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Incidence of and risk factors for totally implantable vascular access device complications in patients with gastric cancer: A retrospective analysis

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Abstract. Totally implantable vascular access devices (TIVADs) are often used to administer chemotherapy by prolonged intravenous infusion. The objective of the present study was to investigate the incidence of long-term complications and identify risk factors associated with TIVAD placement in patients with gastric cancer. A total of 121 patients with gastric cancer who had undergone 150 TIVAD placement procedures for chemotherapy or supportive care were enrolled in the present retrospective cohort study. A number of risk factors were analyzed, including age, sex, hypertension, diabetes mellitus, history of thrombosis, body mass index, disease stage, and site and purpose of TIVAD. In total, 40 TIVADs (26.7%) developed long-term complications, of which 27 (18.0%) were infections, seven (4.7%) were catheter-related deep vein thrombosis (CR-DVT), and six (4.0%) were obstructions. Chemotherapy was associated with an increased rate of infectious adverse events (odds ratio 2.925; 95% CI, 1.104-7.750; P=0.031) according to the multivariate analysis. CR-DVT occurred more frequently in upper arm ports than in chest wall ports; however, this difference was not statistically significant (7.5 vs. 0.0%; P=0.084) according to the univariable analysis. All CR-DVTs developed in the upper arm sites. Chemotherapy and the upper arm site were associated with long-term complications in patients with TIVAD. However, further studies are needed to confirm the findings of the present study and to determine the reasons for the high incidence of long-term complications in these patients.

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Introduction

Gastric cancer is the fourth most frequently diagnosed cancer and the second leading cause of cancer death worldwide (1). The majority of patients with advanced cancer require chemotherapy. Furthermore, supportive care measures, such as medication for preventing chemotherapy-related adverse effects, nutritional support and symptom-relieving drugs have become increasingly important during different phases of cancer treatment (2-4). Implantation of a totally implantable vascular access device (TIVAD) enables repeated administration of chemotherapeutic drugs, parenteral nutrition and intravenous infusion, without multiple peripheral venous punctures and venous toxicities (5,6). TIVADs have been extensively endorsed and used, and the procedure for implanting them is safe and effective (7,8).

TIVADs are placed via the subclavian, external or internal jugular vein through the anterior chest wall, or via the basilic vein through the upper arm; the optimal TIVAD insertion site is controversial (9-23). Placement in the anterior chest wall has been the preferred approach; the advantages of this route include high stability of the system and a low incidence of infection (9). However, complications associated with the operative procedure, such as pneumothorax, arterial puncture and vascular injury, occur in 0.3-15.8% of patients (9-11). For this reason, upper arm sites have been increasingly used; the placement procedure is simple with fewer operative complications, and these sites have cosmetic advantages and an absence of possible interference with radiation therapy (12-14). However, the upper arm route is associated with risk of long-term complications, including catheter-related deep vein thrombosis (CR-DVT), infectious adverse events and mechanical complications (15-18). Furthermore, previous studies have reported that the risk of CR-DVT in patients with cancer is four- to seven-fold that of patients without cancer (19-22). However, although long-term complications are common and potentially serious, the incidence and risk factors in patients with cancer remains unclear. The purpose of the present study was to investigate the incidence of long-term complications and identify risk factors associated with TIVAD placement in patients with gastric cancer.

Patients and methods

Study cohort and data collection. The present study cohort comprised 121 patients with gastric cancer who had undergone TIVAD placement at Kanazawa University Hospital between January 2010 and September 2014; 150 TIVAD ports were placed for chemotherapy and supportive care. Implantation sites were chosen by the surgeon performing the procedure. For the purpose of analysis, each TIVAD placement was counted as a new event. Therefore, all analyses were performed according to TIVAD placements rather than to individual patients. Eligible patients underwent TIVAD placement via the chest wall or upper arm and were followed up for ≥3 years, or until TIVAD removal or death at Kanazawa University Hospital. The surgical procedure and its possible benefits and complications, as well as alternative procedures, were explained to patients, and all patients provided written informed consent before undergoing placement of a TIVAD. The present study was approved by the Research Ethics Committee of Kanazawa University.

Ports and catheters. Open-end type catheters and BARD Slim-Ports (Bard Access Systems) were used initially, and the Vital-Port Vascular Access System (Cook Medical, LLC) later in the study period. Port systems used for the chest and arm sites weighed 8 and 2.5 g, and were 0.5 and 0.2 ml in internal volume, respectively.

Placement of TIVADs. All TIVADs were placed under local anesthesia at the port site using maximal sterile precautions. Routine antibiotic and antithrombotic prophylaxis were not administered. The surgical fields were sterilized with 10% povidone-iodine.

The chest TIVADs were inserted through the subclavian or external jugular vein. Puncture of the subclavian vein was carried out under real-time ultrasonography, whereas puncture of the external jugular vein was via surgical exposure by cut-down. After confirmation of the backflow of blood, a catheter was advanced into the superior vena cava and the catheter tip was inserted to the level of the tracheal bifurcation under X-ray fluoroscopic examination. A subcutaneous pocket was established on the lateral side of the anterior chest wall and the inserted port connected to the catheter through a subcutaneous tunnel. The wound was closed with 4-0 absorbable sutures. Postoperative chest radiography was routinely carried out to determine the position of the catheter tip.

The arm TIVADs were inserted through the basilic vein. Portable ultrasonography was routinely performed before TIVAD placement to identify a suitable vein for insertion. After puncturing the vein with a 22-gauge elastic needle, a catheter was advanced into the superior vena cava. The catheter tip was inserted to the level of the tracheal bifurcation by X-ray fluoroscopic examination. A subcutaneous pocket was shaped distal to the puncture site and the inserted port connected to the catheter in the same manner as the chest port.

Maintenance and follow-up. TIVAD use was started 1-3 days after implantation. Saline was injected to check for leakage or occlusion of the catheter. A semipermeable transparent dressing was used to cover the needle. In patients requiring continuous infusion, the infusion line and needle were changed once a week. Heparinized saline (10 ml; 100 IU/ml) was injected as a flush solution before removing the needle. If the TIVAD was not used for more than a month, heparinized saline was administered monthly. Postoperative ultrasonography was not performed during follow-up provided the patients were asymptomatic.

Study outcomes. The primary end-point of the present study was the cumulative incidence of long-term complications and the secondary end-point was the cumulative incidence of risk factors for long-term complications. Infectious complications included bloodstream infection (BSI) and port-pocket infection. BSI was defined as evidence of inflammation, such as fever or positive blood cultures associated with a long-term venous port. Port-pocket infection was diagnosed on the basis of purulent discharge, tenderness and erythema. Other complications, including CR-DVT and obstructions, were identified. CR-DVT was defined as swelling, redness and tenderness, and diagnosed thrombi were confirmed by ultrasonography. A total of seven variables were analyzed by univariable logistic regression, namely age, sex, risk factor (including hypertension, diabetes mellitus and previous history of thrombosis), body mass index (BMI), disease stage (23), site and purpose of port placement.

Statistical methods. All data were analyzed using the computer software package SPSS 10.0 (SPSS, Inc.). Categorical data were compared using the χ^2 test. Relevant patient characteristics and baseline variables were summarized using descriptive statistics. Univariable and multivariable logistic regression analyses were performed to identify risk factors. $P<0.05$ was considered to indicate a statistically significant difference.

Results

Patient characteristics. In total, 96 of the 121 patients underwent only one TIVAD placement procedure, 21 underwent two procedures and 4 underwent three procedures (Table I). The main characteristics of the included patients are summarized in Table II. The hospital records of 150 TIVAD placements, performed at Kanazawa University Hospital (89 males, 61 females; median age 63 years, range 26-87 years) in 121 patients were retrospectively analyzed. They comprised 57 chest wall procedures (38.0%) and 93 upper arm procedures (62.0%). A total of 88 (58.7%) procedures were for chemotherapy and 62 (41.3%) for supportive care (Table II).

Incidence of late complications. Table III presents the long-term complications after TIVAD placement. In total, 40 TIVADs (26.7%) were associated with long-term complications, of which 27 (18.0%) were infections, seven (4.7%) were CR-DVT, and six (4.0%) were obstructions. There were no port fractures, pinch-offs or catheter tip displacements.

Risk factors for long-term complications. Infectious adverse events occurred significantly more frequently with chemotherapy than with supportive care (23.9 vs. 9.7%; P=0.044; Table IV). Furthermore, according to the multivariable analysis of risk factors with P-values <0.2 in the univariable analysis by logistic regression, chemotherapy was associated

Table I. Number of totally implantable vascular access device placment procedures per patient (n=121).

Placement procedures	n	%
One time	96	79.3
Two times	21	17.4
Three times	4	3.3

Table II. Patient characteristics.

Characteristic	n	%
Sex		
Male	89	59.3
Female	61	40.7
Age, mean (range)	63 (26-87)	
<70 years	109	72.7
≥70 years	41	27.3
Risk factor[a]		
+	53	35.3
-	97	64.7
BMI		
<25	140	93.3
≥25	10	6.7
TNM		
I, II, III	17	11.3
IV, recurrence	133	88.7
Site		
Chest	57	38.0
Upper arm	93	62.0
Purpose		
Chemotherapy	88	58.7
Supportive care	62	41.3

[a]Risk factor includes hypertension, diabetes mellitus and a previous history of thrombosis. BMI, body mass index.

Table III. Incidence of late complications after totally implantable vascular access device placement (n=150).

Complication	n	%
Total	40	26.7
Infection	27	18.0
CR-DVT	7	4.7
Obstruction	6	4.0

CR-DVT, catheter related deep vein thrombosis.

with an increased rate of infectious adverse events, with an odds ratio of 2.925 (95% CI, 1.104-7.750; P=0.031; Table IV).

CR-DVT occurred more frequently in patients with BMI ≥25 than <25 (30.0 vs. 2.9%; P=0.002), in stage I-III than stage IV (11.8 vs. 3.8%; P=0.037), in male than in female patients (7.9 vs. 0.0%; P=0.064) and more often in the upper arm than the chest wall sites (7.5 vs. 0.0%; P=0.084; Table V); however, sex and site were not statistically significant risk factors. A multivariable analysis of risk factors was not conducted, as the study was too small. Notably, CR-DVTs occurred in upper arm sites; however, none occurred in the chest wall (Table V).

Discussion

In the present study, infectious adverse events and CR-DVT were identified as long-term complications of TIVADs in patients with gastric cancer. The incidence of infectious adverse events was greater with chemotherapy use (23.9%) than with supportive care (9.7%). Furthermore, the chest wall and arm sites had different safety profiles, CR-DVT occurring only in arm sites (7.5%).

Risk factors for CR-DVT and infection associated with TIVAD placement belong to three categories: i) Catheter factors, such as the insertion site; ii) patient-related factors, such as presence of malignancy; and iii) medication factors, such as chemotherapy (22).

Catheter factors, including the insertion site, have been shown to be important; previous studies having reported an incidence of CR-DVT of 0.7-8.2% for arm ports (24,25). Lin *et al* (26) reported that the left or right side of TIVAD placement is not associated with occurrence of CR-DVT; however, this factor was not assessed in the present study. At 4.7%, the rate of CR-DVT was significantly higher for arm ports than chest wall ports, where no CR-DVTs developed. CR-DVTs may result in patient inconvenience and the need for anticoagulation therapy, early catheter removal and re-cannulation (15). Arm ports occupy a large proportion of the intravascular lumen as they are in peripheral veins (27). Repetitive arm movements can also contribute to the incidence of CR-DVT (28). Furthermore, TIVADs in the arm require a longer intravenous catheter than chest wall TIVADs (29). Therefore, prolonged contact between the catheter and the intravascular wall may result in endothelial damage, reduction in blood flow and consequent CR-DVT (22).

The second category of patient-related factors is also important. Patients with cancer, who are often immunocompromised and may be malnourished, have been reported to have a higher incidence of infectious complications (30-32) with a substantially higher risk of venous thromboembolism than patients without cancer (33-35). Trousseau (36) first reported the association between malignancy and venous thromboembolism as a documented cause of migratory CR-DVT in patients with cancer. Venous thromboembolism in patients with cancer is typically associated with hypercoagulability, endothelial damage, blood flow stasis, dehydration and malnutrition (37). The clotting process is exacerbated by direct interaction between cancer cells and endothelial cells, which activates blood cells, such as monocytes, macrophages and platelets (34,38). Furthermore, the primary tumor site significantly affects the risk of venous thromboembolism; gastric cancer is associated with a high incidence of this complication (19,39). In

Table IV. Univariable and multivariable analyses of risk factors for infection incidence.

Characteristic	n	Yes	No	%	Univariable analysis P-value	Multivariable analysis OR	95% CI	P-value
Age, <70/≥70 years	109/41	24/3	85/38	22.0/7.3	0.064	2.825	0.784-10.188	0.112
Sex, M/F	89/61	15/12	74/49	16.9/19.7	0.659			
Risk factor[b], +/-	53/97	8/19	45/78	15.1/196.6	0.644			
BMI, <25/≥25	140/10	26/1	114/9	18.6/10.0	0.798			
Stage, I-III/IV, REC	17/133	1/26	16/107	5.9/19.5	0.296			0
Site, Chest/Arm	57/93	8/19	49/74	14.0/20.4	0.441			
Purpose, Chemo/Supportive care	88/62	21/6	67/56	23.9/9.7	0.044[a]	2.925	1.104-7.750	0.031[a]

[a]P<0.05. [b]Risk factor includes hypertension, diabetes mellitus and a previous history of thrombosis. BMI, body mass index; OR, odds ratio; REC, recurrence; M, male; F, female.

Table V. Univariable analyses of risk factors for catheter-related deep vein thrombosis incidence.

Characteristic	n	Yes	No	%	P-value
Age, <70/≥70 years	109/41	6/1	103/40	5.5/2.4	0.720
Sex, M/F	89/61	7/0	82/61	7.9/0.0	0.064
Risk factor[b], +/-	53/97	4/3	49/94	7.5/2.9	0.406
BMI, <25/≥25	140/10	4/3	136/7	2.9/30.0	0.002[a]
Stage, I-III/IV, REC	17/133	3/4	14/129	11.8/3.8	0.037[a]
Site, chest/arm	57/93	0/7	57/86	0.0/7.5	0.084
Purpose, chemo/supportive care	88/62	6/1	82/61	6.8/1.6	0.273

[a]P<0.05. [b]Risk factor includes hypertension, diabetes mellitus and a previous history of thrombosis. BMI, body mass index; OR, odds ratio; REC, recurrence; M, male; F, female.

the present study, CR-DVT occurred more frequently in male patients than in female patients, more often in those with BMI ≥25 than BMI <25, and more often in stage I-III than stage IV. The risk associated with sex remains uncertain as findings of previous studies are conflicting; a higher risk for pulmonary embolism and deep venous thrombosis was reported for both men (40,41) and for women (42). Obesity has long been a known risk factor for venous thromboembolism (43,44). Similar to the present results, a number of previous studies have observed that being male and/or obese are risk factors for CR-DVT (45,46). Typically, advanced disease stages cases are expected to have more CR-DVT (47); however, in the present study, contradictory results were obtained. This could not be considered in detail and requires further investigation in future studies.

Medication factors, such as chemotherapy, are risk factors for CR-DVT and infection (19,4). Chemotherapy may damage the vascular endothelium, cause disequilibrium between procoagulant and anticoagulant molecules, induce apoptosis in tumor endothelial cells, activate cytokines, and increase tissue factor activity (48). The present results suggested that chemotherapy is a risk factor for infectious complications. Development of CR-DVT can also be promoted by central venous catheter-related infection in patients undergoing intensive chemotherapy (20). In the present study, an association between chemotherapy and CR-DVT was not observed. However, careful maintenance of TIVADs for the purpose of chemotherapy is required.

The present study had several limitations. As it was a retrospective single-center study, the present results may not be applicable to other institutions, especially if the type of catheter used and protocol for catheter maintenance differ from those used at Kanazawa University Hospital. The types of catheter and the operation times have important impacts on late complications (49,50). However, in the present retrospective study, it was not possible to evaluate these factors because detailed data had not been recorded. As the present study was not a randomized controlled study, the comparison between chest wall and upper arm ports is not definitive. Additionally, as only symptomatic conditions were recorded, asymptomatic complications could not be identified. Asymptomatic patients did not undergo ultrasonography during follow-up. Overt CR-DVT occurred only in patients with arm TIVADs and patients with chest TIVADs were almost completely asymptomatic. The incidence of asymptomatic CR-DVT is reportedly as high as 66% (51,52). Furthermore, the chemotherapy regimens or cumulative duration of port placement were not compared. Nevertheless, the present study identified an increased risk of infectious complications associated with TIVADs for chemotherapy and an increased risk of CR-DVT associated with arm TIVADs.

In conclusion, the present study identified an association between the objective of chemotherapy and risk of central venous catheter-related infection. Therefore, these patients should be carefully monitored after TIVAD insertion. In addition, CR-DVT may be associated with the upper arm site. Taking the results of the present study and the risk of complications associated with the operative procedure into consideration, it may be necessary to choose the site for TIVAD insertion on an individual basis. However, the present findings require confirmation by a prospective randomized study, including evaluation of the quality of life of the patients. More specifically, to the best of our knowledge, an agreement has not yet been reached on the use of prophylactic anticoagulants and antibiotics in the management of TIVAD (14). Further studies are needed to determine whether such prophylaxis reduces the incidence of long-term complications.

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Availability of data and materials

All data generated or analyzed during the present study are included in this published article.

Authors' contributions

MO, KO and JK conducted the studies, participated in data collection, and drafted the manuscript. MO and KO performed the statistical analysis and participated in the design of the study. JK, TM, HTaj, HTak, IN, SF and TO analyzed and interpreted the data, and reviewed and revised the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by the Research Ethics Committee of Kanazawa University, and written informed consent for placement of TIVADs was obtained from every participant.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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