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Potential Risk Factors Influencing the Formation of Postoperative Seroma After Breast Surgery – A Prospective Study

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Abstract. *Background/Aim: This trial intended to identify patient- and therapy-specific risk factors influencing the genesis of seroma and the extent of its formation. Patients and Methods: Within a prospective randomized controlled trial, 70 patients (n=35 TissuGlu®; n=35 drain) underwent a mastectomy with or without sentinel lymphonodectomy. Specific seroma-associated risk factors were recorded. Regular outpatient aftercare was performed during a 90-day postoperative follow-up. Results: A statistically significant increase in the postoperative seroma rate was demonstrated for those with pre-adiposity compared to normal body weight (p=0.016), as well as for the state of health evaluated by the score of American Society of Anesthesiologists (ASA) (ASA III compared to I; p=0.046), the presence of diabetes mellitus (p<0.001) and the reduction of the length of the surgical procedure (p=0.044). Conclusion: A high body mass index, a poor state of health (ASA score), and diabetes mellitus, as well as a shorter duration of surgery, favor the incidence of postoperative seroma.*

With a yearly incidence of 2.1 million new cases, breast cancer represents one of the most common carcinomas worldwide (1). Depending on the indication, mastectomy is a relevant therapeutic option. Nevertheless, due to the incidence of postoperative seroma, this procedure represents a substantial challenge for both the surgeon and the patient. With an incidence range of 3 to 85%, seroma formation is considered the most frequent complication after breast surgery (2-5). A uniform definition of seroma beyond the description of 'the accumulation of primarily sterile tissue fluid in a pre-formed wound cavity' does not yet exist (5-7). Nevertheless, pro- and inflammatory exudative and transudative processes in the surrounding soft tissue damaged by surgical trauma, as well as intraoperatively injured lymphatic vessels, seem to be causative for the pathophysiological development of seromas (8-11). In addition, increased lymph transudation into the wound area, caused by the intraoperative opening of lymphatic vessels and the postoperative mobilization of the ipsilateral extremity, with in part additionally reduced lymph drainage capacity, promotes the accumulation of lymph and the resulting formation of seroma (8, 12-14). The majority of seroma formed postoperatively is resorbed within 1 month even without intervention (7, 15). Nevertheless, up to 15% of seromas arising postoperatively remain a problem of pronounced clinical relevance due to secondary complications (prolonged wound healing, wound infections, necrosis, lymphedema, pain, esthetic and functional deficits) (8, 16, 17) and the resulting delay of subsequent therapeutic procedures (adjuvant chemotherapy and/or radiotherapy) (18-20). Various patient- and therapy-specific risk factors that may influence the genesis of seroma have been investigated in numerous studies (21-24). However, the results of these studies often diverge. Despite this, studies have been able to identify possible factors that favor the genesis of seroma. Thus, in addition to the type of surgery [mastectomy, breast-conserving therapy with or without removal of locoregional lymph nodes (sentinel lymph node biopsy) (25), the instruments used also appear to

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influence seroma formation. It has been shown that tissue damage provoked mechanically (using a scalpel) or thermally (electrocautery) enhances the production and secretion of postoperative wound fluid (20, 26). Other risk factors that have an unfavorable effect on seroma formation have been identified such as various comorbidities [*e.g.* arterial hypertension (5), high body mass index (BMI) (27)] and patient-specific characteristics [*e.g.* nicotine abuse (27), age ≥40 years (28)]. As for tumor size (29), nodal involvement (21, 30) or neoadjuvant chemotherapy (20), the length of time and number of in situ drains (29) also appear to play a role in the genesis of seroma. While the current standard of seroma prevention is the insertion of a drainage system, studies have shown that in addition to postoperative shoulder immobilization (31, 32), a sufficient reduction of dead space using fibrin (11) or polyurethane-based tissue adhesives (33-35), sutures with the help of which the skin flap is fixed to the underlying breast muscle – known as 'quilting sutures' (4, 36), or the use of an ultrasound dissector (29, 37) utilized for tissue dissection can have a positive effect on reducing the incidence of postoperative seroma. Research groups have also been able to demonstrate a seroma-reducing effect of the use of preoperative steroid injections (38), intraoperative application of a cyanoacrylate-based tissue adhesive (39), and postoperative injections of the somatostatin analog octreotide (40).

The aim of this study was to identify patient- and therapy-specific risk factors and analyze their influence on the postoperative formation of seroma. The analysis was based on a study investigating the use of a polyurethane-based tissue adhesive (TissuGlu®) and its influence on the postoperative complication and intervention rate compared to the use of drainage conducted by Ohlinger *et al.* (34).

Patients and Methods

Within a prospective, randomized, controlled, non-inferiority study conducted by the research group of Ohlinger *et al.* (34), 80 patients were initially included after approval by the local Ethics Committee of the University Medicine Greifswald (internal registration number: BB 049/14). Due to study protocol-based criteria (Table I), 10 patients were subsequently excluded from the study, so that the final study population consisted of 70 participants.

The randomization procedure was carried out by the Institute for Community Medicine Greifswald. All patients treated received a mastectomy, extended by a sentinel lymph node biopsy according to indication. Six of the 70 treated patients received a bilateral mastectomy. Related to all treated breasts, this resulted in a total population of 76 breasts. Dead space reduction and wound closure was achieved by standard wound closure using either the surgical adhesive TissuGlu® (test group; n=35 patients), distributed by Cohera Medical Inc., Pittsburgh, PA, USA, or drainage (control group; n=35 patients). Surgery was conducted by experienced surgeons of the research group of Ohlinger *et al.* (34). To reduce shearing forces, all patients were postoperatively treated with an elastic bandage for 24 hours. The drain was removed when the wound secretion rate was less than 30 ml/24 hours. After the patients were discharged, outpatient follow-up took place for 90 days (day 0=surgical intervention). During this follow-up, patients were treated on four days defined by the study protocol (days 14, 30, 60 and 90, postoperatively). As part of this follow-up, the patients were examined by palpation and sonography. In the case of manifestation of a clinically relevant seroma (pain, swelling, redness, fluctuation), or the sonographic detection of an at least 1 cm-high seroma pocket, measured between the pectoralis major and cutis, the sonographic supported aspiration of seroma was performed as indicated in the study protocol (34). Documentation of examined results and recorded anamnestic data, including data of the procedure performed, as well as of the inpatient stay and daily visits, was performed in the Case Report Form.

For the present study, data collection focused on specific pre-existing conditions or potential risk factors influencing seroma formation. Accordingly, BMI, pre-existing arterial hypertension, diabetes mellitus, the health status measured by the score of American Society of Anesthesiologists (ASA), nicotine abuse and any anticoagulative medication were recorded. For the anticoagulative medication, no differentiation was made between plasmatic anticoagulation and platelet inhibition. Furthermore, the influence of the therapeutic regime on seroma formation was to be investigated, therefore the type of surgical intervention, the intraoperatively created wound area, the weight of the resected tissue and the duration of the surgical procedure were documented and analyzed. The evaluation of demographic data and patient-specific risk factors was carried out not only for the total population of 70 participants, but furthermore also for each study group (n=35 TissuGlu®; n=35 drainage). To investigate the influence of the BMI, the average BMI of the group with seroma as well as the seroma-free group was calculated. Accordingly, no cut-off was determined but rather whether there was a statistically significant difference between the incidence of postoperative seroma and the average BMI between the two study populations (seroma *vs.* no seroma) was examined.

The analysis of the therapy-specific risk factors was performed with reference to all 76 treated breasts. Statistical analysis was conducted by the Institute of Community Medicine using SPSS (version 22; IBM, Armonk, NY, USA). Influences of seroma-associated risk factors were determined by regression analysis using the generalized mixed linear model. Chi-square test was used for significance testing. Statistical significance was assumed for $p<0.05$.

Results

A total of 70 patients were enrolled in the study (n=35 drainage; n=35 TissuGlu® surgical adhesive). Six patients underwent a double-sided mastectomy, therefore with regard to the therapeutic regime there was an indication for surgery on 76 breasts in total.

Referring to age, BMI, relevant previous diseases (arterial hypertension, diabetes mellitus), anticoagulation, nicotine abuse as well as general condition measured by the ASA score, there was a homogeneous distribution for both groups (Table II). In the study, 59 (84.3%) out of the 70 patients developed a seroma (30 in the drainage group; 29 in the adhesive group). Neither age ($p=0.072$) nor nicotine abuse ($p=0.529$), arterial hypertension ($p=0.099$) or anticoagulation ($p=0.233$) had a statistically significant influence on

Table I. *Inclusion and exclusion criteria*.

Inclusion criteria
- ≥18 Years of age
- Provide signed and dated informed consent form
- Willing to comply with all study procedures, schedules and be available for the follow-up evaluations for the duration of the study
- Willing to follow instructions for incision care and follow guidelines related to resumption of daily activities
- Be scheduled for a mastectomy, modified radical mastectomy, extended mastectomy, with or without sentinel node biopsy
- ASA score ≤3

Exclusion criteria
- Pregnancy or lactation
- Known medical condition that results in compromised blood supply to tissues
- Known or suspected allergy or sensitivity to any test materials or reagents
- Any condition known to affect wound healing, such as collagen vascular disease
- Known to have a blood clotting disorder
- Receiving antibiotic therapy for pre-existing condition or infection
- Planned immediate breast reconstruction or axillary dissection
- Concurrent use of fibrin sealants or other internal wound care devices
- Be participating in any current clinical trial with conflicting endpoints or have participated in any conflicting clinical trial within 30 days of enrollment in this study

ASA: American Society of Anesthesiologists.

Table II. *Patient demographics and relevant diseases and their distribution within the study population*.

	Entire cohort (n=70)	Drainage (n=35)	TissuGlu® (n=35)	*p*-Value*
Mean age±SD, years	69.15±10.82	67.71±11.72	70.83±9.83	0.233
Mean BMI±SD, kg/m^2	28.73±5.29	29.67±0.98	27.71±0.81	0.127
Hypertension, n (%)	47 (67.14%)	25 (71.4%)	22 (62.9%)	0.611
Diabetes mellitus, n (%)	17 (24.28%)	11 (31.4%)	6 (17.1%)	0.265
Anticoagulation, n (%)	16 (22.86%)	10 (28.6%)	6 (17.1%)	0.394
Nicotine abuse, n (%)	7 (10%)	5 (14.3%)	2 (5.7%)	0.428
ASA score, n (%)				
I	6 (8.57%)	3 (8.5%)	3 (8.5%)	0.440
II	39 (55.71%)	17 (48.6%)	22 (62.9%)	
III	25 (35.71%)	15 (42.9%)	10 (28.6%)	

ASA: American Society of Anesthesiologists; BMI: body mass index; NE: not evaluated; SD: standard deviation. *Between the two subgroups.

postoperative seroma formation in the total population (n=70) nor in the study group-related analysis.

A significant influence on the postoperative seroma rate was found for BMI (p=0.016). Among the 59 patients who developed a postoperative seroma, the average BMI was 29.55±5.19 kg/m^2. This was significantly higher than for the patients who remained seroma-free postoperatively (BMI= 23.77±5.25 kg/m^2). Seventeen study participants suffered from diabetes mellitus; all of them developed a seroma in the postoperative course, while none of the 11 patients who remained seroma-free was affected by diabetes mellitus. Statistical analysis revealed a highly significant correlation between pre-existing diabetes mellitus and the incidence of postoperative seroma (p<0.001). In addition, the examination of seroma incidence as a function of the general condition determined by the ASA score showed an elevated incidence of postoperative seroma with an increasing ASA score. A statistically significant correlation between an increased seroma incidence and the general condition of affected patients was demonstrated for an ASA score of 3 compared to an ASA score of 1 (p=0.046).

Patient-specific risk factors and their influence on the development of postoperative seroma within the overall study population and the specific study groups are presented with significances in Table III.

With regard to the analysis of therapy-specific risk factors, the seroma rate per surgically treated breast (n=76) was examined. Of 49 breasts that underwent a mastectomy only,

Table III. *Analysis of patient-specific risk factors and their influence on the development of postoperative seroma in relation to the total population of 70 participants.*

	Entire cohort (n=70)		Drainage (n=35)		TissuGlu® (n=35)	
	Seroma (n=59)	No seroma (n=11)	Seroma (n=30)	No seroma (n=5)	Seroma (n=29)	No seroma (n=6)
Mean age±SD, years	69.18±11.73	63.31±7.15	NE	NE	NE	NE
p-Value	**0.072**		NE		NE	
Mean BMI±SD, kg/m^2	29.55±5.19	23.77±5.25	NE	NE	NE	NE
p-Value	**0.016**		NE		NE	
Nicotine abuse (n=7)*	6 (85.7%)	1 (14.3%)	4 (80.0%)	1 (20.0%)	2 (100%)	0 (0.0%)
p-Value	0.529		0.561		>0.999	
Diabetes mellitus (n=17)*	17 (100%)	0 (0.0%)	11 (100%)	0 (0.0%)	6 (100%)	0 (0.0%)
p-Value	**<0.001**		0.157		0.561	
Hypertension (n=47)*	41 (87.2%)	6 (12.8%)	21 (84.0%)	4 (16.0%)	20 (90.9%)	2 (9.1%)
p-Value	0.099		>0.999		0.166	
Anticoagulation (n=16)*	15 (93.8%)	1 (6.2%)	10 (100%)	0 (0.0%)	5 (83.3%)	1 (16.7%)
p-Value	0.233		0.292		>0.999	
ASA score						
I (n=6)*	4 (66.7%)	2 (33.3%)	2 (66.7%)	1 (33.3%)	2 (66.7%)	6 (33.3%)
II (n=39)*	32 (82.1%)	7 (17.9%)	14 (82.4%)	3 (17.6%)	18 (81.8%)	4 (18.2%)
III (n=25)*	23 (92.0%)	2 (8.0%)	14 (93.3%)	1 (6.7%)	9 (90.0%)	1 (10.0%)
p-Value	**0.046****		0.415		0.628	

ASA: American Society of Anesthesiologists; BMI: body mass index; NE: not evaluated; SD: standard deviation. *Related to the respective risk factor examined. **Comparison between ASA I and III. Statistically significant *p*-values are shown in bold.

39 (79.6%) developed a seroma during the postoperative follow-up period. Twenty-seven breasts were mastectomized in combination with a sentinel lymph node biopsy. In comparison, this surgical procedure was associated with an even higher rate of postoperative seroma formation at 88.9%. Nevertheless, no statistically significant influence of the surgical procedure on postoperative seroma formation was established (p=0.417). Concerning the duration of the surgical procedure (incision-suture time), a statistically significant increase of seroma incidence was observed with a shorter incision-suture time (p=0.044). While the surgical intervention of seroma-free patients required an average of 65.00±38.25 min, in patients who developed a seroma in the postoperative course, the duration of surgery was shorter, with an average incision-suture time of 46.31±14.54 min. The average weight of resected breasts of patients who developed a seroma postoperatively was 766.56±394.01 g. This was higher than that of the resected tissue of patients not affected by a seroma (421.01±367.70 g), although not statistically significantly (p=0.129). Investigating the influence of wound size on the rate of postoperative seroma, a larger average wound size was found in the group of patients with postoperative seroma formation (63 breasts: 295.49±138.90 cm^2 *vs.* 229.11±108.33 cm^2). According to this, a larger wound area led to a non significant increase in seroma incidence (p=0.278). A detailed presentation of therapy-associated risk factors and their influence on postoperative seroma, as well as significance levels, is given in Table IV.

Discussion

The study showed that in addition to a high BMI (p=0.016), pre-existing diabetes mellitus (p<0.001), shorter surgery (p=0.044) and poorer health (ASA score; p=0.046) statistically significantly increased the rate of seroma after breast surgery. While results further indicated that age >40 years, as well as pre-existing arterial hypertension, drug-induced anticoagulation, higher weight of resected tissue and greater wound area increased the incidence of postoperative seroma (without evidence of statistical significance), pre-existing nicotine abuse seemed to have no influence on seroma production.

Regarding the BMI, a statistically significant correlation between the incidence of postoperative seroma and patients with pre-adiposity (BMI=29.55±5.19) was identified, whereas the risk of increased seroma production seemed to be lower in a normal-weight study population (BMI=23.77±5.25) (p=0.016). A similar result was achieved by Zielinski *et al.* in a study published in 2005 (22).The working group identified a cut-off for BMI of 30 kg/m^2. A possible reason for an influence on the postoperative seroma rate by an increased BMI might be an effect on wound healing, as already shown in various studies (41-43).

With reference to age, numerous published studies were unable to show any influence on postoperative seroma formation (5, 23, 33, 44, 45). Thus, the general study

Table IV. *Analysis of the influence of therapy-specific risk factors on the incidence of postoperative seroma in relation to the total population of 76 breasts.*

	Seroma (n=63)	No seroma (n=13)	*p*-Value
Mastectomy, n (%)	39 (79.6%)	10 (20.4%)	0.417
Mastectomy + SLNB, n (%)	24 (88.9%)	3 (11.1%)	0.417
Mean±SD duration of surgery, min	46.31±14.54	65.00±38.25	**0.044**
Mean±SD wound area, cm^2	295.49±138.90	229.11±108.33	0.278
Mean±SD resected tissue, g	766.56±394.01	421.07±367.70	0.129

SD: Standard deviation; SLNB: sentinel lymph node biopsy. Statistically significant *p*-values are shown in bold.

situation also represents the results of a not statistically significant correlation (p=0.072) between postoperative seroma formation and age as determined in the present study. Nevertheless, a correlation between age and increasing seroma incidence is conceivable, especially against the background of the theory of seroma genesis developed by Watt-Boolsen *et al*., which is based on an inflammatory reaction in the context of postoperative wound healing after surgical trauma (9). Studies show that age has a considerable influence on the multi-stage wound-healing process (46, 47). For example, advanced age not only leads to a prolongation and change in the second, so-called inflammatory phase of wound healing (48), but also reduces re-epithelialization, collagen synthesis and angiogenesis (49). Although no statistical influence was demonstrated in this study, a tendency towards a negative effect of age on postoperative seroma formation was observed. Accordingly, the present study showed a higher incidence of postoperative seroma with increasing age. Patients who developed a seroma were on average 6 years older than patients who remained seroma-free (69.18 *vs*. 63.19 years). As part of a prospective mastectomy study to identify possible risk factors affecting the genesis of seromas, Zielinski *et al*. even succeeded in identifying a highly significant influence of age on postoperative seroma formation (p=0.001) (22). With a total study population of 150 patients, the working group found an influence of advanced age with a cut-off of 60 years.

According to Guo and DiPietro, comorbidities such as arterial hypertension, diabetes mellitus or nicotine abuse also influence wound healing and lead to a prolongation of these (46). Conversely, an association of these patient-specific risk factors with an increased incidence of postoperative seroma is possible. The results obtained in our study confirm this assumption regarding the presence of diabetes mellitus and show a highly significant influence (p<0.001) on the seroma rate. Studies by others leave doubt about the influence of diabetes mellitus on seroma genesis and did not show a clear correlation (33, 50, 51). When critically reviewing the study by Pan *et al*., it is notable, however, that the number of patients with diabetes mellitus in their retrospective study was not sufficient for a valid statement to be made (51). Of the 102 patients analyzed in total, only four (3.92%) had diabetes mellitus. In the entire study, 23 patients developed a seroma. Of these, only one patient had a history of diabetes mellitus.

Significant influence of arterial hypertension (p=0.099), drug-induced coagulation inhibition (p=0.233) and nicotine abuse (p=0.529) on the postoperative seroma incidence was not established in our prospective validation. With regard to hypertension and nicotine abuse, Ohlinger *et al*. drew the same conclusion (33).

Say *et al*. also confirmed that nicotine abuse apparently has no effect on seroma incidence (50). Nevertheless, studies by others point to a significant influence of smoking behavior. Besides Colwell *et al*. (52), Sforza *et al*. (27) also confirmed a connection between nicotine abuse and the incidence of postoperative seroma. Sforza *et al*. attribute this most likely to a negative impact on wound healing and angiogenesis associated with tobacco consumption. SimilarIy divergent is the situation regarding the frequent occurrence of seroma in dependence on arterial hypertension. While Pan *et al*. (51) and Ohlinger *et al*. (33) were unable to detect significant correlation between hypertension and postoperative seroma incidence, Kumar *et al*. (23) found this risk factor to have a statistically significant influence (p<0.001) and causally suspected prolonged secretion from the wound site with simultaneously prolonged wound healing. This conclusion is supported by a study of Guo *et al*. in which an association between prolonged wound healing and existing hypertension was demonstrated (46).

In our study, the physical condition of the patients was assessed with the help of the ASA score, a non-specific classification system which also takes the prevalence of various comorbidities into account. It was shown that a reduction of general physical condition and a concomitant increase in the ASA score was simultaneously associated with a significantly higher rate of postoperative seroma (ASA score III *vs*. I/II; p=0.046). Other studies also show this correlation. In a retrospective data analysis, Ebner *et al*. showed significantly increased wound secretion depending on the ASA score in patients with primary mastectomy and drainage (53).

However, seromas, in the sense of fluid accumulation in a preformed cavity with clinical relevance, and the influence of the physical condition of the patient were not investigated by that research group. Nevertheless, interdisciplinary correlations between an increased seroma incidence and a reduced general condition were demonstrated. Köckerling *et al*. examined postoperative seroma incidence after inguinal hernia treated with transabdominal preperitoneal patch plasty and showed a high ASA score (III/IV) to be associated with a significant increase in the seroma rate compared to ASA score I (p=0.013) (54).

In addition, the present study demonstrated the influence of the duration of the surgical procedure (p=0.044) on the rate of postoperative seroma. According to the data obtained, the risk of postoperative seroma formation increases with the reduction of the incision-suture time. Pan *et al*. also reported a statistically significant correlation (p=0.006) but, in contrast to the data collected in our study, showed a 30% higher seroma risk with a 10-min increase of incision-suture time (51). Similar results were also obtained by Say *et al*. (50). Ebner *et al*. demonstrated a significant (p<0.001) and clinically relevant correlation between the incidence of postoperative seroma and an increasing duration of the surgical procedure and concluded that an increased postoperative seroma rate is mainly caused by the treating surgeon (53). Srivastava *et al*. (21) and Purushotham *et al*. (55) also demonstrated that a low postoperative seroma rate is the result of optimal surgical treatment. Accordingly, at this point it should be discussed how such a discrepancy between the results of the present prospective study and previous studies might arise. Reduction of surgical time with simultaneously increasing seroma rates being mainly due to patients of the TissuGlu® cohort can be excluded. A closer look at the study group-related analysis of the incision-suture time showed that surgery of patients in the adhesive group (53.70 min) lasted on average 8 min longer than of the drainage group (45.36 min). Looking at the incidence of postoperative seroma as determined by Ohlinger *et al*. in the context of the previous prospective validation, 86.1% of the patients in the drainage group developed a seroma, while the primary seroma rate of the patients receiving the tissue adhesive was 80.0% (34). Despite there being no statistically significant difference (p=0.688), it is conceivable that, as already published by Stehbens *et al*. (56), *in situ* drainage by enhanced shear and frictional forces with subsequent increased wound secretion led to the increased seroma rate in this study and not the duration of the surgical procedure itself. Alternatively, however, it is possible that the relatively high seroma rate despite a comparatively short inscision-suture time, also taking into account pathophysiological aspects, was most likely due to the preparation of the wound site with injury to numerous lymphatic structures which is necessary within the framework of the surgical procedure (10, 15, 39). The evaluation of a reduction in the duration of surgery as an isolated risk factor for the incidence of postoperative seroma should therefore be clearly questioned despite the statistical significance demonstrated in this study.

In addition, numerous studies have shown a correlation between seroma incidence and the type of surgical intervention. For example, some authors pointed to an increased risk of postoperative seroma after mastectomy (25, 56, 57). Furthermore, a considerable influence of additional removal of axillary lymph nodes with increasing incidence of seroma depending on the extent of nodular resection was shown (53, 58). In our study, data analysis also showed a tendency towards an increased seroma risk after additional sentinel lymph node biopsy (seroma rate 88.9%) compared to an isolated mastectomy (seroma rate 79.6%), even though there was no statistically significant correlation. According to Budd *et al*., the correlation between the extent of the surgical intervention and an increase in seroma incidence is most likely to be based on a larger wound surface with simultaneous increase in the number of injured lymphatic and blood vessels, from which an increase in wound secretion develops (59). Although no significance (p=0.278) was demonstrated for this in the present study, a correlation between wound area and seroma incidence is nevertheless apparent. Patients with postoperative seroma had an average intraoperative wound area of 295.49 cm^2±138.50 cm^2, while the extent of the wound in patients without seroma was limited to an area of 229.11 cm^2±108.33 cm^2. Similar results were obtained when considering the influence of the weight of the resected tissue. Here a higher weight of tissue was removed in the seroma population (766.56±394.01 *vs*. 421.07±367.70 g), so that a correlation can be suspected but was without statistical significance in the present study (p=0.129). Nevertheless, the results obtained here are consistent with the current literature (2, 60). Why is an influence of both wound area and weight of the resected tissue nevertheless conceivable? Smooth wound surfaces, small or no dead spaces, and a flat and dry wound bed promote proper and complication-free wound healing with a low seroma rate (7). Comorbidities, the extent of the injury and age, on the other hand, have a negative influence on the wound-healing process (46). In addition, a large wound area which is uneven in mastectomies due to anatomical conditions and has the capacity to form large granulation tissue and a large dead space favor protracted wound consolidation with additional space for the accumulation of exudate and lymph and consequent formation of seroma. Due to the physiological process of respiration and the resulting mobilization of the chest wall, shear forces also act on the wound site, which reduce the adhesive force of the skin flaps and further extend the already protracted wound-healing process (61). However, these pathophysiological processes can be reduced or even stopped by effective dead

space reduction, for example by using tissue adhesives based on polyurethane (33-35) or fibrin (11) or by the special surgical suture technique known as quilting (18, 63). Whether these methods can prevail over the classical wound-closure technique with drainage application, especially with regard to postoperative complications, *e.g.* seroma formation, should be investigated in further prospective validations.

Conclusion

For age, pre-existing arterial hypertension, drug-induced anticoagulation, the extent of the surgical procedure, the weight of the resected tissue and the wound area only a tendency for an increasing incidence of seroma was found, while nicotine abuse did not seem to influence the seroma rate in surgical breast procedures.

Pre-adiposity, pre-existing diabetes mellitus, poor patient health status as measured by the ASA score and a short duration of surgery increased the rate of postoperative seroma with statistical significance. Specifically for these risk factors, perioperative seroma management and dead space-reducing techniques and methods should subsequently be adopted.

Conflicts of Interest

S.P.: Consulting contract with Cohera Medical Inc., Pittsburgh, PA, USA and advanced training assistance and travel cost coverage also by Cohera Medical Inc., Pittsburgh, PA, USA.

Authors' Contributions

Conceptualization, R.O., M.Z. and J.U.; methodology, T.K., R.R; validation, T.K., R.R. and J.U.; formal analysis, T.K., J.U.; investigation, R.O., J.U.; data curation, T.K., J.U.; writing - original draft preparation, J.U., R.O.; writing - review and editing, R.O., R.R., S.P. and M.Z.; visualization, J.U., T.K.; supervision, R.O.; project administration, R.O., S.P., M.Z. All Authors read and agreed to the published version of the article.

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