Abstract. Background/Aim: Totally implanted venous access devices (TIVADs) are increasingly used in the treatment of cancer patients. The aim of this study was to assess the incidence of early and late complications resulting from subcutaneous TIVADs in patients with breast cancer. Materials and Methods: Between 2004 and 2009, we reviewed patients with breast cancer who had a TIVAD placed. Early and late complications, as well as risk factors for TIVAD-associated thrombosis were retrospectively assessed. Results: A total of 281 patients were included. Complications occurred in 26% of patients, the majority of which were late complications (21.4%). The development of TIVAD associated thrombosis was the most frequent late complication (16.4%). In the univariate analysis followed by a multivariate model, risk factors for TIVAD associated thrombosis were not identified. Only within the subgroup of metastatic breast cancer patients an increased risk of TIVAD-associated thrombosis of left compared to right venous access was detected (p=0.015). Conclusion: TIVAD implantation done in a gynecological outpatient setting is feasible and safe.

Totally implanted venous access devices (TIVADs) are increasingly used in the treatment of cancer patients (1, 2). These patients often require for administration of subsequent chemotherapies, nutritional solutions or blood products, especially in metastatic disease. Therefore TIVADs, providing a comfortable, safe and easy-to-handle vascular access, represent a major advance in the treatment of these patients. Different techniques have been established to facilitate and optimize the implantation of these port systems (3-6). The first venous access system was established by Hickmann (7). However, this original method of insertion consisted of percutaneously tunneled device that had an external access and was associated with several infections. The introduction of TIVAD in 1980 lowered the infection rates and facilitated implantation technique (8). The application of ultrasound, radiological and electrocardiography (ECG) guidance further simplified the placement. This advance resulted in a broad use of TIVADs nowadays. Devices are therefore placed by different medical subspecialties, i.e. surgeons, radiologists or gynecologists (1). Most surgeons traditionally use the surgical cut down technique on the cephalic vein. Alternatively, a percutaneous approach by the Seldingers technique to the subclavian or internal jugular vein is possible, often done by radiologists. A recent study suggests that all these insertion modalities are safe and feasible when performed by experienced users (6). Nevertheless, implantable ports also frequently lead to short-term and long-term adverse events (1, 9). They can emerge as immediate intraoperative complications like pneumothorax and malposition or delayed complications such as malfunction, thrombosis or infection. The incidence and association of these complications to clinical parameters for example such as tumor stage may vary between different tumor types. For example, the incidence of catheter-associated vein thrombosis considerably varies between solid tumors and hematological malignancies (10-13). These complications have not yet been broadly analyzed in a homogenous patient cohort with breast cancer (BC). The aim of the present study was to evaluate early and late complications resulting from ECG-guided subcutaneous TIVAD implantation in homogenous cohorts of primary and metastatic breast cancer patients and to identify possible risk factors contributing to these complications.
Materials and Methods

This study included breast cancer patients who had a subcutaneous implantable venous access devise (TIVAD) placed between January 2004 and November 2009 at the Department of Gynecology in the University of Frankfurt. After obtaining ethical approval from the Ethic Committee of Frankfurt University Hospital and patient’s informed consents, we identified 281 breast cancer patients which were planned to receive systemic chemotherapy. All patients were followed through December 2009 or until death, catheter failure, or catheter removal.

Device type and implantation techniques. Two different insertion techniques were used: surgical cut down to the cephalic vein or if not possible direct puncture of the subclavian vein according to the anatomical landmark technique with ultrasound guidance. All devices were inserted by a gynecological oncologist in the operating theater using maximal sterile-barrier precautions in an outpatient setting, predominantly performed in local anesthesia. No prophylactic medications, i.e. antibiotics or anticoagulation, were used. The device was placed on the pectoral fossa after ECG-guided positioning of the catheter tip and being checked postoperatively by chest X-ray. No radiographic guidance was used prior to device placement. Two similar low-profile silicone ports systems were used, different in profile height (12.2 mm vs. 13.5 mm) and external diameter of the tube (2.2 mm vs. 2.8 mm). Selection of device was made according to physician’s discretion. Postoperative assessment of the TIVAD-Position was done by chest-X-ray and described by the radiologist as central (i.e. placement in the lower third of superior vena cava), pre-central (i.e. placement in the upper third of superior vena cava) or malpositioned. Complications. Complications were grouped into two main categories:

(1) Early complications, occurring intraoperatively or prior to device usage such as pneumothorax or malposition.

(2) Late complications, occurring after first usage including TIVAD-dislocation, infection, leakage or thrombosis.

Statistical analysis. Statistical analysis was performed using SPSS 23.0 software. To assess risk factors for thrombosis, univariate analysis was performed using log-rank test or univariate cox. A multivariate Cox regression model was then used to assess the relationship between baseline factors and occurrence of thrombosis. The Kaplan–Meier method was used to calculate event-free survival. Comparison of two or more groups of discrete variables was performed using Fisher’s exact test or the χ² test. All p-values were two sided, and p<0.05 was considered significant. However, because of the retrospective exploratory character of the analyses, even significant p-values were supposed to generate hypotheses only.

Results

In 281 patients with breast cancer a TIVAD was implanted for subsequent chemotherapy between January 2004 and November 2009. Of these women, 203 were primary conditions and 78 patients had metastatic disease. The mean age of the patients was 51.7 in the primary breast cancer group and 56.6 for the metastatic group. The patient characteristics of the whole cohort are displayed in Table I.

Table II summarizes the characteristics of TIVAD-implantation for the whole population. In 79.3% of the patients TIVADs were implanted in the cephalic vein whereas 20.7% in the subclavian vein. A significant difference in the mode of anesthesia between both cohorts was found, as 11.3% of primary breast cancer patients had TIVAD implantation in general anesthesia versus 2.6% in the other group (p=0.019). This higher rate may be due to the more frequent concomitant TIVAD implantation during primary breast surgery in this group of patients.

The median duration of TIVAD indwelling of the entire group with available follow up was 74 weeks (range=1-350 weeks). Primary breast cancer patients had a longer TIVAD indwelling time (84 weeks; range=1-350 weeks) when compared to patients with metastatic breast cancer (62 weeks; range=1-326 weeks). Regarding the side of implantation, no difference could have been identified between both groups as 53.2% of TIVADs were placed on the right side as compared to 46.8% on the left side (p=0.43). The radiographic control postoperatively showed altogether a correct position of the TIVAD in 93.6% of the patients.

### Table I. Patient characteristics.

| Parameter | Primary BC n (%) | Metastatic BC n (%) | p-Value |
|-----------|------------------|---------------------|---------|
| Total     | 203              | 78                  |         |
| Mean age (SD) | 51.7 (11.2) | 56.6 (11.2) | 0.001 |
| Age ≤50  | 97 (47.8%)       | 21 (26.9%)          |         |
| Age >50  | 106 (52.2%)      | 57 (73.1%)          |         |
| Tumor stage |                   |                     |         |
| T1       | 78 (39.4%)       | 21 (30.9%)          |         |
| T2       | 88 (44.4%)       | 25 (36.8%)          |         |
| T3       | 26 (13.1%)       | 5 (7.4%)            |         |
| T4       | 6 (3.0%)         | 17 (25.0%)          |         |
| Nodal stage |                 |                     |         |
| N0       | 92 (45.8%)       | 24 (35.3%)          |         |
| N1       | 75 (36.9%)       | 29 (42.6%)          |         |
| N2       | 19 (9.5%)        | 8 (11.8%)           |         |
| N3       | 15 (7.5%)        | 7 (10.3%)           |         |
| Grade |                   |                     |         |
| G1       | 2 (1.0%)         | 4 (6.5%)            |         |
| G2       | 83 (42.6%)       | 28 (45.2%)          |         |
| G3       | 110 (56.4%)      | 30 (48.4%)          | 0.038   |
| Histology |                   |                     |         |
| Ductal carcinoma | 175 (89.3%) | 58 (81.7%)         |         |
| Lobular carcinoma | 16 (8.2%) | 11 (15.5%)         |         |
| Other    | 5 (2.6%)         | 2 (2.8%)            | 0.21    |
| Surgical procedure |       |                     |         |
| Lumpectomy | 94 (48.7%) | 30 (41.1%)         |         |
| Mastectomy | 89 (46.1%) | 35 (47.9%)         |         |
| Other    | 10 (5.2%)        | 8 (11.0%)           | 0.19    |

BC: Breast cancer.
Early complications were represented in malposition and pneumothorax. Their occurrence showed no significant difference in both cohorts (3.9% and 6.4%, \( p=0.75 \)). The overall rate of pneumothorax was 1.4%. Malposition occurred in 3.2% of all women. Also, regarding late complications no significant difference could have been identified between patients with primary breast cancer and patients with metastatic disease that received a TIVAD for chemotherapy. These late complications occurred in 19.7% and 25.5% of cases with primary and metastatic disease respectively (\( p=0.75 \)). The overall infection rate was 3.2% (9 patients). Of these, 7 ports had to be removed in addition to antibiotic therapy because of progressive infections.

The development of a TIVAD associated venous thrombosis was the most frequent late complication (n=46, 16.4%). The rate of TIVAD associated thrombosis was slightly but significantly higher in the primary breast cancer cohort (17.2% versus 14.1%, \( p<0.001 \)). The median dwelling time in this group of patients was decreased (62.5 weeks, \( \text{range}=13-248 \) weeks) when compared to the non-thrombosis group (81 weeks, \( \text{range}=1-350 \) weeks) (Figure 1). A subgroup analysis pointed out that occurrence of thrombosis did not reduce indwelling duration in metastatic breast cancer (Figure 1). In the univariate analysis followed by multivariate model, no significant impact on the occurrence of a TIVAD thrombosis in the entire population could have been shown (Table IV): Neither for tumor specific prognostic markers like TNM stage, grading, histological subtype nor for patient specific factors like age, treatment modalities, implantation side and type of venous access. Only in the subgroup of metastatic disease the implantation on the left side was associated with shorter time of thrombosis development (Figure 2).

Leakage and dislocations did not occur in the primary group. Only three women with metastatic disease had leakage of their TIVADs as well as 2 patients by whom TIVAD was dislocated.

### Discussion

Venous access device systems are nowadays widely used in cancer patients to facilitate frequent perfusions of chemotherapy (11). The placement of totally implanted venous access devices started 30 years ago (8). Since then different techniques were established to reduce complications and to make the implantation safe and comfortable for patients (14, 15). However, the trials evaluating the incidence of catheter related complications were often inhomogeneous because of the inclusion of various tumor entities and different implantation techniques. Biffi and colleagues were
able to show the equivalence of the three mostly used implantation techniques, i.e., percutaneous puncture of the internal jugular vein ("blind" via anatomical landmarks), ultrasound-guided access to the subclavian vein and surgical cut-down access to the cephalic vein (6). In our series, we only included breast cancer patients that were preplanned to receive an intravenous chemotherapy. Devices were only implanted by surgical cut-down technique or secondary by ultrasound-guided subclavian puncture. Misplacement occurred in only 9 of 281 (3.2%) cases showing that port implantations by a gynecological surgeon in an outpatient setting is feasible.

In terms of early complications, our findings are comparable to the results of other studies described in the literature. We found a total early complication rate of 4.6% (13/281) consisting of 9 misplacements and 4 pneumothoraces. All
patients that experienced a pneumothorax had a secondary “blind” puncture of the subclavian vein due to technique failure. The rate of pneumothorax is similar to the results of Granziera et al. However, our technique failure rate was lower than the reported failure rate of Granziera et al. which may demonstrate that the secondary puncture of the subclavian vein using the landmark technique is feasible and safe even without US-guidance when performed by an experienced surgeon. These results are partly in line with other authors who showed no clear benefit for the ultrasound guided cannulation of the subclavian vein (17, 18). Nevertheless, other authors recommend a systematic use of ultrasound guidance for all vascular access because of a significant advantage for other insertion sites like the internal jugular vein (19). This recommendation is also supported by another trial showing a lower complication rate as artery puncture, hematoma and pneumothorax and a shorter access time even for the US-guided puncture of the subclavian vein (20).

The most frequent complication in both cohorts was the development of a TIVAD associated venous thrombosis with a rate of 16.4%. This result is consistent with data reported by other trials. The occurrence of catheter-related thrombosis was described in a systematic review as a wide range varying from 0.3% to 28.3% (21). In our study the median dwelling time of the TIVAD group of patients experiencing a venous thrombosis was decreased (62.5 weeks, range=13-248 weeks) when compared to the non-thrombosis group reflecting thrombosis as the most significant impact of all complications. In this context, the peripheral position of the catheter tip was not associated with a higher thrombosis rate. On the other hand, the TIVAD-Position control done by postoperative chest-X-ray was central in most patients, stressing on the efficacy of the intraoperative ECG assessment of positioning. Nevertheless these findings differ from other investigations showing a higher rate of thrombosis and malfunction (1, 22, 23). One explanation could be the homogenous cohort of adjuvant breast cancer patients in our trial emphasizing the importance of a separate analysis of various tumor entities.

Another important finding of our study is the missing impact of the implantation side of the TIVAD on the development of thrombosis. Only in the subgroup of metastatic breast cancer patients, the left-sided implantation of the device resulted in a higher risk of thrombosis. These results are similar to other studies. Ignatov et al. showed a higher rate of complications after the implantation on the left side (1). However, in his trial the heterogeneous cohort might have influenced the results. In our study the TIVAD implantations were exclusively done by gynecologic oncologists, performing an ultrasound- and ECG-guided positioning of the catheter without intraoperative radiological imaging. The failure rate was low. Nevertheless, this might lead to a slightly elevated incidence of TIVAD associated thrombotic events because of higher microscopic endothelial lesions during implantation procedure. Regarding the two different types of the TIVAD no significant impact of low vs. standard profile was seen on the incidence of complications.
Furthermore, we did not observe any complications due to high-pressure injections (so called “power injections” of contrast media) like damage of the device. Nevertheless, other authors clearly pointed out this problem (24). In our trial the high rate of adjuvant breast cancer patients did not make it necessary to perform frequent CT scans with high density contrast media, and therefore underrepresenting this type of complication.

Taking into consideration the retrospective nature of our analysis, this failed in terms of identifying any predictive factors for TIVAD-related thrombosis.

Conclusion

The implantation of TIVADs is a safe and beneficial procedure, independently of catheter profile. It can be reliably performed in a gynecological outpatient setting. Our data suggest no difference in terms of early and late complications between primary and metastatic breast cancer patients. Predictive factors for TIVAD-associated thrombosis could not have been identified.

Conflicts of Interest

The Authors have no conflicts of interest to disclose regarding this study.

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