

Appendix. Cancer treatment-related lymphedema

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Search strategy

Ovid

Database(s): EBM Reviews - Cochrane Central Register of Controlled Trials February 2019, EBM Reviews - Cochrane Database of Systematic Reviews 2005 to March 27, 2019, Embase 1974 to 2019 March 29, Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily 1946 to March 29, 2019

Search Strategy:

| # | Searches | Results |
|----|--|----------|
| 1 | exp Neoplasms/rt, su [Radiotherapy, Surgery] (cancer* or neoplasm* or neoplastic or paraneoplas* or tumor* or tumor* or neoplasia* or "section 16" or leukemia* or carcinoma* or lymphoma* or Astrocytoma* or glioma* or adenoma* or carcinoid* or Sarcoma* or ostesarcoma* or histiocytoma* or craniopharyngioma* or ependymoma* or chordoma* or "Chronic Myeloproliferative Disorder*" or craniopharyngioma* or "Mycosis Fungoide*" or "Sézary Syndrome*" or Esthesioneuroblastoma* or melanoma* or retinoblastoma* or histeocytoma* or "gestational trophoblastic disease*" or histiocytos* or burkitt* or Macroglobulinemia* or Mesothelioma* or neuroblastoma* or Papillomatos* or paraganglioma* or "pheochromocytoma* multiple myeloma*" or blastoma* or Rhabdomyosarcoma* or nonmelanoma* or metasta*).ti,ab,hw,kw. | 1391485 |
| 2 | | 9341523 |
| 3 | exp Radiotherapy/ | 648747 |
| 4 | exp surgical procedures, operative/ | 7468924 |
| 5 | (Brachytherap* or irradiat* or operat* or radiation* or "radio therap*" or "radio treatment*" or radiolog* or radiotherap* or radiotreatment* or reconstruction* or repair* or resect* or roentgen* or rontgen* or surg* or "x ray*").ti,ab,hw,kw. | 10191551 |
| 6 | 3 or 4 or 5 | 13342834 |
| 7 | 1 or (2 and 6) | 3626644 |
| 8 | exp Lymphedema/ ("bigfoot disease*" or elephantiasis or elephantiasis or "lymph edema*" or "lymph oedema*" or "lymphatic edema*" or "lymphatic filariases" or "lymphatic filariasis" or "lymphatic oedema*" or lymphedema* or lymphoedema* or lymphooedema* or "lymphostatic edema*" or "lymphostatic oedema*" or "lymphostatic verrucoses" or "lymphostatic verrucosis" or "microcrystal disease*" or "milroy disease" or "milroy meige disease" or "milroy meiges disease" or "milroys disease" or "mossy feet" or "mossy foot*" or podoconioses or podoconiosis).ti,ab,hw,kw. | 30546 |
| 9 | | 38766 |
| 10 | 8 or 9 | 39158 |
| 11 | 7 and 10 | 11153 |
| 12 | exp DISEASE SURVEILLANCE/ | 24791 |
| 13 | (exam or examination* or exams or "patient report outcome*" or "patient reported outcome*" or PROM or surveillance).ti,ab,hw,kw. | 2779044 |
| 14 | exp Massage/ | 19943 |

| | |
|--|---------|
| 15 ("manual lymph drainage" or "manual lymphatic drainage" or massag*).ti,ab,hw,kw. | 38848 |
| 16 exp exercise/ | 505444 |
| 17 exp exercise therapy/ | 127546 |
| 18 (aerobics or anaerobics or bicycling or biking or "endurance training" or exercis* or "fitness training" or isometrics or "physical exertion" or "physical activit*" or "resistance training" or running or "strength training" or swimming or walking or weightlifting).ti,ab,hw,kw. | 1432369 |
| 19 exp Stockings, Compression/ | 4050 |
| 20 exp compression therapy/ | 8299 |
| 21 ("circ aid" or circaid or compression or unna or unnas).ti,ab,hw,kw. | 284949 |
| 22 or/12-21 | 4419563 |
| 23 11 and 22 | 2910 |
| 24 exp evidence based medicine/ | 1145422 |
| 25 exp meta analysis/ | 258169 |
| 26 exp Meta-Analysis as Topic/ | 57039 |
| 27 exp "systematic review"/ | 301029 |
| 28 exp Guideline/ or exp Practice Guideline/ | 522025 |
| 29 exp controlled study/ | 6680981 |
| 30 exp Randomized Controlled Trial/ | 1020185 |
| 31 exp triple blind procedure/ | 204 |
| 32 exp Double-Blind Method/ | 439387 |
| 33 exp Single-Blind Method/ | 79905 |
| 34 exp latin square design/ | 361 |
| 35 exp Placebos/ | 388945 |
| 36 exp Placebo Effect/ | 11206 |
| 37 exp comparative study/ | 3128292 |
| 38 exp intervention studies/ | 39732 |
| 39 exp Cross-Sectional Studies/ | 586142 |
| 40 exp Cross-Over Studies/ | 138371 |
| 41 exp Cohort Studies/ | 2429563 |

| | | |
|----|---|----------|
| 42 | exp longitudinal study/ | 377741 |
| 43 | exp retrospective study/ | 1496634 |
| 44 | exp prospective study/ | 1090455 |
| 45 | exp clinical trial/ | 2198408 |
| 46 | clinical study/ | 156767 |
| 47 | exp case-control studies/ | 1149203 |
| 48 | exp confidence interval/ | 164691 |
| 49 | exp multivariate analysis/ ((evidence adj based) or (meta adj analys*) or (systematic* adj3 review*) or guideline* or (control* adj3 study) or (control* adj3 trial) or (randomized adj3 study) or (randomized adj3 trial) or (randomised adj3 study) or (randomised adj3 trial) or "pragmatic clinical trial" or (doubl* adj blind*) or (doubl* adj mask*) or (singl* adj blind*) or (singl* adj mask*) or (tripl* adj blind*) or (tripl* adj mask*) or (trebl* adj blind*) or (trebl* adj mask*) or "latin square" or placebo* or nocebo* or multivariate or "comparative study" or "comparative survey" or "comparative analysis" or (intervention* adj2 study) or (intervention* adj2 trial) or "cross-sectional study" or "cross-sectional analysis" or "cross-sectional survey" or "cross-sectional design" or "prevalence study" or "prevalence analysis" or "prevalence survey" or "disease frequency study" or "disease frequency analysis" or "disease frequency survey" or crossover or "cross-over" or cohort* or "longitudinal study" or "longitudinal survey" or "longitudinal analysis" or "longitudinal evaluation" or longitudinal* or ((retrospective or "ex post facto") adj3 (study or survey or analysis or design)) or retrospectiv* or "prospective study" or "prospective survey" or "prospective analysis" or prospectiv* or "concurrent study" or "concurrent survey" or "concurrent analysis" or "clinical study" or "clinical trial" or "case control study" or "case base study" or "case referrent study" or "case referent study" or "case referent study" or "case compeer study" or "case comparison study" or "matched case control" or "multicenter study" or "multi-center study" or "odds ratio" or "confidence interval" or "change analysis" or ((study or trial or random* or control*) and compar*)).mp.pt. | 514350 |
| 50 | | 21782897 |
| 51 | or/24-50 | 22337008 |
| 52 | 23 and 51 limit 52 to ("all adult (19 plus years)" or "young adult (19 to 24 years)" or "adult (19 to 44 years)" or "young adult and adult (19-24 and 19-44)" or "middle age (45 to 64 years)" or "middle aged (45 plus years)" or "all aged (65 and over)" or "aged (80 and over)") [Limit not valid in CCTR,CDSR,Embase; records were retained] | 1682 |
| 54 | limit 53 to (adult <18 to 64 years> or aged <65+ years>) [Limit not valid in CCTR,CDSR,Ovid MEDLINE(R),Ovid MEDLINE(R) Daily Update,Ovid MEDLINE(R) In-Process,Ovid MEDLINE(R) Publisher; records were retained] | 1043 |
| 55 | limit 52 to ("all infant (birth to 23 months)" or "all child (0 to 18 years)" or "newborn infant (birth to 1 month)" or "infant (1 to 23 months)" or "preschool child (2 to 5 years)" or "child (6 to 12 years)" or "adolescent (13 to 18 years)") [Limit not valid in CCTR,CDSR,Embase; records were retained] | 1239 |
| 56 | limit 55 to (embryo or infant or child or preschool child <1 to 6 years> or school child <7 to 12 years> or adolescent <13 to 17 years>) [Limit not valid in 227 | |

| | | |
|----|--|---------|
| | CCTR,CDSR,Ovid MEDLINE(R),Ovid MEDLINE(R) Daily Update,Ovid MEDLINE(R) In-Process,Ovid MEDLINE(R) Publisher; records were retained] | |
| 57 | 56 not 54 | 12 |
| 58 | 52 not 57 | 1670 |
| 59 | ("case study" or "case series" or "clinical series" or "case studies" or (case adj3 report)).mp.pt. | 3146591 |
| 60 | 58 not 59 | 1603 |
| 61 | limit 60 to (editorial or erratum or note or addresses or autobiography or bibliography or biography or blogs or comment or dictionary or directory or interactive tutorial or interview or lectures or legal cases or legislation or news or newspaper article or overall or patient education handout or periodical index or portraits or published erratum or video-audio media or webcasts) [Limit not valid in CCTR,CDSR,Embase,Ovid MEDLINE(R),Ovid MEDLINE(R) Daily Update,Ovid MEDLINE(R) In-Process,Ovid MEDLINE(R) Publisher; records were retained] | 20 |
| 62 | from 61 keep 1-3 | 3 |
| 63 | (60 not 61) or 62 | 1586 |
| 64 | remove duplicates from 63 | 1130 |

Scopus

- 1 TITLE-ABS-KEY(cancer* or neoplasm* or neoplastic or paraneoplas* or tumor* or tumor* or neoplasia* or "section 16" or leukemia* or carcinoma* or lymphoma* or Astrocytoma* or glioma* or adenoma* or carcinoid* or Sarcoma* or osteosarcoma* or histiocytoma* or craniopharyngioma* or ependymoma* or chordoma* or "Chronic Myeloproliferative Disorder*" or craniopharyngioma* or "Mycosis Fungoide*" or "Szary Syndrome*" or Esthesioneuroblastoma* or melanoma* or retinoblastoma* or histiocytoma* or "gestational trophoblastic disease*" or histiocytos* or burkitt* or Macroglobulinemia* or Mesothelioma* or neuroblastoma* or Papillomatos* or paraganglioma* or "pheochromocytoma* multiple myeloma*" or blastoma* or Rhabdomyosarcoma* or nonmelanoma* or metasta*)
- 2 TITLE-ABS-KEY(Brachytherap* OR irradiat* OR operat* OR radiation* OR "radio therap*" OR "radio treatment*" OR radiolog* OR radiotherap* OR radiotreatment* OR reconstruction* OR repair* OR resect* OR roentgen* OR rontgen* OR surg* OR "x ray*")
- 3 TITLE-ABS-KEY("bigfoot disease*" OR elephantiasis OR elephantiasis OR "lymph edema*" OR "lymph oedema*" OR "lymphatic edema*" OR "lymphatic filariases" OR "lymphatic filariasis" OR "lymphatic oedema*" OR lymphedema* OR lymphoedema* OR lymphoedema* OR "lymphostatic edema*" OR "lymphostatic oedema*" OR "lymphostatic verrucoses" OR "lymphostatic verrucosis" OR "microcrystal disease*" OR "milroy disease" OR "milroy meige disease" OR "milroy meiges disease" OR "milroys disease" OR "mossy feet" OR "mossy foot*" OR podoconioses OR podoconiosis)
- 4 TITLE-ABS-KEY(exam or examination* or exams or "patient report outcome*" or "patient reported outcome*" or PROM or surveillance)
- 5 TITLE-ABS-KEY("manual lymph drainage" OR "manual lymphatic drainage" OR massag*)
- 6 TITLE-ABS-KEY(aerobics or anaerobics or bicycling or biking or "endurance training" or exercis* or "fitness training" or isometrics or "physical exertion" or "physical activit*" or "resistance training" or running or "strength training" or swimming or walking or weightlifting)
- 7 TITLE-ABS-KEY("circ aid" OR circaid OR compression OR unna OR unnas)
- 8 TITLE-ABS-KEY((evidence W/1 based) or (meta W/1 analys*) or (systematic* W/3 review*) or guideline* or (control* W/3 study) or (control* W/3 trial) or (randomized W/3 study) or (randomized W/3 trial) or (randomised W/3 study) or (randomised W/3 trial) or "pragmatic clinical trial" or (doubl* W/1 blind*) or (doubl* W/1 mask*) or (singl* W/1 blind*) or (singl* W/1 mask*) or (tripl* W/1 blind*) or (tripl* W/1 mask*) or (trebl* W/1 blind*) or (trebl* W/1 mask*) or "latin square" or placebo* or nocebo* or multivariate or "comparative study" or "comparative survey" or "comparative analysis" or (intervention* W/2 study) or (intervention* W/2 trial) or "cross-sectional study" or "cross-sectional analysis" or "cross-sectional survey" or "cross-sectional design" or "prevalence study" or "prevalence analysis" or "prevalence survey" or "disease frequency study" or "disease frequency analysis" or "disease frequency survey" or crossover or "cross-over" or cohort* or "longitudinal study" or "longitudinal survey" or "longitudinal analysis" or "longitudinal evaluation" or longitudinal* or ((retrospective or "ex post facto") W/3 (study or survey or analysis or design)) or retrospectiv* or "prospective study" or "prospective survey" or "prospective analysis" or prospectiv* or "concurrent study" or "concurrent survey" or "concurrent analysis" or "clinical study" or "clinical trial" or "case control study" or "case base study" or "case referent study" or "case referent study" or "case referent study" or "case compeer study" or "case comparison study" or "matched case control" or "multicenter study" or "multi-center study" or "odds ratio" or "confidence interval" or "change analysis" or ((study or trial or random* or control*) and compar*))
- 9 1 and 2 and 3 and (4 or 5 or 6 or 7) and 8
- 10 TITLE-ABS-KEY(newborn* or neonat* or infant* or toddler* or child* or adolescent* or paediatric* or pediatric* or girl or girls or boy or boys or teen or teens or teenager* or preschooler* or "pre-schooler*" or preteen or preteens or "pre-teen" or "pre-teens" or youth or youths) AND NOT TITLE-ABS-KEY(adult or adults or "middle age" or "middle aged" OR elderly OR geriatric* OR "old people" OR "old person*" OR "older people" OR "older person*" OR "very old")

- 11 9 and not 10
- 12 TITLE-ABS-KEY("case study" OR "case series" OR "clinical series" OR "case studies" OR (case W/3 report))
- 13 11 and not 12
- 14 DOCTYPE(ed) OR DOCTYPE(bk) OR DOCTYPE(er) OR DOCTYPE(no) OR DOCTYPE(sh)
- 15 13 and not 14
- 16 INDEX(embase) OR INDEX(medline) OR PMID(0* OR 1* OR 2* OR 3* OR 4* OR 5* OR 6* OR 7* OR 8* OR 9*)
- 17 15 and not 16

Figure S1. Risk of lymphedema (other interventions)

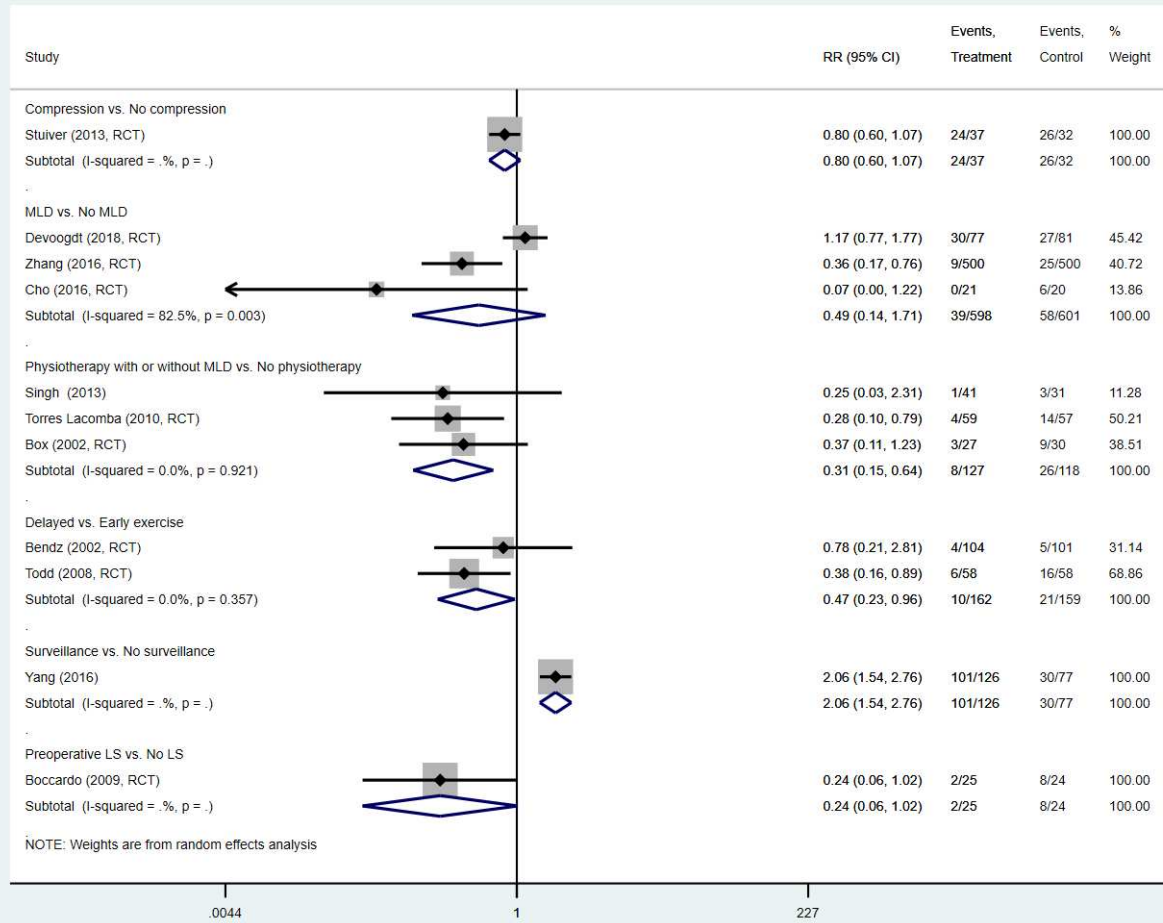


Figure S2. Change in physical activity

(Data are standardized. Higher SMD means improvement in the intervention group)

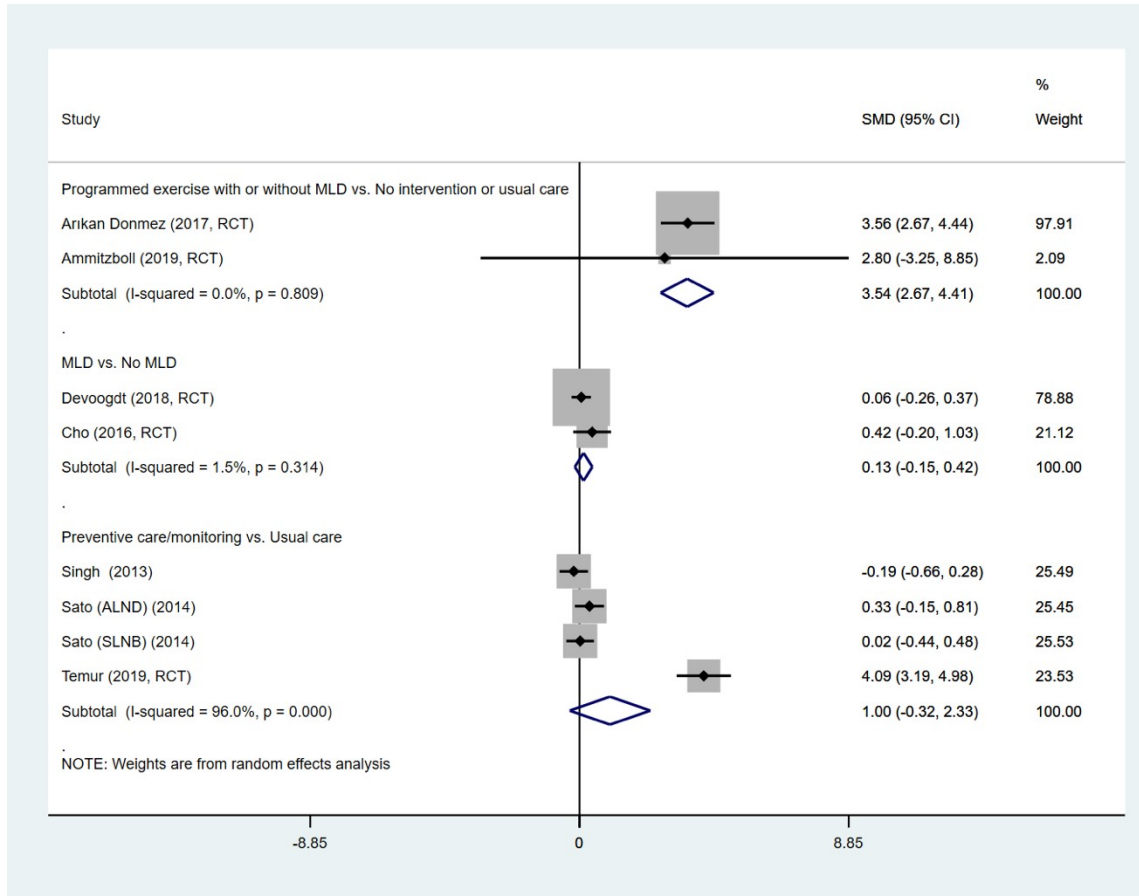


Figure S3. Grip strength

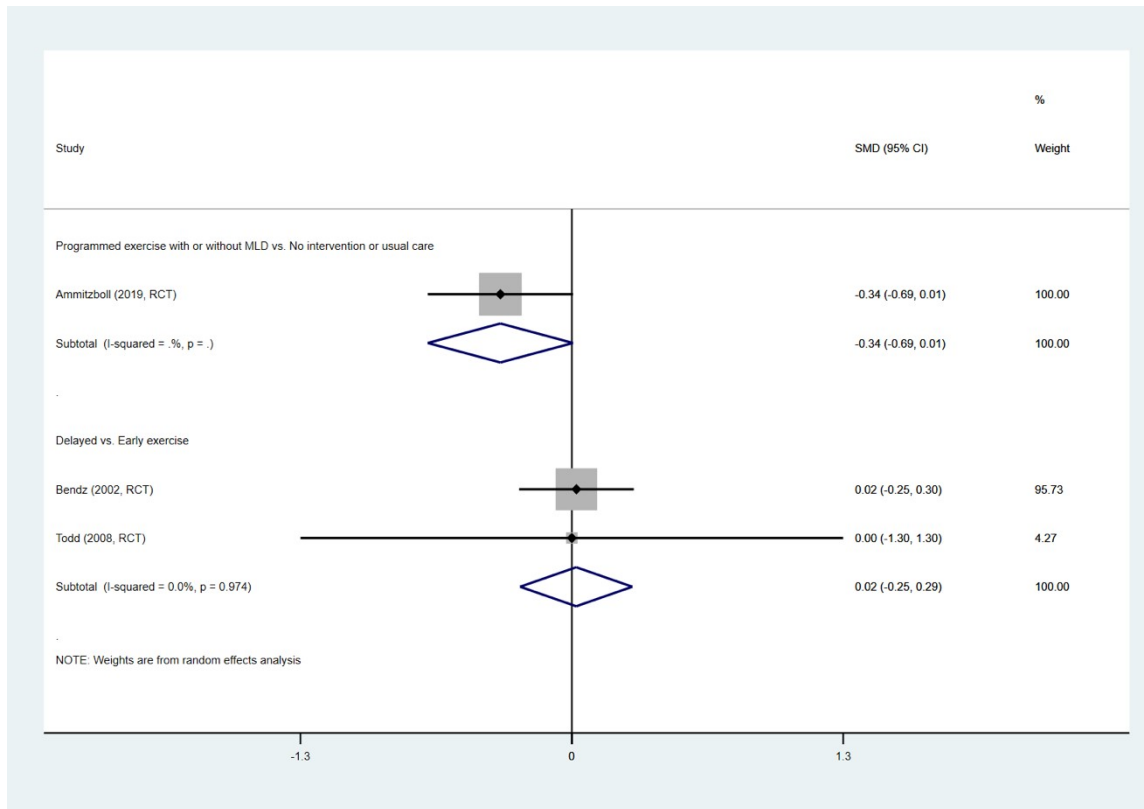
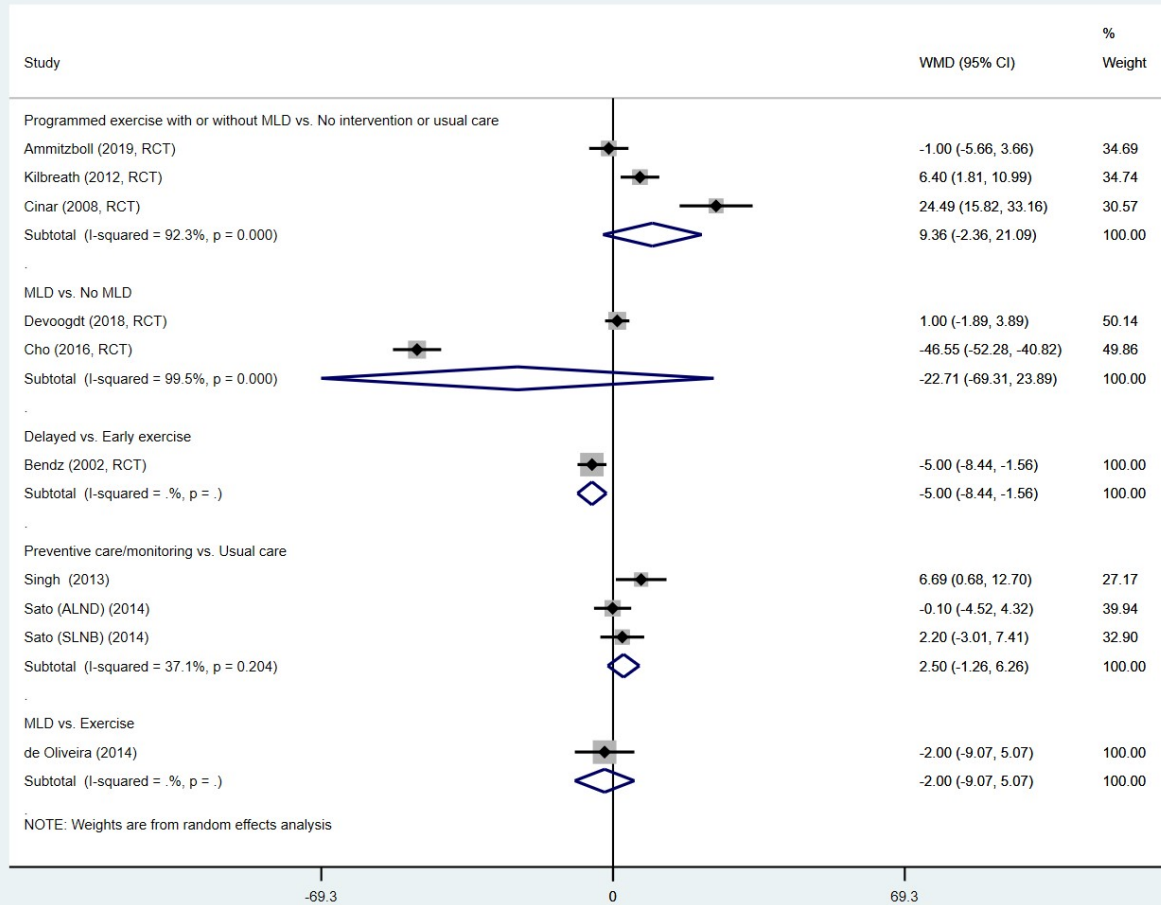
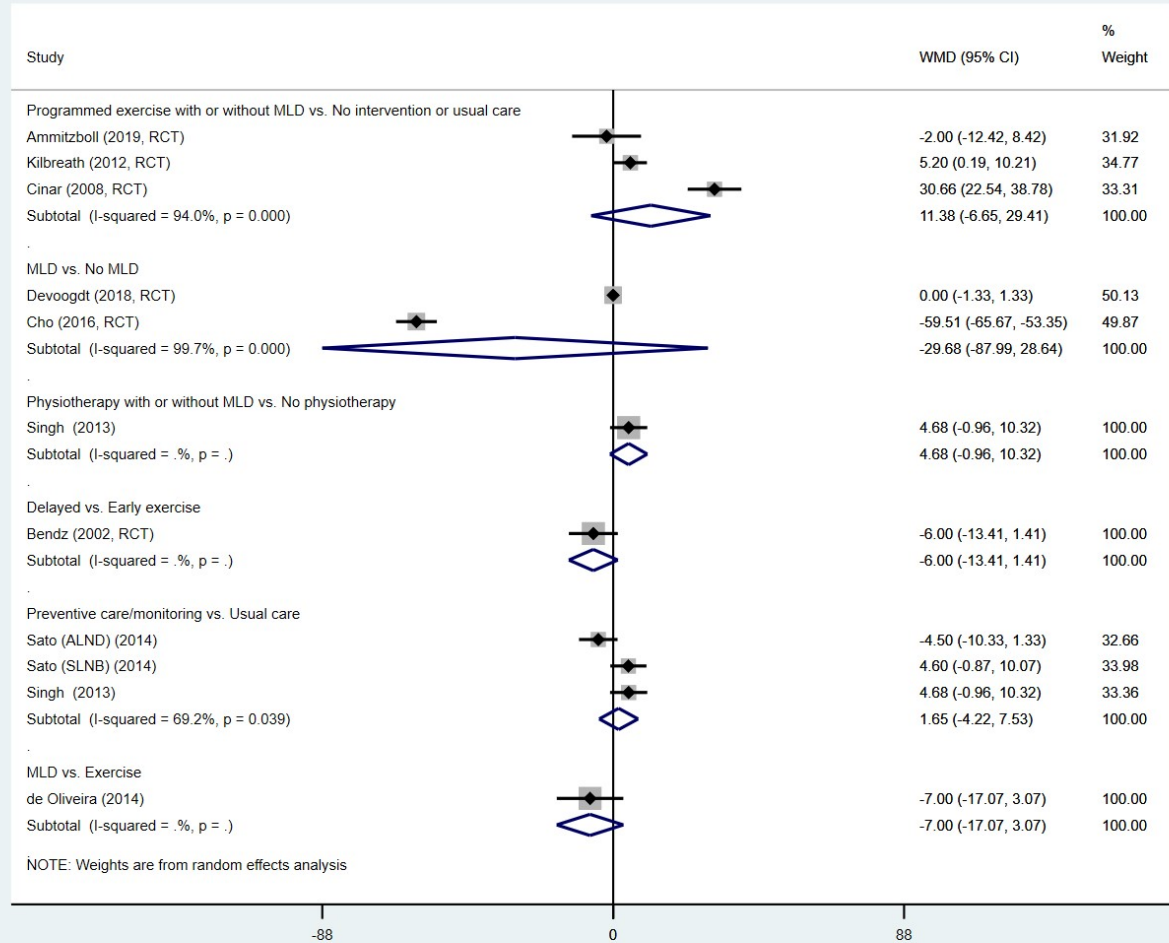


Figure S4. Range of motion

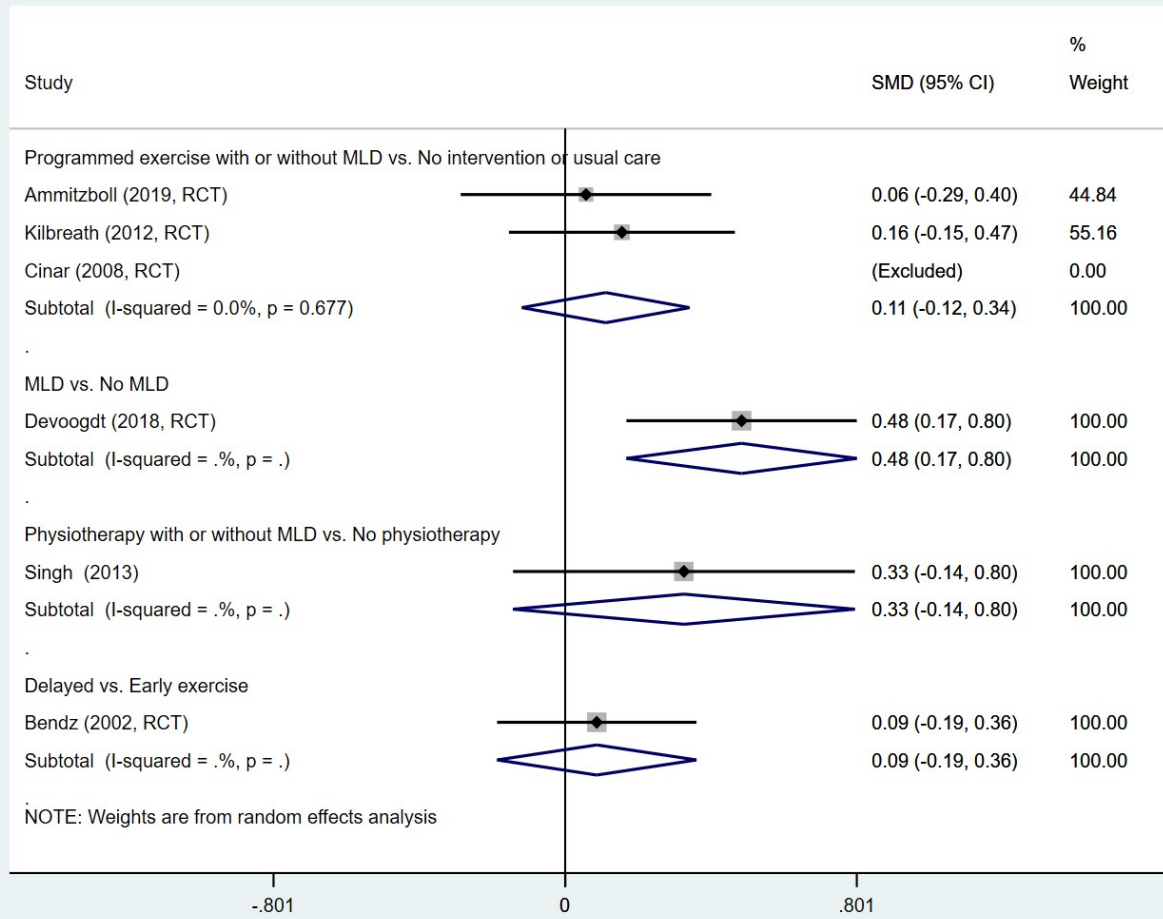
A. Shoulder flexion



B. Shoulder abduction



C. Shoulder external rotation



D. Shoulder horizontal extension

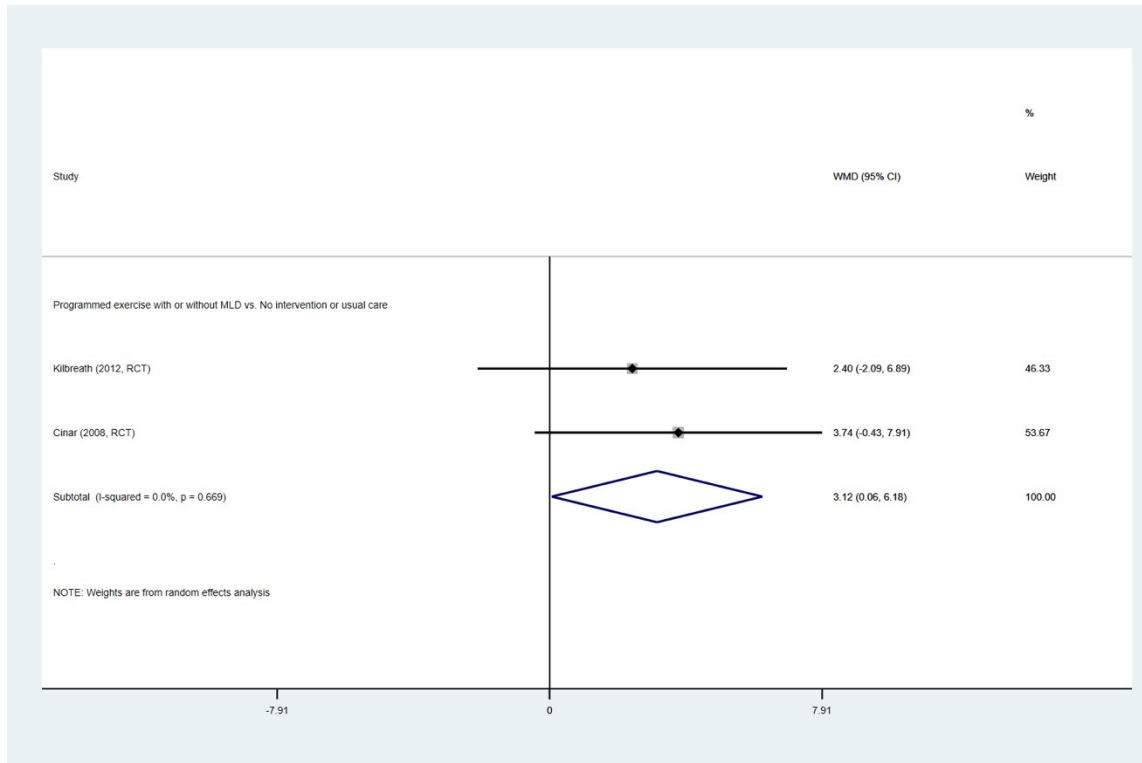


Figure S5. Risk of bias assessment for randomized clinical trials

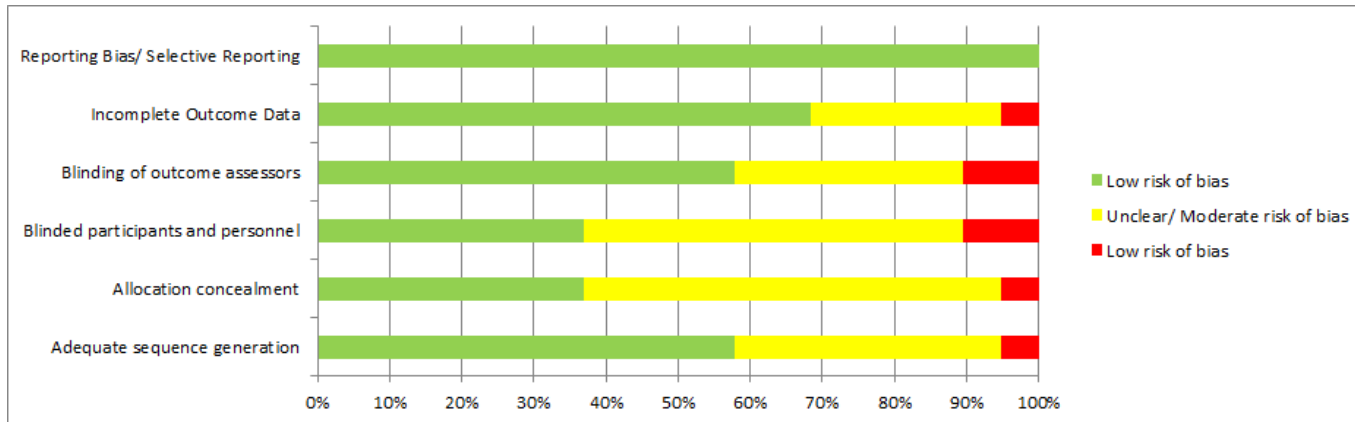


Figure S6. Risk of bias assessment for observational studies and non-randomized clinical trials

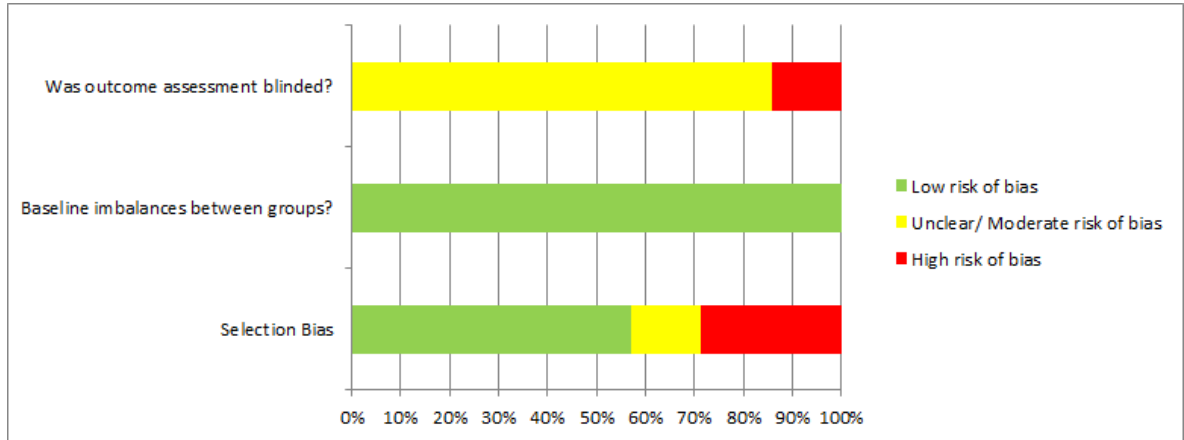


Table S1. Protocol of cancer related lymphedema guideline and systematic review

| Population of interest | Intervention | Comparison | Outcomes | Study designs available to answer this question | Timing |
|--|--|---|--|---|--------|
| Adult patients who have had cancer surgery and/or radiation and are at risk for lymphedema | <ol style="list-style-type: none"> 1. Prospective surveillance, timing 2. Prospective surveillance components/assessment (objective measurements, PROM and clinical examination) | No surveillance | <ol style="list-style-type: none"> 1. Development of lymphedema 2. Missed work or cost of coming in for prospective surveillance 3. # of patients referred to lymphedema specialist (surrogate for development of lymphedema) | Comparative observational studies RCT | Months |
| Adult patients with cancer who are at risk for extremity/trunk lymphedema | <ol style="list-style-type: none"> 1. Prophylactic massage of scar tissue (by patient) 2. Preventive exercises 3. Prophylactic use of compression garments | No treatment or an alternative intervention | <ol style="list-style-type: none"> 1. Development of persistent vs transient stage of lymphedema 2. Change in physical activity 3. Functional impairments (ROM, grip) | Comparative observational studies RCT | Months |

Table S2. Characteristics of studies in the meta-analysis by comparison

A. Compression vs. No compression

| Study Label (Author, Y) | Design* | Number of Patients (total, arm1/ arm 2) | Age in yr (mean, arm 1/ arm 2) | % Males | BMI (mean, arm 1/ arm 2) | Cancer type | Cancer treatment received | Cancer severity | First Arm (Intervention) | Second Arm (Control) | Follow up (Months) | Outcomes Reported |
|--------------------------------------|---------|---|--------------------------------|---------|--------------------------|--|---|-----------------|--------------------------|----------------------|--------------------|--|
| Stuiver, 2013 (Stuiver et al., 2013) | RCT | 80 (41/39) | 59/58 | 49/59 | NR | Melanoma/Ur ogenital Cancer Intervention: 22/18, control: 23/17 | Surgery with inguinal lymph node dissection | NR | Compression stockings | Patient education | 12 | Risk of lymphedema: lower limb/genital, defined as a 10% or greater increase from baseline in volume of the proximal or distal half of the thigh or the lower leg, using the standardized Kühnke's method of surface measurement |

B. MLD vs. No MLD

| Study Label (Author, Y) | Design* | Number of Patients (total, arm1/ arm 2) | Age in yr (mean, arm 1/ arm 2) | % Males | BMI (mean, arm 1/ arm 2) | Cancer type | Cancer treatment received | Cancer severity | First Arm (Intervention) | Second Arm (Control) | Follow up (Months) | Outcomes Reported |
|---------------------------------|---------|---|--------------------------------|---------|--------------------------|---------------|--|--|---|-----------------------|--------------------|---|
| Cho, 2016 (Cho et al., 2016) | RCT | 41 (21/20) | 46.6/50.7 | 0 | NR | Breast cancer | All patients received surgery and some patients also received chemotherapy or radiation. Chemotherapy- Intervention:9 (42.9), control:11 (55). Radiotherapy- intervention:21 (100), control:19 (95). | Stage I: intervention:5 (23.8), control:12 (60) III: intervention:16 (76.2), control:8 (40). | Manual lymph drainage (MLD)+physical therapy (PT) | Physical therapy (PT) | 1 | 1. Risk of lymphedema: ≥ 3 % volume increase from baseline in the affected upper limb 2. Volume change: arm volume calculated from circumference measurements taken at 4-cm intervals from the dorsum of the wrist to the axilla 3. Change in physical activity: EORTC QLQ-C30 and DASH 4. Functional impairment-range of motion: shoulder flexion/ abduction |

| | | | | | | | | | | | | |
|---|-----|-------------|-----------|-----|-----------|---------------|--|---|-----------------------------------|--------|----|---|
| Devoogdt, 2011 (Devoogdt et al., 2011) | RCT | 160 (79/81) | 55.8/54.5 | 1/1 | 26.6/26.2 | Breast cancer | <p>Surgery- Mastectomy: Intervention: 52, Control: 56; Breast conserving: Intervention: 27, Control: 25. Radiotherapy- IMC and medial supraclavicular: Intervention: 69, Control: 67. Radiotherapy- axilla: Intervention: 8, Control: 5. Chemotherapy: Intervention: 50, Control: 58. Neo-adjuvant chemotherapy: Intervention: 14, Control: 14. Trastuzumab: Intervention: 14, Control: 7. Endocrine treatment: Intervention: 55, Control: 66.</p> | <p>Tumor size: pT0: intervention: 1, control: 0; pT1: intervention: 21, control: 26; pT2: intervention: 38, control:39; pT3: intervention: 13, control: 12; pT4: intervention: 6, control: 4.</p> | Manual lymph drainage (MLD) | No MLD | 12 | <p>1. Risk of lymphedema : (1) ≥ 200 mL increase in arm volume up to the reference point 16 cm proximal to the olecranon by water displacement (2) ≥ 2 cm increase in arm circumference at the olecranon and 4, 8, 12, 16, and 20 cm above and under the olecranon (3) using author developed questionnaire 2. Volume change : arm volume change 3. Change in physical activity : SF-36 (QoL : physical health)</p> |
|---|-----|-------------|-----------|-----|-----------|---------------|--|---|-----------------------------------|--------|----|---|

| | | | | | | | | | | | | |
|--|--|-------------|-----------|-----|-----------|---------------|--|---|-----------------------------|--------|----|--|
| Devoogdt, 2018 (Devoogdt et al., 2018) | RCT (the same trial as Devoogdt, 2011) | 160 (79/81) | 55.8/54.5 | 1/1 | 26.6/26.2 | Breast cancer | <p>All patients received surgery and some patients also received chemotherapy or radiation.</p> <p>Radiotherapy- intramammary chain, medial supraclavicular: intervention:69 (87), control:67 (83); axilla: intervention:8 (10), control:5 (6).</p> <p>Chemotherapy- all: intervention:50 (63), control:58 (72); neo-adjuvant: intervention:14 (18), control:14 (17). taxane-based: intervention:45 (57), control:46 (57).</p> | <p>Only for tumor size and node stage.</p> <p>Tumor size, n (%)</p> <p>pT0: intervention:1 (1) control:0 (0)</p> <p>pT1: intervention:21 (27) control:26 (32)</p> <p>pT2: intervention:38 (48) control:39 (48)</p> <p>pT3: intervention:13 (17) control:12 (15)</p> <p>pT4: intervention: 6 (8) control:4 (5)</p> <p>Lymph node stage, n (%)</p> <p>pN0: intervention:23 (29) control:25 (31)</p> <p>pN1: intervention:36 (46) control:39 (48)</p> <p>pN2: intervention:11 (14) control:9 (11)</p> <p>pN3: intervention:9 (11) control:8 (10)</p> | Manual lymph drainage (MLD) | No MLD | 60 | <p>1. Risk of lymphedema : defined as</p> <p>(1) ≥ 200 ml/ ≥ 2 cm increase of absolute arm volume difference compared with pre-surgical value by water displacement</p> <p>(2) ≥ 2 cm increase of arm circumference difference of olecranon at two adjacent measurement points compared with pre-surgical value</p> <p>(3) $\geq 5\%$/ $\geq 10\%$ increase of relative arm volume difference compared with pre-surgical value by water displacement</p> <p>(4) $\geq 5\%$ increase of relative arm volume difference compared with pre-surgical value by water displacement (persistent)</p> <p>2. Volume change : absolute change in difference in arm volume</p> <p>3. % volume change : relative change in difference in arm Volume</p> |
|--|--|-------------|-----------|-----|-----------|---------------|--|---|-----------------------------|--------|----|--|

| | | | | | | | | | | | | |
|-------------------------------------|-----|---------------|----|---|----|---------------|---------|---|---|----------|----|--|
| | | | | | | | | | | | | <p>4. Change in physical activity : physical function (Lymph-ICF) and physical health (SF-36)</p> <p>5. Functional impairment-range of motion: shoulder flexion/abduction/external rotation/internal rotation</p> |
| Zhang, 2016 (Zhang et al., 2016) | RCT | 1000(500/500) | NR | 0 | NR | Breast cancer | Surgery | Tumor-node-metastasis staging: I+II: control:211, intervention:197; III: control:289, intervention:303. | Self-manual lymph drainage (MLD) and exercise | Exercise | 12 | <p>1. Risk of lymphedema: by measuring upper limb circumferences on the surgical side compared with that of the contralateral side</p> <p>2. Functional impairment-range of motion: number of patients achieving 180 degrees of shoulder abduction in 6 months</p> |

C. Physiotherapy with or without MLD vs. No physiotherapy

| Study Label (Author, Y) | Design* | Number of Patients (total, arm1/ arm 2) | Age in yr (mean, arm 1/ arm 2) | % Males | BMI (mean, arm 1/ arm 2) | Cancer type | Cancer treatment received | Cancer severity | First Arm (Intervention) | Second Arm (Control) | Follow up (Months) | Outcomes Reported |
|---|---------|---|--------------------------------|---------|--------------------------|---------------|--|-----------------|--|--|--------------------|--|
| Box, 2002 (Box, Reul-Hirche, Bullock-Saxton, & Furnival, 2002) | RCT | 65 (32/33) | 53.03/59 | 0 | Median 24.3/27.2 | Breast cancer | Surgical Procedure CLE&AD: control:51.5, intervention:46.9; MRM: control: 48.5, intervention:53.1. Radiotherapy control:48.5, interevrntion:65.6. Chemotherapy: control:21.2, interevention:43.8. | NR | Treatment group: received the Physiotherapy Management Care Plan (PMCP), including principles for lymphoedema risk minimization and early management of this condition when it was identified. | Control group: only received an exercise instruction booklet | 24 | Risk of lymphedema : defined by (1) an increase of ≥ 200 ml from the preoperative (VOL (OA-UOA) _{TA}). Arm volumes (VOL) were measured by water displacement. (2) an increase of ≥ 5 cm from the preoperative (CIRC (OA-UOA) _{TA}) (3) MFBIA ratio: number with ratio <95% lower reference limit (4) MFBIA % change: number with >10% decrease from the OA/UOA ratio |

| | | | | | | | | | | | | |
|---|--|-------------------|-----------------|----------|-----------------------------|----------------------|---|-----------|---|---|-----------|---|
| <p>Box, 2002-2 (Box et al., 2002)</p> | <p>RCT (the same trial as Box, 2002)</p> | <p>65 (32/33)</p> | <p>53.03/59</p> | <p>0</p> | <p>Median 24.3/27.2</p> | <p>Breast cancer</p> | <p>Surgical Procedure CLE&AD: control:51.5, intervention:46.9; MRM: control: 48.5, intervention:53.1. Radiotherapy control:48.5, interevntion:65.6. Chemotherapy: control:21.2, interevention:43.8.</p> | <p>NR</p> | <p>Treatment group: Received the Physiotherapy Management Care Plan (PMCP), including principles for lymphoedema risk minimization and early management of this condition when it was identified.</p> | <p>Control group: only received an exercise instruction booklet</p> | <p>24</p> | <p>1. Change in physical activity : measured by compliance with the exercise protocol, which is associated with different patterns of recovery for all movements except external rotation. 2. Functional impairment-range of motion: shoulder abduction</p> |
|---|--|-------------------|-----------------|----------|-----------------------------|----------------------|---|-----------|---|---|-----------|---|

| | | | | | | | | | | | | |
|---|-------------------------|-------------------|------------------|----------|------------------|----------------------|---|---|---|---|----------|--|
| <p>Singh, 2013 (Singh et al., 2013)</p> | <p>Quasi Randomised</p> | <p>72 (41/31)</p> | <p>55.1/62.8</p> | <p>0</p> | <p>27.1/27.0</p> | <p>Breast cancer</p> | <p>All patients received surgery and some patients also received chemotherapy or radiation. Adjuvant radiation: intervention: 22 (53.7), control: 14 (45.2); Adjuvant chemotherapy: intervention: 16 (39), control:16 (32.3).</p> | <p>Cancer stage DCIS or Stage 1: intervention:2 (4.9), control:2 (6.5); Stage II: intervention:14 (34.1), control:10 (32.2); Stage III: intervention:19 (46.3), control:13 (41.9); Unknown: intervention: 6 (14.6), control:6 (19.4).</p> | <p>Clinical care pathway: preoperative education, prospective monitoring, and early physiotherapy</p> | <p>No clinical care pathway: preoperative education alone</p> | <p>7</p> | <p>1. Risk of lymphedema: a 2 cm increase in upper extremities circumference between adjacent points, compared with pre-surgical value 2. Change in physical activity: evaluated by Disabilities of Arm, Shoulder and Hand (DASH) 3. Functional impairment-range of motion: shoulder flexion/abduction/external rotation</p> |
|---|-------------------------|-------------------|------------------|----------|------------------|----------------------|---|---|---|---|----------|--|

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|---|--------------------------------------|--------------------|------------------|----------|------------------|----------------------|--|-----------|---|---------------------------------|-----------|--|
| <p>Torres Lacomba, 2010 (Torres Lacomba et al., 2010)</p> | <p>RCT (ISRCTN9 5870846)</p> | <p>120 (60/60)</p> | <p>52.9/52.9</p> | <p>0</p> | <p>27.9/26.2</p> | <p>Breast cancer</p> | <p>Surgery- Quadrantectomy: Intervention: 24, Control: 26; Modified mastectomy: Intervention: 23, Control: 20; Lumpectomy: Intervention: 13, Control: 14. Postoperative therapy- Radiotherapy: intervention:44, control:49; Chemotherapy: interevntion: 50, control: 45; Hormonal therapy: Intervention: 39, Control: 33</p> | <p>NR</p> | <p>Physiotherapy program, including manual lymph drainage, massage of scar tissue, and progressive active and action assisted shoulder exercises. Also received the educational strategy.</p> | <p>Educational strategy</p> | <p>12</p> | <p>1. Risk of lymphedema: ≥2cm increase in the circumference of any two adjacent points compared with measurements in the other arm 2. % volume change: change in volume ratio</p> |
|---|--------------------------------------|--------------------|------------------|----------|------------------|----------------------|--|-----------|---|---------------------------------|-----------|--|

D. Delayed vs. Early exercise

| Study Label (Author, Y) | Design* | Number of Patients (total, arm1/ arm 2) | Age in yr (mean, arm 1/ arm 2) | % Males | BMI (mean, arm 1/ arm 2) | Cancer type | Cancer treatment received | Cancer severity | First Arm (Intervention) | Second Arm (Control) | Follow up (Months) | Outcomes Reported |
|--|---------|---|--------------------------------|---------|--------------------------|---------------|--|-----------------|---------------------------|-------------------------|--------------------|---|
| Bendz, 2002 (Bendz & Fagevik Olsen, 2002) | RCT | 205 (101/104) | 58/58 | 0 | NR | Breast cancer | All patients received surgery and some patients also received radiation. Mastectomy only: intervention:31, control:22; Incl. radiotherapy: intervention:5, control:7. Quadrant resection only: intervention:20, control:23; Incl. radiotherapy: intervention:45 control:52. | NR | Delayed shoulder exercise | Early shoulder exercise | 24 | 1. Risk of lymphedema: volume on the operated side >10% increased compared with the non-operated side 2. % volume change: the arm volume measured volumetrically 3. Functional impairment-grip : grip strength measured with Vigortmeter 4. Functional impairment-range of motion : shoulder flexion/abduction/external rotation/internal rotation |

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|---------------------------------------|-----|-------------|-----------|---|-----------|---------------|--|---|--|--|----|---|
| Todd, 2008 (Todd et al., 2008) | RCT | 116 (58/58) | 56.5/57.2 | 0 | 27.5/28.4 | Breast cancer | Surgery: wide local excision or mastectomy, including axillary lymph node dissection | Grade I intervention: 8, control: 8; Grade II intervention: 24, control: 27; Grade III intervention: 26, control: 23. | Intervention group (Delayed mobilisation): arm exercises and shoulder movement restricted to below shoulder level for the first 7 days after surgery. | Control group (Early mobilisation): commenced an exercise programme that incorporated exercises above shoulder level within 48 hours. | 12 | 1. Risk of lymphedema: defined by a limb volume difference of 200 ml or more compared with the contralateral arm, measured using volume displacement 2. Functional impairment-grip : grip strength using a hand-held Jamar® dynamometer 3. Functional impairment-range of motion : shoulder abduction |
|---------------------------------------|-----|-------------|-----------|---|-----------|---------------|--|---|--|--|----|---|

E. Preventive care/monitoring vs. Usual care

| Study Label (Author, Y) | Design* | Number of Patients (total, arm1/ arm 2) | Age in yr (mean, arm 1/ arm 2) | % Males | BMI (mean, arm 1/ arm 2) | Cancer type | Cancer treatment received | Cancer severity | First Arm (Intervention) | Second Arm (Control) | Follow up (Months) | Outcomes Reported |
|--------------------------------|---------------------------------|---|---|---------|--------------------------|---------------|--|---|--|----------------------|--------------------|--|
| Sato, 2014 (Sato et al., 2014) | Non-randomized controlled trial | 149 (90/59) | ALND:52.9 SLNB:54.3/ ALND:52.1 SLNB:53.7 | 0 | NR | Breast cancer | All patients received surgery and some patients also received chemotherapy or radiation. Radiotherapy: ALND intervention:69.2, control:83.3; SLNB intervention:58.8, control: 51.7. Chemotherapy, molecular targeting therapy: ALND intervention:79.5, control:86.7; SLNB intervention:11.8, control:24.1. | Stage 0: ALND intervention:0.0, control:6.7; SLNB intervention:25.5, control:44.8. Stage I: ALND intervention:7.7, control:20.0; SLNB intervention:54.9, control:48.3. Stage II: ALND intervention:43.6, control:50.0; SLNB intervention:17.6, control:6.9. Stage III: ALND intervention:41.0, control:23.3; SLNB intervention:2.0, control:0.0. Stage IV:ALND intervention:7.7, control:0.0; SLNB intervention:0.0, control:0.0. | Educational program: monitoring arm function and exercises | Routine care | 3 | 1. Volume change: upper arm/forearm girth 2. Change in physical activity: evaluated by Disabilities of Arm, Shoulder and Hand (DASH) 3. Functional impairment-grip : grip strength 4. Functional impairment-range of motion : shoulder flexion/abduction/horizontal extension |

| | | | | | | | | | | | | |
|---|------------------|------------|-----------|---|---|---------------|--|--|--|--|----------|---|
| Singh, 2013 (Singh et al., 2013) | Quasi Randomised | 72 (41/31) | 55.1/62.8 | 0 | 27.1/27.0 | Breast cancer | All patients received surgery and some patients also received chemotherapy or radiation. Adjuvant radiation: intervention: 22 (53.7), control: 14 (45.2); Adjuvant chemotherapy: intervention: 16 (39), control:16 (32.3). | Cancer stage DCIS or Stage 1: intervention:2 (4.9), control:2 (6.5); Stage II: intervention:14 (34.1), control:10 (32.2); Stage III: intervention:19 (46.3), control:13 (41.9); Unknown: intervention: 6 (14.6), control:6 (19.4). | Clinical care pathway: preoperative education, prospective monitoring, and early physiotherapy | No clinical care pathway: preoperative education alone | 7 | 1. Risk of lymphedema: a 2 cm increase in upper extremities circumference between adjacent points, compared with pre-surgical value 2. Change in physical activity: evaluated by Disabilities of Arm, Shoulder and Hand (DASH) 3. Functional impairment-range of motion: shoulder flexion/abduction/external rotation |
| Temur, 2019 (K. Temur & S. Kapucu, 2019) | RCT | 61 (30/31) | 47.6/45.6 | 0 | >25: 19; <24.9: 11/ >25: 19; <24.9: 12 | Breast cancer | Surgery: modified radical mastectomy and breast-conserving surgery | Stage 1 intervention: 2, control: 2; Stage 2 intervention: 16, control: 16; Stage 3 intervention: 12, control: 13. | Intervention group: Provided training and given a training booklet describing "exercise, massage and prevention methods" | Control group | 6 | 1. Volume change : lateral epicondylitis (10 cm above/below), forearm (wrist joints 10 cm below) and metacarpophalangeal 2. Change in physical activity : physical functioning domain of EORTC QLQ-30 |

F. MLD vs. Exercise

| Study Label (Author, Y) | Design* | Number of Patients (total, arm1/ arm 2) | Age in yr (mean, arm 1/ arm 2) | % Males | BMI (mean, arm 1/ arm 2) | Cancer type | Cancer treatment received | Cancer severity | First Arm (Intervention) | Second Arm (Control) | Follow up (Months) | Outcomes Reported |
|--|---------------------------------|---|--------------------------------|---------|--------------------------|---------------|---|---|---------------------------------|----------------------|--------------------|--|
| de Oliveira, 2014 (de Oliveira et al., 2014) | Non-randomized controlled trial | 96 (48/48) | 55.6/56.7 | 0 | 28/29.1 | Breast cancer | Surgery: Patey Modified Radical Mastectomy: MLD: 17, exercise: 27; Madden MRM: MLD: 25, exercise:19; Halsted RM: MLD: 1, exercise: 0; Neoadjuvant chemo: MLD: 29, exercise: 22. | Surgical staging: I: MLD: 0, exercise: 1; II: MLD: 9, exercise: 17; III/IV: MLD: 34, exercise: 28. | Manual lymphatic drainage (MLD) | Exercise | 2 | 1. Volume change: hand, wrist, arm and forearm 2. Functional impairment-range of motion: shoulder flexion/abduction |

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G. Surveillance vs. No surveillance

| Study Label (Author, Y) | Design* | Number of Patients (total, arm1/ arm 2) | Age in yr (mean, arm 1/ arm 2) | % Males | BMI (mean, arm 1/ arm 2) | Cancer type | Cancer treatment received | Cancer severity | First Arm (Intervention) | Second Arm (Control) | Follow up (Months) | Outcomes Reported |
|--------------------------------|---------------------------------|---|--------------------------------|---------|--------------------------|---------------|---|---|---|----------------------|--------------------|--|
| Yang, 2016 (Yang et al., 2016) | Comparative observational study | 707 (390/317) | 47.6/48.6 | 0 | 24.3/23.3 | Breast cancer | All patients received surgery and some patients also received chemotherapy or radiation. Radiotherapy- Not done: intervention:47 (12.0 %), control:41 (12.9 %); Breast only: intervention:211 (54.0 %), control:174 (54.9 %); Breast and SCRT: intervention:140 (36.0 %), control:102 (32.2 %). Chemotherapy- Doxetaxel: intervention:280 (71.9 %), control:223 (70.3 %). | Histopathologic stage: I(%):intervention:109 (28.0 %), control:92 (29.0 %); II(%):intervention:215 (55.0 %), control:168 (53.0 %); III(%):intervention:66 (17.0 %), control:57 (18.0 %). | Surveillance program for lymphedema management (SLYM) | Standard care | 60 | Risk of lymphedema: defined by reference to the guidelines of the International Society of Lymphology (ISL) consensus document |

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H. Preoperative LS vs. No LS

| Study Label (Author, Y) | Design* | Number of Patients (total, arm1/ arm 2) | Age in yr (mean, arm 1/ arm 2) | % Males | BMI (mean, arm 1/ arm 2) | Cancer type | Cancer treatment received | Cancer severity | First Arm (Intervention) | Second Arm (Control) | Follow up (Months) | Outcomes Reported |
|---|---------|---|--------------------------------|---------|--------------------------|---------------|--|-----------------|--|----------------------|--------------------|---|
| Boccardo, 2009 (Boccardo et al., 2009) | RCT | 49 (25/24) | 53.4/54.6 | 0 | 27.3/29.9 | Breast cancer | Surgical Procedure (n) CLE & AD: intervention:12, control:13; MRM & AD: intervention:13, control:11. All included patients received radiotherapy. | NR | Preventive protocol (PG): Preoperative upper limb lymphscintigraphy (LS), principles for lymphedema risk minimization, and early management of this condition when it was identified. | Control group (CG) | 24 | 1. Risk of lymphedema: a difference of over 200 ml from preoperative VOL measurements VOL (OA-UOA) [operated arm=OA; unoperated arm=UOA] 2. % volume change: arm volumes (VOL) were assessed using water displacement and measured to the nearest 5 ml |

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Table S3. Certainty of evidence of the studies included in the meta-analysis

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| Programmed exercise with or without MLD vs. No intervention or usual care | | | | |
|---|---|-----------------------------------|--|---|
| Outcomes | Studies, Design (patients) | Effect | | Certainty in evidence |
| | | RR, WMD or SMD (95%CI), I-squared | Risk Difference | |
| Development of lymphedema | 7 studies, 5 RCTs (791, events 159) | 0.56 (0.35, 0.89), 59.8% | 93 fewer per 1,000 (137 fewer to 23 fewer) | Low, rated down due to imprecision* and inconsistency [†] |
| | 5 RCTs (among the 7 studies, 706, events 106) | 0.77 (0.54, 1.10), 0% | 40 fewer per 1,000 (79 fewer to 17 more) | Low, rated down twice due to imprecision* |
| Change in physical activity | 2 studies, 2 RCTs (210) | 3.54 (2.67, 4.41), 0% | | Moderate, rated down due to imprecision* |
| Grip strength | 1 study, 1 RCT (129) | -0.34 (-0.69, 0.01) | | Low, rated down due to imprecision* |
| ROM – Shoulder flexion | 3 studies, 3 RCTs (347) | 9.36 (-2.36, 21.09), 92.3% | | Very low, rated down twice due to imprecision* and inconsistency [†] |
| ROM – Shoulder abduction | 3 studies, 3 RCTs (347) | 11.38 (-6.65, 29.41), 94% | | Very low, rated down twice due to imprecision* and inconsistency [†] |
| ROM – Shoulder external rotation | 2 studies, 2 RCTs (290) | 0.11 (-0.12, 0.34), 0% | | Low, rated down twice due to imprecision* |
| ROM – Shoulder horizontal extension | 2 studies, 2 RCTs (217) | 3.12 (0.06, 6.18), 0% | | Low, rated down due to imprecision* and risk of bias [#] |
| Compression vs. No compression | | | | |
| Outcomes | Studies, Design (patients) | Effect | | Certainty in evidence |
| | | RR, WMD or SMD (95%CI), I-squared | Risk Difference | |
| Development of lymphedema | 1 study, 1 RCT (69) | 0.80 (0.60, 1.07) | 163 fewer per 1,000 (325) | Very low, rated down twice due to imprecision* and risk of bias [#] |

| MLD vs. No MLD | | | | |
|--|--------------------------------------|-----------------------------------|---|--|
| Outcomes | Studies, Design (patients) | Effect | | Certainty in evidence |
| | | RR, WMD or SMD (95%CI), I-squared | Risk Difference | |
| Development of lymphedema | 3 studies, 3 RCTs (1,199, events 97) | 0.49 (0.14, 1.71), 82.5% | 49 fewer per 1,000 (83 fewer to 69 more) | Very low, rated down twice due to imprecision*, inconsistency+ and risk of bias# |
| Change in physical activity | 2 studies, 2 RCTs (173) | -0.09 (-1.01, 0.83), 85% | | Very low, rated down twice due to imprecision*, inconsistency+ and risk of bias# |
| ROM – Shoulder flexion | 2 studies, 2 RCTs (199) | -22.71 (-69.31, 23.89), 99.5% | | Very low, rated down twice due to imprecision*, inconsistency+ and risk of bias# |
| ROM – Shoulder abduction | 2 studies, 2 RCTs (199) | -29.68 (-87.99, 28.64), 99.7% | | Very low, rated down twice due to imprecision*, inconsistency+ and risk of bias# |
| ROM – Shoulder external rotation | 1 study, 1 RCT (158) | 0.48 (0.17, 0.80) | | Low, rated down due to imprecision* |
| Physiotherapy with or without MLD vs. No physiotherapy | | | | |
| Outcomes | Studies, Design (patients) | Effect | | Certainty in evidence |
| | | RR, WMD or SMD (95%CI), I-squared | Risk Difference | |
| Development of lymphedema | 3 studies, 2 RCTs (245) | 0.31 (0.15, 0.64), 0% | 152 fewer per 1,000 (187 fewer to 79 fewer) | Moderate, rated down due to imprecision* |
| ROM – Shoulder abduction | 1 study, 0 RCT (72) | 4.68 (-0.96, 10.32) | | Very low, rated down twice due to imprecision* |
| ROM – Shoulder external rotation | 1 study, 0 RCT (72) | 0.33 (-0.14, 0.80) | | Very low, rated down twice due to imprecision* |
| Delayed vs. Early exercise | | | | |
| Outcomes | Studies, Design | Effect | | Certainty in evidence |

| | (patients) | RR, WMD or SMD (95%CI), I-squared | Risk Difference | |
|--|------------------------------------|-----------------------------------|---|---|
| Development of lymphedema | 2 studies, 2 RCTs (321, events 31) | 0.47 (0.23, 0.96), 0% | 70 fewer per 1,000 (102 fewer to 5 fewer) | Low, rated down due to risk of bias [#] |
| Grip strength | 2 studies, 2 RCTs (297) | -0.03 (-0.31, 0.26) | | Very low, rated down due to imprecision* and risk of bias [#] |
| ROM – Shoulder flexion | 1 study, 1 RCT (205) | -5.00 (-8.44, -1.56) | | Low, rated down due to imprecision* and risk of bias [#] |
| ROM – Shoulder abduction | 1 study, 1 RCT (205) | -6.00 (-13.41, 1.41) | | Very low, rated down twice due to imprecision* and risk of bias [#] |
| ROM – Shoulder external rotation | 1 study, 1 RCT (205) | 0.09 (-0.19, 0.36) | | Very low, rated down twice due to imprecision* and risk of bias [#] |
| Preventive care/monitoring vs. Usual care | | | | |
| Outcomes | Studies, Design (patients) | Effect | | Certainty in evidence |
| | | RR, WMD or SMD (95%CI), I-squared | Risk Difference | |
| Change in physical activity | 3 studies, 1 RCTs (282) | 1.00 (-0.32, 2.33), 96% | | Very low, rated down twice due to imprecision* and inconsistency ⁺ |
| ROM – Shoulder flexion | 2 studies, 0 RCT (221) | 2.50 (-1.26, 6.26), 37.1% | | Very low, rated down twice due to imprecision* |
| ROM – Shoulder abduction | 2 studies, 0 RCT (221) | 1.65 (-4.22, 7.53), 69.2% | | Very low, rated down twice due to imprecision* |
| MLD vs. Exercise | | | | |
| Outcomes | Studies, Design (patients) | Effect | | Certainty in evidence |
| | | RR, WMD or SMD (95%CI), I-squared | Risk Difference | |
| ROM – Shoulder flexion | 1 study, 0 RCT (89) | -2.00 (-9.07, 5.07) | | Very low, rated down twice due to imprecision* |

| ROM – Shoulder abduction | 1 study, 0 RCT (89) | -7.00 (-17.07, 3.07) | | Very low, rated down twice due to imprecision* |
|---|-------------------------------|--|---|---|
| Surveillance vs. No surveillance | | | | |
| Outcomes | Studies, Design (patients) | Effect | | Certainty in evidence |
| | | RR, WMD or SMD (95%CI), I- squared | Risk Difference | |
| Development of lymphedema | 1 study, 0 RCT (203) | 2.06 (1.54, 2.76) | 413 more per 1,000 (210 more to 686 more) | Very low, rated down due to imprecision* |
| Preoperative LS vs. No LS | | | | |
| Outcomes | Studies, Design (patients) | Effect | | Certainty in evidence |
| | | RR, WMD or SMD (95%CI), I- squared | Risk Difference | |
| Development of lymphedema | 1 study, 1 RCT (49) | 0.24 (0.06, 1.02) | 253 fewer per 1,000 (313 fewer to 7 more) | Very low, rated down due to imprecision* and risk of bias# |

*Imprecision: without known thresholds, we rated down once for either events < 300 or 95% CI including appreciable benefits and harm (binary outcomes), and patients number < 500 or 95% CI crossing 0 (continuous outcomes).

+Inconsistency: without known thresholds, we rated down for $I^2 > 50\%$ (binary outcomes) and $> 75\%$ (continuous outcomes).

#Risk of bias: For RCT, using Cochrane Collaboration Risk of Bias tool and evaluating according to the two most important domains that may cause bias: the “Random sequence generation” and “Blinding of outcome assessment”;
For non-RCT, using Newcastle-Ottawa quality assessment scale and evaluating according to the two most important domains that may cause bias: the “representative of patients, reported as a consecutive sample of patients” and “comparability of patients”.

Both RCT and non-RCT are evaluated as following: 2 domains of low risk – low risk

1 low risk plus 1 high risk or unclear/ two unclear – unclear

1 unclear plus 1 high risk / two high risk – high risk

When > 50% of studies are RCTs and no inconsistency, we started at high quality; otherwise started at low.

Table S4. Characteristics of included studies comparing Progressive resistance training (RRT) vs Usual care

| Study Label (Author, Y) | Design* | Number of Patients (total, arm1/ arm 2) | Age in yr (mean, arm 1/ arm 2) | % Males | BMI (mean, arm 1/ arm 2) | Cancer type | Cancer treatment received | Cancer severity | First Arm (Intervention) | Second Arm (Control) | Follow up (Months) | Outcomes Reported |
|--------------------------------|-------------------|---|--------------------------------|---------|--------------------------|---------------|--|--|---------------------------------------|----------------------|--------------------|---|
| Ammitzbol 1, 2019 ¹ | RCT (NCT02518477) | 158 (82/76) | 53/52 | 0 | 26.5/26.6 | Breast cancer | Radiation+surgery (all patients) / some patients from each group also received chemotherapy Adjuvant: Control: 45 (59%) Intervention: 48 (59%) Neoadjuvant: Control: 21 (28%) Intervention: 25 (30%) | Histologic stage of malignancy, No. (%) 1: Control:16 (21) Intervention:12 (15) 2 :Control:35 (46) Intervention:48 (59) 3 :Control:18 (24) Intervention:15 (18) | Progressive resistance training (PRT) | Usual care | 12 | Change in physical activity: physical functioning with QLQ C-30 assessing QoL |

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| Study Label (Author, Y) | Design* | Number of Patients (total, arm1/ arm 2) | Age in yr (mean, arm 1/ arm 2) | % Males | BMI (mean, arm 1/ arm 2) | Cancer type | Cancer treatment received | Cancer severity | First Arm (Intervention) | Second Arm (Control) | Follow up (Months) | Outcomes Reported |
|--------------------------------|-------------------|---|--------------------------------|---------|--------------------------|---------------|--|--|---------------------------------------|----------------------|--------------------|--|
| Ammitzbol 1, 2019 ² | RCT (NCT02518477) | 158 (82/76) | 53/52 | 0 | 26.5/26.6 | Breast cancer | Radiation+surgery (all patients) / some patients from each group also received chemotherapy Adjuvant: Control: 45 (59%) Intervention: 48 (59%) Neoadjuvant: Control: 21 (28%) Intervention: 25 (30%) | Histologic stage of malignancy, No. (%) 1: Control:16 (21) Intervention:12 (15) 2 :Control:35 (46) Intervention:48 (59) 3 :Control:18 (24) Intervention:15 (18) | Progressive resistance training (PRT) | Usual care | 12 | 1. Risk of lymphedema: >3% increased interlimb volume difference 2. % Volume change in interlimb volume difference 3. Functional impairment-grip : grip strength-ipsilateral/ contralateral side 4. Functional impairment-range of motion : ipsilateral/ contralateral shoulder flexion, ipsilateral/ contralateral shoulder abduction, ipsilateral/ contralateral shoulder external rotation |

Table S5. Characteristics of included studies comparing Compression vs No compression

| Study Label (Author, Y) | Design* | Number of Patients (total, arm1/ arm 2) | Age in yr (mean, arm 1/ arm 2) | % Males | BMI (mean, arm 1/ arm 2) | Cancer type | Cancer treatment received | Cancer severity | First Arm (Intervention) | Second Arm (Control) | Follow up (Months) | Outcomes Reported |
|----------------------------|---------|---|--------------------------------|---------|--------------------------|--|---|-----------------|--------------------------|----------------------|--------------------|--|
| Stuiver, 2013 ³ | RCT | 80 (41/39) | 59/58 | 49/59 | NR | Melanoma/Ur ogenital Cancer Intervention: 22/18, control: 23/17 | Surgery with inguinal lymph node dissection | NR | Compression stockings | Patient education | 12 | Risk of lymphedema: lower limb/genital, defined as a 10% or greater increase from baseline in volume of the proximal or distal half of the thigh or the lower leg, using the standardized Kühnke's method of surface measurement |

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Table S6. Characteristics of included studies comparing Manual lymph drainage (MLD) vs No MLD

| Study Label (Author, Y) | Design* | Number of Patients (total, arm1/ arm 2) | Age in yr (mean, arm 1/ arm 2) | % Males | BMI (mean, arm 1/ arm 2) | Cancer type | Cancer treatment received | Cancer severity | First Arm (Intervention) | Second Arm (Control) | Follow up (Months) | Outcomes Reported |
|-------------------------|---------|---|--------------------------------|---------|--------------------------|---------------|--|--|---|-----------------------|--------------------|---|
| Cho, 2016 ⁴ | RCT | 41 (21/20) | 46.6/50.7 | 0 | NR | Breast cancer | All patients received surgery and some patients also received chemotherapy or radiation. Chemotherapy- Intervention:9 (42.9), control:11 (55). Radiotherapy- intervention:21 (100), control:19 (95). | Stage I: intervention:5 (23.8), control:12 (60) III: intervention:16 (76.2), control:8 (40). | Manual lymph drainage (MLD)+physical therapy (PT) | Physical therapy (PT) | 1 | 1. Risk of lymphedema: ≥ 3 % volume increase from baseline in the affected upper limb 2. Volume change: arm volume calculated from circumference measurements taken at 4-cm intervals from the dorsum of the wrist to the axilla 3. Change in physical activity: EORTC QLQ-C30 and DASH 4. Functional impairment-range of motion: shoulder flexion/ abduction |

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| Study Label (Author, Y) | Design* | Number of Patients (total, arm1/ arm 2) | Age in yr (mean, arm 1/ arm 2) | % Males | BMI (mean, arm 1/ arm 2) | Cancer type | Cancer treatment received | Cancer severity | First Arm (Intervention) | Second Arm (Control) | Follow up (Months) | Outcomes Reported |
|-----------------------------|---------|---|--------------------------------|---------|--------------------------|---------------|--|--|-----------------------------|----------------------|--------------------|---|
| Devoogdt, 2011 ⁵ | RCT | 160 (79/81) | 55.8/54.5 | 1/1 | 26.6/26.2 | Breast cancer | <p>Surgery- Mastectomy: Intervention: 52, Control: 56; Breast conserving: Intervention: 27, Control: 25.</p> <p>Radiotherapy- IMC and medial supraclavicular: Intervention: 69, Control: 67.</p> <p>Radiotherapy- axilla: Intervention: 8, Control: 5.</p> <p>Chemotherapy: Intervention: 50, Control: 58.</p> <p>Neo-adjuvant chemotherapy: Intervention: 14, Control: 14.</p> <p>Trastuzumab: Intervention: 14, Control: 7.</p> <p>Endocrine treatment: Intervention: 55, Control: 66.</p> | <p>Tumour size: pT0: intervention: 1, control: 0; pT1: intervention: 21, control: 26; pT2: intervention: 38, control:39; pT3: intervention: 13, control: 12; pT4: intervention: 6, control: 4.</p> | Manual lymph drainage (MLD) | No MLD | 12 | <p>1. Risk of lymphedema : (1) ≥ 200 mL increase in arm volume up to the reference point 16 cm proximal to the olecranon by water displacement (2) ≥ 2 cm increase in arm circumference at the olecranon and 4, 8, 12, 16, and 20 cm above and under the olecranon (3) using author developed questionnaire</p> <p>2. Volume change : arm volume change</p> <p>3. Change in physical activity : SF-36 (QoL : physical health)</p> |

| | | | | | | | | | | | | |
|-----------------------------|--|-------------|-----------|-----|-----------|---------------|--|--|-----------------------------|--------|----|--|
| Devoogdt, 2018 ⁶ | RCT (the same trial as Devoogdt, 2011) | 160 (79/81) | 55.8/54.5 | 1/1 | 26.6/26.2 | Breast cancer | <p>All patients received surgery and some patients also received chemotherapy or radiation.</p> <p>Radiotherapy- intramammary chain, medial supraclavicular: intervention:69 (87), control:67 (83); axilla: intervention:8 (10), control:5 (6).</p> <p>Chemotherapy- all: intervention:50 (63), control:58 (72); neo-adjuvant: intervention:14 (18), control:14 (17). taxane-based: intervention:45 (57), control:46 (57).</p> | <p>Only for tumor size and node stage.</p> <p>Tumour size, n (%)</p> <p>pT0: intervention:1 (1) control:0 (0)</p> <p>pT1: intervention:21 (27) control:26 (32)</p> <p>pT2: intervention:38 (48) control:39 (48)</p> <p>pT3: intervention:13 (17) control:12 (15)</p> <p>pT4: intervention: 6 (8) control:4 (5)</p> <p>Lymph node stage, n (%)</p> <p>pN0: intervention:23 (29) control:25 (31)</p> <p>pN1: intervention:36 (46) control:39 (48)</p> <p>pN2: intervention:11 (14) control:9 (11)</p> <p>pN3: intervention:9 (11) control:8 (10)</p> | Manual lymph drainage (MLD) | No MLD | 60 | <p>1. Risk of lymphedema : defined as</p> <p>(1) ≥ 200 ml/ ≥ 2 cm increase of absolute arm volume difference compared with pre-surgical value by water displacement</p> <p>(2) ≥ 2 cm increase of arm circumference difference of olecranon at two adjacent measurement points compared with pre-surgical value</p> <p>(3) $\geq 5\%$/ $\geq 10\%$ increase of relative arm volume difference compared with pre-surgical value by water displacement</p> <p>(4) $\geq 5\%$ increase of relative arm volume difference compared with pre-surgical value by water displacement (persistent)</p> <p>2. Volume change : absolute change in difference in arm volume</p> <p>3. % volume change : relative change in difference in arm Volume</p> |
|-----------------------------|--|-------------|-----------|-----|-----------|---------------|--|--|-----------------------------|--------|----|--|

| Study Label (Author, Y) | Design* | Number of Patients (total, arm1/ arm 2) | Age in yr (mean, arm 1/ arm 2) | % Males | BMI (mean, arm 1/ arm 2) | Cancer type | Cancer treatment received | Cancer severity | First Arm (Intervention) | Second Arm (Control) | Follow up (Months) | Outcomes Reported |
|--------------------------|---------|---|--------------------------------|---------|--------------------------|---------------|---------------------------|---|---|----------------------|--------------------|--|
| | | | | | | | | | | | | <p>4. Change in physical activity : physical function (Lymph-ICF) and physical health (SF-36)</p> <p>5. Functional impairment-range of motion: shoulder flexion/abduction/external rotation/internal rotation</p> |
| Zhang, 2016 ⁷ | RCT | 1000(500/500) | NR | 0 | NR | Breast cancer | Surgery | Tumor-node-metastasis staging: I+II: control:211, intervention:197; III: control:289, intervention:303. | Self-manual lymph drainage (MLD) and exercise | Exercise | 12 | <p>1. Risk of lymphedema: by measuring upper limb circumferences on the surgical side compared with that of the contralateral side</p> <p>2. Functional impairment-range of motion: number of patients achieving 180 degrees of shoulder abduction in 6 months</p> |

| Study Label (Author, Y) | Design* | Number of Patients (total, arm1/ arm 2) | Age in yr (mean, arm 1/ arm 2) | % Males | BMI (mean, arm 1/ arm 2) | Cancer type | Cancer treatment received | Cancer severity | First Arm (Intervention) | Second Arm (Control) | Follow up (Months) | Outcomes Reported |
|------------------------------|---------|---|--------------------------------|---------|--------------------------|---------------|--|---|---------------------------------|--------------------------------|--------------------|---|
| Zimmerman, 2012 ⁸ | RCT | 67 (33/34) | 60.3/58.6 | 0 | 25.6/24.3 | Breast cancer | Breast conserving therapy-MLD: 20, control: 20; Modified mastectomy:-MLD: 13, control: 14; Endocrine therapy-MLD: 14, control: 19; Chemotherapy-MLD: 13, control: 15; Radiotherapy-MLD: 22, control: 25. | Stage I: MLD: 12 (36%), control: 11 (32%); Stage II: MLD: 15 (46%), control: 16 (47%); Stage III: MLD: 6 (18%), control: 7 (21%). | Manual lymphatic drainage (MLD) | No MLD, but with self-drainage | 6 | 1. Risk of lymphedema: defined as >5% volume difference between the upper limbs 2. Volume change: ipsilateral upper limb |

Table S7. Characteristics of included studies comparing Manual lymph drainage (MLD) vs Exercise

| Study Label (Author, Y) | Design* | Number of Patients (total, arm1/ arm 2) | Age in yr (mean, arm 1/ arm 2) | % Males | BMI (mean, arm 1/ arm 2) | Cancer type | Cancer treatment received | Cancer severity | First Arm (Intervention) | Second Arm (Control) | Follow up (Months) | Outcomes Reported |
|--------------------------------|---------------------------------|---|--------------------------------|---------|--------------------------|---------------|--|--|---------------------------------|----------------------|--------------------|--|
| de Oliveira, 2014 ⁹ | Non-randomized controlled trial | 96 (48/48) | 55.6/56.7 | 0 | 28/29.1 | Breast cancer | Surgery: Patey Modified Radical Mastectomy: MLD: 17, exercise: 27; Madden MRM: MLD: 25, exercise:19; Halsted RM: MLD: 1, exercise: 0; Neoadjuvant chemo: MLD: 29, exercise: 22. | Surgical staging: I: MLD: 0, exercise: 1; II: MLD: 9, exercise: 17; III/IV: MLD: 34, exercise: 28. | Manual lymphatic drainage (MLD) | Exercise | 2 | 1. Volume change: hand, wrist, arm and forearm 2. Functional impairment-range of motion: shoulder flexion/abduction |

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| Study Label (Author, Y) | Design* | Number of Patients (total, arm1/ arm 2) | Age in yr (mean, arm 1/ arm 2) | % Males | BMI (mean, arm 1/ arm 2) | Cancer type | Cancer treatment received | Cancer severity | First Arm (Intervention) | Second Arm (Control) | Follow up (Months) | Outcomes Reported |
|------------------------------|---------------------------------|---|--------------------------------|---------|--------------------------|---------------|---|---|---------------------------------|----------------------|--------------------|---|
| Oliveira, 2018 ¹⁰ | Comparative observational study | 106 (53/53) | NR | 0 | NR | Breast cancer | All patients received surgery and some patients also received chemotherapy or radiation. Neoadjuvant chemotherapy: exercise:24 (45.3), MLD:36 (67.9); Adjuvant chemotherapy: exercise:8 (36.4), MLD:18 (62.1); Radiotherapy: exercise:16 (72.7), MLD:26 (86.7). | Clinical Stage I: exercise:1 (2.0) MLD:0 (0.0) II: exercise:17 (34.0) MLD:9 (18.0) III/IV: exercise:32 (64.0) MLD:43 (82.0) Surgical Stage I: exercise:2 (3.8) MLD:1 (1.9) II: exercise:20 (37.7) MLD:11 (20.8) III/IV: exercise:31 (58.5) MLD:41 (77.4) | Manual lymphatic drainage (MLD) | Active exercise (AE) | 30 | Functional impairment-range of motion: shoulder flexion/abduction |

Table S8. Characteristics of included studies comparing Exercise vs No exercise

| Study Label (Author, Y) | Design* | Number of Patients (total, arm1/ arm 2) | Age in yr (mean, arm 1/ arm 2) | % Males | BMI (mean, arm 1/ arm 2) | Cancer type | Cancer treatment received | Cancer severity | First Arm (Intervention) | Second Arm (Control) | Follow up (Months) | Outcomes Reported |
|------------------------------|---------|---|--------------------------------|---------|--------------------------|---------------|--|--|---|----------------------|--------------------|--|
| Anderson, 2012 ¹¹ | RCT | 104 (52/52) | NR | 0 | NR | Breast cancer | Surgery- Lumpectomy only: Control: 25, Intervention: 23; Mastectomy: Control: 24, Intervention: 28. N/A Control: 3, Intervention: 1. Chemotherapy- Control: 31, Intervention: 31; Tamoxifen: Control: 23, Intervention: 26. Radiation therapy: Control: 36, Intervention: 31. | Stage I: intervention 25, control 26; II: intervention 19, control 21 III: intervention 8, control 4 N/A: intervention 0, control 1. | Exercise | Usual care | 18 | Volume change: mean arm volume change |
| Donmez, 2017 ¹² | RCT | 52 (25/27) | 48.6/49.5 | 0 | NR | Breast cancer | Surgery (either MRM: Modified Radical Mastectomy or PS: Breast Protective Surgery) | NR | Physical activity program (PAP) and simple lymphatic drainage (SLD) | Usual care | 1.5 | 1. Volume change: 5cm, 10cm, 15cm, 20cm over arm/forearm and mean metacarpophalangeal (MCP) circumference 2. Change in physical activity: DASH (self-rated questionnaire that measures upper extremity disability and symptoms) |

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| Study Label (Author, Y) | Design* | Number of Patients (total, arm1/ arm 2) | Age in yr (mean, arm 1/ arm 2) | % Males | BMI (mean, arm 1/ arm 2) | Cancer type | Cancer treatment received | Cancer severity | First Arm (Intervention) | Second Arm (Control) | Follow up (Months) | Outcomes Reported |
|---------------------------|---------|---|--------------------------------|---------|--------------------------|---------------|--|-----------------|--|---|--------------------|---|
| Cinar, 2008 ¹³ | RCT | 57 (27/30) | 52.6/51.1 | 0 | 28.7/27.7 | Breast cancer | Modified radical mastectomy 100%. Radiation therapy- Intervention: 10, Control: 14. Chemotherapy- Intervention: 23, Control: 29. | NR | Exercise: 15 sessions of individual rehabilitation program and continued with home-based physical activity program for 8 weeks | Control: only received a form including the exercises, which could be performed by themselves | 6 | <ol style="list-style-type: none"> 1. Risk of lymphedema 2. Volume change: midpoint of the third metacarpophalangeal joint and the ulnar styliod process (0 point) and at 10, 20, 30, and 40 cm proximally from the ulnar styliod process were marked, the circumferences at each marked point were summed to determine the total value and to calculate the difference between the operated and unoperated arm. 3. Functional impairment-range of motion : shoulder flexion/abduction/internal rotation/external rotation/adduction/extension |

| Study Label (Author, Y) | Design* | Number of Patients (total, arm1/ arm 2) | Age in yr (mean, arm 1/ arm 2) | % Males | BMI (mean, arm 1/ arm 2) | Cancer type | Cancer treatment received | Cancer severity | First Arm (Intervention) | Second Arm (Control) | Follow up (Months) | Outcomes Reported |
|-----------------------------|---------------------------------|---|--------------------------------|---------|--------------------------|---------------|---|-----------------|--------------------------|----------------------|--------------------|---|
| Corrado, 2018 ¹⁴ | Comparative observational study | 30 (15/15) | 55.8/54.7 | 0 | NR | Breast cancer | Surgery: modified radical mastectomy and axillary lymph node dissection (ALND). Completed active breast cancer treatment with chemotherapy and radiation therapy. | NR | Home exercise program | No exercise | 3 | Risk of lymphedema : defined as ≥ 4 cm the difference between the sum of the 2 measurements among the affected and the unaffected arm, evaluated by measuring the arm circumference 10 cm above and 10 cm below the olecranon with a standard measuring tape |

| | | | | | | | | | | | | |
|-------------------------------------|--|--------------------|------------------|----------|------------------|----------------------|--|---|-----------------|--------------------|----------|--|
| <p>Kilbreath, 2012¹⁵</p> | <p>RCT (Australian Clinical Trials Registry, ACTRN012606000050550)</p> | <p>160 (81/79)</p> | <p>53.5/51.6</p> | <p>0</p> | <p>26.2/26.5</p> | <p>Breast cancer</p> | <p>Surgery (100%) Mastectomy: Intervention: 48%, Control: 47%; Axillary node dissection: Intervention: 62%, Control: 58%. Chemotherapy: Taxane (Pacli or Docetaxel) Intervention: 0, Control: 5; Anthracycline Intervention: 27%, Control: 27%; Taxane and anthracycline Intervention: 40%, Control: 39%. Other Intervention: 1%, Control: 3%. Radiotherapy (%) Intervention: 79%, Control: 76%.</p> | <p>Intervention- Stage (I/II/III) (%) 17:44:38 Control- Stage (I/II/III) (%) 19:37:44</p> | <p>Exercise</p> | <p>No exercise</p> | <p>6</p> | <p>1. Risk of lymphedema : defined as (1) arm volume \geq10%, derived from circumferential measurements (2) >2 cm in 2 or more measures of interlimb circumference difference, measured at 10-cm intervals from the ulnar styloid to 40 cm proximally on both arms (3) exceeds Bioimpedance Spectroscopy ratio, determined by dividing the impedance from the nonaffected limb by that from the affected limb and this ratio was compared to previously established cut- offs: a ratio \geq1.139 when surgery was on the dominant side and a ratio \geq1.066 when surgery was on the non-dominant side was indicative of lymphedema 2. Functional impairment- range of motion: shoulder forward flexion/ abduction/ horizontal</p> |
|-------------------------------------|--|--------------------|------------------|----------|------------------|----------------------|--|---|-----------------|--------------------|----------|--|

| Study Label (Author, Y) | Design* | Number of Patients (total, arm1/ arm 2) | Age in yr (mean, arm 1/ arm 2) | % Males | BMI (mean, arm 1/ arm 2) | Cancer type | Cancer treatment received | Cancer severity | First Arm (Intervention) | Second Arm (Control) | Follow up (Months) | Outcomes Reported |
|-------------------------------|---|---|--------------------------------|---------|--------------------------|---------------|---|--|--------------------------|----------------------|--------------------|--|
| | | | | | | | | | | | | extension/ external rotation |
| Kilbreath, 2013 ¹⁶ | RCT (Australian Clinical Trials Registry, ACTRN012606000050550) | 160 (81/79) | 53.5/51.6 | 0 | 26.2/26.5 | Breast cancer | <p>Surgery (100%)</p> <p>Mastectomy: Intervention: 48%, Control: 47%;</p> <p>Axillary node dissection: Intervention: 62%, Control: 58%.</p> <p>Chemotherapy: Taxane (Pacli or Docetaxel) Intervention: 0, Control: 5;</p> <p>Anthracycline Intervention: 27%, Control: 27%;</p> <p>Taxane and anthracycline Intervention: 40%, Control: 39%.</p> <p>Other Intervention: 1%, Control: 3%.</p> <p>Radiotherapy (%) Intervention: 79%, Control: 76%.</p> | <p>Intervention- Stage (I/II/III) (%) 17:44:38</p> <p>Control- Stage (I/II/III) (%) 19:37:44</p> | Exercise | No exercise | 15 | Risk of lymphedema: ipsilateral upper limb, swelling was determined using bioimpedance spectroscopy with reference to previously established cut-offs for lymphedema |

| Study Label (Author, Y) | Design* | Number of Patients (total, arm1/ arm 2) | Age in yr (mean, arm 1/ arm 2) | % Males | BMI (mean, arm 1/ arm 2) | Cancer type | Cancer treatment received | Cancer severity | First Arm (Intervention) | Second Arm (Control) | Follow up (Months) | Outcomes Reported |
|-----------------------------|---------|---|--------------------------------|---------|--------------------------|---------------|---|-----------------|--------------------------|----------------------|--------------------|---|
| Kilgour, 2008 ¹⁷ | RCT | 27 (16/11) | 50.6/49.1 | 0 | NR | Breast cancer | All patients received modified radical mastectomy and axillary node dissection. | NR | Home based exercise | Usual care | 14 days | <ol style="list-style-type: none"> 1. Volume change: circumferential tape measurements of the forearm at 5 and 10 cm below the distal border of the lateral epicondyle of the humerus 2. Functional impairment-grip : grip strength using hand-grip dynamometry 3. Functional impairment-range of motion : shoulder flexion/abduction/external rotation using goniometric techniques |

| Study Label (Author, Y) | Design* | Number of Patients (total, arm1/ arm 2) | Age in yr (mean, arm 1/ arm 2) | % Males | BMI (mean, arm 1/ arm 2) | Cancer type | Cancer treatment received | Cancer severity | First Arm (Intervention) | Second Arm (Control) | Follow up (Months) | Outcomes Reported |
|-----------------------------|--------------------------|---|--------------------------------|---------|--------------------------|---------------|---|---|---|---|--------------------|--|
| Sagen, 2009 ¹⁸ | RCT | 204 (104/100) | 54/55 | 0 | NR | Breast cancer | Surgery- Breast ablation: Intervention: 46, Control: 51; Breast conserving: Intervention: 57, Control: 49. Radiotherapy- supraclavicular nodes: Intervention: 47, Control: 40. Radiotherapy-breast: Intervention: 78, Control: 73. Chemotherapy- Intervention: 42, Control: 38. | Histology grade 1: intervention: 25, control: 19; 2: intervention: 54, control: 56; 3: intervention: 24, control: 24. | Exercise: no activity restriction and supervised physical therapy program | No exercise: activity restriction and usual care | 24 | 1. Risk of lymphedema: 10% increase in Voldiff between the affected arm and the control arm 2. Volume change: (1) difference between the volume of the affected arm and the volume of the control arm using the Simplified Water Displacement Instrument (SWDI) (2) change of affected arm volume |
| Schmitz, 2010 ¹⁹ | RCT (NCT0019 4363) | 154 (77/77) | 54/56 | 0 | 27.5/28.6 | Breast cancer | All patients had surgery with at least 2 lymph nodes removed. Chemotherapy: Intervention: 56, Control: 53; Radiation: Intervention: 59, Control: 58. | Cancer stage: Ductal carcinoma in situ- intervention: 1, control: 0; 1- intervention: 43, control:43 2- intervention: 8, control: 6; 3- intervention: 25, control: 28. | Weight lifting | No exercise | 12 | 1. Risk of lymphedema: defined by $\geq 5\%$ increase in arm swelling, measured by water displacement 2. Change in physical activity: International Physical Activity Questionnaire (IPAQ), total physical activity (TPA) in MET-min/week |

| Study Label (Author, Y) | Design* | Number of Patients (total, arm1/ arm 2) | Age in yr (mean, arm 1/ arm 2) | % Males | BMI (mean, arm 1/ arm 2) | Cancer type | Cancer treatment received | Cancer severity | First Arm (Intervention) | Second Arm (Control) | Follow up (Months) | Outcomes Reported |
|----------------------------|---------------------------------|---|--------------------------------|------------|--------------------------|---------------|---|--|--------------------------|----------------------|--------------------|--|
| Sisman, 2012 ²⁰ | Comparative observational study | 55 (45/10) | NR | Totally 2% | NR | Breast cancer | Surgery-Modified radical mastectomy: 53; Breast-conserving surgery:2. Radiotherapy 50 Gy in 25 days: 25 | Stage I: 7 Stage II: 25 Stage III: 20 Stage IV: 3 | Exercise | No exercise | 6 | Risk of lymphedema: measured 7.5 cm over and 7.5 cm below the elbow and the two arms were compared, defined as > 1.5 cm arm circumference measurements |

Table S9. Characteristics of included studies comparing Delayed exercise vs Early exercise

| Study Label (Author, Y) | Design* | Number of Patients (total, arm1/ arm 2) | Age in yr (mean, arm 1/ arm 2) | % Males | BMI (mean, arm 1/ arm 2) | Cancer type | Cancer treatment received | Cancer severity | First Arm (Intervention) | Second Arm (Control) | Follow up (Months) | Outcomes Reported |
|---------------------------|---------|---|--------------------------------|---------|--------------------------|---------------|--|-----------------|---------------------------|-------------------------|--------------------|--|
| Bendz, 2002 ²¹ | RCT | 205 (101/104) | 58/58 | 0 | NR | Breast cancer | All patients received surgery and some patients also received radiation. Mastectomy only: intervention:31, control:22; Incl. radiotherapy: intervention:5, control:7. Quadrant resection only: intervention:20, control:23; Incl. radiotherapy: intervention:45 control:52. | NR | Delayed shoulder exercise | Early shoulder exercise | 24 | 1. Risk of lymphedema: volume on the operated side >10% increased compared with the non-operated side 2. % volume change: the arm volume measured voluminometrically 3. Functional impairment-grip : grip strength measured with Vigormeter 4. Functional impairment-range of motion : shoulder flexion/abduction/external rotation/internal rotation |

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| Study Label (Author, Y) | Design* | Number of Patients (total, arm1/ arm 2) | Age in yr (mean, arm 1/ arm 2) | % Males | BMI (mean, arm 1/ arm 2) | Cancer type | Cancer treatment received | Cancer severity | First Arm (Intervention) | Second Arm (Control) | Follow up (Months) | Outcomes Reported |
|--------------------------|---------|---|--------------------------------|---------|--------------------------|---------------|--|---|---|---|--------------------|---|
| Todd, 2008 ²² | RCT | 116 (58/58) | 56.5/57.2 | 0 | 27.5/28.4 | Breast cancer | Surgery: wide local excision or mastectomy, including axillary lymph node dissection | Grade I intervention: 8, control: 8; Grade II intervention: 24, control: 27; Grade III intervention: 26, control: 23. | Intervention group (Delayed mobilisation): arm exercises and shoulder movement restricted to below shoulder level for the first 7 days after surgery. | Control group (Early mobilisation): commenced an exercise programme that incorporated exercises above shoulder level within 48 hours. | 12 | 1. Risk of lymphedema: defined by a limb volume difference of 200 ml or more compared with the contralateral arm, measured using volume displacement 2. Functional impairment- grip : grip strength using a hand-held Jamar® dynamometer 3. Functional impairment- range of motion : shoulder abduction |

Table S10. Characteristics of included studies comparing Physiotherapy vs No physiotherapy

| Study Label (Author, Y) | Design* | Number of Patients (total, arm1/ arm 2) | Age in yr (mean, arm 1/ arm 2) | % Males | BMI (mean, arm 1/ arm 2) | Cancer type | Cancer treatment received | Cancer severity | First Arm (Intervention) | Second Arm (Control) | Follow up (Months) | Outcomes Reported |
|-------------------------|---------|---|--------------------------------|---------|--------------------------|---------------|--|-----------------|--|--|--------------------|---|
| Box, 2002 ²³ | RCT | 65 (32/33) | 53.03/59 | 0 | Median 24.3/27.2 | Breast cancer | Surgical Procedure CLE&AD: control:51.5, intervention:46.9; MRM: control: 48.5, intervention:53.1. Radiotherapy control:48.5, interevrntion:65.6. Chemotherapy: control:21.2, interevention:43.8. | NR | Treatment group: received the Physiotherapy Management Care Plan (PMCP), including principles for lymphoedema risk minimisation and early management of this condition when it was identified. | Control group: only received an exercise instruction booklet | 24 | Risk of lymphedema : defined by (1) an increase of ≥ 200 ml from the preoperative (VOL (OA-UOA) _{TA}). Arm volumes (VOL) were measured by water displacement. (2) an increase of ≥ 5 cm from the preoperative (CIRC (OA-UOA) _{TA}) (3) MFBIA ratio: number with ratio $< 95\%$ lower reference limit (4) MFBIA % change: number with $> 10\%$ decrease from the OA/UOA ratio |

| Study Label (Author, Y) | Design* | Number of Patients (total, arm1/ arm 2) | Age in yr (mean, arm 1/ arm 2) | % Males | BMI (mean, arm 1/ arm 2) | Cancer type | Cancer treatment received | Cancer severity | First Arm (Intervention) | Second Arm (Control) | Follow up (Months) | Outcomes Reported |
|-------------------------|----------------------------------|---|--------------------------------|---------|--------------------------|---------------|--|-----------------|---|---|--------------------|---|
| Box, 2002 ²⁴ | RCT (the same trial as Box 2002) | 65 (32/33) | 53.03/59 | 0 | Median 24.3/27.2 | Breast cancer | Surgical Procedure CLE&AD: control:51.5, intervention:46.9; MRM: control: 48.5, intervention:53.1. Radiotherapy control:48.5, interevrntion:65.6. Chemotherapy: control:21.2, interevention:43.8. | NR | Treatment group: Received the Physiotherapy Management Care Plan (PMCP), including principles for lymphoedema risk minimisation and early management of this condition when it was identified. | Control group: only received an exercise instruction booklet | 24 | 1. Change in physical activity : measured by compliance with the exercise protocol, which is associated with different patterns of recovery for all movements except external rotation. 2. Functional impairment-range of motion: shoulder abduction |

| Study Label (Author, Y) | Design* | Number of Patients (total, arm1/ arm 2) | Age in yr (mean, arm 1/ arm 2) | % Males | BMI (mean, arm 1/ arm 2) | Cancer type | Cancer treatment received | Cancer severity | First Arm (Intervention) | Second Arm (Control) | Follow up (Months) | Outcomes Reported |
|------------------------------------|-----------------------|---|--------------------------------|---------|--------------------------|---------------|--|-----------------|---|----------------------|--------------------|--|
| Torres Lacomba, 2010 ²⁵ | RCT (ISRCTN9 5870846) | 120 (60/60) | 52.9/52.9 | 0 | 27.9/26.2 | Breast cancer | Surgery- Quadrantectomy: Intervention: 24, Control: 26; Modified mastectomy: Intervention: 23, Control: 20; Lumpectomy: Intervention: 13, Control: 14. Postoperative therapy- Radiotherapy: intervention:44, control:49; Chemotherapy: interevntion: 50, control: 45; Hormonal therapy: Intervention: 39, Control: 33 | NR | Physiotherapy program: including manual lymph drainage, massage of scar tissue, and progressive active and action assisted shoulder exercises. Also received the educational strategy. | Educational strategy | 12 | 1. Risk of lymphedema: ≥2cm increase in the circumference of any two adjacent points compared with measurements in the other arm 2. % volume change: change in volume ratio |

Table S11. Characteristics of included studies comparing Surveillance, education, or clinical care vs No intervention or standard care

| Study Label (Author, Y) | Design* | Number of Patients (total, arm1/ arm 2) | Age in yr (mean, arm 1/ arm 2) | % Males | BMI (mean, arm 1/ arm 2) | Cancer type | Cancer treatment received | Cancer severity | First Arm (Intervention) | Second Arm (Control) | Follow up (Months) | Outcomes Reported |
|------------------------------|---------|---|--------------------------------|---------|--------------------------|---------------|---|-----------------|--|----------------------|--------------------|--|
| Boccardo, 2009 ²⁶ | RCT | 49 (25/24) | 53.4/54.6 | 0 | 27.3/29.9 | Breast cancer | Surgical Procedure (n) CLE & AD: intervention:12, control:13; MRM & AD: intervention:13, control:11. All included patients received radiotherapy. | NR | Preventive protocol (PG); Preoperative upper limb lymphscintigraphy (LS), principles for lymphedema risk minimization, and early management of this condition when it was identified. | Control group (CG) | 24 | 1. Risk of lymphedema: a difference of over 200 ml from preoperative VOL measurements VOL (OA-UOA) [operated arm=OA; unoperated arm=UOA]) 2. % volume change: arm volumes (VOL) were assessed using water displacement and measured to the nearest 5 ml |

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| Study Label (Author, Y) | Design* | Number of Patients (total, arm1/ arm 2) | Age in yr (mean, arm 1/ arm 2) | % Males | BMI (mean, arm 1/ arm 2) | Cancer type | Cancer treatment received | Cancer severity | First Arm (Intervention) | Second Arm (Control) | Follow up (Months) | Outcomes Reported |
|--------------------------|---------------------------------|---|---|---------|--------------------------|---------------|--|--|--|----------------------|--------------------|--|
| Sato, 2014 ²⁷ | Non-randomized controlled trial | 149 (90/59) | ALND:52.9 SLNB:54.3/ ALND:52.1 SLNB:53.7 | 0 | NR | Breast cancer | All patients received surgery and some patients also received chemotherapy or radiation. Radiotherapy: ALND intervention:69.2, control:83.3; SLNB intervention:58.8, control: 51.7. Chemotherapy, molecular targeting therapy: ALND intervention:79.5, control:86.7; SLNB intervention:11.8, control:24.1. | Stage 0: ALND intervention:0.0, control:6.7; SLNB intervention:25.5, control:44.8. Stage I: ALND intervention:7.7, control:20.0; SLNB intervention:54.9, control:48.3. Stage II: ALND intervention:43.6, control:50.0; SLNB intervention:17.6, control:6.9. Stage III: ALND intervention:41.0, control:23.3; SLNB intervention:2.0, control:0.0. Stage IV: ALND intervention:7.7, control:0.0; SLNB intervention:0.0, control:0.0. | Educational program: monitoring arm function and exercises | Routine care | 3 | 1. Volume change: upper arm/forearm girth 2. Change in physical activity: evaluated by Disabilities of Arm, Shoulder and Hand (DASH) 3. Functional impairment-grip: grip strength 4. Functional impairment-range of motion: shoulder flexion/abduction/horizontal extension |

| Study Label (Author, Y) | Design* | Number of Patients (total, arm1/ arm 2) | Age in yr (mean, arm 1/ arm 2) | % Males | BMI (mean, arm 1/ arm 2) | Cancer type | Cancer treatment received | Cancer severity | First Arm (Intervention) | Second Arm (Control) | Follow up (Months) | Outcomes Reported |
|---------------------------|------------------|---|--------------------------------|---------|---|---------------|--|--|--|--|--------------------|---|
| Singh, 2013 ²⁸ | Quasi Randomised | 72 (41/31) | 55.1/62.8 | 0 | 27.1/27.0 | Breast cancer | All patients received surgery and some patients also received chemotherapy or radiation. Adjuvant radiation: intervention: 22 (53.7), control: 14 (45.2); Adjuvant chemotherapy: intervention: 16 (39), control:16 (32.3). | Cancer stage DCIS or Stage 1: intervention:2 (4.9), control:2 (6.5); Stage II: intervention:14 (34.1), control:10 (32.2); Stage III: intervention:19 (46.3), control:13 (41.9); Unknown: intervention: 6 (14.6), control:6 (19.4). | Clinical care pathway: preoperative education, prospective monitoring, and early physiotherapy | No clinical care pathway: preoperative education alone | 7 | 1. Risk of lymphedema: a 2 cm increase in upper extremities circumference between adjacent points, compared with pre-surgical value 2. Change in physical activity: evaluated by Disabilities of Arm, Shoulder and Hand (DASH) 3. Functional impairment-range of motion: shoulder flexion/abduction/external rotation |
| Temur, 2019 ²⁹ | RCT | 61 (30/31) | 47.6/45.6 | 0 | >25: 19; <24.9: 11/ >25: 19; <24.9: 12 | Breast cancer | Surgery: modified radical mastectomy and breast-conserving surgery | Stage 1 intervention: 2, control: 2; Stage 2 intervention: 16, control: 16; Stage 3 intervention: 12, control: 13. | Intervention group: Provided training and given a training booklet describing "exercise, massage and prevention methods" | Control group | 6 | 1. Volume change : lateral epicondylitis (10 cm above/below), forearm (wrist joints 10 cm below) and metacarpophalangeal 2. Change in physical activity : physical functioning domain of EORTC QLQ-30 |

| Study Label (Author, Y) | Design* | Number of Patients (total, arm1/ arm 2) | Age in yr (mean, arm 1/ arm 2) | % Males | BMI (mean, arm 1/ arm 2) | Cancer type | Cancer treatment received | Cancer severity | First Arm (Intervention) | Second Arm (Control) | Follow up (Months) | Outcomes Reported |
|--------------------------|---------------------------------|---|--------------------------------|---------|--------------------------|---------------|---|---|---|----------------------|--------------------|--|
| Yang, 2016 ³⁰ | Comparative observational study | 707 (390/317) | 47.6/48.6 | 0 | 24.3/23.3 | Breast cancer | All patients received surgery and some patients also received chemotherapy or radiation. Radiotherapy- Not done: intervention:47 (12.0 %), control:41 (12.9 %); Breast only: intervention:211 (54.0 %), control:174 (54.9 %); Breast and SCRT: intervention:140 (36.0 %), control:102 (32.2 %). Chemotherapy- Doxetaxel: intervention:280 (71.9 %), control:223 (70.3 %). | Histopathologic stage: I(%):intervention:109 (28.0 %), control:92 (29.0 %); II(%):intervention:215 (55.0 %), control:168 (53.0 %); III(%):intervention:66 (17.0 %), control:57 (18.0 %). | Surveillance program for lymphedema management (SLYM) | Standard care | 60 | Risk of lymphedema: defined by reference to the guidelines of the International Society of Lymphology (ISL) consensus document |

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