Review Article

Regional nodal irradiation in the setting of sentinel node biopsy

Crystal Seldon[1], Anna Lee[2]^

[1]Department of Radiation Oncology, Miller School of Medicine, Sylvester Comprehensive Cancer Center, University of Miami, Miami, FL, USA; [2]Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Contributions: (I) Conception and design: A Lee; (II) Administrative support: A Lee; (III) Provision of study materials or patients: C Seldon; (IV) Collection and assembly of data: C Seldon; (V) Data analysis and interpretation: Both authors; (VI) Manuscript writing: Both authors; (VII) Final approval of manuscript: Both authors.

Correspondence to: Anna Lee, MD, MPH. Department of Radiation Oncology, University of Texas MD Anderson Cancer Center, 1840 Old Spanish Trail, Houston, TX 77054, USA. Email: alee13@mdanderson.org.

Abstract: The need for axillary lymph node dissection (ALND) in patients with invasive breast cancer (IBC) has been a topic of great debate in the last decade. The role of axillary management in patients with sentinel lymph node biopsy (SLNB) negative or micrometastatic disease is well established after multiple trials demonstrated no survival benefit with the addition of ALND (NSABP B32, IBCSG 23-01, AATRM048); yet, there remains controversy in the management of SLNB positive disease. ALND has traditionally been the standard of care following positive SLNB, however, results from recent studies have identified that further surgical exploration of the axilla may be overtreatment in these patients. In order to de-escalate treatment, non-surgical options such as regional nodal irradiation (RNI) and neoadjuvant chemotherapy (NAC) have been increasingly explored. Trials evaluating the role of RNI following positive SLNB have suggested that RNI is non-inferior to ALND and provides superior outcomes with an improved toxicity profile (AMAROS, MA.20, EORTC 22922). NAC has been explored in the treatment paradigm in patients with locally advanced disease, however, the role of SLNB and RNI in this setting remains unequivocal. This review aims to provide an update on the role of RNI following SLNB in IBC using an evidence-based approach.

Keywords: Regional nodal radiation treatment (regional nodal RT); sentinel lymph node biopsy (SLNB); breast cancer

Received: 12 October 2020; Accepted: 05 March 2021; Published: 30 March 2022.
doi: 10.21037/abs-20-125
View this article at: http://dx.doi.org/10.21037/abs-20-125

Introduction

The management of the axilla in breast cancer has evolved considerably over the past several decades as new evidence emerges regarding the role and efficacy of systemic therapy as well as reduction in the extent of surgery performed (1-3). While axillary lymph node dissection (ALND) remains the standard of care for clinically node-positive disease, sentinel lymph node biopsy (SLNB) is now the gold standard for early-stage clinically node-negative disease as it allows axillary pathologic assessment with decreased morbidity (4,5). The pathological assessment of sentinel lymph nodes have evolved over time as previously bisected nodes are now microsectioned and further evaluated with immunohistochemistry (6). In patients with positive sentinel nodes, subsequent clinical decision-making involves how to achieve local control including the role of radiation therapy

^ ORCID: 0000-0002-9114-1815.

to the area. In patients with negative sentinel nodes, the question arises as to which patients warrant regional nodal irradiation (RNI) given other risk factors. Neoadjuvant chemotherapy (NAC) has been increasingly employed in this population, however, radiation plans based on chemotherapy response and nodal status is of considerable debate. This review will provide an update on the role of RNI using an evidence-based approach.

RNI following positive SLNB

Whole breast irradiation (WBI) following breast-conserving surgery (BCS) for early-stage breast cancer is the standard of care. WBI typically consists of tangent fields, which include level I axillary lymph nodes in the treatment field. In the setting of a positive sentinel lymph node following BCS, patients historically underwent completion ALND, however, there is evidence that SLNB is non-inferior to completion ALND (7-9) and the role of RNI in this setting has been further elucidated with the following studies.

The EORTC 10981-22023 AMAROS trial randomized 4,806 patients with T1–2 clinically node negative (cN0) tumors with a positive SLNB to either ALND or RNI. All patients received breast conserving treatment or mastectomy with or without chest wall irradiation. RNI was delivered to all levels of the axilla and to the supraclavicular fossa with 10% (65/681) receiving radiation to the internal mammary nodes. While underpowered for non-inferiority due to the low number of events, the primary endpoint of locoregional recurrence (LRR) at 5 years was 0.43% (95% CI: 0.00–0.92) in the ALND group and 1.19% (95% CI: 0.31–2.08) in the RNI group. There was also no significant difference in disease-free survival (DFS) (HR: 1.18; 95% CI: 0.93–1.51; P=0.18) or overall survival (OS) (HR: 1.17; 95% CI: 0.85–1.62; P=0.34) between the two arms. The risk of lymphedema was 11% *vs.* 23% in favor of those who received RNI (P<0.0001) (10). The 10-year update presented at the San Antonio Breast Cancer Symposium (SABCS) confirmed the conclusion that RNI is the preferred treatment to ALND in early breast cancer patients (11).

The ACOSOG Z0011 was a surgical phase III study of 891 patients with clinical T1–2N0 breast cancer who had 1–2 positive lymph nodes on SLNB. All underwent BCS followed by adjuvant WBI and were randomized to SLNB with ALND versus SLNB alone. At 10 years, there was no difference in LRR (HR: 0.87; one-sided 95% CI: 0.62–1.22; noninferiority P=0.41) or OS (HR: 0.85; one-sided 95% CI: 0.00–1.16; noninferiority P=0.02) between the two groups despite over a quarter of patients in the ALND group having additional positive nonsentinel nodes (8). A subanalysis of radiation fields by Jagsi *et al.* found radiation to the lower axilla may have been compensated with the radiation field design, however, the distribution in tangent fields were not significantly different between the two arms as over half in each arm received high tangents (12).

These two studies reveal that nodal irradiation to the axilla can replace ALND in early-stage patients with macrometastases revealed on SLNB. Axillary recurrence rates remain low with RNI with comparable DFS and OS while minimizing lymphedema. To reassess the Z0011 results, the SENOMAC trial is underway comparing ALND versus no ALND in cN0 patients with up to two nodes on SLNB that are positive for macrometastatic disease. The inclusion criteria was expanded to this with T3 disease and those treated with mastectomy (NCT02240472). Furthermore, they will require electronic reporting of regional nodal volumes. The SERC trial is also accruing in France, which compares ALND versus no ALND in patients with cN0 breast cancer with positive SLNB following lumpectomy (NCT01717131). In this study, those with macrometastatic lymph node disease will receive nodal irradiation to the supraclavicular nodes and/or level III axilla while treatment to the internal mammary chain will be up to the treating institution (*Table 1*).

Studies addressing regional radiotherapy have been able to show that higher-risk patients benefit from RNI. The National Cancer Institute of Canada MA.20 trial randomized 1,832 post-lumpectomy patients with 1–3 positive lymph nodes to either WBI or WBI and RNI, which included axillary, supraclavicular and IMN nodal regions. SLNB positive patients underwent ALND to levels I and II. There was a significant improvement with RNI in 10-year isolated locoregional DFS (HR: 0.59; 95% CI: 0.39–0.88; P=0.009), DFS (HR: 0.76; 95% CI: 0.61–0.94; P=0.01) and distant DFS (HR: 0.76; 95% CI: 0.60–0.97; P=0.03) but not in OS (HR: 0.91; 95% CI: 0.72–1.13; P=0.38) (13). This may be due to several reasons; namely, effective systemic therapy agents utilized contemporaneously were not widely administered during the study period between 2000 and 2007. Furthermore, the median number of axillary nodes examined in the study was 12, thus the benefit seen with RNI may be due to the limited axillary dissection.

The EORTC 22922 trial included over 4,000 patients with stage I–III invasive breast cancer (IBC). All underwent

Table 1 Ongoing trials

Trial name	Start year	Target accrual	Patient population	Comparison	Primary endpoint	Other endpoints	Expected closing date
SENOMAC (ClinicalTrials.gov NCT02240472)	2015	3,500	cT1–3N0 with 1–2 nodes with macrometastatic disease on SLNB	ARM 1: ALND; ARM 2: no ALND	Breast cancer specific survival	DFS, axillary recurrence rate, OS	2021
SERC (ClinicalTrials.gov NCT01717131)	2012	3,000	cT1–2N0 with SLNB positive disease	ARM 1: ALND; ARM 2: no ALND	DFS	Axillary recurrence rate, OS	2028
BOOG 2013-07 (ClinicalTrials.gov NCT02112682)	2014	52	cT1–2N0; pN1mi or pN1	ARM 1: axillary management (ALND or axillary RT); ARM 2: no axillary management	Regional recurrence rate		2018
POSNOC (ClinicalTrials.gov NCT02401685)	2014	1,900	cN1	ARM 1: no axillary management; ARM 2: axillary management (ALND or Axillary RT)	Axillary recurrence	Arm morbidity, QOL, anxiety, economic evaluation, LR, regional recurrence, DM, time to axillary recurrence, axillary recurrence free survival, DFS, OS, contralateral breast cancer, non-breast malignancy	2023
MA39 (ClinicalTrials.gov NCT03488693)	2018	2,140	pT1–2N1 disease	ARM 1: WBI following BCS or no RT following mastectomy; ARM 2: WBI and RNI (Supraclavicular, non-dissected axilla, internal mammary) following BCS or chest wall RT and RNI following mastectomy	BCRFI	IDFS, breast cancer mortality, OS, LRRFI, DRFI, adverse events, lymphedema, PROs, QOL, cost-effectiveness	2027
Alliance A011202 (ClinicalTrials.gov NCT01901094)	2014	1,660	cT1–3N1M0 breast cancer who have SLNB positive disease after NAC	ARM 1: ALND and RNI; ARM 2: RT to levels I–III of the axilla, supraclavicular and internal mammary nodes	IBC-RFI	OS, ILR-REC, lymphedema, RCB, adequacy of radiation fields, dose delivered to supraclavicular and axillary nodes	2024
NSABP B-51/ RTOG 1304 (clinicaltrials.gov: NCT01872975)	2013	1,636	cT1–3N1M0 breast cancer who have SLNB negative disease after NAC	Group 1A lumpectomy: no RNI with WBI; Group 1B mastectomy: no RNI or chest wall XRT; Group 2A lumpectomy: RNI with WBI; Group 2B mastectomy: RNI and chest wall RT	IBC-RFI	OS, LRRFI, DRFI, DFS-DCIS, time to SPC, cosmetic outcome, adverse events, molecular predictors of recurrence	2023

SLNB, sentinel lymph node biopsy; ALND, axillary lymph node dissection; DFS, disease-free survival; OS, overall survival; RT, radiation treatment; QOL, quality of life; LR, local recurrence; DM, distant metastasis; RNI, regional nodal irradiation; BCS, breast-conserving surgery; WBI, whole breast irradiation; BCRFI, breast cancer recurrence-free interval; IDFS, invasive disease-free interval; LRRFI, locoregional recurrence-free interval; DRFI, distant recurrence-free interval; PROs, patient reported outcomes; NAC, neoadjuvant chemotherapy; IBC-RFI, invasive breast cancer recurrence-free interval; ILR-REC, ipsilateral/local/regional invasive breast cancer recurrence; RCB, residual cancer burden; DFS-DCIS, disease-free survival to ductal carcinoma in situ; SPC, second primary cancer.

either lumpectomy or mastectomy with SLNB. If SLNB was positive, they underwent ALND. Patients were randomized to RNI or no RNI, which included treatment to the supraclavicular and internal mammary nodes (14). Results showed significant improvement in 15-year distant DFS (HR: 0.92; 95% CI: 0.83–1.04; P=0.178) and breast cancer-specific mortality (HR: 0.81; 95% CI: 0.69–0.94; P=0.005) with the addition to RNI but similar to MA.20, there was no improvement in OS (HR IM-MS RT *vs.* control: 0.95; 95% CI: 0.84–1.06; P=0.358) (15).

There are two ongoing studies that will further assess the benefit of axillary management. Namely, the POSNOC British trial is enrolling patients with early-stage breast cancer and 1–2 positive SLN. Following breast conserving treatment or mastectomy, patients are randomized to no further treatment of the axilla versus ALND or RNI with the primary endpoint of axillary recurrence (NCT02401685). Another ongoing study is the Dutch BOOG 2013-07 trial, which is also enrolling patients with early-stage disease (≤T2) following mastectomy with up to three positive nodes on SLNB including micrometastases. Patients are randomized to no further axillary treatment versus completion axillary treatment with either ALND or RNI with a primary endpoint of regional recurrence at 5 years (NCT02112682). Results from these studies will help ascertain which patients we can safely de-escalate axillary treatment in the setting of positive sentinel lymph nodes.

Post mastectomy

Patients with SLNB positive disease who do not require any radiation following mastectomy have the option to undergo ALND, however, the question arises whether these patients can undergo SLNB alone. A retrospective study from Memorial Sloan Kettering examined patients who underwent mastectomy with a positive SLNB and no further treatment. Fifty-four percent of patients had isolated tumor cells, 37% had micrometastatic disease and 9% had macrometastatic N1 disease. Recurrence rates were very low with 4-year LRR at 1.7% and regional recurrence rate at 2.5% (16). These results are interesting and prospective evaluation are needed to explore this treatment option and to ascertain which patients we can omit further treatment.

With respect to RNI in the setting of post-mastectomy radiation therapy (PMRT), randomized studies have shown improved outcomes in patients with T1–2 disease and 1–3 positive lymph nodes (14,17-20), however, the role of PMRT is evolving with improved systemic therapy and more sensitive nodal staging. Further discussion regarding PMRT can be found in the sister article on the topic.

Role of RNI after neoadjuvant systemic treatment

Randomized trials have demonstrated improved disease free-survival after adjuvant RNI (13,14), however there are no randomized trials currently available that clarify the role of RNI following NAC. NAC can lead to downsizing or elimination of clinical gross tumor and nodal volume with the goal to achieve a complete pathologic response (pCR). When defined as ypT0N0, pCR is associated with favorable outcomes (21). For those with clinically node positive disease, NAC has been associated with pCR in axillary lymph nodes in 40–75% of patients (22,23). Higher rates observed in patients with HER2 positive and triple negative disease, high-grade tumors, and lower T stages (24-26). Per NCCN guidelines, pCR in the axilla can allow for less extensive surgical exploration of the area as well as lead to reduced radiation to this site by decreasing radiation fields due to exclusion of the axilla (7).

One topic of much debate is the rate of false negative results (FNRs) of SLNB following NAC, mainly in patients with clinically node positive disease prior to NAC, as well as the feasibility of SLNB following NAC. A few non-prospective studies have examined the feasibility of SLNB after NAC in patients with initial clinical N1 disease and deemed it a viable option given its acceptable FN rates (12), while others have shown unacceptable FN rates (27,28).

The following prospective studies sought to further investigate this topic. The SENTINA study was a multicenter cohort with the primary endpoint of identifying the FNR of SLNB in patients with clinically node positive disease who converted to clinically node negative (ycN0) following NAC. One thousand seven hundred and thirty-seven patients were randomized to four arms. Arm A included patients with clinically node negative disease (cN0) who underwent SLNB before NAC and received no further axillary management due to negative SLNB ($pN0_{sn}$). Arm B included patients with cN0 disease with a positive SLNB before NAC ($pN1_{sn}$) who then underwent a second SLNB and subsequent ALND following NAC. Arms C and D contain patients who were cN1–2 who underwent NAC. For patients who had conversion to clinically node negative disease (ycN0), they subsequently received SLNB and ALND (Arm C). For patients who continued to have clinically node positive disease after NAC (ycN1), ALND

was performed (Arm D). The detection rate (DR) of the 1,022 women who underwent first SLNB before NAC was 99.1% (95% CI: 98.3–99.6) (Arms A and B). The DR did not differ among the detection techniques of using combined radiocolloid and blue dye versus radiocolloid alone. In Arm C, the DR was 80.1% (95% CI: 76.6–83.2) and the overall FNR was 14.2% (95% CI: 9.9–19.4). Of note, the FNR was 16.0% using radiocolloid alone and decreased to 8.6% with the addition of blue dye. Also, the removal of three or more lymph nodes reduced the FNR below 10%. These results suggest that SLNB has worse DRs and FNR following NAC in previously clinically node positive patients who convert to ycN0 compared to patients who undergo SLNB first. The results also suggest that the use of a combined radiotracer may improve the FNR (29).

The ACOSOG Z1071 study enrolled 656 patients with clinical T0–4 N1–2 disease who underwent SLNB then subsequent ALND following NAC. The primary endpoint was to determine the FNR in patients who had clinically node positive disease prior to NAC. The FNR of patients with initial cN1 breast cancer and at least two SLNs identified at the time of surgery was 12.6% (90% Bayesian credibility interval: 9.85–16.05), higher than the prespecified threshold of 10%. Of note, this threshold was acquired from those reported in studies of SLNB following NAC in cN0 participants (2). The FNR decreased when three or more nodes were samples compared to two (9.1% *vs.* 21.2) and was significantly lower with combined radiotracer mapping compared to single agent mapping (10.8% *vs.* 20.3) (30). These findings reflect those observed in the SENTINA trial.

The SN FNAC study was a multicenter trial that investigated the FNR in patients who underwent NAC followed by SLNB then subsequent ALND. This trial was closed early to accrual due to its similarity to ACOSOG Z1071 after reaching 51% of its target size. In an interim analysis, the FNR of SLNB following NAC was 8.4% in all patients (95% CI: 2.4–14.4), under the threshold of 10%. This supports that SLNB following NAC has an acceptable FNR unlike the results from Z1071 (31).

The use of targeted staging procedures are used more frequently in this setting. During neoadjuvant SLNB, positive nodes are marked with a clip or other marker. A targeted SLNB (TLNB) or targeted axillary dissection (TAD) requires the removal of these marked nodes for evaluation of treatment response. The SenTa study was a prospective registry study that aimed to identify the accuracy of TLNB and TAD after neoadjuvant systemic therapy. Five hundred and forty-eight were included in the study. After NST (n=473), the clipped TLN was intraoperatively resected in 77.8% of the patients. (95% CI: 74.0–82.0). TAD had a DR of 86.9% (95% CI: 81.8–91.0) while the DR of SLN and TLN were both 64.8%. FNRs were 7.2% (95% CI: 3.1–13.6) for TLNB followed by and 4.3% (95% CI: 0.5–14.8) for TAD followed by ALND.

Although trial results were variable, several conclusions were made. Although SLNB has a FNR rate of greater than 10%, per the NCCN guidelines, this can be improved by removing more than two SLNs, using dual tracers, and marking biopsied lymph nodes to document their removal (7).

The treatment approach for patients who present with clinically positive lymph nodes and achieve pCR following NAC is a matter of considerable debate. The role of RNI in this patient population is controversial given inconsistent data and lack of clinical trials. The following studies suggest there may be an indication for RNI following NAC (32,33). A meta-analysis of 4,756 patients with early-stage breast cancer from ten randomized trials evaluating outcomes after NAC found that tumors that decreased in size following NAC had higher rates of local recurrence compared to those of the same dimensions who did not receive NAC implying the need for adjuvant radiation therapy (32). In a retrospective series from MD Anderson, 541 patients treated with NAC and adjuvant radiation were compared to 134 patients who did not receive adjuvant radiation. It was found that adjuvant radiation therapy improved local control and survival for patients with four or more positive lymph nodes (33).

Publications based on comparative cohort data give conflicting results on the benefit of RNI following NAC (34-36). In a study utilizing the National Cancer Database, 15,315 patients with cN1 disease who received NAC and surgical resection were grouped into cohorts based on the surgical approach taken and nodal response to NAC. They received adjuvant breast radiation therapy. It was found that post-mastectomy radiation was associated with improved OS for all pathological nodal subgroups, however, there was no difference in OS with the addition of RNI among the patients who received BCS regardless of their nodal pathologic response to NAC (34). A combined analysis of two prospective trials involving NAC (NSABP B-18/B-27) revealed that regardless of surgical procedure, ypN+ disease was the strongest predictor of LRR. The rates of LRRs were low in patients who presented with cN+ disease and achieved ypN0 status with 10-year rates ranging from

0–12.4% (36).

Ongoing clinical trials will clarify the role of axillary management after NAC in cN1 patients. In the Alliance A011202 trial, the role of ALND versus axillary nodal irradiation is addressed. Patients with clinical T1–3, N1 breast cancer treated with NAC and subsequent positive SLNB are randomized to receive ALND or axillary nodal irradiation along with radiotherapy to the whole breast or chest wall. Both groups will receive radiotherapy to the supraclavicular fossa. Patients in the ALND arm will receive radiotherapy to the undissected axilla. The target accrual is 1,660 patients and the primary study endpoint is invasive breast cancer recurrence-free interval (IBC-RFI) (NCT01901094). The NSABP B-51/RTOG 1304 trial is investigating the role of RNI in the same patient population who achieve pCR at ALND following NAC. Patients who present with clinical T1–3 tumors and N1 disease who achieve pCR post NAC are randomized to receive axillary RNI versus no further axillary treatment. Patients who receive RNI will also receive radiation to the whole breast or chest wall. The target accrual is 1,636 patients with the primary study endpoint of IBC-RFI (NCT01872975).

Future directions

There are several upcoming studies that will provide guidance for axillary management after SLNB (*Table 1*). After the publication of Z0011, the question remains on whether it is beneficial to pursue additional axillary management in patients with early-stage breast cancer and positive disease on SLNB. The SENOMAC and SERC trials seek to determine the utility of ALND in this patient population with the primary endpoints being breast cancer specific survival and DFS respectively (NCT02240472, NCT01717131).

The BOOG 2013-07 and POSNOC trials aim to determine the safety of omitting complete axillary management in SLNB positive patients treated with mastectomy, with complete axillary management including ALND or axillary irradiation [NCT02112682, NCT02401685, (37)]. The POSNOC study will include patients treated with lumpectomy as well (NCT02401685).

MA39, a non-inferiority study, will be comparing IBC-RFI in RNI versus no RNI in patients with biomarker low risk disease. Biomarker low risk disease is defined as patients with ER positive, HER2 negative breast cancer with an Oncotype Dx score less than 18 who have macrometastatic disease in 1–3 lymph nodes (NCT03488693).

While RNI following SLNB has been proven to be a safe choice compared to ALND among women with cN1 disease (10), the best approach of surgery and radiation therapy post NAC remains undetermined. Ongoing clinical trials have developed that will clarify the role of axillary management after NAC in cN1 patients. The Alliance A011202 study randomizes cN1 patients to ALND and XRT of the regional nodes and the undissected axilla versus axillary and regional nodal radiation of the regional nodes (eliminate XRT) after achieving ypN0 post-NAC. After SLNB identifies a positive node, patients are randomized to either arm (NCT01901094). If SLNB does not identify persistent nodal disease, these patients can be registered on the NSABP B-51/RTOG 1304 trial where they are randomized to RNI or no RNI (NCT01872975).

There are efforts to further reduce dose to the heart when treating with RNI as cardiac dose has been linked to increased risk of cardiovascular events in women treated for breast cancer (38). Intensity modulated radiation therapy (IMRT) and volumetric modulated arc therapy (VMAT) has shown to be dosimetrically superior to three-dimensional conformal radiation therapy with respect to coverage but can be at the cost of increasing integral dose to normal structures (39). An improvement upon this has been pencil beam scanning with proton therapy, which offers excellent target coverage and lower dose to normal structures (39). Currently, a randomized study of proton versus photon therapy for patients with breast cancer is ongoing (RADCOMP; NCT02603341) with a primary endpoint of reduction in major cardiovascular events.

Conclusions

There has been a movement for axillary de-escalation in the setting of node positive disease to spare patients from associated morbidity. Results from upcoming trials should clarify the role of continued axillary management following SLNB. As we continue to expand our knowledge and systemic therapies, it is important to evaluate each patient and cancer individually. Treatment should be discussed with a multidisciplinary team of physicians to determine the best plan of action. Centers may want to consider performing a gene expression assay or assessing clinicopathologic factors to evaluate the benefit of axillary management as well as the patient's prognosis.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the Guest Editors (William Small Jr and Parul Barry) for the series "Advancements and Opportunities for Breast Irradiation" published in *Annals of Breast Surgery*. The article has undergone external peer review.

Peer Review File: Available at https://abs.amegroups.com/article/view/10.21037/abs-20-125/prf

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://abs.amegroups.com/article/view/10.21037/abs-20-125/coif). The series "Advancements and Opportunities for Breast Irradiation" was commissioned by the editorial office without any funding or sponsorship. AL receives funding and salary support unrelated to this project from the National Institutes of Health (NIH) National Institute of Biomedical Imaging and Bioengineering (NIBIB) Research Education Programs for Residents and Clinical Fellows Grant (R25EB025787-01). The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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doi: 10.21037/abs-20-125
Cite this article as: Seldon C, Lee A. Regional nodal irradiation in the setting of sentinel node biopsy. Ann Breast Surg 2022;6:7.