

# Partial-Breast Radiation for Early Staged Breast Cancers: Hypothesis, Existing Data, and a Planned Phase III Trial

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## Key Words

Breast cancer, partial-breast irradiation, breast conservation

## Abstract

This review of clinical data from partial-breast treatment studies discusses results from a single institution's experience using brachytherapy catheters, the MammoSite balloon (Proxima Company, Alpharetta, GA), and three-dimensional external beam partial-breast treatment. Rationale, techniques, dose schedules, and available results are presented. Intra-operative single-dose radiation to the lumpectomy site is also reviewed. The National Surgical Adjuvant Breast and Bowel Project (NSABP) and Radiation Therapy Oncology Group (RTOG) cooperative groups are opening a phase III trial to compare partial-breast treatment to the standard 5- to 6-week course of whole-breast radiation. The design of this study is also presented in this review. (*JNCCN* 2005;3;301–307)

In the early 1970s, the first reports of successful treatment results in North America for early staged breast cancer using breast-conserving surgery and external beam whole breast radiation appeared in medical literature. The reports came from the experience of single institutions such as the Harvard Joint Center, Yale University, Albert Einstein College of Medicine, the M. D. Anderson Cancer Center, and Princess Margaret Hospital in Toronto.<sup>1–5</sup> Six centers in France reported similar results at the American Radium Society Meeting in 1976.<sup>6</sup> This historic body of literature did not represent the first time breast conservation surgery had been used.<sup>7–10</sup> However,

because of influences such as increased mammographic screening and early detection, availability of linear accelerators to deliver the treatment rather than orthovoltage equipment, early reports of success with adjuvant systemic chemotherapy,<sup>11,12</sup> and the women's movement, this alternate to mastectomy became a highly controversial issue. To quote Levene, Harris, and Hellman, "Few topics in medicine engender as much emotional response as the treatment of primary breast cancer. This appears true of both patient and physician alike. The medical literature contains emotionally charged, strongly worded statements for and against the necessity of mastectomy."<sup>11</sup>

Fortunately for both patients and doctors, breast conservation surgery and radiation were tested against mastectomy in a number of phase III trials in both the United States and Europe. Twenty-year follow-ups from both the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-06 trial and the Milan Cancer Institute trial were reported recently and confirmed the equivalency of the two treatments found in all the studies over time.<sup>13,14</sup> Of note for this review, the NSABP B-06 trial contained three treatment arms—mastectomy, lumpectomy, and whole-breast radiation, and lumpectomy alone—which tested the concept of partial breast treatment with surgery alone.

Although negative margins were an entry requirement for this trial, the cumulative incidence of local failure was 39.2% in the lumpectomy-only arm, compared with 14.3% in the lumpectomy-plus-radiotherapy arm. For comparison, the local failure rate in the mastectomy arm was reported as a "first reported event" in 60 patients (or 10.2% in the most recent publication).

The Milan group<sup>13</sup> also ran a prototype partial-breast treatment with surgery in the follow-up study to their better-known phase III trial comparing mastectomy with

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McCormick

quadrantectomy and whole-breast radiation.<sup>14</sup> A follow-up phase III trial was designed to compare the same quadrantectomy and radiation versus the surgical quadrantectomy alone. The crude local failure rate reported at 10 years was 5.8% for the radiated group compared with 23.5% for the surgery-only group.<sup>15</sup>

Fentiman et al.<sup>16</sup> reported a partial-breast radiation technique using low-dose iridium implants after lumpectomy, delivering 55 Gy at a dose rate of 10 Gy per day. Although the first reports for both cosmesis and tumor control were promising, Fentiman et al.'s later publication noted local failure in 10 of 27 cases, or 37%.<sup>17</sup>

### Rationale for Partial-Breast Treatment

Breast-conserving surgery and whole-breast radiation are accepted as equivalent to mastectomy in every standard medical textbook (based on excellent phase III trial evidence). Yet a recent study for the American College of Surgeons and the American College of Radiology concluded that breast-conserving surgery was performed in only 42.6% of women with stage I and II disease in the United States, and that radiation was delivered in only 89% of the conserved cases. Living in the Northeast part of the United States was the strongest predictor for this treatment.<sup>18</sup> Data were SEER (Surveillance, Epidemiology, and End Results) generated using a sample size of over 16,600 patients treated in 1994.

Based on this reasoning, a strong case can be made for increasing the number of women offered treatment with breast conservation surgery. For those who have the surgery and need radiation, the time course for the delivery of the radiation could be decreased. Women in rural areas might have better access to treatment if the delivery time could be changed from 6 weeks to a few days.

A general principle of radiation therapy delivery is that the larger the proportion of an organ included in the radiation field, the smaller the daily radiation fraction size should be to minimize normal tissue damage. To shorten the course of radiation, the proportion of the breast included in the radiation field would need to be reduced. Studies of long-term patterns of recurrence after quadrantectomy and whole-breast radiation showed that most recurrences are within the original quadrant of presentation at first diagnosis.<sup>15</sup> This is the rationale for partial-breast radiation

with higher doses delivered to the area of the primary lesion with a margin in an accelerated time course. Clearly, if partial-breast radiation proves as efficacious as the traditional 6-week course of whole breast radiation, this significantly shorter technique would have wide appeal to women living in any part of the country.

This article reviews the experience of centers reporting on partial-breast radiation using catheter brachytherapy including the MammoSite (Proxima Company, Alpharetta, GA) balloon experience, the work performed to date with external beam partial-breast radiation, and the ongoing studies employing intra-operative single-dose delivery of radiation. The article also reviews the design of the new NS-ABP/Radiation Therapy Oncology Group (RTOG) phase III trial.

### Catheter Techniques

Traditional catheter brachytherapy with low dose rate (LDR) radioisotopes has been used for decades in the treatment of early staged breast cancer. Historically, this technique was used to deliver a "boost" dose to the lumpectomy site after completion of the whole-breast external beam portion of the treatment.<sup>1,2,4,6</sup>

In the early 1990s, two centers in the United States independently initiated treatment programs using catheter brachytherapy as the sole radiation treatment for breast cancer after conservation surgery. The group at the Ochsner Clinic in New Orleans treated 50 women between 1992 and 1993, offering the study treatment to women with stage Tis, T1, or T2 tumors measuring up to 4 cm in diameter. Negative surgical margins were required with involvement of no more than 3 axillary lymph nodes. The catheters were placed at the time of lumpectomy with a target volume of the surgical bed with a margin of 2 to 3 cm. Alternating groups of 10 patients were treated with an LDR technique of 45 Gy over 4 days or a high dose rate (HDR) technique of 4 Gy twice a day to 32 Gy. With a median follow-up time of 75 months, 1 breast and 3 nodal recurrences were seen. Cosmetic outcome at a median follow-up time of 20 months was scored by health care professionals reviewing photographs as "good to excellent" in 75% compared with 84% "good to excellent" results in women treated at that center with external beam whole-breast radiation.<sup>19</sup> Of note, one

surgeon and one radiation oncologist performed this treatment for the entire group.

The group at William Beaumont Hospital used a similar brachytherapy catheter technique with a similar target margin to treat 198 women with the following entry criteria: infiltrating ductal histology and a maximum tumor size of 3 cm; negative surgical margins; negative nodes; and age older than 40 years. Of note, 158 women met these strict criteria and another 41 were treated although they were ineligible for minor reasons. LDR treatment, consisting of 50 Gy in 96 hours, was prescribed for 120 women, and 79 patients received HDR radiation with 3.4 Gy given twice per day for 10 fractions. As with the Ochsner experience, the treatment was well tolerated. Cosmetic outcome in 79 women followed up 5 years or more was “good to excellent” in 99%. The actuarial ipsilateral breast recurrence rate at 5 years was 1%.<sup>20</sup> Again, a limited number of physicians participated in the delivery of this treatment.

In 1997, the RTOG cooperative group opened a phase II trial using catheter brachytherapy in women with early staged breast cancer. The maximum tumor size allowed was 3 cm and ductal carcinoma in situ (DCIS) was excluded. Both node-negative and node-positive cases (up to 3 involved nodes) were allowed. The treatment schedule for the LDR arm was 45 Gy and for the HDR arm, 34 Gy in 5 to 7 days using twice a day treatment. Despite the large number of centers with membership in the RTOG group, only 10 institutions participated in this trial over its accrual time from 1997 to 2000. This included participation by the Ochsner Clinic and the William Beaumont Hospital. Early reports from the study suggest that results will be excellent, with a 3% local failure rate noted at median follow-up time of 3.7 years.<sup>21</sup> Of note is the limited number of centers that participated in this trial. Although the concept of partial-breast radiation was supported by the group, the technical expertise required to hand place these catheter implants is not widely taught in residency programs in the United States.

There have been other reports from single institutions documenting similar results using catheter brachytherapy that corroborate the findings from the above-mentioned trials.

In 2002, the FDA approved of a new kind of catheter for use in breast cancer called the MammoSite Balloon. This catheter looks much like a Foley

catheter, with a channel to expand the balloon with saline and a second channel that receives a radioactive source. Unlike the traditional catheters used to date, the MammoSite Balloon is easily placed in a lumpectomy cavity and expanded to receive a radioactive source. Since the device was marketed, experts estimate that more than 6,000 have been used in the treatment of breast cancer.<sup>22</sup> Forty-three women were treated with this device from 2000 to 2001 as part of the FDA approval process. All were treated with the same HDR treatment scheme of 34 Gy delivered in 10 doses twice per day over 5 to 7 days as used in the RTOG study. With a median follow-up time of 29 months, no local failures were reported and cosmesis was scored as “good to excellent” in 84% of women in the study.<sup>23</sup>

### External Beam Partial-Breast Treatment

With the increasing sophistication of treatment planning and radiation delivery with computed tomography (CT)-based planning and multi-leaf collimation on linear accelerators, the group at William Beaumont Hospital developed a partial-breast radiation technique using noninvasive three-dimensional conformal therapy. The target was again the lumpectomy cavity, and a slightly larger margin of normal tissue was used than for the brachytherapy techniques because of the possibility of some breathing motion. The first patients treated in the study were given a total dose of 34 Gy in 10 treatments twice per day over 5 to 7 days. Because of some radiobiologic differences between external beam isodose curves and those generated by a brachytherapy implant, the prescribed dose was increase to a total of 38.5 Gy using the same time and fractionation. The feasibility of this technique was first reported in 2003.<sup>24,25</sup>

The RTOG, working with Vicini et al., opened its own phase II partial-breast three-dimensional external beam study in 2003, using the same entry criteria as for the catheter brachytherapy study.<sup>22</sup> The dose of 38.5 Gy CT scanning was required for planning. The study was designed for 42 women, but because of the rapid accrual and timing of the protocol completion announcement, it actually accrued 58 patients from 24 different centers. Initial evaluation of the cases revealed the technique to be both feasible and reproducible across the institutions.<sup>22</sup>

McCormick

**Table 1 Accelerated Partial Breast Irradiation Brachytherapy (HDR and LDR) and IORT Studies**

Series	Patients (n)	Age (y)	Tumor size (cm)	N stage	EIC	Margin status	Dose Fractionation	Median follow-up (mo)	CTV margin (cm)	5-y Ipsilateral Recurrence rate (%)
Guy's Hospital Trial <sup>16,17</sup>	27	<70	<4	N0	Positive	Positive	HDR 55 Gy/5 d	72	2	37
Ochsner Clinic <sup>19</sup>	50	All	Tis and <4	N1	Positive	Negative	LDR 45 Gy/4 d	75	2–3	2
William Beaumont Hospital <sup>20</sup>	199	>40	<3	N0	Negative	Negative	HDR 4 Gy × 8 LDR 50 Gy/4d	65	1–2	1
London Regional Cancer Centre, Canada <sup>21</sup>	39	All	<5	N0	Positive	Positive	HDR 4 Gy × 8, 3.4 Gy × 10 HDR 3.72 in 10 Fx b.i.d.	91	0	16.2
RTOG 95-17 <sup>21</sup>	100	All	<3	N1	Excluded	Negative	HDR 3.4 Gy × 10 b.i.d. LDR 45 Gy/4 d	32	2	—
Virginia Commonwealth University <sup>22</sup>	44	All	<4	N1	Excluded	Negative	LDR 45 Gy/4 d	42	1–2	0
Mammosite Multicenter Trial <sup>23</sup>	43	>45	<2	N0	Excluded	Negative	HDR 3.4 Gy × 10 b.i.d. HDR 3.4 Gy × 10 b.i.d.	21	>1	—
National Institute of Oncology, Hungary <sup>23</sup>	Phase I-II, 45	All	<2	N0	Excluded	Negative	Ph I-II, HDR 4.33 Gy × 7, 5.2 Gy × 7: Phase III, HDR 5.2 Gy × 7	Phase I-II, 57	1–2	Phase I-II, 4.4
European Institute of Oncology <sup>27</sup>	Phase III, 63 101	All	<2.5	—	Excluded	Negative	IORT electron beam therapy 10–21 Gy	8	0	—

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Abbreviations: HDR = high dose rate; LDR = low dose rate; IORT = intraoperative radiotherapy; EIC = extensive intraductal component; CTV = clinical target volume; b.i.d. = twice daily

Using a somewhat different approach, Formenti et al.<sup>26</sup> developed a partial-breast external beam technique with the patient treated prone. This technique also uses CT-based treatment planning. Dose was prescribed to the lumpectomy cavity with a 1.5-cm margin, and 30 Gy total dosage was given using 5 daily fractions of 6 Gy. With a median follow-up time of 18 months, the treatment regimen was also well-tolerated and no recurrences have been reported.<sup>26</sup>

### Intra-Operative Partial-Breast Radiation

Using the same rationale for fractionated partial-breast radiation, several centers have started radiation treatment programs using intra-operative radiation (IORT) delivered to the lumpectomy cavity during the actual surgery. The Milan group began its intra-operative

program in 1999 by using a dose escalation model. The source of the radiation was a portable linear accelerator, the Novac7 unit from Hitesys SpA (Aprilia, Italy). The linear accelerator has electron beam energies ranging from 3 to 9 MeV. Women with a tumor size of 2.5 cm or smaller were offered this treatment as a boost dose for the lower doses of 10 Gy and 15 Gy, and as whole treatment for the higher doses from 17 to 21 Gy. The unit has custom delivery cones for use in the operating room. The group also uses a small aluminum-lead shield placed behind the breast tissue on the pectoralis muscle to further shield normal tissue.<sup>27</sup> Based on this demonstration of feasibility and patient tolerance, the Milan group has now opened a prospective randomized trial comparing IORT versus the standard 6 weeks of external beam breast radiation.

In London, an IORT study is underway using a device called the Intrabeam (Photoelectron Corporation, Lexington, MA), a miniature low photon energy generator. The device, which comes with different spherical-sized applicators, is placed directly into the lumpectomy cavity at surgery. Feasibility has been established, and a phase III trial is now underway. The device generates x-rays in the 50 kV range and has an advantage over other IORT techniques because it does not require a lead-shielded operating room. The planned dose is 5 Gy at a distance of 1 cm from the applicator surface.<sup>28</sup>

In New York, the Memorial Sloan-Kettering group has a pilot IORT study open using a custom HAM silastic applicator (Mick Radio-Nuclear Instruments, Mount Vernon, NY) and an HDR unit already in use for many other brachytherapy procedures in the department. This study is open to women 60 years of age and older with a tumor size of 2 cm or smaller. The dose within 1 cm of the applicator is 20 Gy, chosen based on the experience of the Milan group with their IORT protocol. The study is planned for 50 patients, most of whom have been accrued and treated as of this writing.<sup>29</sup>

## Discussion and Future Directions

As noted previously, variation exists in both the dose and delivery techniques for partial-breast treatments used to date. Rosenstein et al.<sup>30</sup> summarized the published partial-breast experience through 2004 (Table 1), comparing eligibility criteria, dose, follow-up time,

and results if available. Table 2 compares the three-dimensional partial-breast protocols used at the William Beaumont Hospital and New York University Medical Center.<sup>30</sup> Even with these two “similar” techniques, the median volume of breast tissue treated in each center is quite different as is the ratio of the actual treated volume or planning target volume (PTV) to the total breast volume. Perera et al.<sup>31</sup> provide more detailed comparisons, with information on biologically effective doses.

With the widespread interest in partial-breast radiation, as confirmed by MammoSite catheter placement estimates and the initial success of the catheter trials, both the NSABP and the RTOG cooperative groups expressed an interest in designing a phase III trial to compare standard whole-breast radiation to some form of partial-breast therapy. With prompting from the Cancer Therapy Evaluation Program (CTEP) of the NCI, the two groups agreed to work together and opened a phase III trial in early 2005. The trial will compare standard whole radiation therapy to partial-breast treatment using the RTOG phase II trial dose delivery schedule of twice daily treatments for 5 days or 10 fractions. The trial will be open to women with early stage I and II breast cancer as well as those with DCIS.

After surgery and before trial entry, patients will undergo radiation treatment planning CT scanning to assess the size of the lumpectomy cavity to the whole breast. The protocol has defined ratios of partial-breast to whole breast volumes to insure that the two groups will not overlap. In other words, a woman with a very

**Table 2 Dosimetric Comparison of EBRT Partial Breast Techniques**

Ipsilateral Breast Coverage Series	PTV (cm <sup>3</sup> )	PTV/TBV* (%)	PTV/TBV* (%)				Lung Dose† (%)	Cardiac Dose ‡ (%)
			100%	75%	50%	25%		
NYU (26)								
Median	192	22	27	40	46	53	0	0
Range	57–118	10–55	10–45	20–68	23–75	27–82	0	0
WBH <sup>20</sup>								
Median	240	17	21	35	46	60	16	0‡
Range	82–482	11–22	14–39	26–53	34–60	39–92	0–37	0–7

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Abbreviations as in Table 1.

\*Planning target volume/total breast volume

†Percentage of lung volume that received 5 Gy

‡Percentage of cardiac volume that received 5 Gy (NYU) or 10 Gy (WBH)

McCormick

small breast and a large lumpectomy cavity may not meet the eligibility criteria. After negative margins have been confirmed, patients will be randomly assigned to receive either 5 to 6 weeks of standard whole breast radiation with a boost if indicated or partial-breast treatment delivered using brachytherapy catheter placement, MammoSite balloon, or external three-dimensional conformal treatment. For women assigned to the partial-breast arm, the physician will choose the technique on a case-by-case basis, considering both physician expertise and patient anatomy. Details of this study can be found at both cooperative groups' Web sites ([www.RTOG.org](http://www.RTOG.org); [www.NSABP.org](http://www.NSABP.org)).

The treatment of breast cancer has developed over the past three decades in a deliberate, evidence-based progression of studies that has benefited both patients and those who care for them. Partial-breast radiation has been successful in a limited number of centers when performed with specific physician expertise. The NSABP/RTOG phase III trial will now answer the question of whether this same treatment will be as effective as the time-tested whole-breast radiation in terms of both local tumor control and cosmetic outcome.

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## Partial-Breast Radiation

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