Editorial Commentary

A promising step forward: early results from a randomized clinical trial support the efficacy of immediate lymphatic reconstruction following axillary lymph node dissection

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Breast cancer related lymphedema (BCRL) is a persistent challenge following axillary lymph node dissection (ALND) (1). Based on a systematic review from our own institution, BCRL can affect up to 32% of patients undergoing ALND, leading to lifelong functional and social challenges (2). The microsurgical community has developed innovative procedures to try to reduce limb volume in women with BCRL, such as lymphovenous anastomosis (LVA) and vascularized lymph node transplant (3). Even more exciting to consider is a preventative approach, named immediate lymphatic reconstruction (ILR), using LVA completed at the time of ALND (4). This procedure involves the identification and preservation of length on arm lymphatic vessels during the ALND and subsequent anastomosis of these lymphatics into branches of regional veins, thereby allowing for ongoing lymphatic drainage through existing lymphatic channels, which would have otherwise been divided and scarred off (4).

While initial use of LVA focused on treating lymphedema, its use for ILR was first described by Boccardo *et al.* in 2009 (4,5). Since that time, interest in the procedure has grown, with recent studies demonstrating a reduction in the absolute risk of BCRL of 27.3% (6.7% BCRL in the ILR group *vs.* 34% BCRL in the standard care group) (2). This represents a risk ratio of 0.22 and a number needed to treat of 4 (2). ILR has also recently been shown to be oncologically safe, as well as cost effective (6,7). These promising early studies have sparked ongoing interest in the procedure and the need for further research into its efficacy, particularly in the form of a randomized clinical trial (RCT) which has not yet been presented in the literature. Fortunately, such a trial is currently underway by Coriddi *et al.*, who have just published their preliminary results (8). This trial is the first of its kind to randomize breast cancer patients undergoing ALND to either ILR or standard care, ALND only, and will provide valuable information into the true efficacy of this procedure. We have been given the pleasure of providing an editorial commentary on this paper. First of all, we commend the authors for taking on this trial, and persevering with it throughout the coronavirus disease 2019 (COVID-19) pandemic. As we await the final report of their trial, the preliminary results are already demonstrating promise.

In their preliminary results, Coriddi *et al.* present an analysis of their first 99 patients (49 intervention and 50 control), who all had at least 12 months of follow-up, with a median follow-up of 18 months. Patients were well balanced between groups in terms of age, body mass index (BMI), race and cancer treatments. Very promisingly, they

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found the cumulative incidence of BCRL to be significantly lower in the ILR group than in the control group (9.5% *vs.* 32%; P=0.014), which provides support for the procedure. The authors plan to ultimately report on 174 patients with 24 months of follow-up in their final analysis which we anticipate will further strengthen their results, although it is important to note that statistical significance may change once all patients have been analyzed, depending on the number of patients that develop lymphedema.

As we have identified through our own lymphedema research, this field of research is not without its challenges, the first of which is the diagnosis of lymphedema itself (9,10). Past studies have used a variety of methods and measurements to diagnose lymphedema, ranging from changes in limb volume over time to imaging modalities such as lymphoscintigraphy and SPY-PHI technology (Stryker Endoscopy, San Jose, CA, USA) and more recently disease-specific patient reported outcomes measures (PROMs) (9). In their RCT, Coriddi *et al.* chose to use relative volume change (RVC) to diagnose lymphedema, with a >10% difference being used for a diagnostic cutoff, where limb measurements taken at 4 cm interval starting at the wrist are then used to calculate limb volume based on a truncated cone formula (11). Although widely used as a common diagnostic method, the authors themselves comment that this number is arbitrary, but the team needed to employ a commonly used method (8). Through conducting our own studies, we agree that this is a practical and reproducible method that is reasonably efficient and does not add additional cost to patient care, though one limitation might be user variability in how exactly the tape measure is used in terms of placement and tightness.

A challenge that we have identified in both this paper and in our own research on ILR (LYMbR Trial; NCT05136079) is the use of compression in both patients who develop lymphedema and those who experience some swelling but do not meet the 10% RVC definition of lymphedema. In this paper, patients in both the ILR (26%) and control (49%) groups used compression at their 18-month follow-up. As patients are followed prospectively in a trial, even a whiff of lymphedema begets a rehabilitation specialist referral and early compression. This early use of compression may be impacting the natural history of lymphedema and possibly be preventing unreconstructed patients from going on to meet the diagnostic threshold, effectively dampening the apparent impact of ILR in the trial. This idea of at least some lymphedema prevention through early compression and physiotherapy has been demonstrated in a prior study and therefore it is possible, that by compressing sub-threshold patients, we are preventing them from otherwise meeting the >10% diagnostic threshold (12).

A strength of this paper is the use of PROMs, including the validated Lymphedema Quality of Life (LYMQOL) questionnaire. Although no statistically significant differences were noted across the various PROMs used, the authors noted a trend towards better function scores in the ILR group. As noted above, the diagnosis and measurement of lymphedema remains a challenge, and measurement cutoffs are largely arbitrary. Patients may more accurately detect changes in limb volumes through symptom reporting even before volume based diagnostic criteria are met or at volume changes lower than current diagnostic thresholds (13). PROMs therefore may perhaps be a better diagnostic and assessment tool for BCRL and even the success of ILR than the clinical evaluation of lymphedema alone. We also appreciate and use the LYMQOL questionnaire but note that it was designed to assess patients with established lymphedema and may not be the most useful to assess ILR patients without the index condition. It is also important to note that patients were not blinded in this trial, so it is possible that control patients may have been more anxious about their symptoms possibly making them more motivated to report them. We agree with the authors that perhaps in the future, once the LYMPH-Q is available for instance, it might be able to pick up more subtle differences between groups and possibly further strengthen results.

Another strength of the paper is their method of randomization, which was done after completion of the ALND, presumably to prevent the oncologic surgeon from knowing the treatment allocation, and subconsciously being more or less aggressive with the ALND, based on their opinion of the efficacy of ILR. One exclusion to randomization in the trial was the lack of suitable donor and recipient vessels, which occurred in 10% of cases. Interestingly, while carrying out ILR at our own institution for the last several years, we have not yet found a non-reconstructable patient. Perhaps this is because the plastic surgeon is scrubbed throughout the case, doing a "dance" with the resecting surgeon, alternating operating, to be sure lymphatics and veins are advocated for, whilst not impacting the oncologic procedure (14). Although we find this to be very helpful, this is a large human resource commitment on the part of the plastic surgeon, and we envision that in this trial, the plastic surgeons were called upon following the completion of the ALND. Presumably, 10% of patients

had their lymphatics cut too short, or venous tributaries foreshortened, making the procedure impossible.

Although this paper represents the preliminary results of the RCT, the minimum 12 months of follow-up may be too short to capture some patients who may go on to develop lymphedema. Noted in their results was an increase in the cumulative incidence of lymphedema in both the ILR and control groups as follow-up time increased. There was just a 2% incidence of lymphedema in the ILR group by 12 months, which had then increased to 9.5% by 18 months. The incidence of lymphedema in the control group similarly increased from 18% at 12 months up to 32% by 24 months. It is therefore possible that the incidence of lymphedema may continue to increase over time, especially since so many patients were radiated, which may lead to late fibrosis. Reassuringly, although the incidence of lymphedema did increase in both groups, when comparing the cumulative incidence of lymphedema between groups, the incidence was significantly lower in the ILR group. Therefore, although more patients will go on to develop lymphedema over time even with ILR, ILR does seem to continue to prevent more cases from occurring than in patients who did not have the procedure. Given the amount of time and resources required for the procedure, future research that focuses on better understanding exactly which patients undergoing ALND are the most at risk for developing lymphedema and over what time period, will help surgeons to select the best candidates for ILR.

Overall, the preliminary results of the RCT by Coriddi *et al.*, show promise for the efficacy of ILR and represent an essential step in moving this procedure forward. Despite challenges with the definition and measurement of lymphedema, we cannot continue to advance this field without trials such as this one, which serve to greatly improve the body of evidence for the procedure.

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