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Treatment for lymphedema following head and neck cancer therapy: A systematic review

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ABSTRACT

Objective: To perform the first systematic review evaluating all established treatment modalities of head and neck lymphedema resulting from head and neck cancer therapy. Since craniofacial lymphedema treatment represents unique challenges not addressed by extremity lymphedema therapies, a systematic review and evaluation of treatment modalities specific to this area is needed to guide clinical management and further research.
Data sources: Four electronic databases were searches from inception to September 2018. These included Scopus (Embase), PubMed (Medline), Clinicaltrials.gov, and Cochrane Databases.
Review methods: A search string was developed, and all databases queried for keywords on three subjects: head and neck cancer, lymphedema, and therapy. Results were uploaded to an EndNote database where relevant items were identified by hand-searching all titles and abstracts. Subsequently results were combined, duplicates removed, and full papers screened according to eligibility criteria.
Results: Of a total 492 search results, twenty-six items met eligibility criteria for this review. These included fourteen cohort studies, seven case reports, two randomized controlled trials, two systematic reviews, and one narrative review totaling 1018 study subjects. The manual lymph drainage group had the largest number of studies and participants, with fewer studies investigating selenium, liposuction, and lymphaticovenular anastomosis.
Conclusion: Evidence for the efficacy of all types of lymphedema therapy is limited by paucity of large randomized controlled trials. While manual lymph drainage is best studied, liposuction and surgical treatments have also been effective in a small number of patients.

1. Introduction

As head and neck cancer survival rates continue to improve, there is an increasing focus on improving the quality of life for survivors by reducing the debilitating side effects resulting from cancer treatment [1]. Lymphedema is a common, and well-studied side effect in breast, genitourinary, and gynecologic cancer treatments, occurring as a result of direct tumor invasion, radiation therapy, or surgical resection which disrupts lymphatic drainage [2]. However is not as well studied following head and neck cancer (HNC) therapy [3].

Cosmetic sequelae remain the most common complication of head and neck lymphedema (HNL), with 84% of patients reporting complaints about their appearance. However, 33% of patients also report functional deficits such as pain, dysphagia and dysphonia [4].

The diagnosis and measurement of HNL is challenging, and reproducible measurements can be problematic as reference points in patients with HNL are inconsistent and often obscured [5]. As a result, the prevalence of HNL is understudied, but is estimated to be as high as 75.3% [6].

Treatment for HNL is largely based on extremity edema literature due to the paucity of research on lymphedema specific to the head and neck. Manual lymphatic drainage (MLD) is recommended as the first-line therapy for HNL according to American Cancer Society Guidelines [7]. Originally developed by Dr. Vodder, it consists of tissue massage,

Abbreviations: HNC, head and neck cancer; CDT, complete decongestion therapy; HNL, head and neck lymphedema; LVA, lymphaticovenular anastomosis; MLD, manual lymph drainage

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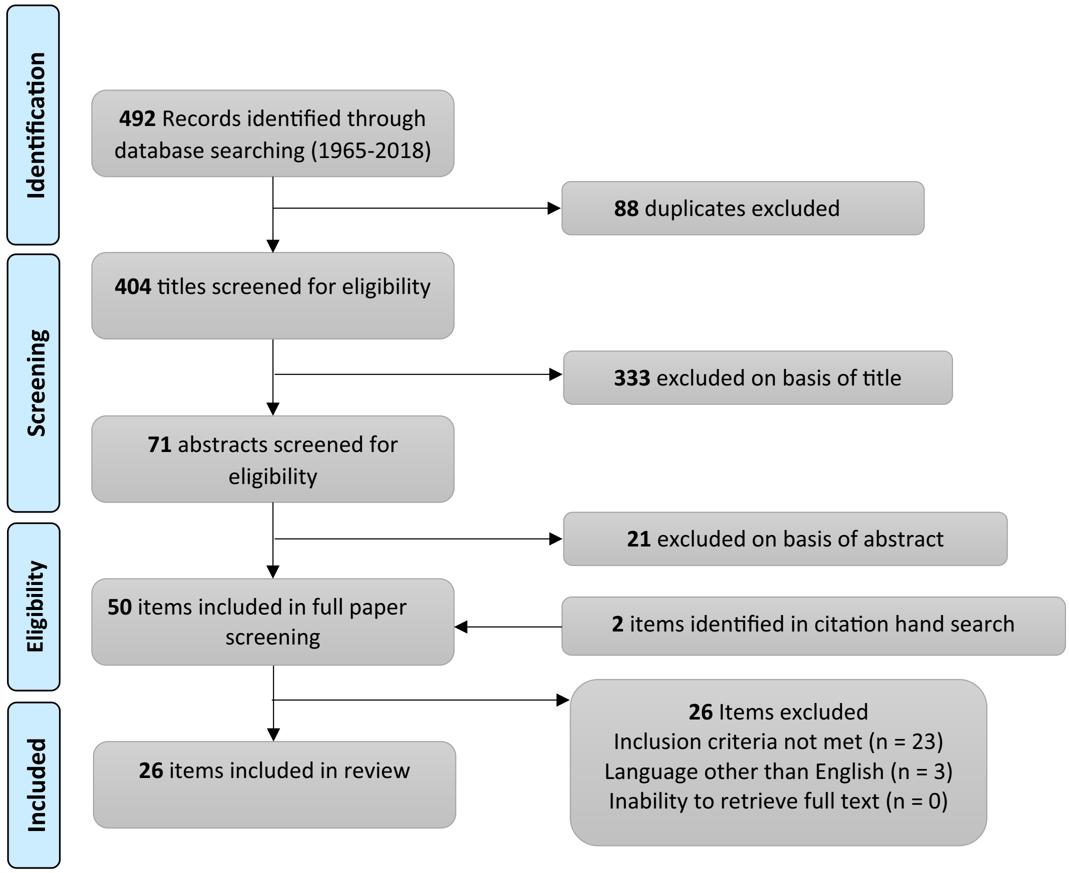

Fig. 1. Article selection flow diagram.

joint manipulation, and stretching exercises performed by a trained therapist [8].

Complete decongestion therapy (CDT), a newer therapy, is the most widely used treatment for HNL today and combines MLD with the use of custom compression garments, physical exercise, and skin care [9]. Despite their frequent use by healthcare providers, compliance with compression garments of the head and neck is a barrier for many patients who seek alternative therapies.

Selenium compounds, thought to reduce lymphedema by increasing the activity of reactive oxygen species clearing enzymes, as well as amifostine, and acupuncture have been studied as alternatives and adjuncts to compressive therapy, though their use is not yet widespread [10,11].

Recently, surgical management has been increasingly used for refractory cases. This includes liposuction and microvascular surgery. Lymphaticovenular anastomosis (LVA) is one such novel technique in which a diseased or absent lymphatic drainage pathway is bypassed by identifying local functioning lymphatic vessels and surgically anastomosing them to a suitable venule, thereby creating a functional drainage pathway [12–14].

Unfortunately, there continues to be a lack of consensus on the most effective way to diagnose and treat lymphedema following HNC, and current recommendations are not evidence based [15]. Our goal is to review the current literature on HNL treatment and assess which treatment modalities have evidence demonstrating their effectiveness, to better inform clinical management and to suggest avenues of further investigation.

2. Methods

This systematic review was conducted using the PRISMA 2009 checklist to ensure compliance with current guidelines.

2.1. *Eligibility criteria*

Any study investigating lymphedema treatment outcomes for one or more patients who underwent chemotherapy, radiation therapy or surgical excision of a head or neck cancer was included. To meet inclusion criteria lymphedema had to be present in the head or neck within one year of cancer treatment. Any study focused on extremity lymphedema treatment that included a cohort of HNL patients was also included. Studies of all lymphedema interventions present in our literature search including manual lymph drainage (MLD), complete decongestive therapy (CDT), surgical interventions, acupuncture, and chemotherapeutics were also included. Primary review outcomes were statistically significant improvement in lymphedema as measured by the study investigator or perceived by the patient using any metric to determine which, if any modalities were effective. Due to the paucity of randomized controlled trials (RCTs), all study types were included, and studies were not required to include a control arm. Studies were limited to the English language and all publication years were included. Ongoing and completed clinical trials were also included if preliminary data was available.

2.2. *Search strategy and study selection*

Four electronic databases were searched from inception to September 2018: MEDLINE (PubMed), EMBASE (Scopus), Cochrane Library, and clinicaltrials.gov. A research librarian was consulted for the development of appropriate search terms. The search strategy had three components: head and neck cancer, lymphedema, and therapy. These components were used to identify corresponding MeSH terms and combined to develop the following search string for PubMed search: (treatment) AND ((lymphedema) AND ((((submental) OR oral tumor) OR laryngocarcinoma) OR (head and neck cancer))). Search

Table 1
Characteristics of included studies.

Study	*n*	Cancer treatment	LE location	Assessment tool	Baseline severity	Median follow-up	Outcome
MLD & CDT – level 4 evidence							
Cohort							
Tacani et al. 2016 [5]	32	Surgery 100% Neck dissection 85% Rad 90% Chemo 50%	Submental 90% Face 65% Neck 35%	Visual Analog Scale (VAS)-pain	Fibrosis 70% Pain score: 7.8	9–39 treatment sessions (time unspecified)	Significant reduction in pain (VAS 7.8 ± 2.2 to 3.6 ± 1.6); ($p < 0.001$) and lymphedema ($p < 0.05$)
Smith et al. 2015 [4]	733	Surgery 12% Rad 30% Surgery + Rad 58%	Submental 89% Face 53% Neck 90% Intra oral 18%	MDACC[a] HNL evaluation protocol (modified Foldi scale)	Soft non-pitting edema 28% Reversible pitting edema 62% Firm pitting edema 9%	69 days	74% of patients in full compliance with treatment demonstrated improvement ($p < 0.001$)
Piso et al. 2001 [19]	11	Resection with neck dissection 100% Rad 9%	Not specified	Distance measurements	Pretherapy sum of distances 93.5 cm	3–9 weeks after 6 weeks therapy	Decrease in sum distance measured by 9 cm ± 7.1 at 6 weeks ($p < 0.05$), non-significant decrease until 12 weeks
Krisciunas, 2016 [23]	5	Rad 100%	Not specified	10-point Wong-Baker Pain Faces Scale	Mean Wong-Baker Pain Faces Score 2.9	4–7 weekly sessions	Decrease in mean score from 2.9 to 0.9 (significance not reported)
Doke et al. 2018 [20]	34	Radical neck dissection 53% Rad 100%	Not specified	10-point Wong-Baker Pain Faces Scale, neck circumference, cervical range of motion	Pain score 4.3 ± 2.6 Post-rad neck circumference 138.1 cm ± 10.2	3–12 months (during treatment)	Pain score reduced by 3.1 points at 6 months ($p < 0.0001$) 38.4% decrease in neck circumference ($p < 0.05$) 44.6–55.3% increase in cervical range of motion
Nixon et al. 2018 [48]	10	Surgery 100% Bilateral dissection 80% Rad 90% Chemo 20% Rad. Iodine 10%	Not specified	Distress Thermometer (0–10 scale), EORTC-QLQ H&N35[b]	Median EORTC-QLQ[b] 64.58	22 weeks (during treatment)	Subjectively decreased lymphedema ($p = 0.001$) and distress ($p = 0.007$) at 22 weeks compared to baseline
Pigott et al. 2018 [21]	10	Surgery 90% LN resection 70% Rad 90% Chemo 20% Rad. Iodine 10%	Neck or submental 100%	Size measurements (tape measure), tissue dielectric constant (TDC)	Upper neck circumference 46.9 cm, lower neck circumference 44.3 cm	22 weeks (during treatment)	Significant reduction in lower and upper neck circumference ($p = 0.004$ and $p < 0.001$) and TDC ($p < 0.001$)
Case report							
Crane et al. 2015 [24]	1	Right radical neck dissection Maxillectomy Rad	Neck edema	Patient Specific Functional Scale (PSFS), 10-point numeric pain rating scale (NPRS), facial measurement	PSFS 13/30 NPRS 9/10 Neck girth 46.7 cm	After 4 weeks of treatment and by phone 3 months later	Increase in PSFS score to 27/30 Decreased pain (NPRS) to 4/10 Neck girth 35.2 cm (significance not reported)
Maus et al. 2012 [29]	1	Hemi-mandibulectomy Hemiglossectomy Rad Chemo	Neck fibrosis Facial edema (eyelid, tongue, cheek)	Distance between facial structures using 3D fluorescence imaging of facial structures	Majority of color rendering in +3 mm range	4 weeks	Color rendering in −3 mm range representing decreased edema at week 3 followed by recurrence due to metastatic disease in week 4 (significance not reported)
Systematic review							
Cohen et al. 2016 [26]	–	Surgery Rad Chemo	Internal LE 9.8% External LE 39% Combined LE 51%	n/a	n/a	n/a	No clinical trials demonstrate efficacy of isolated MLD, one trial demonstrates efficacy of CDT [19]
Acupuncture/moxibustion – level 4 evidence							
Cohort							
de Valois et al. 2012 [27]	8	Not reported	Not reported	Measure Yourself Medical Outcome Profile (MYMOP), Positive and Negative Affect Schedule (PANAS)	Mean MYMOP Score 4.00, Positive Affect PANAS 35.5, Negative Affect PANAS 16.6	12 weeks (after 12 sessions)	No significant change in either PANAS or MYMOP
Selenium – level 2B evidence							
RCT							
Zimmermann et al. 2005 [10]	20	Oral tumor resection 100%	Not reported	Distance measurements	Tragus-chin tip distance 18 cm in placebo at 1 week	2 weeks for LE, 1 year for selenium levels	Max tragus-chin tip distance 17 cm in selenium group ($p = 0.005$) at 1 week, non-significant difference at 2 weeks

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Table 1 (*continued*)

Study	*n*	Cancer treatment	LE location	Assessment tool	Baseline severity	Median follow-up	Outcome
Cohort							
Micke et al. 2003 [30][c]	36	Bilateral neck dissection 38% Rad 100%	Not reported	Score adopted from the LENT-SOMA system, VAS, scale modified from Foldi, scale modified from Miller et al	VAS 7.9 ± 2.3	4–6 weeks (treatment duration)	VAS 3.5 ± 2.4, reduction in VAS by 4.4 pts. ($p < 0.05$), no significant difference in any other scale
Bruns et al. 2004 [31][c]	36	Bilateral neck dissection 38% Rad 100%	Not reported	Score adopted from the LENT-SOMA system, VAS, scale modified from Foldi, scale modified from Miller et al	VAS 7.9 ± 2.3	4–6 weeks (treatment duration)	Reduction in VAS by 4.4 pts. ($p < 0.05$), no significant difference in any other scale
Buntzel et al. 2002 [32]	30	Surgery + Rad + Chemo 54% Rad + Chemo 46%	Cutaneous 33% Cutaneous and supraglottic 67%	Laryngoscopic evaluation, subjective questionnaire	Not reported (images of one patient provided)	8 weeks (treatment duration)	"Substantial reduction of edema" in 18/30 patients (significance not reported), significant subjective breathing improvement in all patients (*p* value not reported)
Narrative review							
Muecke et al. 2011 [34]	–	Not reported	Not reported	n/a	n/a	n/a	Selenium supplementation is "advisable" in cases of deficiency
Systematic review							
Dennert, 2006 [33]	–	Not reported	Not reported	n/a	n/a	n/a	No basis for any recommendation in favor or against selenium supplementation
Surgical excision/anastomosis/lymphatic bridge – level 4 evidence							
Cohort							
Ayestaray et al. 2013 [49]	4	Intra-oral resection 100%	Chronic unilateral (2+ years) 75% Chronic bilateral (2+ years) 25%	Average reduction in circumference, volume, cross sectional area	Mean circumference 48.6-51 cm	12 months	Significant reductions of 3.7% (*p* 0.006), 6.9% (*p* 0.05), 7.2% ($p = 0.007$) respectively
Case series/report							
Mihara et al. 2011 [50]	1	Oropharyngeal and neck dissection Radiotherapy	Non-pitting upper eyelid and cheek	CT of subcutaneous fat, edema appearance	Buccal fat thickness of 20 mm, visible eyelid edema	10 months	Decrease in buccal fat thickness by 14 mm (no significance reported), visible decrease in eyelid edema
Withey et al. 2001 [37]	1	Modified radical neck dissection Radiotherapy	Full face and neck	Ability to open eyes, speak, visible appearance	Marked visible edema, inability to speak or open eyes, airway obstruction	3 months	Able to open left eye spontaneously
Inatomi et al. 2018 [39]	1	Maxillectomy Glossectomy Bilat. neck dissection Radiotherapy Chemo	Bilateral face and upper eyelids	Ability to open eyes, edema appearance	Unable to open eyes	6 months	Able to open both eyes spontaneously, facial edema visibly improved on photograph
Sagili et al. 2013 [51]	3	Bilateral neck dissection 67% Unilateral neck dissection 33% Chemo 67% Rad 67%	Bilateral eyelid 67% Unilateral eyelid 33% Oropharyngeal 33%	Vision restriction, edema appearance	Marked visible edema, decreased field of vision, new obstructive sleep apnea	2 weeks to 4 months	"Cosmetic and functional improvement" in 2/3 patients who underwent surgical excision, 1 patient did not undergo surgery and had unchanged LE
Sandner et al. 2013 [17][d]	1	Neck dissection Radiotherapy Chemotherapy	Bilateral eyelid, tongue, face	Distance measurements, vision restriction	R. lower lid protuberance of 5 cm, L lower lid "tennis ball-sized" protuberance	18 months	5 cm protuberance completely resolved, vision no longer restricted, visible improvement on photograph
Liposuction – level 2B evidence							
RCT							
Alamoudi et al. 2018 [41]	20	Neck dissection 55% Rad 100%	Submental 100%	MBOE[e], DAS59[f]	Pre-procedure MBOE, DAS59 scores not reported	6 months	Significant MBOE and DAS59 score improvement ($p < 0.001$; $p = 0.001$) in liposuction group
Cohort							
Brake et al. 2014 [40]	10	Neck dissection 50% Rad 100%	Submental 100%	MBOE[d], DAS59[e], "objective observer score" by otolaryngologists	Pre-procedure average MBOE scores reported	6 months or more following liposuction	Overall self-perceived improvement in appearance and reduction of distress ($p = 0.0078$) and decreased objective observer score ($p = 0.016$)

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Table 1 (*continued*)

Study	*n*	Cancer treatment	LE location	Assessment tool	Baseline severity	Median follow-up	Outcome
Taylor et al. 2012 [14]	10	Neck dissection 50% Rad 100%	Submental 100%	Patient satisfaction	Not reported	6 months following liposuction	100% patient satisfaction per authors

n = total participants, Chemo = chemotherapy, Rad = radiotherapy, LN = lymph node, RCT = randomized placebo-controlled double blinded trial, LE = lymphedema.
[a] MD Anderson Cancer Centre Head and Neck Lymphedema Rating Scale.
[b] European Organization for Research and Treatment of Cancer Quality of Life Questionnaire: Head and Neck.
[c] Two cohort studies published results using the same data set.
[d] Surgical resection was combined with subsequent MLD in this case report.
[e] Modified Blepharoplasty Outcome Evaluation.
[f] Derriford Appearance Scale.

terms were modified for all other databases not employing MeSH terms to ensure all three components were adequately represented resulting in a second search string: ((head AND neck AND cancer) OR (submental) OR (oral AND tumor) OR (laryngocarcinoma)) AND (lymphedema OR lymphoedema) AND (treatment OR therapy).

Results of each search were uploaded to an EndNote database where relevant items were identified by hand-searching all titles and abstracts. Subsequently results were combined, duplicates removed, and full papers screened according to eligibility criteria. All titles and abstracts were screened for relevance with full papers reviewed for eligibility. Additional studies were identified by hand searching study citations (Fig. 1).

2.3. Data collection and bias assessment

For each full paper screened, data regarding the site and severity of lymphedema, cancer treatment type, treatment modality used, follow-up duration, lymphedema assessment tool employed, final treatment outcome, and level of evidence was extracted and charted (Table 1). The level of evidence for each treatment modality was determined using the Oxford Centre for Evidence-based Medicine criteria [16]. The highest level of evidence associated with each treatment is reported. Bias was assessed at the study level using the Cochrane Handbook v.5.1.0 (Table 2). Due to heterogenous data, poor study data quality, and a paucity of studies neither subgroup analysis nor meta-analysis was conducted.

Table 2
Evaluation of study bias broken down by subtype.

	Selection Bias	Blinding of participants (performance bias) (performanceconcealment	Incomplete outcome data (attrition)	Blinding of outcome assessment (objective detection)	Selective reporting	Other bias
Tacani et. al. 2014	Yellow	Red	Yellow	Red	Green	Yellow
Smith et. al. 2015	Yellow	Red	Red	Yellow	Green	Yellow
Piso et. al. 2001	Yellow	Red	Yellow	Red	Green	Yellow
Krisciunas, 2015	Yellow	Red	Red	Red	Yellow	Red
Crane et. al. 2015	Red	Red	Green	Red	Yellow	Red
Maus et. al. 2012	Red	Red	Red	Yellow	Green	Yellow
Cohen et. al. 2016	Yellow	Grey	Grey	Yellow	Grey	Red
Doke et. al. 2018	Yellow	Red	Green	Red	Green	Yellow
Nixon et. al. 2018	Yellow	Red	Green	Red	Green	Red
Pigott et. al. 2018	Yellow	Red	Green	Red	Green	Yellow
de Valois et. al. 2012	Yellow	Red	Yellow	Red	Green	Yellow
Zimmermann et. al. 2005	Yellow	Yellow	Green	Yellow	Yellow	Yellow
Micke et. al. 2003	Yellow	Red	Yellow	Red	Red	Yellow
Bruns et. al. 2004	Yellow	Red	Yellow	Red	Red	Yellow
Buntzel et. al. 2002	Yellow	Red	Yellow	Red	Red	Red
Muecke et. al. 2011	Red	Grey	Grey	Red	Red	Red
Dennert & Horneber 2017	Green	Grey	Grey	Red	Grey	Yellow
Ayestaray et. al. 2012	Yellow	Red	Green	Red	Green	Yellow
Mihara et. al. 2011	Grey	Red	Green	Red	Yellow	Yellow
Withey et. al. 2001	Grey	Red	Green	Red	Red	Yellow
Inatomi et. al. 2018	Red	Red	Green	Red	Red	Red
Sagili et. al. 2013	Red	Red	Green	Red	Red	Red
Sandner et. al. 2013	Red	Red	Green	Red	Yellow	Red
Alamoudi et. al. 2018	Yellow	Red	Green	Red	Green	Yellow
Brake et. al. 2014	Yellow	Red	Yellow	Green	Green	Yellow
Taylor et. al. 2012	Red	Red	Green	Red	Red	Red

Categories amended from the Cochrane handbook v.5.1.0. Green = low risk of bias. Yellow = unclear risk of bias. Red = high risk of bias. Grey = not applicable (systematic or narrative review).

3. Results

The initial search yielded 492 results. After the exclusion of duplicates and studies not meeting inclusion criteria, twenty-six items were excluded after full paper screening (Fig. 1). Due to the paucity of RCTs all study types were included. These consisted of fourteen cohort studies, seven case reports or case series, two RCTs, two systematic reviews, and one narrative review totaling 1018 study subjects (Table 1). No eligible ongoing clinical trials with preliminary results were found during our search. Participants were predominantly men over the age of sixty who had undergone some combination of radiotherapy, surgical excision and/or chemotherapy for head and neck cancer. Cancer type and lymphedema location was not specified in some studies. Furthermore, there was extreme heterogeneity in the use of lymphedema assessment tools, the time at which diagnosis was made and treatment initiated, and duration of follow-up both within and among the different treatment modalities. No studies directly comparing two treatment modalities were found though a case report by Sandner et al. combined surgical and manual therapy [17]. Thus, it was not possible to directly compare efficacy between treatment modalities or perform meta-analysis on study results.

3.1. Manual lymph drainage, complete decongestion therapy and acupuncture (level 4 evidence)

Despite being the current standard of care only ten studies report on the efficacy of MLD and CTD (Table 1). Seven of these are retrospective cohorts encompassing 837 participants. A single 2015 study by Smith et al. was the most significant contributor with 733 participants [18]. Of these, five studies including Smith et al., used objective measurements (size, circumference, range of motion) made by non-blinded investigators, alone or in combination with subjective measures [5,18–21]. The remaining two relied solely on subjective pain and distress scales [22,23]. Six of seven studies reported statistically significantly decreased lymphedema measurements after a follow-up period which ranged from three to twelve weeks. An additional two case reports by Crane et al. and Maus et al. demonstrated changes in patient function and facial measurements respectively though significance was not reported [24,25]. One systematic review by Cohen et al., which evaluated the studies by Piso et al. and Smith et al. found they demonstrated efficacy of MLD combined with compression garment use, while noting that compression garments were poorly tolerated in this patient population [26]. Finally, one eight-patient cohort which studied the effect acupuncture and moxibustion found no change in HNL subsequent to treatment [27].

3.1.1. Bias assessment

While all studies report that MLD alone or combined with physical therapy is an effective treatment for HNL, the validity of these results is undermined by methodological inconsistencies among a majority of studies. There are no published RCTs studying MLD or CDT, and cohort studies are often unclear on selection criteria for participants with incomplete reporting of their previous oncologic and treatment history [5,19,21,23,28]. Furthermore, there is a complete lack of blinding of outcome assessment across all studies with principal study investigators personally performing patient measurements (Table 2). The only exceptions to this are studies by Maus et al. and Smith et al. which did not specify who was responsible for data collection and interpretation [18,29]. The largest study, by Smith et al. suffered from incomplete outcome data reporting, failing to identify why only 733 of the originally recruited 1202 patients received treatment. This study also allowed patients to self-select into outpatient and self-administered treatment groups resulting in a comparison of two unmatched cohorts [18].

The heterogeneity in treatment strategies categorized as MLD and CTD make it difficult to draw conclusions from this group of studies, many of which do not fully describe what physical therapy maneuvers were used and if they conform to the original definition of MLD as described by Dr. Vodder [8]. This is compounded by the wide variety in HNL assessment scales and measurement strategies described. Studies that used subjective scales to assess HNL often do not use them in the population for which they are validated. For example, the Wong-Baker Pain Faces Scale has shown validity in chronic pain, when studied in children.

3.2. Selenium (level 2B evidence)

The use of orally administered sodium selenite has been investigated in only four studies specific to HNL. One RCT by Zimmermann et al. measured HNL reduction in patients treated with 1000 μg sodium selenite and found postoperative neck lymphedema to be significantly reduced one week following treatment, but no significant difference compared to placebo at two weeks [10]. Of three remaining retrospective cohort studies, two by Micke and Bruns found significant reduction in lymphedema, however both studies used the same methodology and patient data set [30,31]. The third, by Buntzel et al. reported “a substantial reduction in edema” but did not report any statistical significance associated with these findings [32]. A 2006 Cochrane review by Dennert & Horneber found no basis to recommend selenium as a therapeutic for HNL [33]. A more recent narrative review by Muecke et al. did recommend supplementation in cases of deficiency, though no clear evidence for this recommendation is given [34].

3.2.1. Bias assessment

All three unique studies investigating the effect of selenium on HNL suffer from methodological issues resulting in a high risk of bias (Table 2). There is a low number of participants across selenium studies, with a total of only eighty-six once the duplicate publication is excluded. Of these only twenty participated in the RCT. While the Zimmerman study is reported as a double-blind trial, participants in the treatment arm were informed they would be receiving the drug [33]. The method of random allocation in this trial is not described, and patient characteristics of each arm are not reported.

Furthermore, only the studies by Bruns and Micke used validated lymphedema scales to measure change in HNL [30,31]. In the Zimmermann study a single individual conducted arbitrary face distance measurements while Butzel used subjective laryngoscope evaluation by one individual to draw conclusions [10,30,32]. Finally, all studies in this category have an extremely short follow-up period ranging from 2 to 8 weeks after treatment as compared to 3–12 months for most other treatment modalities.

3.3. Surgical treatment (level 4 evidence)

One prospective cohort by Ayestaray et al. demonstrated a significant reduction in HNL circumference, volume, and cross-sectional area in all four participants after insertion of an LVA [35]. All five remaining studies investigating surgical treatments were case reports or case series with a total of seven participants. These five studies reported decreased HNL after surgical intervention for all participants, in two cases based on raw measurements made by investigators, and in three cases based on improvement in appearance and function as noted by investigators [17,36–39].

3.3.1. Bias assessment

Due to the invasive nature of surgical treatment for HNL all study participants had first failed conservative treatment with MLD and CTD, thus selecting for patients with refractory HNL. As with other treatment modalities there was a lack of blinding of both study participants and investigators in all studies. Despite reporting improvement for all participants, only the study by Ayestaray provided any analysis of statistical significance. None of the studies used validated HNL scales or measurements and five of a total eleven participants were evaluated based only on the investigators' visual assessment of appearance and functionality. These studies also commented on overall improvement but did not specify which metrics were assessed resulting in a high risk of selective reporting bias. Finally, more than any other treatment modality, studies of HNL treatments suffer from a lack of power making it difficult to draw conclusions regarding effectiveness.

3.4. Liposuction (level 2B evidence)

There is only one RCT and two prospective cohort studies investigating submental liposuction in HNL [14,40,41]. The 2018 RCT by Alamoudi et al. demonstrated significant self-perceived improvement in appearance and reduction of distress in the liposuction arm compared to the control arm using two subjective lymphedema scales [41]. Similarly, significant findings were also reported in the study by Brake et al. which used the same scales, combined with an objective observer score in nine participants [40]. Taylor et al. reported 100% patient satisfaction in ten study participants but did not characterize how patient satisfaction was assessed [42].

3.4.1. Bias assessment

Liposuction studies are limited by their small sample sizes with only thirty-nine participants across all studies. All liposuction was performed for submental lymphedema. Due to the lack of objective measurements across all studies, results are indicative of an improvement in self-perception rather than a decrease in HNL. The sole RCT by Alamoudi blinded neither study participants nor investigators and enrolled only ten participants in the treatment arm [41]. The methodology and reporting for this study was otherwise sound with low risk of bias. However, while both subjective scales used in the Alamoudi and Brake studies are validated for HNL, there was no objective measurement of lymphedema in either study [40,41]. Though the objective observers in the Brake study were blinded and demonstrated good interrater reliability, they did not use a validated grading scale, and criteria for improvement was unclear [40]. The prospective cohort by Taylor et al. is particularly sparse in describing its methodology. It does not explicitly state selection criteria, patient characteristics, or how the primary outcome of was assessed [14].

4. Discussion

4.1. Summary of evidence

There appears to be a paucity of evidence regarding the most effective way to treat HNL after head and neck cancer therapy. MLD and CDT are the best studied therapies for HNL, yet there have been no RCTs investigating these treatments. Almost all cohort studies which exist on the subject have found a significant decrease in HNL after therapy, and the remaining studies demonstrate a non-significant decrease suggesting this is still the most effective first line treatment for HNL.

However, factors unique to HNL may necessitate the use of treatments other than MLD and CDT. For example, compression garments, which have been extremely beneficial to patients with lymphedema of the extremities, present a challenge for HNL patients due to the unique anatomy of the head and neck. The cost of outpatient treatment, compliance with neck compression garment use, and a lack of adherence to a regular at-home therapy program also present significant challenges to patients attempting these therapies and to those attempting to evaluate efficacy of the treatments.

Effectiveness of other treatment modalities is more difficult to assess. Selenium, studied in four trials all of which suffered from problematic study designs, has shown mixed results which may partly attributed to their extremely short follow-up duration. Unlike MLD and CDT, selenium has also not been evaluated for long term efficacy and safety. While literature on surgical approaches such as LVA appears promising with decreased HNL reported in all patients, there are too few studies to draw conclusions from. The efficacy of liposuction is slightly better studied with improvement shown in all three trials, including one small RCT. This modality has shown particular promise in 5-year prospective trials demonstrating total and stable resolution of extremity edema following breast cancer treatment [43]. Furthermore, it has been well documented that compression therapy following liposuction is required to prevent extremity lymphedema recurrence [44]. This combination has not been tested in HNL and presents a future avenue of study. Thus, both liposuction and LVA represent promising new therapies to be explored in this patient population. Despite small sample sizes all studies of surgical modalities included our review have shown significant improvement, particularly among patients with very severe or chronic edema (Table 1) who may not benefit from MLD and CDT.

Overall poor study quality has significantly hampered our ability to draw conclusions regarding the effectiveness of all HNL therapies. All studies in our review suffer from short follow-up times, lack of blinding and randomization of participants, heterogenous patient populations, and low numbers of participants. There are several ongoing RCTs which address some of these issues including several trials of pneumatic compression devices but have yet to publish any results. However, there is an ongoing need for large multi-center RCTs which directly compare treatment modalities.

Perhaps the greatest challenge in assessing treatment efficacy has been the absence of a universal HNL assessment tool by which to measure study outcomes. In our literature search only eleven of twenty-six studies used one or more standardized assessment tool to evaluate lymphedema or its sequelae. Within this group there were twelve unique tools used demonstrating the challenge in directly comparing treatment modalities across studies. Currently, Foldi's Scale is referenced most frequently in the extremity lymphedema literature. However, portions of the evaluation criteria in Foldi's Scale, such as the presence of pitting edema or elephantiasis, are not appropriate for HNL staging, as they occur with a much lower frequency than in peripheral lymphedema, or do not occur at all in HNL [45]. Many scales specific to HNL rely on anatomical landmarks that may lack consistency [19]. Though novel methods of quantifying HNL including ultrasound and computed tomography have been investigated, they have not been widely accepted into practice [46,47]. Therefore, the establishment of a comprehensive, universal assessment protocol for submental lymphedema continues to be an unmet pre-requisite to ensure uniform patient evaluation.

4.2. Strengths and limitations

While there are systematic reviews on lymphedema treatment modalities, some of which include a cohort of HNL patients, there are no reviews which include all treatment types limited to this patient population. As previously stated, addressing the unique challenges of HNL requires dedicated research into treatment effectiveness. This is the only systematic review to date which summarizes the current available literature on all treatment modalities for HNL and identifies several key gaps in the literature which must be addressed.

One limitation of this review is the exclusion of publications written in languages other than English that did not have a readily available translation. Furthermore, while the methodology was reviewed by all authors, a single author determined study eligibility and assessed bias. This author was not blinded to either the study authors names or institutions during assessment. Finally, while meta-analysis would allow for more robust conclusions regarding the effectiveness of each treatment modality, this was possible due to the heterogenous study data both within and between different treatment types. This has prevented us from making recommendations regarding which patients benefit from which treatment modalities.

5. Conclusion

There are few robust studies investigating the effectiveness of HNL therapies. While there is stronger evidence for the effectiveness of MLD and CDT trials of other treatment modalities such as liposuction and LVA have demonstrated HNL reduction in a small group of patients necessitating further study. Surgical intervention has shown particular promise in patients with severe or refractory edema, and these patients may benefit from early surgical referral. However, it is vital to expand the body of literature on HNL evaluation, staging, and treatment. Until robust clinical data is made available, HNL will remain a challenge to both diagnose and manage.

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Declaration of competing interest

The authors have no conflicts of interest to disclose.

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