Toxicity and Cosmesis from RTOG 95-17: A Phase I/II Trial to Evaluate Brachytherapy as the Sole Method of Radiation Therapy for Stage I and II Breast Carcinoma

Rachel Rabinovitch[1], Kathryn Winter[2], Marie Taylor[3], Robert Kuske[4], John Bolton[5], Doug Arthur[6], Julia White[7], William Hanson[8], Ray Wilenzick[9] and Beryl McCormick[10]

[1]University of Colorado Cancer Center, Aurora, CO, [2]RTOG Statistical Center, Philadelphia, PA; [3]Washington University, Saint Louis, MO, [4]Arizona Oncology Services, Scottsdale, AZ; [5]Ochsner Clinic, New Orleans, LA; [6]Medical College of Virginia, Richmond, VA; [7]Medical College of Wisconsin, Milwaukee, WI; [8]MD Anderson Cancer Center, Houston, TX; [9]Ochsner Clinic, New Orleans, LA, and [10]Memorial Sloan-Kettering Cancer Center, New York, NY.

ABSTRACT

Background: RTOG 95-17 is the only completed cooperative group trial evaluating multi-catheter brachytherapy (BTx) for early stage breast cancer. Cosmesis and toxicity outcomes are presented.

Materials/Methods: Following lumpectomy and axillary dissection, patients with invasive non-lobular breast cancer <3 cm, - margins, and <3 positive lymph nodes were treated with either high dose rate (HDR) or low dose rate (LDR) BTx via a multi-catheter implant - 45 Gy over 3.5-6 days or 34 Gy in 10 BID fractions, respectively. 100 women were enrolled from 1997-2000, 99 were eligible; 66 were treated with HDR and 33 with LDR. Chemotherapy, if given, was delivered after BTx. Median follow up (f-up) is 7.6 years (0.9-9.2). F-up included cosmesis evaluation assessed separately by pt, treating radiation oncologist (RO) and surgeon (S) at 6 months, 1 year, and then annually. The study was not designed to test for toxicity or cosmesis differences between HDR and LDR techniques.

Results: Grade 3 toxicity at any time during f-up was reported in 8%/21% of HDR/LDR pts, and consisted of breast infection (n=0/2 in HDR/LDR), erythema (0/1), wound dehiscence (1/0), skin thickening (1/3), skin fibrosis (2/4), pain (2/0), and telangectasias (1/4). Fat necrosis developed in 27%/21% of HDR/LDR pts. No G3 skin ulceration, breast edema or tenderness was reported. Treatment effects as reported by RO and S at 2 years are listed in Table 1. Table 2 lists reported excellent-good cosmesis assessments at intervals following therapy by evaluator. At 2 years, poor cosmesis was reported for HDR/LDR as follows: Pt 2%/8%, RO -0%/14%, and S-0%/10%.

Conclusion: Toxicity of multi-catheter breast BTx in the cooperative group setting is acceptable and similar to single institution series. Good-excellent cosmesis is achieved in the majority of pts at 3 years. Pts tend to rate cosmesis most favorably, and surgeons, most critically.

BACKGROUND

- **Whole Breast Irradiation** – lumpectomy followed by whole breast radiation (RT) +/- a tumor bed boost is the standard local treatment for early stage breast cancer, established by numerous randomized trials. This approach results in high rates of tumor control at 20 years and good/excellent cosmesis rates (>80%)[1]. This approach, however, typically requires 5-6.5 weeks for the RT component of therapy.
- **Partial Breast Irradiation (PBI)** – data on in-breast failure following lumpectomy alone or lumpectomy followed by RT demonstrate that the overwhelming majority of recurrences (85-100%) are true local recurrences, i.e. immediately surrounding the originally resected tumor. This suggests that the primary role of RT following lumpectomy is to eradicate tumor cells surrounding the lumpectomy bed and not in more remote areas of the breast.
- **Radiobiologic Implications of PBI** – basic radiobiologic principles support the feasibility of treating smaller volumes of breast tissue with higher doses/fraction and fewer total fractions, while preserving tumor control and cosmesis rates of the treated tissue. PBI delivered with multi-catheter BTx over 5-7 days was the first technique in single institution series supporting the tumor control efficacy and toxicity acceptability of this approach.
- **RTOG 95-17** - this phase I/II clinical trial was the first cooperative group study investigating PBI in North America and the only one to date evaluating multi-catheter BTx. Long term toxicities and cosmesis rates have not previously been available in the literature for this technique in either single institution or cooperative group settings. Excellent inter-institutional reproducibility and ipsilateral breast tumor control rates have previously been reported by RTOG for this trial; updated toxicity and cosmesis data is presented here.

OBJECTIVES

- **Toxicities and Cosmesis** – to evaluate the toxicity and cosmesis profile of PBI delivered with multi-catheter BTx in the cooperative group setting (presented below). The study was not designed to test for toxicity or cosmesis differences between the HDR and LDR
- **Technical Feasibility and Reproducibility** – to evaluate the feasibility and reproducibility of multi-catheter breast BTx in the first cooperative group clinical trial investigating this approach (*presented elsewhere*).
- **Ipsilateral Breast Tumor control** – to evaluate the rate of Ipsilateral breast tumor control and compare to published rates for whole breast RT (*presented elsewhere*).

ELIGIBILITY

- **Stage** – T1-2 (≤3cm) and N0-1 (0-3 positive lymph nodes) following lumpectomy and axillary staging (dissection or sampling with >6 lymph nodes identified; dissection was required if any positive lymph node identified).
- **Histology** – any non-lobular invasive breast cancer histology with negative surgical inked margins (no tumor at ink). Tumors with an extensive intraductal component or lymph nodes with extracapsular extension were excluded.
- **Other** – 6 clips marking the borders of the lumpectomy cavity were required.
- **Systemic Therapy** – Tamoxifen during BTx was allowed. Chemotherapy could be administered no sooner than 2 weeks following catheter removal.

STUDY DESIGN

RECORD
•Institutional Brachytherapy Credentialing by RTOG
•Institutional Selection of HDR or LDR as Treatment Technique
•Breast Conserving and Axillary Surgery
•Catheter Placement – 2 plane implant
•Verification of Histology and Eligibility Criteria

REGISTER
•Approval of Treatment Plan through Rapid Review Process
•Treatment (as previously identified by treating institution/nonrandomized):

Arm 1	Arm 2
LDR BTx	HDR BTx
45 Gy	34 Gy -10 fractions BID
3.5-6 days	5-7 days

•Follow Up
Cosmesis Evaluation at 6 months, 1 year, then annually by Patient (Pt), Radiation Oncologist (RO) and Surgeon (S)

RESULTS

Methods/Materials/Follow-up

- **Enrolled** – 100 pts enrolled from 1997-2007 Pretreatment characteristics were well balanced between LDR and HDR treated patients
- **Follow up** – analysis updated in May 2007, with median follow up of 7.6 years (range .9-9.2 years).

Table I. Status of Cases

	LDR	HDR	Total
Registered	34	66	100
Ineligible	1	0	1
Analyzable	33	66	99
With Toxicity Information	33	66	99

Table II. Worst Reported Toxicity During Follow-Up by Grade and Toxicity Type

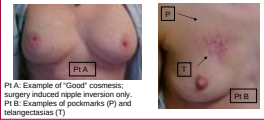
	LDR (n=33)			HDR (n=66)		
Toxicity Type	**Toxicity Grade**					
	1	**2**	**3**	**1**	**2**	**3**
Arm Edema	4	4	0	5	7	0
Breast Edema	7	4	0	21	7	0
Breast Erythema	6	2	1	14	6	0
Breast Infection	0	0	2	0	2	0
Breast Pain	10	2	0	15	8	2
Breast Tenderness	13	3	0	28	5	0
Skin Fibrosis	7	13	4	28	10	2
Skin Thickening	10	9	3	26	4	1
Skin Ulceration	0	1	0	2	2	0
Telangectasias	7	3	4	20	10	1
Wound Dehiscence	0	1	0	0	0	1
Worst Overall Toxicity	**6 18%**	**16 48%**	**7 21%**	**29 44%**	**27 41%**	**5 8%**

Table III. Other Toxicities During Follow-Up

	LDR (n=33)	HDR (n=66)
Pockmarks	32 (97%)	61 (92%)
Any Fat Necrosis	7(21%)	18(27%)
Distribution of Fat Necrosis by Grade*:		
Grade 1	3 (9%)	7 (11%)
Grade 2	2 (6%)	8 (12%)
Grade 3	1 (3%)	3 (4%)
Not Specified	1 (3%)	0 (0%)

*Fat necrosis defined as G1-Assymptomatic, detected clinically or mammographically; G2–Mildly symptomatic (mild inflammation and tenderness +/- skin erythema); G3-Moderate-severe inflammation and pain managed non-surgically except for needle aspiration.

Examples of Cosmesis/Toxicities



Pt A: Example of "Good" cosmesis; surgery induced nipple inversion only. Pt B: Examples of pockmarks (P) and telangectasias (T)

Table IV. Comparison of 2-year Toxicities as Reported by Radiation Oncologist (RO) and Surgeon (S)

	LDR		HDR	
	RO n=22	S n=10	RO n=40	S n=18
Atrophy	9%	10%	0	23%
Dimpling	32%	50%	20%	56%
Erythema	5%	10%	8%	11%
Fibrosis	50%	60%	23%	67%
Hyperpigmentation	23%	10%	3%	22%
Pockmarks	68%	40%	63%	56%
Telangectasias	27%	20%	23%	11%

Table V. Cosmesis Rates by Evaluator and Length of Follow-up

		LDR (n=33)			HDR (n=66)		
Evaluator	**Cosmesis Score**	**1 yr %**	**2 yr %**	**3 yr %**	**1 yr %**	**2 yr %**	**3 yr %**
Patient	n	31	25	19	44	48	21
	Excellent	32	32	26	39	42	47
	Good	58	28	37	45	44	30
	Fair	6	28	21	11	6	20
	Poor	3	8	16	2	2	0
Radiation Oncologist	n	27	22	16	39	40	28
	Excellent	37	23	6	33	53	21
	Good	37	32	50	46	25	43
	Fair	19	32	25	15	18	32
	Poor	7	14	19	3	0	0
Surgeon	n	22	10	6	29	18	16
	Excellent	32	40	33	38	28	25
	Good	27	10	33	52	44	50
	Fair	27	30	33	10	22	25
	Poor	9	10	0	0	0	0

CONCLUSIONS

- **PBI with multi-catheter BTx results in excellent-good cosmesis in the majority of patients at 3 years following treatment**
- **These toxicity and cosmesis results, delivered in the cooperative group setting, are similar to single institution multi-catheter BTx series**
- **Surgeons tend to grade individual toxicities more critically than radiation oncologists; Patients tend to grade cosmesis more favorably than physicians**
- **Randomized clinical trial data will be required to accurately compare toxicity and cosmesis profiles of PBI to whole breast irradiation. RTOG 0413/NSABP B-39 is currently accruing patients toward this end.**

REFERENCES

1. Taylor ME, Perez CA, Halverson KJ, et al: Factors influencing cosmetic results after conservation therapy for breast cancer. Int J Radiat Oncol Biol Phys. 1995 Feb 15;31(4):753-64.
2. King, Bolton, Kuske, et al: Long-Term Results of Wide-Field Brachytherapy as the Sole Method of Radiation Therapy after Segmental Mastectomy for Tis,1,2 Breast Cancer. American J Surg 2000 180(4):299-304