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Review

Factors Predicting Seroma Formation Following Breast Cancer Surgery: A Concise Review

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Seroma formation is the most prevalent postoperative complication following breast cancer surgery. The aim of this systematic review was to identify evidence based risk factors for seroma formation. Articles published in English in the last decade were obtained from searches of Medline and additional references were found in the bibliographies of these articles. Risk factors were graded according to the quality and strength of evidence and to the direction of association. One meta-analysis, 15 randomized controlled trials, 6 prospective studies and 2 retrospective studies were identified. There was no risk factor supported by strong evidence, but there was moderate evidence to support a risk for seroma formation in individuals with heavier body weight, extended radical mastectomy as compared with simple mastectomy, and greater drainage volume in the initial 3 days. On the other hand, the following factors did not have a significant influence on seroma formation: duration of drainage; hormone receptor status; immobilization of the shoulder; intensity of negative suction pressure; lymph node status or lymph node positivity; number of drains; number of removed lymph nodes; previous biopsy; removal of drains on the fifth postoperative day versus when daily drainage volume fell to minimal; stage; type of drainage (closed suction versus static drainage); and use of fibrinolysis inhibitor. In contrast, sentinel lymph node biopsy reduced seroma formation. Although a number of factors have been correlated with seroma formation, strong data on factors associated with seroma formation are still rare, and it seems to be difficult to identify patients who will ultimately suffer from seroma. However, this study has provided findings that are useful for identifying commonly cited risk factors that have no evidence to support them.

Key words: Breast cancer; Seroma; Risk factors .

INTRODUCTION

Ever since mastectomy was first carried out by Halsted in 1882, surgeons have faced several problems such as necrosis of the skin flaps, breakdown of the wound, hematoma, seroma, and infection (Kuroi *et al.,* 2006b). Among them, seroma, a subcutaneous collection of serous fluid, is a common complication in breast cancer surgery. As it usually resolves within a few weeks, many surgeons view this problem as an unavoidable nuisance rather than a serious complication (Kuroi *et al.,* 2006b; Pogson *et al.,* 2003). However, excessive accumulation will stretch the skin and cause it to sag, resulting in patient discomfort and sometimes prolongation of hospital stay (Tadych and Donegan, 1987). To prevent seroma formation, it is important to estimate individual risk of seroma formation. In this study, we carried out a systematic review to identify evidence based risk factors for seroma formation.

METHODS

The primary outcome of interest was the incidence of

Seroma formation following breast surgery in patients with breast cancer. To identify published articles on seroma, a computer assisted MEDLINE search was conducted from 2003 up to September 2013. The reference terms 'breast cancer', 'mastectomy', 'breast-conserving surgery' and 'seroma' were used as both keyword and subject terms. We included meta-analysis, randomized controlled trials (RCTs), prospective studies, systematic review of RCTs or prospective studies, and retrospective studies if they included at least 100 patients. The search was limited to studies published in English, and unpublished data were not located. Data were extracted and checked independently by the author.

The direction of association was defined as follows: increase, significant association between a factor and increase of seroma formation; decrease, significant association between a factor and decrease of Seroma formation; no association, no significant association between a factor and seroma formation. The quality of evidence was ranked as follows according to the 'levels of evidence and grades recommendation' of the Oxford Center for Evidence-based Medicine (Burns *et al.,* 2011): level 1, systematic review of RCTs, and individual RCT; level 2, systematic review of cohort studies, and individual cohort study including low-quality RCT; level 3, systematic review of case– control studies, and individual case–control study; level 4, case series, and poor quality cohort and case–control studies; level 5, expert opinion without explicit critical appraisal, or based on physiology, bench research or first principles. The strength of evidence was categorized as grade A (strong), consistent level 1 studies; grade B (moderate), consistent level 2 or 3 studies, or extrapolations from level 1 studies; grade C (weak), level 4 studies or extrapolations from level 2 or 3 studies; grade D (unproven), level 5 evidence or troublingly inconsistent or inconclusive studies of any level. When there was no consistency, extrapolations were made either if there was predominance in the direction with at least two study differences or if evidence was based on a study and troublingly inconsistent was considered if there was bidirectionality. Otherwise, the evidence was regarded as 'inconclusive'.

MAIN FACTORS

One meta-analysis, 15 randomized controlled trials (RCTs), 6 prospective studies and 2 retrospective studies were included in this review (Table 1). Considering the quality of the RCTs, all of them were graded as level 2, as these were usually underpowered, and the method of random allocation and concealment and sample size justification were not described in detail. Risk factors for seroma formation were subdivided into three categories: patients and tumor characteristics, surgical factors and nonsurgical modalities.

Patients and Tumor Characteristics

In this category, age, body mass index, breast size, grade, histological type, hormone receptor status, hypertension, nodal status or positivity of lymph nodes (LNs), number of positive LNs, side, stage, tumor location and tumor size were assessed. Among them, one study had found a positive association between body weight and seroma formation (Zielinski *et al.* 2013). In contrast, as for hormone receptor status, nodal status or positivity of LNs, and stage, studies consistently showed no association with seroma formation (Gonzalez *et al.* 2003; Hashemi *et al.,* 2004; Lumachi *et al.,* 2004; Zielinski *et al.,* 2013). Similarly, no individual study found a significant association with other factors such as neoadjuvant chemotherapy (Gonzalez *et al.,* 2003; Zielinski *et al.,* 2013), side (Lumachi *et al.,* 2004) and grade (Lumachi *et al.,* 2004). On the other hand, existing evidence was inconclusive for histological type and hormone receptor status. Three studies had found a positive association between age and seroma formation.

Extent of Mastectomy

With respect to the extent of mastectomy, four studies have demonstrated that modified radical mastectomy (MRM) increases seroma formation as compared with simple mastectomy (Akinci *et al.,* 2009; Loo and Chow, 2007; Pogson *et al.,* 2003; Watt-Boolsen *et al.,* 1989). In contrast, one study has indicated that immediate following MRM decreases seroma formation (Jeon *et al.,* 2012). However, no association was found between preservation or removal of the pectoral fascia and seroma formation (Dalberg *et al.,* 2004), and association was inconclusive when radical mastectomy was compared with modified radical mastectomy (MRM) and was bidirectional among six studies comparing MRM and breast-conserving surgery. With respect to axillary dissection, four studies have consistently indicated that the number of removed LNs does not influence seroma formation (Akinci *et al.,* 2009; Andeweg *et al.,* 2011; Boostrom *et al.,* 2009; Burak *et al.,* 1997). Similarly, one study has demonstrated that the extent of axillary dissection does not affect seroma formation (Douay *et al.,* 2008). On the other hand, a study of Purushotham et al has demonstrated that sentinel LN biopsy (SLNB) is associated with significantly less seroma formation than conventional axillary dissection (Purushotham *et al.,* 2002).

Wound Drainage

In this category, intensity of negative suction pressure, no drainage, number of drains, type of drainage (closed

Table1: Showed Summary of risk factors of seroma formation.

Author, year	Level of evidence	Sample size	Type of surgery	Intervention and seroma formation (%)	Factors and direction of association
Purushotham *et al.(* 2002)	2	375	MRM, BCS	No drainage with suture flap fixation versus Drainage without suture flap fixation 61 versus 55 (NS) in MRM, 47 versus 51 (NS) in BCS	→ No drainage with suture flap fixation versus drainage without suture flap fixation
Schuijtvlot *et al.* (2002)	2	97	BCS	Suture flap fixation (buttress suture) without drainage versus Conventional surgery	→ Number of positive LNs ↓ Suture flap fixation
Talbot and Magarey (2002)	2	90	MRM, BCS	Prolonged suction drainage versus Short drainage versus No drain	↑ No drainage → Timing of drain removal
Galatius *et al.* (2003)	2	59	MRM	Use of ultrasonic scalpel versus scissors and electrocautery in flap dissection	→ Surgical device (ultrasound scalpel versus scissors and electrocautery)
Gonzalez *et al.* (2003)	,3	359	MRM, BCS	___	↑ Type of mastectomy (MRM > BCS) → Age, presence or number of positive LNs, no. of removed LNs, tumor size, body weight, Neoadjuvant chemotherapy
Langer *et al.* (2003)	2	55	MRM	Fibrin glue versus None	→ Use of fibrin glue versus not using
Puttawibul *et al.* (2003)	2	60	MRM	Axillary drainage versus Axillary and pectoral drainage	→ Number of drain
Ulusoy *et al.* (2003)	2	54	MRM	Use of fibrin glue versus None	→ Use of fibrin glue versus not using
Dalberg *et al.* (2004)	2	250	MRM	Removal versus Preservation of pectoral fascia	→ Preservation of pectoral fascia
Jain *et al.* (2004)	2	116	MRM, BCS	Drainage versus No drainage	→ No drainage versus drainage
Hashemi *et al.* (2004)	3	158	MRM, BCS	_	↑ Type of surgery (MRM > BCS) → Age, tumor size, and lymph node status
Lumachi *et al.* (2004)	3	92	MRM, BCS	Use of ultrasound scissors versus Scissors and ligation in axillary dissection →	↑ Tumor size (larger), total drainage volume (greater), no. of involved nodes (greater), type of surgery (MRM > BCS) Age, side, grade, ER, nodal status, number of LNs, use of ultrasonic scissors
Chintamani *et al.* (2005)	2	85	MRM	Half (350 mg/m^2) versus full (700 mg/m^2) vacuum suction drainage	→ Extent of negative suction pressure
Johnson *et al.* (2005)	2	82	MRM, BCS	Use of fibrin glue without drainage versus Drainage	→ Use of fibrin glue without drainage versus Drainage

Table 1. Contd.

Soon *et al.* (2005)	2	87	ALND	Drain versus no drain	→ With or without drainage
Shamley *et al.* (2005)	1	444	MRM, BCS	Delay versus early shoulder exercise Odds ratio: 0.41 (95%CI 0.27–0.61)	↑ Early shoulder exercise
Loo and Chow (2007)	2	119	MRM	—	↑ Age > 45, hypertension, delayed breast reconstruction → Operative blood loss, transfusion requirements and operation time, experience of surgeons
Lin *et al.* (2011)	2	158	MRM	Age (years), total serum protein concentration (g/L). 15.2% of patients developed seroma.	↑ Age, low values of total protein and albumin
Okholm and Axelsson (2011)	2	42	MRM	Intravenous injection of a bolus of 125 mg of methyl prednisolone sodium succinate before mastectomy versus None	→ Methylprednisolone sodium succinate
Yilmaz *et al.* (2011)	2	82	MRM	Use of ultrasonic dissector versus Scalpel and electrocautery	↓ Use of ultrasonic dissector
Axelsson *et al.* (2012)	2	160	MRM	injection of methyl prednisolone acetate versus saline in the mastectomy cavity	→ Local injection of Methylprednisolone sodium succinate
Miri Bonjar *et al.* (2012)	2	60	MRM	Use of fibrin glue plus conventional drain placement versus conventional drain placement. Seroma formation rate was 24.1% in the control group and 16.1% in the fibrin glue group.	→ Use of fibrin glue
Sakkary (2012)	2	40	MRM	Mastectomy flaps fixation versus Drainage without flaps fixation Seroma formation was significantly lower in the flap fixation group ($p < 0.001$).	↓ Mastectomy flaps fixation
Zielinski *et al.* (2013)	2	150	MRM	The amount of seroma formed were correlated with selected demographic, clinical and pathological parameters.	↑ Age ,obesity and TNM staging (1&2) → Number of lymph nodes resected, Neoadjuvant chemotherapy

Abbreviations: ALND, axillary lymph node dissection; BCS, breast-conserving surgery; BMI, body mass index; ER, estrogen receptor; Ext, extended mastectomy; IR, immediate reconstruction; LN, lymph node; MRM, modified radical mastectomy; NOS, not otherwise specified; NS, not significant; PgR, Progesterone receptor; POD, postoperative day; Rad, radical mastectomy; RCT, randomized controlled trial; SLNB, sentinel lymph node biopsy.
*Direction of association: " = increase, current evidence demonstrates an association with significant increase of seroma formation;! = no association, current evidence demonstrates no association with seroma formation; # = decrease, current evidence demonstrates an association with significant decrease of seroma formation. According to author's reply, difference between MRM and BCS was significant ($P < 0.01$), type of mastectomy was strictly related to the tumor size, and also use of ultrasonic scissors was associated with seroma formation in logistic regression analysis. ALND was performed in node-positive patients as a second procedure if the SLN was positive for metastasis.

suction versus passive drainage), type of drainage unit (evacuated bottle type versus bellow type) and type of drainage tube (multiple hole type versus multiple channel type) were assessed. As for no drainage, 3 out of 6 studies had reported that this policy increases seroma formation (Divino *et al.,* 2000; He *et al.,* 2011; Kuroi *et al.,* 2006a). However, seroma formation was not influenced by the intensity of negative suction pressure, by the number of drains, or by the choice of closed suction drainage or passive drainage. These findings were consistent among studies. Similarly, in an RCT by Barton et al., choice of evacuated bottle type or bellow type did not affect the number of aspirations required (Barton *et al.,* 2006). In contrast, in a study of Porter et al. a flat-type

drain with multiple channels running the length of the drain reduced seroma formation as compared with a flat-type drain with multiple holes (Porter *et al.,* 1998). It was speculated that the holes might clog more easily than the channels, which could lead to premature removal of drains. However, this study was not primarily planned to assess drain type, and the drain was selected according to the attending surgeon's preference.

Suture Flap Fixation

Suture flap fixation is a surgical technique for securing flaps to underlying tissues to close the dead space with sutures. Although this technique is not commonly performed, it is interesting to note that an RCT by Coveney et al. has demonstrated that this technique reduces seroma formation in patients undergoing mastectomy (Hashemi *et al.,* 2004). In association with this, a RCT by Purushotham et al. has demonstrated that mastectomy without drainage does not increase seroma formation when this technique is applied (Purushotham *et al.* 2002). Also, a prospective study by Schuijtvlot et al. has revealed that seroma formation is reduced by the use of this technique in patients undergoing BCT without axillary drainage (Schuijtvlot *et al.,* 2002).

Miscellaneous

Moreover, several factors such as previous biopsy, blood loss, blood transfusion, operation time, skin incision, skin graft, surgeon and type of anesthesia have been assessed, and individual study has demonstrated that a longer operation time and diagonal skin incision as compared to vertical skin incision increase seroma formation. On the other hand, no association was found for previous biopsy, type of anesthesia (local or general) or blood transfusion. Available evidence was inconclusive for whether or not skill or experience of the surgeon influences seroma formation, for quantity of blood loss, and for use or non-use of a skin graft.

Nonsurgical Modalities

This category includes radiation, neoadjuvant chemotherapy, use of adhesive glue and antifibrinolytic agents. With respect to radiation, a retrospective study of Say et al. has demonstrated that pre- or postoperative radiation therapy does not affect seroma formation in patients who have undergone radical mastectomy (Kuroi *et al.,* 2006b). Similarly, neoadjuvant chemotherapy did not influence seroma formation in an RCT comparing Neoadjuvant chemotherapy with immediate surgery (Unalp and Onal 2007). With regard to the use of adhesive glue such as fibrin glue or bovine thrombin, four RCTs found no significant effect on seroma formation, and an RCT by Vaxman et al. even revealed that the use of fibrin glue increased seroma formation (Miri Bonjar *et al.,* 2012; Ulusoy *et al.,* 2003; Zielinski *et al.,* 2013). Similarly, in an RCT by Jain et al., patients were randomized to receive suction drainage or to receive no drain, and those allocated to no drainage were further randomized for application of fibrin sealant to the dissected area or to no intervention (McCaul *et al.,* 2000). Overall, this RCT failed to show any significant effect of the use of fibrin sealant on seroma formation. Similarly, the use of fibrin glue and fibrinolysis inhibitor or perioperative and postoperative administration of fibrinolysis inhibitor did not reduce seroma formation. The concept of the use of fibrinolysis inhibitor was based on the hypothesis that fibrinolytic activity of the plasmin system in serum and lymph might contribute to fluid accumulation.

CONCLUSION

The following factors did not have a significant influence on seroma formation: the duration of drainage; hormone receptor status; immobilization of the shoulder; intensity of negative suction pressure; LN status or positivity of LNs; number of drains; number of removed LNs; previous biopsy; removal of drains on the fifth POD versus when the daily drainage volume fell to a minimal; stage; type of drainage (closed suction versus static drainage); and use of fibrinolysis inhibitor. In contrast, as might have been expected, SLNB reduced seroma formation. For the other factors that were commonly cited in the literature, evidence was weak or unproven. Thus, although a number of factors have been correlated with seroma formation, strong data on factors associated with seroma formation are still rare, and it seems to be difficult to identify patients who will ultimately suffer from seroma. However, this study has provided findings that are useful for identifying commonly cited risk factors that have no evidence to support them.

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