Update on the NSABP B-39/RTOG 0413 Clinical Trial

Comparing Partial to Whole Breast Irradiation Therapy

by Deborah Norris, DO, and Thomas B. Julian, MD

Although breast conservation therapy now provides an option equal in terms of overall survival to mastectomy,[1] some women with breast cancer and some physicians still choose mastectomy, for many reasons. A major factor in this decision is often the length of treatment. The six- to seven-week course of daily radiation treatment[2,3] has been an obstacle to many women who would otherwise be able to have successful breast conserving treatment.[4] Up to 43 percent of cancer patients who are eligible to receive breast conservation therapy instead elect to have a mastectomy.[2] Even more worrisome, 15 to 30 percent of women who have lumpectomies do not receive prescribed radiation therapy.[2,3] This leaves them at significant risk for local recurrence, as was evidenced in the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-06 study.[1]

Partial Breast Irradiation

Partial breast irradiation (PBI), administered in several forms in an abbreviated treatment time of five days, is now demonstrating early effective data.[3,4,6] The three common PBI methods are the MammoSite® intracavitary balloon catheter, interstitial multi-catheter brachytherapy, and 3-D conformal external beam radiation (3D CRT). MammoSite®, a single-channel, intracavitary balloon catheter placed either at the time of breast surgery or afterwards, has resulted in positive data over the past five years.[2,6] Interstitial multi-catheter brachytherapy, which is a complex system of multiple catheters placed by freehand technique or with CT and template guidance surrounding the tumor bed after surgical excision, has also been used with cosmetic success for local disease control over five years.[3] These two modalities use a radioactive source that is passed into the breast via catheter(s) to treat the lumpectomy site.[3] The third PBI modality, 3D CRT, is noninvasive and uses computerized radiation for precision-targeted treatment of the lumpectomy bed plus a 1-2 cm margin.[4,8]

Partial breast irradiation may provide solutions for problems related to travel and lodging, work, and caregiving responsibilities that many women seeking treatment for breast cancer need to address.[2,3] PBI may also reduce the rate of post-radiation complications that can occur with whole breast irradiation (WBI).[2,4,7] Unfortunately, PBI lacks long-term clinical outcome results. Though most true in-breast tumor recurrence occurs at the site of lumpectomy,[4] there have been no randomized comparison data to show that PBI can reduce the risk of local recurrence as effectively as can current standard WBI.[6] In addition, each delivery form for PBI has distinct advantages and disadvantages and the most efficacious system has not yet been determined.[4]

NSABP B-39/RTOG 0413 Clinical Trial

With the encouragement of the National Cancer Institute (NCI), the National Surgical Adjuvant Breast and Bowel Project (NSABP), Radiation Therapy Oncology Group (RTOG) developed the NSABP B-39/RTOG 0413 trial to determine the efficacy of these new radiation treatment modalities compared to WBI and to each other, in addressing local recurrence, disease-free survival, overall survival, quality of life, and cosmesis in several stages of breast cancer. This type of study is felt to be necessary if PBI is to be established as a standard of care.

The NSABP B-39/RTOG 0413 study includes patients with Stage 0, I, or II breast cancer who have had lumpectomy for a tumor ≤ 3cm and who have no more than 3 positive lymph nodes. Patients are stratified by disease stage (DCIS, invasive, 0 or 1-3 positive nodes), menopausal status, hormone receptor status, and intention to receive chemotherapy. These patients are then randomized into two groups following lumpectomy and axillary staging (see Figure 1).

Those in group 1 are assigned to receive WBI, consisting of the conventional 50 – 50.4 Gy (2.0 to 1.8 Gy/ fraction) with a 10 – 16 Gy boost to the tumor bed. Treatment takes place over six to seven weeks. Those in group 2 receive one of three forms of PBI: multi-catheter brachytherapy, MammoSite® balloon catheter, or 3D CRT. Patients are dosed at 34 Gy in 3.4 Gy BID (twice a day) fractions for the catheters and 38.5 Gy in 3.85 Gy fractions BID for the external beam. All PBI is given for 5 days in a 5-10 day time span for a total of 10 treatments, with no boost.

The intent of this study is to determine if PBI is as effective in preventing in-breast tumor recurrence as is WBI. Quality of life issues such as fatigue, cosmesis, and convenience will be evaluated in patients who do and do not undergo chemotherapy (480 patients each).

Patient Accrual

Since opening in March 2005, the trial has rapidly accrued patients, and a sufficient number of low-risk patients have now been entered, resulting in a decision to restrict further accrual to only high-risk patients and to increase the total accrual so that we can properly address the primary endpoint of in-breast tumor recurrence. Today accrual is currently open to patients who are younger than 50 years of age and who 1) have DCIS, regardless of receptor status or 2) are diagnosed with invasive breast cancer, N0, N1, and any receptor status. Accrual is also open to those older than 50 with invasive breast cancer that is 1) hormone receptor negative, regardless of node status or 2) hormone receptor positive, node positive. The new target accrual is 4,300 patients. Definitive analysis will take place after there are 175 in-breast tumor recurrences, which is approximately 10 years away.

NSABP B-39/RTOG 0413 is a critical Phase III trial to determine the efficacy of PBI in both low- and high-risk breast cancer patients. The study has the potential to alter breast care in terms of less breast irradiation, as NSABP B-06 altered surgical breast care to give women a choice between mastectomy and lumpectomy.

You and your patients are encouraged to participate in this trial and to help determine and improve the future of breast cancer care. Clinicians who are interested in participating can contact the NSABP at 412.330.4624 or via its website at *www.NSABP.Pitt.edu*, or RTOG at 215.574.3205 or via its website at *www.RTOG.org*.

Deborah Norris, DO, is surgical breast fellow, Department of Human Oncology, Allegheny General Hospital, Pittsburgh, Pa. Thomas B. Julian, MD, is associate professor of Human Oncology, Allegheny General Hospital and associate medical director, National Surgical Adjuvant Breast and Bowel Project, Pittsburgh, Pa.

References

[1] 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(16):1233-1241.
[2] Pruthi S, Boughey JC, Brandt KR, et al. A multidisciplinary approach to the management of breast cancer, part 2: therapeutic considerations. *Mayo Clin Proc.* 2007; Sep;82(9):1131-1140.
[3] Vicini FA, Baglan KL, Kestin LL, et al. Accelerated treatment of breast cancer. J Clin Oncol. 2001;Apr 1;19(7)1993-2001.
[4] Kuerer HM, Julian TB, Strom EA, et al. Accelerated partial breast irradiation after conservative surgery for breast cancer. *Ann Surg.* 2004; Mar;239(3):338-51.
[5] Guerrero Urbano MT, Nutting CM. Clinical use of intensity-modulated radiotherapy: part II. *Br J Radiol.* 2004;77(915): 177-182.
[6] Benitez PR, Keisch ME, Vicini F, et al. Five-year results: the initial clinical trial of MammoSite balloon brachytherapy for partial breast irradiation in early-stage breast cancer. *Am J Surg.* 2007;194(4):456-462.
[7] Hiatt JR, Evans SB, Price LL, et al. Dose-modeling study to compare external beam techniques from protocol NSABP B-39/RTOG 0413 for patients with highly unfavorable cardiac anatomy. *Int J Radiat Oncol Biol Phys.* 2006;65(5):1368-1374.
[8] Cuttino LW, Todor D, Arthur DW. CT-guided multi-catheter insertion technique for partial breast brachytherapy: reliable target coverage and dose homogeneity. *Brachytherapy.* 2005;4(1):10-17.

Figure 1. Schema for the NSABP B-39/RTOG 0413 Trial