breast cancer patients in 1994.[16] Sentinel lymph node biopsy is dependent upon the known, orderly pattern of the lymphatic drainage of the breast. Radioactive Technetium-99m and/or blue dye (isosulfan or methylene blue), are injected directly into the breast or into the skin of the breast. Subsequently, the lymph nodes that either turn blue or have the most radioactive uptake, typically one to fourlymph nodes, are selected for removal (See Figure 2) and evaluated for metastatic disease. Since these sentinel lymph nodes

would be the first ones to which metastatic disease would spread, if there is no evidence of metastases in the sentinel nodes, there is a very low risk of additional nodes having metastases.[17]

Multiple randomized controlled trials have evaluated whether sentinel node biopsy is as effective as axillary lymph node dissection in patients with no evidence of metastases on final nodal pathology.[17] These trials have revealed sentinel node biopsy to be equivalent to complete axillary lymph node dissection in terms of survival and recurrence. Additionally, sentinel node biopsy has lower rates of lymphedema, neuropathic pain, and sensory deficits, when compared to axillary lymph node dissection.[17] With the introduction and validation of the sentinel node biopsy technique, sentinel node is the standard option for routine axillary staging in clinically node negative patients in the United States.[18-21] For patients with evidence of axillary metastases in their sentinel nodes however, complete axillary lymph node dissection was still recommended to obtain additional staging and prognostic information in order to help guide adjuvant therapies.

Pathology Analysis of Sentinel Nodes

When complete axillary lymph node dissection was routinely performed, 10-40 lymph nodes were typically removed. The accepted approach to analysis of these nodes was a single hemotoxylin and eosin (H&E) stained section of each node.[22] Historically, analysis of these nodes occurs by dividing the node in half and evaluating either side of the bisected node. With the advent of sentinel node biopsy, and the fewer number of lymph nodes removed, serial sectioning of these nodes became the standard.[22] This more thorough serial sectioning of axillary nodes has shown increased sensitivity in identifying axillary node metastases. Tan et al.[22] studied paraffin blocks from 368 patients who underwent complete axillary lymph node dissection at Memorial Sloan-Kettering Cancer Center from 1976-1978. All these patients had been found to have no evidence of axillary metastases on the original pathology analysis. For their study, the paraffin embedded nodes underwent serial sectioning utilizing current sentinel node techniques. This more careful evaluation revealed a 23% rate of upstaging-i.e. a diagnosis of axillary metastases-that were missed with the original analysis. Kahn et al.[23] reported similar results even when just two additional sections of the node were evaluated. Given the increased identification of axillary metastases and specific staging information gained via sentinel node biopsy, and the known lack of a survival benefit with complete axillary lymph node dissection, the utility of completion axillary lymph node dissection even in the setting of a positive sentinel node biopsy started to be questioned.

Sentinel Node Biopsy Alone in the Setting of Axillary Metastases

In 1999, a study to challenge routine axillary lymph node dissection for patients with sentinel node metastases undergoing breast conserving therapy was initiated by the American College of Surgeons Oncology Group (ACoSOG), this was called the Z11 trial.[24, 25] Z11 randomized patients undergoing breast conserving therapy with sentinel node metastases to completion axillary lymph node dissection or no further specific treatment directed towards the axilla. This trial included patients with clinical T1-T2N0M0 breast cancers undergoing partial mastectomy with sentinel lymph node biopsy. Key exclusion criteria were patients not receiving standard whole breast radiation, T3/T4 tumors, patients presenting with palpable/matted suspicious axillary lymph nodes, and patients with ≥3 metastatic lymph nodes. Patients with metastases in the sentinel nodes were randomized to either observation alone or completion axillary lymph node dissection. All patients received adjuvant whole breast radiation, and 97% received adjuvant systemic therapy per institutional protocols. Study endpoints were survival and recurrence. Unfortunately, this trial was closed early due to poor accrual and an unexpectedly low rate of recurrence events; however, 891 patients were randomized. With a median follow-up of 6.3 years, two of 420 axillary lymph node dissection patients (0.5%) had an axillary recurrence, versus 4 of 436 (0.9%) in the sentinel node alone group ($p=0.45$).[5] The results of Z11 revealed that there was no benefit in terms of regional failures and survival rates for patients who had axillary lymph node dissection. For patients with small tumors, a clinically negative axilla, undergoing partial mastectomy with adjuvant radiation and systemic therapy omitting completion axillary lymph node dissection does not increase the risk of axillary recurrence nor impact survival. Recent results from a European trial-After Mapping of the Axilla: Radiotherapy Or Surgery (referred to as the AMAROS trial),[26] similar to ACOSOG Z11, also support sentinel node biopsy alone, even in

the setting of axillary metastases for patients receiving multimodality therapy for breast cancer.

The Future

In the current era of personalized therapy treatment decisions are based on tumor biology, frequently gleaned from genomic and proteomic sequencing. The information gained from complete axillary lymph node dissection is becoming increasingly unnecessary in guiding adjuvant therapy decisions. In addition, approaches towards less invasive sentinel node evaluation utilizing enhanced magnetic resonance imaging,[27] ultrasound guided percutaneous sentinel node excision,[28] and intra-operative assessment without removal[29] are being explored. These new techniques have the potential to completely replace surgical axillary staging in the future.

Conclusion

For nearly 30 years, it has been known that axillary lymph node dissection, even in the setting of nodal metastases, does not improve survival; however, this information was required to guide decisions regarding adjuvant treatments and achieve regional disease control. Currently, and in the future, multimodality treatment will be more dependent upon primary tumor features, including molecular markers, rendering the staging information obtained via axillary lymph node dissection irrelevant. As studies such as the ACoSOG Z11 are applied to practice, it is critical to ensure patients are the same in stage and access to multimodality treatment regimens as those who were in the trials described. In patients where these multimodality treatments are not readily available, the previously described indications for axillary lymph node dissection may still apply.

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Disclosure

None reported.

MM

Blood Conservation Strategies and Liver Transplantation

Transfusion-Free Techniques Derived from Jehovah's Witness Surgical Cohorts

by Mansi Sheth, BS, Sujit Kulkarni, MD, Kiran Dhanireddy, MD, Alexander Perez, Randy Henderson & Rick Selby, MD

Mainstream transfusion avoidance strategies are important to implement in order to decrease costs and improve clinical outcomes.



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Abstract

Red blood cell and component transfusions are a frequent and widely accepted accompaniment of surgical procedures. Although the risk of specific disease transmission via allogeneic blood transfusions (ABT) is very low, the occurrence of transfusion related immune modulation (TRIM) still remains a ubiquitous concern. Recent studies have shown that ABT are linked to increased morbidity and mortality across various specialties, with negative outcomes directly correlated to number of transfusions. Blood conservation methods are therefore necessary to reduce ABT.

Acute normo-volemic hemodilution (ANH) along with pre-operative blood augmentation and intraoperative cell salvage are blood conservation techniques utilized in tertiary and even quaternary (transplantation) surgery in Jehovah's Witnesses with excellent outcomes. The many hematologic complications such as anemia, thrombocytopenia and coagulopathies that occur with liver transplantation present a significant barrier when trying to avoid ABT. Despite this, living donor liver transplantation (LDLT) has been successfully performed in a transfusion-free environment, providing valuable insight into the possibilities of limiting ABT and its associated risks in all patients.

Introduction

Allogeneic blood transfusions (ABT) have been routine practice during operations for many decades, well integrated into surgical standard of care guidelines. However, reducing blood transfusions in patients has both financial and clinical implications. The cost of blood products makes up a significant portion of a hospital budget and in the era of DRG reimbursement, these expenses no longer pass through to payers. Further, there are also hidden costs to blood transfusions related to the intrinsic immune-suppressing nature of allogeneic blood product administrations.[1]

While the risk of disease transmission from banked blood is very low, there still remains a considerable risk of TRIM. This immune modulation has been shown

Study	Results: Transfusion Associated With …
Engoren et al (2002) (n = 1915)	1. Mortality at 5 years: RR 1.7
Koch et al (2006) (n = 11,963)	1. Higher postoperative morbidity and mortality OR 1.77 2. Renal failure OR 2.06 3. Prolonged ventilator support OR 1.79 4. Serious infection OR 1.76 5. Cardiac complications OR 1.55 6. Neurologic events OR 1.37
Murphy et al (2007) (n = 8,598)	1. Infection and ischemic outcomes Adjusted OR 3.38 and 3.35 2. Increased length of stay HR 0.63 3. Death within 30 days HR 6.69

Table 1
Outcomes in Cardiac surgery between transfusion-free and transfusion-eligible patients. Transfusion is associated with an increased number of major complications such as renal failure and serious infection as well as increased mortality.

to have a negative effect on a patient's postoperative recovery. ABT has been linked to an increased risk of infection post-operatively.[2] These negative outcomes are directly proportional to the number of units transfused.[3] Avoidance of blood transfusion is, therefore, key to improving patient outcomes following surgery. The aim of this paper is to: 1) Highlight the use of acute normovolemic hemodilution (ANH) as the most effective blood conservation strategy; 2) Examine successful blood augmentation and blood conservation strategies used during live donor liver transplantation (LDLT) to prevent blood loss; and 3) Demonstrate the results of a Jehovah's Witness (JW) cohort study comparing transfusion-free and transfusion-eligible patients across multiple surgical specialties.

Increased Patient Risk With Blood Transfusions

While banked blood is safe, transfusion can be potentially quite harmful. The risk of contracting viral infections during an ABT is very low, with a 1:200,000-500,000 chance of HBV transmission and a 1:2 million chance of HIV transmission. The risk of CMV transmission is highest at 12:100.[4] The real risk of transfusion for the patient is not disease transmission but rather immune suppression. ABT results in the infusion of large amounts of foreign antigens and WBCs, which modulate the recipient immune system. The severity of this immune suppression is correlated with the number of units of blood transfused[5] and the WBC aliquot that accompanies it. Negative effects of TRIM include increased risk of infections, increased risk of cancer reoccurrence and increase in other post-operative morbidities.[6]

A meta-analysis of 23 peer-review articles published between 1986 and 2000 showed overwhelming evidence that ABT is associated with significantly increased risk of post-op bacterial infection in the surgical patient.[7] Nosocomial infection rates are higher in transfused patients.[8] In a study published by Crabtree et al. looking at 8,405 cardiac surgery patients between 1997 and 2004, blood product transfusion was shown to be an independent prognostic factor in elective cardiac procedures for C. Difficile infection (OR =3.277). Blood product transfusion had a greater odds ratio for C. Difficile infection than advanced age, female sex and increased cumulative days of antibiotic administration.[9]

Table 1 shows a compilation of comparative transfusion studies in cardiac surgery that all demonstrate an association between transfusion and increased morbidity and mortality. The 2006 cohort study of 11,963 patients by Koch et al. shows that transfusion is associated with an increase in serious complications such as renal failure, cardiac arrhythmias and neurologic events. Murphy et al. showed in their large 2007 cohort study that transfusions lead to increased length of hospital stay and short-term mortality with corresponding increased costs. This result challenged the long-held notion that older individuals with coronary disease should have a lower threshold for transfusion.[10]

Increased cancer recurrence and decreased survival in patients with transfusion during surgery has also been shown in studies across different cancer types including colorectal[11] and hepatocellular carcinoma.[12]

With ABT linked to increased morbidity and mortality, appropriate blood conservation measures are essential to decrease post-operative risk in patients. Blood conservation strategies are associated with similar or better clinical outcomes as well as decreased costs.

ANH is the Best Blood Conservation Tool

Acute normovolemic hemodilution (ANH) involves placement of a large-bore IV with gravity drainage of whole blood into a CPD bag following anesthesia

induction. Whole blood is removed while albumin or crystalloid IV restoration of intravascular volume occurs simultaneously. This is maintained until the patient's hematocrit drops to a level between 18-30%. Any blood loss that occurs during surgery results in the loss of diluted blood. The whole blood collected pre-operatively stays in the operating room and all ANH blood is returned to the patient as needed during the procedure and all is returned by the end of the operation[13].

The major benefits of ANH include: 1) Simplicity- it does not require any preoperative preparation whereas with blood augmentation using erythropoietic drugs there is a time delay for erythropoiesis as well as a pharmaceutical cost increment. 2) ANH contains whole blood including platelets and coagulation factors. It takes advantage of the natural redundancy of the coagulation system which allows removal of a significant portion of the protein pro-coagulant and platelet compartments while preserving 100% platelet and plasma protein clotting system activities. 3) ANH provides a valuable cushion for safety, usually 400-800 cc, in the event of unexpected blood loss.

The basic principle behind ANH is that isovolemic anemia is a safe situation in most patients and that it will be well tolerated. ANH builds upon the concept that hematologic redundancy, in this case of the red cell mass, is present and allows manipulation of this red cell mass compartment to the benefit of the patient.

Vascular volume is preserved so cardiac output and oxygen delivery are maintained. ANH to a hemoglobin level as low as 5gm/dl in conscious healthy resting humans did not produce inadequate systemic oxygenation. Studies have shown that ANH decreases systemic vascular resistance (SVR) and increases heart rate (HR) and stroke volume (SV). Plasma lactate levels stay constant over a wide range of hemoglobin.[14] Even in the event of significant blood loss, post-operative anemia is safe. A 2005 study conducted by the American Society of Hematology found that six out of seven patients (85.7%) with a hemoglobin as low as 2.5-3.0 g/dL survived. Out of a total of 128 patients with profound anemia (hemoglobin ranging from 2.5-7.0 g/dL), 95.3% survived[15]. Patients with profound post-operative anemia treated without blood transfusions have a high survival rate.

Blood Conservation Strategies in LDLT

Transfusion-free techniques were first performed on Jehovah's Witnesses (JW) because of their religious beliefs that do not allow them to accept whole blood transfusions. Solid organ transplantation, ANH, heart lung bypass and intraoperative cell saver are considered a matter of personal choice under JW religious guidelines.[16] Blood conservation strategies used on JW cohorts serve as a valuable prototype for transfusion-free surgery in a secular population.

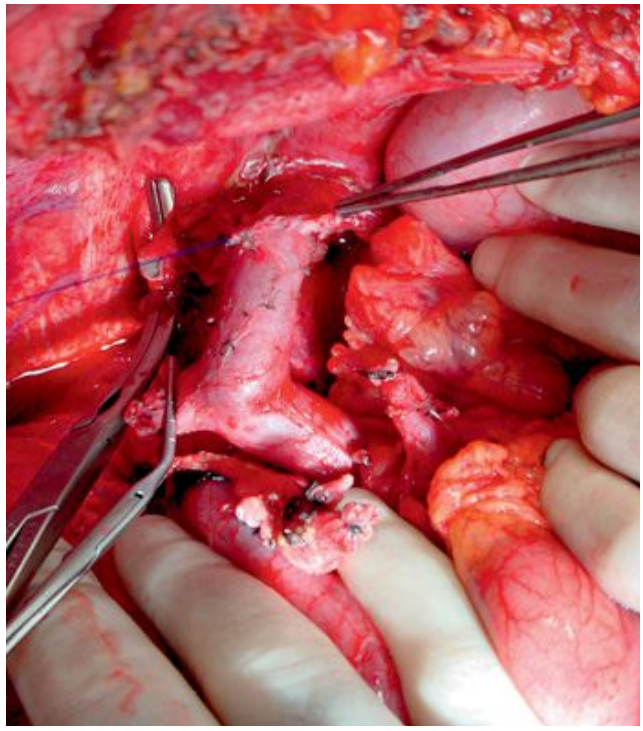


Figure 1
Completed left portahepatic shunt in transfusion-free recipient of a live donor liver transplant. The portahepatic shunt reduces blood loss and helps control intra-abdominal hypertension.

Several blood conservation strategies are currently used in JW during live donor liver transplantation (LDLT). These are either pre-operative, intraoperative or postoperative. Pre-operative strategies consist of raising hemoglobin through blood augmentation using iron, folate and EPO. Post-operative blood conservation involves limited blood draws and the use of pediatric drainage tubes. Intraoperative techniques include ANH, cell salvage, and specialized surgical techniques. Combining pre-operative blood augmentation with ANH can be especially effective in LDLTs, allowing the removal of greater quantities of whole blood without causing significant pre-operative anemia.

Surgical techniques to control portal hypertension and blood loss during LDLT operations in recipients are also essential for blood conservation. Hepatic congestion is a problem unique to LDLT and is associated with impaired function of the transplanted lobe. A temporary

Procedure	N		Procedure	N
Liver Transplantation	31		Major Liver Lobectomy	48
Kidney Transplantation	27		Distal Pancreatx-Splenx	4
Heart Transplantation	5		Whipple Procedure	12
CABG	13		Total Hysterectomy	24
Valve Replacement	21		Pelvic Floor Reconstruction	7
Cardiac Resection	2			
			Radical Cystectomy	6
Esophagectomy	2		Radical Prostatectomy	12
Radical Gastrectomy	2		RP Lymph Node Dissection	5
Esophageal Fundoplication	26		Robotic Nephrectomy	23
Abdomino-Perineal Resection	7		Pneumonectomy/Lobectomy	4
Colectomy	26		Diaphragm Hernia Repair	4
Total Knee Replacement	46		AAA repair-Open	3
Redo Total Knee Replacement	38		Carotid Endarterectomy	5
Total Hip Replacement	11		Renal or Fem-Tib repair	3
Redo Total Hip Replacement	16			
			Radical Neck Dissection	9
Craniotomy w Resection/Clipping	6		Pharyngectomy/Laryngectomy	4
Pituitary Excision	15		Sinusectomy	18
Cervical Spinal Fusion	18		Mandibulectomy	5
Lumbar Spinal Fusion	31			

Table 2
Tertiary and quaternary surgical procedures associated with substantial blood loss and likelihood of blood product transfusions that have been performed at Keck Hospital of USC on Jehovah's Witness patients between 1997 and 2013.

left portahepatic shunt – constructed by doing an end-to-end anastomosis of the left branch of the portal vein to the left hepatic vein - relieves the intra-abdominal hypertension while volume homeostasis is restored.[17] The completed shunt is shown in Figure 1.

A comparison between transfusion-free (JW) patients and transfusion eligible recipients in LDLT showed decreased estimated blood loss, decreased ICU stay and decreased need for reoperation in those who did not receive blood. There was a 100% survival in the JW liver recipients compared to 90% in the transfusion-eligible patients. All of the transfusion free patients received ANH as well as cell saver.[18]

JW Cohort studies across surgical specialties

Beginning in 1997, Keck Hospital of USC has tracked cohorts of JW that underwent major elective surgeries across multiple specialties (See Table 2). The results were compared to the outcomes for transfusion-eligible patients in 25 different operations where there is an anticipation of significant blood loss (between 300-500cc). There was no mortality in any of the elective cases in transfusion-free patients. Transfusion-free patients who received cadaveric liver transplants had the worst outcomes (50% survival) but also had the most severe pre-operative liver disease.[19]

Future Implications for Blood Conservation

Successfully performing major operations in a transfusion-free setting opens the door for implementing blood conservation in transfusion-eligible patients.

Mainstream transfusion avoidance strategies are important to implement in order to decrease costs and improve clinical outcomes. Blood loss by surgical case type is now predictable and transfusions are coming under increased scrutiny as a quality metric-likely to be a core measure in the near future.

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Disclosure

None reported.

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