UT Southwestern

THE TARGET

News from the Department of Radiation Oncology

SUMMER 2015

SABR with a twist: A new approach for prostate cancer treatment

UT Southwestern was the first medical center to test a high-dose, five-treatment radiotherapy regimen for prostate cancer. Now physicians are investigating a method to reduce potential side effects using an injectable spacer.

Radiation oncologist Dr. Michael Folkert and urologist Dr. Yair Lotan are leading a clinical trial to further improve the safety of stereotactic ablative radiotherapy (SABR) for prostate cancer patients.

What's Inside

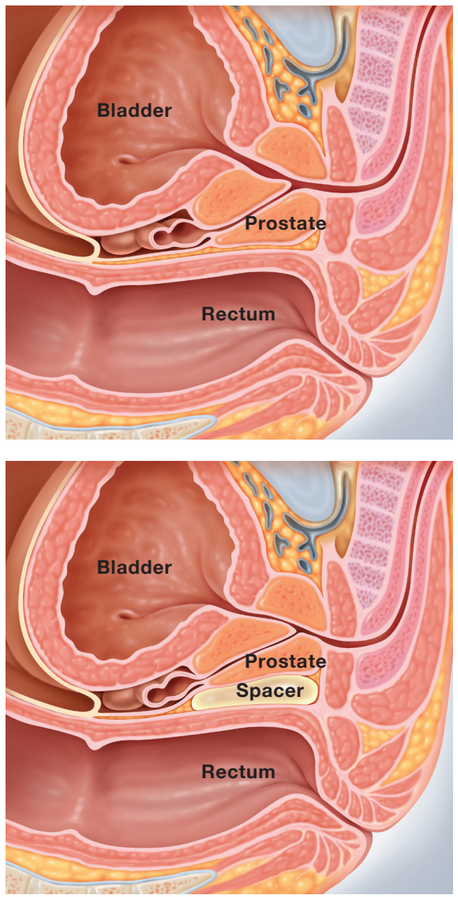
In a multidisciplinary effort to improve the safety of extreme high-dose radiation treatments administered for prostate cancer, UT Southwestern researchers have begun investigating the use of an injectable, biodegradable gel to physically move one sensitive organ—the rectum—out of the high-dose radiation field.

The prostate gland has always presented a challenge to radiation therapy treatment due to its location in close proximity to sensitive vital structures such as the urethra, bladder, and rectum.

In theory, stereotactic radiation (radiation delivered in fewer treatments at a higher dose using multiple angles and advanced targeting) is ideally suited to treating prostate cancer. The tighter dose conformity achieved with stereotactic ablative radiation (SABR, also known as SBRT) can better avoid organs at risk and thus lead to fewer side effects, while the more potent individual doses are known to result in better disease control.

Yet early studies at UT Southwestern and elsewhere have shown that the powerful ablative dose delivered by SABR can be associated with an elevated risk of toxicity in certain circumstances.
UT Southwestern researchers were the first to perform a dose-escalation safety study of SABR for the treatment of prostate cancer. The findings revealed that while SABR was initially well tolerated, a pattern of ulceration in the rectal wall emerged in the months after treatment.

"Our phase I/II study clearly demonstrated that delayed rectal toxicity events can occur, but this is likely preventable if we can respect rectal tolerance by reducing the radiation dose to the rectal wall," says co-lead investigator and Assistant Professor of Radiation Oncology Michael Folkert, M.D., Ph.D. Simply reducing the total given dose, however, would likely result in some patients receiving suboptimal treatment for their cancer.



Illustrated sagittal views pre-implantation (above) and post-implantation (below) of the spacer material. Illustration courtesy of Augmenix Inc.

Another innovative option, which has already been tested successfully in both conventional and intensity-modulated radiation therapy (IMRT), is to use a rectal spacer implant to increase the separation between the two organs. Studies using the spacer with both modalities have reported it as safe and effective, with no evidence of damage (ulceration, stricture, or necrosis) to rectal tissue after 12 months.

"All we need is a few extra millimeters to separate the prostate and rectal wall, and the spacer will help us achieve that," Dr. Folkert says. "SABR is very effective at treating prostate cancer, but we want to be able to offer it with the fewest possible side effects."

Composed of a patented hyaluronic acid gel, the spacer is inserted via transperineal needle injection under ultrasound guidance by surgeons in the Department of Urology. The procedure is done at the same time gold fiducial markers are placed for SABR image guidance, so the hydrogel placement causes no additional inconvenience to patients.

Following spacer and fiducial placement, patients then have a total of five radiation treatments, far fewer than the seven to 10 weeks of daily treatment given with standard radiation therapy. The tumor target receives a therapeutic dose of 45 Gy (9 Gy per fraction) with a dosimetric limit of 24 Gy delivered to 50 percent or less of the rectal circumference. The gel dissipates in the body after about 12 weeks.

The *International Journal of Radiation Oncology • Biology • Physics* in April published the results of a multicenter trial using perirectal spacing in conjunction with IMRT, reporting that the technique "shows promise in reducing rectal dose during prostate cancer radiation therapy."

"As already demonstrated in lung and liver cancers, SABR offers hope for improved local control that may translate into gains in survival relative to conventional radiation therapy, especially for smaller early-stage lesions," Dr. Folkert says. "So the need to make this treatment one that patients can safely tolerate is important. By working closely with our colleagues in Urology, we believe that we can significantly reduce the risk of long-term rectal toxicity."

While there are already several relatively good options for early- and intermediate-stage prostate cancer, including active surveillance, physicians at UT Southwestern believe SABR offers several key benefits.

"There are populations that cannot tolerate the invasiveness of surgery or that may find the inconvenience of long-term daily traditional radiotherapy impractical," Dr. Folkert says. "So the convenience and relative noninvasiveness of SABR is helpful to some who might otherwise be deterred from getting treatment.

"Furthermore, there also is evidence that prostate cancer behaves differently than other cancers when subjected to radiation. Its damage repair profile suggests that it may be more effectively eradicated with fewer, more powerful doses than with longer lower-dose treatment courses. Thus, the shorter, more convenient treatment may offer superior cancer control.

"As the medical community's interest grows in SABR, we are pleased to be the first center to offer this treatment to our patients on a clinical trial basis with an additional safeguard to improve the incidence of side effects."

New physicians join Radiation Oncology Department

Dr. David Sher

David Sher, M.D., M.P.H., has joined the faculty as Associate Professor of Radiation Oncology and leader of the department's head and neck team.

Dr. Sher earned his medical degree from Harvard Medical School, where he also completed his residency training. A board-certified radiation oncologist, he is currently an active participant in several national committees of the American Society for Radiation Oncology (ASTRO) and is a senior reviewer for the prominent *International Journal of Radiation Oncology • Biology • Physics.* Dr. Sher has extensive experience in the formal teaching of residents, fellows, and postdocs, and he has authored numerous papers advancing the field of radiation oncology.

In addition to caring for patients with head and neck cancer, Dr. Sher will be developing a new outcomes research program to further characterize the benefits of different types of radiation treatments, including heavy particle therapy. His training at the Harvard School of Public Health, as well as his work at the Dana Farber Center for Outcomes and Policy Research, have made him well-suited for this role. Dr. Sher will have a secondary appointment in the Department of Clinical Science's Division of Outcomes and Health Services Research.

"Dr. Sher's expertise in the field of outcomes study will be a significant enhancement to our radiation oncology program and the Simmons Comprehensive Cancer Center as a whole," says Chair of Radiation Oncology Hak Choy, M.D.

Dr. Aaron Laine

The department's second new faculty member is Aaron Laine, M.D., Ph.D., Assistant Professor of Radiation Oncology.

Dr. Laine graduated from the medical science training program at Mount Sinai School of Medicine in New York and completed a postdoctoral fellowship at the Tokyo Metropolitan Institute for Medical Science in Japan prior to joining UT Southwestern's radiation oncology residency program. Dr. Laine was promoted to a faculty position upon completion of his residency this spring.

Dr. Laine will focus on genitourinary cancer, participating in innovative trials such as the new five-fraction stereotactic prostate cancer treatment using a rectal spacer. Dr. Laine will also spend dedicated time in the laboratory exploring the cellular mechanisms of cancer cachexia, the characteristic "wasting" of muscle and adipose tissue seen in many cancer patients. This work builds on his residency research conducted under the mentorship of Assistant Professor of Radiation Oncology Puneeth Iyengar, M.D., Ph.D.

"Dr. Laine is a compassionate physician whose early research shows great promise," Dr. Choy says. "His interest in newer therapies such as heavy ion complements the direction of our department, and his addition to our faculty speaks highly both of his credentials and of the superior caliber of our residency program."

Physicians pioneer the use of stereotactic body radiation to treat inferior vena cava tumor thrombus

UT Southwestern Medical Center Kidney Cancer Program investigators have published what is believed to be the first successful use of stereotactic body radiation therapy for inferior vena cava tumor thrombus (IVC-TT), an often deadly complication of kidney cancer.

Two case studies reported in the May issue of *Cancer Biology and Therapy* provide an important potential new avenue for treatment of these types of tumors, which are resistant to traditional radiation therapies and difficult to manage even with surgery, the current standard of care.

"Our case studies showed similar survival with the use of stereotactic radiation therapy compared with surgery," says lead author Dr. Raquibul Hannan, Assistant Professor of Radiation Oncology and co-leader of the Kidney Cancer Program at Harold C. Simmons Comprehensive Cancer Center. "This result is important because people with this disease have a traditionally poor prognosis and few options."

Adds Dr. Vitaly Margulis, Associate Professor of Urology: "Removing the tumor surgically is currently the only treatment proven effective. It is still considered an extremely difficult and delicate surgery, with high rates of complications and cancer recurrence." As detailed in a recent study by Dr. Margulis in *The Journal of Urology*, "Patients with the disease who undergo surgery have a mortality rate that can be as high as 10 percent, depending on the location of the tumor and its growth into the venous system. There are currently no alternatives for those who are not surgical candidates."

"For these reasons, finding new therapies such as stereotactic radiation therapy is desperately needed," Dr. Hannan says. "This innovative proof-of-principle was a critical first step for determining whether our approach will ultimately prove to be effective."

Left untreated, IVC-TT can lead to severe complications, including pulmonary tumor embolus (tumor clots in the lung), Budd-Chiari syndrome (a serious liver condition), and even fatality.

Dr. Raquibul Hannan (left) and Dr. Robert Timmerman led a team that successfully used stereotactic body radiation therapy for the first time to treat an often deadly complication of kidney cancer.

The case studies—one a case of recurrent and another of unresectable IVC-TT—demonstrate that stereotactic ablative radiotherapy (SABR) can be an effective treatment. The reported survival times of 18 months and 24 months were comparable to standard surgical outcomes, and both patients improved symptomatically and did not experience any acute or late treatment-related toxicity, the researchers reported. UT Southwestern's kidney cancer team hopes to follow up with a study to evaluate the neoadjuvant use of SABR for IVC-TT in conjunction with surgery.

Dr. Robert Timmerman, Professor of Radiation Oncology and Neurological Surgery and the senior author of the study, was one of the first researchers in the world to use SABR, also known as stereotactic body radiation therapy (SBRT), for cancers in the body. This revolutionary technique, originally developed to treat brain cancer, relies on highly advanced imaging, treatment planning, and radiation delivery technology to administer an extremely potent dose with extreme precision from multiple angles, which has been shown to offer better cure rates for many cancers. Dr. Timmerman, who holds the Effie Marie Cain Distinguished Chair in Cancer Therapy Research, has championed the use of SABR globally and has served as the lead investigator in several national trials designed to evaluate the efficacy and safety of SABR to treat cancer in the lungs, liver, spine, and prostate.

Other UT Southwestern faculty members involved in the study were Dr. Ramzi Abdulrahman, Associate Professor of Radiation Oncology; Dr. Arthur Sagalowsky, Professor of Urology and Surgery; Dr. Ivan Pedrosa, Associate Professor of Radiology and the Advanced Imaging Research Center; Dr. Hak Choy, Chair and Professor of Radiation Oncology; Dr. James Brugarolas, Associate Professor of Internal Medicine and Developmental Biology; and other researchers, including Dr. Stephen Chun, Dr. Nathan Cannon, and Dr. Nathan Kim.

Clinical Trials

BRAIN

New– NRG BN001 Randomized phase II trial of hypofractionated dose-escalated photon IMRT or proton beam therapy versus conventional photon irradiation with concomitant and adjuvant temozolomide in patients with newly diagnosed glioblastoma

042011-075 Interstitial radioactive iodine implants for the treatment of pan-invasive pituitary macroadenomas

042011-050 Phase II trial of hippocampal-avoiding whole brain irradiation with simultaneous integrated boost for treatment of brain metastases

BREAST

092012-058 Randomized, double-blind, vehicle-controlled pilot study of the efficacy and safety of HylaCare™ in the treatment of acute skin changes in patients undergoing external beam radiotherapy for tumors of the breast

072010-015 A phase I study of CyberKnife partial breast irradiation (PBI) for early-stage breast cancer

GASTROINTESTINAL

032012-025 Phosphatidylserine-targeting antibody bavituximab in combination with capecitabine and radiation therapy for the treatment of stage II and III rectal adenocarcinoma

GENITOURINARY

092013-013 Phase II study of stereotactic ablative radiotherapy (SABR) for low-risk prostate cancer with injectable rectal spacer

RTOG 924 Androgen deprivation therapy and high-dose radiotherapy with or without whole-pelvic radiotherapy in unfavorable intermediate or favorable high-risk prostate cancer: a phase III randomized trial

122013-030 A phase II trial of stereotactic ablative body radiation therapy (SABR) for patients with primary renal cancer (RCC)

12013-041 A phase II trial of high-dose IL-2 and stereotactic ablative body radiation (SABR) for patients with metastatic clear-cell renal cell cancer (mRCC)

102012-026 Phase II trial of sipuleucel-T and stereotactic ablative body radiation (SABR) for patients with metastatic castrate-resistant prostate cancer (mCRPC)

RTOG 0815 A phase III prospective randomized trial of dose-escalated radiotherapy with or without short-term androgen deprivation therapy for patients with intermediate-risk prostate cancer

RTOG 0534 A phase III trial of short-term androgen deprivation with pelvic lymph node or prostate bed-only radiotherapy (SPPORT) in prostate cancer patients with a rising PSA after radical prostatectomy

GYNECOLOGIC

082013-064 A phase II study for image-guided hypofractionated radiation boost therapy for definitive treatment of locally advanced cervical cancer

RTOG 1203 A randomized phase III study of standard vs. IMRT pelvic radiation for postoperative treatment of endometrial and cervical cancer (TIME-C)

HEAD AND NECK

New– 052014-085 A phase I trial of stereotactic HYpofractionateD RadioAblative (HYDRA) treatment of advanced laryngeal cancer

112013-007 A phase I study of reduced-volume hypofractionated, PET-directed, intensity-modulated radiotherapy concurrent with weekly cisplatin chemotherapy for T1/NO-2 squamous cell carcinoma of the head and neck

NRG-HN001 Randomized phase II and phase III studies of individualized treatment for nasopharyngeal carcinoma based on biomarker Epstein Barr virus (EBV) deoxyribonucleic acid (DNA)

RTOG 3501 Tryhard: a phase II, randomized, double-blind, placebo-controlled study of lapatinib (Tykerb) for non-HPV locally advanced head and neck cancer with concurrent radiation

06213-052 A phase 1 CyberKnife accelerated hemilarynx stereotactic radiotherapy study for early-stage glottic larynx cancer

RTOG 1216 Randomized phase II/III trial of surgery and postoperative radiation delivered with concurrent cisplatin versus docetaxel versus docetaxel and cetuximab for high-risk squamous cell cancer of the head and neck

RTOG 0920 A phase III study of postoperative radiation therapy (IMRT)/- cetuximab for locally advanced resected head and neck cancer

LUNG

Small Cell Lung Cancer

CALGB 30610/RTOG 0538 A phase III comparison of thoracic radiotherapy regimes with cisplatin and etoposide in limited small cell lung cancer

Non-Small Cell Lung Cancer

RTOG 839 Randomized phase II study of preoperative chemoradiotherapy +/- panitumumab followed by consolidation chemotherapy in potentially operable locally advanced (stage Iia, N2+) non-small cell lung cancer

92013-070 Maintenance chemotherapy versus consolidative stereotactic body radiation therapy (SBRT) plus maintenance chemotherapy for stage IV non-small cell lung cancer (NSCLC): a randomized phase II trial

RTOG 1306 A randomized phase II study of individualized combined modality therapy for stage III non-small cell lung cancer (NSCLC)

062012-53 A randomized phase I/II study of nab-paclitaxel, or paclitaxel, plus carboplatin with concurrent radiation therapy followed by consolidation in patients with favorable-prognosis inoperable stage IIIA/B NSCLC

052011-093 Phase III randomized study of standard versus accelerated hypofractionated image-guided radiation therapy (IGRT) in patients with stage II-III non-small cell lung cancer and poor performance status

SPINE

072010-134 A phase II study of stereotactic body radiation therapy (SBRT) and vertebroplasty for localized spine metastasis

RTOG 0631 A phase II/III study of image-guided radiosurgery/SBRT for localized spine metastasis

For more information, please contact Clinical Research Manager Jean Wu at 214-633-1753 or jean.wu@utsouthwestern.edu

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Accelerated partial breast irradiation (APBI): Options and new horizons

After completing this activity, the participant should be better able to:

- Determine good candidates for hypofractioned whole-breast irradiation and accelerated partial-breast irradiation
- Differentiate between the various modalities of partial-breast irradiation
- Describe newer modalities and technology currently under investigation for partial-breast irradiation

Breast cancer is the second most common cancer diagnosed in women. (Skin cancer is the most common.) With better screening modalities such as annual mammography and MRI, more women are diagnosed with breast cancer at earlier stages. Depending on the location of the tumor and patient breast size, breast conservation therapy is usually an option for many women instead of mastectomy. Several randomized trials have demonstrated that breast irradiation substantially reduces the risk of local recurrence and prevents the need for subsequent mastectomy in patients with invasive breast cancer.[1-5]

Breast conservation therapy typically requires lumpectomy surgery with or without nodal evaluation and whole-breast radiation treatments. Whole-breast radiation treatments have historically required 6-6.5 weeks of treatment (30-33 fractions). Hypofractionated whole-breast radiation (involving a higher dose of radiation per fraction, with fewer total fractions), has become another option for early-stage breast cancer, constituting 42.5 Gy in 16 fractions of radiation therapy.[6] Whelan et al., in their phase III randomized trial, compared standard fractionation to hypofractionated whole-breast irradiation and found similar local control and cosmetic results at 10 years. However, hypofractionated whole-breast radiation is not an option for every candidate for breast conservation therapy as ASTRO consensus guidelines require favorable dosimetric parameters that usually rely on breast size, T1 or T2N0 disease, age >/= 50 years old, and no prior chemotherapy.[7]

Over the years, it has been discovered that 15-30% of women fail to complete whole-breast radiation therapy treatments as part of their breast conservation therapy (BCT).[8-9] Contributing factors for this high incompletion percentage include inaccessibility to a nearby radiation facility, development of toxicity, and/or the inconvenience of 6.5 weeks of daily radiation treatments. Common early toxicities include fatigue, edema, and skin erythema or blistering, all of which can have an impact on quality of life.

Clinical trials evaluating the role of breast irradiation following breast-conserving surgery suggest that if local recurrences occur, they are most likely (70-80% of cases) to develop at the site of the primary tumor with or without radiation therapy. The risk of recurrence in the breast away from the primary tumor site is only 1.5-3.5%.[10-11] These observations have led to the hypothesis that limiting radiation therapy to the primary tumor site—a technique called accelerated partial-breast irradiation (APBI)—rather than treating the whole breast may result in potentially less morbidity and shorter overall treatments in early-stage breast cancer.

Partial-breast radiation therapy allows for completion of radiation in a faster time frame, thus allowing a more convenient treatment for women. Larger doses per fraction are used while limiting the volume of normal breast tissue exposed to radiation. The lumpectomy cavity is treated with a 1-2.5 cm margin, depending on the technique of APBI used. Even though the standard of care is still whole-breast radiation, the frequency of partial-breast radiation in breast conservation therapy has increased due to promising clinical data and perceived patient convenience.

Several consensus guidelines outline the ideal candidate for partial-breast radiation outside of a clinical trial setting. As more institutions have started implementing PBI techniques in their practices, different medical societies have published guidelines—among them the American Society for Radiation Oncology (ASTRO), Groupe Européen de Curietherapie-European Society of Therapeutic Radiation Oncology (GEC-ESTRO), American Society of Breast Surgeons (ASBS), and American Brachytherapy Society (ABS). There are minor variations among the different societies regarding the definition of a suitable candidate. Briefly, these include early-stage, low-risk breast cancer: T1 or T2 invasive ductal breast carcinoma less than 3 cm; estrogen positive; age greater than 60; and node negative12 (see Table 1 for ASTRO consensus guidelines).

Treatment options

Partial-breast radiation can be delivered via several different modalities, including interstitial brachytherapy, intracavitary brachytherapy (SAVI, Contura, or Mammosite), intraoperative radiation and 3-D external beam radiation therapy. Brachytherapy and conventional 3-D external beam radiation therapy treatments are usually given over a five-day period twice per day while intraoperative radiation is delivered at the time of surgery in the operating room in a single fraction.

Interstitial brachytherapy is the oldest technique for APBI. This technique uses multiple interstitial catheters that are placed in the breast with either a template or free-hand and usually with some image guidance (ultrasound or CT scan). This technique is very operator-dependent and requires an experienced physician to produce an implant of excellent quality. The catheters can be loaded with either low dose rate (LDR) or high dose rate (HDR) sources. HDR is the most common because iridium-192 sources can be used on an outpatient basis.

Intracavitary balloon (Mammosite and Contura) or strut-based brachytherapy (SAVI) are another modality of breast brachytherapy. These devices come in different sizes, have single or multiple lumens (strut-based or balloon-based catheters), and the entire device is placed into the lumpectomy cavity. The lumens are then connected to an HDR unit, and treatments are given twice daily for five days to a dose of 34 Gy in 10 fractions. This treatment is invasive, and the device stays within the lumpectomy cavity for the duration of the radiation treatments (five to seven days, typically). The ASBS registry trial has reported 1,449 patients treated with balloon-based brachytherapy with a median follow-up of 53.3 months. The five-year actuarial rate of ipsilateral breast tumor recurrence is only 2.59%.[13]

Intraoperative radiation (IORT) is a single high-dose fraction of radiation delivered to the lumpectomy cavity at the time of surgery. This can be done with either megavoltage electrons or 50KV photons prescribed to 20-21 Gy. The advantage of this technique is that radiation treatment can be completed at the time of surgery, tissues can be physically displaced out of the radiation beam as needed, and radiation can be delivered theoretically before residual tumor cells have time to proliferate postoperatively. One disadvantage is that some women will still require whole-breast radiation after IORT when unexpected findings are found on the final pathology report because final pathology results are not available at the time of surgery.

Figure A

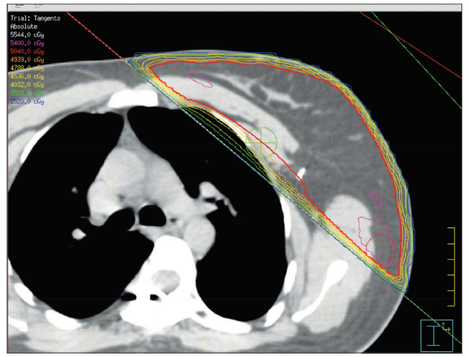
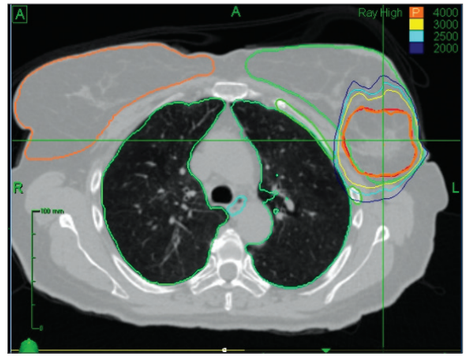


Figure B



Tangential whole-breast radiation (Fig. A) versus CyberKnife stereotactic partial-breast radiation (Fig. B).

Clinical evidence for partial-breast irradiation

The TARGIT, a phase III non-inferiority trial, compared single-dose targeted intraoperative radiotherapy (TARGIT) versus fractionated external beam radiotherapy (EBRT) for breast cancer.[14] From 2000-2012, a total of 3,451 patients were randomized between APBI and whole-breast radiation in 33 centers in 11 countries. Fifteen percent of women in the APBI arm were treated with additional EBRT due to adverse pathological features. With a median follow-up of two years and five months for the whole cohort, the five-year risk of local recurrence was 3.3% with TARGIT and 1.3% with the WBRT, (p=0.04). The ELIOT trial using megavoltage electrons has a median follow-up of 5.8 years.[15] The five-year risk of ipsilateral breast recurrence was 4.4% with IORT and 0.4% with the standard WBRT (p<0.0001). The overall mortality was not different between both groups, with a five-year survival rate around 97%.

Initial phase II trials have reported low rates of local recurrences and acceptable rates of cosmesis (with at least 80% good-to-excellent cosmesis outcomes) following APBI with 3DCRT. Currently, the largest U.S. randomized control trial (RTOG 0413 / NSABP 39) comparing whole-breast radiation to partial-breast radiation has finished accruing, and we are awaiting final results. More than 4,000 women participated in this trial nationwide. PBI treatments were delivered via interstitial brachytherapy, intracavitary brachytherapy, or 3-D external beam radiation at the discretion of the treating

radiation oncologist. The clinical target volume (CTV) and planning target volume (PTV) (with expansions to cover potential microscopic disease and set-up error, including chest wall movement with respiratory variation, respectively), included a total expansion of 2.5 cm from the lumpectomy cavity. Patients treated with 3-D CRT were treated to 38.5 Gy in 10 fractions (treatments given twice daily over five days).

Meanwhile, the Canadian RAPID trial has reported cosmesis outcomes with a median follow-up of 36 months.[16] This phase III trial involved 2,135 women randomized to whole-breast irradiation and 3-D conventional external beam partial-breast radiation (CRT) with CTV and PTV expansions from the lumpectomy cavity totaling 2.0 cm. Adverse cosmesis at three years was increased among those treated with APBI compared with WBI as assessed by trained nurses (29% v 17%; p=.001), by patients (26% v 18%; p=0.002), and by physicians reviewing digital photographs (35% v 17%; p=.001). In this trial, 3D-CRT APBI was associated with increased rates of adverse cosmesis and late radiation toxicity compared to standard WBI. This publication cautioned physicians and patients against the use of 3-D APBI outside of a clinical trial.[16] One factor that potentially contributed to these adverse cosmetic outcomes was the 3-D CRT technique that was used. Not only were there a limited number of beams, but the margins used to create the PTV were large, allowing a large volume of normal breast tissue to receive the prescription dose.

Future directions

At UT Southwestern Medical Center, we have pioneered a new modality for PBI utilizing stereotactic body radiation therapy (SBRT, also known as stereotactic ablative radiotherapy or SABR). Currently, a robotic stereotactic system is being utilized in a phase I institutional dose escalation trial of PBI, decreasing the total number of fractions from 10 to five fractions while escalating the dose of radiation. Sixty-eight women have been reported thus far, and early cosmetic results seem promising. Physicians have scored cosmesis post-SBRT as excellent or good at baseline, 6, 12, and 24 months in 94.9%, 100%, 97.7%, and 100% of patients, respectively (p=0.28), while patients scored the same periods as 82.7%, 96.2%, 95.4%, and 92.8% (p=0.04) (results presented at ASCO Chicago 2015).

The benefit of using the robotic stereotactic system is that the respiratory cycle is continuously tracked, allowing total lumpectomy cavity expansions to be minimized because there is no need to account for major variations in chest wall movement during the respiratory cycle. This reduces the volume of breast tissue being irradiated, which we hope will translate to better long-term cosmetic outcomes. In comparison to interstitial and balloon brachytherapy, this treatment is noninvasive and is given in five daily fractions rather than 10 twice-daily fractions. This ongoing phase I dose-escalation trial demonstrates that a dedicated stereotactic unit —or in fact simply a stereotactic radiation technique—can be implemented and used for APBI. This technique also is less operator-dependent compared to brachytherapy procedures.

Further on the horizon is the development of dedicated stereotactic external beam radiation technology to treat breast cancer. UT Southwestern soon will be one of five centers worldwide to obtain a device called the GammaPod™ (Xcision Medical Systems LLC, Columbia, Maryland). The design goal of the GammaPod™ is to deliver ablative doses with sharp gradients under stereotactic image guidance. Highly focused radiation is achieved at the isocenter due to the cross-firing from 36 radiation arcs generated by 36 rotating individual cobalt-60 beams while using vacuum-assisted breast cups for immobilization of the breasts.

Currently, APBI still is an investigational treatment for breast cancer; however, preliminary data seem promising, and we are all awaiting the final results of the several large phase III trials comparing whole-breast radiation therapy to partial-breast radiation.

References:

1. Early Breast Cancer Trialists' Collaborative Group. Favourable and unfavourable effects on long-term survival of radiotherapy for early breast cancer: An overview of the randomized trials. Lancet. 2000;355:1757-69.

2. Fisher B, Anderson S, Bryant J, et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. N Engl J Med. 2002;347:1233-41.

3. Liljegren G, Holmberg L, Bergh J, et al. 10-year results after sector resection with or without postoperative radiotherapy for stage I breast cancer: A randomized trial. J Clin Oncol. 1999;17(8):2326-33.

4. Clark RM, Whelan T, Levine M, et al. Randomized clinical trial of breast irradiation following lumpectomy and axillary dissection for node-negative breast cancer: An update. J Natl Cancer Inst. 1996;88(22):1659-64.

5. Veronesi U, Luini A, Del Vecchio M, Greco M, Galimberti V, Merson M, Rilke F, Sacchini V, Saccozzi R, Savio T, et al. Radiotherapy after breast-preserving surgery in women with localized cancer of the breast. N Engl J Med. 1993;328(22):1587-91.

6. Whelan TJ, Pignol JP, Levine MN, et al. Long-term results of hypofractionated radiation therapy for breast cancer. N Engl J Med. 2010; 362(6):513-20.

7. Smith BD, Bentzen S, Correa CR, et al. Fractionation for whole breast irradiation: An American Society for Radiation Oncology (ASTRO) evidence-based guideline. Int J Radiat Oncol Biol Phys. 2011;81(1):59–68.

8. Nattinger AB, Hoffmann RG, Kneusel RT, Schapira MM. Relation between appropriateness of primary therapy for early-stage breast carcinoma and increased use of breast-conserving surgery. Lancet. 2000;356(9236):1148-53.

9. Tyldesley S, Foroudi F, Barbera L, et al. The appropriate rate of breast conserving surgery: An evidence-based estimate. Clin Oncol (R Coll Radiol). 2003;15(3):144-55

10. Clark RM, McCulloch PB, Levine MN, et al. Randomized clinical trial to assess the effectiveness of breast irradiation following lumpectomy and axillary dissection for node-negative breast cancer. J Natl Cancer Inst. 1992;84:683-89.

11. Imamura H, Haga S, Shimizu T, et al. Relationship between the morphological and biological characteristics of intraductal components accompanying invasive ductal breast carcinoma and patient age. Breast Cancer Res Treat. 2000; 62:177-84.

12. Smith BD, Arthur DW, Buchholz TA, et al. Accelerated partial breast irradiation consensus statement from the American Society for Radiation Oncology (ASTRO). Int J Radiat Oncol Biol Phys. 2009;74(4):987-100.

13. Shaitelman SF, Vicini FA, Beitsch P, et al. Five-year outcome of patients classified using the American Society for Radiation Oncology consensus statement guidelines for the application of accelerated partial breast irradiation: An analysis of patients treated on the American Society of Breast Surgeons MammoSite Registry Trial. Cancer. 2010; 116(20):4677-85.

14. Vaidya JS, Wenz F, Bulsara M, et al. Risk-adapted targeted intraoperative radiotherapy versus whole-breast radiotherapy for breast cancer: 5-year results for local control and overall survival from the TARGIT-A randomised trial. Lancet. 2014;383(9917):603-13.

15. Veronesi U, Orecchia R, Maisonneuve P, et al. Intraoperative radiotherapy versus external radiotherapy for early breast cancer (ELIOT): A randomised controlled equivalence trial. Lancet Oncol. 2013;Dec;14(13):1269-77.

16. Olivotto IA, Whelan TJ, Parpia S, et al. Interim cosmetic and toxicity results from RAPID: A randomized trial of accelerated partial breast irradiation using three-dimensional conformal external beam radiation therapy. J Clin Oncol. 2013;31(32):4038-45.

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Table 1 ASTRO Consensus Guidelines for APBI

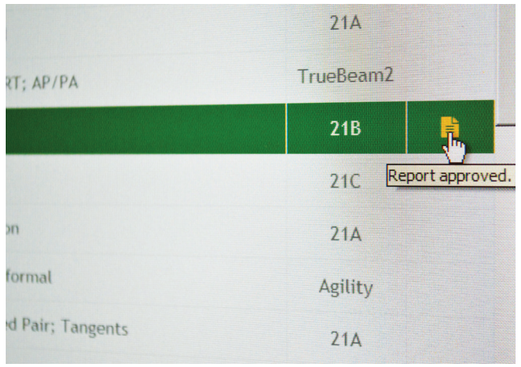
Patients are "suitable" for APBI if all criteria are present

Factors	Criterion
Age	>/= 60 years
BRCA1/2 mutation	Not present
Tumor size	</= 2 cm
T stage	T1
Margins	Negative by at least 2 mm
Grade	Any
LVSI	No
ER status	+
Multicentricity	Unicentric
Multifocality	Clinically unifocal
Histology	Invasive Ductal, mucinous Tubular, colloid
Pure DCIS	Not allowed
EIC	Not allowed
Associated LCIS	Allowed
N stage	N0 (i-,i+)
Nodal surgery	SN Bx or ALND
Neoadjuvant therapy	Not allowed

First automated chart-checking program to improve safety

Radiation oncology is quite different from other cancer specialties in its heavy reliance on technology, which ranges from giant linear accelerators to highly advanced computer-based treatment planning systems.

"We generate a lot of data—thousands of treatment parameters per plan," says Professor Steve Jiang, Ph.D., Radiation Oncology's Director of Medical Physics and Engineering.



CACCI: Computer-Assisted Chart Checking and Inspection

And with multiple parameters comes the potential for multiple errors. Historically, physicists here and elsewhere have conducted manual checks of each patient's chart on a regular basis to look for inconsistencies or errors. Data generated by the treatment machines representing the actual dose delivered to a patient were compared with the data contained in the patient's chart representing the intended dose delivery method, a familiar process known as the "chart check."

"Not only was this inefficient, but it was impossible to check every parameter of a patient's treatment, particularly when using modern technologies such as IMRT," Dr. Jiang says. "Instead, we would have to look at a subset of the data."

To address the shortcomings of this method, UT Southwestern physicists have developed a new software program called CACCI—Computer-Assisted Chart Checking and Inspection—to improve the chart-checking process. CACCI compares and verifies individual patient plans as well as general rules, such as "a signed chart check must be performed with every five fractions of treatment." Nonmatching parameters or rules are flagged with a warning sign for a physicist to manually check.

"The main goal is to make radiation treatment even safer," says Professor Yulong Yan, Ph.D., Director of Computational Physics in the Division of Medical Physics and Engineering. "Computers are very good at repetitive work, whereas human eyes are limited in terms of both accuracy and the amount of data that can be processed."

The computerized chart check is the first such program developed specifically for radiation therapy quality control. The CACCI application is also Web-based, allowing users to perform chart checks wherever it is convenient rather than just at clinic workstations.

Dr. Jiang says the next step will be to utilize machine learning to enhance the performance of CACCI. The development team, including Dr. Yan, lead developer Jun Tan, Ph.D., and other clinical physicists in the division, plans to publish the results of their accuracy validation studies and then make the software available to the radiation therapy community.

News Briefs

Single-dose SABR for liver reported

A dose-escalation study to determine the highest safe dose for single-fraction stereotactic ablative radiotherapy (SABR) for the liver was recently reported in the *Annals of Surgical Oncology*. The study, led by UT Southwestern Assistant Professor of Radiation Oncology Jeffrey Meyer, M.D., encompassed 14 patients with 17 liver metastases. No dose-limiting toxicities were observed at either the 35 Gy or 40 Gy dose level. Nine of the 13 lesions assessable for treatment response showed a complete radiographic response to treatment; the remainder showed partial response. Local control of irradiated lesions was 100 percent at a median imaging follow-up of 2.5 years.

Grants awarded to Radiation Oncology investigators

NASA has renewed its Specialized Center of Research on Radiation Carcinogenesis, a multi-institution grant ($952,282 / 5 years) with UT Southwestern, Colorado State University (institutional lead), and UT Medical Branch in Galveston participating. Colorado State's Michael Weil, Ph.D., is the overall principal investigator, while UT Southwestern's Michael Story, Ph.D., Professor of Radiation Oncology and Director of Molecular Radiation Biology, is principal investigator.

Puneeth Iyengar, M.D., Ph.D., Assistant Professor of Radiation Oncology, has been awarded an American Cancer Society research scholar grant for his project, "Unchecked Adipocyte Lipolysis and Tumor Progression in Cachexia" ($600,000/4 years).

Heavy ion meeting scheduled

The next International Symposium on Ion Therapy (ISIT) will be held Oct. 15-16 in Dallas. This event brings together global leaders in the field of heavy particle therapy to share emerging advances in patient treatment, clinical trials, technology, and basic science. For registration and abstract submissions, please visit isit-sw.org.

Survivor Story: Former cancer patient comes back—as a radiation therapy student

After overcoming brain cancer, Lisa Liter changed her career plans to seek training at the same place she received treatment.

Tall and confident, 28-year-old Lisa Liter wears navy blue scrubs and her hair in a ponytail as she moves around the CT scanner in the radiation clinic, preparing the room for the next patient. It's hard to believe that less than three years ago she was patient here herself.

"I was inspired by the radiation therapist who treated me, who also was a cancer survivor," says Ms. Liter. "Radiation therapists have direct relations with patients. They see, talk to, and comfort them every day. I like that interaction."

A native of Lawton, Okla., Ms. Liter was already on track to enter the medical profession in some capacity. After high school, she worked for years both part time and full time as a pharmacy tech and simultaneously worked in finance for Oklahoma's Department of Mental Health, where she rapidly rose to a supervisory position.

She was studying to become a licensed pharmacist in the fall of 2012 when she started having violent headaches—so severe that they woke her in the middle of the night vomiting.

"I was surprised because I had always been healthy. I did weight training five times a week," says Ms. Liter, a former state tennis champion. She went to a holistic medicine practitioner who prescribed pain medication, and later on, steroids. When the headaches didn't subside, she had an MRI.

Within 30 minutes of undergoing her MRI, Ms. Liter, who was already driving home, received a call from the imaging technicians directing her to go to the nearest hospital. There was a large mass on her brain, which further testing revealed was a grade 3 anaplastic astrocytoma.

The Oklahoma neurosurgeon Ms. Liter consulted with agreed to send her to UT Southwestern due to the size and complexity of the mass removal. She was transported to Dallas by ambulance.

Once here, Professor of Neurological Surgery Bruce Mickey, M.D., performed the complex surgery to remove the tumor from Ms. Liter's brain. The surgery was mostly successful, but radiation was a key next step to kill residual cancer cells. However, Ms. Liter's state-sponsored insurance plan wanted her to have her radiation treatments in Oklahoma.

"UT Southwestern specializes in brain radiotherapy treatment; I was convinced they wouldn't know how to take care of me if I went somewhere else," Ms. Liter says. "After meeting with Dr. [Robert] Timmerman, I decided I was going to have my treatment here even if it bankrupted me."

Fortunately, just 24 hours before Ms. Liter was scheduled to receive her planned CT at UT Southwestern, an Oklahoma neurosurgeon provided her with a letter of medical necessity to allow her treatment to be covered and to receive continuity of care. Ms. Liter underwent seven weeks of intensity-modulated radiation therapy (IMRT) at UT Southwestern, followed by 18 months of oral chemotherapy (temozolomide).

With little to no side effects from her ongoing treatment, Ms. Liter began making some new plans.

"I was surprised when she told me on her six-month follow-up visit that she had applied to our radiation therapy program—surprised and really proud that she thought so highly of the care we were able to provide her," says Dr. Timmerman, Professor of Radiation Oncology. "I asked her if she was sure that she could handle the emotional aspect of dealing with other cancer patients with her same diagnosis."

"I feel like everything happens for a reason, and my cancer experience was actually rewarding," Ms. Liter says. Now she spends three days every week in the clinic, performing tasks that fulfill the two-year program's requirements for demonstrating clinical competency. Occasionally she shares her story with other patients when it seems appropriate.

She says, "I'm here for a reason: It's to give back and give hope."

> "Radiation therapists have direct relations with patients. They see, talk to, and comfort them every day. I like that interaction."
>
> — *Lisa Liter*

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Physicians who would like to make a referral may call the department's main clinic number at 214-645-8525 or UT Southwestern's physician referral line at 214-645-8300 (toll-free 866-645-5455) for adult patients, or 877-445-1234 for pediatric patients.

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