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Risk Factors for Totally Implantable Central Venous Access Port-related Infection in Patients With Malignancy

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Abstract. *Background: We sought to identify the risk factors of totally implantable central venous access port (TICVAP)-related infections in patients with malignant disease. Patients and Methods: Overall, 324 consecutive patients who received a TICVAP at our institution were retrospectively analysed. We further analysed cases of TICVAP-related complications. The risk factors for TICVAP-related infection were investigated using Cox regression hazard models. Results: With a median TICVAP duration of 268 days (range=1-1,859 days), TICVAP-related complications were observed in 36 cases and infectious complications in late phase were the most common, seen in 19 cases (9.26%). A multivariate analysis showed that patients with head and neck malignancy (p<0.001) and patients who received TICVAP insertion in the upper arm (p<0.001) were independently at a higher risk for TICVAP-related infections. Conclusion: Patients with head and neck malignancy or TICVAP insertion in the upper arm have potentially increased risk for late-phase TICVAP-related infections.*

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Malignant disease is a major public health problem worldwide, with the number of patients with malignancy increasing (1). Multimodality treatments, consisting of chemotherapy, radiotherapy, and surgery have been increasingly utilised in malignant diseases to improve prognosis in the recent decade. Chemotherapy is usually administered for local and distant disease control in patients whose disease has not responded to combined radiation and surgery (2). The use of a totally implanted central venous access port (TICVAP), which was initiated in the early 1980s, has been standard practice for patients with malignant disease to facilitate the safe delivery of chemotherapy, hydration, and parenteral nutrition (3, 4). TICVAP offers several advantages over central venous catheters, including their semi-permanent nature and ease of use, especially in ambulatory patients (5, 6). Although TICVAP-associated complications have generally been very rare, several studies have reported complications after TICVAP insertion, such as infection (5-26%), thrombosis (2-26%), catheter malposition, catheter fracture, and catheter migration (7, 8). Once TICVAP-related complications are suspected, special care, such as extraction of the TICVAP, wound management, antibiotic therapy, and anticoagulation therapy, is needed. TICVAP-related complications result in an increased rate of sepsis-related mortality, a delay of hospitalisation, and impairment of the patient's quality of life (9).

To date, the risk factors for TICVAP-related complications in patients with malignancy have not been completely elucidated. Thus, in this study, we retrospectively investigated

the incidence of TICVAP-related complications and sought to identify their risk factors in patients with malignancy.

Patients and Methods

Study setting. This was a retrospective cohort study conducted at a single institution (Second Department of Surgery, Hamamatsu University School of Medicine). This study was approved by the Ethics Committee at Hamamatsu University School of Medicine (approval number: 20-299), and followed the tenets set by the Declaration of Helsinki. Patient confidentiality was protected by anonymising patient chart data and removing non-pertinent identifiers prior to analysis.

Patients. A total of 328 patients underwent surgery for TICVAP insertion at our institution between January 1, 2015, and October 31, 2019. Among them, four patients were excluded due to having no malignant disease, resulting in 324 patients who were enrolled for analysis. The following data were collected from each patient chart: Patient baseline characteristics at the time of TICVAP insertion including age, sex, and body mass index, purpose of insertion, Eastern Cooperative Oncology Group performance status (ECOG PS) (10), presence of diabetes mellitus, laboratory data such as serum albumin and C-reactive protein, underlying malignant disease, experience of the previous TICVAP insertion, and the vein involved (subclavian, jugular, cephalic, upper arm) with its laterality (right or left).

TICVAP placement. All operations for TICVAP insertion were performed by a team of surgeons in operating rooms under strict aseptic conditions with standard sterile precautions (mask, cap, sterile gloves, and large sterile drape). Catheter site dressings were used as recommended by Disease Control and Prevention guidelines to prevent intravascular catheter infection (11). A prophylactic antibiotic (cefazolin) was administered before the procedure. Ultrasound and radiographic guidance for catheter insertion were used in all cases. Implantation from a subclavian vein, jugular vein, cephalic vein at the deltoid-pectoralis groove, or vein of the upper arm (brachial or basilic vein in the antecubital fossa) was chosen. Seldinger technique was used for the subclavian and jugular approach, and the cutdown method was used for the cephalic vein. Either the Seldinger or cutdown method was applied for veins of the upper arm. Generally, we chose the subclavian approach for venous access. However, considering patient characteristics or commodities, such as vein diameter at the preoperative ultrasound view, presence of venous occlusion, radiodermatitis, or anti-platelets, or anticoagulation therapy, an approach from the jugular, cephalic, or vein of upper arm was chosen instead. Regarding laterality, we considered quality-of-life factors such as hand dominance and seatbelt orientation while driving, in addition to the aforementioned patient characteristics and commodities. The side of the non-dominant hand was generally chosen wherever possible. A variety of port systems were used consisting of a titanium reservoir with a 5-Fr Anthron P-U catheter kit (Toray Industries, Inc., Tokyo, Japan), 6-Fr Orphis CV kit (Sumitomo Bakelite Company Limited, Tokyo, Japan), and a polyurethane catheter (6-Fr or 8-Fr), Powerport isp M.R.I. (Bard Access Systems, Inc., Salt Lake City, UT, USA), or SlimPort (Bard Access Systems). The choice of devices for each case was based on the underlying disease, patient anatomy, availability of the device, and the type of chemotherapy regimen. A catheter tip was placed at a level of one vertebral body unit below the tracheal bifurcation under radiographic guidance. The port device was generally fixed with subcutaneous tissue using a non-absorbable thread, while the skin was closed with absorbable threads. Same-day X-ray confirmed proper positioning of TICVAP post-procedure. The TICVAP was then declared available for use the next day.

Follow-up. The TICVAP duration was defined as the number of days from insertion to removal of the port due to completion of therapy, TICVAP-related complication, transfer to another hospital, home care, or patient death (12).

Cases with any suspected TICVAP-related complications were referred to the Second Department. of Surgery, Hamamatsu University School of Medicine. The timing of any complication was categorised based on the time of occurrence either as procedure-related (<24 hours), early (24 hours to 30 days), or late (>30 days) (13).

TICVAP-related infections were defined as a local infection (the presence of signs of local inflammation, including erythema, warmth, tenderness, and pus formation) or bloodstream infection (bacteraemia, or fungemia) in a patient with a TICVAP and more than one positive blood culture with no other apparent source of bloodstream infection (14, 15). The microorganisms isolated from TICVAP-related infection were recorded.

Statistical analysis. Descriptive statistics with mean ± standard deviation and median (range) were used to characterise the study population. Categorical variables are described as counts and percentages. TICVAP insertion days were calculated as the sum of the TICVAP durations in each patient cohort. The incidence rate of TICVAP-related infectious complications was calculated as the number of complications/1,000 TICVAP insertion days.

The Cox proportional hazard model was used to evaluate the hazard ratio for each variable in univariate and multivariate analyses. Factors with a *p*-value of less than 0.1 on univariate analysis were selected for a multivariate analysis. For analysing the infection-free TICVAP duration, the Kaplan–Meier method and log-rank test were used. *p*-Values of less than 0.05 were considered statistically significant. All calculations were performed with SPSS ver. 24.0 software (IBM, Armonk, NY, USA)

Results

Patient characteristics. The clinical characteristics of the 324 consecutive patients who underwent TICVAP insertion at our institution are shown in Table I. Their median age was 67 years with a range of 24-90 years. A total of 217 (67.0%) patients were male. The mean body mass index was 21.1±4.32 kg/m^2. The purpose of TICVAP insertion was for chemotherapy (n=262, 80.9%) or nutrition (n=62, 19.1%). The majority of patients (n=255, 78.7%) had ECOG PS of 0-1. Forty-four patients (13.6%) had diabetes mellitus. The median albumin and C-reactive protein values immediately before the TICVAP insertion were 3.6 (range=1.4-4.8) g/dl and 0.66 (range=0.01-21.12) mg/dl, respectively. The primary site of malignant disease was the colorectum (n=107, 33.0%). Thirteen patients (4.0%) had had previous

Table I. *Characteristics of patients who underwent surgery for insertion of totally implantable central venous access ports (TICVAP) (n=324).*

Factor	Value
Age, years	
Mean±SD	64.1±12.30
Median (range)	67 (24-90)
Gender, n (%)	
Male	217 (67.0)
Female	107 (33.0)
BMI, kg/m^2	
Mean±SD	21.1± 4.32
Median (range)	20.7 (13.1-37.5)
Purpose of insertion, n (%)	
Chemotherapy	262 (80.9)
Nutrition	62 (19.1)
ECOG PS, n (%)	
0	127 (39.2)
1	128 (39.5)
2-4	69 (21.3)
Diabetes mellitus, n (%)	
No	280 (86.4)
Yes	44 (13.6)
Albumin, g/dl	
Mean±SD	3.5±0.69
Median (range)	3.6 (1.4-4.8)
CRP, mg/dl	
Mean±SD	1.87±2.77
Median (range)	0.66 (0.01-21.12)
Malignant disease, n (%)	
Colorectum	107 (33.0)
Head and neck	48 (14.8)
Hepatobiliary-pancreas	46 (14.2)
Stomach	36 (11.1)
Oesophagus	31 (9.6)
Bone and soft tissue	23 (7.1)
Gynaecological	15 (4.6)
Haematological	5 (1.5)
Lung	4 (1.2)
Urological	4 (1.2)
Other	5 (1.5)
Previous insertion, n (%)	
No	311 (96.0)
Yes	13 (4.0)
Vein used, n (%)	
Subclavian	257 (79.3)
Jugular	26 (8.0)
Cephalic	21 (6.5)
Upper arm	20 (6.2)
Inserted side, n (%)	
Right	118 (36.4)
Left	206 (63.6)
TICVAP duration, days	
Median (range)	298 (1-1,859)

BMI: Body mass index; CRP: C-reactive protein; ECOG: PS: Eastern Cooperative Oncology Group performance status; SD: standard deviation.

TICVAP insertion. Regarding procedure aspects, in the majority of cases the subclavian vein (79.3%), and the left side (63.6%) were used.

Table II. *List of totally implantable central venous access port-related complications.*

Complication	Cases, n (%)
Procedure-related (<24 h)	
Total	5 (1.54)
Arterial puncture	3 (0.93)
Pneumothorax	2 (0.62)
Early (24 h to 30 days)	
TotaI	1 (0.31)
Pain when swallowing	1 (0.31)
Late (>30 days)	
Total	30 (9.26)
Infection	19 (5.86)
Local infection	12 (3.70)
Bloodstream infection	7 (2.16)
Catheter-related	5 (1.54)
Fraction	2 (0.62)
Kinking	1 (0.31)
Malposition	1 (0.31)
Deviation	1 (0.31)
Port-related	4 (1.23)
Exposed	3 (0.93)
Inversion	1 (0.31)
Thrombosis	2 (0.62)

Table III. *Frequency distribution of species isolated from cases with totally implantable central venous access port-related infection.*

	Infection, n	
Species	Local	Bloodstream
Gram-positive bacteria		
Staphylococcus aureus	4	3
Staphylococcus epidermidis	2	0
Gram-negative bacteria		
Serratia marcescens		1
Stenotrophomonas maltophilia		1
Pseudomonas aerginosa	1	1
Bacillus cereus		1
Fungus		
Candida albicans		2

Numbers include overlapping cases.

Follow-up and TICVAP-related complication. The median TICVAP duration was 268 days (range=1-1,859 days). One hundred and forty-two (43.8%) patients died, and 145 (44.7%) patients were transferred to another hospital or home care. A total of 37 port devices were removed due to a TICVAP-related complication (n=31) or completion of treatment (n=6) during the observed study period.

TICVAP-related complications were observed in a total of 36 cases (Table II). The microorganisms detected in TICVAP-

Table IV. *Univariate and multivariate analyses of risk factors associated with totally implantable central venous access port-related infection.*

Variable		n	Infection events	Insertion days*	Incidence rate	Univariate		Multivariate	
						HR (95% CI)	*p*-Value	HR (95% CI)	*p*-Value
Age	<66 Years	151	8	67,375	0.119	1			
	≥66 Years	173	11	59,727	0.184	1.742 (0.572-3.564)	0.445		
Gender	Male	107	6	76,337	0.079	1			
	Female	217	13	50,765	0.256	1.280 (0.486-3.375)	0.617		
BMI	<20.7 kg/m^2	169	13	56,647	0.229	1		1	
	≥20.7 kg/m^2	155	6	70,455	0.085	0.419 (0.159-1.104)	0.078	0.85 (0.279-2.586)	0.774
Purpose	Chemotherapy	262	15	119,492	0.126	1		1	
	Nutrition	62	4	7,610	0.526	2.705 (0.874-8.370)	0.084	1.490(0.407-5.453)	0.547
ECOG PS	0-1	255	13	116,990	0.111	1		1	
	2-4	69	6	10,112	0.593	3.861 (1.438-10.368)	0.007	1.913(0.623-7.198)	0.227
Diabetes mellitus	No	280	16	114,259	0.140	1			
	Yes	44	3	12,843	0.234	1.409 (0.408-4.859)	0.588		
Albumin	≥3.5 g/dl	177	9	87,493	0.103	1		1	
	<3.5 g/dl	147	10	39,609	0.252	2.146 (0.866-5.320)	0.099	0.707(0.241-2.075)	0.527
CRP	<1.0 mg/dl	265	16	109,656	0.146	1			
	≥1.0 mg/dl	59	3	17,446	0.172	1.186 (0.345-4.077)	0.787		
Malignant disease	Colorectum	107	1	62,981	0.016				
	Head and neck	48	9	13,770	0.654				
	Hepatobiliary-pancreas	46	1	12,672	0.079				
	Stomach	36	2	9,409	0.213				
	Oesophagus	31	1	5,406	0.185				
	Bone and soft tissue	23	4	10,804	0.370				
	Gynaecological	15	1	7,029	0.142				
	Haematological	5	0	1,944	0				
	Lung	4	0	683	0				
	Urological	4	0	1,433	0				
	Other	5	0	971	0				
Malignant disease	Other	276	10	113,332	0.088	1		1	
	Head and neck	48	9	13,770	0.654	6.441 (2.611-15.888)	<0.001	5.775 (2.314-14.410)	<0.001
Previous insertion	No	311	17	119,597	0.142	1			
	Yes	13	2	7,505	0.266	2.318 (0.535-10.037)	0.261		
Inserted side	Right	118	8	36,341	0.220	1			
	Left	206	11	90,761	0.121	0.651(0.260-1.630)	0.359		
Vein used	Subclavian	257	11	112,405	0.098				
	Jugular	26	1	4,349	0.230				
	Cephalic	21	1	5,263	0.190				
	Upper arm	20	6	5,085	1.180				
Vein used	Other	304	13	122,017	0.107	1		1	
	Upper arm	20	6	5,085	1.180	1.788 (1.403-2.279)	<0.001	1.651 (1.266-2.151)	<0.001

BMI: Body mass index; CRP: C-reactive protein; ECOG: PS: Eastern Cooperative Oncology Group performance status. *TICVAP insertion days were calculated as the sum of the TICVAP durations in each patient cohort.

related infections were as follows: Gram-positive bacteria in nine cases, gram-negative bacteria in five cases, and fungus in two cases (Table III).

Risk factors associated with TICVAP-related infection. Risk factors of TICVAP-related infectious complications were analysed in a total of 19 patients in this study. All TICVAP-related infections occurred as late complications, and the median interval from TICVAP insertion to infection was 95 days (range=31-676 days). The total infection incidence rate was 0.149 infections per 1,000 insertion days. Patients with head and neck cancer had the highest incidence rate (0.654 infections per 1,000 insertion days), and those with TICVAP in the upper arm had the highest (1.180 infections per 1,000 insertion days) (Table IV). In a univariate analysis using the Cox regression hazard model, TICVAP-related infection was significantly correlated with ECOG PS 2-4) (p=0.007), head and neck malignancy (p<0.001), and insertion in the vein of

the upper arm ($p<0.001$) (Table IV). The multivariate analysis showed that head and neck malignancy and TICVAP in the vein of the upper arm remained significant as independent risk factors associated with late TICVAP-related infection (Table IV). Kaplan–Meier analysis revealed that patients with head and neck malignancy and those with TICVAP in the upper arm had a significantly shorter infection-free interval than those without (Figure 1).

Discussion

This study reviewed our daily clinical practice for TICVAP insertion and evaluated risk factors for TICVAP-related complications. During the study period, a total of 36 TICVAP-related complications occurred, with late phase being most frequent (30 cases, 9.26%), followed by procedure-related (five cases, 1.54%), and early (one case, 0.31%), respectively, which were all comparable to those reported in a previous study (13). We chose to focus on late complications since procedure-related and early complications might be influenced by technical factors, and found that infectious complications were the most frequent kind encountered during the study period. In the multivariate analysis using the Cox regression hazard model, patients who had head and neck malignancy and those who received TICVAP insertion into the upper arm were noted as at independently higher risk for TICVAP-related infection. The overall incidence of TICVAP-related infection was 0.149 infections per 1,000 insertion days, which was slightly lower compared to that reported previously (0.16-0.35 infections per 1,000 insertion days) (16-18). In contrast, the incidence rate of infection in patients with head and neck malignancy and those with upper arm approach were 0.654 and 1.180 infections per 1,000 insertion days, respectively, which were higher than those reported in the aforementioned studies.

The assumed mechanisms of TICVAP-related infection are as follows: i) Extra-luminal contamination (*i.e.* migration of organisms along the external surface of the catheter) during TICVAP insertion; ii) extra-luminal colonisation during port maintenance (inappropriate disinfection of the skin before insertion of the Huber needle); iii) intraluminal (*i.e.* migration of organisms into the lumen of the catheter after contamination of the catheter hub or, less frequently, after infusion of contaminated solutions); and iv) haematogenous (*i.e.* contamination from blood-borne bacteria coming from a distant source) (19, 20). Regarding late infectious events, possible mechanisms of infection are extra-luminal colonisation or from an intraluminal route. The most frequent bacterial species detected in this study were gram-positive coccus (Staphylococcus aureus), which exist as dermatopathogenic bacteria. This finding supports the hypothesis that TICVAP-related infection in the late phase would mainly be caused by extra-luminal colonisation during port maintenance.

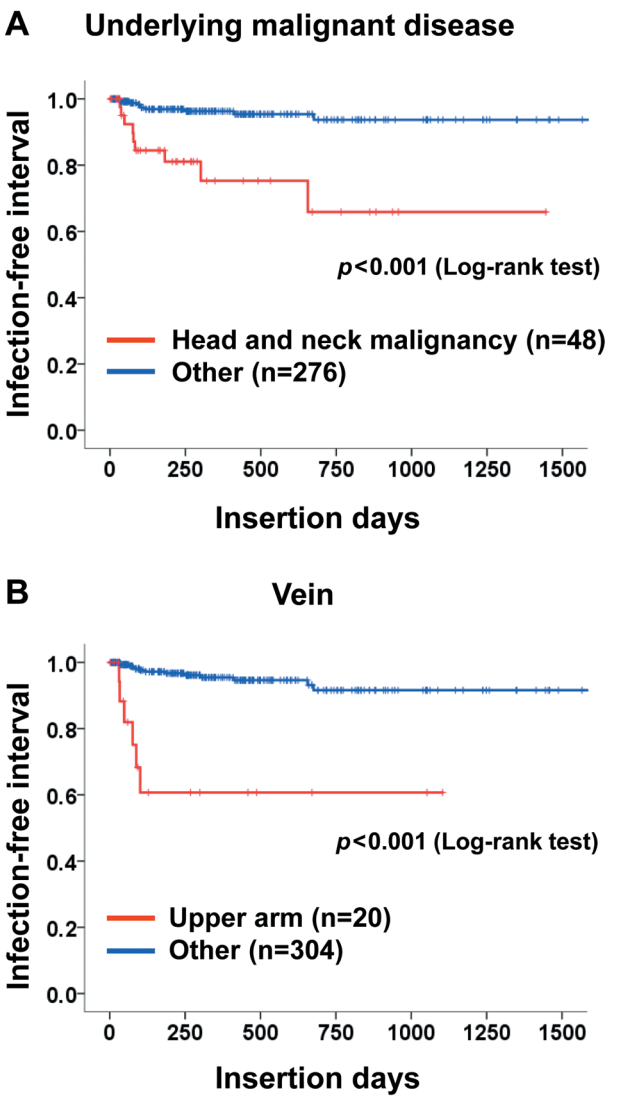

Figure 1. *Kaplan–Meier curves of the infection-free interval for patients who received a totally implantable central venous access port stratified by malignancy (A) and vein location (B).*

In this study, patients with head and neck malignancy were noted as independently being at a higher risk for late TICVAP-related infection. To the best of our knowledge, this is the first report to indicate that patients with head and neck malignancies are at risk for TICVAP-related infection after 30 days from insertion. This may be since they are prone to prolonged severe neutropenia, induced by high-dose chemotherapy or prolonged radiation therapy (21). Moreover, radiation-induced mucositis of the mouth and nasopharynx disrupts the mucosal barrier function, leading to microbial invasion (22). Furthermore, patients with head and neck malignancy have difficulties with oral intake based on organ-specific features. In addition to immuno-nutritional factors,

they tend to have poor skin condition caused by stiffness due to radiation therapy, dermatitis induced by molecular target therapy, and difficulties keeping skin clean because of tracheostomy, which all seem to increase the risk of infection. These speculations are in line with a previous report (23, 24).

Interestingly, our results indicated that patients with TICVAP insertion in the vein of the upper arm were also indicated as independently being at a higher risk for TICVAP-related infection in late disease stages. The procedure and the feasibility of TICVAP insertion in the upper arm have been detailed and insertion at this site has been widely accepted as a safe procedure (25-29). However, few reports have focused on late-phase infectious complications and the potential relationship with a port insertion site. Shiono *et al*. suggested that skin temperature and skin aerobic/anaerobic flora density were different over the forearm compared with over the subclavian area, potentially affecting adverse infection incidence (30). In addition, Akahane *et al*. suggested that phlebitis occurred most frequently in upper arm sites, and thrombophlebitis was correlated with infection-related adverse events (21). In our study, there were no obvious cases that developed thrombophlebitis from clinical manifestation or imaging findings. However, one must still consider the potential increased risk of phlebitis-related infectious complications caused by TICVAP insertion in the upper arm. Furthermore, the difference in needle care between an arm port and a chest port must be considered, especially in an ambulatory setting. Patients have to take the needle out of a port with one hand themselves if they cannot get in-home support, which may increase the risk for inadequate safety precautions.

This study has important limitations. Firstly, this was a retrospective single-centre study that featured a study cohort with various underlying malignancies, cancer stage, chemotherapy regimen, and type of chemotherapy cycle, consequently influencing the device service interval. Next, the analysis of the differences in the results between veins used must consider the differences between groups. In other words, as the patients were not randomised, the differences in results may either be due to the different veins used or inherent to the different populations. Thus, randomised prospective studies are warranted for further evaluation. Our results indicate that patients with head and neck cancer or those who receive TICVAP insertion in the upper arm have increased potential risks for TICVAP-related infectious complications 30 days after insertion. When following up such patients, we need to be mindful of the high risk involved, careful port management, and adequate patient and family instruction.

Conflicts of Interest

The Authors declare that they do not have anything to disclose regarding funding or conflict of interest with respect to this article.

Authors' Contributions

SF: Design of the work, data acquisition, data analysis, drafting of the work. Y. Morita: Design and drafting of the work. SI, RM, RK, K. Suzuki, YS, K. Sugimoto, MT, HI, Y. Maekawa, H. Mineta and H. Miyake: Data acquisition, and drafting of the work. HK, YH, KK, and HT: Drafting of the work. All Authors read and approved the final article.

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