

# Evidence Mapping of the Treatments for Breast Cancer–related Lymphedema

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**Background:** Women treated for breast cancer are facing a lifetime risk of developing lymphedema, which occurs in up to 40% of this population. There is a lack of evidence and limited knowledge regarding the treatment of breast cancer–related lymphedema (BCRL). The aim of this study was to identify, describe, and organize the currently available evidence in the treatment of BCRL.

**Methods:** We conducted an evidence mapping review study according to the methodology proposed by Global Evidence Mapping. We performed a systematic search in Medline, Embase, Central (Cochrane), and Epistemonikos, from 2000–2020. We included studies about all treatment types for BCRL, including surgical and nonsurgical treatment. Results were summarized in narrative and tabular forms.

**Results:** A total of 240 studies were included in this mapping review, distributed as follows: 147 experimental studies [102 randomized clinical trials (RCTs) and 45 quasi-experimental clinical trials], 48 observational studies (34 prospective and 14 retrospective studies), and 45 systematic reviews (17 of them with metaanalysis). Most of the RCTs were on nonsurgical interventions. Only two RCTs addressed surgical intervention.

**Conclusions:** In the last 20 years, there were an average of 12 publications per year on the treatment of BCRL. Recently this lack of attention has been partially corrected, as the majority were published in the past 5 years. However, most of them were on nonsurgical interventions. Well-designed RCTs on surgery are needed to measure the effectiveness of the applied interventions. (*Plast Reconstr Surg Glob Open* 2022;10:e4045; doi: [10.1097/GOX.0000000000004045](https://doi.org/10.1097/GOX.0000000000004045); Published online 18 January 2022.)

## INTRODUCTION

More than 1.38 million women worldwide were estimated to be diagnosed with breast cancer in 2008, accounting for 23% of all diagnosed cancers among women.<sup>1</sup>

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Given that the 5-year survival rate for breast cancer is now 90%, experiencing breast cancer is ultimately about quality of life.<sup>1</sup> Women treated for breast cancer face a lifetime risk of developing lymphedema, which occurs in up to 40% of this population and negatively affects breast cancer survivors' quality of life.<sup>2–5</sup>

Patients with lymphedema have a significantly decreased quality of life, with frequent infections, reduced range of motion, and a cosmetic deformity that is difficult to conceal.<sup>6</sup> Treatment for breast cancer–related lymphedema (BCRL) has mostly been symptomatic in nature and designed mainly to prevent swelling progression.<sup>7</sup> BCRL treatment might involve (1) surgical treatments, which currently include the different microsurgery techniques and liposuction, or (2) nonsurgical treatments, which might include pharmacotherapy, diet, exercise, and physiotherapy options.

In the past decades, major advancements in the lymphatic imaging and surgical instruments and techniques have rekindled broader interest among surgeons in the pursuit of a more effective treatment for lymphedema.<sup>8</sup> Nonsurgical

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treatments are taking part in both prevention and treatment of BCRL, and they include a great variety of options, mainly physiotherapy like complex physical therapy, intermittent pneumatic compression, or compressive garments.<sup>9</sup>

The limited knowledge regarding the treatment of BCRL, together with the insufficient standardization of the different therapeutic options, warrants highlighting the available evidence using an innovative approach provided by evidence mapping, combined with a detailed description of the available randomized clinical trials (RCTs) published in the literature.

Evidence mapping allows a visual understanding of the evidence base of any treatment, apart from supporting the process of decision-making by facilitating information in a user-friendly format.<sup>10</sup> Furthermore, it is the best study design when there is an abundance and a diversity of research and an excellent way to identify gaps in a topic area.<sup>10</sup>

Thus, the main objective of this study was to identify, describe, and organize the currently available evidence in the treatment of BCRL, with an additional focus on RCTs, especially in relation to surgical interventions. In addition, the study aimed to identify the existing gaps of knowledge and to provide recommendations for future research.

## PATIENTS AND METHODS

### Study Design

An evidence mapping study was conducted according to the methodology proposed by Global Evidence Mapping.<sup>11</sup> This evidence mapping adhered to the PRISMA-Extension for Scoping Reviews.<sup>12</sup> All methods were specified a priori in a protocol (available on request).

### Eligibility Criteria

We have used the PICOS framework (population, intervention, comparison, outcome and study design) to formulate the eligibility criteria.<sup>13</sup> We considered eligible patients (older than 18 years old) with BCRL. We included all treatment types for BCRL, including surgical and nonsurgical treatment. We considered studies with all kinds of comparison and studies without comparison groups. Due to the nature of the study, all types of outcomes were eligible. We included the following study designs from the year 2000 to 2020: RCTs, quasi-experimental clinical trials, observational studies (retrospective, prospective), and systematic reviews (SRs) with or without metanalysis. We selected the most updated publication when we identified studies published on the same topic and by the same team. We excluded animal studies, in vitro studies, single case reports, case series, letters to the editor, narrative reviews, studies including different types of edema or mixed edema, studies including less than 10 patients or reviews with fewer than three studies and studies addressing other than treatment of BCRL or addressing both prevention and treatment together.

### Search Strategy

The search strategy was conducted in MEDLINE (via PubMed), Embase (via Ovid), Cochrane Central Register of Controlled Trials (CENTRAL) via The Cochrane

## Takeaways

**Question:** There is a lack of evidence and limited knowledge regarding the treatment of breast cancer-related lymphedema.

**Findings:** A total of 240 studies were included in this mapping review, most of them nonsurgical interventions. Among these studies, there were 102 randomized clinical trials, with only two RCTs addressing surgical interventions

**Meaning:** More surgical randomized clinical trials are needed in the future to measure the real effectiveness of the applied interventions.

Library, and Epistemonikos. A search algorithm was designed, including a combination of controlled vocabulary, Medical Subject Headings (MeSH) descriptors, free text terms and thesaurus terms when available, with no language restriction. We did not search for grey literature.

### Study Selection and Data Extraction

The studies retrieved by titles and abstract were uploaded to Mendeley and then managed with the software Rayyan QCRI. After removing duplicates, three reviewers (AMA, AIS, and LVC) independently screened all titles and abstracts, with each article being screened by at least two reviewers. Afterward, a full-text screening was done by the same reviewers who confirmed eligibility based on the inclusion and exclusion criteria. Disagreements between two reviewers were resolved mainly by the third reviewer or by consensus. For each individual study, data extraction was conducted separately by the two reviewers (AMA and AIS). Results were then compared, and in case of disagreement, the third reviewer (LVC) acted as a referee to reach consensus.

### Data Synthesis and Analysis

The obtained results are presented in a narrative and visual format using tables, graphs, and a bubble plot. A flow chart for the whole process of study selection was elaborated based on the PRISMA-P diagram.<sup>14</sup> The analysis of the selected studies was divided in two parts: a general mapping description of all studies included in this mapping review, and a detailed description of the included RCTs.

## RESULTS

### Studies Selection

The flow chart of the studies selection is shown in [Figure 1](#). The search yielded a total of 4993 studies. After removing 1751 duplicates, we proceeded with 3242 studies to screen by title and abstract. In total, 2889 studies were excluded for not being related to the review's main topic. Then, a full-text review was done for 353 studies. After the resolution of discrepancies by consensus between researchers, we excluded 106 studies. Similarly, seven studies where the full-text was missing were also excluded

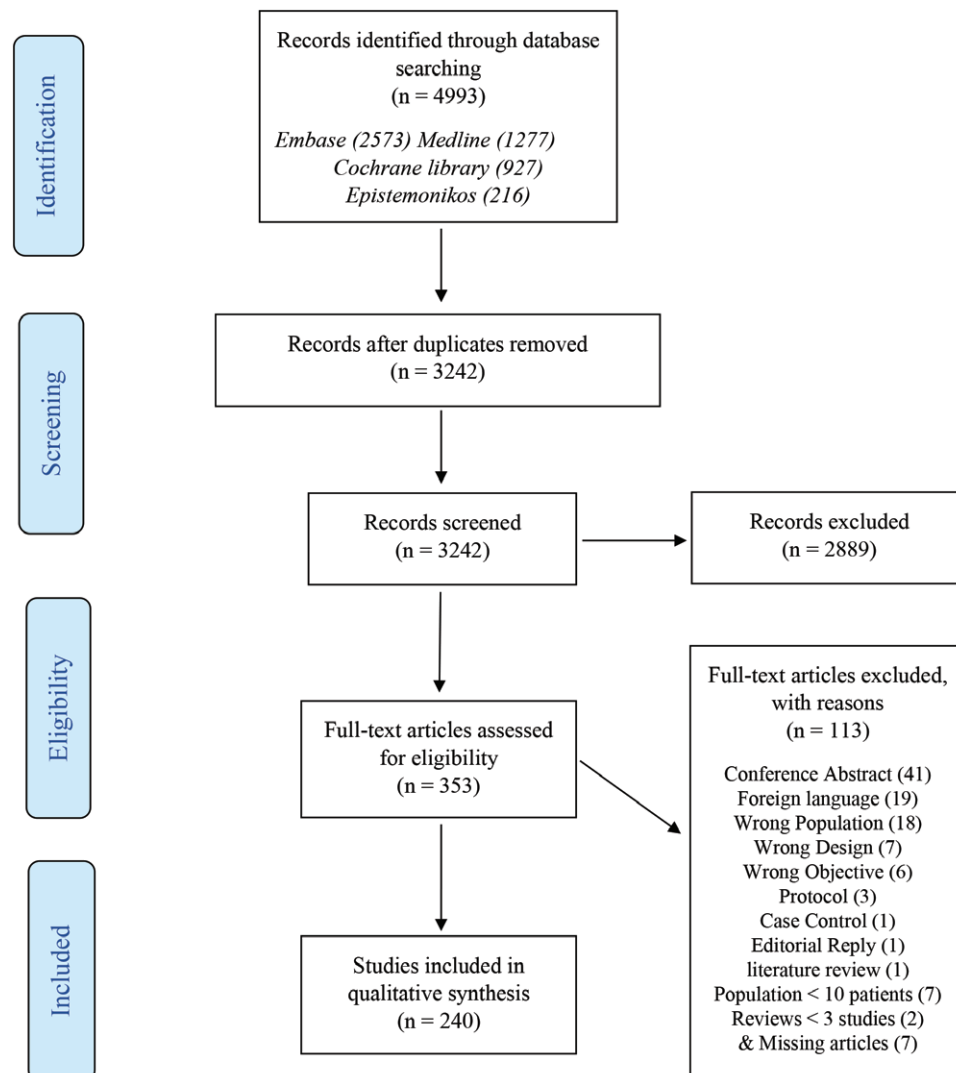


Fig. 1. PRISMA flow diagram and selection process of studies on BCRL.

from the descriptive analysis. Finally, a total of 240 studies were included in this mapping review.

The main reason for excluding studies was that the articles were published as conference abstracts (41); other reasons included foreign languages (other than English and Spanish) (19), wrong population (18), wrong design (7), wrong objective (6), published protocol (3), case report (1), editorial reply (1), literature review (1), population less than 10 patients (7), reviews including less than three studies (2), and the aforementioned missing full-text (7).

#### Characteristics of All Included Studies

##### Publication Year and Language

We observed a marked increase in the number of publications in the past 5 years; 139 (58%) of the published studies in the treatment of BCRL were from 2016 to 2020 (Table 1). As defined in the eligibility criteria, we included only studies published in English and Spanish. Overall, only two studies were published in Spanish, and the rest (238 studies) were all in English.

##### Countries

The published studies were distributed among different countries worldwide. The United States of America had the highest number of publications (32) followed by Turkey (19), Australia (17), China (16), South Korea (14), Brazil (12), the United Kingdom (12), and Iran (10). The rest of the countries had fewer than 10 published studies (Fig. 2).

##### Study Design

We identified 147 experimental studies (102 RCTs and 45 quasi-experimental clinical trials), 48 observational studies (34 prospective studies and 14 retrospective studies), and 45 SRs (28 SRs without meta-analysis and 17 with meta-analysis) (Table 2).

##### Intervention Type

The identified studies included different types of intervention (42 surgical treatment and 198 nonsurgical treatment). Most of the surgical interventions were combined with a nonsurgical treatment, such as garment, exercise, or

**Table 1. Distribution of the Total Studies and RCTs on BCRL by Publication Year**

Years	Total Studies, N (%)	RCTs, N (%)
2000–2004	15 (6.25)	9 (9)
2005–2009	33 (13.75)	13 (13)
2010–2014	53 (22)	28 (27)
2015–2020	139 (58)	52 (51)
Total	240 (100)	102 (100)

others. The distribution of the intervention type according to the study design is described in [Figure 3](#).

**Characteristics of the RCTs**

**Publication Year and Language**

Out of the total RCTs, 52 (51%) were published in the past 5 years, and they all were published in the English language ([Table 1](#)).

**Countries**

During the last 20 years, RCTs have been published in many different countries, the main ones being Australia

(12), the USA (11), Turkey (8), South Korea (8), the UK (7), China (5), and Poland (5). The remaining countries published fewer than five clinical trials.

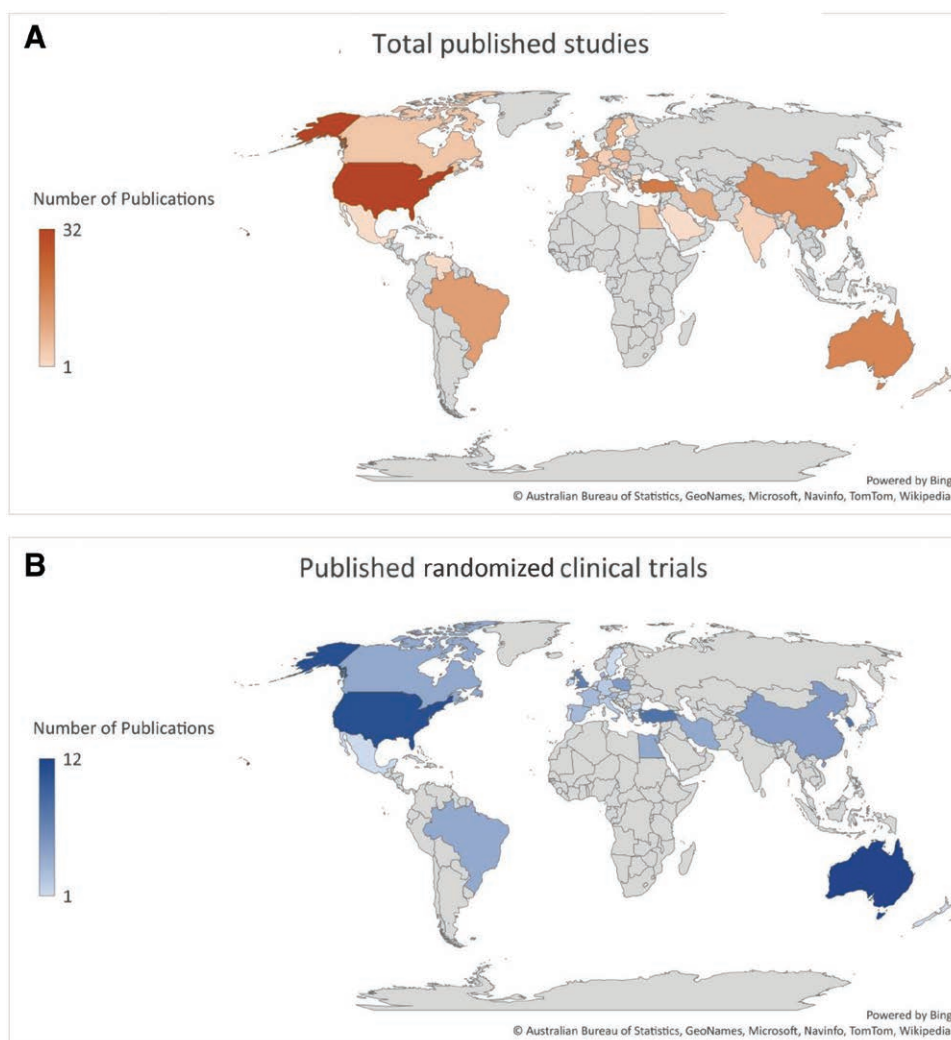
**Population Characteristics and RCTs Design**

These RCTs included patients with BCRL affecting the ipsilateral arm, but three studies described breast or chest lymphedema secondary to breast conservative treatment or mastectomy. Three trials studied BCRL only in overweight or obese patients. All were parallel with two arm groups, but there were five crossover design trials, and five RCTs comparing three arm groups.

We encountered some RCTs that included the same population and methodology protocol and were performed by the same team but measuring different outcomes and/or describing subgroup analysis. These studies have been included as separate studies and analyzed independently.

**Intervention Type**

Overall, most of the RCTs were on nonsurgical treatment, and there was a large diversity in nonsurgical



**Fig. 2.** Geographic distribution of the published studies on BCRL. A, Total number of studies B, Randomized clinical trials.



**Table 2. Frequency of the Study Design among Total Studies in the Treatment of BCRL**

Study Design	No. Studies (%)
Interventional	147 (61.25)
RCTs	102 (42.5)
Quasi experimental	45 (18.75)
Observational	48 (20)
Prospective	34 (14.16)
Retrospective	14 (5.84)
Systemic reviews	45 (18.75)
SR without meta-analysis	28 (11.67)
SR with meta-analysis	17 (7.08)
Total	240 (100)

treatment options, mostly regarding physiotherapy treatments, such as different kinds of sleeves/bandages, kinesio tape, manual lymphatic drainage, pneumatic compression pump, decongestive compression therapy, exercise protocols (active, resistant, aqua exercise), yoga, weight loss, acupuncture or different pharmacotherapy, laser therapy, satellite ganglionic block, etc.

Among the nonsurgical treatment trials, we also found two studies addressing autologous stem cell transplantation (ASC), which is considered a minimally invasive medical intervention; both studies were done in a surgery setting (Table 3).

There were only two RCTs on surgical treatment: the first trial about lymphovenous anastomosis (LVA), and the second trial about vascularized lymph node transfer (VLNT). The characteristics of the included RCTs on surgical intervention are described in Table 4.

### Measured Outcomes

There was a wide variety of outcomes measured in these trials and most of the trials focused on more than one outcome. The main outcome measured was the arm volume and circumference, followed by lymphedema symptoms like heaviness or pain, arm function and range

of movements, and quality of life. Other measured outcomes were patient adherence, satisfaction, safety and adverse events, skin changes, infection and inflammatory markers, cost of treatments, or intervention duration (Fig. 4).

### Effect of Intervention

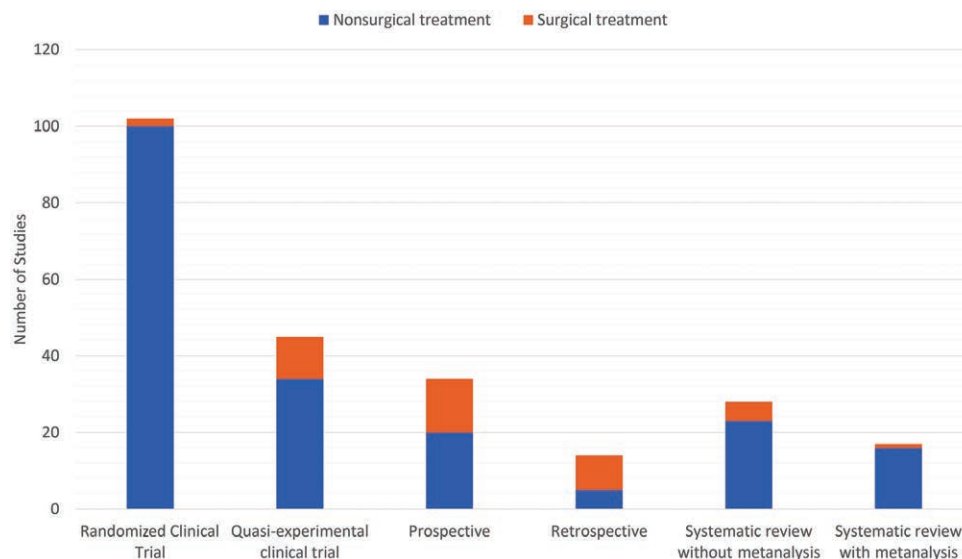
Most of the RCT results favored toward intervention (59). Some other studies favored toward the comparison group (7), and the rest of the trials had no difference of effect by applying the intervention (37). The therapeutic results according to the intervention type among the RCTs are described in Figure 5.

## DISCUSSION

As we perceived that the available evidence of the treatment for BCRL is not proportional to the importance of this health condition, which is considered as significant problem for women who had been treated for breast cancer, we decided to conduct a mapping review to identify and to make a broad picture of the current situation of this important topic.

There is a variety of methodological standards to develop a mapping review, but we decided to follow the Global Evidence Mapping initiative because it is very rational and systematic.<sup>11</sup> This methodology includes three core tasks: setting the topic area's boundaries and the context in question, searching and selecting relevant studies, and reporting on search results and study characteristics.<sup>11</sup>

In the last 20 years, we identified 240 publications about the treatment for BCRL, which means an average of 12 publications per year. Recently, this lack of attention has been partially corrected when the majority of these articles (58%) were published in the past 5 years. We assume that this is due to the availability of new treatment options and techniques in the recent years, as well as an increase in the interest of clinical research among



**Fig. 3.** Distribution of the intervention type according to the study design among the total studies (total: n = 240) on BCRL.

**Table 3. Frequency of the Specific Treatment on BCRL according to the Intervention Type among the RCTs**

Intervention Type	Specific Treatment	No. RCTs
Surgical treatment (N = 2)	Lymphovenous anastomosis (robot-assisted)	1
	Vascularized lymph node transfer	1
Nonsurgical treatment (N = 100)	Exercise (active, resistant, aqua exercise)	18
	Compression sleeve/bandage	14
	Kinesio tape	10
	Manual lymphatic drainage	10
	Pneumatic compression pump	10
	Pharmacotherapy	8
	Laser therapy/electrical therapy	8
	Yoga	4
	Acupuncture	3
	Decongestive compression therapy	3
	Satellite ganglionic block	3
	Diet and weight loss	3
	Autologous stem cells transplantation	2
	Hyperbaric oxygen therapy	1
Extra corporal shock wave therapy	1	
Others	2	
Total		102

health professionals about the effectiveness and safety of these treatments. Due to the extreme importance of BCRL and its physical and psychosocial consequences, more research is needed in this field to strengthen the evidence base and ensure patients receive clinically effective treatment.<sup>17</sup>

We have observed in this review that surgical interventions in these articles were mainly distributed between microsurgical techniques (LVA, vascularized lymph node transfer) and liposuction. These surgical procedures focused on re-establishing the function of the lymphatic system and reducing the volume, respectively, which might reflect the common surgical practice nowadays.<sup>18</sup> On the other hand, there was great diversity of nonsurgical interventions, and usually there was a mix of different options that have been used to treat a considerably large number of patients with BCRL.<sup>19</sup>

Our results show that the country with the most research on this topic was the USA, followed by three main countries: Turkey, Australia, and China. Moreover, there was significant variability among the countries in the treatment options that have been assessed in these studies, which supports the diversity of the treatment worldwide.<sup>20, 21</sup>

In our findings, of the total 240 articles that we have identified, about 81% were primary studies, which include a considerably large number of interventional studies (61%) and observational studies (20%). However, about 19% of the total publications were SRs, which might indicate a considerable gap in secondary studies. Even though well-conducted SRs are considered higher quality evidence than other studies in decision-making for clinical practice and health policy,<sup>22</sup> it was not the goal of this study to analyze these SRs.

Due to the fact that RCTs are highly controlled and managed studies, and their level of evidence is higher than other types of primary studies,<sup>23</sup> on this mapping review, we have decided to focus more on these RCTs and to provide more description of their data.

Of the total 102 RCTs that we have identified, there were 100 RCTs on nonsurgical treatment and only two studies addressing surgical treatment,<sup>15,16</sup> which indicates the insufficient number of RCTs in the field of lymphedema surgery. This could be mainly due to the usual and general difficulties to design RCTs to assess the surgical procedures compared with pharmaceutical agents.<sup>24</sup> Therefore, despite the progressive use of the different surgical interventions in clinical practice, there is currently not enough high-quality research to assess their effectiveness.<sup>25</sup> This highlights the current need for well-designed RCTs to compare the effectiveness of the broad range of these surgical modalities, as well as in relation to nonsurgical therapy.

Sometimes the scarcity of RCTs has been justified due to the difficulty of blinding, but this requirement is not absolutely necessary in designing RCTs and could be overcome with alternative designs to maximize the validity and to reduce the chance of assessment bias.<sup>26</sup> However, we assumed that well-designed non-randomized prospective studies were conducted on surgical intervention.

We observed that many RCTs described combined treatment options for patients with BCRL. Likewise, we have identified that studies addressing the surgical interventions were also accompanied by garments and/or physiotherapy. This signifies the importance of a multidisciplinary team in lymphedema treatment provided by a group of healthcare professionals.<sup>27</sup>

Among the total number of RCTs, three studies assessed exclusively the treatment effectiveness in overweight and

**Table 4. Characteristics of the Included Randomized Clinical Trials on Surgical Intervention for BCRL**

Study	Country	Title	No. Patients	Intervention	Comparison Group	Outcome Measured	Reported Results
van Mulken et al <sup>15</sup>	Netherlands	First-in-human robotic supermicrosurgery using a dedicated microsurgical robot for treating breast cancer-related lymphedema: a randomized pilot trial	20	Robot-assisted supermicrosurgical lymphaticovenous anastomosis	Manual supermicrosurgical lymphaticovenous anastomosis	Upper limb volume, quality of life, duration of surgery, and quality of anastomosis	No difference
Dionysiou et al <sup>16</sup>	Greece	A randomized control study of treating secondary stage II breast-cancer-related lymphoedema with free lymph node transfer	36	Vascularized lymph node transfer, physiotherapy, and compression	Physiotherapy and compression alone	Upper limb volume, infection, and lymphedema symptoms	Favors toward intervention

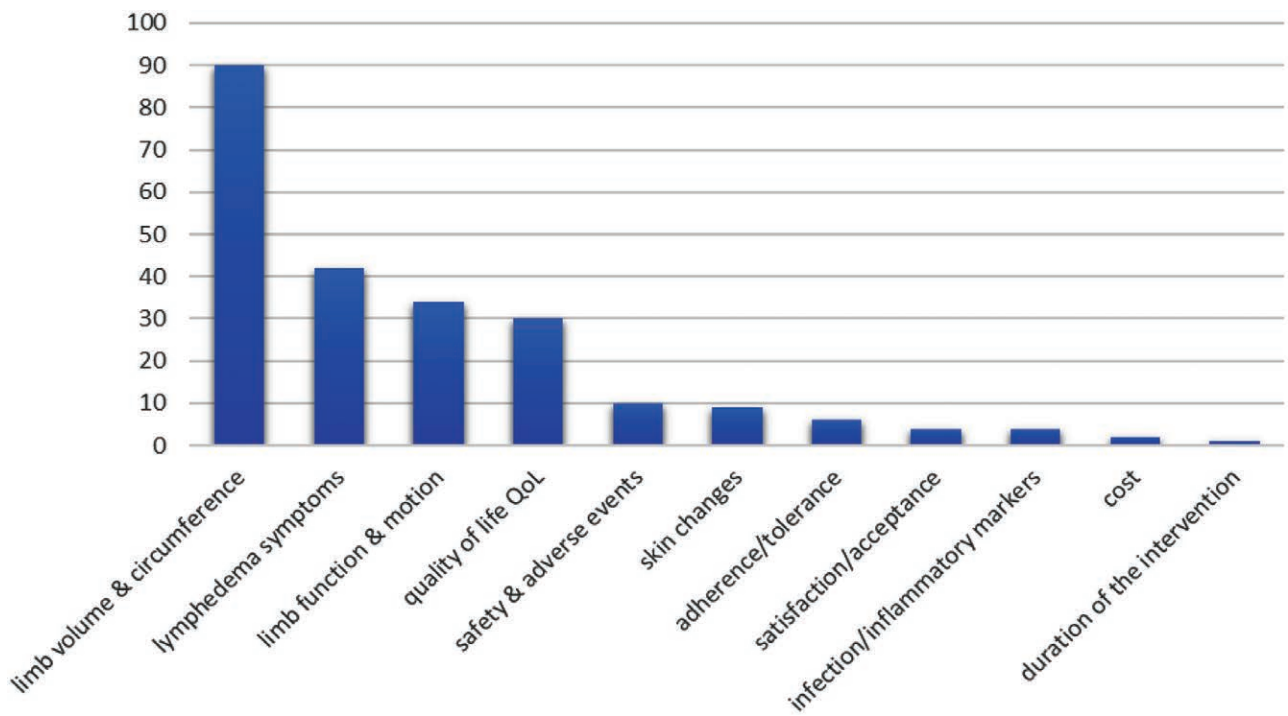
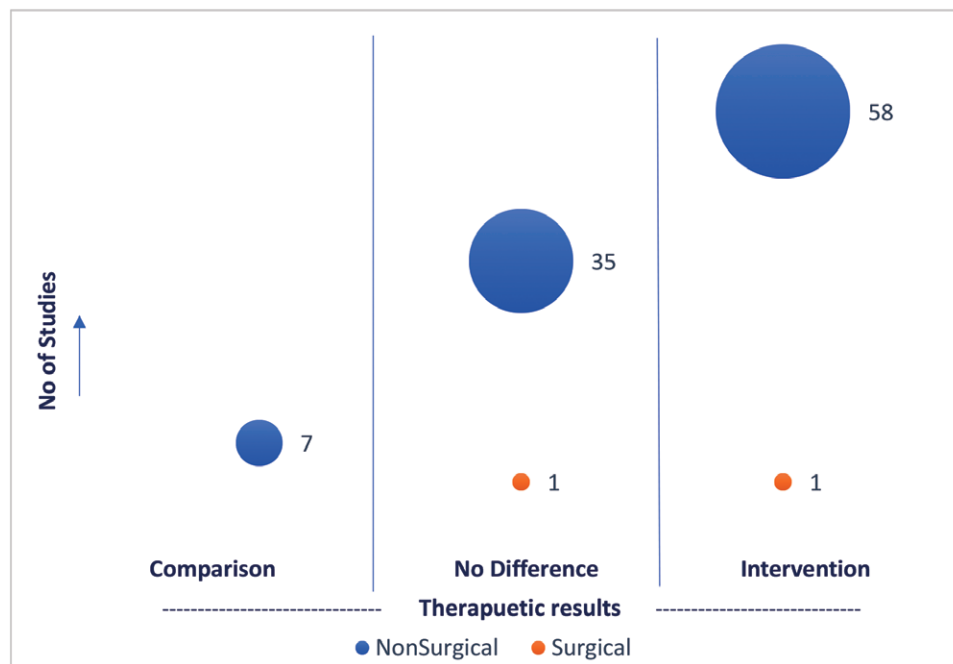


Fig. 4. Distribution of the measured outcomes in the randomized control trials on BCRL.



- Therapeutic results: Favors toward comparison / No difference effect / Favors toward intervention
- Total studies N=102; Nonsurgical studies N=100, Surgical studies N=2

Fig. 5. Evidence mapping of the therapeutic results according to the type of intervention among the randomized clinical trials on BCRL.

obese patients.<sup>28–30</sup> Given the fact that obese individuals have three times the risk of developing lymphedema compared with the non-obese population,<sup>31</sup> we assumed that this population was well represented in the totality of RCTs. Moreover, there were three RCTs that assessed the treatment effectiveness for lymphedema of the breast and chest, which could combine the arm lymphedema.<sup>32–34</sup> Unfortunately, these lymphedema sites are usually missed during the clinical assessment and treatment of BCRL.

There was a wide heterogeneity among the published studies in terms of population characteristics, intervention types, measured outcomes, and study design. This should be addressed clearly for future research to provide evidence about the treatment effectiveness and could be complemented by SRs if the primary studies are valid and available in number.

Even though there was a great variability of the measured outcomes in these RCTs and the majority focused on more than one outcome, almost 90% of them measured the limb volume and circumference, which is considered the most relevant objective and subjective outcome for patients' follow-up after the applied intervention. It depends mainly on the detectable volume and circumference difference between the involved and the uninvolved limb.<sup>35</sup>

As there were no reported harmful interventions, we classified the conclusions of the RCT results as favoring toward the intervention (59 articles), toward comparison (only seven articles) or no different effect (36 articles). We have presented these results on a bubble plot to obtain a broader outlook of the available evidence (Fig. 5).

This study presents some limitations. Firstly, the absence of the methodological quality assessment of primary studies that is not conducted in a mapping review. Secondly, the nature of the mapping review is descriptive and not to provide sufficient evidence to support the applied intervention. And finally, the mapping review requires additional expertise for creating the visual output.

Among the strengths of this study, we have made an extensive search using standard methodology that contributes to the descriptive objectives. Moreover, there was a consistency between the reviewers, and the screening part was done in a systematic way by three different reviewers, which ensures confidence of the reported results.

Although the quality assessment part is not a core task of evidence mapping,<sup>10</sup> we took into consideration the methodological quality when we defined the eligibility criteria by excluding low evidence studies such as case reports. Also, we presented the results in a relatively easy way to interpret and understand. The results of this evidence mapping review might be used to address more focused research in the future, particularly in the field of surgery. Finally, this might be the first evidence mapping about therapeutic interventions for BCRL, as per our knowledge.

## CONCLUSIONS

In the last 20 years, there were an average of 12 publications per year on the treatment of BCRL, even though lymphedema is considered an important health problem for women who undergo breast cancer treatment.

Recently this lack of attention has been partially corrected, as the majority of the studies were published in the past 5 years. However, most of these studies were on nonsurgical interventions.

Most of the RCTs focused on nonsurgical treatment, and only two RCTs addressed the effectiveness of surgical treatment. Therefore, well-designed RCTs on surgical interventions are needed to measure their real effectiveness before wider use in regular clinical practice.

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