

Sentinel Lymph Node Mapping in Post-Mastectomy Chest Wall Recurrences: Influence on Radiation Treatment Fields and Outcome

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ABSTRACT

Background and Objectives. Invasive chest wall recurrences (CWR) following mastectomy are typically treated with surgical excision, radiation therapy (RT) to the chest wall and supraclavicular (SCV) region, and appropriate systemic therapy. Repeat axillary surgery is not routinely performed if the axilla is clinically negative. We evaluated sentinel node biopsy (SNB) in patients with an isolated invasive CWR, for identification and biopsy rates, non-axillary drainage, and clinical implications for radiation fields and outcome.

Methods. Between 2008 and 2013, 12/19 women with an isolated invasive CWR had sentinel node (SN) mapping with Tc99m. Median age was 53 years, and 92 % (11/12) had initial path N0 disease. All had prior SNB, with axillary dissection in one patient.

Results. Overall, 83 % (10/12) had successful mapping, with 70 % (7/10) having an axillary SN. Ninety percent (9/10) had successful axillary node biopsy, with one patient having positive nodes. SCV RT was omitted in those with negative axillary nodes. With a median follow-up of 4.6 years from recurrence, there have been no SCV recurrences and no instances of lymphedema.

Conclusions. SNB is possible in women with an isolated CWR with acceptable identification and biopsy rates. Omission of routine irradiation of the SCV region has not jeopardized regional control and results in decreased morbidity.

Despite the demonstrated equivalence in randomized trials of breast-conserving therapy with radiation and mastectomy,¹ recent studies have reported an increase in mastectomy rates in the US, with a parallel increase in immediate reconstruction.^{2,3} The skin-sparing or total skin-sparing mastectomy has replaced the modified radical mastectomy in these women. Sentinel lymph node biopsy (SLNB) has become the standard axillary staging procedure in clinically node-negative women, based on the reported experience of single institutions and the results of randomized trials comparing axillary dissection (AD) and SLN mapping and biopsy.^{4–6}

Despite these surgical advances in the primary treatment of breast cancer, there have been few advances in the treatment of an isolated chest wall recurrence (CWR) post-mastectomy. Historically, conventional treatment included surgical resection of the CWR (when feasible), radiation, and systemic therapy. If the initial surgery included an AD, re-exploration of the axilla was not performed unless the nodes were clinically positive. Standard radiation fields included the chest wall and supraclavicular (SCV) region based on older series in which AD was performed at the time of initial diagnosis.^{7,8} Halverson et al.⁷ reported a 16 % recurrence in the SCV region in the absence of elective radiation to this area. However, AD and SCV radiation are independently associated with the risk of lymphedema and the combination of the two has resulted in a lymphedema risk of 20 %.^{9,10} SCV radiation has also been associated with an increased risk of symptomatic pneumonitis and brachial plexopathy.^{11–14}

While advances in diagnostic imaging, including axillary ultrasound, magnetic resonance imaging (MRI), and positron emission tomography/computed tomography (PET/CT), have improved our ability to assess the extent of disease at the time of a CWR, the pathologic status of the

axillary nodes remains an important prognostic factor.¹⁵ Repeat sentinel node biopsy (SNB) has primarily been evaluated in patients with an ipsilateral breast tumor recurrence (IBTR) with clinically negative axillae after breast-conserving surgery and prior SLNB or AD. A meta-analysis of 25 studies¹⁶ of 636 women demonstrated successful mapping in 73 % of patients and successful biopsy of sentinel nodes (SNs) in 66 % of patients. Aberrant SN drainage was found in 40 % of patients. This meta-analysis included only 62 patients from nine studies whose primary treatment had been mastectomy with SLNB and/or AD. In these women, successful mapping occurred in 76 % of patients, with successful biopsy occurring in 69 % of patients. Aberrant drainage was reported in 77 % of patients.

The finding of histologically positive axillary nodes at the time of an apparent isolated CWR has clinical implications for systemic therapy and radiation. The CALOR trial recently reported an improved 5-year disease-free survival with chemotherapy for isolated locoregional recurrences, especially those that were estrogen receptor (ER)-negative.¹⁷ Omission of regional node irradiation could be considered if the SNs were negative. Identification of non-axillary SNs may direct radiation to these regions, and the finding of positive nodes would support radiation to the regional nodes. Avoidance of routine irradiation of the regional nodes will diminish treatment-associated morbidity.

The purpose of this retrospective study was to evaluate repeat SNB in women with an isolated CWR following mastectomy, for identification and biopsy rates, non-axillary drainage patterns, clinical implications for radiation, and outcome.

METHODS

The medical records of 19 patients diagnosed with an isolated invasive CWR following mastectomy during the years 2008–2013 were retrospectively reviewed. Patients with a prior history of radiation or with clinically- or imaging-positive axillary nodes were excluded. The study was approved by the University of California San Francisco Committee on Human Research.

Stage distribution at initial diagnosis was 0 in 21 % of patients, I in 32 %, II in 42 %, and III in 5 %. At initial diagnosis, T-stage ranged from Tis–T3. Of the initial 15 invasive cancers, two were grade 1, six were grade 2, and seven were grade 3. Four patients had lymphovascular invasion. ER was positive in 74 % of patients, progesterone (PR)-positive in 63 % of patients, and human epidermal growth factor receptor 2 (HER2)-positive in 26 % of patients. Sixty-eight percent of patients were pathologic N0 at the time of initial diagnosis (13/19 patients). For the six

patients with positive nodes, the median number of positive lymph nodes was 1 (range 1–5). The mastectomy was skin-sparing or total skin-sparing, with tissue expander/implant immediate reconstruction in 12 patients, latissimus flap and implant in one patient, and autologous reconstruction in two patients [deep internal perforator flap (DIEP) in one patient, and transversus abdominis muscle flap (TRAM) in one patient]. Four patients had mastectomy without reconstruction. Initial axillary surgery was SNB in 14 patients and AD in 5 patients. Initial chemotherapy was administered in 11/19 patients. At diagnosis, the chemotherapy was doxorubicin and/or taxane-based and included trastuzumab for HER2-positive. Endocrine therapy was administered in 8/19 patients, and four patients had no systemic therapy.

Median age at the time of CWR was 53 years (range 36–62), and the median interval from mastectomy to CWR was 25 months (range 3–77). Eighteen of 19 recurrences were identified by clinical examination. The median size of CWR was 1.2 cm (0.5–5.2 cm), and the receptor status of CWR was ER-positive in 74 % (14/19) of patients, PR-positive in 53 % (10/19) of patients, and HER2-positive in 10 % (2/19) of patients. One recurrence was invasive lobular histology, one was poorly differentiated carcinoma not otherwise specified, one was mucinous, and all others ($n = 16$) were invasive ductal cancers. All patients underwent surgical excision of the CWR, with negative margins in 11 patients, positive margins in five patients, and close margins (<1 mm) in three patients.

Repeat SLN mapping was performed with Tc 99m sulfur colloid with or without lymphazurin. The injection was intradermal into the mastectomy skin flap, and a lymphoscintigram was performed following the isotope injection. Surgical exploration of non-axillary SNs was not performed. All patients received radiation at the University of California San Francisco, with 5000–5040 cGy (180–200 cGy per fraction) delivered to the chest wall. A boost of 1000 cGy was delivered to the excision site. The SCV field delivered a dose of 4500–4600 cGy in 180–200 cGy per fraction. Systemic therapy for the CWR included chemotherapy in 68 % of patients. Chemotherapy was taxane-based with carboplatin and included trastuzumab and pertuzumab for HER2-positive patients ($n = 1$ patient). Endocrine therapy was administered in 74 % of patients, while six patients did not receive any systemic chemotherapy at the time of recurrence. One patient only had neither chemotherapy nor hormonal therapy at the time of recurrence. Lymphedema was scored as present or not present, based on clinical measurements of the arm circumference before and after radiation. Recurrences were noted either on imaging follow-up or on physical examination during clinic visits.

RESULTS

Of the 19 patients with an invasive CWR after mastectomy, 63 % (12/19) underwent attempted SLN mapping with Tc99m sulfur colloid injection with or without blue dye. Ninety-two percent (11/12) had a history of prior SNB, and one had a prior AD (Table 1).

Of the 12 patients who underwent repeat SLN mapping, 83 % had successful mapping (10/12). The majority of these [7/10 (70 %)] localized to the axilla (levels I or II), and two patients localized to the retropectoral (Rotter's) nodes. Other non-axillary SNs were SCV nodes (1), parasternal node (1), and the clavicular head (1). The SLNB was negative in 100 % (7/7) of those who had successful mapping to the axilla. In one patient, two of six lymph nodes were positive (one 3 mm tumor deposit and isolated tumor cells in a second lymph node). One patient underwent an axillary lymph node dissection after successful mapping to the SCV nodes, but 0/10 axillary nodes were positive, and one patient whose SN was parasternal had axillary surgery with six negative nodes. One of the

two patients with unsuccessful mapping underwent removal of two negative axillary nodes, while the other patient had no axillary surgery. Patient number 11 (Table 2) had a tracer localized to the left axilla and left subpectoral region, but exploration of the axilla did not identify any lymph nodes.

The results of successful repeat SLN mapping were used to influence radiation treatment fields. All patients received radiotherapy to the chest wall/reconstructed breast, and 3/12 patients with attempted repeat lymph node mapping had SCV radiation. Reasons for SCV irradiation included one patient with an SCV SN, one patient with unsuccessful SLN mapping, one patient who requested SCV lymph node irradiation despite successful mapping and a negative biopsy. A single patient had internal mammary node (IMN) irradiation due to localization of the SN to the parasternal area/clavicular head.

Median follow-up for patients who underwent repeat SLN mapping was 55.5 months (range 8–76). There have been no chest wall or SCV recurrences to date. One patient developed an IMN recurrence (SN was in the axilla and was negative) and one patient had in-field axillary recurrence (unsuccessful SLN mapping, two negative axillary nodes sampled, and radiotherapy included the level 1–2 axillary nodes without SCV irradiation) (see Fig. 1). None of these patients have developed lymphedema, as assessed by clinical measurements of the arm circumference on serial follow-up visits. There have been no cases of symptomatic pneumonitis or brachial plexopathy.

TABLE 1 Treatment characteristics ($n = 12$)^a

Median age at chest wall recurrence	53 years
Median interval (mastectomy to chest wall recurrence)	25 months (range 3–77)
Prior axillary dissection	1/12
Chemotherapy	68 % (8/12)
Hormones	74 % (9/12)
Successful repeat SLN Mapping	83 % (10/12) ^d
Sentinel node mapped to:	
Axilla	70 % (7/10)
Retropectoral (Rotter's) ^b	2/10
Supraclavicular nodes	1/10
Parasternal lymph nodes	1/10
Clavicular head	1/10
Repeat SLN biopsy negative	90 % (9/10) ^a
Chest wall RT	All
Supraclavicular radiation	3/12 ^c

SLN sentinel lymph node, RT radiation therapy, SCV supraclavicular

^a Twelve patients underwent attempted SLN mapping, ten of whom had successful mapping of sentinel nodes (83 % success rate). Nine of these ten patients had a negative SLN node (90 % pathologically node-negative)

^b One patient had primary drainage to the retropectoral (Rotter's) nodes and one patient had drainage to the axilla and Rotter's. One patient mapped to a parasternal node and a node near the clavicular head

^c Supraclavicular irradiation was administered in three cases due to (i) SLN in the SCV region; (ii) no SLN identified; and (iii) patient choice

^d Two of the twelve patients did not have successful mapping. One of the patients had axillary node sampling, and the second patient did not have any axillary surgery

DISCUSSION

Repeat SLN mapping has been more commonly studied in patients with an IBTR with a clinically negative axilla following breast-conserving surgery and radiation. A meta-analysis of 25 studies¹⁶ of 636 women demonstrated successful mapping in 73 % of patients, and successful biopsy of SNs in 66 % of patients. Aberrant SN drainage was found in 40 % of patients. Only 62 patients in this meta-analysis had an initial mastectomy. In these women, successful mapping was reported in 76 %, with successful biopsy reported in 69 %, and aberrant drainage in 77 % of patients. Table 3 presents a summary of relevant series in the literature for mastectomy patients. A registry study from 35 hospitals in The Netherlands identified only 21 patients who had repeat SNB for a post-mastectomy CWR.¹⁸ Successful mapping occurred in 76 % of patients, with successful biopsy occurring in 71 % of all patients and 94 % of those with successful mapping. Non-axillary SNs were identified in 75 % of patients, including 100 % of the nine patients with prior AD and 43 % of those with prior SNB. There were no positive axillary nodes. Three

TABLE 2 Treatment outcomes. Clinical N0 patients who underwent attempted repeat sentinel lymph node mapping and the influence on the SCV RT field

Patient	Initial stage	Prior ax. surgery	Ax. LN removed	Reconstruction	Repeat SLN mapping successful	Interval to CWR (months)	Type of CWR	Nodes +	SCV RT	Status interval	Time NED (months)
1	pT1cN0	SLNB	4	LD flap	N	43	IDC	0/2	N	LRR- L Ax.	36
2	pT1bN0	SLNB	5	None	Y – axilla	5	IDC	0/3	N	NED	64
3	pT1cN0	SLNB	2	DIEP	N	24	Mucinous adeno	0/0	Y^a	NED	75
4	ypTisN0	SLNB	9	None	Y – SCV	22	Carcinoma NOS	0/10	Y^b	NED	8
5	pTisN0	SLNB	4	None	Y – axilla	77	IDC	0/9	N	NED	18
6	pTisN0	SLNB	3	TE	Y – axilla	18	IDC	0/2	N	NED	57
7	pT1cN1mic	AxLND	7	TE	Y – retropectoral ^c	36	IDC	2/6	N	NED	51
8	pT1aN0	SLNB	1	TRAM	Y – axilla	52	IDC	0/2	N	LRR– IMN	37
9	pTisN0	SLNB	3	Implant	Y – parasternal, clavicular	68	IDC	0/6	N ^c (IMN RT)	NED	46
10	pTisN0	SLNB	0	TE	Y – axilla	27	IDC	0/2	N	NED	54
11	ypT2N0	SLNB	6	TE	Y – axilla, retropectoral ^c	9	IDC	0/0	N	NED	43
12	ypTisN0	SLNB	1	TE	Y – axilla	19	IDC	0/2	Y^d	NED	69

Bold indicates patients with recurrence

LD latissimus dorsi, DIEP deep internal perforator flap, TE tissue expander, TRAM transversus abdominis muscle flap, NED no evidence of disease, LRR locoregional recurrence, IMN internal mammary node, SLNB sentinel lymph node biopsy, AxLND axillary lymph node dissection, SCV supraclavicular, RT radiation therapy, Ax. axillary, LN lymph node, SLN sentinel lymph node, CWR chest wall recurrences, Y yes, N no, IDC invasive ductal carcinoma, NOS not otherwise specified, SLNB sentinel lymph node biopsy, IMN internal mammary node

^a The SCV field was included due to no sentinel nodes being identified

^b The SCV field was included because sentinel nodes were mapped to the SCV region. This patient had a full AxLND at the time of recurrence. All others had SLNB only

^c Treated with an IMN field since the sentinel node was localized to the parasternal area

^d The SCV field was included due to patient choice

^e Retropectoral nodes are also known as Rotter's nodes

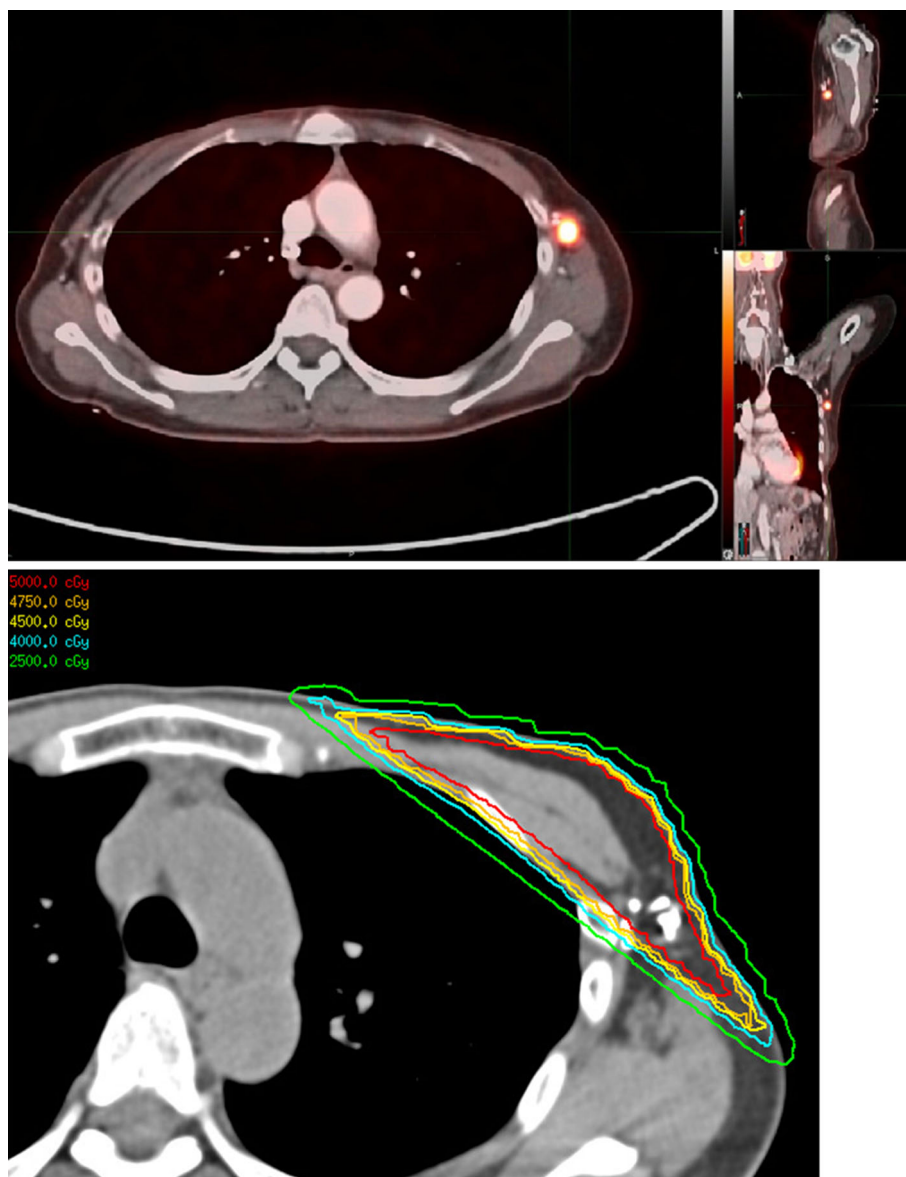
^f Median follow-up was 46 months (range 8–76)

patients had positive IMNs, with one patient having a macrometastasis and two micrometastases. Similarly, only 14 patients were identified from five institutions in Denmark.¹⁹ Successful mapping occurred in 69 % of patients, with successful biopsy in 64 %. Aberrant drainage was identified in 31 % of patients. The largest single-institution series, which included 17 patients, was reported by investigators from the Memorial Sloan Kettering Cancer Center.²⁰ Nine of these patients had prior AD, four had SNB, and four had no prior axillary surgery. Mapping was to the axilla in all 15 patients with a positive lymphoscintigram, with two patients having additional non-axillary SNs (IMN and SCV). Repeat SNB was successful in 12 of the 17 patients (71 %), and in all patients who had prior SNB or no axillary surgery, but only 44 % of those with prior AD. Success rates for repeat SNB were lower for patients who had undergone immediate reconstruction when compared with those did not (50 vs. 87.5 %).

Positive axillary nodes were found in 15 % of patients. These results are comparable to our series (second largest single-institution series reported), in which repeat SN mapping was successful in 83 % (10/12) of patients and repeat biopsy was successful in all seven patients with localization to the axilla. It should be noted that only one of our patients had a prior AD. Non-axillary SNs were identified in two patients (parasternal, SCV) and these nodes were not biopsied. Repeat SLNM was unsuccessful in two of nine patients who had reconstruction of any kind. Repeat SLNM was successful in all three patients who did not undergo reconstruction. Of the seven patients who had repeat axillary surgery after successful mapping to the axilla, only one was found to have positive nodes (one 3 mm metastatic focus and one lymph node with isolated tumor cells).

The clinical implications of the pathologic findings from repeat SNB for an isolated CWR have been infrequently

FIG. 1 Patient with an in-field axillary recurrence



addressed in the literature. The accuracy of the SNB was reported by Maaskant-Braat et al.¹⁸ and Uth et al.¹⁹ The false negative rate was 0 % in those who had confirmatory AD in both studies. Maaskant-Braat et al.¹⁸ reported a change in plans for additional therapy (systemic therapy or regional node irradiation) in 10 % of patients. We used the information from the repeat SNB to determine radiation fields. If the SN was axillary in location and the repeat SNB was negative, we did not recommend irradiation of the SVC or axillary regions. To date, there have been no SCV failures or axillary failures in these women. One patient developed an in-field axillary recurrence. SN mapping was unsuccessful and two non-sentinel axillary nodes were negative. Radiation included the level 1–2 axillary nodes and, despite this, the patient developed an axillary recurrence (see Fig. 1). In addition, one patient

developed an IMN recurrence. SN mapping was successful and two axillary SNs were negative. The IMN node was resected and the patient remains alive without evidence of disease. No patient has developed distant metastatic disease. However, it should be noted that these recurrences were relatively favorable, with all being clinically node-negative and amenable to surgical resection. Seventy-five percent of patients were ER-positive and 11/12 patients received systemic chemotherapy and/or hormonal therapy at the time of recurrence.

Our series compares favorably to the literature. In a publication by Halverson et al., 16 % of patients with CW recurrence after mastectomy experienced an SCV failure if radiotherapy was omitted compared with 6 % who had radiotherapy (CW + SCV) at the time of recurrence.⁷ The difference between our series and theirs is that all of the

TABLE 3 Reported series on repeat SNB for isolated chest wall recurrence post-mastectomy

Series	No. of patients	Prior axillary surgery	Mapping successful (%)	Biopsy successful (%)	Pathologically node-negative (%)	Non-axillary drainage (%)
Meta-analysis ¹⁶	62	NS	76	69	NS	77
Registry Netherlands ¹⁸	21	SNB, 9 pts	78	78	100	42
		AD, 12 pts	75	67	63	100
Registry Denmark ¹⁹	14	AD, 10 pts	69	64	NS	31
		SNB, 4 pts				
Memorial Sloan Kettering ²⁰	17	SNB, 4 pts		100	82, all pts	0
		AD, 11 pts		36		
		None, 3 pts		100		
MD Anderson ²¹	4	AD	NS	50	100	50
European Institute of Oncology ²²	4	None	100	100	50	0
Present series	12	SNB, 11 pts	82	54	90	30
		AD, 1 pt	100	100	100	0

SNB sentinel node biopsy, *pts* patients, *AD* axillary dissection

patients in the series by Halverson et al. had an AD. We observed no SCV failures, which suggests patients with a CWR may avoid the morbidity of combined AD and SCV irradiation. We encourage further investigation.

CONCLUSIONS

Our limited, single-institution experience confirms that repeat SNB is possible in the setting of an isolated post-mastectomy CWR. As SNB becomes the primary axillary procedure, the feasibility of repeat SNB at the time of recurrence will increase. The pathologic findings from repeat SNB can direct radiation fields, provide prognostic information, and enhance regional control by identifying occult regional disease and non-axillary drainage patterns. Omission of routine irradiation of regional nodes diminishes treatment-associated morbidity and in our series did not jeopardize regional control. We encourage further investigation.

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