

**ORIGINAL****Safe central venous catheters for esophageal cancer treatment**

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**Abstract : Introduction :** Central venous catheter (CVC) use is essential for treating esophageal cancer. Peripherally inserted central catheters (PICC) are commonly used recently for improved patient comfort and safety. We compared centrally inserted central catheters (CICC) and PICC insertions and examined their safety. **Methods :** We retrospectively investigated complications at the catheter insertion and post-insertion for 199 patients' esophageal cancer treatment (CICC : 45, PICC : 154) from 2013 to 2018. In addition, we summarized the results of catheter tip culture. **Results :** No serious complications occurred at the catheter insertion in either group. The rate of complications at catheter insertion was 5.8% for PICC and 6.7% for CICC patients. Post-insertion complications were observed in 6.5% and 11.1% of patients with PICC and CICC, respectively, and this difference was not significant. The incidence of catheter-related blood stream infection (CRBSI) was significantly lower in PICC than CICC patients (0.3 vs. 1.8/1,000 catheter-days ;  $p = 0.029$ ). Catheter-related thrombosis was observed in PICC : 0.5 and CICC : 0.6, and occlusion due to blood flow reversal was observed in PICC : 0.5 and CICC : 0.6. **Conclusion :** PICCs are safer and more effective than CICCs for the treatment of esophageal cancer, and reduce the incidence of CRBSI. We hope to standardize the insertion procedures, conventionalize techniques, and establish training systems. *J. Med. Invest.* 67:298-303, August, 2020

**Keywords :** peripherally inserted central venous catheter (PICC), centrally inserted central catheter (CICC), catheter-related bloodstream infection (CRBSI), catheter-related thrombosis, esophageal cancer

**INTRODUCTION**

In the treatment of esophageal cancer, the insertion of a central venous catheter (CVC) for chemotherapy and/or nutritional management is indispensable, but complications associated with catheters have been reported, such as pneumothorax and hemothorax. Several deaths due to serious CVC-related complications were reported in Japan. In 2017, a Japan Medical Safety Research Organization survey revealed underlying issues with CVC use, e.g., incorrect indications, unfamiliarity with procedures, and insufficiently developed training systems. As an alternative approach to improve the comfort, management convenience, and safety of the catheterization, the use of a peripherally inserted central catheter (PICC) has increased (1-4).

PICCs are a new type of catheter that are suggested to have a lower risk of complications/infections associated with the puncture, easier insertion by a trained physician, and reduced patient anxiety at insertion compared to CVCs (5-10). PICCs have become the standard in the U.S., but in Japan their use remains infrequent. Few studies have compared the usefulness of PICCs with that of CICCs. In our hospital, PICCs have been used since 2013 with fluoroscopic or ultrasound guidance, but no analysis of their performance and safety in comparison with CICCs has been performed. Herein we compared the safety of PICC insertion and CICC insertion for the treatment of esophageal cancer.

**PATIENTS AND METHODS***Patients*

We studied 199 esophageal cancer patients who had undergone CVC insertion during treatment at our department from April 2013 to March 2018. PICC was defined as a catheter inserted from the vein of the brachial arm with its tip placed in the superior vena cava.

*Materials and Methods*

In this retrospective study we compared the safety of PICC insertion and CICC insertion for the treatment of patients with esophageal cancer. We first investigated the complications associated with the catheter insertion procedures, and then analyzed the complications occurring after insertion. Based on a review of the patients' records, we examined each of the following : the patient demographics and characteristics ; insertion site ; purpose of the catheter insertion and reasons for its removal ; complications at the catheter insertion ; duration of catheter placement and post-insertion complications ; and catheter tip cultures. The complications at catheter insertion included changing the side of the puncture site, neuralgia, changing the catheter and hematoma. Post-insertion complications included catheter-related blood stream infection (CRBSI), catheter-related thrombosis, occlusion due to blood flow reversal and self-removal. Serious complications were defined as severe conditions requiring additional treatment such as pneumothorax or hemothorax.

CRBSI was diagnosed according to the US National Hospital Infection Surveillance System CRBSI criteria (11). CRBSI was diagnosed when both the peripheral blood culture and the catheter tip culture were positive, with the same bacteria detected and no relationship with other infections, and when the patient presented with one or more of the following during catheter placement : fever of 38°C or higher, shaking with chills, and blood pressure decrease. The CRBSI incidence was determined

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as CRBSI events per 1,000 catheter-days.

The PICCs used were from a polyurethane (16G) 50 cm-long PICC kit (cat. no. PR-35041-HPSL ; Teleflex Medical Japan, Tokyo) with a 0.046 mm-diameter guidewire (length 130 cm) and a 7.0 cm-long 22G puncture short needle. The CICC were from a polyurethane (20G) 20-cm-long Microneedle Seldinger Kit (cat. no. 1320-12G ; Covidien Japan, Tokyo) with a 0.44 mm-diameter guidewire (length 60 cm) and a 6.7 cm-long 22G puncture long needle.

*Catheter insertion methods*

Table 1 summarizes the insertion method for the catheters. The maximal barrier precaution technique was used for insertion of all PICCs and CICCs. In all patients, the catheter was inserted in a fluoroscopy room by a physician wearing a surgical hat, mask, gloves, and gown after the disinfection of a wide area and the securing of a clean field with large sterile sheets. For the pre-insertion disinfection, 10% povidone iodine was used. Local anesthesia (1% lidocaine) was administered at the puncture site. For the PICCs, the puncture was performed with ultrasound real-time guidance by positioning the ultrasound probe in the short-axis direction relative to the vein. For the CICCs, the puncture was performed after confirming the course of vessels using ultrasound.

The first-choice puncture vein when a PICC was used was the brachial vein, and a position cranial to the elbow joint was selected. The first-choice puncture vein when a CICC was used was the subclavian vein ; the selection of the femoral vein was avoided whenever extent possible. When the subclavian vein was punctured, the conventional landmark technique (12) was used, and when puncturing the internal jugular vein, the ultrasonic-guided technique (13) was used. After the needle was inserted into the vein through the blood-vessel puncture site, the guidewire was inserted, and using a dilator, the opening was expanded further from the insertion site in the skin to the vein’s insertion site.

In all cases, X-ray fluoroscopy was used to confirm that the catheter tip was located in the superior vena cava at the level of the bifurcation of the trachea. Each PICC was fixed using its set’s fixture, and the CICCs were all fixed by tying two 2-0 silk sutures around the catheter. A sterile film dressing agent was used. Senior residents who had been trained by attending physi-

cians for both PICC and CICC insertions performed the catheter insertions under an attending physician’s supervision.

*Catheter management*

For both types of catheters, the dressing was changed 1×/week and the route was changed 1×/4 days by a nurse. When the catheter was not in use, heparin was administered into the catheter and a clamp was placed. Each catheter was removed when its purpose was fulfilled. For removal, the insertion site was disinfected with 10% povidone iodine and the catheter tip was immediately placed in a sterile centrifuge tube. Only the catheter tip was cut off and submitted for culture. The presence/absence of catheter-related thrombosis was assessed using contrast-enhanced CT images taken after the completion of the esophageal cancer treatment.

*Statistical analyses*

SPSS 22 software was used for all analyses. We used Fisher’s exact test or Pearson’s chi-square test to compare proportions and the t-test to compare mean values. To compare the infection rates, the log rank test was used with consideration of the in-dwelling period. The log rank test used the Kaplan-Meier method to perform a between-group test, with CRBSI occurrence as the event and with the duration as the period from catheter insertion to CRBSI onset. Continuous variables were expressed as the median and interquartile range (IQR) and were examined with a nonparametric Mann-Whitney U test. The significance level was set at p < 0.05.

**RESULTS**

*Patient characteristics and the state of catheter placement*

Table 2 shows the patients’ characteristics. The study population consisted of 199 patients, with 154 and 45 receiving PICC and CICC, respectively. The age and sex distribution were not significantly different between the two groups. Regarding concomitant diseases, more patients had circulatory system diseases than other diseases in both catheter groups. Fourteen (9.1%) PICC patients and two (4.4%) CICC patients were taking anticoagulants at their catheter insertion.

Table 2 shows the purpose and site of catheter insertion and

Table 1. The insertion method details for the catheters

	PICC	CICC
<b>Insert operation</b>	Maximal barrier precaution technique	
<b>Position</b>	Upper extremity abduction	Spine position
<b>Antiseptic solution</b>	10% povidone iodine	
<b>Insertion location</b>	Fluoroscopy room	
<b>Local anesthesia</b>	1% lidocaine	
<b>Puncture needle</b>	Plastic cannula short needle (22G)	Plastic cannula long needle (22G)
<b>Ultrasound</b>	Real time guidance	Landmark technique or Ultrasonic-guided technique
<b>Puncture vein</b>	Brachial vein	Subclavian vein or Internal jugular vein or Femoral vein
<b>Catheter fixation</b>	Using the fixture in the set Covered with film dressing	Tying two 2-0 silk sutures Covered with film dressing
<b>Practitioner</b>	The senior residents who had undergone training	
<b>Management</b>	One weekly film dressing changing The route exchanged once every four days by a nurse	

the reasons for catheter removal. The most common reason for insertion was chemotherapy, followed by perioperative management and the securing of vascular access for fluid infusion during long-term fasting. The insertion site was the upper arm in all 154 PICC patients and the subclavian vein in 41 of the CICC patients. In both catheter groups, the puncture was made on the right-hand side.

#### Complications at the catheter insertions

Table 3 shows the complications at catheter insertion. The complication rates at catheter insertion were 5.8% for PICC and 6.7% for CICC, and the difference was not significant ( $p = 0.536$ ). No serious complications occurred in either group. The complications at catheter insertion were the following: changing the side of the puncture site (4.5%), switching from a PICC to CICC (0.6%). Neuralgia, a PICC-specific complication observed at the puncture site, occurred in only one patient (0.6%). In the CICC group, the complications at catheter insertion consisted of switching from a CICC to a PICC (2.2%) and development of hematoma due to subclavian artery puncture (4.4%).

#### Catheter placement duration and post-insertion complications

The median numbers of days of catheter placement were 41.0 (33.0-47.0) days for PICC and 38.0 (27.5-43.5) days for CICC, and

the difference was not statistically significant ( $p = 0.194$ ) (Table 4). Post-insertion complications were observed in 6.5% of PICC patients and 11.1% of CICC patients ( $p = 0.337$ ). The incidence of CRBSI was significantly lower in the PICC than the CICC group (0.3 versus 1.8/1,000 catheter-days;  $p = 0.029$ ) (Fig. 1). Regarding the incidence of others complications, catheter-related thrombosis was observed in PICC: 0.5 and CICC: 0.6/1,000 catheter-days, and occlusion due to blood flow reversal was observed in PICC: 0.5 and CICC: 0.6/1,000 catheter-days. The incidence of self-removal was 0.3/1,000 catheter-days for PICC group.

#### Catheter tip cultures

Table 5 shows the results of catheter tip culture. The rate of positive PICC catheter tip culture was 5.2% and that of positive CICC catheter tip culture was 11.1%. The causative bacteria of CRBSI were *Staphylococcus caprae*, *Staphylococcus hominis*, and *Serratia marcescens* for the PICC group and *Staphylococcus haemolyticus*, *Staphylococcus capitis*, *Citrobacter freundii*, and *Candida parapsilosis* for the CICC group. Other bacteria detected, which were not diagnosed as CRBSI, were methicillin-resistant *Staphylococcus aureus* (MRSA) in two cases, *Chryseobacterium indologenes*, and *Candida dubliniensis*.

Table 2. Patient characteristics and the states of catheter placement

	PICC (n = 154)	CICC (n = 45)	P-Value
<b>Sex (Male / Female)</b>	132 / 22	37 / 8	0.636
<b>Age (year) Median (IQR)</b>	68.0 (61.0-75.0)	68.0 (65.0-76.5)	0.288
<b>Concomitant disease (%)</b>			
Respiratory disease	5 (3.2)	3 (6.6)	0.383
Liver disease	17 (11.0)	3 (6.6)	0.574
Cardiovascular disease	27 (17.5)	6 (13.3)	0.650
Taking anticoagulants	14 (9.1)	2 (4.4)	0.532
Cerebral hemorrhage	2 (1.2)	1 (2.2)	0.538
Kidney disease	2 (1.2)	0 (0)	0.598
Diabetes mellitus	6 (3.8)	2 (4.4)	0.574
Other	4 (2.5)	4 (8.8)	0.079
<b>Insertion purpose (%)</b>			
Chemotherapy	134 (87.0)	34 (75.6)	—
Perioperative management	8 (5.2)	8 (1.8)	—
Nutrition management	12 (7.8)	3 (6.6)	—
<b>Insertion site</b>	Brachium : 154	Subclavian : 41 Jugular : 3 Femur : 1	—
<b>Insertion side (%)</b>			
Right side	119 (77.3)	41 (91.1)	—
Left side	35 (22.7)	4 (8.9)	—
<b>Detention length (cm) Median (IQR)</b>	35.0 (32.0-38.0)	15.0 (15.0-16.5)	—

Table 3. Complications at the catheter insertion

	PICC (n = 154)	CICC (n = 45)	P-Value
<b>Number (%)</b>	9 (5.8)	3 (6.7)	0.536
<b>Content (%)</b>	Changing the side of puncture site (4.4) Neuralgia (0.6) Switched to CVC (0.6)	Hematoma (4.5) Switched to PICC (2.2)	—

Table 4. Duration of catheter placement and post-insertion complications

	PICC (n = 154)	CICC (n = 45)	P-Value
<b>Duration of catheter Placement (days)</b>			
Median (IQR)	41.0 (33.0-47.0)	38.0 (27.5-43.5)	0.194
<b>Post-insertion complications</b>			
All (%)	10 (6.5)	5 (11.1)	0.337
CRBSI (/total insertion days) (incidence / 1,000 catheter-days)	2/ 6252 0.3	3/ 1670 1.8	0.029*
Catheter-related thrombosis (/total insertion days) (incidence / 1,000 catheter-days)	3/ 6252 0.5	1/ 1670 0.6	0.731*
Occlusion due to blood flow reversal (/total insertion days) (incidence / 1,000 catheter-days)	3/ 6252 0.5	1/ 1670 0.6	0.912*
Self-removal (/total insertion days) (incidence / 1,000 catheter-days)	2/ 6252 0.3	0/ 1670 0.0	0.459*

\*Log-rank test.

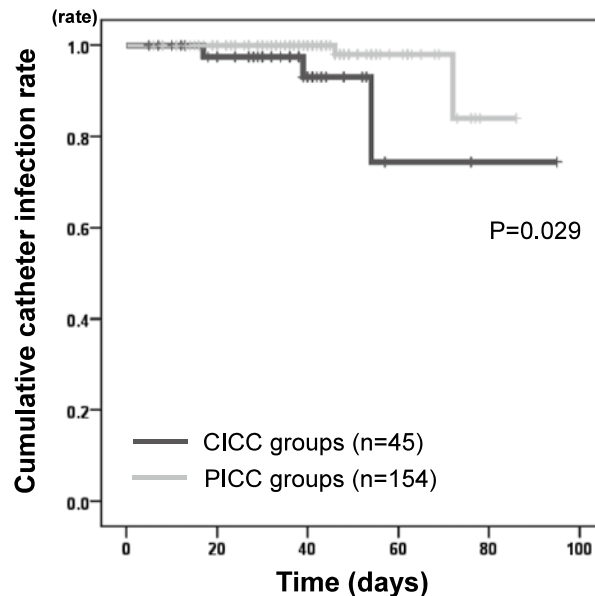


Fig 1. Comparison of CRBSI incidence by catheter group  
The figure showed that the incidence of CRBSI was significantly lower in the PICC group than the CICC group (P=0.029). To compare the infection rates, the log rank test was used with consideration of the indwelling period. The log rank test used the Kaplan-Meier method to perform a between-group test, with CRBSI occurrence as the event and with the duration as the period from catheter insertion to CRBSI onset.

Table 5. Results of catheter tip cultures

	PICC (n = 153*)	CICC (n = 45)	P-Value
<b>Positive catheter tip cultures</b>	8 (5.2%)	5 (11.1%)	0.262
<b>Causative bacteria</b>	Staphylococcus hominis Staphylococcus caprae Serratia Marcescens	Staphylococcus haemolyticus Staphylococcus capitis Citrobacter freundii Candida parapsilosis	—
<b>Other bacteria</b>	MRSA Staphylococcus capitis Candida dubliniensis	Chryseobacterium indologenes	—

\*One patient in the PICC group was excluded due to self-removal.

## DISCUSSION

PICCs are generally associated with fewer complications than CICC (1,3,5). Our present retrospective analysis also showed that PICCs were associated with lower incidence of CRBSI than CICC, suggesting that PICCs are a safe device to secure access for intravenous fluid administration. On the other hand, PICCs were reported to have many catheter tip abnormalities (2,6) and too often result in catheter-related thrombosis (5,14).

In this study, all of the present patients had esophageal cancer; many were male and  $\geq 65$  years old. Esophageal cancer patients generally have many comorbidities and a relatively high risk of complications due to central venous puncture. However, neither PICCs nor CICC showed any serious complications in this study. Although neuralgia was observed as a specific complication associated with PICC insertion, this complication can be avoided with the knowledge that the median nerve runs along the brachial veins, and by confirming the course of nerve fibers by means of ultrasound. Thus, once PICC insertion procedures become established and the anatomy is understood, PICCs might be the safest catheters.

CRBSI risk has been reported to be lower with PICCs than CICC (15,16), because compared to the chest and neck regions, the forearm has lower temperature and humidity and fewer resident bacteria and is less susceptible to contamination due to its distance from the nose and mouth. The incidence of CRBSI was 1.8/1,000 catheter-days in the CICC group and 0.3/1,000 catheter-days in the PICC group, and was significantly lower in the PICC group compared to the CICC group. Previous studies of venous catheter placement indicated that the incidence of CRBSI was 2.2–2.4 for CVCs and 0.2–0.7 for PICCs (8,9,17–21), which is consistent with our data. Thus, in light of the risk of developing infections, PICCs are ideal central venous catheters. Regarding the disinfectants used prior to a catheter insertion, although 2% chlorhexidine gluconate is recommended, 10% povidone iodine was used in our patients. The dressing was changed only 1×/week, although it is recommended that it be changed 2×/week; these protocol features thus need to be modified.

The typical causative agents of catheter infections are coagulase-negative Staphylococcus (CNS), *S. aureus* (including MRSA), *Candida*, *Enterococcus*, and Gram-negative bacillus (22,23). Catheter infection due to *Serratia marcescens* was observed in our study. Members of the genus *Serratia* are considered highly likely to be transmitted via the hands of medical personnel (24). It is thus possible that infections occur at the time of catheter insertion or when the dressing is changed. Bacteria that did not develop CRBSI but were identified from catheter tip cultures were MRSA, *C. indologenes*, and *C. dubliniensis*. We suspect that these patients were latently infected but did not quite develop CRBSI, as their host immune system response was activated. Clinicians can make use of these findings, and we plan to change our management and insertion methods to further decrease the rates of infection.

Regarding post-insertion complications, it was reported that PICCs have higher incidences of thrombosis, phlebitis, and catheter failure (2,14). Although we observed no onset of phlebitis or catheter failure herein, thrombosis occurred in 1.9% of the patients, and in all thrombosis cases, contrast-enhanced CT after the esophageal cancer treatment revealed the thrombosis; the thrombosis was not identified because the patients presented with symptoms. The thrombosis disappeared with anticoagulants without the development of organ embolism in all patients. Because catheter insertion presents a thrombosis risk, clinicians must remain aware that thrombosis may occur. When the duration of placement is expected to be prolonged, the possible formation of blood clots must be checked by vascular ultrasound

or contrast-enhanced CT.

In our analysis, PICCs were associated with a lower incidence of CRBSI and higher safety than CICC. Therefore, PICCs could reduce the cost of treating catheter-related complications and shorten the length of the hospital stay. Although the PICC insertion procedure requires some skill, senior residents can perform catheter insertion safely without complications as long as training is provided by an attending physician using a blood vessel model. However, the anatomic knowledge pertaining to PICC insertion and training procedures has not been conventionalized. Future challenges are the creation of training manuals to convey such knowledge and procedures and the improvement of training systems, including workshops for PICC insertion procedures.

## CONCLUSION

PICCs in the treatment of esophageal cancer are safer and more useful than CICC, and reduce the incidence of CRBSI. We hope to standardize the insertion procedures, conventionalize the techniques, and establish a puncture training systems for using PICCs.

## DISCLOSURES

Ethical Statement: All procedures followed were in accordance with the ethical standards of the institutional responsible committee on human experimentation and with the Helsinki Declaration of 1964 and later versions.

Conflict of interest: All authors have no conflicts of interest associated with this study.

Informed consent: The requirement for informed consent was waived in light of the retrospective nature of the study.

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