



Clinical Investigation

Long-Term Cancer Outcomes From Study NRG Oncology/RTOG 9517: A Phase 2 Study of Accelerated Partial Breast Irradiation With Multicatheter Brachytherapy After Lumpectomy for Early-Stage Breast Cancer

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Summary

Study NRG Oncology/Radiation Therapy Oncology Group 9517, a phase 2, multi-institutional, single-arm, prospective trial, evaluated one of the earliest methods of accelerated partial breast irradiation (APBI),

Purpose: To examine 10-year rates of local, regional, and distant recurrences, patterns of recurrence, and survival rates for breast cancer patients enrolled on Study NRG Oncology/Radiation Therapy Oncology Group 9517, a multi-institutional prospective trial that studied one of the earliest methods of accelerated partial breast irradiation (APBI), multicatheter brachytherapy (MCT).

Methods and Materials: Eligibility included stage I/II unifocal breast cancer <3 cm in size after lumpectomy with negative surgical margins and 0 to 3 positive axillary nodes without extracapsular extension. The APBI dose delivered was 34 Gy in 10 twice-daily fractions over 5 days for high-dose-rate (HDR); and 45 Gy in 3.5 to 5 days for low-dose-rate (LDR) brachytherapy. The primary endpoint was HDR and LDR

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multicatheter brachytherapy, and accrued a total of 100 patients. This combined analysis of those who received low- and high-dose-rate APBI demonstrates durable local control outcomes at a median follow-up of 12.1 years.

MCT reproducibility. This analysis focuses on long-term ipsilateral breast recurrence (IBR), contralateral breast cancer events (CBE), regional recurrence (RR), and distant metastases (DM), disease-free, and overall survival.

Results: The median follow-up was 12.1 years. One hundred patients were accrued from 1997 to 2000; 98 were evaluable; 65 underwent HDR and 33 LDR MCT. Median age was 62 years; 88% had T1 tumors; 81% were pN0. Seventy-seven percent were estrogen receptor and/or progesterone receptor positive; 33% received adjuvant chemotherapy and 64% antiendocrine therapy. There have been 4 isolated IBRs and 1 IBR with RR, for 5.2% 10-year IBR without DM. There was 1 isolated RR, 1 with IBR, and 1 with a CBE, for 3.1% 10-year RR without DM. The 10-year CBE rate was 4.2%, with 5 total events. Eleven patients have developed DM, 8 have died of breast cancer, and 22 have died from other causes. The 10-year DFS and OS rates are 69.8% and 78.0%, respectively.

Conclusion: This multi-institutional, phase 2 trial studying MCT-APBI continues to report durable in-breast cancer control rates with long-term follow-up. © 2016 Elsevier Inc. All rights reserved.

Introduction

Accelerated partial breast irradiation (APBI) that targets radiation therapy after lumpectomy to only the breast tissue surrounding the postexcision surgical cavity considered at highest risk of cancer recurrence, instead of the whole breast, has been the subject of investigation for more than a decade. Recently, 2 phase 3 randomized, controlled trials have published 5-year outcomes demonstrating noninferior results from APBI versus standard whole-breast irradiation (WBI) for conservative therapy in early-stage invasive breast cancer (1, 2). Several additional phase 3 randomized control trials that compare APBI with WBI after lumpectomy have completed accrual and have results pending. Until all of these trials report their findings, the potential trade-off of more convenient radiation therapy against the risk for local recurrence needs to be weighed for the individual breast cancer patient. Despite this, APBI has gained increasing acceptance into clinical practice (3). This has resulted in considerable discussion and debate about which patients are best suited for treatment with APBI after lumpectomy for breast conservation. Several groups have examined the status of evidence for APBI and generated consensus statements and recommendations as to who should be treated with APBI after lumpectomy until outcomes from clinical trials are known (4-6). One of the central challenges regarding APBI evidence in current breast cancer management is the paucity of long-term outcomes beyond 5 years for a disease that can have a prolonged natural history. Multicatheter brachytherapy (MCT) is one of the earliest forms of APBI developed. It was first evaluated in the multi-institutional setting in a single-arm phase 2 NRG Oncology/Radiation Therapy Oncology Group (RTOG) 9517 clinical trial that completed accrual in 2000 and therefore can uniquely provide long-term cancer outcomes for women treated with APBI. The goal of this updated analysis is to examine 10-year rates of local, regional, and distant recurrences, patterns of recurrence, and survival rates for breast cancer patients enrolled on Study NRG Oncology/RTOG 9517.

Methods and Materials

Study NRG Oncology/RTOG 9517 is a phase 2 clinical trial that demonstrated that MCT APBI as the sole radiation therapy method after lumpectomy for breast conservation was technically feasible and reproducible, with acceptable complication rates in a multi-institution setting (7). The secondary objectives of NRG Oncology/RTOG 9517 included cosmetic results and cancer control rates, each of which has been previously reported (8, 9). Long-term cancer control rates are the focus of this analysis. The methods for this trial have been published previously (7-10) but are summarized below. The trial schema is seen in Figure 1.

Eligibility

Enrollment on Study NRG Oncology/RTOG 9517 was open to women with stage I or II breast cancer who had undergone lumpectomy and axillary node dissection and who were considered to be good technical candidates for MCT and who met the following criteria: unicentric breast cancer with pathologic tumor size <3 cm; negative surgical margins; invasive ductal, medullary, papillary, colloid (mucinous), or tubular histology; and surgical clips in place delineating the margins of the lumpectomy cavity. This trial was conducted before widespread adoption of sentinel node biopsy, so to be eligible, an axillary dissection must have been done and at least 6 axillary nodes recovered. Negative axillary nodes (N0) and those with up to 3 axillary nodal metastases (N1) without extracapsular extension were eligible. Notable ineligibility criteria for enrollment on Study NRG Oncology/RTOG 9517 included ductal carcinoma in situ, ductal carcinoma in situ with micro-invasion, or invasive lobular histology, presence of an extensive intraductal component, prior existing collagen vascular disorder, or those who had a fair or poor cosmetic appearance of the affected breast after lumpectomy, before radiation therapy. There was no limit placed on patient age as an eligibility or ineligibility criteria.

R	Dose Rate	R	
E	1. LDR	E	APBI Brachytherapy
C	2. HDR	G	
O		I	
R	Surgery	S	Arm 1: LDR 45 Gy/3.5-6 days
D	1. Lumpectomy/Reexcision	T	
	2. Catheter Placement	E	Arm 2: HDR 34 Gy/10 fractions/5-7 days
	3. Axillary Dissection	R	(3.4 Gy b.i.d. separated by 6 hours)

Fig. 1. NRG Oncology/RTOG 9517 study design. *Abbreviations:* HDR = high dose rate; LDR = low dose rate.

Treatment

Brachytherapy catheters could be placed either at the time of lumpectomy, re-excision, or axillary surgery, or through a separate closed procedure. For Study NRG Oncology/RTOG 9517, the treatment target volume was defined as lumpectomy cavity plus 1 cm superficial (toward skin) and deep (toward chest wall) and 2 cm in all other dimensions. Brachytherapy could be either low (LDR) or high (HDR) dose rate. The protocol was not designed to make any comparisons between HDR and LDR methods. The radiation therapy dose delivered to the target volume for LDR ABPI was 45 Gy with a target dose rate of 45 cGy/h (30-60 cGy/h dose rate acceptable); and for HDR APBI was 34 Gy over 10, 3.4-Gy fractions delivered 2 times daily with a minimal 6-hour daily interfraction interval. Protocol-specific credentialing was required by each institution before participation, consisting of completion of a questionnaire and a benchmark case. Planning was based on orthogonal films; computed tomography-based planning was not used (10). A rapid dosimetry review was done before treatment to ensure dose delivery per protocol. The dose specification and quality assurance for the APBI brachytherapy delivered on NRG Oncology/RTOG 9517 has been published previously (10). Briefly, two-thirds of the patients were treated with HDR (n = 65) and one-third with LDR (n = 33). On average, approximately 17 catheters were used regardless of modality. Most implants used 2 (74%) or 3 (22%) planes (10). Brachytherapy for APBI was to begin within 6 weeks after the last surgical procedure and before delivery of any chemotherapy. Catheter removal was completed directly after completion of dose delivery. Systemic therapy was per the treating physician recommendation, with anti-endocrine therapy allowed and chemotherapy when indicated to be initiated no sooner than 2 weeks after completion of APBI.

Analysis

This trial was designed to evaluate the feasibility of post-lumpectomy multicatheter APBI with LDR and HDR methods for breast conservation. For this analysis LDR and HDR groups were combined in an exploratory manner to evaluate durability of loco-regional recurrence results and patterns of failure. The goal of this analysis was to examine ipsilateral breast, regional, and distant recurrences and contralateral breast cancer events, as well as disease-free and overall survival of all eligible patients enrolled on NRG Oncology/RTOG 9517 with 5- and 10-year follow-up. The

study was not designed to test efficacy of this treatment regimen against a historical control or to test efficacy between HDR and LDR brachytherapy methods. Because the patient characteristics were numerically similar in the HDR and LDR treated groups, these patients were combined for reporting of this analysis. Local, regional, loco-regional, and distant recurrences and contralateral breast events were estimated with the cumulative incidence method (11). Recurrences included in disease-free survival are local, regional, or distant recurrence and death from any cause. Disease-free and overall survivals were estimated with the Kaplan-Meier method (12).

Results

One hundred patients from 11 institutions were enrolled to NRG Oncology/RTOG 9517 from May 16, 1997, through

Table 1 Pretreatment patient and tumor pathology characteristics (n = 98)

Age (y)	
Median	62
Range	33-83
Race (%)	
White	86.7
Hispanic/Latino	4.1
African American	7.1
Asian	1.0
American Indian/Alaskan Native	1.0
Karnofsky performance status (%)	
100	76.5
90	19.4
80	2.0
Unknown	2.0
Menopausal status (%)	
Post-	79.6
Pre-	14.3
Peri-	4.1
Unknown	2.0
T stage (%)	
T1	87.8
T2	12.2
N stage (%)	
N0	80.6
N1	19.4
Estrogen receptor (ER) (%)	
Positive	74.5
Negative	21.4
Not done	1.0
Unknown	3.1
Progesterone receptor (PR) (%)	
Positive	68.4
Negative	27.6
Not done	1.0
Unknown	3.1
ER and/or PR (%)	
Positive	76.5
ER and PR (%)	
Negative	19.4
Not done/unknown	4.1

Table 2 Local and regional cancer events

Event	No. of events	5-y			10-y		
		Estimates (%)	95% CI (%)	At risk	Estimates (%)	95% CI (%)	At risk
Isolated in-breast recurrence*	4	3.1	(0.0-6.6)	86	4.1	(0.1-8.1)	69
In field	3	2.1	(0.0-4.9)	86	3.1	(0.0-6.6)	69
Out of field	1	1.0	(0.0-3.1)	86	1.0	(0.0-3.1)	69
In-breast and regional recurrence†	2	1.0	(0.0-3.1)	84	2.1	(0.0-5.1)	68
In-breast without distant metastases	5	3.1	(0.0-6.6)	86	5.2	(0.7-9.6)	69
All in-breast recurrences	6	4.1	(0.1-8.1)	86	6.2	(1.4-11.1)	69
Isolated regional recurrence‡	2	2.1	(0.0-4.9)	87	2.1	(0.0-4.9)	71
Regional recurrence without distant metastases	3	2.1	(0.0-4.9)	87	3.1	(0.0-6.6)	71
All regional recurrences	5	4.1	(0.1-8.1)	87	5.2	(0.7-9.6)	71
Any loco-regional recurrence (with or without distant metastases)	9	7.2	(2.0-12.4)	84	9.3	(3.5-15.1)	68
Contralateral breast cancer	5	3.1	(0.0-6.6)	88	4.2	(0.1-8.2)	70
Mastectomy	11	8.2	(2.7-13.7)	83	10.3	(4.2-16.4)	66

Abbreviation: CI = confidence interval.

* Excludes patients that had regional and/or distant metastases with their ipsilateral breast recurrence (IBR).

† One regional recurrence (RR) with distant metastases (DM) and one RR without DM.

‡ Excludes patients that had IBR and/or DM with their regional recurrence.

March 1, 2000. Two patients did not meet eligibility criteria and were excluded from analysis. (One case underwent sentinel node biopsy only, and the other case had nodal extra capsular extension present.) The median follow-up overall was 12.1 years (range, 0.9-14.3 years), and for surviving patients the median follow-up was 12.7 years (range, 0.9-14.3 years).

Patient and pathology characteristics

The median age of the patients enrolled on NRG Oncology/ RTOG 9517 was 62 years. As seen in Table 1, most patients were white, postmenopausal, and had an excellent performance status. Tumor pathology characteristics are also seen in Table 1. Most had T1 tumors. The median tumor size was 1.3 cm (range, 0.3-3.0 cm). Nineteen percent had metastases in 1 to 3 axillary nodes; 89.5% had 1 axillary nodal metastasis; 10.5% had 2; and 0% had 3. The majority of tumors were either

estrogen- or progesterone-receptor—positive, whereas 19% were both estrogen- and progesterone-receptor—negative. Testing for HER2 was not consistently used during the era in which this trial accrued, so it was not collected. Sixty-four percent enrolled received anti-endocrine therapy, and 33% received chemotherapy for systemic treatment.

Local and regional cancer recurrences

There have been 4 ipsilateral breast recurrences (IBRs) as the isolated first site of relapse and 1 IBR that occurred concomitantly with an axillary recurrence, for 5.2% (95% confidence interval [CI] 0.7%-9.6%) 10-year IBR without distant metastases (DM). One IBR occurred with simultaneous axillary, internal mammary recurrences and DM, making a total of 6 IBRs with or without DM, 6.2% (95% CI 1.4%-11.1%) at 10 years (Table 2). The median time to in-

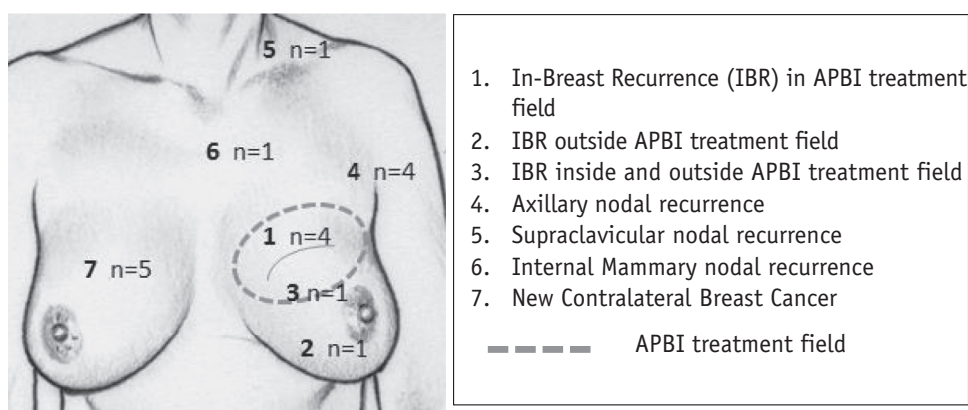


Fig. 2. Patterns of failure in 13 women that experienced loco-regional events after treatment with multicatheter brachytherapy accelerated partial breast irradiation (APBI) after lumpectomy on Study NRG Oncology/RTOG 9517, with a median follow-up of 12.1 years. Patients can experience more than one site of failure.

Table 3 Patterns of local, regional, and distant recurrence and contralateral breast cancers

Failure pattern	n (%)
Local only within or outside APBI volume	4 (4.1)
Local within APBI volume and regional (ipsilateral axillary nodes)	1 (1.0)
Local within and outside volume and regional (ipsilateral axillary and internal mammary nodes) and distant	1 (1.0)
Regional only (ipsilateral supraclavicular nodes)	1 (1.0)
Regional (ipsilateral axillary nodes) and contralateral	1 (1.0)
Regional (ipsilateral axillary nodes) and distant	1 (1.0)
Distant and contralateral	1 (1.0)
Distant only	8 (8.2)
Contralateral only	3 (3.1)
No local, regional, contralateral, or distant events	77 (78.6)
Total	98

Abbreviation: APBI = accelerated partial breast irradiation.

breast recurrence was 49 months (range, 23.5-73.6 months). Of the 6 IBR events, 4 occurred within the brachytherapy APBI treatment field, 1 elsewhere in the breast, and 1 was recorded as both in and out of the treatment field (Fig. 2). There were 5 new breast cancers diagnosed in the contralateral breast (10 years: 4.2% [95% CI 0.1%-8.2%]). Two of these contralateral breast cancers occurred along with events from the index cancer: 1 an ipsilateral axillary recurrence and the other a distant recurrence.

There was 1 regional recurrence in the supraclavicular nodes as the isolated first site of relapse, 1 axillary recurrence with an IBR, and 1 axillary recurrence with a CBE, for 3.1% 10-year regional recurrence without DM. Two regional recurrences occurred simultaneously with DM: 1 axillary nodal recurrence with DM, and 1 axillary recurrence with an IBR (within and outside the APBI field) as well as internal mammary recurrence and DM. There were a total of 5 regional nodal recurrences with and without DM (10-year: 5.2% [95% CI 0.7%-9.6%]). The pattern of regional recurrences is shown in Figure 2 and listed in Table 3.

Distant metastases and survival

There were a total of 11 cases that developed DM (10-year: 10.3% [95% CI 4.2%-16.4%]). In 2 cases, DM occurred with an IBR and/or regional recurrence (Table 3). There were a

total of 8 deaths from breast cancer and 22 from other causes, for a 10-year overall survival of 78% (Table 4).

Discussion

The results of Study NRG Oncology/RTOG 9517 have demonstrated durable local control at 10 years after delivery of multicatheter APBI as the sole radiation therapy method after lumpectomy. The 10-year IBR rate was 5.2% in those who experienced an IBR without DM. The 6.2% 10-year overall IBR with or without DM was stable in comparison with what was previously reported for the 5-year outcome (9). The 5.2% overall 10-year regional recurrence at first glance seems higher than expected; however, on closer inspection it is only 3.1% for regional recurrences without DM and includes 1 supraclavicular nodal recurrence and 2 axillary recurrences, one of which occurred with an IBR. The 10.3% 10-year DM reflects the overall good outcome of these early-stage breast cancer patients treated with multicatheter APBI after lumpectomy.

There are very few prospective APBI studies with reported 10-year cancer outcomes to serve as a point of comparison for this study. Polgár et al (13) recently reported 10-year cancer outcomes from multicatheter APBI after lumpectomy on the Budapest randomized, controlled trial. This trial randomized 258 women between 1998 and 2004 who had undergone lumpectomy for early-stage breast cancer to standard WBI (n = 130) or multicatheter APBI (n = 128). This trial population included a similar median patient age of 58.5 years but overall had on average more favorable pathology than was enrolled on NRG Oncology/RTOG 9517; 89% were estrogen receptor-positive, all tumors were ≤ 2 cm, and nearly all patients were node negative (3.5% had microscopic nodal metastases or were N1^{mic}). With a median follow-up of 10.2 years, rates of isolated IBR were 5.5% in the multicatheter APBI arm compared with 4.6% in the WBI arm (13). The 10-year regional recurrence rate was 2.3% in the APBI arm and 0.8% with WBI. A retrospective matched-pair analysis from William Beaumont Hospital compared 199 cases prospectively treated with multicatheter APBI after lumpectomy on 3 different prospective clinical trials from 1993 to 2001 with 199 patients treated between 1980 and 1997 with standard WBI (14). The population characteristics reveal that the median age was somewhat older at 64 years, 82.5% were estrogen receptor-positive, and 12% had 1 to 3 positive axillary nodal metastases. The median follow-up for the APBI patients was 9.6 years. Ten-year IBR rates that are also

Table 4 Distant metastases and survival

Event	No. of failures	5-y			10-y		
		Estimates (%)	95% CI (%)	At risk	Estimates (%)	95% CI (%)	At risk
Distant metastases	11	7.2	(2.0-12.4)	87	10.3	(4.2-16.4)	72
Disease-free survival	39	83.5	(74.5-89.6)	81	69.8	(59.5-77.9)	65
Overall survival	30	92.8	(85.5-96.5)	90	78.0	(68.3-85.1)	73

Abbreviation: CI = confidence interval.

comparable to those in Study NRG Oncology/RTOG 9517 were reported: 5% in the APBI group and 4% in the WBI group. The 10-year regional rates were 0.5% and 1.6%, respectively, for the APBI and WBI groups (14).

The strength of this analysis is that it reflects a cohort of patients who were prospectively enrolled from 11 institutions within defined eligibility criteria and treated with MCT APBI that met stringent quality assurance review before treatment. The outcomes from NRG Oncology/RTOG 9517 provide reassurance that APBI can yield durable local control outcomes at 10 years as the sole radiation therapy modality after lumpectomy for breast conservation. Unfortunately, these results cannot provide any insight into what these cancer outcomes may have been if these patients had instead been treated with standard WBI. However, it is notable that the loco-regional cancer outcomes reported here for women treated with APBI on NRG Oncology/RTOG 9517 are numerically similar to the 10-year breast relapse rates recently reported from the START-A and -B phase 3 clinical trials that randomized patients after lumpectomy to various fractionation schemes for WBI (15). The START-A and -B trials accrued breast cancer patients between 1999 and 2002 in the United Kingdom; 85% and 92% of which, respectively, had undergone breast-conserving surgery. Patients in START-A (n=2236) were randomly assigned to WBI of either 50 Gy in 25 fractions (control group) or 41.6 Gy in 13 fractions or 39 Gy in 13 fractions over 5 weeks; and START-B (n=2215) patients to WBI of either 50 Gy in 25 fractions (control group) over 5 weeks or 40 Gy in 15 fractions over 3 weeks. With a median follow-up of 9.3 years, the START-A trial demonstrated a 10-year local relapse rate of 6.7%, 5.6%, and 8.1% in the 50-Gy, 41.6-Gy, and 39-Gy arms, respectively. Similarly, with a median follow-up of 9.9 years, the START-B trial demonstrated 10-year local relapse rates of 5.2% and 3.8% in the 50-Gy and 40-Gy arms, respectively. In comparison, the 10-year local relapse in the breast was 5.2% for the patients treated with MCT APBI on Study NRG Oncology/RTOG 9517 using a similar definition that excludes DM.

Numerous methods of partial breast irradiation have emerged since Study NRG Oncology/RTOG 9517 was conducted. These include single entry brachytherapy devices, external beam methods with 3-dimensional conformal or intensity modulated planning, and intraoperative radiation therapy. Many of these methods have reported outcome data so far from phase 3 randomized controlled trials, with median follow-up ranging from 2.5 to 5.75 years (1, 2, 16-18). The median time to in-breast recurrence on Study NRG Oncology/RTOG 9517 of 49 months emphasizes the need for long-term follow up when evaluating PBI after lumpectomy to ensure durable results.

Conclusion

This multi-institutional phase 2 trial studying multicatheter APBI continues to report durable loco-regional cancer control outcomes at 10 years with a 12.1 year median follow-up.

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