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The Feasibility of Radiation Therapy after Breast-Conserving Surgery for Multiple Ipsilateral Breast Cancer: An Initial Report from ACOSOG Z11102 (Alliance) Trial

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Abstract

Purpose: Historically, multiple ipsilateral breast cancer (MIBC) has been a contraindication to breast-conserving therapy. We report the feasibility of radiation therapy (RT) after breast-conserving therapy in MIBC from the Alliance Z11102 trial.

Methods and Materials: Delineation of targets and organs at risk was performed according to the Radiation Therapy Oncology Group contouring consensus definitions. RT was delivered to the whole breast to 45 to 50 Gy in standard daily fractions of 1.8 to 2.0 Gy. A boost of 10 to 16 Gy in 2.0-Gy daily fractions to each tumor bed was mandatory.

Results: A total of 236 eligible patients were enrolled in the study between July 23, 2012 and August 19, 2016. Of those, 195 (83%) completed RT. No patient underwent mastectomy for failure to meet the RT dose constraints. Higher absolute boost volume was associated with increased incidence of grade 2 or higher dermatitis (odds ratio, 1.21; 95% confidence interval, 1.041.41; $P = .014$). Higher relative boost volume as a percentage of the overall breast volume was

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not associated with increased dermatitis. Neither absolute nor relative boost volume appeared to significantly influence overall cosmesis.

Conclusions: Breast conservation followed by whole breast RT plus boost to each tumor bed was feasible in the majority of patients with MIBC. Increasing radiation boost volume was associated with increased incidence of acute dermatitis, but was not associated with worse overall cosmesis.

Introduction

Historically, the treatment for women who present with multiple ipsilateral breast cancers (MIBC) has been mastectomy. This recommendation was based on retrospective analyses that suggested that the risk of local failure with breast-conserving surgery and radiation therapy (RT) was unacceptably high in patients with multiple tumors.[1–3] These studies were published long before the introduction of modern imaging techniques and before comprehensive evaluation of surgical margins became routine. Because these studies reported local failure in up to 40% of patients, breast conservation had not been recommended in this population.

More recently, the introduction of improved breast imaging techniques such as digital mammography, tomosynthesis, contrast mammography, and magnetic resonance imaging (MRI) has allowed for the diagnosis of smaller cancers that would have been radiographically undetectable using older technologies. This, in turn, has likely led to a rising incidence of MIBC.[4–14] Increasing numbers of patients are now being diagnosed with MIBC and often presented with mastectomy as their only or best surgical option.

At the same time, local control after breast-conserving surgery and RT continues to improve. Some reports have even suggested superior outcomes with breast-conserving surgery and RT for certain tumor types compared with mastectomy.[15–17] More recent retrospective analyses of patients with MIBC treated with breast conservation therapy have found rates of local recurrence comparable to those observed with unifocal disease.[18–22]

The Alliance Z11102 trial prospectively evaluated the feasibility and safety of breast conservation in women with MIBC. The primary endpoint of Alliance Z11102 is locoregional recurrence at 5 years. Secondary endpoints include rate of conversion to mastectomy (due to persistent positive margins, poor cosmesis, or inability to satisfy radiation dose constraints), cosmesis, incidence of lymphedema, adverse effects of breast-conserving surgery, and adverse effects of whole breast RT. Herein, we report the feasibility of RT after breast conserving therapy in MIBC from the Z11102 trial.

Methods and Materials

Alliance Z11102 is a prospective, single-arm trial designed to assess the feasibility of breast conservation therapy in women with 2 or 3 sites of malignancy in a single breast. The American College of Surgeons Oncology Group is now part of the Alliance for Clinical Trials in Oncology. All sites received approval from their institutional review boards, and written, informed consent was obtained from patients before study enrollment.

Inclusion criteria required biopsy of all suspicious lesions before surgery and a minimum of one site of invasive carcinoma. The remaining lesions could be ductal carcinoma in situ or invasive carcinoma. Additional eligibility criteria included female sex, life expectancy >5 years, age >40 years, and cN0 or cN1 disease. Initially, MRI within 60 days before surgery was required in addition to mammogram. The MRI requirement was removed in an amendment activated May 2015. Exclusion criteria included pregnancy, neoadjuvant hormone therapy or chemotherapy, a single radiographic site of disease larger than 5 cm, bilateral breast cancer (synchronous or metachronous), comorbidity precluding whole breast radiation, history of ipsilateral breast irradiation, plan for partial breast irradiation, or a known BRCA mutation.

Patients were initially all registered for the study preoperatively. An amendment effective May 2015 allowed postoperative registration if this occurred before initiation of RT. For women registered before surgery, enrollment was based on radiographic distance between lesions. The protocol required a minimum of 3 cm of normal-appearing breast tissue between lesions before an amendment (effective January 2014) that decreased the minimum distance between lesions to 2 cm.

Resection through a single or multiple incisions was allowed. Where possible, surgical clips were placed to outline the surgical bed for all patients. For patients in whom an oncoplastic approach to the surgical resection was undertaken, clips were required to outline the surgical bed. At the outset of the trial, negative margins were defined as a minimum of 2 mm, excepting anterior and posterior margins if skin and/or fascia were taken. Re-excision was recommended for patients with margins <2 mm. After the publication of the Society of Surgical Oncology/American Society of Radiation Oncology consensus guidelines on margins, the protocol was amended, effective May 2015, defining negative margin for invasive breast cancer as “no ink on tumor.” For patients with persistently positive margins after attempted breast-conserving surgery, mastectomy was recommended. Oncoplastic reconstruction was allowed. Adjuvant systemic therapy was prescribed at the discretion of the treating oncologist. Hormone receptor positivity was defined per individual institutional policies.

Patients undergoing breast-conserving surgery received adjuvant whole breast radiation with a boost to the lumpectomy bed of each site of disease. The boost was limited to 2 quadrants of the breast only. Women who could not undergo radiation boost were excluded from the trial. Delineation of radiation targets and organs at risk were performed according to the Radiation Therapy Oncology Group (RTOG) contouring consensus definitions (http://www.rtog.org/CoreLab/ContouringAtlases/BreastCancerAtlas.aspx). The lumpectomy gross tumor volume was created using all available clinical and radiographic information, including the excision cavity volume, architectural distortion, lumpectomy scar, and seroma and/or extent of surgical clips. Patients without a clearly identifiable lumpectomy bed were not eligible for protocol participation. The tumor bed boost clinical target volume was defined as the lumpectomy gross tumor volume plus a 10 mm expansion, and the boost planning target volume was the clinical target volume plus a 3 to 5 mm expansion.

Radiation was delivered with standard fractionation of 1.8 to 2.0 Gy daily for a total whole breast dose of 45 to 50 Gy. Prone positioning was permitted. Hypofractionation was not allowed. A radiation boost of 10 to 16 Gy in 2 Gy daily fractions to each tumor bed was mandatory (10 Gy for those receiving 50–50.4 Gy to the whole breast, 14 Gy for those receiving 46 Gy to the whole breast, and 16 Gy for those receiving 45 Gy to the whole breast). The protocol required that ≥90% of the lumpectomy planning target volume receive ≥90% of the boost prescription dose. Higher boost target coverage (≥95%) was not required, in an effort to minimize the high dose volume relative to the total breast volume. No more than 50% of the target breast tissue was to receive over 60 Gy. If dose constraints were not met, patients were rescanned no later than 10 weeks after lumpectomy (or final margin re-excision) to allow for cavity shrinkage. If the seroma decreased in size during the course of RT, adaptive planning was not allowed because plan data were submitted for central review before treatment start.

Three-dimensional computed tomography−based treatment planning was required. Intensity modulated RT with inverse planning was allowed. Image guidance for the boost phase was not required.

Addition of nodal radiation fields was at the discretion of the treating radiation oncologist. For those patients with 1 to 2 positive sentinel lymph nodes not undergoing axillary lymph node dissection, the use of either standard tangent fields or “high tangent fields,” defined as covering part or all level II axillary nodes, was permitted. The use of high tangents was clinically determined during centralized review. For those patients with ≥3 positive sentinel lymph nodes undergoing axillary lymph node dissection, regional nodal irradiation was encouraged, especially in those with extracapsular extension, nodal ratio >20%, high-grade disease, and lymphovascular space invasion. Coverage of the supraclavicular fossa and high axillary lymph node regions was recommended. Coverage of the internal mammary nodes was at the discretion of the radiation oncologist. For those patients with ≥3 positive sentinel lymph nodes not undergoing axillary lymph node dissection, regional nodal irradiation was required. If regional lymph nodes were treated, contouring of regional lymph nodes per the RTOG breast contouring atlas was required. If treated, the dose to the regional nodes was 46 to 50 Gy in 2 Gy daily fractions or 50.4 Gy in 1.8 Gy daily fractions, 5 days a week.

All radiation plans were submitted for central review. Data collection and statistical analyses were conducted by the Alliance Statistics and Data Center. Data quality was ensured by review of data by the Alliance Statistics and Data Center and by the study chairperson, following Alliance policies. The Alliance Data Safety Monitoring Board reviewed safety data for this trial at least twice per year. Data for these analyses were frozen on April 9, 2020, when all patients had at least 2 years of follow-up.

Dermatitis was graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 and reported at the conclusion of RT. Patients’ perception of cosmesis were assessed at their initial postoperative visit as well as 1, 6, 12, and 24 months after completion of whole breast irradiation using the BREAST-Q questionnaire, a patient-reported outcome instrument for breast surgery patients. This study used the independent scales of satisfaction with breasts, satisfaction with overall outcome, adverse

effects of radiation, and physical well-being from the breast-conserving therapy module of the BREAST-Q. Higher scores (up to 100 for each scale) are associated with better outcome.

Analyses

Categorical data are summarized by counts and relative frequency, and continuous data are summarized with the median (minimum value, maximum value). A χ^2 test (or Fisher's exact test if the χ^2 test was not appropriate) was used to compare 2 categorical values. The association between boost volume and dermatitis is summarized with an odds ratio and corresponding 95% confidence interval. The analysis of the breast cosmesis scores over time used the area under the curve (AUC). Specifically, for each patient, a curve was determined by plotting the cosmesis score by timepoint (points were connected with a straight line), and the AUC was computed. If patients were missing a timepoint, a line was used to connect the available points on either side of the missing value. If patients were missing a score for the last follow-up time point(s), the AUC was normalized for the duration of time for which values were collected. The mean AUC was compared between groups using a 2-sample *t* test (or Wilcoxon rank sum test, if more appropriate). All statistical tests were 2-sided, and a .05 level of significance was used. Analyses were done using SAS 9.4.

Results

A total of 236 eligible patients were enrolled in the study between July 23, 2012 and August 19, 2016. Patient demographics and tumor characteristics are summarized in Table 1. A total of 195 (83%) eligible patients completed RT. Of the 41 patients who did not complete protocol treatment, 13 (32%) required mastectomy due to persistently positive margins, 14 (34%) withdrew consent, and 14 (34%) went off study for other reasons (including inability to define the tumor bed due to degree of oncoplastic reconstruction, patient receiving treatment at an outside facility, and patient refusal of standard fractionation). Only 2 patients were excluded due to inability to deliver a boost. One patient was excluded because constraints could not be met, and another patient was excluded because the cavity could not be visualized. No patient underwent mastectomy for failure to meet the RT dose constraints. As previously reported, only 14 of 198 patients (7.1%) enrolled preoperatively required conversion to mastectomy, and 134 of 198 women (67.6%) successfully achieved breast conservation with negative margins in a single operation.[23] After central review before starting RT of 154 cases, no plan modifications were required in 144 cases (95%). Modifications were required and made in 7 cases (4%) and required but not made in 1 case. Review was not performed before start of treatment in 42 cases (22%).

A total of 182 patients had information on the use of high tangents, 55 patients (30.22%) were treated with "high" tangents to cover the low axilla, 111 (61.0%) patients were treated with standard tangents, and 16 (8.8%) patients had no specified tangent technique listed. High tangents were more frequently used in patients with node positive disease than in node negative disease: 38 of 140 patients (27.1%) with N0 disease and 17 of 40 patients (42.5%) with node-positive disease were treated with high tangents ($P < .0001$) (Table 2). More N0 patients than expected were treated with high tangents, likely because the definition of

high tangents was clinical (not target volume based) and at the discretion of the treating physician. Eighteen patients (10%) received regional RT.

Of patients who completed RT (n = 195), 192 (98%) received the required boost to the lumpectomy site(s). At the time of central review, 184 (94%) of plan contours were per RTOG guidelines, and 134 (68%) RT plans were appropriate per protocol in terms of contours, target coverage, and dose to organs at risk. Minor deviations from protocol treatment were observed in 42 patients (22%) and included acceptable variations in target coverage, acceptable variations in doses to organs at risk, and use of nonprotocol boost prescription dose. Major deviations were seen in 12 patients (6%) and use of hypofractionation, maximum dose >120% of the prescription, and failure to contour targets and organs at risk per the RTOG guidelines. Six plans (3%) were unevaluable, and review was not performed in 1 case.

RT was very well tolerated, with the vast majority of patients experiencing only grade 1–2 acute dermatitis. Only 5 patients (3%) experienced grade 3 or higher dermatitis. Higher absolute boost volume was associated with increased incidence of grade 2 or higher dermatitis (odds ratioOR, 1.21; 95% CI, 1.04–1.41; $P = .014$). Higher relative boost volume as a percentage of the overall breast volume was not associated with increased dermatitis (Table 3).

In terms of cosmesis, neither absolute nor relative boost volume appeared to significantly influence overall cosmesis. However, there was an association between larger absolute boost volume and worse BreastQ scores (Table 4). The use of high tangents was not associated with increased incidence of dermatitis or overall cosmesis (Table 2).

Discussion

There is a paucity of prospective data regarding the suitability of breast-conserving surgery and radiation in women with early stage operable breast cancer who present with MIBC. This has become an increasing clinically important issue facing women with breast cancer, who now routinely undergo modern comprehensive and sophisticated imaging with MRI, 3-dimensional mammography, and ultrasound, where additional small lesions may be detected. These patients likely differ from patients in several prior retrospective studies, where additional cancers in the breast may have been detected by physical examination or with less sensitive imaging technology. Many of these women may be recommended mastectomy due to the paucity of prospective data and guidelines regarding the suitability of breast-conserving surgery with radiation in this setting.

The data from Alliance Z11102 demonstrate that breast-conserving surgery followed by whole breast RT with boost to all tumor beds is feasible in the majority of women with MIBC. Few women required conversion to mastectomy, and no women required mastectomy due to failure to meet RT constraints. To our knowledge, Z11102 is the first trial to require use of the RTOG contouring guidelines for RT planning. The majority of plans reviewed were compliant with contours and the required dose parameters and constraints; 90% of plans met all protocol requirements or had only minor deviations. Radiation boost to all sites

of disease, while sparing at least 50% of the whole breast volume, was possible in 98% of patients who completed RT.

RT with boost to all lumpectomy sites was very well tolerated. Only 3% of patients experienced grade 3 or higher acute dermatitis, and only 3.6% reported poor cosmesis, which compares quite favorably with the toxicity reported after RT for unifocal disease.[24–27] As expected, increasing radiation boost volume was associated with increased incidence of acute dermatitis, but importantly was not associated with worse overall cosmesis. There was a higher proportion of grade 1 or higher dermatitis among patients receiving high tangents compared with those receiving standard tangents (81.8% vs 68.5%) but this did not reach statistical significance. The observed higher proportion in the high tangent group may be attributed to the increased field length over the axilla. Due to its anatomy, the low axillary region tends to have more dose inhomogeneity, thus leading to a higher propensity for acute radiation dermatitis. Because only 18 patients received regional RT, no relationship between addition of nodal fields and cosmesis could be established.

This trial demonstrates that high-quality RT is possible after breast-conserving surgery for women with MIBC and that adherence to the RTOG contouring guidelines and strict dose constraints is feasible across multiple institutions. The adverse event rate was not increased compared with that expected after RT for unifocal disease. Because the trial did not allow hypofractionation, we cannot comment on the feasibility of this approach using hypofractionated whole breast radiation. Given that hypofractionation has evolved as the preferred standard of care, clinicians and patients likely would want to understand why hypofractionation could not be used in the setting of multiple lesions in the breast. Given that data on hypofractionation from START B and other studies demonstrate at least equivalent toxicity,[28] fibrosis, and cosmesis, it is likely that hypofractionation in the setting of multiple lesions should be acceptable, provided appropriate dose constraints are met. Given these data, although it may be reasonable to extrapolate the results of this study to the setting of hypofractionation, this trial demonstrates that standard fractionation in the setting of multiple lesions in the breast in accordance with the dose constraints and guidelines is feasible with good cosmetic outcomes.

A number of retrospective studies have evaluated the locoregional recurrences and outcomes of patients with multiple lesions treated with breast-conserving surgery plus RT, with some showing slightly higher rates of local recurrence. As noted earlier, many of these prior studies were conducted with women in whom the additional lesions may have been detected by physical examination or with less sophisticated comprehensive imaging. We are awaiting longer follow-up to reports on the locoregional recurrence data from this study. The prospective data from this trial will ultimately serve to demonstrate the effectiveness of this approach with respect to local control. The current manuscript helps to establish some guidelines regarding acceptable dose-volume constraints that will result in acceptable toxicity and cosmesis in the increasing number of patients presenting with MIBC.

Conclusions

Breast-conserving surgery followed by whole breast RT plus a boost to each tumor bed was feasible in the majority of patients with MIBC. To our knowledge, this is one of the first breast cancer trials to require contouring of target volumes and organs at risk per the RTOG consensus guidelines. The majority of plans reviewed were compliant with the required volume definition, target coverage, and doses to organs at risk. No patients on this trial converted to mastectomy because of failure to meet RT dose constraints. RT was very well tolerated, with acute skin adverse events rates comparable to that expected with treatment of unifocal disease. Increasing radiation boost volume was associated with increased incidence of acute dermatitis but was not associated with worse overall cosmesis.

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Table 1

Patient demographics and tumor characteristics

	All eligible patients who had RT (n = 195)
Patient age, y	
Median (range)	61.0 (40.0–87.0)
No. of lesions (preop imaging)	
1	3 (1.5%)
2	186 (95.4%)
3	6 (3.1%)
No. of lesions (preop biopsy)	
2	189 (96.9%)
3	6 (3.1%)
No. of lesions (path)	
0	1 (0.5%)
1	7 (3.6%)
2	172 (88.2%)
3	15 (7.7%)
Size of largest lesion (preop) in centimeters	
Median (range)	1.6 (0.4–5.2)
Size of largest lesion (path)	
Median (range)	1.5 (0.1–6.5)
Minimum distance between lesions (preop)	
Median (range)	38 (2.0–15.0)
ER status	
All positive	178 (91.3%)
All negative	9 (4.6%)
Mixed	8 (4.1%)
PR status	
All positive	164 (84.1%)
All negative	15 (7.7%)
Mixed	16 (8.2%)
Any Her2 positive disease	
Yes	19 (9.7%)
No	171 (87.7%)
Not done	5 (2.6%)
Histology	
DCIS	1 (0.5%)
Invasive ductal	115 (59.0%)
Invasive lobular	17 (8.7%)
Invasive ductal/DCIS	39 (20.0%)
Invasive lobular/DCIS	5 (2.6%)
Invasive ductal/lobular	16 (8.2%)

	All eligible patients who had RT (n = 195)
Other	2 (1.0%)
Tumor grade	
1 (low)	51 (26.2%)
2 (intermediate)	93 (47.7%)
3 (high)	50 (25.6%)
x (grade cannot be assessed)	1 (0.5%)
Type of first surgery	
Single lumpectomy	59 (30.3%)
Two lumpectomies	131 (67.2%)
Three lumpectomies	5 (2.6%)
Axillary surgery done	
No axillary surgery	3 (1.5%)
SLN only	162 (83.1%)
ALND only	9 (4.6%)
Both SLN and ALND	21 (10.8%)
Path N category	
N0	150 (76.9%)
N1	38 (19.5%)
N2	3 (1.5%)
N3	2 (1.0%)
NX	2 (1.0%)

Abbreviations: ALND = axillary lymph node dissection; DCIS = ductal carcinoma in situ; ER = estrogen receptor; RT = radiation therapy; SLN = sentinel lymph node.

Table 2

Use of high tangents and association with dermatitis and nodal status

	High tangents		
	Yes N = 55	**No N = 111**	***P***
Grade 1 or higher dermatitis			.069
Yes	45 (81.8%)	76 (68.5%)	
No	10 (18.2%)	35 (31.5%)	
Grade 2 or higher dermatitis			.35
Yes	25 (45.4%)	42 (37.8%)	
No	30 (54.6%)	69 (62.2%)	
Grade 3 or higher dermatitis			.26
Yes	2 (3.6%)	1 (0.9%)	
No	53 (96.4%)	110 (99.1%)	
Path N status			<.0001
N0	38 (27.1%)	101 (72.1%)	
N1–3	17 (42.5%)	101 (72.1%)	
NX	0	2 (100%)	

Table 3

Boost volume and dermatitis

	Grade 1 or higher dermatitis		Grade 2 or higher dermatitis		Grade 3 or higher dermatitis	
	OR (95% CI)	***P***	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***
Boost total volume	1.01 (0.86–1.19)	.91	1.21 (1.04–1.41)	.014	1.53 (0.97–2.40)	.067
Boost volume %	1.08 (0.97–1.21)	.15	1.05 (0.95–1.17)	.33	0.85 (0.63–1.14)	.28

* For boost total volume a unit change corresponds to 500 cm^3 and for boost volume percentage a unit change corresponds to 5%

Abbreviations: CI = confidence interval; OR = odds ratio.

Table 4

Boost absolute volume (cm^3), relative boost volume (%), high tangents, and association with cosmesis over time

	Boost total volume			Boost volume %			High tangents		
	Low (≤1000) n = 71	**High (>1000) n = 87**	***p***	**Low (≤25%) n = 37**	**High (>25%) n = 104**	***p***	**Yes n = 51**	**No n = 89**	***p***
BreastQ score: Satisfaction with breast									
Mean AUC	226.4	216.2	0.19	227.9	217.6	0.29	213.9	226.5	0.12
BreastQ score: Adverse effects of radiation									
Mean AUC	271.6	254.9	0.015	265.7	260.9	0.60	257.5	264.9	0.36
BreastQ Score: Physical well-being									
Mean AUC	228.3	215.0	0.18	233.7	213.8	0.091	211.6	222.4	0.30
Patient breast cosmesis score									
Mean AUC	5.42	5.86	0.19	5.58	5.83	0.55	5.94	5.43	0.18

Abbreviation: AUC = area under the curve of cosmesis scores over time.

Higher AUC scores are associated with better outcome.