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Clinical Investigation

The Risk of Subclinical Breast Cancer-Related Lymphedema by the Extent of Axillary Surgery and Regional Node Irradiation: A Randomized Controlled Trial

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Purpose: To compare the risk of subclinical breast cancer–related lymphedema (sBCRL) using bioimpedance spectroscopy (BIS) or tape measure (TM) by the extent of axillary surgery and regional nodal irradiation (RNI).

Methods and Materials: Patients were randomized to surveillance with TM or BIS. A BIS ≥6.5 L-Dex units or TM volume change ≥5 and <10% above presurgical baselines "triggered" sBCRL. The incidence of sBCRL by sentinel node biopsy or axillary lymph node dissection (ALND) with or without RNI was examined for 484 patients. Radiation was categorized as "limited RNI" (axilla level I/II only) or "extensive RNI" (axilla level III or supraclavicular fossa with or without level I/II).

Results: At a median follow-up of 20.5 months, 109 of 498 patients (21.9%) triggered sBCRL (BIS 13.5% vs TM 25.6%; $P < .001$). In patients not receiving RNI, BIS triggered 12.9% of patients undergoing SNB and 25.0% undergoing ALND ($P = .18$). Extensive RNI significantly increased triggering with BIS versus no RNI after sentinel node biopsy (SNB; 33.3% vs 12.9%; $P = .03$) but not ALND (30.8% vs 25.0%; $P = .69$). Triggering by TM was greater than 25% for most subgroups and was inferior to BIS in discriminating the risk of sBCRL by utilization of RNI or axillary surgery.

Conclusions: The lower triggering rates with BIS and its better discrimination of the risk of sBCRL by receipt and type of RNI compared with TM support its use for posttreatment surveillance to detect sBCRL and to initiate early intervention. The

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risk of sBCRL increased with more extensive axillary treatment. Patients having ALND or extensive RNI require close surveillance for BCRL. Longer follow-up is required to determine rates of progression to clinical lymphedema.

Introduction

In the modern era of breast cancer treatment, there is an increasing trend to "de-escalate" axillary management to avoid the morbidity of an axillary lymph node dissection (ALND). The dilemma is that more aggressive treatment to the regional nodes is associated with higher rates and earlier onset of breast cancer–related lymphedema (BCRL).[1] Less aggressive treatments, however, are potentially associated with higher rates of locoregional recurrence and breast cancer mortality. It is also unclear why some patients develop BCRL and others do not. Understanding the risk of subclinical BCRL (sBCRL) by the extent of surgical or radiation treatment to the axilla may help with lymphedema screening strategies to prevent progression to clinical lymphedema, which can adversely affect quality of life.

An important, but mostly unanswered, question is how to balance the extent of treatment to the axilla, which has a small effect on breast cancer mortality to the higher risk of BCRL. The Oxford overview found a survival benefit for chest-wall and regional node irradiation (RNI; including the supraclavicular fossa [SCF] and internal mammary chain [IMC]) even for patients with 1 to 3 positive nodes (after ALND) and current guidelines advise RNI in this setting.[2] However, many patients had a limited ALND so that those classified as 1 to 3 positive nodes would have had $\geq$4 positive nodes involved with a more extensive dissection.[3] A question arises as to whether long-term meta-analysis data applies to patients treated today with more effective systemic treatments, such as taxanes[4] and trastuzumab, likely means that it is probably safe to omit post-mastectomy radiation for some patients with early nodal disease and limit the extent of radiation for others.[5-7]

The Oxford overview, performed in the ALND era, might not apply now where there has been a trend to irradiate the axilla for patients who are clinically node-negative with a positive sentinel node. The AMAROS randomized trial compared axillary and SCF irradiation after a positive sentinel node to an ALND. The 5-year incidence of BCRL was double for patients undergoing ALND compared with RNI (13% versus 6%; $P = .009$) with no difference in rates of metastases. The authors concluded that "if further axillary treatment is needed in clinically node-negative, sentinel-node–positive patients, axillary radiation therapy could be chosen instead of axillary lymph node dissection because it provides comparable axillary control and less morbidity."[8]

With the increasing use of neoadjuvant systemic therapy, the radiation oncologist is often left with the dilemma of potentially undertreating or overtreating the regional nodes after a positive sentinel node biopsy (SNB). On the one extreme, one could argue to treat all regional nodes including the SCF, infraclavicular fossa (ICF), and the IMC to the other extreme of treating levels I and II of the axilla as part of a "high tangent" field, to potentially ignoring the axilla when isolated tumor cells are found. For example, although the Z011 trial mandated radiation therapy to the breast only with either an axillary dissection or axillary observation after a positive SNB (no neoadjuvant therapy), a subsequent subset analysis, found that 53% were treated with "high tangents" that included level I-II of the axilla (as defined by as defined as being within 2 cm of the inferior aspect of the humeral head), and 17% had an SCF field. Despite guidelines, rates of nodal recurrence balanced against the rates of BCRL are not well documented.[9]

Chronic changes of BCRL are preceded by a subclinical and early stage and timely intervention with complex decongestive physiotherapy (CDP) is thought to reduce the progression to clinical symptoms and signs.[10] The 2020 National Cancer Control Network has recommended early detection of lymphedema, and the radiation oncologist is in an ideal position to discuss this and other survivorship issues during radiation treatment. For many patients, baseline measures of arm girth using a tape measure (TM) or Bio-impedance Spectroscopy (BIS) and lymphedema education might not have previously been done nor prioritized by the patient or clinician at the time of diagnosis.

Measures for BCRL vary across institutions in frequency, technique, and accuracy. Techniques such as perometry and circumference measure girth and derived volume changes, which can vary by the extent of fat changes owing to weight gain, muscle changes (from exercise or sarcopenia), or lymphedema.[11]

BIS detects extracellular fluid changes that predate clinically evident BCRL. BIS uses an "impedance ratio" methodology to assess unilateral lymphoedema of the arm. The resistance at 0 kHz in the affected or at-risk arm is compared with the resistance at 0 kHz in the unaffected arm as represented by the following ratio (unaffected:affected or at-risk). By this method, the unaffected arm acts as an internal and subject-specific control. Alternatively, this ratio can be linearized and expressed as an L-Dex score, which can be generated by the device. An abnormal L-Dex value is defined as $>$10 L-Dex units (in the absence of a pre-treatment baseline) or a change of $\geq$6.5 (2 standard deviations) from the baseline value. Subsequent intervention with noninvasive measures (including skincare, self-massage, and a 23- to 32-mm compression garment) are

less intensive and less costly than CDP.[12,13] BIS, particularly when performed using newer upright scale-like devices, provides immediate reproducible and objective feedback and can be done by any trained staff members in a few minutes.[14]

Studies have found that BIS is a reliable objective measure for patients with early lymphedema with a score of >7.1, consistent with clinical BCRL.[12] BIS, particularly when performed using newer upright scale-like devices, provides immediate feedback and can be done by any trained staff in a few minutes.[14]

Ridner (2019) compared early detection using TM or BIS over 3 years in a multicenter international randomized control trial. Trigger points defining sBCRL requiring intervention were a BIS change of ≥6.5 L-Dex units and, for the TM group, a volume change in the at-risk arm that was between ≥5 and <10% above presurgical baselines (without a similar change in the non−at-risk arm). The interim analysis found that compared with TM, BIS had a lower rate of trigger (15.8% vs. 28.5%; $P < .001$) and longer times to trigger (9.5 vs. 2.8 months; $P = .002$). BIS also reduced the absolute rates of progression of clinical BCRL requiring CDP by approximately 10% (TM, 14.7%; BIS, 4.9%), which is a clinically meaningful improvement.[15]

As noted earlier, deintensification of axillary management has shifted the landscape from ALND to RNI. A difficult decision for patients with limited nodal disease is whether to treat the SCF or add a posterior axillary boost, which increase the risk of lymphedema over and above an axillary dissection.[16-18] Although it makes intuitive sense that irradiation of more lymphatic basins after axillary surgery will increase the risk of BCRL, prospective data on the risk of BCRL by surgical and radiation treatment are limited.[18-20] Previous cadaveric and indocyanine green (ICG) studies identified the axillary lymphatic pathways of the arm but also a "lateral pathway" that bypasses the axilla.[21] These lymphatic vessels run along the cephalic vein in the outer aspect of the upper arm and pass between the pectoralis major and deltoid muscle, pierce the coracoclavicular fascia, cross the axillary artery, and end in the axillary vein just below the clavicle. That is, this lateral pathway communicates with level III of the axilla in the subclavicular region. An important unanswered question is whether protection of this group of lymph nodes when the risk of cancer in this region is low (by not dissecting or irradiating level III of the axilla or the SCF) can reduce the risk of lymphedema.

A secondary aim of the study, reported here, is to evaluate the influence of potential surgical and radiation risk factors on sBCRL, which can guide the treatment team about advising screening and at what frequency. For this secondary analysis, the incidence of sBCRL by SNB or ALND with or without radiation (limited RNI: level I or II only or extensive RNI: level III/SCF with or without limited RNI) was examined for 484 patients who had surgery to the axilla. To our knowledge, this randomized prospective study is the first to document, using BIS or TM, the risk of sBCRL by the extent of specific radiation fields.

The key questions were:

1. What proportion of patients develop sBCRL based on either BIS or TM-derived volume change by treatment extent to the regional nodes?
2. Was more treatment to the axilla associated with earlier onset sBCRL?
3. Does extensive RNI increase the risk of sBCRL?

Methods and Materials

Participants

This randomized study compares posttreatment surveillance with volume measurements derived from TM with BIS. Postsurgical inclusion criteria included stage I-III invasive breast cancer or ductal carcinoma in situ with at least one the following: mastectomy, axillary treatment (ALND, SNB with greater than 6 nodes), radiation therapy, or taxane-based chemotherapy.[22] Most patients who underwent SNB with less than 6 nodes dissected also had radiation and were eligible on that basis. Approval for the study was obtained from the Vanderbilt University Institutional Review Board and the Vanderbilt Ingram Cancer Center Scientific Review Committee before participant enrollment. Study activities were conducted under the guidelines outlined in the Declaration of Helsinki. The local ethical committees approved the trial of all the participating centers. The trial is registered with ClinicalTrials.gov, number NCT02167659.

Intervention and control conditions

The trial design is a 2-group (BIS versus TM) stratified randomized clinical trial being conducted in 9 hospitals in the USA and 4 in Australia.[22] After giving consent, patients underwent baseline presurgical measurements with BIS (L-Dex U400, Impedimed) and volume (circumference) measurements (Gulick II tape) and randomized after surgery.

Both the TM and BIS arms underwent planned postoperative assessments at 3, 6, 12, 18, 24, and 36 months (optional visits at 15 and 21 months) and at the end of any intervention. Patients with a BIS change from baseline of ≥6.5 L-Dex units or TM volume change ≥5% and <10% above presurgical baselines "triggered" for sBCRL. BIS ≥ 7.0 and TM volume change ≥10% was considered clinical BCRL. Once triggered, patients underwent 4 weeks of wearing a class 2 (23-32 mm Hg) compression sleeve and gauntlet therapy for 12 hours per day.

Measurement techniques

Tape measure

Circumferential measurements were made by research assistants who underwent training (with at least annual audit and fidelity visits) by the senior author and chief investigator (S.R.) using a nonflexible Gulick II TM with spring-loaded tension to facilitate equal tension being applied around the limb. Measurements for the unaffected and then the at-risk limb were made in 10-cm increments from the ulna styloid process to 40 or 50 cm above the wrist, depending on arm length. Each location was measured twice, and the average of each measure was used to calculate volume using a truncated cone formula.[15]

Bioimpedance spectroscopy

For BIS measurements, participants were placed in the supine position, and skin preparation and electrode placement followed the manufacturer's instructions (Impedimed U400). Detailed written and visual instructions were provided to the research assistants. Electrodes were disposable and used only once.

Statistical methods

Enrollment commenced in June 2014. An interim analysis of lymphedema progression has been published with detailed methods.[15] The study completed accrual in March 2018, and a final report is expected after March 2021, when all patients have been at risk for 3 years. Study nominal and ordinal data values were summarized using frequency distributions based on 2 main groups—patients who had an SNB only (n = 380) or patients who had an ALND with or without SNB (n = 104). Fourteen patients (usually ductal carcinoma in situ) who met the criteria for the primary study had no axillary surgery and were excluded from this analysis of axillary treatment. For this analysis, radiation location was categorized as breast/chest-wall, SCF, ICF, and IMC and by axillary level (level I-III) as defined by the Radiation Therapy Oncology Group. Patients who had "high tangents" were categorized as having levels 1 to 2 radiation. Individual plans were not routinely reviewed, and patients who were reported by the treating radiation oncologist to have treatment to the whole breast only were recorded as having no RT to the axilla. Radiation fields were obtained by the research staff members having access to the electronic record and included review of correspondence, treatment summaries and, in cases of ambiguity, the radiation oncologist was contacted directly to clarify which regional nodes were included in the treatment plan. The ICF was rarely specified but always associated with SCF RT; therefore, it was not analyzed. In this series, only 6 patients received radiation to the IMC, and all these patients had SCF radiation. There was no statistical difference in the incidence of BCRL between patients who did or did not receive IMC radiation, and these patients were not evaluated further.

We calculated the incidence of "triggering" representing sBCRL by BIS or TM for all 498 patients and separately for SNB alone or an ALND for 3 radiation subgroups:

1. No radiation to the axilla or SCF
2. Limited RNI: radiation to level I and/or II axilla
3. Extensive RNI: radiation to level III or SCF with or without limited RNI

Chi-squared tests of independence (±Yates correction) compared baseline treatment characteristics of the 2 study groups. Depending on the scenario, medians were compared using nonparametric 2-sample tests to delineate samples. For follow-up time, the median was calculated for patients who had not triggered and measured from the date of surgery. Analyses were conducted with SAS (version 9.4; SAS Institute, Cary, NC) and Microsoft Excel. The cumulative incidence of sBCRL was calculated with the Kaplan-Meier method[23] and compared using the log-rank test.[24] A Cox multivariate analysis was deferred until the final primary analysis to increase its statistical validity. A consort diagram is shown in the Appendix E1.

Results

This analysis consisted of 498 women with newly diagnosed breast cancer, with a median follow-up of 20.5 months (interquartile range = 16-25). Patient demographics are summarized in Table 1 by axillary surgery; the median age was 58.8 years (interquartile range, 51.0-67.0 years), with 76% of patients (n = 389) being white. Clinical characteristics are summarized in Table 2. Most patients had stage I disease (57.0%), and breast conservation was undertaken in 78.9% of patients. As expected, patients who underwent an axillary dissection had higher UICC stage ($P < .001$), higher median number of positive nodes ($P < .001$), and were more likely to undergo mastectomy, standard fractionation radiation therapy ($P < .01$), and chemotherapy ($P < .0001$).

The crude incidence of triggering for potential sBCRL detected by either screening technique was 30.8% for patients who underwent ALND versus 19.2% for patients undergoing SNB ($P = .01$). The corresponding rates of triggers for BIS were 24.0% after ALND and 13.5% after SNB ($P = .07$); for TM, the incidence was 37.0% and 25.6%, respectively ($P = .10$). The 12-month actuarial incidence of triggers was 7.3% for BIS compared with 19.9% for TM ($P < .0001$). The corresponding 24-month actuarial incidence for BIS was 16.7% compared with 30.3% for TM ($P = .0001$; Fig. 1). The median time for triggering by BIS was longer than for TM for patients having an SNB (13.1 vs 7.5 months; $P = .0025$) or an ALND (12.7 vs 9.3 months; $P = .04$). The incidence of triggers by the extent of RNI, regardless of the screening technique, is shown in Table 3. The incidence of triggers was 30.8% for patients who underwent an axillary

Table 1 Patient demographics

Characteristic	Total		SNB		ALND		*P* value
	no.	%	no.	%	no.	%	
No. of patients	498		380		104		
Age, years	498		380		104		
Median [IQR]	58.8		59.4		55.3		.0005
IQR	51-67		51-67		47-63		
<34	7	1.4	4	1.1	3	2.9	
35-50	107	21.5	69	18.2	32	30.8	
>50-69	318	63.9	253	66.6	59	56.7	
70-79	58	11.6	47	12.4	9	8.7	
≥80	6	1.2	6	1.6	0	0.0	
Not known	2	0.4	1	0.3	1	1.0	
Menstrual status	498		380		104		.5300
Premenopausal	74	14.9	53	13.9	17	16.3	
Postmenopausal	424	85.1	327	86.1	87	83.7	
Years of education	495		378		104		.6808
Median	14.6		14.6		14.5		
IQR	12-16		12-16		12-16		
Race	498		379		104		.78
Do not care to respond	6	1.2	4	1.1	2	1.9	
Multiracial or other*	36	7.2	27	7.1	9	8.7	
Asian	40	8.0	33	8.7	6	5.8	
Black or African American	36	7.2	25	6.6	8	7.7	
White	380	76.3	290	76.5	79	76.0	
Marital status	495		378		93		.190
Single	61	12.3	42	11.1	4	4.3	
Single, living with partner	16	3.2	13	3.4	3	3.2	
Married	359	72.5	273	72.2	77	82.8	
Widowed	32	6.5	25	6.6	7	7.5	
Separated	17	3.4	16	4.2	1	1.1	
Other	10	2.0	9	2.4	1	1.1	
Employment	495		377		104		.21
Employed full-time	205	41.4	151	40.1	47	45.2	
Employed part-time	59	11.9	40	10.6	18	17.3	
Homemaker	43	8.7	34	9.0	9	8.7	
Retired	151	30.5	125	33.2	21	20.2	
Unemployed	7	1.4	5	1.3	2	1.9	
On Disability	5	1.0	4	1.1	1	1.0	
Other	25	5.1	18	4.8	6	5.8	
Residence	495		378		103		.96
City/urban	119	24.0	90	23.8	26	25.2	
Country/rural/small town	113	22.8	86	22.8	23	22.3	
Suburb	263	53.1	202	53.4	54	52.4	
Insurance	498		380		104		.56
Any government insurance	315	63.3	248	65.3	61	58.7	
Any non-government insurance	384	77.1	295	77.6	76	73.1	
No Insurance	2	0.4	1	0.3	1	1.0	

Abbreviations: ALND = Axillary lymph node dissection +/- SNB; IQR = interquartile range; SNB = sentinel node biopsy.
* Including American Indian, Alaskan Native, Native Hawaiian, Pacific Islander, Aboriginal, and Torres Strait Islander.

dissection and 19.2% for patients undergoing an SNB (P = .01). The likelihood of BCRL increased with the extent of surgery and radiation.

The crude incidence of triggers by the extent of RNI and screening method is shown in Table 4. The likelihood of triggers increased with the extent of surgery and radiation. Screening by BIS consistently had lower rates of potential sBCRL than for TM. BIS triggered 12.9% of patients undergoing SNB and 25.0% undergoing ALND (P = .18) without RNI. Only 1 of 22 patients (4.5%) who had an SNB and limited RNI developed sBCRL. Extensive RNI increased triggering with BIS compared with no RNI after

Table 2 Clinical and pathologic characteristics

Characteristic	Total		SNB		ALND		*P* value
	no.	%	no.	%	no.	%	
No. of patients	498		380		104		
Side of cancer	494		376		104		.72
Left	236	47.8	181	48.1	48	46.2	
Right	258	52.2	195	51.9	56	53.8	
UICC Stage	498		380		104		<.001
0 (DCIS)	22	4.4	13	3.4	0	0.0	
I	284	57.0	257	67.6	23	22.1	
II	160	32.1	109	28.7	50	48.1	
III	32	6.4	1	0.3	31	29.9	
Nodes dissected (median)	3		2		14		<.0001
Range	0-45		1-11		2-45		
Nodes Positive (median)	0		0		2		<.0001
Range	0-24		0-3		0-24		
Treatment to the breast	498		380		104		
WLE alone	8	1.6	5	1.3	3	2.9	.27
WLE + whole breast RT	378	75.9	310	81.6	54	51.4	<.001
WLE + partial breast RT	7	1.4	6	1.6	1	1.0	.63
Mastectomy	72	14.5	55	14.5	17	16.2	.66
Mastectomy + RT	33	6.6	4	1.1	29	27.6	<.001
Reconstruction	105		59		46		
No	46	43.8	24	40.7	23	48.9	.34
Yes, immediate implant	47	44.8	28	47.5	18	38.3	.39
Yes, immediate flap*	7	6.7	4	6.8	3	6.4	.95
Yes, delayed	5	4.8	3	5.1	2	4.3	.86
Radiation therapy	498		380		104		
Yes	418	83.9	320	84.2	84	80.8	.402
No	80	16.1	60	15.8	20	19.2	.402
Standard fractionation	226	54.1	149	46.6	73	86.9	<.001
Hypofractionation	176	42.1	161	50.3	7	8.3	<.001
Unknown fractionation	9	1.9	4	1.3	3	3.6	.356
Partial breast irradiation	7	1.7	6	1.9	1	1.2	1.00
Boost after whole breast radiation							
No	85	22.5	74	23.9	7	13.0	
Yes	293	77.5	236	76.1	47	87.0	.08
Chemotherapy	498		380		104		
No	291	58.4	249	65.5	28	26.9	<.00001
Yes	207	41.6	131	34.5	76	73.1	
Neoadjuvant chemotherapy	20	9.7	7	5.3	13	17.1	
Adjuvant chemotherapy	163	78.7	116	88.5	47	61.8	
Both	24	11.6	8	6.1	16	21.1	
Chemotherapy type	207		131		76		
Any taxane	186	37.3	113	29.7	73	70.2	<.00001
Other (nontaxane)	21	4.2	18	4.7	3	2.9	
Hormone therapy	388	77.9	293	77.1	85	81.7	.31

Abbreviations: ALND = Axillary lymph node dissection +/- SNB; DCIS = ductal carcinoma in situ; SNB = sentinel node biopsy; UICC = Union for International Cancer Control; WLE = wide local excision.

* Patients who had combined flap and implant procedure were scored as flap.

SNB (33.3% vs 12.9%; $P = .03$) or ALND (30.8% vs 25.0%; $P = .69$). Triggering by TM was greater than 25% for most subgroups, and it did not discriminate the risk of sBCRL by receipt and type of RNI as well as BIS. In fact, for patients screened with TM, 6 of the 6 treatment groups had rates of sBCRL greater than 15% (red or amber cells in Table 3) compared with 3 of 6 groups screened by BIS. The difference was particularly marked for patients undergoing an SNB and no RNI where the incidence of sBCRL by BIS was 12.9% versus 26.0% for TM ($P = .003$; Table 4).The 24-month actuarial incidence of triggering potential sBCRL by BIS was 13.1% (SNB only), 25.0% (ALND only), 4.5% (SNB + limited RNI), 0% ALND + Limited RNI, 28.0% (SNB + Extensive RNI) and 42.9% (ALND + Extensive

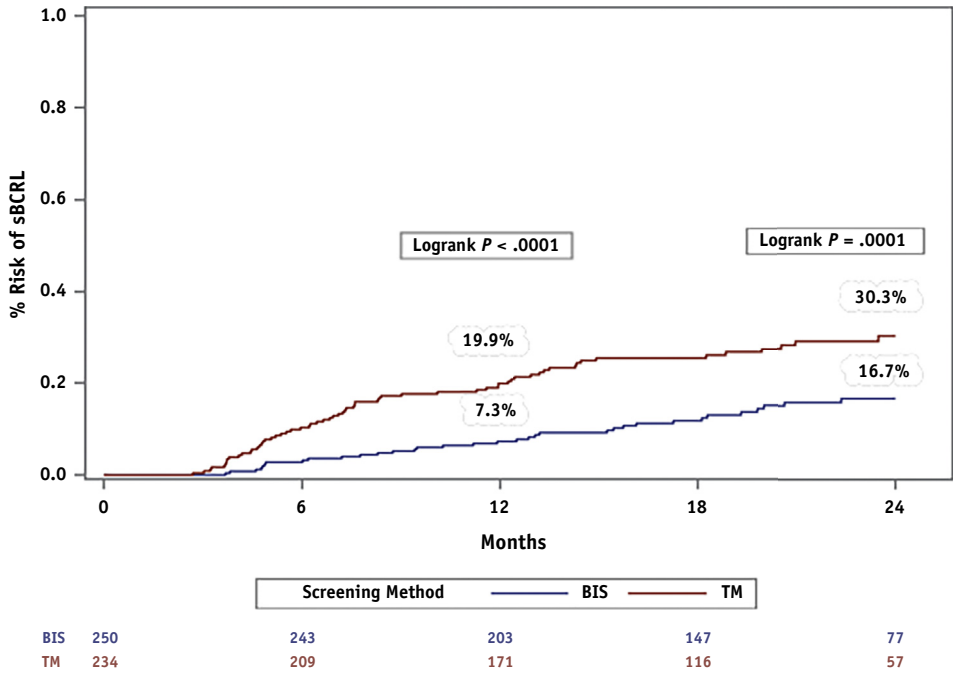

Fig. 1. The cumulative risk of triggering for sBCRL by screening method. Patients with a BIS ≥ 6.5 L-Dex units or TM volume change ≥5% and <10% above presurgical baselines "triggered" for sBCRL. *Abbreviations:* BIS = bioimpedance spectroscopy; sBCRL = subclinical breast cancer-related lymphedema; TM = tape measure.

RNI) (SNB only vs SNB + extensive RNI; $P = .015$; all other comparisons not significant).

Discussion

In this randomized controlled trial screening for sBCRL, we found that the lower triggering rates with BIS and its better risk discrimination by receipt and extent of RNI compared with TM support its use for posttreatment surveillance. The risk of triggering increased with more extensive axillary treatment. In particular, patients having ALND or SNB with extensive RNI require close surveillance for BCRL. Longer follow-up is necessary to determine whether triggering thresholds and rates defining sBCRL will predict progression to clinical lymphedema. The ongoing use of SCF irradiation for all node-positive patients in this era of "de-escalation" needs to be balanced with the increased risk of BCRL.

Although modern studies such as the MA20 and the EORTC 22922/10925 that mainly included patients with 1 to 3 positive nodes, investigated the merit of RNI compared with breast/chest-wall radiation, the relative contribution of the SCF irradiation to the reduction in distant metastases over and above RT to the IMC or axilla is unknown. It is likely, however, that the effect of radiation is more significant on first-echelon nodes like the axilla or IMC compared with the SCF. In one large study of breast lymphatic mapping, the drainage to the SCF was 0.5%, IMC was 21.8%, and axilla was 95.3%, suggesting that the

Table 3 Probability of triggering for lymphedema by extent of radiation irrespective of surgical extent to the axilla or type of monitoring (TM or BIS)

Radiation extent	No SCF	SCF	SCF + IMC	IMC	Total	Trigger*	%
No axilla or SCF	351	—	—	0	351	71	20.2
L1 or L2	52	—	—	0	52	6	25.0
L3 or SCF (no L1 or L2)	—	56	1	0	57	20	33.3
L3 or SCF +/− L1 or L2	3	66	6	0	75	27	36.0
L3 or SCF + L1 or L2	3	13	5	—	21	9	42.9
Any Level 3, no SCF	3	—	—	0	3	2	66.7

Abbreviations: BIS = bioimpedance spectroscopy; IMC = internal mammary chain irradiation; L = level; SCF = supraclavicular fossa radiation; TM = tape measure.

* Patients with a BIS ≥ 6.5 L-Dex units or TM volume change ≥5% and <10% above presurgical baselines "triggered" for sBCRL.

Table 4 Probability of triggering for sBCRL by extent of radiation by axillary surgery and screening by TM or BIS

Screening	Group	SNB	Triggered (n)	%	Group	ALND	Triggered(n)	%	*P* value
Bioimpedance spectroscopy*									
No RNI	A	163	21	12.9%	C	16	4	25.0%	.18
Limited RNI†		22	1	4.5%		8	0	0.0%	
Extensive RNI‡	B	15	5	33.3%	D	26	8	30.8%	.87
A vs B									.03
C vs D									.69
Tape measure*									
No RNI	E	150	39	26.0%	G	25	6	24.0%	.83
Limited RNI		18	3	16.7%		5	2	40.0%	.26
Extensive RNI	F	12	4	33.3%	H	24	12	50.0%	.55
E vs F									.80
G vs H									.06
A vs E									.003
C vs G									.94

Abbreviations: ALND = axillary lymph node dissection; BIS = bioimpedance spectroscopy; RNI = regional node irradiation; sBCRL = subclinical breast cancer-related lymphedema; SNB = Sentinel node biopsy; TM = tape measure.

<15% shown in green; 16-30% amber; >30% red.

* Patients with a BIS ≥ 6.5 L-Dex units or TM volume change ≥5% and <10% above presurgical baselines "triggered" for sBCRL.

† Radiation to axilla level I and/or II.

‡ Radiation to level III or supraclavicular fossa with or without limited RNI.

benefit of radiation to this region is low when the tumor burden in the axilla is low.[25]

Axillary dissection is classified as levels I, II, or III with nodes defined on the basis of their relationship to the pectoralis minor muscle.[26] Although not skeletonizing the axillary vein may preserve lymphatics, this does not explain why some SNB patients develop lymphedema or why rates might not vary by the extent of ALND.[27,28] Recent ICG studies have found repair and restoration of the lymphatics through the axilla after ALND so that the majority of patients do not develop BCRL. In addition, as BCRL progresses, a higher proportion of patients develop aberrant lymphatic flow through the lateral cephalic bypass pathway.[29]

Our study is similar to the MGH study that prospectively measured the incidence of BCRL (relative increase in arm volume of 10%) by perometry for patients attending a radiation oncology department. RNI was defined as RT to the SCF or upper axilla using a posterior axillary boost. Five-year incidence of BCRL was 9% for SNB, 12% for SNB and RNI, 25% for ALND, and 31% for ALND and RNI.[1] In an earlier publication, the same group found no difference in rates of BCRL between SCF (21.9%) or SCF/axilla radiation using a posterior axillary boost (21.1%).[1,30] Unfortunately, perometry is expensive and not readily suitable for everyday clinical practice. Our study differed as it aimed to detect sBCRL with lower thresholds than clinical BCRL, as BIS is a measure of extracellular fluid and not arm volume and are not directly comparable.[31,32]

In a recent UK study, BIS was compared with perometry for patients treated with ALND. Of note, 83% received postoperative radiation (84% in our study), and 47% had a mastectomy (21% in our study). Twenty-four−month data were presented using various previously published definitions of lymphedema, although less than half of the patients were followed at that time. The gold standard for clinical lymphedema was self-defined as a relative arm volume increase (RAVI) >10% of the affected compared with the unaffected arm measured by perometry and found in 22.4% of patients. A BIS ≥ 7.5 or ≥10 was measured in 57.6% and 45.2% of patient, respectively. The authors, in their introduction, noted a RAVI ≥ 5% as more suitable for early intervention, where 51.4% met this criterion that closely correlated with BIS and symptoms. Early intervention is best implemented when there is sBCRL before adipose differentiation, and subsequent fibrosis occurs and a RAVI > 10% is too late in the disease development for intervention to make a meaningful difference.[11]

It is difficult to compare the 2 series. For example, for patients who received only axillary dissection in our study, without radiation, the triggering rate detected by TM was 25% and 24% for BIS, almost half the rate in the UK study. This triggering discrepancy might reflect our use of dedicated staff members under strict protocol conditions with regular audit and better follow-up in our study.

Although other retrospective studies of BCRL after SCF radiation have been reported, interpretation is difficult because of treatment, lymphedema definition, and measurement variations. In contrast to our study and the MGH study, the AMAROS trial defined clinically significant BCRL as a ≥10% increase in arm circumference (15 cm above or below the medial epicondyle) as measured by study clinicians. The 5-year incidence of BCRL was double for patients undergoing ALND compared with RNI (13% versus 6%; $P = .0009$). In this study, only the medial SCF was treated with potential underdosing of the SCF fossa and possibly the cephalic lateral bypass pathway, perhaps explaining some of the differences with our study.[33] The

AMAROS study also differed from a pooled analysis, where the incidence of BCRL for 4379 patients who received breast or chest-wall RT was 7.4% but doubled to 15.5% for 1882 patients in whom the SCF was treated.[34] Using BIS, the incidence of potential sBCRL was 12.9% for patients having SNB, 25.0% after an ALND (without any nodal radiation), but >25% when extensive RNI including the SCF or level III of the axilla was added to surgery (Table 4). These data suggest that SCF radiation over and above axillary surgery is an important risk factor for lymphedema, possibly by affecting the "lateral (bypass) pathway" of lymphatics.[1] This pathway is also likely to be affected by posterior axillary boost or techniques that encompass the full SCF, ICF, and axillary nodes.[18,35] Triggering by TM was >25% for most subgroups and was inferior to BIS in discriminating the risk of sBCRL by receipt and type of RNI. Longer follow-up and analysis of the full data set will provide a better understanding of the natural history of sBCRL and progression to clinical lymphedema.

This study shows that triggering for potential sBCRL is less frequent with BIS compared with TM, and it suggests that TM might be associated with a higher rate of false-positive results. Initially, because of recent changes in subclinical threshold criteria, there was concern that BIS would have more false-positive results, which would increase patient distress compared with TM.[36] If the lower rate of triggers and the lower rates of CDP persist for the BIS arm, this condition suggests that BIS may is more specific than TM measurements, reducing rather than increasing the rate of false positives. The interim analysis found that compared with TM, BIS had a lower rate of trigger (15.8% vs 28.5%; $P < .001$) and longer times to trigger (9.5 vs 2.8 months; $P = .002$). BIS also reduced the absolute rates of progression of BCRL requiring CDP by approximately 10%, (TM, 14.7%; BIS, 4.9%) but longer follow-up is required. It must be stressed that not all patients with sBCRL progress to clinical lymphedema. The rates of progression in the primary analysis suggest lower rates of clinical BCRL, consistent with previous research showing that early detection and intervention can reduce progression to more advanced fatty or fibrotic stages of lymphedema.

Large randomized studies comparing ALND to axillary radiation or observation for clinically node-negative patients found no survival difference.[37,38] However, the results were questioned, and concern raised that patients exist where ineffective locoregional therapy might compromise survival rates.[39] This debate regarding where to set the threshold to maximize locoregional tumor control versus minimizing quality-of-life treatment effects continues today, often with limited data. The Oxford meta-analysis explored the issue of less surgery versus more radiation to the axilla in its metanalysis and found that patients who had axillary sampling (n = 2541) had higher locoregional recurrence rates and inferior 20-year survival compared with patients who had an axillary dissection or axillary sample and radiation therapy. Twenty-year breast cancer mortality was 68.2% for mastectomy and axillary sample versus 55.6% for the addition of radiation ($P < .00001$) (Ref. [2]; Webfigure 27). For patients who had an adequate axillary dissection, were node-positive, and had systemic therapy, the reduction in breast cancer mortality after radiation to the chest wall and regional nodes (including the internal mammary and SCF nodes) was 8% for patients with 4 or more positive axillary nodes (Ref. [2]; Webfigure 19) and, almost identical at 7.9% for patients with 1 to 3 positive nodes (Ref. [2]; Webfigure 27). One drawback of the meta-analysis is that treatment techniques today vary both in terms of breast surgery, reconstruction techniques, less utilization of an ALND, greater use of taxanes, anti-HER2 agents, and radiation to the regional nodes after a positive SNB.[8]

The question of the extent of radiation treatment by surgical treatment and nodal status has not been well studied. For a patient with 4 or more positive nodes, the risk of level III axillary involvement is as high as 39%; therefore, it is logical to treat the SCF. What is less clear is the extent of RNI for patients with 1 to 3 positive nodes where level III involvement is approximately 2%[40] with rates of SCF recurrence of <2%.[17,41] The HERA trial explored the effects of postmastectomy radiation (PMRT) for HER2-positive patients, with 1 to 3 positive nodes. Of the 517 patients, 48% received PMRT (of whom, 48% received SCF irradiation). The locoregional recurrence (LRR) rate was 3% for PMRT versus 10% for no PMRT ($P = .004$) with a nonsignificant improved overall survival after PMRT ($P = .06$).[42] Similarly, of the 684 lower-risk 1 to 3 node-positive patients in the BIG-02-98 trial, 49% received PMRT, of whom 74% had SCF irradiation. LRR was 2.5% for PMRT and 6.5% for the no-PMRT ($P = .005$).[43] These modern studies show that LRR is lower than historical studies and that there is a benefit to PMRT even when a proportion of patients (26%-52% in the postmastectomy RT arms) do not receive SCF irradiation. None of these studies reported SCF recurrence rates, which were often considered metastatic disease. Using radiation to level I-II of the axilla for patients with limited disease after an SNB could be a reasonable option for selected patients at higher risk of lymphedema.[44,45]

This study allows a unique opportunity to analyze the incidence of sBCRL and, with more follow-up, its potential progression to clinical lymphedema by the extent of surgery and radiation therapy. Limitations of this study include the short follow-up period of 20.5 months and the low rates of clinical BCRL requiring CDP.[15] However, in a previous large series of surgery and radiation to the axilla, 80% of clinical BCRL occurred within 24 months.[46] Although other studies using perometry have found clinical BCRL occurring later in some subgroups receiving radiation, evidence suggests that sBCRL can be detected 8 to 12 months earlier, which represents an essential window of opportunity to intervene with a compression garment and therapy to assist lymphatic flow.[47] It could be argued that some

patients might not progress to clinical BCRL and that intervention can cause unnecessary distress. In our main study, we continue to collect data on quality of life using validated instruments FACT-B plus 4 and Lymphedema Symptom Intensity and Distress Survey-Arm Version. However, the fact that BIS is associated with a lower 24-month actuarial incidence of sBCRL than TM (16.7% versus 30.3%; $P = .0001$) means that it is an objective measure of extracellular fluid that is less influenced by fat or muscle changes that affect girth measures.

Some subgroups were small, such as patients having limited RNI. Patients who triggered were prescribed a compression garment for 4 weeks, and lower rates of BCRL are anticipated than in historical nonrandomized studies.[15,22] In a study of 196 patients who underwent ALND, 21 of 35 patients with ICG changes consistent with lymphatic dysfunction did not have any appreciable volume changes. A compression garment reversed the early ICG changes of lymphedema, such as dermal backflow, in approximately one third of patients.[48] Although one small retrospective study has compared BIS to ICG and found a false-negative rate of 36%; this was not surprising as most patients had advanced stage 2 or 3 BCRL associated with less tissue fluid and increased fat deposition and cannot be compared with our study screening patients for stage 0, sBCRL.[49] Our trial now has more than 1000 patients, and with longer follow-up, an updated analysis of sBCRL by treatment extent and progression to clinical lymphedema will be undertaken. We have also not evaluated competing risk factors such as body mass index, the number of removed nodes, or the use of taxane chemotherapy, but we plan to do so with longer follow-up. Some of these factors, including the time-course for the development of BCRL, have been explored elsewhere. For example, Vicini et al[50] in a prospective nonrandomized study using BIS found that the median time for 25% of patients to develop at least an L-Dex score >7.0 was 4.3 months for ALND/RNI/taxane patients versus 30.8 months for SNB-alone patients.[50] This critical issue of time to the development of lymphedema was also explored by Taghian et al[1] using perometry; they also found that the lymphedema risk peaked earlier for patients who had an ALND.[1]

Conclusion

The lower triggering rates with BIS and its better discrimination of the risk of sBCRL by receipt and type of RNI compared with TM support its use for posttreatment surveillance to detect sBCRL and to initiate early intervention. The risk of sBCRL increased with more extensive axillary treatment. Patients having ALND or extensive RNI require close surveillance for BCRL. Consideration could be given to avoiding the SCF/Level III of the axilla for selected patients with other risk factors for BCRL. Longer follow-up is required to determine rates of progression to clinical lymphedema.

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