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Neue Methoden in der Brustchirurgie: Maximale Therapie mit minimalen Narben

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Inhalt

Summery

This cumulative dissertation summarizes five publications on the topic of surgical therapy of breast cancer. Four these publications are first descriptions of methods which have proved that there exist oncologically safe alternatives to already established methods. These produce along with less invasivity and thus less morbidity better cosmetic results than all the other methods known to date. The doctoral candidate has developed these methods and has described them in various publications. One publication deals with the controversy about the impact of invasive lobular and invasive ductal breast cancer histology including the surgical procedure. All publications came out in a peer-reviewed international journal with a current impact factor of 1.28, which is among the top 80 % of the ISI-listing.

Zusammenfassung

In dieser kumulativen Dissertation werden fünf Publikationen zum Thema operative Therapie des Mammakarzinoms zusammengefasst. Vier Arbeiten sind Erstbeschreibungen von Methoden die gezeigt haben, dass es onkologisch sichere Alternativen zu den etablierten Methoden gibt. Diese führen bei geringerer Invasivität und damit Morbidität zu besseren kosmetischen Ergebnissen als die bis dato bekannten Methoden. Der Doktorand hat diese Methoden entwickelt und in diversen Publikationen beschrieben. Eine Arbeit befasst sich mit der Bedeutung der lobulären und duktalen Mammakarzinomsubtypen u.a. auf die chirurgischen Verfahren. Alle Arbeiten sind in einem peer-reviewed international journal mit einem Impact Factor von derzeit 1,28 erschienen die zu den oberen 80% der ISI Auflistung zählen.

Introduction

Breast cancer is for women in the Western industrial nations the most frequent malignant disease. In Germany almost one in ten is taken ill with it in her lifetime. More than half of the persons affected are aged 60 or younger when diagnosed, among them approximately 20 % aged under 40. Nowadays the surgical treatment of breast cancers is still an essential part of the therapy. When the clinical picture changed from a local into a systemic disease, the type of surgical concept changed though: From the initially highly radical surgeries (Halsted 1894) to the modified radical mastectomy (Patey 1948) up to the breast-conserving surgical techniques (Atkins 1972, Veronesi 1977, Fisher 1977). (1-4)

The demand for further surgical procedures which meet the female patients' desire to keep their physical integrity along with less morbidity led to considerations as to how this could be achieved.

Four publications summarized in this dissertation are first descriptions of methods that proved to be oncologically safe alternatives to the already established ones. They produce along with less invasivity and thus less morbidity better cosmetic results than all the other methods known to date.

The doctoral candidate has developed these methods and has described them in various publications.

One publication deals with the long controversy about the impact of invasive lobular and invasive ductal histology in breast cancer on overall survival (OS) and disease-free survival (DFS). The amount of mastectomies in invasive lobular is still higher than in ductal breast cancer. In order to contribute further in this controversy we have analysed our database of 5689 female patients with invasive breast cancer by univariate and multivariate survival analyses.

We especially examined five standard situations for female patients with a breast cancer:

Status Post Mastectomy and the Request for a Reconstruction in Case of Big Contralateral Breast

So far the reconstructions were made by using the female patients' autologous tissue mainly from the lower abdomen. Since in the case of female patients with big breasts the reconstruction is mostly combined with a contralateral reductory plastic, it seems reasonable to use this tissue for the reconstruction. There exist only two publications dealing with this approach. Both used the caudal area of the contralateral breast for the reconstruction.

Marshall et al conducted a two-step procedure, consisting of a first session, in which a rough transfer of breast tissue was made, and a second session 4 to 6 weeks later, in which the vessel pedicle was cut through, the breast was formed and the MAK was transferred back. Schoeller et al performed this as a single-step procedure. As a result, the majority of the flap turned necrotic so that it became necessary to use a Latissimus-dorsi flap for the covering.

We thought that the difficult reproduction of the procedure in a single session can be put down to the unfavourable pediculation. Since the mamaria interna vessels supply the breast often in the form of a fan from the medial and the axillary ones from the lateral area, we decided to divide the breast along the longitudinal axis. This would have the additional advantage that the volumina will be divided evenly so that a single-procedure reconstruction becomes possible.

The possible risk of a carcinoma in a breast which was reconstructed with this particular procedure has to be taken into consideration. But there is no reason to believe that the risk of a carcinoma in a divided breast should be higher than a breast left in one piece on the healthy side.

We therefore described a new mamma-splitting technique and showed that it is a promising method of the single-procedure reconstruction with own tissue without donation site morbidity or implants. Meanwhile we treated six female patients with this technique. In all cases the

cosmetic results were good. There occurred no complications. Further centres have in the meantime successfully been using this technique and published its good results.

Indication for Mastectomy and Request for Reconstruction in Case of Bigger Ipsilateral Breast

In this case the reconstruction with own tissue from the lower abdomen would also be a possibility. Another one would be to insert an implant and cover it with de-epithelialized skin from the lower part of the breast – ending to the IMF –sutured to the lower boundary of the pectorlis muscle, thus maintaining the IMF with a good aesthetic result.

Herein, a skin-reducing mastectomy without any implant insertion is presented. To our best knowledge this is the first time ever that such an approach has been presented in the specialist literature.

Despite the current trend supporting the thesis that skin-reducing mastectomy should be accompanied by the insertion of sub-pectoral implants, we believe that the avoidance of implants when possible could present certain advantages. Firstly it costs significantly less than the currently applied approach, since no implants or Acellular Dermal Matrix (ADM) are inserted. Additionally, in case of prophylactic bilateral skin-reducing mastectomies performed in rather young patients, the breasts are expected to present a natural ptosis with time, thus imitating aesthetically the normal breast. This would not happen if implants were inserted; on the contrary, implants make the breasts rather resistant to ptosis and present the risk of implant migration or exposure, not to mention the long-term complication of capsular contracture. Compared to autologous reconstruction techniques, the approach presented herein is expected to be of lower risk for necrosis since no translocated myocutaneous flap has been used. From the oncological point of view, avoiding the insertion of an implant is expected to assist the mammographic follow-up of the high-risk patient; implants are

described to obscure visualization of adjacent breast tissue, while they cannot be adequately compressed during mammography. Mammography loses up to a 50 % of its sensitivity when the implant presents with capsular formation.

Indication for Mastectomy and Request for Reconstruction in Case of Moderate to Small Ipsilateral Breast

In such cases the reconstruction with autologous tissue from the lower abdomen is usually applied. A reconstruction with implants is not promising due to the lack of coverage in the caudal area. The most frequently occurring long-term complication in implant-based breast reconstruction is the fibrotic capsule formation in the recipient site with concurrent dysaesthesia and poor aesthetic result. The integrity of soft tissues is a basic aspect of successful reconstructive and plastic surgical procedures in breast surgery. Porcine Acellular Dermal Matrix (P-ADM) as connective tissue graft is supposed to improve the quality and quantity of soft tissue in implant-based breast reconstruction. We were the first to use ADM in Europe and have the broadest experience with this new technology. This study investigates the indications, the results and the costs for the use of PADM for correction or prevention of implant-associated breast deformities. We found out that ADM-assisted implant-based breast reconstruction has a satisfying safety profile. The use of ADM as interface matrix for implant-based breast reconstruction includes a predictable good aesthetic and haptic result by preventing capsular contracture, rippling, implant malposition, soft tissue thinning and failure of the silicone implant based breast augmentation. The actual high cost of PADM may be limiting to widespread use.

Big Thoracic Wall Recurrence Which Cannot Be Covered with Advancement Flaps

Frequently within the context of the resection of these recurrences a masking with autologous tissue becomes necessary, as e.g. with the latissimus dorsi muscle flap. This is a relatively laborious operation with a poor general prognosis. Serious complications of this procedure are partial necrosis up to the complete loss of the graft. In case of latissimus-dorsi-flap operations, this is the consequence reported for up to 8 % of the female patients. Since in case of a loco-regional recurrence often an axilla dissection was previously performed, one has to be prepared for a more difficult depiction of the latissimus-flap-vessels. Accordingly, the rate of (partial) loss of flaps will be higher. Autologous tissue from the abdomen could be an alternative here and could improve the cosmetic result in terms of a reconstruction, but because of the additional tension it is often not practical. Furthermore, the often bad general health of the female patients would have an additional negative influence in this respect. The donor site morbidities are among the most common complications. This could be a limited movement and, in the case of pediculated grafts from the abdomen, hernias. Furthermore, there are the general risks of surgery, such as thrombosis, seromas, hematomas, wound infection and secondary haemorrhage. Among them the development of seromas is frequent due to the big operation area. In case of a big contra-lateral breast, the latter can also be used for masking the defect. On the other hand, the ten-year survival rate after recurrence sanitation following a mastectomy is 30 % and the one after breast conserving treatment 50 %.

By means of the Vacuum Assisted Closure Therapy (VAC-Therapy) many successful closures of bigger wounds were reported. Randomized studies showed that VAC-Therapy has improved the healing of open wounds significantly.

We considered whether this could also be applied within the context of the recurrence resection, in order to avoid laborious maskings with autologous tissue and thus to lower

morbidity. Especially for loco-regional recurrences with simultaneous axilla infestation as well as in a condition after axilla dissection with iatrogenic severance of the thoracodorsal vessel bundles this procedure could prove to be a good alternative.

Often necessary additional therapies, like radiation and chemotherapy, can be carried out in the course of a VAC-Therapy.

We found out that by applying the VAC –Therapy in cases of thoracic wall recurrences or extensively therapy-resistant local recurrences after breast reconstruction, a masking with autologous tissue can be avoided. Since as a rule the prognosis is reduced, this therapy with low morbidity is a good alternative. Particularly additional necessary therapies, such as radiation and chemotherapy, can be performed during a VAC-Therapy.

Comparison of patients with invasive lobular and invasive ductal histology in breast cancer

In our study population of 5689 patients with IDC and ILC who were followed over a median period of 57 months, we found a significant difference in OS both in univariate and in multivariate survival analyses. This is most likely due to the more favourable tumour biology of ILC and applies despite the fact that we excluded all patients who had any adjuvant chemotherapy and hormonal treatment, which possibly would have led to an additional OS benefit. The fact that differences in DFS are not statistically significant could be attributable to the fact that ILC initially presents in a more diffuse pattern leading to increased rates of positive margins after BCT. This phenomenon, in turn, could lead to more frequent local recurrences, which have a negative impact on DFS. Since the local disease in invasive breast cancer is secondary concerning OS, the more favourable tumour biology of ILC could still ultimately lead to better OS.

Mastectomy in invasive lobular breast cancer could reduce the differences in DFS between IDC and ILC.

Article 1: Worldwide First successful splitting of the breast for a single-procedure reconstruction after mastectomy with maintaining the sensitivity

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ORIGINAL ARTICLE

Worldwide first successful splitting of the breast for a single-procedure reconstruction after mastectomy with maintaining the sensitivity

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Abstract
Purpose Breast reconstructions are made autologously, that is with the body's own tissue, or heterologously by means of implants. This either causes donor site morbidity or a foreign body is implanted. Both are disadvantages which could not be avoided up to now. By using tissue of the still remaining (contralateral) breast both could be avoided. The object of this paper is to check whether this technique is feasible.
Method By dividing the existing breast and transferring it to the contralateral side, we were able to successfully conduct a single-procedure breast reconstruction with one female patient.
Results The operation technique as well as the post-operative progression of the female patient will be presented.
Conclusion Mamma-splitting is a new and promising method of reconstruction with own tissue, without donor site morbidity or implant. The use within a bigger group of female patients will show the method's validity.

Keywords Breast · Cancer · Mastectomy · Reconstruction · Splitting · Contralateral

Introduction

Each year about 50,000 women contract breast cancer in Germany. In approxiamtely 30% of the persons concerned one breast has to be removed. Such a surgical operation does not only change the outer appearance, but can occasionally effect the whole personality. With regard to the patient's quality of life, the reconstruction of the breast is therefore an important part of the therapy, in which psychological and aesthetic aspects ought to be taken into adequate consideration next to the oncological ones.

Breast reconstructions are made autologously, with own tissue, or heterologously, with implants. This either causes donor site morbidity or a foreign body is implanted. Both are disadvantages which could not have been avoided up to now. By using tissue of the still remaining (contralateral) breast both could be avoided. The object of this study is to evaluate whether this technique is feasible.

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Materials and methods

The first time that we exercised this technique successfully was with a 67-year-old female patient: in her case a mastectomy was performed in July 2007 outside in another hospital with an invasive ductal breast carcinoma pT2, pN1a (1/10), G3. Afterwards the patient received chemotherapy, a radiation was not indicated. The subsequent check study did not show any signs of a relapse. The current diagnosis—including palpation, mammography and ultrasound of the left breast—was without pathological findings. She introduced herself to us with the desire for a reconstruction.

The patient is of 169 cm height and weighs 93 kilos. As to the family's anamnestic background, there are no breast carcinomas or ovarian cancer known. As a secondary finding a hypertonus was diagnosed 10 years ago, which has been treated with drugs. There is no consumption of nicotine, no diabetes mellitus. The physical examination shows that the right ablation scar does not cause irritations. On

both sides of the ablation scar are tori. The left breast is soft, big and ptotic. The distance between jugulum and areola is 42 cm.

Due to the size and ptosis of the left breast a reduction plastic would be necessary. We explained to the patient that the surplus tissue of the reduction plastic is usually rejected so that there is the possibility of using this tissue to perform the reconstruction. If this was not successful, the usual reconstruction from the underbelly would be necessary. The patient agreed to this procedure. Preoperatively the Doppler sonographic depiction of the perforations of the vasa mamaria interna is conducted. Afterwards the cut figures for the division of the breast are outlined as well as the new submammary fold. At the beginning of the operation the perforators are once more verified and outlined by means of the Doppler. The area between the ablation scar and the future submammary fold is deepithelialised. The ablation scar is incised and the cranial area of sebaceous matter is separated from the pectoral muscle. The preparation is made up to the desired starting point of the reconstructed breast (Fig. 1a). Afterwards the breast is divided along the middle line. Thus two skin-fat-gland areas of equal size are created (Fig. 1b). The lateral part is vascularized by cranio-latero-caudal, the medial part by cranio-medio-caudal. The medial part is laid free up to the perforators. The Doppler is once more used to identify the vascularization. At the end of this preparation, the medial flap is just supplied by the two preoperative perforators (Fig. 1c). The caudal and cranial supply do no longer exist. Now the deepithelialised area is moved over to the side which is to be reconstructed so that it keeps a caudal pedicle in the lateral area (Fig. 1d). This area is placed laterally underneath the transplant and is in charge of the lateral projection. Furthermore, the medial over-projection is thus reduced by the pedicle. The medial flap, which is only supplied by the perforators, is now rotated 180° and moved onto the contralateral side (Fig. 1e). The lateral flap is swivelled into the defect like a rotary plastic. Along the middle line the surplus skin is deepithelialised and the wound closed.

At the end of the operation the nipple is situated on the reconstructed side in the area of the axillary trail. After the wound has healed, the nipple is divided and transplanted as free transplant to the correct position under local anaesthetic.

Results

The operation of this patient took four hours. During the operation no complications occurred. The loss of blood was approximately 100 ml. During the hospital stay antibiotics were admitted for 3 days postoperatively. No rheologic drugs were necessary. The patient was able to leave the hospital in a good general condition on the eighth day after the operation. During her stay at the hospital no problems occurred. The patient was mobile on the day of the operation. The scars are healing. The sensitivity of the reconstructed breast was completely maintained. The MAK-complex still has full sensitivity. Figure 2 shows the situs preoperatively and on the sixth day after the operation. The volumina are evenly spread and a good symmetry is achieved. The nipple reconstruction has not been performed yet and will proceed 3 month postoperatively.

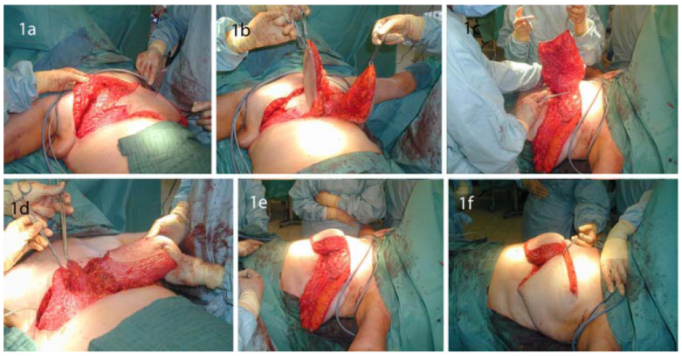

Fig. 1 Photos of the various operative steps. **a** The ablation scar is incised and the cranial area of sebaceous matter is separated from the pectoral muscle, **b** division of the breast along the middle line, **c** medial flap is only supplied by two perforators **d**: epilated area of the side which is to be reconstructed is lifted, **e** the medial flap is rotated 180° and placed on the contralateral side

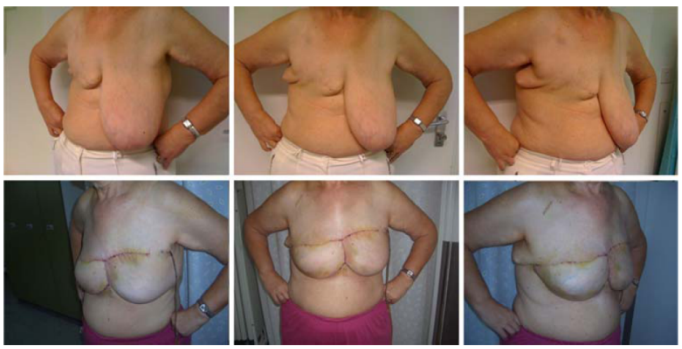

Fig. 2 Preoperative (*top series of photos*) and postoperative (*bottom series*) situs

Discussion

Breast reconstructions are made autologously, that is with the body's own tissue, or heterologously by means of implants.

The implants cannot be placed directly underneath the skin of the breast. Thus the skin, which has been correctly thinned out during a mastectomy, can result in a capsular fibrosis within a short period of time. That is the reason for placing the expander and afterwards the implants underneath the pectoral muscle. The cosmetic success is often not very satisfying, since a ptosis cannot be imitated. Thus a tightening of the contralateral side or the use of reductory plastics are mostly necessary. Lately materials have been offered which are meant to prevent a capsular fibrosis by partially or completely covering the implants. The resulting data are still due. Even if this procedure should prove itself feasible, it would still need an implant and thus a foreign body. That is why the autologous procedures have been gaining extensive acceptance during the last years. In this context, the donor site morbidity was minimized by micro-surgical techniques. In 1991, reconstructions with pure skin vessels (SIEA-flap) were described for the first time [1]. Thus one can do without muscle tissue, but there remains a scar in the belly area.

Since in the case of female patients with big breasts the reconstruction is mostly combined with a contralateral reductory plastic, it seems reasonable to use this tissue for the reconstruction. There exist only two publications dealing with this approach. Both used the caudal area for the reconstruction.

Marshall et al. [2] conducted a two-step procedure, consisting of a first session, in which a rough transfer of breast tissue was made, and a second session 4–6 weeks later, in which the vessel pedicle was cut through, the breast was formed and the MAK was transferred back. Schoeller et al. [3] performed this as a single-step procedure. As a result, the majority of the flap became necrotic so that it became necessary to use a Latissimus-dorsi flap for the covering.

We think that the difficult reproduction of the procedure in a single session can be put down to the unfavourable pediculation. Since the mamaria interna vessels supply the breast often in the form of a fan from the medial and the axillary ones from the lateral area, we decided to divide the breast along the longitudinal axis. This would have the additional advantage that the volumina will be divided evenly so that a single-procedure reconstruction becomes possible. This method is limited to female patients with a big ptotic breast and is a replenishment to the repertoire of a plastic surgeon specialized in breasts.

The possible risk of a carcinoma in a breast which was reconstructed by this particular procedure would be possible. But there is no reason to believe that the risk of a carcinoma in a divided breast should be higher than if one leaves the breast in one piece on the healthy side.

Comment

The described mamma-splitting technique is a new and promising method of the single-procedure reconstruction with own tissue without donation site morbidity or implants. Its administration in a bigger group of female patients will show the validity of this method.

Conflict of interest statement The authors declare that there are no considerations or conflicts of interest

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Article 2: Bilateral prophylactic skin-reducing nipple-sparing mastectomy with immediate breast reconstruction using only a vascularized dermal–subcutaneous pedicle: technique and possible advantages

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GYNECOLOGIC ONCOLOGY

Bilateral prophylactic skin-reducing nipple-sparing mastectomy with immediate breast reconstruction using only a vascularized dermal–subcutaneous pedicle: technique and possible advantages

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Abstract
Purpose To present a new surgical technique regarding breast reconstruction after skin-reducing nipple-sparing mastectomy.
Method The current trend for immediate breast reconstruction after skin-reducing mastectomy mainly supports the insertion of subpectoral implants or the use of autologous breast reconstruction techniques. Herein for the first time, we present a case of bilateral prophylactic skin-reducing nipple-sparing mastectomy with immediate breast reconstruction, using only a dermal–cutaneous pedicle.
Results The postoperative course was uneventful. Forty days postoperatively the aesthetic result was excellent.
Conclusions We believe that such technique in selected cases can present several advantages as low cost, reduced possibilities for complications associated to implant insertion or autologous reconstruction techniques and an easier mammography follow-up.

Keywords Breast reconstruction · Mastectomy · Breast implants

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Introduction

Mastectomy is a common surgical option in case of breast cancer treatment or prophylaxis. It is considered as an operation that is associated with several problems for the patient, affecting the overall postoperative quality of life. Altered body image, diminished self worth, loss of a sense of feminity along with anxiety, and depression have been reported so far in women that underwent a mastectomy procedure [1]. In the aim of alleviate such issues, breast reconstruction has been proposed as the second step in the management of the oncology patient [2].

Several techniques have been developed so far regarding breast reconstruction involving both autologous and heterologous approaches. Good aesthetic results have been reported especially after the introduction of skin-sparing and nipple-sparing mastectomies. As far as large breast reconstruction is concerned, the up-to-date trend is the skin-reducing mastectomy followed by insertion of subpectoral implants [3].

Herein, we present for the first time a variation of this surgical technique: skin-reducing mastectomy using the excess of skin—instead of inserting subpectoral implants—to restore the breast mound. We believe that this approach apart from being feasible, it may hold advantages compared to the standard implant-based technique.

Patient and method presentation

Patient characteristics

A 55-year old woman was referred to our Department for breast screening due to family history of breast cancer

(daughter died of breast cancer at the age of 34). Her medical and surgical history was null. She had not received any sort of hormonal treatment before. On clinical examination, both breasts were found large and ptotic with no evidence of palpable lesion. Both axillas were also free of palpable lymph nodes. Mammography did not reveal any suspicious lesion for breast cancer. After being properly informed and having consented, the patient was investigated for BRCA-1/BRCA-2 mutations and proved to be BRCA-2 mutation carrier. In the context of her being a high-risk patient for breast cancer development, the patient opted for a bilateral skin-reducing/nipple-sparing mastectomy with breast reconstruction. She was also informed of the additional need for further follow-up postoperatively—as the risk is definitely reduced but is not eradicated with the operation [4]—and for the possibility of inserting definite implants during the operation. The patient preferred if possible not to have any implants inserted. The option of using the excess of skin and subcutaneous tissue to fill the breast mould was then presented to the patient, notifying her that if not successful, standard treatment would be offered to her. The patient gave her informed consent for the procedure.

Preoperative planning

The operation was designed according to the Wise breast-reducing pattern, in the view of a reverse-T end result (Fig. 1a). Nipple-sparing and translocation to a higher position was also scheduled (Fig. 1).

Operative procedure

Initially, the skin included in the marked area (as this is presented in Figs. 1, 2a) was de-epithelialized (Fig. 2b). The boundaries of de-epithelialized area were then incised to create a window through which a standard skin-sparing mastectomy was performed (Fig. 2c, d). The nipple-areolar complex (NAC) was spared, emphasizing that no residual breast tissue was left behind it (Fig. 2e). The dermal–subcutaneous pedicle (involving the infra-mammary fold—IMF) was then folded in a way that: (a) it filled the skin envelope created by the skin-sparing mastectomy and (b) the nipple-areolar complex (NAC) was placed right on its new site (Fig. 2f, g). Finally the skin was sutured in a reverse-T pattern with intra-cutaneous Monocryl® 4-0. At the same time, the NAC was also sutured to its new elevated position adjacent to the skin (Fig. 1h). Negative pressure drainages were placed to both breasts.

Postoperative course and follow-up

The patient's postoperative course was uneventful. Drainages were removed when they drained less than 30 ml/day. She received prophylactic antibiotics for 3 days and was discharged at the 7th postoperative day presenting a good aesthetic result (Fig. 1). Forty days after being discharged, her healing proved to progress well, without any complications; the aesthetic result was excellent (Fig. 1). She was thus referred to regular breast screening with clinical examination every 6 months and mammography yearly.

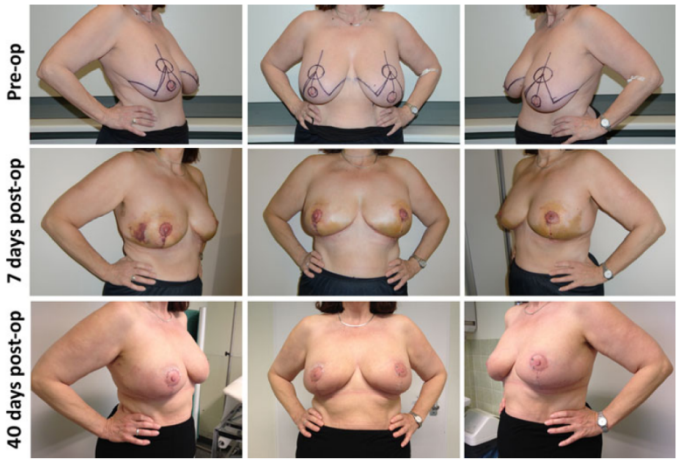

Fig. 1 Presentation of the aesthetic result of the bilateral skin-reducing nipple-sparing mastectomy using only a dermal–cutaneous flap for breast reconstruction. Both breasts appear large and ptotic preoperatively. Appropriate marking of the skin has been done according to breast-reducing Wise technique. Seven days postoperatively the healing is satisfactory; only skin bruising is visible with no sign of complications. Forty days postoperatively, skin bruising has disappeared; healing has progressed to an acceptable result

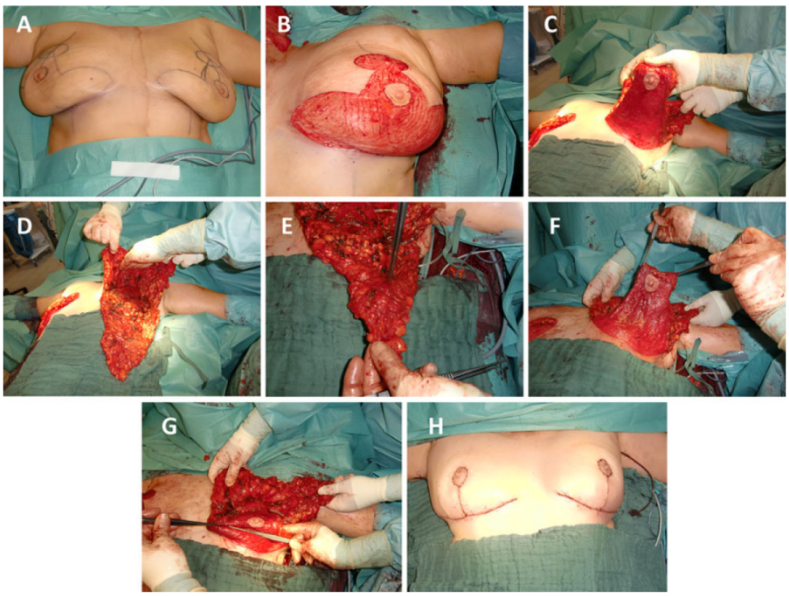

Fig. 2 Salient steps of the described surgical method. **a** Both breasts appear with substantial ptosis immediately prior to surgery, **b** de-epithelialization of the marked area has been performed, **c** the limits of this area are used as a window to perform a standard skin-sparing mastectomy, **d** after mastectomy the skin envelope is ready for reconstruction, **e** detail of the area behind the nipple-areolar complex (NAC) where no residual breast tissue has remained, **f** the dermal–cutaneous pedicle is held by two forceps in order to be folded into the skin envelope, **g** final placement of the folded dermal–cutaneous pedicle in way that the NAC is in its new anatomical position, **h** final result after intracutaneous suturing

Discussion

Breast reconstruction techniques addressed the aesthetic and psychological issues raised by women that have opted for mastectomy.

After the introduction of skin-sparing mastectomy in the early 1990s [5], the thesis of immediate breast reconstruction was implemented. Indeed skin-sparing mastectomy was efficient in creating a skin envelope for the reconstructed breast to maintain both its shape and colour. The breast mound was thus reconstructed either by inserting a definitive prosthesis [6] or by translocating myocutaneous flaps from other sites like the transverse rectus abdominus, the latissimus dorsi, the deep inferior epigastric, the buttocks and the thighs [7]. Several techniques have been developed in order for an implant to be inserted. The initial insertion above the pectoralis major (PM) muscle was rapidly replaced by techniques inserting the implant below the PM, with or without elevating further the anterior serratus muscle [3]. It was easily recognized though, that a complete coverage of the implant by the PM was problematic in the context of creating a result that could not imitate the normal breast. The low breast pole was more or less missing, while the implant was forced to project in the upper quadrants of the breast [6]. These problems were overcome by applying techniques expanding the submuscular pocket towards the lower breast pole. De-epithelialized skin from the lower part of the breast—ending to the IMF—was sutured to the lower boundary of the PM, maintaining in this way the IMF with a good aesthetic result [8]. This technique was further evolved by the use of acellular dermal matrices (ADM) sutured to the lower end of the PM and to the IMF [9].

The current operation scheme changed further as skin-sparing mastectomy involved also patients with large breasts or even macromastia. Such patients are usually offered a skin-sparing mastectomy and a simultaneous breast reduction following the well-accepted Wise methodology [10]. In that context skin is de-epithelialized and re-sutured, yielding a reverse-T scar. This combination of

operations, now addressed as skin-reducing nipple-sparing mastectomy was decided to be offered to our patient as well.

Of note is the contribution of the NAC to the aesthetic result during breast reconstruction. Although the oncological risk of maintaining the NAC has not been completely delineated, the sparing of NAC—as is the presented case—is an acceptable option [11].

Herein, a skin-reducing mastectomy without any implant insertion is presented. To our best knowledge this is the first time that such approach has been presented in the literature.

Despite the current trend supporting the thesis that skin-reducing mastectomy should be accompanied by the insertion of sub-pectoral implants, we believe that the avoidance of implants when possible could present certain advantages. Firstly it costs significantly less than the currently applied approach, since no implants or ADM are inserted. Additionally, in case of prophylactic bilateral skin-reducing mastectomies performed in rather young patients, the breasts are expected to present a natural ptosis with time, thus imitating aesthetically the normal breast. Such thing would not happen if implants were inserted; on the contrary, implants make the breasts rather resistant to ptosis and present the risk of implant migration or exposure, not to mention the long-term complication of capsular contracture [6]. Compared to autologous reconstruction techniques the approach presented herein is expected to be of lower risk for necrosis as no translocated myocutaneous flap has been used [7]. From the oncological point of view, avoiding inserting an implant is expected to assist the mammographic follow-up of the high-risk patient; implants are described to obscure visualization of adjacent breast tissue, while they cannot be adequately compressed during mammography [12]. Mammography loses up to a 50 % of its sensitivity when the implant presents with capsular formation [12].

The currently discussed patient will definitely be enrolled in an intense follow-up program; without any implants in place, mammography will continue to serve as a primary screening tool. If any implant was inserted, mammography would be difficult to interpret, a fact that would easily lead to screening with magnetic resonance breast imaging.

Opposed to these advantages, it could be argued that there is still a risk—in the view of a good cosmetic result—that the surgeon might tend to leave a thicker layer of subcutaneous tissue, increasing the risk of residual breast tissue in the reconstructed breast and, therefore, contributing to an increased risk for breast cancer recurrence or occurrence. A prerequisite for applying our technique is the adherence to the basic principles of a *lege artis* oncological skin-sparing mastectomy. Thus, in the view of oncological safety, our technique is considered suitable exclusively for women with large-sized breasts. In the case of large-sized breasts, the tissue used for breast reconstruction is extensive in surface and satisfactorily thin. Thus, no residual breast tissue is expected to be left. On the contrary, in case of small or moderate size breasts, the tissue anticipated to be used for breast reconstruction is not of sufficient surface for the current technique to be applied. The approach to increase the volume by increasing the thickness of the layer—although it would succeed in filling the breast mould—is not recommended, since it would definitely increase the risk of residual breast tissue and consequently the risk of breast cancer occurrence or recurrence. Taking, thus, into account that the current technique is suggested as unsuitable for women with small or medium size breasts, a careful patient selection is imperative, if a case-series with good cosmetic and oncological results is to be organized and studied.

Conclusions

This is the first time that a skin-reducing nipple-sparing mastectomy without the insertion of implants or any myocutaneous flap is presented. The technique is cheaper compared to standard options at the moment, offering better terms of follow-up at least on a prophylactic scheme. An adequate case-series study with proper inclusion criteria, will clarify, in a statistically significant way, whether such technique can be applied as a routine option when a skin-reducing mastectomy is decided.

Conflict of interest The authors declare no conflict of interest.

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Article 3: The use of porcine acellular dermal matrix in silicone implant-based breast reconstruction

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GYNECOLOGIC ONCOLOGY

The use of porcine acellular dermal matrix in silicone implant-based breast reconstruction

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Abstract
Introduction The most frequently occurring long-term complication in implant-based breast reconstruction is fibrotic capsule formation at the recipient site, with concurrent dysesthesia and poor aesthetic results. Using porcine acellular dermal matrix (PADM) as a connective tissue graft material is supposed to improve the quality and quantity of soft tissue in implant-based breast reconstruction. This study investigates the indications for and the results and the costs of using PADM for the correction or prevention of implant-associated breast deformities.
Materials and methods This study reviewed a single surgeon's experience in the correction or prevention of implant-associated breast deformities with PADM in breast cancer-related breast reconstruction from 2009 to 2011. A total of 23 patients (27 breasts) were included in the study. The aesthetic outcome, the incidence and the type of complication were analysed. Twenty-three women underwent breast cancer-related breast reconstruction: 19 women underwent single-breast reconstruction and four women underwent bilateral reconstruction.
Results Of the 23 patients who underwent breast reconstruction, 18 (78%) were "satisfied" with the aesthetic and haptic outcome after implant-based reconstruction with PADM. One patient (one breast) required another breast operation because of ipsilateral breast cancer recurrence during the follow-up period. PADM-assisted implant-based breast reconstruction has a satisfactory safety profile.
Conclusion The use of PADM as an interface matrix for implant-based breast reconstruction yielded predictable and acceptable aesthetic and haptic results by preventing capsular contracture, rippling, implant malposition, soft-tissue thinning and failure of the silicone implant-based breast augmentation.

Keywords Acellular dermal matrix · Reconstructive tissue matrix · Breast reconstruction · Breast cancer

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Introduction

A variety of predictable and aesthetically acceptable autogenous procedures using axial and microvascular (musculo) cutaneous composite flaps as well as implant materials exist for breast reconstruction. The use of implant-based techniques in reconstructive breast surgery due to primary deformities or acquired deformities after trauma or breast surgery and in plastic breast surgery is indicated immediately in a single-stage procedure or in a delayed fashion after skin-expanding procedures. There are many reasons for breast reconstruction procedures to fail to achieve the desired aesthetic results. Some patients may have already undergone multiple prior corrective surgeries for asymmetry, ridging, undefined inframammary folds or fibrotic capsule formation, making additional revisions more difficult. Almost every type of inserted foreign material is sealed

within a fibrous capsule. This fibrous capsule may thicken and contract over time [1]. Deformities, distortion, dislocation and dysesthesia of breast implants typically follow fibrotic capsule development [2]. The integrity of muscle and soft tissues is a basic factor in successful reconstructive and plastic surgeries.

The insertion of a connective tissue graft can improve the quality and quantity of breast reconstruction. The use of an interface matrix to separate the silicone compartment from the immunogenic surrounding tissue compartment to prevent fibrotic capsule formation may lead to satisfying long-term outcomes after implant-based breast reconstruction. Porcine acellular dermal matrix (PADM, Strattice™ LifeCell Corporation) may eliminate the disadvantages of capsule formation by providing a structure for connective tissue growth. LifeCell Corporation received clearance from the United States Food and Drug Administration for the production of Strattice™ tissue matrix in June 2007. The Strattice™ product was commercially launched in December 2008. Strattice™ reconstructive tissue matrix is a sterile porcine-derived reconstructive tissue matrix that supports tissue regeneration. It is derived from porcine dermis and undergoes processing to retain the structural integrity of the extracellular matrix and to remove cells and DNA and minimises the presence of galactose–alpha [1, 3]-galactose terminal disaccharide (alpha-Gal) via specific enzymatic cleavage. The immune response to xenogenic epitopes is, therefore, significantly reduced and may allow the scaffold to support regeneration of native tissue [3]. In a primate excisional repair model of abdominal wall tissue, Strattice™ tissue matrix demonstrated rapid revascularization, cell repopulation and white cell migration as early as 2 weeks post-implantation and mature vascular structure at 6 months post-implantation [4]. Strattice™ tissue matrix, used in breast augmentation revision surgery, is a tool that may help control breast pocket size and location, acting as an "internal bra" to help support and hold the implant in place, support fold repairs, offer an additional layer of tissue that may mask implant visibility and reduce fibrotic capsule formation. Complications following breast plastic surgery that may be addressed with the use of Strattice™ tissue matrix include bottoming out, malposition of the inferior or lateral fold and wrinkling or rippling. The use of PADM for the repair of bottoming out is similar to the breast reconstruction technique in which PADM acts as an "internal bra" to provide additional support to the implant. PADM is attached to the pectoralis major muscle (PMM) and the new inframammary fold to secure the pocket and help hold the implant in the desired location. The utilisation of PADM along the new fold may provide the extra support needed to keep the implant in the desired location and to prevent inferior or lateral fold malposition [3]. The correction of wrinkling and rippling involves a delicate balance between pocket size correction and coverage. It is often a result of thin tissues that do not mask the ripples on the implant. PADM may help to support and hold the implant in the desired location and diminish wrinkling or rippling in the lower pole [5]. Many studies have been performed to prevent or decrease capsule formation and contraction which tends to develop around implants. This report presents the outcomes of treating breast cancer patients with PADM. PADM was used as a biological barrier for silicone implant-based breast reconstruction between the wound and the implant.

Methods

The results of 23 patients who underwent implant-based breast reconstruction using PADM performed by one surgeon in a university hospital from August 2009 to April 2011 were reviewed. The adjuvant treatment, the incidence and types of complications, the aesthetic outcomes and the costs were analysed. Twenty-three patients aged 29–68 years (median 48 years) were treated with PADM for silicone implant-based breast reconstruction. The PADM sheet was prepared according to the manufacturer's instructions. This material was rehydrated with room-temperature, sterile saline for a minimum of 2 min, prior to implantation. The soft reconstructive tissue matrix, we used in our institution, measured 8 × 16 cm and was trimmed to cover (without folds) the silicone implant exposed by the PMM at the inferior, medial and lateral borders of each breast. On average, one sheet of PADM was used per breast. The silicone implants (Mentor®, Inamed®) were placed in a submuscular pocket. Therefore, the PMM was released inferolaterally on both sides and elevated off the chest wall. An implant pocket was dissected under the PMM. The silicone implant was introduced into the pocket under the elevated PMM. The inferior border of the PMM was brought over the implant and sutured to the superior border of the prepared acellular dermis. The PADM sheet was anchored inferiorly at the inframammary fold and medially and laterally to the chest wall using size 2-0 polydioxanon (PDS®) sutures created using the single-knot technique. The incisions were then closed according to the anatomical layers. Two drainage tubes with suction were inserted subcutaneously and behind the implant. The patient was treated with cephalosporine 1.5 g intravenously every 8 h for 5 days postoperatively. The healing of the surgical site, including the nipple–areola complex, was monitored precisely. The drains were removed when the secretion level fell below 30 ml per day. The stitches were removed after 1.5 weeks. The patient was instructed to wear a firm bra from day one postoperatively until the first follow-up visit, 4 weeks later. The patient was examined daily for the first postoperative

week, as well as 4 weeks after surgery and 6 months after surgery. Skin complications, fibrosis, rippling, soft-tissue thinning and implant malposition were evaluated by the surgeon. Each patient's subjective evaluation of the aesthetic, haptic and sensory outcomes of the surgery was obtained by questionnaire, with a ranking from "not satisfied" to "satisfied" and "very satisfied", during the follow-up visits, 4 weeks and 6 months postoperatively.

Results

The results of implant-based breast reconstruction using PADM performed on 23 patients by one surgeon from August 2009 to April 2011 were reviewed. The patients with a median of 48 years (29–68 years) were treated with PADM for silicone implant-based breast reconstruction. The median duration for wound drainage were 5 days to reach a daily secretion below 30 ml. Clinical follow-up was performed 1 month and 6 months after PADM surgery by the same surgeon. The median follow-up was 19 months (range 8–36 months).

Five out of 23 patients (22%) had non-invasive breast tumours measuring 0.8–7.5 cm (including the resection margins), with a retromammarian distance of more than 0.6 cm. Seventeen of 23 patients (74%) had invasive breast cancer (pT1–pT3) with a retromammarian distance of more than 1.4 cm. One of 23 patients (4%) with invasive breast cancer had nodal macro-metastasis. Three patients had BRCA mutations (one patient had a BRCA-1 mutation; two patients had BRCA-2 mutations).

Postoperative seroma

Postoperative seroma was detected by palpation and ultrasound in two out of 23 patients during the follow-up period (8%). One of the mentioned two patients had the wound drainage for 3 days; the other patient had the wound drainage for 4 days. Four weeks after surgery both asymptomatic patients presented with little seroma, puncture was not indicated. In these two patients there was no evidence of seroma at the time of the 6-month follow-up examination.

Adjuvant treatment

Three out of five patients with ductal carcinoma of the breast received endocrine treatment with tamoxifen. Sixteen out of 17 patients with breast cancer received standard chemotherapy. Nine out of 17 breast cancer patients received radiation treatment before PADM-based surgery; one out of 17 breast cancer patients received radiation treatment after PADM-based surgery. Fifteen out of 17 breast-cancer patients are currently receiving endocrine treatment.

Incidence of skin and nipple–areola complex complications

The first patient presented with flare-like, diffuse, painless redness without any signs of systemic inflammation until the 5 month after surgery. Revision of the breast was performed. Intra-operatively, there was no sign of inflammation of the soft tissue, the pocket of the implant or the PADM sheet. The microbiology smear showed no growth. In subsequent patients, this flare-like redness was seen regularly after PADM-based surgery and resolved 6–8 months after initial surgery without any treatment. These signs were considered to represent a local, harmless immunologic reaction.

One out of 23 patients (4%) presented partial nipple–areola complex necrosis on both sides after 3 months. This condition was treated by excision of the necrosis.

One out of 23 patients (4%) presented with complete nipple–areola complex necrosis and tissue thinning with implant perforation 7 weeks after PADM-based surgery. Wound dehiscence was not observed.

The skin and nipple–areola complex complications observed are assumed to be related to radical retro-areolar resection, a history of surgery in the same site, impaired perfusion and smoking history. In 1–3.5% of patients, partial or complete necrosis of the nipple–areola complex occurs as a complication, when radical excision in the retro-areolar plane is performed after skin- and nipple–areola complex-sparing mastectomies [8–10]. There was no complication related to simultaneous xenograft application. No major skin necrosis was seen. There was no reason to remove the PADM sheet in any patient.

Fibrotic formation

Two out of 23 (9%) patients presented with fibrotic retraction of the upper and ventral poles of the breast 3 and 5 months after surgery, respectively. No capsular contracture ranking higher than Baker class I arose during the follow-up period.

Rippling

Rippling was not be detected in any patient during the follow-up period.

Implant malposition

Implant malposition was seen in one patient with lateral protrusion of the implant and consecutive breast asymmetry. The implant malposition was due to initial iatrogenic lateral positioning and fixation rather than to postoperative dislocation, PADM herniation or suture dehiscence. There was no significant bottoming-out deformity in any patient.

Soft-tissue thinning

Soft-tissue thinning with consecutive dermal fistula was seen in one patient 7 weeks after surgery. The patient had a history of breast conservation in the same breast; the same segment had been identified as benign by histology 23 years ago. Minor perfusion of the scar tissue in this region in combination with nicotine-induced vasculopathy was assumed to have caused the soft-tissue thinning, which resulted in skin failure and skin fistula of the ventral implant. This condition was treated by excision of the fistula.

Aesthetic results

Twenty-one out of 23 patients (91%) were "very satisfied" or "satisfied" with the aesthetic results, when answering the questionnaire administered 4 weeks, postoperatively. This result was confirmed by physical examination at the same time-point. One patient had a nipple–areola hypoperfusion during the first week, and one patient was "not satisfied" with the aesthetic outcome. Eighteen out of 23 patients (78%) were "very satisfied" or "satisfied" with the aesthetic results after 6 months, as determined by questionnaire and confirmed by physical examination. One patient was "not satisfied" with the aesthetic outcome, one out of 23 patients (4%) displayed nipple–areola asymmetry of 1 cm, one out of 23 patients (4%) had complete nipple–areola complex necrosis and one out of 23 patients (4%) had partial nipple–areola complex necrosis on both sides.

Haptic results

Eighteen out of 23 patients (78%) were "very satisfied" or "satisfied" with the haptic results 4 weeks postoperatively, as determined by questionnaire and examination. Eighteen out of 23 patients (78%) were "very satisfied" or "satisfied" with the haptic results after 6 months, as determined by questionnaire and examination.

Sensory results

Eighteen out of 23 patients (78%) were "very satisfied" or "satisfied" with the sensory results after 4 weeks, as determined by questionnaire. Eighteen out of 23 patients (78%) were "very satisfied" or "satisfied" with the sensory results after 6 months, as determined by questionnaire.

Disease-free survival

One patient with invasive breast cancer experienced an ipsilateral intramammary recurrence, 6 months after the initial PADM-based surgery.

Table 1 Patient characteristics

	Patients
Indications	
Indication BC	16
Indication DCIS	5
Indication BC rec	2
Indication fibrous capsule	1
Indication BRCA 1/2	3
Reconstruction	
Single-stage reconstruction	15
Two-stage reconstruction	12
Risk situation	
Former radiation	10
Bilateral	4
Smoking history	2

Table 2 4-Week patient outcome

	Patients
Skin complications	1
Sensory result	
Good	18
Poor	5
Aesthetic result	
Good	20
Poor	3
Haptic result	
Good	18
Poor	5

Table 3 6-Month patient outcome

	Patients
Skin complications	2
Fibrosis	2
Rippling	0
Implant malposition	1
Soft-tissue thinning	1
Aesthetic result	
Good	18
Poor	5
Haptic result	
Good	18
Poor	5

Costs

The PADM material is available in firm and soft versions. The soft PADM version appears to be optimal for encapsulation of the convex implant. The soft PADM material

exists in two different sizes: 5 × 16 cm and 8 × 16 cm, both of which are disposable mesh. At the author's institution, the soft PADM material typically employed measured 8 × 16 cm and costs the patient 2350€ plus tax (currently 19% in Germany) per breast. The German health insurance system covers all or part of the cost, under the condition of prior application for PADM cost reimbursement for each surgery.

Discussion

Implant-based reconstruction is currently the method of breast reconstruction, most commonly performed after invasive and non-invasive ablative breast cancer surgery. Unfortunately, breast reconstruction with implants also has a number of disadvantages. Interaction of the anatomical site with the implant has a cumulative effect on the outcome of implant-based reconstruction. As a result of this interaction, numerous complications may arise after reconstruction. These include rippling, fibrotic capsular formation, implant dislocation, bottoming out and soft-tissue thinning with implant exposure [13]. The majority of these complications results from periprosthetic atrophy, capsular formation, inadequate soft-tissue coverage and inappropriate filling of the patient's breast pocket. In addition, the patient's individual tissue characteristics, such as history of radiation and smoking, degree of ptosis and lifetime soft-tissue changes, affect the implant–site interaction and the long-term outcome. In implant-based breast reconstruction, complete submuscular implant coverage ensures the best protection against implant exposure. This is achieved by reliable soft-tissue interface recruitment between the implant and the skin, resulting in a reconstructed breast with a natural contour. However, complete PMM coverage

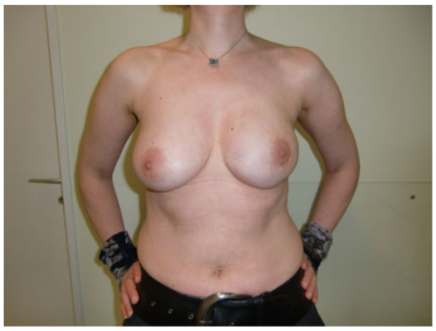

Fig. 1 Patient after breast conserving treatment, preoperative photo before skin sparing mastectomy and PADM based reconstruction

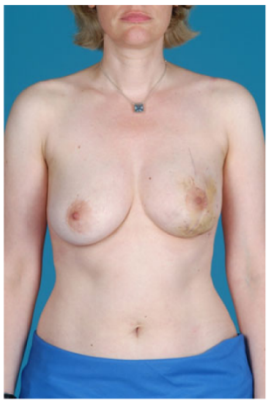

Fig. 2 Postoperative photo, patient after skin sparing mastectomy and PADM based reconstruction

results in more frequent upper-pole expansion and restricts lower-pole expansion [14]. Another challenging aspect of immediate implant-based breast reconstruction is that after skin-sparing mastectomy, the skin envelope loses all of the perforator-based blood supply emerging from the resected breast parenchyma and integrated adipose tissue. The insertion of a breast implant that is too large or overfilled further compromises the impaired postextirpative circulation [12]. Techniques using acellular allogeneic or xenogenic tissue as a PMM extension can allow for more rapid filling of the expander or safer immediate implant insertion and better control of the inframammary fold [6, 7]. The use of PADM as a connective tissue graft material in implant-based reconstruction is a new and promising surgical approach. PADM acts as a web with revascularizing functionality and as a biological barrier-scaffold for epithelial cell migration, allowing the tissue to achieve the appropriate contour [11]. The present case series demonstrates the application of a xenogenic dermal graft to create a submuscular space for the appropriately sized implant, to secure the perfusion of the vulnerable overlying skin and to supplement the muscle deficit of the lower breast pole. Alternatively, autologous tissue can be taken from the latissimus dorsi to supplement the lower pole. This technique has its own disadvantages, such as donor site morbidity, scarring and seroma formation [15].

During the follow-up period, the smoothing and emulating function of PADM was reproducible in our case series of 27 reconstructed sites. No graft problem arose during follow-up. The perfusion failure in the nipple–areola region occurring in two patients was due to extensive but oncologically necessary retro-areolar resection, and explainable by

patient history. The use of PADM at the inferolateral border helped to maintain the inframammary fold and to prevent implant exposure and camouflage rippling. Because of the short follow-up period, the safety profile could not be definitively assessed but was determined to be satisfactory during the follow-up period. The majority of the patients were "satisfied" with the aesthetic, haptic and sensory outcomes after PADM-based surgery. The high cost of PADM may limit widespread use of the material.

Conclusion

The use of PADM as an interface matrix for breast reconstruction is promising. Our study showed predictable, positive aesthetic results and reduced risks of fibrosis and failure of the silicone implant-based breast augmentation. The xenograft technique allowed immediate breast reconstruction with less risk of periprosthetic atrophy by achieving optimal breast contouring, simultaneously maintaining thicker muscle coverage in the upper and medial pole areas and stronger lower pole support. This eliminated many of the current disadvantages of implant-based reconstruction. Further follow-up and clinical trials are necessary to evaluate the efficacy and the long-term safety profile of PADM-assisted implant-based breast reconstruction. Our results are encouraging and should be validated in a larger cohort of women undergoing breast reconstruction (Tables 1, 2, 3; Figs. 1, 2).

Conflict of interest Neither the authors nor their immediate family members have indicated a financial interest or a personal relationship with persons or with the manufacturer organisations that could inappropriately influence their work. No conflict exists for devices used in the reported investigation.

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Article 4: Worldwide first experiences with vacuum-assisted closure as alternative treatment method to repair defects of an extended thoracic wall recurrence of breast cancer

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GYNECOLOGIC ONCOLOGY

Worldwide first experiences with vacuum-assisted closure as alternative treatment method to repair defects of an extended thoracic wall recurrence of breast cancer

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Abstract
Introduction Loco-regional recurrences of the breast cancer are associated with a bad prognosis. Often costly autologous-tissue treatment as a surgery aiming at repairing the defects is necessary.
Patients and methods Four female patients were treated with the vacuum-assisted closure (VAC)-system in context with the recurrence resection. In all cases a primary local masking was not possible.
Results In the described cases the wounds healed well during the post-operative phase. There occurred no problems either during the radiation treatment or during chemotherapy in the case of lying VAC-Systems.
Conclusion Using vacuum-assisted wound closure one can avoid autologous-tissue treatment in the case of extensive loco-regional recurrences.

Keywords Breast · Cancer · Recurrence · Vacuum-assisted closure (VAC)

Introduction

The 10-year loco-regional relapse rate after mastectomy comes to 10–15% and after breast conserving technique to 10–20% [1, 2]. There is no difference here between ductal and lobular carcinomas [3]. Frequently, within the context of the resection of these recurrences a masking with autologous tissue becomes necessary, as, e.g. with the latissimus dorsi muscle flap. This is a relatively laborious operation with a poor general prognosis. Serious complications of this procedure are partial necrosis up to the complete loss of the graft. In the case of latissimus-dorsi-flap operations this is the consequence reported for up to 8% of the female patients. Since in the case of a loco-regional recurrence often an axilla dissection has been previously performed, one has to be prepared for a more difficult depiction of the latissimus-flap-vessels. Accordingly, the rate of (partial) loss of flaps will be higher. Autologous tissue from the abdomen could be an alternative here and could improve the cosmetic result in terms of a reconstruction, but because of the additional tension it is often not practical [4]. Furthermore, the often bad general health of the female patients would have an additional negative influence in this respect. The donor-site morbidities are among the most common complications. This could be a limited movement and, in the case of pediculated grafts from the abdomen, hernias. Furthermore, there are the general risks of surgery such as thrombosis, seromas, hematomas, wound infection and secondary haemorrhage. Among them the development of seromas is frequent due to the big operation area [5]. In case of a big contra-lateral breast the latter can also be used for masking the defect [6]. On the other hand, the 10-year survival rate after recurrence sanitation following a mastectomy is 30% and after breast conserving treatment 50% [7].

By means of the vacuum-assisted closure therapy (VAC-therapy) many successful closures of bigger wounds were reported. Randomized studies have shown that VAC-therapy has improved the healing of open wounds significantly [8, 9].

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We considered whether this could also be applied within the context of the recurrence resection, in order to avoid laborious maskings with autologous tissue and thus to lower morbidity. Especially for loco-regional recurrences with simultaneous axilla infestation as well as in a condition after axilla dissection with iatrogenic severance of the thoracodorsal vessel bundles this procedure could prove to be a good alternative.

Often necessary additional therapies like radiation and chemotherapy can be carried out in the course of a VAC-therapy.

Patients and methods

VAC-therapy is a non-invasive wound closure system which causes a controlled, locally limited, negative pressure and thus accelerates the healing process in acute and chronic wounds. A sterile foam bandage with an open-cell structure is introduced into the wound defect, the area is sealed with an adhesive transparent plastic membrane, and afterwards a controlled negative pressure is used on the wound, either continually or intermittently, according to the type of wound and the therapeutic goal.

This helps to support the reduction of interstitial oedemas and at the same time increases the nutritive perfusion. The increased perfusion also leads to a better oxygenation as well as to the reduction of growth inhibitors and inflammatorily acting substances in the wound exudate. In different publications the mechanical tension induced on the tissue is declared the reason for the release of mediators which lead chemotaxically to an increase of the fibroblast migration and thus to a rise of the mitosis rate [10, 11].

For thousands of years silver has been used in the topical treatment of wounds, in previous times in the form of silver nitrate (Credé-Prophylaxis) as antiseptics or in burn ointments; nowadays it is mainly inserted in wound pads. Silver has an antimicrobial effect and is only slightly toxic. Thus, foams with a silver layer are available for the VAC-therapy of infected wounds.

At present the Vacuum Therapy is contraindicated in the case of patients with the following:

- incomplete debridement
- bare vessels or organs
- malignancy within the wounds
- non-treated osteomyelitis
- non-explored fistulas
- active haemorrhages
- anticoagulants
- difficult wound hemostasias.

At first the treatment of the wound is given on an in-patient basis. After the debridement, appropriate foam is inserted and connected to the VAC-System. During this process it is important to ensure that the vacuum does not escape through points in the membrane which are not airtight. Every 4–5 days the foam has to be changed. The therapeutic goal is the closure of the wound or rather the granulation at skin level. This would be the final point of the VAC-therapy. Problems during the VAC-therapy occur due to improper application. If the foam gets into direct contact with organs such as, e.g. skin surface, intestine or blood vessels, it will result in erosions. A variety of training seminars shall secure the correct handling of the system. Meanwhile, a lot of nurses, specialized in this system, assure the patients good medical care, not only at the in-patient level but also at the out-patient level. The good wound-treatment by trained nurses makes a regular medical wound control dispensable. In the case of problems though, medical wound control becomes necessary. Therefore, it is important for the nursing care that the patients are connected with specially trained nurses and that there is a good co-operation with likewise trained medical personnel. A further prerequisite is a good compliance of the female patients. The latter should inform the nurses as soon as the VAC-System has a leak or blood has entered the system. Furthermore, one should take care that the foam is positioned well in order to avoid contact with any organs.

It cannot be stated how much the patients' quality of life is reduced by the permanent carrying of the VAC-System. The studies which examine the quality of life in correlation with the VAC-therapy compared it with the conventional treatment of open wounds. There is an improvement of the quality of life was achieved [12–17]. Through the introduction of the portable VAC-Systems the satisfaction of the patients has certainly increased, since it allows them the integration into everyday life.

Examples of VAC-Systems are the Vacuum Assisted Closure (VAC®) (KCI, San Antonio, Texas, USA) and the Chariker-Jeter® Wound Sealing Kit (BlueSky Medical Group, Carlsbad, California, USA).

Altogether four female patients with local recurrences of breast cancer were treated with the VAC -System.

The first patient was a 61-year-old woman. She was diagnosed with breast cancer on the outside left, close to the submammary fold in 1993: G2, pT1c, pN0 (28), M0. The breast-conserving therapy with ensuing radiation was conducted. Because of asymmetry an equalization-reduction mammaplasty was applied on the right. In 2005, a local recurrence in the submammary fold/parasternal was found and completely excised. Because of the danger of overlapping radiation fields, radiation was not performed after consultation with the radiotherapist who was in charge then. Afterwards, the patient with a hormone-receptor-positive result received a therapy with Anastrozol 1 mg (Arimidex®), which was changed due to intolerance 7/2006

to Letrozol 2.5 mg (Femara®). Once again, in September 2006 a local recurrence was located in the same area. The area on which a resection was to be performed measured 10 × 5 cm. The options of chemotherapy versus surgical sanitation were discussed with the patient. On September 5, 2006 the excision with inserting the V.A.C.-Foam System was conducted. After about 4 weeks a radiation was performed for 5 weeks on the lying system. Overall, there were 25 sessions (20 × fractionated + 5 × boost) of radiotherapy with altogether 50.0 Gy applied. During the entire radiotherapy the granulation progressed. After additional 4 weeks the wound had spontaneously closed (Fig. 1).

During the entire time the foam was changed every 4–5 days. The period from the primary excision to the skin closure lasted 95 days. The costs for the therapy amounted to 2,850 €. In the further course the patient was diagnosed at the end of 2007 with osseous metastases in the entire area of the thoracic and the lumbar spines, axilla metastases and smaller skin metastases were found. A therapy with Bisphosphonate (Aredia®) was started. Furthermore, a conversion to Exemestan (Aromasin®) was undertaken. The patient died 2.3 years after the masking of the defect as a result of the diffuse metastatic invasion.

The second patient was a 66-year-old woman. She was diagnosed with an inflammatory breast carcinoma on the left in January 2007. Already in the computed tomography there were primarily described diffuse hepatic, pulmonary and osseous metastases. She received a primary systemic therapy with six cycles FEC as well as Bisphosphonate infusions (Aredia®); furthermore, an endocrine therapy with Anastrozol 1 mg (Arimidex®), which was due to the progress was changed to Exemestan 25 mg (Aromasin®) in January 2008. Under the chemotherapy a partial remission of the liver metastases (25% volume reduction) and clinically complete remission in the breast area developed. But in December 2007, the liver values were increasing again and with a sonography a progress of the metastatic invasion of the liver was diagnosed. Locally there was also a tumour progress with impending ulceration. The ablation and the inserted VAC-System were discussed with the patient and performed on 31 January 2008 (Fig. 2). The post-operative progression was without any complications. The wound had clearly shrunk under the repeated change of the VAC-Pump and was about to heal. An endocrine therapy with Tamoxifen was started and the Bisphosphonate therapy carried out. On 20 February 2008, the patient's general health deteriorated rapidly and she died on 29 February 2008 mainly due to her pulmonary complications.

In the case of the third patient, a 64-year-old woman, breast cancer on the left with primary pulmonary metastases was diagnosed in February 2007. In the same month the atypical complete lung resection followed. She primarily received a weekly palliative chemotherapy with Epirubicin (02–06/07). Afterwards, the lumpectomy of the left mamma followed with an axilla dissection and completion of the chemotherapy (Epirubicin) over altogether 21 cycles. A palliative radiation of the left breast, including the drainage areas, took place from October to December 2007. Since a lymphangiosis carcinomatosa of the left breast occurred in February 2008, a therapy with Taxol 80 mg/m^2 (8 cycles) followed. Nevertheless the result progressed further. With impending ulceration the ablatio mammae followed with inserted VAC-System on April 2008 (Fig. 3). Afterwards followed the therapy with Vinorelbin (Navelbine®) on an extended lymphangiosis carcinomatosa in the area of the left thoracic wall of the left axilla with extensions into the back. The wound clearly shrunk after repeated change of the VAC-Pump and was about to heal. This patient also died as a result of a diffuse metastatic invasion 6 months after the masking of the defect.

In the case of the fourth patient, a 64-year-old woman, breast cancer was diagnosed in August 2007. Because of its size, a neoadjuvant chemotherapy with FEC was performed. It was followed by a lumpectomy and axilla dissection (3/08: ypT1b, ypN2a, L1, V0, G2, R0, M0) with post-operative radiation. Already in January 2009 mastectomy and axilla revision were conducted at a local recurrence. Only 2 months later a new thoracic wall recurrence without distant metastasis appeared. In March 2009

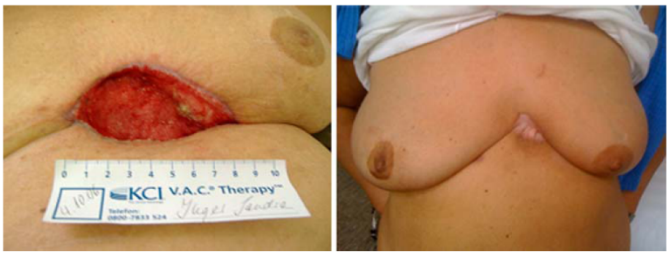

Fig. 1 Patient 1; post-operative (wound w/h/d:10/8/4 cm) and after 13.5 weeks

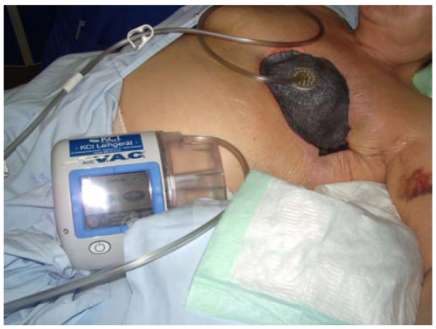

Fig. 2 Patient 2 after the VAC-System was applied

followed another excision with inserted VAC-System. The wound granulated at skin level and was covered with mesh in May 2009 (Fig. 4).

Results

In the case of the first patient, the wound above the sternum was covered with granulation tissue by means of the VAC-System within 4 weeks. Afterwards radiotherapy was performed. The course of the healing process was unproblematic. The skin defect was closed after 13.5 weeks. The patient died 2.3 years after the masking of the defect as a result of the diffuse metastatic invasion.

In the case of the second patient, we were able to identify a wound reduction, but she died before the complete wound closure as a result of her metastatic invasion.

In the case of the third patient, there was also a wound reduction visible. The chemotherapy with Vinorelbin (Navelbine®) was performed simultaneously without any complications. This patient also died as a result of her metastatic invasion 6 months after the masking of the defect.

In the case of the fourth patient, we covered the wound granulation on skin level with mesh. Three months later the local recurrence appeared once again with an extensive lymphangiosis up to the middle of the back. At present she is receiving a chemotherapy with Vinorelbin (Navelbine®).

Discussion

In the cases of all these patients a laborious operation to mask the defect with autologous tissue was avoided by using the VAC-System. With a lying VAC-System it was even unproblematic to conduct the radiotherapy with the first patient and the chemotherapy with the third patient. Thus, a necessary additional therapy was no contraindication. It has to be noted that foams with silver particles should not be used during the radiation.

The costs of the VAC-therapy have to be individually negotiated with the company according to the respective

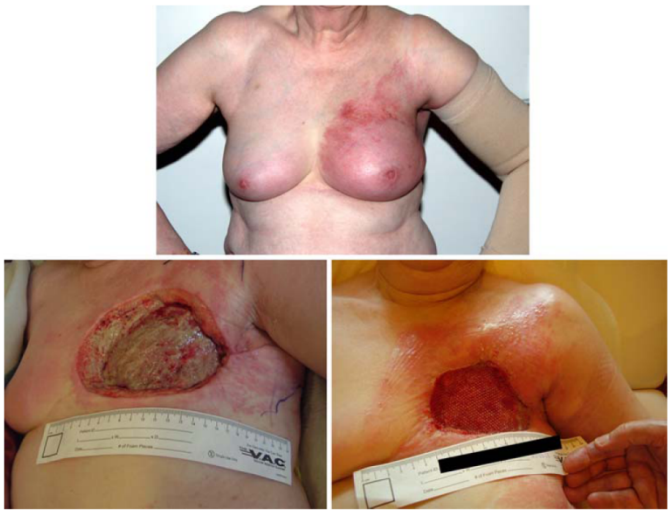

Fig. 3 Patient 3; pre-operative, post-operative (wound w/h/d: 22/16/4 cm) and after 10 days of treatment (w/h/d: 9/5/1 cm)

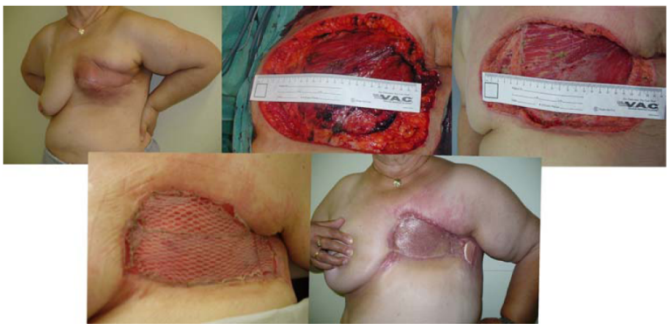

Fig. 4 Patient 4; pre-operative, intra-operative (wound w/h/d: 25/22/4 cm), after 57 days of treatment (w/h/d: 16/20/1 cm), after covering with mesh on the 67th day. Local recurrence 40 days after covering with mesh

hospital. 7 days of VAC-therapy consists of two dressing changes with foam and a canister to collect the secretion. The total costs amount to 210.28 €/week in the case of the company KCI. The stated price is valid for the clinics of the University of Munich.

Usually the patient can leave the clinic after 5 days. The vacuum pump is put into a portable bag so that the mobility does not get limited. There are data on the quality of life of patients under VAC-therapy versus the conventional therapy for the treatment of open wounds. They show an improvement of the quality of life [12–17]. Until now a comparison between the VAC-therapy and the primary masking with autologous tissue has not been undertaken though. The fact that from time to time the female patients have to live with the VAC-System for several weeks argues in favour of a surgical masking. This would have to be investigated. The change of the dressing has to be conducted every 4 days and can be done during out-patient care.

A latissimus-dorsi transfer of autologous tissue would be the operative alternative in all three cases. The proceeds of the two procedures clearly differ (Table 1).

Mostly the saved operation time for the plastic covering of the defect cannot balance this difference. Thus, the clinic has to optimize this in the negotiations with the health insurance companies. As to the cases of the second and the third patients, the question is whether the ablation would have improved the prognosis. Since metastatic conditions of the above-mentioned patients differed, one can only speculate. The impending ulceration confronts women with cosmetic problems though and is mostly accompanied by the development of a distinct smell. In these cases we prefer the ablation after a failed systemic therapy. Especially the second, third and fourth cases show that the masking with autologous tissue increases morbidity, while having the same unfavourable prognosis.

During our research we reviewed the literature and did not find any other publication on the topics "Vacuum-Assisted Closure" and "Cancer", so this seems to be the first approach to this surgical technique in the case of cancer.

Comment

By applying the VAC-therapy in cases of thoracic wall recurrences or extensively therapy-resistant local recurrences after breast reconstruction, a masking with autologous tissue can be avoided. Since as a rule the prognosis is reduced, this therapy with low morbidity is a good

Table 1 Cost difference among various techniques according to the DRG at the LMU-München

Type of the operative care	DRG-costs (LMU München)
Excision of a thoracic wall recurrence with an inserted latissimus-dorsi flap	5.976 €
Excision of a thoracic wall recurrence and VAC-therapy	1.917 €
Difference	−4.059 €
Ablation in the context of an extensive local recurrence with an inserted latissimus-dorsi flap	5.977 €
Ablation in the context of an extensive local recurrence and VAC-therapy	4.275 €
Difference	−1.702 €

Article 5: Survival analysis between patients with invasive ductal and invasive lobular breast cancer

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ORIGINAL ARTICLE

Survival analysis between patients with invasive ductal and invasive lobular breast cancer

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Abstract
Objective Differences in overall survival (OS) and disease-free survival (DFS) between patients with invasive ductal (IDC) and invasive lobular breast cancer (ILC) are controversial.
Study design The study population was selected from a database of 5,689 female patients with invasive breast cancer. In order to focus on the impact of tumour histology, all primary metastatic patients and patients with adjuvant chemotherapy or anti-hormonal treatment were excluded. Only patients with pure invasive lobular and invasive ductal histology were included.
Results Multivariate survival analyses of 2,058 eligible patients confirmed tumour histology as an independent prognostic factor for OS in invasive breast cancer ($p = 0.046$) but not for DFS ($p = 0.599$). Kaplan–Meier survival analysis of OS between IDC and ILC patients showed a statistically significantly better OS for patients with ILC ($p = 0.0302$). DFS was not statistically different ($p = 0.6659$) between IDC and ILC. Univariate survival analyses of tumour size, tumour grading and nodal status in our study population were highly statistically significant for OS and DFS ($p < 0.0000$).
Conclusion Patients in our study population with ILC have significantly better OS than patients with IDC. Differences in DFS are not statistically significant.

Keywords Breast cancer · Ductal · Lobular · Survival

Darius Dian and Hannes Herold contributed equally to this manuscript.

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Introduction

Breast cancer is a histologically heterogeneous malignancy. It is the most commonly diagnosed carcinoma in women, in the industrialized world. Invasive ductal carcinoma (IDC) is the most frequent histological subtype comprising approximately 75–80% of all invasive breast cancers. Incidence rates of invasive lobular carcinoma (ILC) are increasing and range between 5 and 17% [1–6].

There has long been controversy about the impact of invasive lobular and invasive ductal histology in breast cancer on overall survival (OS) and disease-free survival (DFS). Some authors have found a difference between IDC and ILC [7–12] while most authors have not found any significant discrepancies between the two histological subtypes [13–21]. Looking at the date of publication of the individual studies there is no trend indicating changing differences in survival over time. Also, the quality of the studies which find a difference in survival and of those that don't is rather similar. Thus, the controversy about which histological type has better OS or DFS remains.

In order to contribute further in this controversy we have analysed our database of 5,689 female patients with invasive breast cancer by univariate and multivariate survival analyses.

Materials and methods

Study population

Our study population was selected from a database of 5,689 female patients with invasive breast cancer at the Departments

of Gynaecologic Oncology at the Free University of Berlin-Charlottenburg between 1963 and 1987 and at Ludwig Maximilian University of Munich between 1987 and 2004. The switch occurred because the initiator of the database transferred from Berlin to Munich. This database was established in 1963 and has been continuously updated. Follow-up of all patients has been conducted according to the regularly updated guidelines by the interdisciplinary Munich Tumor Center [http://tzm.web.med.uni-muenchen.de/] founded by the Medical faculties of the Ludwig-Maximilians-University and the Technical University of Munich.

We included all female patients on whom information on age at primary diagnosis, tumour histology, tumour size, histological grading and nodal status was available. Histological diagnoses at the Free University Berlin were made by the Division of Gynaecologic Pathology within the Department of Obstetrics & Gynaecology. At the University of Munich histological diagnoses were made by the Division of Gynaecologic Pathology within the Department of Obstetrics & Gynaecology until December 2002 and by the Institute of Pathology of the University of Munich from December 2002 to 2004. Patients with mixed ductal and lobular histology were excluded from our analysis as were patients with special histological subtypes, such as tubular, mucinous or medullary carcinomas. Information on hormonal receptor status as well as data on HER-2/neu status was not used in our current analysis.

Our focus of interest was the pure impact of different histological subtypes on OS and DFS. We therefore, excluded all metastatic patients and all patients who had received adjuvant anti-hormonal therapy or adjuvant chemotherapy. This was decided upon as the dramatic impact of today's evolving adjuvant regimes and the metastatic situation would have significantly altered the patients' prognosis. Hereby, the focus on the pure histology would have been disturbed. Patients who were only microscopically positive for micrometastases in the bone marrow were not excluded.

Statistical methods

Statistical tests were performed using the SPSS 12.0® statistical software for Windows (SPSS Inc., Chicago, IL, USA) and SAS Version 8.0 (SAS Institute Inc., Cary, NC, USA). Statistical analyses were conducted by a professional statistics agency [www.estimate.de].

OS was defined as the period between the first diagnostic biopsy and death caused by breast cancer-related complications, death being counted as an event. Patients who were still alive were censored at the time of the last follow-up. Other causes of death were also censored.

DFS was defined as the period between the first diagnostic biopsy and the first local or distant recurrence, each being counted as an event. All patients were censored at the time of the last follow-up.

OS and DFS survival analyses were conducted using the Kaplan–Meier product-limit method [22] and were compared using log rank tests. Multivariate analyses of OS and DFS were conducted using Cox proportional hazard regression models.

Results

First, we analysed differences in OS between IDC and ILC patients. A systematic search of our data base of $n = 5{,}689$ patients with invasive breast carcinoma resulted in a study population of $n = 2{,}058$ eligible female patients on whom data on OS was available and who were non-metastatic and had received no adjuvant hormonal- or chemotherapy. Population's characteristics are shown in Table 1. Patients were followed over a median period of 57 months with a maximum follow-up period of 583 months. Of the patients eligible for OS analysis, 80% were characterized by pure invasive ductal histology and 20% were classified as pure invasive lobular histology. The percentage of patients with ILC hereby is larger than frequently stated in the literature. Moreover, in the whole study population there is a marked and disproportionate increase of the incidence of patients with ILC breast cancer when looking at incidence rates before 1985 and between 1985 and 2002. An increase in the incidence of ILC has also been noticed by other authors [1, 5].

Multivariate Cox regression analyses were performed to see whether tumour histology was an independent prognostic factor for OS. Nodal status, tumour size and tumour grading were included as covariates in the model. Results regarding OS were calculated for breast cancer-related death and showed that tumour histology was a statistically significant prognostic factor for OS ($p = 0.046$). Nodal status ($p < 0.000$), tumour size ($p < 0.000$) and tumour grading ($p = 0.000$) were also significant in the multivariate analyses. Kaplan–Meier survival analysis of OS between IDC and ILC patients resulted in a statistically significant better OS for patients with ILC ($p = 0.0302$/Hazard-Ratio 0.732/95%-CI 0.543–0.986) (Fig. 1).

In order to confirm that our study population is representative regarding OS as far as the other established prognostic factors are concerned we also conducted univariate survival analyses. Hereby, tumour size, tumour grading and nodal status were highly statistically significant ($p < 0.0000$).

Analogously, we analysed differences in DFS between IDC and ILC patients. Again, multivariate Cox regression analyses were performed to see whether tumour histology was an independent prognostic factor for DFS. Nodal status, tumour size and tumour grading were included as

Table 1 Population characteristics

	Duct	Lobular	Total
Tumour size			
0–10	250	91	341
11–20	833	170	1,003
21–30	384	100	484
≥31	163	47	210
Missing	17	3	20
Total	1,647	411	2,058
Not involved			
0 LN	1,383	356	1,739
1–3 LN	152	32	184
4–9 LN	84	12	96
≥10 LN	20	8	28
Missing	8	3	11
Total	1,647	411	2,058
Grading			
G1	160	68	228
G2	1,002	158	1,160
G3	367	34	401
Missing	118	151	269
Total	1,647	411	2,058
Age			
≤49	385	88	473
50–59	425	123	548
60–69	429	111	540
70–79	333	66	399
≥80	71	23	94
Missing	4	0	4
Total	1,647	411	2,058

covariates in the model. Results regarding DFS did not reach statistical significance as far as tumour histology is concerned ($p = 0.599$). The other established prognostic factors incorporated in the multivariate analysis all reached statistical significance ($p = 0.000$).

Also, Kaplan–Meier survival analysis resulted in no statistically viable differences in DFS between IDC and ILC patients ($p = 0.6659$) (Fig. 2).

In order to confirm that our study population is representative regarding DFS as far as the other established prognostic factors are concerned we again conducted univariate survival analyses. Hereby, tumour size, tumour grading and nodal status were statistically significant ($p < 0.0000$).

Discussion

There has long been controversy about the impact of different histological subtypes on OS and DFS in invasive breast

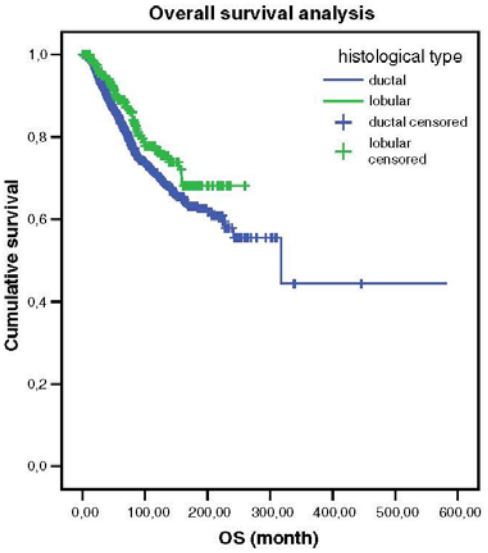

Fig. 1 Kaplan–Meier survival analysis of overall survival (OS) between invasive ductal (IDC) and invasive lobular (ILC) breast carcinomas: $N = 2058$. The cumulative survival time (Cum. survival) is shown. $p = 0.0302$

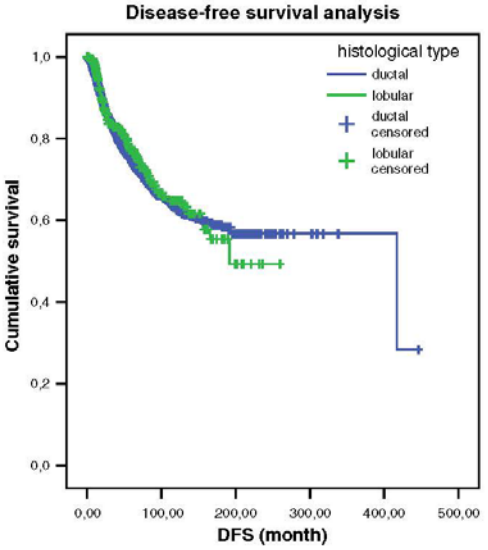

Fig. 2 Kaplan–Meier survival analysis of disease-free survival (DFS) between invasive ductal (IDC) and invasive lobular (ILC) breast carcinomas: $N = 2,058$ The cumulative survival time (Cum. survival) is shown. $p = 0.6659$

This phenomenon, in turn, could lead to more frequent local recurrences, which have a negative impact on DFS. Since the local disease in invasive breast cancer is secondary concerning OS, the more favourable tumour biology of ILC could still ultimately lead to better OS.

Considering the increasing numbers of patients with ILC both in Europe and in US it will be interesting to follow these patients in the future with regard to DFS and OS.

Conflicts of interest The authors declare that there are no considerations or conflicts of interest.

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alternative. Particularly additional necessary therapies, such as radiation and chemotherapy, can be performed during a VAC-therapy. The costs have to be negotiated with the insurance companies.

Conflict of interest statement None.

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Eidesstattliche Versicherung

Ich, Darius Dian, erkläre hiermit an Eides statt, dass ich die vorliegende Dissertation mit dem Thema:

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