Breast Conservation Therapy with Tumor Bed Brachytherapy Alone in Stage I Breast Cancer: Results of a Phase II Trial

Leela Krishnan M.S., M.D., F.A.C.R.O.[1], William R. Jewell, M.D., F.A.C.S.[2], Carol Connor, M.D.[2], Ossama W. Tawfik, M.D., Ph.D.[3], Alvaro Alvarez-Farinetti, M.D.[1], Fen Wang, M.D., Ph.D.[1], Eashwer K. Reddy, M.D., F.A.C.R.[1], Srivani Thatikonda, M.D.[1], Engikolai C. Krishnan, M.S., M.D.[2], Bruce F. Kimler, Ph.D.[1]

University of Kansas Medical Center, Kansas City, KS

[1]Department of Radiation Oncology

[2]Department of Surgery

[3]Department of Pathology and Laboratory Medicine

Abstract

Background. Radiotherapy after breast conserving surgery increases local control. Standard radiotherapy includes whole breast irradiation delivered in a daily fashion over 5 or 5½ weeks. All patients may not require entire breast treatment. We tested the feasibility of limited surgery with limited irradiation using interstitial brachytherapy to the tumor bed in a selected group of patients with stage I breast cancer in a phase II trial.

Methods. Women aged 55 years or older with low or intermediate grade stage I tumors were treated with placement of interstitial catheters at the time of lumpectomy and axillary node dissection. The tumor bed was treated peri-operatively, using either low-dose-rate or high-dose-rate brachytherapy with Iridium-192 to deliver 16 to 25 Gy to the tumor bed over one to two days.

Results. Ninety-five breasts (94 women) were treated on the protocol. There were four (4%) local recurrences in the breast at a median follow-up interval of 66 months (range, 2.8 - 152). Cosmetic appearance ranged between good to excellent. There were no long-term radiation related complications.

Conclusions. In a selected group of patients, lumpectomy and immediate peri-operative low-dose interstitial brachytherapy to the tumor bed yielded local control equivalent, without significant morbidity, to that observed in a historical series of whole breast irradiation.

KJM 2009; 2(2):33-40.

Introduction

Several randomized trials clearly have established that breast conservation therapy with irradiation and mastectomy have equivalent survival results for early stage breast cancer.[1-6] The standard of care for breast conservation therapy includes whole breast irradiation. Over the last decade, there has been increasing interest in the feasibility of doing partial breast irradiation in selected cases with interstitial brachytherapy[7-13], external beam therapy[14,15], or intra-operative radiotherapy.[16,17] The rationale for reducing the volume of breast irradiated includes improved cosmesis, improved function, greater convenience for patients, reduced radiation dose, and decreased risk of second malignancy.

At our institution, we initiated a single arm Phase II trial in June 1993 to assess the efficacy of a low dose of tumor bed brachytherapy immediately following lumpectomy in a selected subset of patients with invasive breast cancer.[18] This report represents an update of our continued accrual into this

trial including a larger number of patients and a longer period of follow-up.

Methods

Study procedures, including obtaining informed consent, were conducted in accord with the ethical standards of the institution's Human Subjects Committee. The trial was initiated in June 1993. For enrollment in the study, prospective subjects were required to meet all four of the following criteria: patient age ≥ 60 years, tumor size ≤ 2 cm, low or intermediate histologic grade, and pathologically negative axillary nodes. Subsequently, the study was modified to include patients ≥ 55 years of age based on the finding that local recurrence rate in women over 55 years with quadrantectomy was not significantly different from those who received immediate breast irradiation.[19]

The requirement for pathologically negative axillary lymph nodes was modified to include clinically negative nodes in tumors ≤ 1 cm, if an axillary lymph node dissection was deemed medically inappropriate by the treating surgeon. However, with the advent of sentinel lymph nodal sampling, this procedure replaced axillary lymph node dissection. Tumors with the following histologic types made a patient ineligible for the protocol: infiltrating ductal carcinoma with extensive intraductal component, pleomorphic type of infiltrating lobular carcinoma, ductal carcinoma in situ, or lobular carcinoma in situ.

The primary outcome of the trial was to assess the rate of local recurrence with limited radiotherapy. The stopping rule specified that the study would be stopped if the local recurrence rate was higher than the local recurrence rate obtained at our institution in operable breast cancer treated with the conventional approach of breast conservation therapy plus brachytherapy to the tumor site and entire breast irradiation. The recurrence rate at a median follow-up of 69 months in our series was 14 of 250 breasts or 5.6%.[20]

Pathologic diagnoses were established by either excisional, incisional, mammotest core biopsies, or fine needle aspiration biopsies. Patient eligibility was determined based upon the previously outlined criteria. Eligible patients were advised about the option of partial breast irradiation following lumpectomy utilizing peri-operative brachytherapy and informed consent was obtained.

Margin status of the wide excision specimens was evaluated by frozen section examination. Patients with clear margins of invasive or intraductal carcinoma underwent placement of interstitial catheters into the tumor bed by the technique described in our previous papers.[21,22] Patients were treated with low-dose-rate brachytherapy (LDRB) between December 1993 and June 1999, when the new technique of high-dose-rate brachytherapy (HDRB) became routinely available. Subsequently, all patients were treated using HDRB.

Prior to July 1999, axillary node dissections were performed and a final pathologic evaluation was obtained within 24 hours from the time of surgery. Subsequently, when sentinel lymph node sampling became the standard, a frozen section examination of the nodes was performed and node negative patients were treated according to the protocol. If the final pathology report revealed positive nodes, the patient was deemed ineligible for the protocol of brachytherapy alone and in addition received whole breast irradiation.

After the operation, simulation films were performed for localization of the catheters in the tumor bed and computation of isodose curves was carried out in the Department of Radiation Oncology. In those treated with LDRB, the catheters were after-loaded with low-dose-rate Iridium-192, varying in strength between 0.33 and 0.44 mg radium equivalent. A 20 to 25 Gy dose

was delivered to an isodose line that encompassed all the iridium ribbons and was at least one cm deep to the tumor bed over 24 to 48 hours.

In HDRB cases, a biological equivalent dose (BED) of 16 to 22 Gy was delivered in four fractions. Not all the patients received adjuvant systemic therapy; some patients were not recommended treatment and others refused treatment. Forty-eight patients received hormonal treatment, either tamoxifen or anastrozole. Three patients received adjuvant chemotherapy. The patients were followed on a regular basis and regular mammograms were obtained.

Results

A total of 94 post-menopausal patients enrolled in the protocol between December 1993 and November 2005. One African-American patient in her 60's had bilateral breast cancer with diagnoses one year apart and each breast was treated to the tumor bed with brachytherapy. Patient demographics are outlined in Table 1. Tumor characteristics are outlined in Table 2. Tumors ranged in size from a largest dimension of 0.3 cm to 2.0 cm, with a median of 1.0 cm. Sixty-five of 95 tumors were as expected, of the invasive ductal carcinoma type, not otherwise specified (Table 3). The treatment details are provided in Table 4.

Median time of follow-up was 69 months with a range of three to 152 months. Eighty of the 94 patients (85%) were alive in 2008, 78 (83%) with no evidence of disease and two (2%) with evidence of distant disease. Of the 14 deaths, there was evidence of breast cancer (distant disease but no local recurrence) at time of death for 10 of the women. Of the 95 breasts treated, a local recurrence occurred in only four women (4%; Figure 1) who were subsequently treated with mastectomy or whole breast irradiation (Table 5). With only four events, it would not be possible to identify potential prognostic factors for recurrence with any statistical power. All four patients were alive

Table 1. Demographics of 94 women treated on the protocol.

Demographics	Number of Patients	Percent
Age at Diagnosis, years		
55-59	11	12
60-69	34	36
70-79	39	41
80-89	8	9
91-100	2	2
Race		
African-American	12	13
Caucasian	82	87

Table 2. Characteristics of 95 tumors at diagnosis.

Tumor Characteristics	Number of Tumors	Percent
Detection		
Mammographic findings alone	74	78
Palpable	19	20
Bloody nipple discharge	2	2
Laterality		
Left	45	47
Right	50	53
Site of primary		
Upper outer quadrant	54	57
Upper inner quadrant	19	20
Lower outer quadrant	4	4
Lower inner quadrant	6	6
Central	1	1
Contiguous	11	12

Table 3. Pathologic characteristics of 95 tumors.

Pathologic Characteristics	Number of Tumors	Percent
Histology		
Invasive ductal carcinoma, NOS	65	68
Invasive tubular carcinoma	5	5
Invasive colloid (mucinous) carcinoma	7	7
Invasive lobular	12	13
Mixed invasive ductal and lobular	6	6
T1 Categories		
T1mic	1	1
T1a	10	11
T1b	38	40
T1c	46	48
Histological Grade*		
Grade 1	59	62
Grade 2	36	38
Estrogen Receptor Status**		
Positive	79	83
Negative	6	6
Unknown	10	11

*Tumor grade is based on the Elston and Ellis modification of the Bloom and Richardson's grading system.[24]

**Estrogen receptor status is determined by immunohistochemical analysis with expression of >10% nuclear staining considered positive.

Table 4. Treatment characteristics of 95 tumors.

Treatment	Number of Tumors	Percent
Axillary Procedure		
None	7	7
Level I dissection	1	1
Sentinel node sampling	54	57
Axillary node dissection	33	35
Brachytherapy		
LDRB; BED = 20 – 25 Gy	27	28
HDRB; BED = 14 – 22 Gy	68	72
Systemic Treatment		
None	44	46
Anti-hormone therapy	48	51
Chemotherapy	3	3

Figure 1. Freedom from local recurrence of the affected breast (n=95) as a function of time after diagnosis.

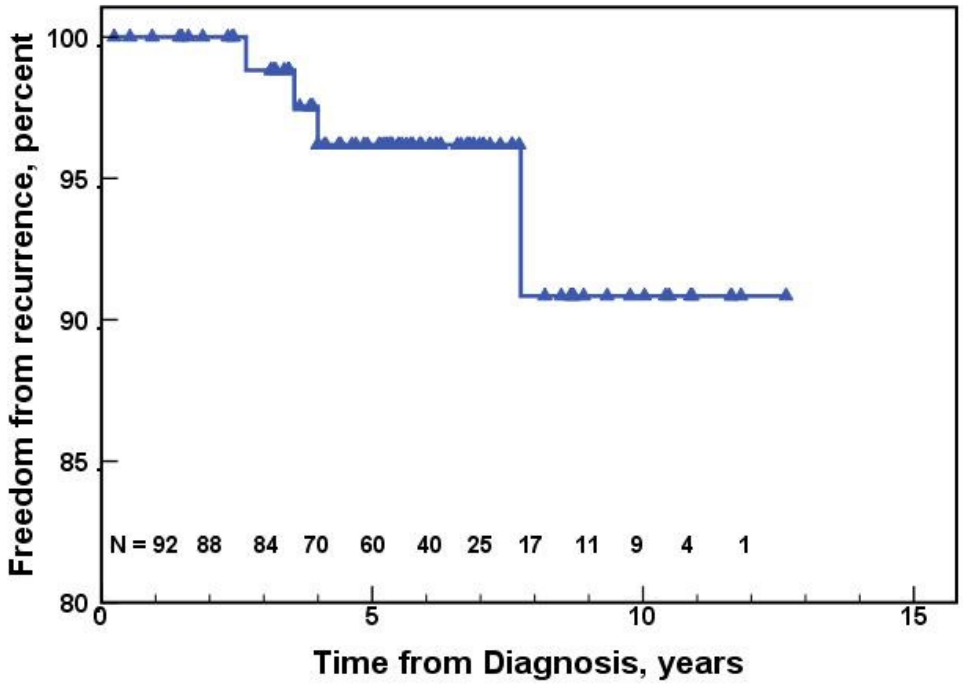

Table 5. Local tumor recurrence in four patients.

Interval from Diagnosis (in months)	Quadrant	Initial Treatment	Treatment of Recurrence	Status
32	Different	HDRB 22 Gy	Whole Breast Radiotherapy	NED* 57 months
43	Same	HDRB 16 Gy	Mastectomy	NED 13 months
48	Different	HDRB 22 Gy	Whole Breast Radiotherapy	NED 43 months
93	Same	LDRB 20 Gy	Mastectomy	NED 25 months

*NED: No evidence of disease.

at last follow-up, ranging from 13 to 57 months after time of recurrence. Cosmetic appearance of the breast, judged according to our criteria,[23] was deemed to be good to excellent in all patients. Radiation-related complications were evaluated during follow-up and no long-term sequelae were observed.

Discussion

Several randomized studies have established the validity of breast conservation surgery followed by irradiation in early stage breast cancer.[1-6] The National Surgical Adjuvant Breast and Bowel Project (NSABP) B-06 clearly demonstrated that omission of radiotherapy leads to an

unacceptably high local recurrence rate.[5] Other trials have attempted to identify subsets of patients who could be at a low risk for breast relapse without breast irradiation.[25-27] In each such trial, the local recurrence rate without irradiation was significantly higher than with irradiation.

Pathological analysis of local breast recurrences following lumpectomy in the NSABP B-06 trial determined 86% of local recurrences to be in the same quadrant as the initial primary.[28] Gump et al.[29] noted 90% of multicentric foci in 657 mastectomy specimens to be in close proximity to the primary. Similarly, Holland et al.[30] determined that in 43% of 282 invasive cancers tumor foci were present within two cm from the reference tumor.

A viable compromise between full-scale radiation and no radiation would be radiation restricted to the tumor bed. There are several such trials published in this respect. The doses of radiation to the tumor bed have varied among the different investigators from 30 to 55 Gy. The results of the current on-going NSABP protocol which randomized patients with tumors less than three cm to tumor bed irradiation versus whole breast irradiation would probably standardize radiotherapy in particular subsets of women who desire breast conservation therapy.

When we initiated our phase II trial, we decided on a dose of 20 to 25 Gy to the tumor bed with LDRB on a very conservative principle. Our previous work had revealed that peri-operative irradiation to tumor bed, accomplished by placement of implant catheters under direct visualization, enhanced local control.[20-22,31,32] The dose was prescribed to the periphery of tumor bed. The center of the tumor bed would receive at least 150% of the dose (i.e., 30 to 37.5 Gy) which yielded a radiobiological equivalent of approximately 40 to 45 Gy of external beam radiation given at 1.8 Gy per fraction.[33,34]

When we replaced LDRB with HDRB, equivalent doses were calculated and delivered in four fractions to facilitate delivery within two days of surgical excision. Further, if any of our patients suffered a recurrence in the breast, at that point, wide excision with external beam radiotherapy to the entire breast could still be offered as an option versus a mastectomy, without risk of tissue necrosis or rib fractures. If the recurrence happened to be in another quadrant, an interstitial boost to the tumor bed in addition could be offered.

In summary, the results presented in this study supported our original preliminary review.[18] Our local recurrence rate at 66 months was 4%, which was comparable to results reported by other investigators.[7-13] In addition, this rate was lower than the 5.6% obtained in our series with standard radiotherapy.[20] The doses used in our trial were lower than those used by other investigators.[7-13] However, our trial was in a selected group of patients, who were 55 or older, with stage I tumors with low or intermediate grade.

Our results may be due to the close collaboration between the surgeon and radiation oncologist, meticulous attention to margins, placement of interstitial catheters into the open surgical bed under direct visualization, generous coverage of the tumor cavity, and the biological advantage of immediate (within 24 to 48 hours of surgery) brachytherapy to the tumor bed.

References

[1] Veronesi U, Cascinelli N, Mariani L, et al. Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. N Engl J Med 2002; 347:1227-1232.

[2] Blichert-Toft M, Rose C, Andersen JA, et al. Danish randomized trial comparing breast conservation therapy with mastectomy: Six years of life–table analysis. J Natl Cancer Inst Monogr 1992; 11:19-25.

[3] van Dongen JA, Bartelink H, Fentiman IS, et al. Randomized clinical trial to assess the value of breast-conserving therapy in stage I and II breast cancer, EORTC 10801 trial. J Natl Cancer Inst Monogr 1992; 11:15-18.

[4] Sarrazin D, Lê MG, Arriagada R, et al. Ten-year results of a randomized trial comparing a conservative treatment to mastectomy in early breast cancer. Radiother Oncol 1989; 14:177-184.

[5] 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; 347:1233-1241.

[6] Lichter AS, Lippman ME, Danforth DN Jr, et al. Mastectomy versus breast-conserving therapy in the treatment of stage I and II carcinoma of the breast: A randomized trial at the National Cancer Institute. J Clin Oncol 1992; 10:976-983.

[7] Fentiman IS, Poole C, Tong D, et al. Inadequacy of iridium implant as sole radiation treatment for operable breast cancer. Eur J Cancer 1996; 32A:608-611.

[8] Perera F, Engel J, Holliday R, et al. Local resection and brachytherapy confined to the lumpectomy site for early breast cancer: A pilot study. J Surg Oncol 1997; 65:263-267.

[9] Samuel LM, Dewar JA, Preece PE, Wood RAB. A pilot study of radical radiotherapy using a perioperative implant following wide local excision for carcinoma of the breast. Breast 1999; 8:95-97.

[10] King TA, Bolton JS, Kuske RR, Fuhrman GM, Scroggins TG, Jiang XZ. Long-term results of wide-field brachytherapy as the sole method of radiation therapy after segmental mastectomy for T(is, 1, 2) breast cancer. Am J Surg 2000; 180:299-304.

[11] Vicini FA, Baglan KL, Keslin LL, et al. Accelerated treatment of breast cancer. J Clin Onc 2001; 19:1993-2001.

[12] Wazer DE, Berle L, Graham R, et al. Preliminary results of a Phase I/II study of HDR brachytherapy alone for T1/T2 breast cancer. Int J Radiat Oncol Biol Phys 2002; 53:889-897.

[13] Polgár C, Sulyok Z, Fodor J, et al. Sole brachytherapy of the tumor bed after conservative surgery for T1 breast cancer: Five-year results of a Phase I-II study and initial findings of a randomized phase III trial. J Surg Oncol 2002; 80:121-128.

[14] Ribeiro GG, Magee B, Swindell R, Harris M, Banerjee SS. The Christie Hospital breast conservation trial: An update at 8 years from inception. Clin Oncol (R Coll Radiol) 1993; 5:278-283.

[15] Formenti SC, Rosenstein B, Skinner KA, Jozsef G. T1 stage breast cancer: Adjuvant hypofractionated conformal radiation therapy to tumor bed in selected postmenopausal breast cancer patients-pilot feasibility study. Radiology 2002; 222:171-178.

[16] Veronesi U, Orecchia R, Luini A, et al. A preliminary report of intraoperative radiotherapy (IORT) in limited-stage breast cancers that are conservatively treated. Eur J Cancer 2001; 37:2178-2183.

[17] Vaidya JS, Baum M, Tobias JS, et al. Targeted intra-operative radiotherapy (Targit): An innovative method of treatment for early breast cancer. Ann Oncol 2001; 12:1075-1080.

[18] Krishnan L, Jewell WR, Tawfik OW, Krishnan EC. Breast conservation therapy with tumor bed irradiation alone in a selected group of patients with stage I breast cancer. Breast J 2001; 7:91-96.

[19]Veronesi U, Luini A, Del Vecchio M, et al. Radiotherapy after breast-preserving surgery in women with localized cancer of the breast. N Engl J Med 1993; 328:1587-1591.

[20]Krishnan L, Jewell WR, Mansfield CM, Reddy EK, Thomas JH, Krishnan EC. Early-stage breast cancer: Local control after conservative surgery and radiation therapy with immediate interstitial boost. Radiology 1993; 187:95-98.

[21]Jewell WR, Krishnan L, Reddy EK, Thomas JH, Mansfield CM. Intraoperative implantation radiation therapy plus lumpectomy for carcinoma of breast. Arch Surg 1987; 122:687-690.

[22]Krishnan L, Jewell WR, Mansfield CM, Reddy EK, Thomas JH, Krishnan EC. Perioperative interstitial irradiation in the conservative management of early breast cancer. Int J Radiat Oncol Biol Phys 1987; 13:1661-1665.

[23]Krishnan L, Jewell WR, Mansfield CM, et al. Cosmetic results in early breast cancer treated with lumpectomy, peri-operative interstitial irradiation, and external beam radiation. Int J Radiat Oncol Biol Phys 1988; 15:205-211.

[24]Elston CW, Ellis IO. Pathological prognostic factors in breast cancer. I. The value of histological grade in breast cancer: Experience from a large study with long-term follow-up. Histopathology 1991; 19:403-410.

[25]Uppsala-Orebro Breast Cancer Study Group. Section resection with or without postoperative radiotherapy for stage I breast cancer: A randomized trial. J Natl Cancer Inst 1990; 82:277-282.

[26]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; 88:1659-1664.

[27]Forrest AP, Stewart HJ, Everington D, et al. Randomized controlled trial of conservation therapy for breast cancer: 6-year analysis of the Scottish trial. Scottish Cancer Trials Breast Group. Lancet 1996; 348:708-713.

[28]Fisher ER, Sass R, Fisher B, Gregorio R, Brown R, Wickerham L. Pathologic findings from the National Surgical Adjuvant Breast Project (Protocol 6). II. Relation of local breast recurrence to multicentricity. Cancer 1986; 57:1717-1724.

[29]Gump FE, Shikora S, Habif DV, Kister S, Logerfo P, Estabrook A. The extent and distribution of cancer in breasts with palpable primary tumors. Ann Surg 1986; 204:384-390.

[30]Holland R, Veling SH, Mravunac M, Hendriks JH. Histologic multifocality of Tis, T1-2 breast carcinomas. Implications for clinical trials of breast-conserving surgery. Cancer 1985; 56:979-990.

[31]Krishnan EC, Krishnan L, Cytacki EP, et al. Radiobiological advantages of an immediate interstitial boost dose in conservative treatment of breast cancer. Int J Radiat Oncol Biol Phys 1990; 18:419-424.

[32]Krishnan L, Jewell WR, Krishnan EC, Cherian R, Lin F. Breast cancer with extensive intraductal component: Treatment with immediate interstitial boost irradiation. Radiology 1992; 183:273-276.

[33]Orton CG. Time-dose factors (TDFs) in brachytherapy. Br J Radiol 1974; 47:603-607.

[34]Orton CG, Ellis F. A simplification in the use of the NSD concept in practical radiotherapy. Br J Radiol 1973; 46:529-537.

Keywords: breast conserving surgery, brachytherapy, breast cancer, radiotherapy