

# Avoiding the Swell: Advances in Lymphedema Prevention, Detection, and Management

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OVERVIEW

Lymphedema is a feared complication of cancer treatments that negatively affects survivors' quality of life. The true incidence of lymphedema is difficult to determine given its long latency period. As the number of survivors of cancer is increasing in the United States, lymphedema is poised to be a major health concern. The most noteworthy risk factor for lymphedema is comprehensive lymph node dissection. The last 2 decades have witnessed a dramatic shift in cancer treatment in an attempt to systematically de-escalate therapeutic interventions, specifically seeking to shift treatment away from routine lymph node dissection in favor of sentinel node biopsy or radiation strategies, thereby reducing the risk for lymphedema while maintaining survival outcomes. A growing body of robust evidence supports prospective screening and thereby a prospective surveillance model (PSM) for early diagnosis and intervention for the prevention and treatment of lymphedema. Finally, investigators are actively evaluating the effectiveness of contemporary surgical procedures in ameliorating the symptoms and disability of patients with lymphedema and reducing the risk of future episodes of cellulitis, with outcomes of surgery significantly better than with conservative therapy alone. In this article, we review the current data surrounding these initiatives.

## INTRODUCTION

Lymphedema occurs when protein-rich lymphatic fluid accumulates in the interstitial tissue, causing swelling. In the developed world, cancer treatments remain the most common cause of secondary lymphedema development. Clinicians caring for patients with cancer should recognize the clinical manifestations of lymphedema, as its incidence is likely higher than reported. Further, lymphedema confers a profound negative impact on the functional status and overall quality of life of survivors of cancer. Current advances in lymphedema science center around reducing lymphedema risk by minimizing and personalizing cancer treatment strategies, prevention and early diagnosis, and novel therapeutic interventions for those affected with lymphedema.

The true incidence of lymphedema is unknown, likely due to its prolonged latency requiring diligent long-term follow-up and lack of consistent definitions used by clinicians for diagnosis. Although lymphedema has long been considered synonymous with breast cancer treatment, it has been reported after most cancers requiring lymph node removal.<sup>1</sup> It is interesting to note that incidence of lymphedema varies across cancer type, even if the affected nodal basin is consistent. Also, lymphedema risk appears higher when the at-risk limb is a lower extremity. Finally, few published manuscripts on cancer-related lymphedema focus on

populations without breast cancer. Regardless, given that the National Cancer Institute suggests over 19 million survivors of cancer will be living in the United States by 2024, lymphedema is poised to be a major public health concern.<sup>2</sup>

## CANCER SURGERY AND RADIATION CONSIDERATIONS

For years, physicians believed lymph node removal was therapeutic. As such, patients willingly endured considerable risk and anxiety for lymphedema, choosing survival over long-term morbidity. However, since the dawn of the 21st century, landmark clinical trials in surgical and radiation oncology have challenged this long-held notion that more comprehensive treatment and nodal extirpation equates to improved survival. Instead, these trialists have argued that most cancers are systemic diseases, benefit from multimodality therapy, allow for personalized approaches, and support lymph node removal in most cases as a diagnostic tool as opposed to a therapeutic intervention in the setting of early-stage or biologically favorable disease.

Further, advancements in cancer treatments and documented low rates of isolated regional nodal recurrences have reinforced lymph node evaluation as a likely diagnostic and not a therapeutic. This conclusion is critical, as it is clear that the extent of nodal surgery and the synergistic effect of surgery and radiation on the affected lymphatic basin remain the

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## PRACTICAL APPLICATIONS

- In the developed world, secondary lymphedema is most commonly caused by cancer treatments. Although lymphedema is frequently linked to breast cancer, it can occur after lymph nodes have been removed or radiated in any lymph node basin.
- Stepwise surgical trials have evaluated the role of minimizing lymph node dissection in favor of sentinel node biopsy or radiation therapy alone. This de-escalation in care has resulted in a lower sustained incidence of lymphedema.
- The PSM for lymphedema is a clinically effective intervention to promote early detection and management of lymphedema, as well as a feasible practice for oncology providers.
- Surgical treatments can be broadly categorized into physiologic procedures, including lymphovenous bypass and VLNT, and debulking procedures, including SAL with controlled compression therapy and direct excision.
- Evidence supports the efficacy of surgical treatments for lymphedema at reducing the excess limb volume, reducing the occurrence of cellulitis, decreasing the need for conservative therapy, improving patient quality of life, and improving physical function.

primary drivers of lymphedema development. Acknowledging lymphedema is a serious concern after treatment of many different cancers, a focused review of the stepwise progression of clinical trials in breast cancer research provides a robust framework of level 1 evidence for the systematic de-escalation of lymph node treatment. Although these trials aimed to promote personalized intervention strategies and evaluate survival, most also addressed lymphedema risk and incidence as secondary endpoints.

## BREAST CANCER SURGICAL TRIALS

Axillary dissection remained the standard of care for breast cancer lymph node assessment until the early 2000s. Shaitelman et al<sup>3</sup> reviewed 5,354 patients, finding a pooled incidence of lymphedema of 28% (range 11%–57%) in those undergoing axillary lymph node dissection (ALND). The breast cancer community adopted sentinel lymph node biopsy (SLNB) for axillary assessment around the year 2000. The randomized controlled trials designed to evaluate the efficacy of SLNB (all mandated backup ALND) not only demonstrate accurate axillary staging but also less lymphedema after SLNB when compared with ALND, 0% to 7% versus 12% to 16%, respectively.<sup>4-6</sup> A pooled analysis of 6,711 patients with breast cancer undergoing SLNB

validated these trials, noting the incidence of lymphedema to be 6.3% with a range of 0% to 23%.<sup>3</sup> Interestingly, the American College of Surgeons Oncology Group (ACOSOG) Z0010 trial<sup>7</sup> reported higher rates of subjective lymphedema after both SLNB (objective 12%; subjective 24%) and ALND (objective 40%; subjective 41%), which underscore the controversies on how lymphedema should be defined and the value of both objective and subjective measures. Regardless, it is clear that less extensive axillary surgery results in less lymphedema, and therefore, surgical research has focused on how to extend SLNB to more patients.

Further review of the randomized SLNB clinical trials gave way to critical study on the extent of nodal positivity among patients proceeding to ALND. Specifically, it was recognized that in about 70% of patients undergoing ALND, the sentinel nodes were the only positive lymph nodes. This finding empowered the ACOSOG to investigate whether every patient with a positive SLNB benefits from completion ALND. The ACOSOG Z0011 trial prospectively and randomly selected women undergoing breast-conserving surgery with one or two positive sentinel lymph nodes to either completion ALND or no further axillary surgery.<sup>8</sup> They reported regional recurrence rates of less than 1% in both arms and no differences between overall survival (SLNB: 86.3% vs. ALND: 83.6%; noninferiority  $p = .02$ ) or disease-free survival (SLNB: 80.2 vs. ALND: 78.2%;  $p = .32$ ) at 10 years, thus proving in this population of patients with early-stage breast cancer that SLNB alone was not inferior to ALND. Although fiercely debated for several years, Z0011 has since been widely adopted after its initial publication in 2011, further extending the benefits of minimal axillary exploration (SLNB) and lower lymphedema risk to more patients.

After the practice-changing success of Z0011, the next major question was how to further reduce axillary node treatment to patients presenting with clinically positive nodes at diagnosis and the efficacy of SLNB after neoadjuvant therapy. The ACOSOG 1071, SENTINA, and SN FNAC trials confirmed the feasibility of SLNB in this population.<sup>9-11</sup> The subsequent trials (Alliance 11202 and NRG B-51) are now actively evaluating the role of selective ALND with or without axillary radiation in patients treated with neoadjuvant chemotherapy who remain pathologically node positive or downstage to being node negative. Lymphedema is a secondary endpoint.

Finally, although not currently being evaluated in a prospective, randomized clinical trial, the benefit of targeted axillary dissection is being studied by breast surgeons. Specifically, patients presenting with a clinically positive axillary node undergo needle biopsy to confirm metastatic disease and to leave a marking clip. After neoadjuvant chemotherapy, the node is localized for surgical excision, and targeted axillary dissection is performed in addition to

SLNB. Targeted axillary dissection reduces the false-negative rate of SLNB in these high-risk patients and therefore helps better target which patients might benefit from completion ALND due to chemotherapy-resistant residual disease.<sup>9</sup> Its effect on lymphedema has not specifically been documented but it is expected to parallel that of SLNB. This evolution in breast cancer clinical trials serves as the gold standard for intervention de-escalation strategies documenting sustained excellent survival rates while systematically reducing lymphedema risk

### BREAST CANCER RADIATION TRIALS

Although surgeons have focused on de-escalation of surgery, radiation oncologists have investigated the equipoise of axillary radiation and axillary dissection in the setting of a positive sentinel node. The After Mapping of the Axilla: Radiotherapy Or Surgery? (AMAROS) trial<sup>10</sup> randomly selected patients with a positive SLNB to receive standard ALND or axillary radiation therapy. The trial reported significantly less lymphedema after axillary radiation therapy (objective 5%; subjective 11%) when compared with ALND (objective 13%; subjective 23%). A recent prospective study of 1,811 patients evaluated breast cancer–related lymphedema (BCRL) risk according to extent of axillary surgery and axillary regional lymph node radiation (RLNR).<sup>11</sup> At 5 years, the authors found the following cumulative lymphedema incidences: SLNB alone, 7.7%; SLNB plus RLNR, 10.8%; ALND alone, 29%; and ALND plus RLNR, 38.7%. Interestingly, in the setting of similar local control rates, multivariable analysis found no noteworthy difference in lymphedema rates between axillary surgery groups regardless of use of RLNR, and the ALND groups consistently had higher lymphedema risks than the SLNB groups. These data lend further support to the findings of the AMAROS trial, documenting that in patients with only one or two positive sentinel lymph nodes, lymphedema could be significantly reduced if axillary regional nodal radiation replaced ALND.

The combination of ALND and comprehensive nodal radiation can act synergistically to nearly double the risk of lymphedema. In a systematic review, Cormier et al reviewed radiation and reported lymphedema risk after breast or chest wall radiation to be 14.5% but was 31.5% after breast/chest wall plus supraclavicular radiation and 41.4% when a posterior axillary boost was added.<sup>1</sup> Shah et al<sup>12</sup> also evaluated the impact of radiation on survivors of breast cancer completing breast-conserving surgery and whole-breast radiation, citing less lymphedema risk than Cormier et al<sup>1</sup> (8.3% to 14.7%), but noted lymphedema risk varied according to whether supraclavicular, posterior axillary, or internal mammary nodes were treated. Risk factors for lymphedema included having more nodes removed, extracapsular extension, advanced nodal status, grade 3

disease, or receipt of adjuvant systemic therapy (all  $p < .02$ ).<sup>12</sup>

### MELANOMA SURGERY TRIALS

Melanoma research focusing on de-escalation nodal strategies to minimize treatment morbidity has paralleled breast cancer research. Overall, the pooled incidences of lymphedema after melanoma surgery are reported as 4.1% after SLNB, 3% after ALND, and 18% after inguinofemoral lymph node dissection.<sup>3</sup> Hyngstrom et al<sup>13</sup> prospectively followed 182 patients with melanoma for 12 months and found, similar to breast cancer data, that lymph node dissection resulted in significantly more lymphedema than SLNB (odds ratio 3.18;  $p < .01$ ). Data from the Multicenter Selective Lymphadenectomy Trial I (MSLT 1) prospectively, randomly selected patients undergoing wide excision of a primary melanoma to receive SLNB or observation alone. Those with a positive SLNB completed immediate or early lymph node dissection.<sup>14</sup> If patients developed a regional nodal recurrence, they completed delayed lymph node dissection. This allowed restriction of lymph node dissection to only those patients who might benefit, again validating SLNB. At 5-year median follow-up, patients undergoing immediate/early lymph node dissection had less lymphedema than those undergoing delayed lymph node dissection (12.4% vs. 20%;  $p = .04$ ). Further, inguinofemoral dissection was significantly more likely to result in lymphedema than ALND (26% vs. 9%;  $p < .001$ ). The DeCoG and MSLT 2 trials build upon the results of MSLT 1.

### EMERGING STRATEGIES FOR SURGICAL PREVENTION OF LYMPHEDEMA

Beyond limiting surgical dissection, surgeons are actively investigating prevention techniques that can be combined with routine axillary surgery to further limit lymphedema risk. Axillary reverse mapping (ARM) seeks to preserve upper-extremity lymphatics and nodes, identifying them separately from those draining the breast and thereby reducing lymphedema. The surgeon isolates the lymph nodes draining the breast with technetium and those draining the arm with blue dye. A systematic review found lymphedema in 0% to 6% of patients undergoing ARM plus SLNB and 5.9% to 24% of patients undergoing ARM plus ALND.<sup>15</sup> Concerns surrounding ARM include reliable and consistent ARM identification rates, crossover lymph nodes/lymphatics (breast SLNB is also ARM node), and feasibility axillae with heavy tumor burden. The Alliance A221702 trial is currently evaluating SLNB or ALND with and without ARM to formally evaluate the feasibility and utility of ARM (NCT03927027).

A few surgeons are performing the lymphatic microsurgical preventive healing approach (LYMPHA). LYMPHA seeks to identify arm lymphatics in the axillary field and then perform lymphatic to venous anastomoses via microsurgical techniques when a competent venous valve is present.

Boccardo et al<sup>16</sup> published the first series noting lymphedema in 4% of patients receiving LYMPHA after ALND that increased to 10.5% if they included those patients with transient postoperative lymphedema. More recently, Feldman et al<sup>17</sup> found lymphedema in 8% of patients at 24 months, which increased to 12.5% when those with transient lymphedema were included. Collectively, these studies suggest some benefit to immediate lymphovenous anastomosis during ALND; however, further investigation is needed, as the added operative time and need for specialized microsurgical training must be considered if LYMPHA is to be widely adopted for all patients undergoing ALND.

## RISK AND SURVEILLANCE

Although SLNB procedures have reduced the extent of axillary clearance, there remains a 6% to 25% risk for developing BCRL.<sup>3</sup> This risk is attributed to the extent of axillary dissection and whether radiation therapy (whole breast with or without regional nodal irradiation) is applied. Notably, the onset of BCRL is commonly slow and progressive. Most cases present more than 6 months after the breast surgical procedure and antineoplastic therapies, with reported incidence escalating for at least the first 3 years after surgery.<sup>18</sup> Moreover, the risk of arm morbidity reducing physical function beyond the completion of cancer treatments is also relevant and necessitates attention.<sup>19</sup>

Knowing that this latent time to onset exists, there is an unprecedented opportunity to characterize an individual's risk and monitor their limb prospectively to identify self-reported symptoms and clinically measurable changes associated with early-onset lymphedema.<sup>20</sup> When early lymphedema is identified, it can be treated conservatively, possibly preventing the progression to a more advanced, chronic condition.<sup>21</sup> To optimize early identification and management, a standardized methodology for surveillance is necessary.<sup>22</sup>

## THE PROSPECTIVE SURVEILLANCE MODEL

The PSM is recognized as an optimal framework to guide clinical implementation of a screening methodology for early identification and management of breast cancer treatment-related impairments.<sup>22,23</sup> Using the PSM in clinical practice enables the early identification and treatment of lymphedema, sometimes in a subclinical stage, when intervention can prevent the progression to a more chronic form of the condition.<sup>21</sup> The PSM suggests a clinical pathway that starts with a baseline assessment of the individual's limb at the point of breast cancer diagnosis, prior to initiating cancer treatments, and proceeds with interval screening at punctuated intervals through the duration of treatment in an effort to identify clinically meaningful change from baseline. [Figure 1](#) highlights the PSM clinical pathway.

## Baseline Assessment

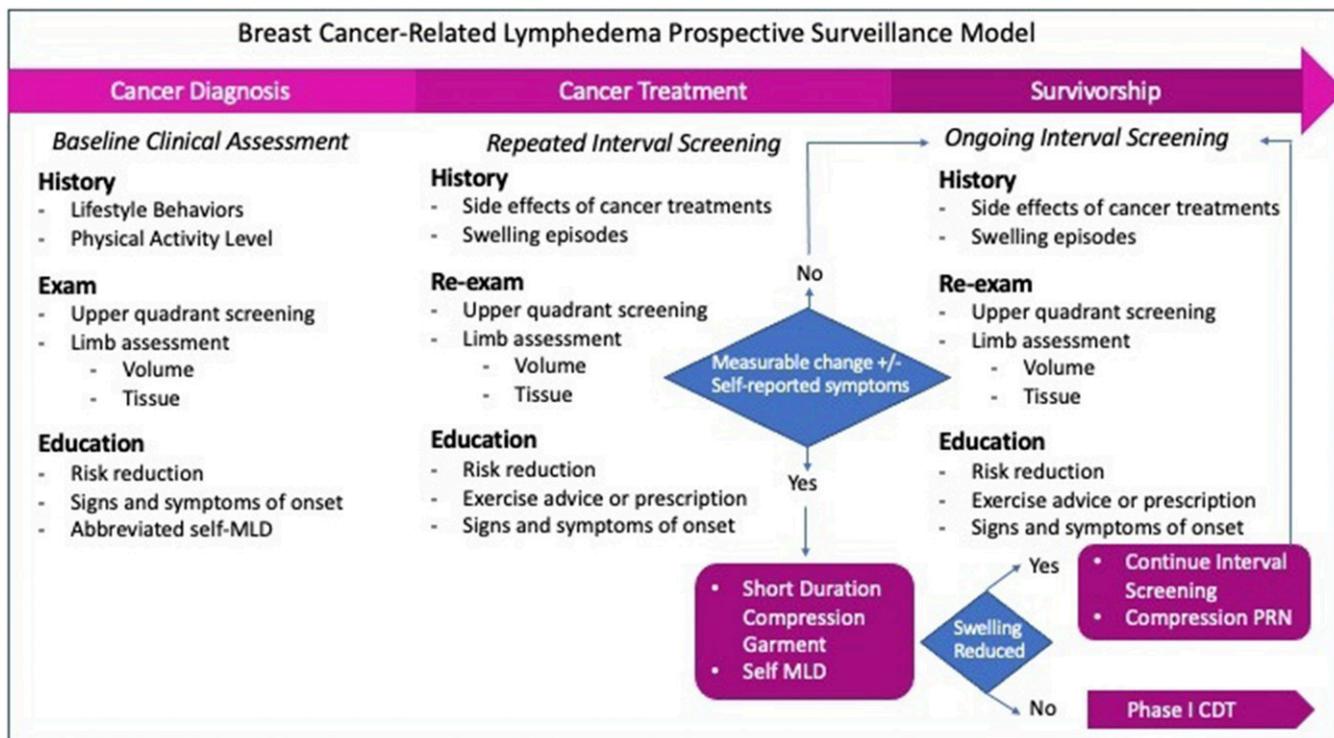
Prior to the onset of breast cancer treatment, an assessment of the individual's baseline is warranted. The baseline assessment establishes a premorbid level of function and should obtain clinical measures of the limb and any self-reported limb problems. Ideally, this preoperative visit is conducted in conjunction with a presurgical physician office visit or nurse case-manager visit to reduce the individual's burden of multiple tests and appointments. This engagement also provides an opportunity for education about what lymphedema is and why prospective monitoring is warranted. Proactive education and awareness about conditions such as lymphedema are perceived by patients to be of high importance.<sup>24,25</sup>

The baseline assessment should include valid tests that have demonstrated efficacy in enabling early identification of limb changes. Superior tests for clinical screening include optoelectronic perometry and bioelectrical impedance analysis.<sup>26</sup> These screening measures are highly sensitive and specific to identifying early lymphedema when used in PSM for BCRL<sup>21</sup>; there is also good concordance between these measures.<sup>27,28</sup> The baseline measure is requisite to standardize and optimize early identification of lymphedema, leading to more precise diagnoses.<sup>29</sup>

A holistic view of the individual's level of physical function is warranted and should be assessed at baseline. Although the PSM is ideal for early detection and management of lymphedema, other common breast cancer treatment-related problems such as shoulder morbidity and fatigue occur prevalently and can be identified and managed proactively using PSM.<sup>30,31</sup> Suggested patient-reported outcome measures for upper-quadrant function include the Disabilities of the Arm, Shoulder, and Hand questionnaire and the Functional Assessment of Cancer Therapies Breast + 4.<sup>32</sup>

## Interval Screening

Through the trajectory of breast cancer treatment, different and varied antineoplastic therapies are introduced, each with side effects that may affect the risk profile for the development of lymphedema. Especially concerning is reduced physical activity and exercise during treatment and the tissue changes associated with radiotherapy.<sup>33,34</sup> Considering the varied nature of treatment side effects and the need for individualized patient pathways, a tailored approach is warranted and should be driven by the individual's risk for lymphedema. The timing of the repeated interval assessment ranges in the literature from 3-month intervals through the first year of active medical treatment of individuals at higher risk to 6-month intervals for those with less risk and lower potential symptom burden.<sup>23,35</sup> The interval follow-up schedule should be planned in accordance with the individual's treatment pathway and should



**FIGURE 1. Breast Cancer–Related Lymphedema Prospective Surveillance Model**

Abbreviations: +/-, with or without; CDT, complete decongestive therapy; MLD, manual lymphatic drainage; PRN, as necessary.

minimize the burden of additional or unnecessary appointments outside of the cancer care plan. Therefore, incorporating these repeated screening measures into oncology practice is critical. This can be achieved by introducing a clinically integrated rehabilitation professional into the cancer care clinical pathway,<sup>36</sup> incorporating screening through navigation pathways,<sup>37</sup> or instituting system-specific processes for repeated measures.

The critical element of the repeated interval screening is assuring that a sensitive threshold for diagnosis is standardized and that clinical triage pathways are developed to promote intervention by a qualified lymphedema specialist when warranted. Subclinical lymphedema was first identified by Stout et al<sup>21</sup> and described as a 3% or higher increase in the affected limb from the baseline measure with consideration for the contralateral limb. However, the individuals diagnosed through these initial studies demonstrated clinically meaningful change at 5% volume change. The standard for clinical diagnosis is recognized as 5% or higher volume change from baseline. Using circumferential measurement methodology with tape measures, optoelectronic perometry, or water displacement requires attention to the contralateral limb to control for weight gain or loss when assessing change over time.<sup>26</sup> Bioelectrical impedance analysis, however, uses a ratio of resistance and

reactance in the tissue, derived from an electrical wave that is sent through the tissue, to determine if early fluid congestion is occurring. Prospective studies suggest that bioelectrical impedance analysis, when standardized through a PSM, enables early identification of BCRL.<sup>38,39</sup>

Upon early identification of BCRL, it is imperative that the clinical pathway include evidence-based clinical interventions to reduce limb volume, prescribe individualized self-management strategies to prevent the progression of severity of lymphedema, and reduce the impact on function. Application of compression garments, fitted and prescribed on an individualized basis,<sup>21,40</sup> is recommended along with self-manual lymphatic drainage techniques,<sup>41</sup> and exercise<sup>42</sup> is a recommended intervention for early lymphedema.

**Outcomes and Feasibility of the PSM**

The emergence of evidence regarding PSM largely favors the model as a clinically effective intervention to promote early detection and management of lymphedema, as well as a feasible practice for oncology providers. Additionally, the PSM construct is favorable to early identification and management of breast cancer–related upper-extremity morbidity, and therefore, a holistic approach to measuring the individual’s function over time should be considered part of this standard of care.<sup>43,44</sup>

The clinical outcomes overwhelmingly suggest that early identification of lymphedema is best achieved using the PSM and standardizing measurement methodology, including timing, assessment measures, and clinical interventions. Recent guidelines recommend PSM as a standard of care to improve the detection and treatment of lymphedema.<sup>45,46</sup> The 2019 National Comprehensive Cancer Network Guidelines for Survivorship update recognizes the subclinical stage of lymphedema and provides guidance aligned with the PSM for early detection and management of lymphedema.<sup>47</sup> The feasibility of the model has also been examined and found to be favorable to implementation.<sup>44,48</sup> Additionally, preliminary cost analysis demonstrates that PSM may be a cost-mitigating strategy when early intervention strategies are effective to prevent the progression to chronic, later-stage lymphedema.<sup>49,50</sup>

### Implementation as a Standard of Care

Greater attention is being directed toward proactively supporting individuals throughout the continuum of cancer care.<sup>51</sup> The concepts of risk stratification, prospective monitoring for symptom burden, and early detection and management of morbidity are gaining broad recognition across survivorship research and are being heralded as critical components to optimize cancer outcomes.<sup>52</sup> The PSM is a framework that could support larger implementation efforts around cancer survivorship care. Although the early research on PSM was directed to breast cancer, scaling this model to other cancer disease types is aligned with current initiatives and could provide a clinical pathway to prospectively assess broad domains of function, including cognitive, sexual, and psychosocial, in addition to physical, function.<sup>53</sup> The extension of the PSM has been proposed and is currently being studied in this regard.<sup>54,55</sup>

## SURGICAL INTERVENTIONS FOR THE TREATMENT OF SYMPTOMATIC LYMPHEDEMA

### Background

A growing body of evidence supports the effectiveness of surgical procedures in ameliorating the symptoms and disability of patients with lymphedema and reducing the risk of future episodes of cellulitis with outcomes of surgery significantly better than with conservative therapy alone. These surgical procedures can be broadly categorized as physiologic or debulking. Physiologic surgeries, including the lymphovenous bypass or vascularized lymph node transplant (VLNT) procedures, aim to restore lymphatic fluid drainage in the affected extremity. Vascularized lymph node flaps may be harvested from regional lymphatic basins (axillary, inguinal, or cervical) or from within the abdomen. Once established, the chronic lymphedema phenotype is characterized by hypertrophy of fibroadipose tissue that can only be removed directly by suction-assisted lipectomy (SAL) or excisional procedures.

### Diagnosis and Staging

For patients with symptoms and signs consistent with a lymphedema diagnosis and with clinically remarkable volume and/or bioimpedance spectroscopy differences between the limbs (or compared with preoperative measurements),<sup>56,57</sup> the presence of dermal backflow on contrast-enhanced imaging of the lymphatic system is diagnostic for lymphedema. The severity and distribution of this backflow correlates closely with the pathologic condition of the lymphatic vessels and the stage of the disease.<sup>58</sup> Imaging modalities specific to the lymphatic system include indocyanine green fluorescent lymphography, magnetic resonance lymphography, and radioisotope lymphoscintigraphy.

### Patient Selection for Surgical Intervention

For patients presenting early following a lymphedema diagnosis, a trial of conservative therapy, including daily use of a compression garment, directed by a lymphedema therapist for 3 to 6 months is typically instituted and may be curative in some patients with upper-extremity lymphedema.<sup>59</sup> In patients with persistent lymphedema following this, surgical intervention is indicated in those who are medically fit for it.<sup>60</sup>

Patients presenting with advanced-stage lymphedema with considerable pitting edema, in particular those with recurrent bouts of cellulitis, benefit from complete decongestive therapy until the maintenance phase is achieved before proceeding with surgery.<sup>61</sup> Patients with recurrent episodes of cellulitis may benefit from prophylactic antibiotics.

Those with untreated or uncontrolled primary cancer or locoregional recurrence are not generally candidates for surgical intervention and are better served by nonsurgical management. Patients with a very high body mass index can develop lymphedema spontaneously and should be managed by weight-loss interventions, which can result in substantial improvements in lymphedema, prior to being considered for surgical intervention.<sup>62</sup>

### Algorithms for Surgical Management

An algorithmic approach to surgical intervention for lymphedema with standardization improves outcomes.<sup>60</sup> Evidence supports that lymphovenous bypass is indicated in earlier-stage lymphedema in which there are still patent lymphatic vessels, VLNT in advanced lymphedema, and debulking procedures for advanced lymphedema with considerable soft tissue excess. Combination of these procedures extends indications for physiologic surgery to those with advanced-stage chronic lymphedema phenotypes.<sup>63</sup>

**Lymphovenous bypass procedure** Using a fluorescent lymphography imaging system, intradermal injection of indocyanine green into the webspaces of the affected extremity

allows the lymphatic vessels to be mapped, and discrete obstructed lymphatic vessels distal to areas of dermal backflow, ranging in caliber from 0.3 to 0.8 mm, are identified and targeted for supermicrosurgical anastomosis to adjacent small venules.<sup>58</sup> This procedure requires specialist surgical techniques, specialist instruments and 11-0 nylon suture, and a high-powered surgical microscope.

**Vascularized lymph node transplant procedures** VLNT procedures are indicated in advanced presentation lymphedema to import new lymphatic function into an affected extremity. Although the exact mechanisms of action of vascularized lymph node flap transplantation are yet to be fully elucidated, spontaneous lymphatic reconnection mediated by lymphangiogenic growth factor secretion from the transplanted lymph nodes (bridging mechanism),<sup>64</sup> as well as with establishment of new lymphaticovenous drainage within these driven by perfusion gradients between the arterial inflow and venous outflow (pumping mechanism), have been demonstrated in both the clinical and experimental settings.<sup>65</sup> These procedures involve microvascular anastomosis of a functional lymph node flap into an extremity, either to an anatomic (orthotopic) or nonanatomical (heterotopic) location, to restore lymphatic flow. Orthotopic VLNT to the axilla has the additional advantage of allowing for radical scar release and decompression of the subclavian vein, where there is venous insufficiency, which may decrease the lymphatic load with subsequent improvement of the lymphedema.

Vascularized lymph node flaps may be harvested from within the superficial inguinal (groin), lateral thoracic, supraclavicular, or submental regional lymph node basins.<sup>60</sup> For patients wishing to avoid any risk of iatrogenic donor extremity lymphedema or visible donor site scars, intra-abdominal lymph node flap options are increasingly being performed, in particular the omental (gastroepiploic) vascularized lymphatic flap, which may be harvested laparoscopically to reduce donor-site morbidity.<sup>66</sup> In patients undergoing postmastectomy breast reconstruction, VLNT may be performed by transferring a deep inferior epigastric artery perforator flap with a chimeric groin lymph node transplant.<sup>67</sup> Vascularized lymph node transfer from the inguinal or axillary regions must be performed under reverse lymphatic mapping guidance to reduce the risk of iatrogenic donor extremity lymphedema.<sup>68</sup>

**Debulking procedures** Once established, the chronic lymphedema phenotype is characterized by hypertrophy of fibroadipose soft tissues, which can only be removed by direct excision. Traditional excisional surgeries that resulted in unacceptable scarring and morbidity have been replaced, except in the most severe cases, by minimally invasive SAL with postoperative controlled compression therapy.<sup>69</sup> SAL with controlled compression therapy is effective at reducing

the limb volume, improving function and quality of life, and decreasing the risk of future infections.<sup>70,71</sup> As this procedure provides only minimal physiologic improvement of the lymphatic system, patients must continue wearing compression garments lifelong to prevent recurrence. For patients with large-volume advanced fibrotic disease, SAL is ineffective at extracting this tissue, and excisional techniques are required. These include staged direct excision (modified Homan procedure) and, in extreme cases, excision and skin grafting (Charles procedure).

## CLINICAL OUTCOMES OF SURGICAL PROCEDURES

Clinical outcome studies, including randomized controlled trial evidence, support the efficacy of surgical treatment of lymphedema at reducing the occurrence of cellulitis, decreasing the need for compression garments and other conservative therapy, reducing the excess limb volume, improving patient quality of life, and improving physical function.<sup>63,70,72-74</sup> Research supports that physiologic procedures, including lymphovenous bypass and VLNT, are effective at decreasing the symptoms of lymphedema, reducing the risk of future infections, and decreasing the amount of time spent daily for lymphedema care; selected patients may be able to discontinue use of their compression garments. Several studies have confirmed the efficacy and long-term stability of large-volume SAL debulking with controlled compression therapy for reducing limb volume to that similar to the unaffected side for both the upper and lower extremities and improving patient quality of life.<sup>63,70</sup> Additionally, the incidence of cellulitis is dramatically reduced postoperatively.<sup>71</sup> Outcomes for these surgical interventions are significantly better than with maximal conservative therapy alone.<sup>69,72</sup>

## ASSESSING OUTCOMES OF SURGICAL INTERVENTION

Outcome metrics for lymphatic surgery include limb volume, incidence of cellulitis, physiologic downstaging, and patient-reported outcomes. Change in limb volume is most commonly measured by limb circumferential measurements (including derived volumetric calculations) or by using a perometer (optoelectronic limb volumeter). Bioimpedance spectroscopy can also be used to comparatively measure the extracellular fluid, and a growing body of evidence supports its use in response to intervention. Physiologic downstaging can be evaluated either using radioisotope lymphoscintigraphy or by indocyanine green lymphography. The Lymphedema Quality of Life scale, Upper Limb Lymphedema 27 questionnaire, and Lymphedema Life Impact Scale are validated tools specific for patient-reported outcomes in patients with lymphedema.

## CONCLUSION

Secondary lymphedema in the developed world is most commonly attributed to cancer treatment. Serial clinical

trials in many cancer subtypes are actively seeking to de-escalate nodal treatment strategies, recognizing that comprehensive nodal extirpation frequently does not add benefit to long-term survival. Widespread adoption of prospective lymphedema screening models and consistent patient education are needed to raise awareness and early intervention in at-risk patients. Exciting advancements in

microsurgery for prevention and treatment of lymphedema are actively being studied. These may provide durable long-term therapeutic options for at-risk and affected patients with lymphedema. It is critical that all clinicians treating patients with cancer understand available resources for lymphedema prevention and treatment.

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## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

Disclosures provided by the authors and data availability statement (if applicable) are available with this article at DOI <https://doi.org/10.1200/JCO.2019.17.3324>.

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