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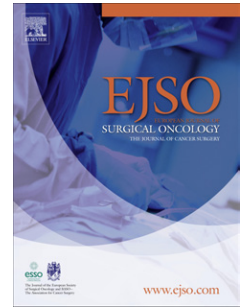
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Prevention of seroma formation after axillary dissection in breast cancer: a systematic review.

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Background: The most common complication after breast cancer surgery is seroma formation. It is a source of significant morbidity and discomfort. Many articles have been published describing risk factors and preventive measures. The aim of this paper is to provide a systematic review of studies and reports on risk factors and preventive measures. Surgery lies at the core of seroma formation; therefore focus will be placed on surgical ways of reducing seroma.

Methods: A computer assisted medline search was carried out, followed by manual retrieval of relevant articles found in the reference listings of original articles.

Results: 136 relevant articles were reviewed. Though the level of evidence remain varied several factors, type of dissection, tools with which dissection is carried out, reduction of dead space, suction drainage, use of fibrin glue and octreotide usage, have been found to correlate with seroma formation and have been shown to significantly reduce seroma rates.

Conclusion: Seroma formation after breast cancer surgery can not be avoided at present. There are however several methods to minimize seroma and associated morbidity. Future research should be directed toward the best ways of reducing seroma by combining proven methods.

Keywords: Seroma, breast cancer, lymphadenectomy, risk factors, prevention.

Introduction

Seroma formation, an abnormal collection of serous fluid, is known for being the most common complication following breast cancer surgery. Viewed by some surgeons as a necessary evil, it accounts for prolonged patient discomfort which translates as pain, delayed wound healing, skin flap necrosis and infection.^{1 2} Additional financial burden is caused by late onset seroma formation; which in most cases requires multiple visits with manual evacuation of accumulated fluid.

With incidence rates varying from 15 up to 90 percent there is extensive literature on this subject.^{3 4 5} Consensus however is lacking with respect to pathophysiology as well as preventive measures. This article provides an up to date review of available literature in an attempt to clarify seroma formation. Pathophysiology and preventive measure will be discussed. Emphasis will be placed on surgical aspects, as it is surgery that lies at the root of seroma formation.

Pathogenesis

Although not yet fully understood the pathogenesis of seroma formation has been linked to several precipitating factors.⁶ The dead space created by dissected tissue is filled with serous fluid.⁷ This fluid changes composition in the days following surgery. At first it simulates lymph like fluid with blood clots, indicating broken lymph and blood vessels due to the dissection. A few days later it imitates an exsudate, which seems to be formed as the body reacts to the acute inflammatory condition following surgery.⁸ Skin flaps, the result of

dissecting through different layers of tissue, which already had to adhere to the irregular chest wall are further hindered by seroma.⁹ This leads to a prolonged primary wound union process.¹⁰ Lymphatic and blood vessels which are damaged by the operation start to ooze blood and lymphatic fluid, which adds to the seroma, as the patient resumes moving her arm.¹¹ The pathophysiology for seroma formation seems to be multifactorial with surgery at its core.¹²

Materials and methods

Articles were collected via a computer assisted medline search up to February 2010, and additional references were found in bibliographies of these articles. As reference terms 'seroma', 'lymphadenectomy', 'breast cancer', 'mastectomy' and 'lymphocele' were used in combination with the following search strategy: (("seroma"[MeSH Terms] OR "seroma"[All Fields]) OR ("lymphocele"[MeSH Terms] OR "lymphocele"[All Fields])) AND (("lymph node excision"[MeSH Terms] OR "lymph node excision"[All Fields] OR "lymphadenectomy"[All Fields]) OR ("mastectomy"[MeSH Terms] OR "mastectomy"[All Fields])) Included articles were limited to studies published in English. Randomized controlled trials, prospective studies, retrospective studies as well as smaller descriptive studies were selected from the list of found articles and extensively reviewed. Quality of evidence was categorized according to the levels of evidence and grades of recommendation as used by the Oxford centre of Evidence –based Medicine.

Results

Risk factors

A multitude of research has tried to provide characteristics of patients at risk of developing seroma formation after breast cancer surgery. Bodyweight and hypertension have shown to be significant influencing factors for seroma formation.^{13 14 15} Age, number of lymph nodes and extent of lymph nodes involved remain controversial factors as some studies show significant seroma formation^{16 17 18 19 20} while others found no significant association.^{21 22 23}²⁴ The following factors were shown to have no significant influence on seroma formation: tumour size, neoadjuvant therapy, smoking, breast size, diabetes mellitus.^{25 26}

Surgical risk factors

There are several factors concerning surgical involvement in the formation of seroma. First and foremost is the type of dissection carried out. The more extensive the dissection will be the more blood and lymphatic vessels will be damaged; resulting in larger seroma formation. This was shown when studies compared modified radical mastectomy with mastectomy and modified radical mastectomy with wide local excision and axillary dissection.^{15 16 17 27} When modified radical mastectomy was compared to breast conserving therapies results were mixed. Yet breast conserving therapies have an overall lower seroma formation.^{28 29 30 31} Axillary dissection has been shown to negatively influence seroma formation. With the introduction of sentinel lymph node biopsy a means to assess the need for axillary dissection has become available. Sentinel lymph node biopsy has been associated with significantly lower seroma formation in comparison to axillary dissection.^{12 32} Not only is the actual dissection, and with that the damage to lymphatic and blood vessel, smaller with dissection of one sentinel node, it also prevents in many cases the need for a larger dissection. Interesting to note is that a recent RCT showed that concurrent axillary dissection, when needed after sentinel node biopsy, is better to be carried out in a secondary procedure. Patients who

underwent concurrent axillary dissection in the same operation as the sentinel lymph node biopsy had significantly more seroma formation in comparison to patients who underwent two separate procedures.³³

The choice of instruments with which surgery is performed has also been shown to influence seroma formation. Electrocautery for haemostasis is the preferred method due to decreased operating time and reduced blood loss. It has however been linked with significantly more seroma formation when compared to knife dissection.^{34 35 36 37 38} Other techniques include argon diathermy, laser scalpel and ultrasonic tools. All of the aforementioned show equal amounts of seroma formation when compared with knife dissection, yet every technique reports better haemostasis.^{23 39 40 41 42 43 44 45 46 47} A recent prospective study which used the electrothermal bipolar vessel sealing system showed promising result. 60 patients with locally advanced breast cancer (T2 or T3) were treated by modified radical mastectomy with axillary dissection. All operations were carried out by the same surgical team using the electrothermal bipolar vessel sealing system. No seroma formation was found in 60 patients with haemostasis reported equal to electrocautery.⁴⁸

Preventive measures

Suction drains, first described in 1947, have brought forth many an article.⁴⁹ When compared to no drain usage suction drainage resulted in significantly lower seroma formation.^{50 51 52 53} The negative pressure applied by the drain is thought to obliterate the dead space left after excision, thus facilitating skin flap apposition and enforcing wound healing. Negative pressure is also thought to reduce wound dehiscence, necrosis, wound infection and seroma formation.^{54 55 56 57 58} Whether this negative pressure is applied by a single drain or multiple drains at several locations does not seem to affect seroma formation.^{26 59 60} The amount of suction, high or low pressure and active or passive suction, used by the drain is also of no consequence on seroma formation.^{61 62 63 64 65 66 67} With respect to the type of drain used, a flat type drain with multiple channels has been show to correlate with lower seroma formation.^{27 57} The duration of drainage is also subject to discussion. It has been shown that 74% of total seroma formation is drained in the first 48 hours postoperative.⁶⁸ Recent studies have shown that volume drained in the first 48 hours predicts seroma formation.^{69 70 71} However studies comparing removal after max 3 days postoperative, with removal ranging form 6 until 16 days postoperative, have not been associated with significant decrease of seroma formation.^{45 47 72 73 74 75 76 77 78 79 80} No significant seroma increase has been correlated to leaving the hospital with a drain in situ.^{81 82 83 84 85 86 87}

Shoulder immobilisation has been thought to decrease seroma formation. Multiple studies however have shown that immobilisation of the shoulder does not correlate with a decrease in seroma formation.^{8 88 89 90 91 92} Active shoulder exercise however, such as physiotherapy, has been linked with decreased seroma formation when the exercise was postponed until at least one week after surgery.^{93 94 95 96 97}

External compression dressings in the axilla have claimed to reduce the dead space created after surgery. Nevertheless studies have shown that they do not reduce seroma formation. The idea of axillary padding in the reduction of seroma formation has long been forfeited.^{98 99}

Surgical prevention

Due to the lack of fibrinogen found in aspirated serous fluid, the hypothesis was raised that fibrin enriched fluid could decrease seroma formation.^{6 100} Although a few small studies have shown promising result,^{101 102 103 104 105} a multitude of large trials report that fibrin glue does not reduce seroma formation.^{11 106 107 108 109 110 111 112 113 114} Recent trials, though

limited in patient numbers, show reduced seroma formation however no differences are observed.^{103 115 116} A recent trial using fibrin glue also did not show a decrease in seroma formation; however it did show significantly reduced drainage duration and overall drain output.¹¹⁷

Another investigated chemical means for obliterating dead space has been tetracycline sclerotherapy. Although successful in decreasing seroma formation the process proved too painful for patients to endure, while another study showed a high rate of infection.^{118 119 120 121 122}

The secretion suppressing qualities of octreotide have led to its study in the decrease of seroma formation. A large randomized controlled trial showed a significant decrease in seroma formation after surgery in comparison to controls.^{123 124 125}

The dead space left after surgery seems to be one of the key factors in the formation of seroma. Research has gone toward obliterating dead space, not only by chemical means but also by using a mechanical way.^{1 126 127} Flap fixation to reduce dead space has been performed in many different places: axilla, skin edge, in the line of wound closure and at the site of flaps.^{46 128 129 130} Many different techniques and materials were used in the fixation: skin to fascia, mattress type sutures, through the skin sutures, subcutaneous sutures, sutures approximating the axillary aponeurosis to proximate muscle, flaps to underlying muscle and buttress sutures. These sutures were made using surgical silk, fine cotton thread and absorbable thread.^{9 14 131 132} These techniques were carried out after various forms of breast cancer surgery: breast conserving therapy, radical and extended mastectomy and functional axillary lymphadenectomy.^{3 19 133} All of the used techniques showed a significant decrease in seroma formation. Interesting to note is that two recent studies showed that after flap fixation there was no need for suction drainage. No increase in seroma formation was found after flap fixation without drain when compared to drain usage.^{55 134} While cosmetic appearance after fixation was reported to be satisfactory, the downside of fixation can be found in increased operating time required. Increases have been reported up to 20 minutes.^{20 46 135 136}

Discussion

Seroma formation is the most common complication after breast cancer surgery. With an incidence of up to 90 percent seroma formation is a common problem. Left untreated it can lead to delayed wound healing, pain, skin necrosis and infection. This literature research has not found a single way to prevent seroma formation; however there are many proven methods to significantly reduce seroma formation.

Several factors have been linked to seroma formation. The dissection creates a large dead space with skin flaps in different layers and damage to lymphatic and blood vessels. The spilled fluids, which leak through the damaged lymphatic and blood vessels as patients resume their daily routine, is collected in the dead space area. The skin flaps, which already had a hard time adhering to the irregular underlying tissue, are further hindered by this accumulation of fluid leading to secondary wound union. Seroma is maintained through this secondary wound union as the space where this fluid accumulates is not reduced rapidly enough.

Every woman undergoing breast cancer surgery is at risk for creating seroma yet it has been demonstrated that some factors correlate with an increase of aforementioned risk. Increased bodyweight and hypertension have shown to be significant influencing factors for seroma formation. Not all risk factors however are patient related, the type of surgery corresponds with seroma formation; the more extensive the dissection the more blood and lymphatic vessels will be damaged, resulting in increased seroma formation. Aside from the type of surgery the tools with which to perform said operation have also been shown to alter seroma

formation. Though electrocautery provides an excellent means for haemostasis, it also significantly increases seroma formation. At present there are other techniques available, argon diathermy, laser scalpel, ultrasonic tools and bipolar, which show better haemostasis compared to knife dissection, with significantly lower seroma rates. The type of dissection to be carried out is linked to the stage of disease, however the tools with which to operate can be chosen.

At present no means to prevent seroma is readily available, yet ways for reducing seroma formation are widely available. Suction drainage, thought to reduce dead space through negative pressure, significantly lowers seroma formation after surgery. A single flat type drain with multiple channels used for 48 hours produces the best results. Though 48 hours in hospital stay is irregular after breast cancer surgery, patients can also be discharged with drain in situ as this did not increase seroma rates. Use of the arm at the affected site has been linked to seroma formation since it pressures lymph and blood towards the damaged lymph and blood vessels. Restricting the use of aforementioned arm however has not decreased seroma formation, yet has led to disability of the shoulder. No immediate physiotherapy correlated with decreased seroma rates. Therefore patients should be encouraged to use their arm in normal routines; physiotherapy on the other hand should be started at least one week after surgery. Compression dressings, which were thought to decrease dead space extracorporeal, have been demonstrated to cause no effect on seroma formation.

The reduction of dead space after surgery can be achieved through chemical and mechanical means. The chemical way, through either fibrin enriched fluid tetracycline or octreotide, shows promise of reducing seroma formation yet it has its shortcomings. Fibrin enriched compounds have shown seroma reduction in smaller studies but in large randomized trials effect seems to be missing. Tetracycline showed significant seroma reduction yet the present method of administering proved too painful. Octreotide, a secretion suppressing compound equal to somatostatin, showed significant seroma reduction. At present however this was only shown in one study. Mechanical means of reducing seroma through minimizing dead space have proven to be very successful. All of the different methods, using different materials after different kind of operations, show significantly lower seroma rates. While cosmetic results have been reported to be acceptable there is a cost however: operating time is increased by as much as 20 minutes.

With incidence as high as 90% seroma is a given for these patients. There are however measures that can be taken significantly reduce seroma, through good use of drains and mechanical dead space closure as well as other means such as delaying physiotherapy. At present we recommend, especially in patients with increased risk factors, to utilize a combination of proven seroma reducing measures. Future research concerning decreasing seroma should be directed towards the reduction of seroma formation through the combined use of proven seroma reduction methods.

Conflict of interest

There are no conflicts of interest.

Table 1 Risk factors per level of evidence

| Grade | Direction of association | | |
|----------------|--|---|---|
| | Increase | No association | Decrease |
| Level 1 | none | none | none |
| Level 2 | Body weight extended radical mastectomy | Duration of drainage Immobilization of the shoulder LN status Intensity of negative suction Use of fibrinolysis inhibitor Number of LN's | Sentinel LN biopsy Suction drainage Octreotide use |
| Level 3 | Hypertension Multiple holes type drains No drainage Operation time Use of electrocautery | Use of adhesive glue Use of laser scalpel Use of argon diathermy Use of pressure garment Breast size Diabetes mellitus Smoking Neoadjuvant therapy | Suture fixation techniques Use of ultrasonic scissors Use of electrothermal bipolar vessel system Extent of dissection Postponed active shoulder exercise Tetracycline sclerotherapy |
| Level 4 | none | Age Tumor Size Total drainage volume | none |

Table 2 Randomized controlled trials**Dead space reduction through fixation**

| Year | Author | n | Intervention | Incidence of seroma% |
|------|-------------|-----|---|----------------------|
| 1990 | Hamy | 53 | Surgical wadding vs none | 27 vs 80 |
| 1993 | Coveney | 40 | Suture fixation vs none | 25 vs 85 |
| 2002 | Purushotham | 375 | Suture fixation without drain vs conventional surgery | 47 vs 51 |

Suction drainage

| Year | Author | n | Intervention | Incidence of seroma % |
|------|---------------|-----|---|-----------------------|
| 1973 | Morris | 53 | suction drainage vs static drainage | 12 vs 29 |
| 1979 | Britton | 46 | high vacuum vs low vacuum drainage | not significant |
| 1988 | Cameron | 40 | drain vs no drain | 10 vs 15 |
| 1991 | Inwang | 84 | drain removal at 5th vs < 20 ml | 49 vs 28 |
| 1992 | Petrek | 65 | single vs multiple drains | not significant |
| 1992 | Somers | 227 | suction drain vs no drain | 73,1 vs 89,1 |
| 1992 | Terrel | 84 | axillary drainage vs axillary and pectoral drainage | 19 vs 13 |
| 1992 | Parikh | 100 | drain removal at 3d vs 6th POD | not significant |
| 1995 | Heurn | 78 | low versus high vacuum drainage | 30 vs 42 |
| 1997 | Ackroyd | 120 | drain removal at 5th vs < 30 ml | 29 vs 25 |
| 1998 | Zavotsky | 46 | suction drain vs no drain | 8,3 vs 50 |
| 1999 | Kopelman | 90 | drain removal 3d POD vs < 35 ml | 21 vs 2 |
| 2001 | Gupta | 121 | drain removal 5th vs 8th POD | 48 vs 28 |
| 2003 | Puttawibul | 60 | axillary drainage vs axillary and pectoral drainage | 20 vs 37 |
| 2004 | Dalberg | 250 | drain removal at first POD vs < 40 ml | 48,5 vs 22,2 |
| 2005 | Soon | 87 | drain vs no drain | 94 vs 96 |
| 2005 | Chintamami | 85 | half versus full vacuum drainage | 2,8 vs 4 |
| 2005 | Baas-Vrancken | 100 | short versus long term postoperative drainage | 76 vs 64 |

Shoulder immobilisation

| Year | Author | n | Intervention | Incidence of seroma % |
|------|---------|-----|---|-----------------------|
| 1979 | Flew | 64 | 7 days immobilisation vs exercise starting 2d POD | 7 vs 20 |
| 1990 | Petrek | 57 | mobilization from 2nd POD vs 5th POD | not significant |
| 1990 | Janssen | 144 | exercise from 1st POD vs 8 days of immobilization | not significant |
| 1996 | Browse | 67 | 10 days immobilization vs none | 31 vs 43 |
| 1998 | Abe | 116 | mobilization from 1st POD vs 7th pod | significant |

Shoulder exercise

| Year | Author | n | Intervention | Incidence of seroma % |
|------|---------|-----|---|-----------------------|
| 1997 | Schultz | 163 | shoulder exercise form 1st POD vs 7th POD | 38 vs 22 |
| 2005 | Shamley | 444 | Delayed vs early shoulder exercise | 27 vs 46 |

Compression dressing

| Year | Author | n | Intervention | Incidence of seroma % |
|------|--------|-----|---|-----------------------|
| 1998 | Chen | 40 | 14 days compression dressing vs none | 0 vs 4,8 |
| 1999 | O'hea | 135 | Compression dressing vs conventional dressing | 2,9 vs 1,8 |

Fibrin glue

| Year | Author | n | Intervention | Incidence of seroma % |
|------|----------|-----|--|-----------------------|
| 1993 | Uden | 53 | fibrin glue vs none | 64 vs 53 |
| 1995 | Vaxman | 40 | fibrin glue vs none | 20 vs 5 |
| 1998 | Gilly | 108 | fibrin glue vs none | 2 vs 1.7 |
| 2000 | Dinsmore | 27 | fibrin glue vs none | 43 vs 23 |
| 2001 | Moore | 79 | fibrin glue vs none | 16 vs 29 |
| 2001 | Berger | 60 | fibrin glue vs none | 39 vs 42 |
| 2003 | Ulusoy | 54 | fibrin glue vs none | 18 vs 11 |
| 2003 | Langer | 55 | fibrin glue vs none | 4 vs 3 |
| 2004 | Jain | 116 | fibrin glue vs none | 38 vs 26 |
| 2004 | Mustonen | 40 | fibrin glue and fibrinolysis inhibitor vs none | not significant |
| 2005 | Johnson | 82 | fibrin glue without drainage vs drainage | 36,8 vs 45,5 |

Octreotide

| Year | Author | n | Intervention | Incidence of seroma % |
|------|-----------|-----|-----------------------------------|-----------------------|
| 2003 | Carcoforo | 261 | octreotide subcutaneously vs none | significant |

Tetracycline

| Year | Author | n | Intervention | Incidence of seroma % |
|------|--------|----|----------------------|-----------------------|
| 2000 | Rice | 62 | tetracycline vs none | 53 vs 22 |

Bovin thrombine

| Year | Author | n | Intervention | Incidence of seroma % |
|------|--------|-----|-------------------------|-----------------------|
| 1997 | Burak | 101 | bovine thrombin vs none | 37 vs 40 |

Surgical prevention

| Year | Author | n | Intervention | Incidence of seroma % |
|------|-------------|-----|--|-----------------------|
| 1993 | Wyman | 40 | laser scalpel vs scalpel | 50 vs 55 |
| 1996 | Kerin | 50 | aron diathermy vs scalpel | 12 vs 17 |
| 1998 | Porter | 80 | electrocautery vs scalpel | 38 vs 13 |
| 2004 | Lumachi | 92 | ultrasound scissors vs scissors and ligation | 20 vs 40 |
| 2005 | Purushotham | 298 | SLND vs ALND | 11 vs 24 |
| 2006 | Mandar | 160 | electrocautery vs scalpel | 88,3 vs 82,2 |

¹ Halsted W, et al. Developments in the skin grafting operations for cancer of the breast. *JAMA* 1913; 60: 416-451.

² Tadych K, et al. Postmastectomy seromas and wound drainage. *Surg Gyn Obstet* 1987; 165: 483-7.

³ Alvandy L, et al. Preliminary results of conservative treatment of early breast cancer with axillary dissection. *Aust N Z J Surg* 1991; 9: 670-74.

⁴ Osteen R, et al. The national cancer data base report on breast cancer. *Cancer* 1994; 73: 1994-2000.

⁵ Roses D, et al. Complications of level I and II axillary dissection in the treatment of carcinoma of the breast. *Ann Surg* 1999; 230: 194-201.

⁶ Agrawal A, et al. Concepts of seroma formation and prevention in breast cancer surgery. *ANZ J Surg* 2006; 76: 1088-1095.

⁷ Bonnema J, et al. The composition of serous fluid after axillary dissection. *Eur J Surg* 1999; 165: 9-13.

⁸ Watt-Boolsen S, et al. A study of the nature and origin of seroma after mastectomy. *Dan Med Bull* 1989; 36:487-9.

⁹ Aitken D, et al. Complications associated with mastectomy. *Surg Clin North Am* 1983; 63: 1331-52.

¹⁰ Chilson T, et al. Seroma prevention after modified radical mastectomy. *Am Surg* 1992; 58: 750-54.

- ¹¹ Budd DC, et al. Surgical morbidity after mastectomy operations. *Am J Surg* 1978; 135: 218-20.
- ¹² Kuroi K, et al. Evidence based risk factors for seroma formation in Breast surgery. *Jpn J Clin Oncol* 2006; 36: 197-206.
- ¹³ Burak W, et al. Seroma formation following axillary dissection for breast cancer, *J surg Oncol* 1997; 4: 293-7.
- ¹⁴ Kumar S, et al. Post mastectomy seroma, *J R Coll Surg Edinb* 1995; 40: 292-4.
- ¹⁵ Loo W, et al. Factors predicting seroma formation after mastectomy for Chinese breast cancer patients. *Indian J Cancer* 2007; 44: 99-103.
- ¹⁶ Petrek J, et al. Axillary lymphadenectomy. *Arch. Surg* 1990; 125: 378-82.
- ¹⁷ Salmon RJ, et al. Prevention of post-mastectomy seromas, *Presse Med* 1985; 14: 27-9.
- ¹⁸ Bryant M, et al. Postoperative seroma following mastectomy and axillary dissection. *Br J Surg* 1987; 74: 1187.
- ¹⁹ Lucci A, et al. Surgical complications associated with sentinel lymph node dissection (SLND) plus axillary lymph node dissection compared with SLND alone in the American College of Surgeons Oncology group trial Z0011, *J Clin Onc* 2007; 25: 3657-63.
- ²⁰ Randolph L, et al. Predictions of postoperative seroma after latissimus dorsi breast reconstruction. *Plas and Recon Surg* 2005; 116: 1287-1290.
- ²¹ Tejler G, et al. Complications and hospital stay after surgery for breast cancer: a prospective study of 385 patients, *Br J Surg* 1985; 72:542-4.
- ²² Schuijtvlot M, et al. A prospective audit of the use of a buttress suture to reduce seroma formation following axillary node dissection without drains, *Breast* 2002;11:94-6.
- ²³ Gonzalez EA, et al. Seroma formation following breast cancer surgery. *Breast* 2003; 9: 385-8.
- ²⁴ Hashemi E, et al. Seroma formation after surgery for breast cancer. *World J. Surg. Oncol* 2004; 2: 44.
- ²⁵ Say CC, et al. A biostatistical evaluation of complications from mastectomy. *Surg Gynecol Obstet* 1974;138:370-6.
- ²⁶ Woodworth PA, et al. Seroma formation after breast cancer surgery: incidence and predicting factors. *Am Surg* 2000;66:444-50; discussion 450-1.
- ²⁷ Aitken D, et al. Prevention of seromas following mastectomy and axillary dissection. *Surg Gynecol Obstet* 1984; 158: 327-30.
- ²⁸ Petrek JA, et al. .A prospective randomized trial of single versus multiple drains in the axilla after lymphadenectomy. *Surg Gynecol Obstet* 1992;175:405-9.
- ²⁹ Abe M, et al. A Randomized controlled trial on the prevention of seroma after partial or total mastectomy and axillary lymph node dissection. *Breast Cancer* 1998;5:67-9.
- ³⁰ Lumachi F, et al. Seroma prevention following axillary dissection in patients with breast cancer by using ultrasound scissors: a prospective clinical study. *Eur J Surg Oncol* 2004;30:526-30.
- ³¹ Medl M, et al. The application of fibrin glue after axillary lymphadenectomy in the surgical treatment of human breast cancer. *Anticancer Res* 1995; 15:2843-5
- ³² Purushotham AD, et al. Morbidity after sentinel lymph node biopsy in primary breast cancer: results from a randomized controlled trial. *J Clin Oncol* 2005;23: 4312-21.
- ³³ John A, et al. Impact of immediate versus delayed axillary node dissection on surgical outcomes in breast cancer patients with positive sentinel nodes. *J Clin Oncol* 2008;26:3530-3535.
- ³⁴ Porter KA, et al.. Electrocautery as a factor in seroma formation following mastectomy. *Am. J. Surg.* 1998; 176: 8-11.
- ³⁵ Keogh GW, et al.. Seroma formation related to electrocautery in breast surgery: a prospective randomised trial. *The Breast* 1998; 7: 39-41.
- ³⁶ Hoefler RA Jr.,et al. Wound complications following modified radical mastectomy: an analysis of perioperative factors. *J. Am. Osteopath. Assoc.* 1990; 90: 47-53.
- ³⁷ Hongying W, et al. Origin and countermeasure for common skin flap complications after radical operation for breast cancer. *Kath Univ Med J* 2006; 13: 14-17.
- ³⁸ Mandar S, et al. Influence of surgical technique on axillary seroma formation. *ANZ J. Surg.* 2007; 77: 385-389.
- ³⁹ Kerin MJ, et al. Argon-enhanced cutting and coagulation confers advantages over conventional electrocautery for mastectomy. *Eur J Surg Oncol* 1996;22:571-3.
- ⁴⁰ Ridings P, et al.. Argon beam coagulation as an adjunct in breast-conserving surgery. *Ann. R. Coll. Surg. Engl.* 1998; 80: 61-2.
- ⁴¹ Wyman A, et al. Randomized trial of laser scalpel for modified radical mastectomy. *Br. J. Surg.* 1993; 80: 871-3.

- ⁴² Lumachi F, et al. Usefulness of ultrasound scissors in reducing serous drainage after axillary dissection for breast cancer: a prospective randomized clinical study. *The American Surgeon* 2004;70: 80.
- ⁴³ Deo SV, et al. Modified radical mastectomy using harmonic scalpel. *J. Surg. Oncol.* 2000; 74: 204–7.
- ⁴⁴ Deo SV, et al. A comparative study of modified radical mastectomy using harmonic scalpel and electrocautery. *Singapore Med. J.* 2002; 43: 226–8.
- ⁴⁵ Galatius H, et al. Mastectomy using ultrasonic dissection: effect on seroma formation. *Breast* 2003; 12: 338–41.
- ⁴⁶ Irshad K, et al. Use of harmonic scalpel in mastectomy and axillary dissection for breast cancer. *Eur. J. Cancer* 2002; 38 (Suppl. 3): 104.
- ⁴⁷ Adwani A, et al. Ultracision reduces acute blood loss but not seroma formation after mastectomy and axillary dissection: a pilot study. *Int J Clin Pract*, May 2006, 60, 5, 562–564.
- ⁴⁸ Manouras A, et al. Modified radical mastectomy with axillary dissection using the electrothermal bipolar vessel sealing system. *Arch Surg.* 2008;143(6):575-580.
- ⁴⁹ Murphey D, et al. The use of atmospheric pressure in obliterating dead space. *South Surg* 1947; 13: 372-5.
- ⁵⁰ Cameron A, et al. Suction drainage of the axilla. *Br J Surg* 1988; 75: 1211.
- ⁵¹ Zavotsky J et al. Evaluation of axillary lymphadenectomy. *Ann Surg Oncol* 1998; 5: 227-31.
- ⁵² Kopelman D, et al. Postoperative suction drainage of the axilla. *Eur J Surg* 1999; 165: 117-20.
- ⁵³ Soon P, et al. Seroma formation after axillary lymphadenectomy with and without the use of drains. *The Breast* 2005; 14: 103-107.
- ⁵⁴ Coveney E, et al. Effect of closing dead space on seroma formation. *Eur J Surg Oncol* 1993; 19: 143-6.
- ⁵⁵ Somers R., et al. The use of closed suction drainage after lumpectomy. *Ann Surg* 1992; 215: 146-9.
- ⁵⁶ Bonnema J, et al. A Prospective trial of high versus low vacuum drainage. *Am J Surg* 1997; 173: 76-9.
- ⁵⁷ Moss J, et al. Historical and current perspectives on surgical drainage. *Surg Gynecol Obstet* 1981; 152: 517-27.
- ⁵⁸ Morris A, et al. A controlled trial of closed wound suction. *Br J Surg* 1973; 60: 357-9.
- ⁵⁹ Terrel G, et al. Axillary versus combined axillary and pectoral drainage after modified radical mastectomy. *Surg Gynecol Obstet* 1992; 175: 437-40.
- ⁶⁰ Puttawibul P, et al. Mastectomy without drain at pectoral area. *J Med Assoc Thai* 2003; 86: 325-31.
- ⁶¹ Whitfield P, et al. Suction versus siphon drainage after axillary surgery for breast cancer. *Br J Surg* 1979; 81: 547.
- ⁶² Purushotham A, et al. Randomized clinical trial of no wound drains and early discharge in the treatment of women with breast cancer. *Br J Surg* 2002; 89: 286-92.
- ⁶³ Pogson C, et al. Seroma following Breast cancer surgery. *Eur J Surg Oncol* 2003; 29: 711-17.
- ⁶⁴ Britton B, et al. A comparison between disposable and non disposable suction drainage units. *Br J Surg* 1979; 66: 279-80.
- ⁶⁵ Chintmani, et al. Half versus full vacuum suction drainage after modified radical mastectomy. *BMC Cancer* 2005; 5: 11.
- ⁶⁶ van Heurn L, et al. Prospective randomized trial of high versus low vacuum drainage after axillary lymphadenectomy. *Br J Surg* 1995; 82: 931-2.
- ⁶⁷ Wedderburn A, et al. Comparison between low and high suction pressure drainage following axillary clearance. *Eur J Surg Oncol* 2000; 26: 142-4.
- ⁶⁸ Barwell J, et al. How long should suction drains stay in after breast surgery. *Ann R Coll Surg Engl* 1997; 79:435-7.
- ⁶⁹ Haluk U, et al. Analysis of risk factors affecting the development of seromas. *Breast J* 2007; 13: 588-592.
- ⁷⁰ Baas-vrancken Peeters, MJ, et al. Short versus long-term postoperative drainage of the axilla. *Br Can Res Treat* 2005; 93: 271-275.
- ⁷¹ Akinci M, et al. Factors affecting seroma formation after mastectomy with full axillary dissection. *Acta Chir Belg* 2009; 109: 481-483.
- ⁷² Parikh H, et al. Early drain removal following modified radical mastectomy. *J Surg Oncol* 1992; 51: 266-9.
- ⁷³ Inwang R, et al. A controlled trial of short term vs standard axillary drainage. *Ann R Coll Surg Engl* 1991; 73: 326-8.
- ⁷⁴ Yui M, et al. Early Removal of drains and discharge of breast cancer surgery patients. *Ann R Coll Surg Engl* 1995 77; 77: 377-9.
- ⁷⁵ Liu C, et al. Overnight closed suction drainage after axillary lymphadenectomy for breast cancer. *Am Surg* 1997; 63: 868-70.
- ⁷⁶ Ackroyd R, et al. A prospective randomized trial of the management of suction drains following breast cancer surgery. *The Breast* 1997; 6: 271-4.
- ⁷⁷ Dalberg K, et al. A randomised study of axillary drainage. *Eur J Surg Oncol* 2004; 30: 602-9.

- ⁷⁸ Barton A, et al. Early removal of postmastectomy drains is not beneficial: results from a halted randomized controlled trial. *Am J Surg* 2006; 191: 652-656.
- ⁷⁹ Talbot m, et al. Reduced use of drains following axillary lymphadenectomy. *ANZ J Surg* 2002; 72: 488-90.
- ⁸⁰ Gupta R, et al. A comparison of 5 day and 8day drainage following mastectomy. *Eur J Surg oncol* 2001; 27: 26-30.
- ⁸¹ Holcombe C, et al. The satisfaction and savings of early discharge with drain in situ following axillary lymphadenectomy. *Eur J Surg Oncol* 1995; 21: 604-6.
- ⁸² Wagman LD, et al.. Evaluation of a short-stay program for patients undergoing mastectomy. *J Surg Oncol* 1989; 41: 98-102.
- ⁸³ Boman L, et al. Effects of early discharge from hospital after surgery for primary breast cancer. *Eur J Surg* 1993; 159: 67-73.
- ⁸⁴ Tan LR, et al. Outpatient definitive breast cancer surgery. *Am Surg* 1997; 63: 865-7.
- ⁸⁵ Edwards M, et al. Economic impact of reducing hospitalization for mastectomy patients. *Ann Surg* 1988; 208: 330-6.
- ⁸⁶ Orr R, et al. Early discharge after mastectomy. A safe way of diminishing hospital costs. *Am Surg* 1987; 53: 161-3.
- ⁸⁷ Hoehn JL. Definitive breast cancer surgery as an outpatient: a rational basis for the transition. *Semin Surg Oncol* 1996; 12: 53-8.
- ⁸⁸ Flew T, et al. Wound drainage following radical mastectomy. *Br J Surg* 1979; 66: 302-5.
- ⁸⁹ Jansen R, et al. Immediate versus delayed shoulder excercises after axillary lymph node dissection. *Am J Surg* 1990; 160:481-4.
- ⁹⁰ Browse D, et al. Axillary node clearance; who wants to immobilize the shoulder. *Eur J Surg Oncol* 1996; 22:569-70.
- ⁹¹ Chen S, et al. Timing of shoulder exercise after modified radical mastectomy. *Changgeng Yi Xue Za Zhi* 1999; 22: 37-43.
- ⁹² Knight C, et al. Prevention of seromas in mastectomy wounds. *Arch Surg* 1995; 130: 99-101.
- ⁹³ Lotze M, et al. Early verus delayed shoulder motion following axillary dissection. *Ann Surg* 1981; 193: 288-95.
- ⁹⁴ Schultz I, et al. Delayed shoulder excercises in reducing seroma frequency. *Ann Surg Oncol* 1997; 4:293-7.
- ⁹⁵ Rodier J, et al. Influence of the timing of physiotherapy upon the lymphatic complications of axillary dissection. *Int Surg* 1987; 72:166-9.
- ⁹⁶ Shamley D, et al. Delayed versus immediate exercises following surgery for breast cancer: a systematic review. *Breast Can Res Treat* 2005; 90: 263-271.
- ⁹⁷ Van der Horst C, et al. Shoulder function following early mobilization of the shoulder after mastectomy. *Neth J Surg* 1985; 37: 105-8.
- ⁹⁸ O'Hea B, et al. External compression dressing versus standard dressing after axillary lymphadenectomy. *Am J Surg* 1999; 177: 450-53.
- ⁹⁹ Chen C, et al. The effect of a pressure garment on post surgical drainage and seroma formation. *Singapore Med J* 1998; 39: 412-15.
- ¹⁰⁰ Rousou J, et al.Fibrin glue: an effective hemostatic agent for non suturable intra opertive bleeding. *Ann Thorac Surg* 1984; 38: 409-10.
- ¹⁰¹ Jain P, et al. Randomized clinica trial investigating the use of drains and fibrin sealant following surgery for breast cancer. *Br J Surg* 2004; 91: 54-60.
- ¹⁰² Sanders R et al. Effect of fibrinogen and thrombin concentrations on mastectomy seroma prevention. *J Surg Res* 1996; 61: 65-70.
- ¹⁰³ Gioffre Florio M, et al. The use of fibrin glue in the surgery of breast cancer. *G Chir* 1993; 14: 239-41.
- ¹⁰⁴ Gilly F, et al. Prevention of lymphorrhoea by means of fibrin glue. *Eur Surg Res* 1998; 30: 439-43.
- ¹⁰⁵ Moore M, et al. Fibrin dealant reduces the duration and amount of fluid drainage after axillary dissection. *J Am Coll Surg* 2001; 192: 591-9.
- ¹⁰⁶ Ulusoy A, et al. Effect of fibrin glue on lymphatic drainage and on drain removal time. *Breast J* 2003; 9: 393-6.
- ¹⁰⁷ Uden P et al. Fibrin adhesive in radical mastectomy. *Eur J Surg* 1993; 159: 263-5.
- ¹⁰⁸ Vaxman F, et al. Biological glue does not reduce lymphorrhoea after lymph node excision. *Ann Chir* 1995; 49: 411-16.
- ¹⁰⁹ Johnson L, et al. Influence of fibrin glue on seroma formation after breast surgery. *Am J Surg* 2005; 189: 319-23.
- ¹¹⁰ Dinsmore R, et al. Effect of fibrin glue on lymphatic drainage after modified radical mastectomy. *Am Surg* 2000; 66: 982-5.

- ¹¹¹ Carless P, et al. Systematic review and meta-analysis of the use of fibrin sealant to prevent seroma formation after breast cancer surgery. *Brit J Surg* 2006; 93: 810-819.
- ¹¹² Berger A, et al. Sealing of postoperative axillary leakage after axillary lymphadenectomy. *Breast Cancer Res Treat* 2001; 67: 9-14.
- ¹¹³ Langer S, et al. Does fibrin sealant reduce drain output and allow earlier removal of drainage catheters. *Am Surg* 2003; 69: 77-81.
- ¹¹⁴ Mustonen P, et al. The effect of fibrin sealant combined with fibrinolysis inhibitor on reducing the amount of lymphatic leakage. *Scand J Surg* 2004; 93: 209-12.
- ¹¹⁵ Ruggiero R, et al. Effectiveness of fibrin glue in conjunction with collagen patches to reduce seroma formation. *Am J Surg* 2008; 196: 170-174.
- ¹¹⁶ Ruggiero R, et al. New trends on fibrin glue in seroma after axillary dissection. *G Chir* 2009; 30: 306-310.
- ¹¹⁷ Ko E, et al. Fibrin glue reduces the duration of lymphatic drainage after lumpectomy and level II or III axillary lymph node dissection for breast cancer: a prospective randomized trial. *J Korean Med Sci* 2009; 24: 92-96.
- ¹¹⁸ Rice D, et al. Intraoperative topical tetracycline sclerotherapy. *J Surg Oncol* 2000; 73: 224-7.
- ¹¹⁹ Sitzmann J et al. The use of sclerotherapy for treatment of postmastectomy wound seromas. *Surgery* 1983; 93: 345-7.
- ¹²⁰ Nichter I, et al. Rapid management of persistent seromas by sclerotherapy. *Ann Plast Surg* 1983; 11: 233-6.
- ¹²¹ McCarthy P. An aborted prospective randomised trial of sclerotherapy for prolonged drainage after mastectomy. *Surg Gynaecol Obstet* 1986; 162: 418-20.
- ¹²² Trockmorton AD, et al. Sclerotherapy for the treatment of postmastectomy seroma. *Am J Surg* 2008; 196: 541-544.
- ¹²³ Shamley D, et al. Delayed versus immediate exercises following surgery for breast cancer. *Breast Cancer Res Treat* 2005; 90: 263-71.
- ¹²⁴ Carcoforo P, et al. Octreotide in the treatment of lymphorrhoea after axillary node dissection. *J Am Coll Surg* 2003; 196: 365-9.
- ¹²⁵ Mahmoud S, et al. Octreotide can control lymphorrhoea after axillary node dissection in mastectomy operations. *Breast* 2007; 13: 108-9.
- ¹²⁶ Kuroi K, et al. Effect of mechanical closure of dead space on seroma formation after breast surgery. *Breast Can* 2006; 13: 260-265.
- ¹²⁷ Stehbens W. Postmastectomy serous drainage and seroma. *ANZ J Surg* 2003;73: 877-880.
- ¹²⁸ Orr T, et al. An incision and method of wound closure for radical mastectomy. *Ann Surg* 1951; 133: 565-566.
- ¹²⁹ Hamy A, Wading of the axilla in conservative treatment of cancer of the breast. *J Chir* 1990; 127: 99-102.
- ¹³⁰ O'Dwyer P, et al. Effect of closing dead space on incidence of seroma after mastectomy. *Surg Gynecol Obstet* 1991; 172: 55-56.
- ¹³¹ Keyes E, et al. Basting the axillary flap for wounds of radical mastectomy. *AMA Arch Surg* 1953;66: 446-451.
- ¹³² Garnier J, et al. A new approach to the axilla. *J Gynecol Obstet* 1993; 22: 237-242.
- ¹³³ Urban J, et al. Radical mastectomy in continuity with en bloc resection of the internal mammary lymph node chain. *Cancer* 1952; 5: 992-1008.
- ¹³⁴ Classe J, et al. Axillary padding as an alternative to closed suction drain. *Arch Surg* 2002; 137: 169-172.
- ¹³⁵ Kuroi K, et al. The effect of tacking suture on seroma formation after mastectomy. *Jpn J Breast Cancer* 2002; 17: 311-315.
- ¹³⁶ Larsen B, et al. Fixation of skin flaps by subcutaneous sutures in radical mastectomy. *J Am Med Assoc* 1955; 159: 24.