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INITIAL EFFICACY RESULTS OF RTOG 0319: THREE-DIMENSIONAL CONFORMAL RADIATION THERAPY (3D-CRT) CONFINED TO THE REGION OF THE LUMPECTOMY CAVITY FOR STAGE I/ II BREAST CARCINOMA

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Abstract

Purpose—This prospective study (Radiation Therapy Oncology Group 0319) examines the use of three-dimensional conformal external beam radiotherapy (3D-CRT) to deliver accelerated partial breast irradiation (APBI). Initial data on efficacy and toxicity are presented.

Methods and Materials—Patients with Stage I or II breast cancer with lesions≤3 cm, negative margins and with≤3 positive nodes were eligible. The 3D-CRT was 38.5 Gy in 3.85 Gy/fraction delivered 2×/day. Ipsilateral breast, ipsilateral nodal, contralateral breast, and distant failure (IBF, INF, CBF, DF) were estimated using the cumulative incidence method. Mastectomy-free, disease-free, and overall survival (MFS, DFS, OS) were recorded. The National Cancer Institute Common Terminology Criteria for Adverse Events, version 3, was used to grade acute and late toxicity.

Results—Fifty-eight patients were entered and 52 patients are eligible and evaluable for efficacy. The median age of patients was 61 years with the following characteristics: 46% tumor size <1 cm; 87% invasive ductal histology; 94% American Joint Committee on Cancer Stage I; 65% postmenopausal; 83% no chemotherapy; and 71% with no hormone therapy. Median follow-up is

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4.5 years (1.7–4.8). Four-year estimates (95% CI) of efficacy are: IBF 6% (0–12%) [4% within field (0–9%)]; INF 2% (0–6%); CBF 0%; DF 8% (0–15%); MFS 90% (78–96%); DFS 84% (71–92%); and OS 96% (85–99%). Only two (4%) Grade 3 toxicities were observed.

Conclusions—Initial efficacy and toxicity using 3D-CRT to deliver APBI appears comparable to other experiences with similar follow-up. However, additional patients, further follow-up, and mature Phase III data are needed to evaluate the extent of application, limitations, and value of this particular form of APBI.

Keywords

Partial breast irradiation; External beam radiation therapy; Breast cancer; Breast-conserving therapy

INTRODUCTION

Over the past decade, accelerated partial breast irradiation (APBI) has been explored as a possible option to deliver adjuvant irradiation after lumpectomy in selected patients undergoing breast-conserving therapy (BCT). Most Phase I/II studies using this technique have demonstrated acceptable 5- and 10-year rates of local control and cosmesis in highly selected, low-risk patients (1, 2). Early studies using catheter-based interstitial brachytherapy as the APBI technique have provided the largest group of patients with the longest follow up (3–5). Despite good results, application of this method of APBI has proven technically challenging. Even using the best placement methods available, the technique can be complex and requires a great deal of experience and skill to position the needles or catheters to cover the required target volume (6). As a result, widespread adoption of this method of APBI has not yet been demonstrated.

In recognition of these issues, several different treatment techniques have been explored for the delivery of APBI. In the United States, two different techniques have dominated and include balloon-based catheter brachytherapy (*i.e.*, the MammoSite applicator) and three-dimensional conformal external beam radiotherapy (3D-CRT) (7–9). Despite their popularity and ease of application, data on both of these newer techniques are limited, with only a handful of studies reporting outcome in patients followed up to 5 years.

Radiation Therapy Oncology Group (RTOG) 0319 was the first cooperative group trial to examine the use of 3D-CRT to deliver APBI. Reproducibility, as measured by technical feasibility, was the primary end point of this Phase II trial with the goal of demonstrating whether or not the technique could be widely adapted in a multicenter setting before undertaking a Phase III trial. The technique was determined to be reproducible and the initial results were published in 2005 (10). This subsequently led to the incorporation of 3D-CRT in the combined Phase III trial National Surgical Adjuvant Breast and Bowel Project B39/RTOG 0413. Secondary end points of the RTOG 0319 trial were efficacy and toxicity and are the purpose of this analysis.

METHODS AND MATERIALS

Patients eligibility

All patients with American Joint Committee on Cancer Stage I or II (T1N0, T1N1, T2N0, T2N1) invasive ductal, breast cancer including not otherwise specified, medullary, papillary, colloid (mucinous), or tubular histologies with lesions ≤3 cm were eligible. Patients were required to have unifocal breast cancer (single focus, which can be encompassed by one lumpectomy). Patients with an extensive intraductal component were excluded. Patients

with up to three positive axillary nodes were allowed. Patients were required to have negative margins (>2 mm). Patients were ineligible for the study if they had a history of prior malignancy within the past 5 years (except for non-melanomatous skin cancer).

Treatment technique and imaging

Treatment planning and delivery were required to be performed with the patient in the supine position. A treatment planning computed tomography scan was required to define the clinical target volume (CTV) and planning target volume (PTV). The CTV was defined by uniformly expanding the excision cavity volume by 10–15 mm. Six surgical clips were required and used to help define the boundaries of the cavity volume. However, the CTV was limited to 5 mm from the skin surface and lung–chest wall interface. This study required the computed tomography scan to start at or above the mandible and extend several centimeters below the inframammary fold (including the entire lung). These structures required contouring: CTV, PTV, ipsilateral breast, thyroid, contralateral breast, ipsilateral and contralateral lung, and heart. The shoulders, chin, and contralateral breast were included in the scan (computed tomography scan thickness of ≤0.5 cm). The CTV and PTV and normal tissues were outlined on all computed tomography slices.

The PTV was designed to provide a margin around the CTV to compensate for the variability of treatment setup and motion of the breast with breathing. A minimum of 10 mm around the CTV was required (superior, inferior, medial, and lateral dimension). The PTV was saved and used to generate the beam aperture (with an additional margin to take penumbra into account). Because a substantial part of the PTV often extends outside the patient (especially for superficial cavities) the PTV was then copied to a PTV for evaluation (PTV_EVAL), which was edited. This PTV was limited to exclude the part outside the patient and the first 5 mm of tissue under the skin (to remove most of the build up region for the dose–volume histogram analysis) and excluding (if applicable) the PTV expansion within the lung. This PTV_EVAL was the structure used for dose–volume histogram constraints and analysis. This PTV for evaluation could not be used for beam aperture generation.

Treatment could only be given using 3D-CRT fields. Intensity-modulated radiation therapy was not allowed. Field arrangements were at the discretion of the physician and determined by 3D treatment planning to produce the optimal conformal plan in accordance with volume definitions (see the following section). The treatment plan used for each patient was based on an analysis of the volumetric dose including dose–volume histogram analyses of the PTV and critical normal tissues.

Radiotherapy was recommended to begin within 8 weeks of surgery, if no chemotherapy was given. If chemotherapy was given first, RT was recommended to start a minimum of 2 weeks after the last cycle of chemotherapy. A total of 38.5 Gy in 10 fractions were prescribed to the International Commission on Radiation Units and Measurements 50 reference point dose (usually isocenter). Two fractions per day, each of 3.85 Gy, separated by at least 6 h, were given in 5 consecutive working days (Monday–Friday). Dose calculations with tissue inhomogeneity correction were required. Portal films or portal images of each beam and an orthogonal pair (anteroposterior and lateral) were obtained for the first fraction. Subsequent films or images were obtained on fraction numbers 2, 5, and 9 including an orthogonal pair. Additional individual port films could be taken at the investigator’s discretion.

Dose–volume constraints/normal tissue tolerances

Dose–volume constraints were established for the protocol and have been previously published (10). These included limitations in dose to: (1) uninvolved breast tissue, (2) ipsilateral and contralateral lung, (3) contralateral breast, (4) heart (different values for right and left-sided lesions), and thyroid. In addition, quality assurance evaluations were established with an ideal plan having the 95% isodose surface covers 100% of the PTV and the maximum dose to the PTV should not exceed the prescription dose by >10%.

Toxicity evaluation

Acute and late radiation effects were evaluated and scored using the National Cancer Institute Common Terminology Criteria for Adverse Events v3.0 (CTCAE v3.0) (MedDRA v6.0). The values stated represent the patient's worst toxicity at any time point.

Statistical considerations

The current analysis focuses on the following protocol-specified secondary efficacy end points: ipsilateral breast recurrence, ipsilateral nodal failure, distant metastases, mastectomy-free survival (MFS), disease-free survival (DFS), and overall survival (OS). An ipsilateral breast failure (IBF) is defined as biopsy-proven invasive or noninvasive recurrence (except lobular carcinoma in situ) in the ipsilateral breast. Failure rates will also be subdivided by within field, peripheral (in the skin of the treated breast), or extra- field locations. An ipsilateral nodal failure (INF) is defined as an ipsilateral axillary, internal mammary, or supraclavicular recurrence only if accompanied by an IBF. IBF, INF, contralateral breast (CBF), and distant failure (DF) rates were estimated using the cumulative incidence method in which death is a competing risk. For MFS, a failure is defined as a simple mastectomy, a modified radical mastectomy, or death from any cause. For DFS, a failure is any tumor recurrence—including local recurrence, nodal recurrence, distant metastases, contralateral breast cancer—or death. MFS, DFS, and OS rates were estimated using the Kaplan-Meier method.

RESULTS

Study accrual

A total of 58 patients were enrolled on the trial between August 2003 and April 2004, of which 52 were evaluable for efficacy and toxicity assessments. Three patients did not receive any protocol treatment and 3 patients were ineligible. The median follow-up for all patients is 4.5 years (range, 1.7–4.8). For the 49 patients who are still alive, the median follow-up is 4.5 years (range, 2.7–4.8) and all of these patients have been followed for more than 2 years; 47 (96%) ≥3 years; and 41 (84%) ≥4 years.

Patient characteristics

Pretreatment characteristics for all eligible patients are shown in Table 1. The median patient age was 61 and the median tumor size was 9 mm. Tumor size was <10 mm in 24 patients (46%) and ≥2 cm in only 3 (6%). For the 48 cases where estrogen receptor status was reported, 39 (81%) were estrogen receptor(+) and 9 (19%) were negative. Of the 52 patients included in the analysis, 17 had axillary nodes sampled and 35 had a sentinel lymph node biopsy. Of the 17 with axillary nodes sampled, positive nodes were reported in 4 cases. Of the 35 with a sentinel lymph node biopsy, no positive nodes were reported (4 of 52 total cases [7.6%] had positive nodes). There were no cases of pure ductal carcinoma *in situ* and all patients had negative margins pathologically. Eight patients (16%) received systemic chemotherapy, 15 (29%) hormonal therapy, and no patients received both.

Toxicity

Toxicity scores are presented in Tables 2 and 3. A total of 2 patients (4%) developed Grade 3 toxicities that were felt to be treatment related. This included 1 patient who experienced Grade 3 skin fibrosis and telangiectasias and 1 patient that developed Grade 3 radiation dermatitis and myositis. No other Grade 3 toxicities were observed. Grade 1 and 2 pain was reported in 9 patients (17%) and 7 patients (13%), respectively. Cosmesis scores are not yet available.

Efficacy

IBF—Four-year estimates (95% CI) of efficacy are presented in Table 4. A total of three IBFs were recorded for a 4-year actuarial rate of 6% (0–12%) The 4-year rate of infield IBF was 4% (0–9%). One of these three IBFs developed concurrently with DF and in the skin of the breast. The 4-year rate of isolated IBF (without concurrent DF) was 4%.

INF—A total of three INFs were observed (axilla only) at any point in follow-up (before or after DF or at mastectomy performed for nononcologic reasons). Only one of these INFs met the protocol criteria (patients also had to have an IBF) with a 4-year actuarial rate of 2% (0–6%). For the 3 cases that experienced an INF, all were node negative at diagnosis (all 3 had a sentinel node biopsy only). No patient with positive lymph nodes at diagnosis ($n = 4$) experienced a nodal failure of any type.

MFS—A total of 3 patients underwent mastectomy (all are still alive) and 3 additional patients died for a 4-year MFS rate of 90% (78–96%). Two patients underwent mastectomy for IBF and 1 patient for nononcology reasons (patient requested after experiencing breast pain).

DFS and OS—The 4-year DFS rate was 84% (71%, 92%), with a total of 8 failures. Table 5 shows pretreatment, treatment, and tumor characteristics of these 8 patients. The 4-year OS rate was 96% (85–99%), with a total of 3 deaths.

DISCUSSION

The primary purpose of RTOG 0319 was to examine the use of 3D-CRT to deliver APBI. Reproducibility, as measured by technical feasibility, was the primary end point with the goal of demonstrating whether or not the technique was widely applicable in a multicenter setting before undertaking a Phase III trial. The technique was determined to be reproducible and the initial results were published in 2005 (10). This subsequently led to the use of the technique in the combined Phase III trial: NSABP B39/RTOG 0413. A secondary end point of the RTOG 0319 trial was efficacy and toxicity and is the purpose of this analysis. With a median follow-up of 4.5 years, the 4-year actuarial rate of IBF was 6%, and only 2 patients (4%) experienced Grade 3 toxicities. There is, however a wide confidence interval to the reported IBF rate, a result of the small sample size used for this Phase II trial. These results are comparable to other experiences with similar, limited follow-up (see the following section). Analysis of data resulting from larger patient numbers, longer follow-up and a Phase III trial design (*i.e.*, RTOG 0413/NSABP B-39 trial) will be needed to thoroughly evaluate the efficacy, extent of application, limitations, and complete value of this particular form of APBI.

Efficacy

The acceptable 5- and 10-year rates of local tumor control and cosmesis using interstitial brachytherapy to deliver APBI were achieved using a relatively consistent dose fractionation

schedule of 34 Gy given in 10 fractions delivered over 5 days (1, 11, 12). Radiobiologic calculations using 3D-CRT to deliver APBI suggest that a slightly higher dose (38.5 Gy in 10 fractions) might be required (13, 14). Despite the fact that this total dose and fractionation schedule is now the most frequently employed in clinical practice (when applying 3D-CRT to deliver APBI), its long-term efficacy remains uncertain. There are other doses and treatment schedules that have been recommended and used successfully (Table 6). Some groups have employed 30 Gy in 5 fractions (over 10 days), whereas others have conducted does escalation trials attempting to establish the most appropriate dose (15–18). The early results in this trial using 38.5 Gy in 10 fractions are encouraging but must be viewed cautiously. Only long-term clinical data from large patient populations addressing both local tumor control, cosmesis, and acute/chronic toxicities using this and different dose schedules will resolve the issue of identifying the most efficacious fractionation scheme to employ.

Toxicity

Unlike brachytherapy, in which the implanted volume is the treated volume, the use of 3D-CRT to deliver APBI must account for respiratory motion and treatment setup uncertainties (19, 20). Previous studies addressing this issue suggested that a 10-mm margin (added to the CTV) was needed to adequately account for these concerns (PTV). Unfortunately, it is still uncertain if this PTV expansion is sufficient in all patients or, conversely, if it unnecessarily irradiates excessive volumes of nontarget tissue in others. In addition, these substantially increased target volumes limit the practical application of this technique from restrictions placed on doses to nontarget breast and other normal tissues.

As discussed previously, the delivery of 3D-CRT for APBI requires the use of multiple conformal beams that incidentally irradiate significant nontarget breast and normal tissues to comprehensively cover the CTV. For many of these tissues, it is uncertain what the maximum acceptable dose–volume limitations should be. Recent concerns have been expressed that the application of these large fraction sizes and volumes may potentially increase the rate of unacceptable cosmesis or the development of late effects such as severe fibrosis, pain, telangiectasia, and fat necrosis (21). For example, using α/β values derived from recent clinical trials on hypofractionated whole breast irradiation (*e.g.*, the START A and B trials), biologically equivalent dose calculations now suggest that the late tissue injury of 3D-CRT APBI using 38.5 Gy in 10 fractions may be more severe than that predicted for either conventionally fractionated whole-breast irradiation or brachytherapy APBI delivered at 34 Gy in 10 fractions (22–24).

Two recent reports (abstract form) suggest potentially unacceptable toxicities/cosmesis when applying the RTOG 0319 fractionation schedule and the dose–volume limitations of the NSABP B-39/RTOG 0413 Phase III trial. For example, Hepel *et al.* (Tufts University) recently reported data on 64 patients treated with similar guidelines as found in the NSABP B-39/RTOG 0413 Phase III trial (25).With a median follow-up of 15 months, 10% of their patients experienced moderate-to-severe late toxicity and 81.7% of patients were scored with good/excellent cosmesis (11.7% fair and 6.7% poor). The most significant late toxicity was subcutaneous fibrosis: 25% Grade 2–4 and 8.3% Grade 3–4. Univariate regression analysis demonstrated that the development of fibrosis was related to the maximum dose within the breast (Dmax), the size of the 3D-CRT target volume (PTV_EVAL), and the size of the low, intermediate, and high dose volumes (V5–80) in proportion to the overall volume of the nontarget breast.

In a separate study at the University of Michigan, Jagsi *et al.* treated 34 patients in a prospective, institutional review board–approved trial delivering 38.5 Gy in 10 fractions with an inverse-planned, beamlet intensity-modulated radiation therapy plan at deep breath

hold (26). According to the authors, similar dose–volume guidelines/limitations as in the NSABP B-39/RTOG 0413 Phase III trial were employed. With a minimum cosmetic follow-up of at least 1 year in all patients studied (19 patients were followed more than 2 years), adverse cosmesis was observed in 7 patients, leading to the premature closure of their trial.

It is important to note that these two analyses represent small numbers of patients, mostly from single institutions. Other studies suggest this fractionation schedule may actually reduce fibrosis compared with conventional whole-breast RT. In a recent dosimetric study, Jothy Basu *et al.* compared the normal tissue complication probability for radiation-induced fibrosis in the treated breast using Lyman's relative- seriality model and the breast fibrosis normal tissue complication probability model fitting parameters for the study. Their analysis concluded that APBI (using 3D-CRT to deliver 38.5 Gy in 10 fractions) may reduce ipsilateral breast fibrosis compared with conventional whole-breast treatment in early-stage breast cancer (27).

To determine the relevance of all these reports to future participants of the NSABP B-39/RTOG 0413 Phase III trial, a detailed analysis of toxicity for all enrolled patients on this trial by treatment group was recently presented to the NSABP Data Monitoring Committee (28). No issues/concerns related to significant toxicity were raised in a recent report from the trial. Furthermore, there was little difference in serious adverse events (to date) between whole-breast irradiation and the three APBI techniques with a mean follow-up time of 19.4 months (<1% Grade 3 toxicities were observed). Of note in this trial, about 70% of women randomized to receive APBI are treated with the external beam technique used in RTOG 0319. Therefore, with more than 3200 patients enrolled in this large prospective randomized Phase III trial (with careful reporting of adverse events), there has been no confirmation of the Tufts University or University of Michigan experiences regarding toxicity concerns.

In the current study with a median follow-up 4.5-years, only 4% of patients developed Grade 3 or greater toxicities. These results are similar to those recently reported by the Beaumont group using the same fractionation scheme and treatment volumes (29). In 94 patients treated with a median follow-up of 4.2 years, they reported a 4-year actuarial rate of IBF of 1% with only 4% of patients developing Grade 3 toxicities and 89% of patients achieving a good/excellent cosmetic result. A recent interim analysis of a Phase III trial (from Spain) comparing partial (3D-CRT giving 38.5 Gy in 10 fractions) vs. whole-breast irradiation in 46 patients was presented at the 2008 meeting of the European Society for Therapeutic Radiology and Oncology (30). With a median follow-up of 18 months, the authors noted no significant differences in Grade 1, 2, or 3 toxicities between both treatment groups (Table 6).

Finally, there are noteworthy differences that exist between the 3D-CRT treatment approach employed in this current study (RTOG 0319) and the presently ongoing NSABP B39/RTOG 0413 Phase III trial. The Phase III 3D-CRT treatment approach was defined based on the early experience of this RTOG -0319 Phase II trial with appropriate modifications in an attempt to improve the usability of this treatment technique in the Phase III trial and to further reduce potential toxicities. These modifications included relaxation of target coverage/dose–volume constraints and the use of bolus was prohibited. Despite our basic understanding of this treatment technique, however, conflicting toxicity data following the use of 3D-CRT to deliver APBI exist. In response, it would appear prudent to emphasize the importance of clinical trial accrual as the appropriate vehicle for 3D-CRT use as a treatment approach for APBI. Otherwise, careful use of this fractionation schedule and dose–volume limitations is warranted until additional long-term outcome data are available.

CONCLUSIONS

Initial efficacy results (locoregional control and toxicities) using 3D-CRT in RTOG 0319 to deliver APBI appear comparable to other experiences with similar, limited follow-up. However, additional patients, further follow-up, and mature Phase III trial data (*i.e.*, RTOG 0413/NSABP B-39 trial) will be needed to thoroughly evaluate the extent of application, limitations, and complete value of this particular form of APBI.

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Table 1

Pretreatment characteristics for all eligible patients ($n = 52$)

Characteristic	Finding	
Age		
Median	61	
Range	38–89	
Tumor dimension (cm)		
Median	0.9	
Range	0.1–2.6	
	n	%
Tumor dimension		
<1 cm	24	46
Between 1 cm and 2 cm	19	37
≥2 cm	3	6
Missing	6	12
Histology		
Invasive ductal	45	87
Colloid	2	4
Tubular	5	10
Stage		
I (T1, N0–1, M0)	49	94
II (T2, N0–1, M0)	3	6
Nodes		
N0	48	92
N+	4	8
Menopausal status		
Premenopause	7	7
Postmenopause	34	34
Surgically menopausal	11	11
Location of tumor		
Upper outer	22	42
Upper inner	9	17
Lower outer	2	4
Lower inner	6	12
Upper central	9	17
Lower central	1	2
Subareolar	3	6
Final surgical margins		
Negative	49	94
Positive margin, negative at reexcision	3	6
Chemotherapy		
None	43	83

Characteristic	Finding	
Yes, before radiotherapy	5	10
Yes, after radiotherapy	3	6
Unknown	1	2
Hormonal therapy		
None	37	71
Yes	15	29

Table 2

All adverse events reported as definitely, probably, or possibly related to treatment ($n = 52$)

	Grade		
	1	**2**	**3**
Blood/bone marrow	2	0	0
Cardiovascular (general)	1	0	0
Constitutional symptoms	13	1	0
Dermatology/skin	19	18	2
Endocrine	3	0	0
Gastrointestinal	2	0	0
Lymphatics	6	0	0
Musculoskeletal/soft tissue	5	7	1
Pain	9	7	0
Pulmonary	1	1	0
Sexual/reproductive function	4	5	0
Worst nonhematologic	17 (33%)	24 (46%)	2 (4%)
Worst overall	17 (33%)	24 (46%)	2 (4%)

Table 3

Grade 3+ adverse events reported as definitely, probably, or possibly related to treatment (n = 2 patients)

Case	Category	Adverse event	Grade
A	Dermatology/skin	Skin fibrosis	3
		Telangiectasia	3
B	Dermatology/skin	Dermatitis radiation NOS	3
	Musculoskeletal/soft tissue	Myositis	3

Abbreviation: NOS = not otherwise specified.

Table 4

Treatment outcome

End point	No. failures	4-year estimates	95% CI	At risk
All ipsilateral breast failure (IBF)	3	6%	(0–12%)	40
Within field, invasive	2	4%	(0–9%)	40
Within field, noninvasive	0	0%	—	40
Outside field	1	2%	(0–6%)	40
Peripheral (skin)	1	2%	(0–6%)	40
IBF without concurrent distant failure	2	4%	(0–9%)	40
Ipsilateral nodal failure (protocol-defined)	1	2%	(0–6%)	42
Contralateral breast failure	0	0%	—	42
Distant failure	4	8%	(0–15%)	40
Mastectomy-free survival	6	90%	(78–96%)	39
Disease-free survival (see Table 5 for details)	8	84%	(71–92%)	37
Overall survival	3	96%	(85–99%)	42

Table 5

Characteristics of the 8 disease-free failure patients

Case	Age	Stage	Tumor size (cm)	Node+	ER+	Menopausal status	Tumor location	Margins	Chemo	Tam	Failure type
A	67	I	0.7	No	Yes	Postmenopausal	LIQ	Neg	No	No	INF (axilla) DF
B	73	I	1.7	Yes	Yes	Surgical menopause	UOQ	Neg	No	Yes	DF Death (spine metastases)
C	50	I	0.3	No	Yes	Postmenopausal	UC	Neg	Yes, after XRT	No	IBF (outside field) Simple mastectomy
D	80	I	1.3	No	Yes	Postmenopausal	UIQ	Neg	No	Yes	INF (axilla) Bilateral mastectomy
E	84	I	0.7	No	NR	Postmenopausal	UOQ	Neg	No	No	IBF (within field, invasive) IBF (skin of treated breast) INF* (axilla), DF Death (liver metastases)
F	70	I	1.4	No	Yes	Postmenopausal	LOQ	Neg	No	No	Death (bladder, second primary)
G	60	I	1.2	No	NR	Surgical menopause	UOQ	Initially Pos	No	No	IBF (within field, invasive) Bilateral mastectomy
H	53	I	0.6	Yes	NR	Postmenopausal	UOQ	Neg	Yes, prior to XRT†	No	DF

Abbreviations: IBF = ipsilateral breast failure; chemo = chemotherapy; ER = estrogen receptor status; DF = distant failure; INF = ipsilateral nodal failure; LOQ = lower inner quadrant; NR = not reported; tam = tamoxifen; UC = upper central; UIQ = upper inner quadrant; UOQ = upper outer quadrant; XRT = radiation therapy.

*This failure met the protocol-specified criteria for INF.

†202 days from surgery to radiation therapy.

Table 6

Partial breast irradiation studies using external beam radiation

Institution/series	No. cases	Follow-up (months)	Fractionation schedule	IBF rate	Cosmetic result (good/excellent)	≥Grade 3 toxicity
RTOG 0319 (current study)	52	54 (median)	385 cGy × 10 (b.i.d.)	6%	NS	4%
William Beaumont Hospital (8,29)	94	50 (median)	340 or 385 cGy × 10 (b.i.d.)	1.1%	89%	4%
Harvard (31)	99	36	3200 cGy 4 Gy/bid	2%	97%	NS
New York University/Keck School of Medicine (32)	10	36 (minimum)	500, 550, or 600 cGy × 5 (10 days)	0%	100%	NS
Formenti (15)	47	18 (median)	600 cGy × 5 (10 days)	0%	NS	NS
Christie Hospital/ Holt Radium Institute (33)	353	96 (mean)	500–531 cGy × 8 (10 days)	25%	NS †	NS
National Institute of Oncology, Hungary (Phase III Trial) *	40	86 (median)	200 cGy × 25	2.5%	70%	NS
Rocky Mountain Cancer Center (34)	55	34	385 cGy × 10 (b.i.d.)	0%	NS	NS
NSABP B39/ RTOG 0413 Phase III Trial (28)	3200	19.4 (mean)	385 cGy × 10 (b.i.d.)	NS	NS	<1%
Hospital de la Esperanza Barcelona, Spain Phase III Trial (30)	46	18 (median)	375 cGy × 10 (b.i.d.)	0%	NS	0%
Tufts University Brown University (25)	64	15 (median)	385 cGy × 10 (b.i.d.)	NS	81.7%	8.3%
University of Michigan (26)	34	>24	385 cGy × 10 (b.i.d.)	NS	79.5%	NS

Abbreviations: b.i.d. = twice daily; IBF = ipsilateral breast failure; NS = not stated.

* Personal communication.

† Partial breast irradiation patients had a greater incidence of fibrosis, telangiectasias, and fat necrosis.