



# THE SAHLGRENKA ACADEMY

## A comparison of Catheter-Related Infection in oncology patients with Peripherally Inserted Central Catheter versus Totally Implantable Central Access Device.

Degree project in Medicine

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## Abbreviations

CLABSI	Catheter-Line Associated Blood Stream Infection
CRBSI	Catheter-Related Blood Stream Infection
CRI	Catheter-Related Infection
CRP	C-Reactive Protein
CTI	Catheter-Tip Infection
CVAD	Central Venous Access Device
CVC	Central Venous Catheter
IVAD	Implantable Venous Access Device
PICC	Peripherally Inserted Central Catheter
RCT	Randomized Controlled Trial
SFAI	Swedish Society of Anesthesiology and Intensive Care
SIRS	Systemic Inflammatory Response Syndrome
SÄS	Södra Älvsborg Hospital (Swe: Södra Älvsborgs Sjukhus)
tCVC	Tunneled Central Venous Catheter
TIVAD	Totally Implantable Venous Access Device
TIVAPS	Totally Implantable Venous Access Port System

## Abstract

Degree project, Programme in Medicine. *A comparison of Catheter-Related Infection in oncology patients with Peripherally Inserted Central Catheter versus Totally Implantable Central Access Device*. Lisa Bjerling, 2017, Department of Infectious Diseases and Infection Control, Södra Älvsborg Hospital, Borås, Sweden. University of Gothenburg, Gothenburg, Sweden. Supervisor: Maria Werner, MD, PhD.

**Introduction:** Catheter-Related Infection (CRI) is an important factor for morbidity in patients with a Central Venous Access Device (CVAD). The CRI-incidence differ between CVADs. In oncological care, CVADs used are for example Totally Implantable Venous Access Device (TIVAD) and Peripherally Inserted Central Catheter (PICC).

**Aim:** To find whether PICC or TIVAD gives the lowest incidence of CRI in patients with solid tumors.

**Method:** Records from 556 patients with CVADs (328 PICC and 228 TIVAD) inserted between 2015-2016 at Södra Älvsborg Hospital (SÄS) in Sweden were reviewed. The comparison of the CRI-incidence was made in two groups: Confirmed CRI and Total CRI (Uncertain CRI-episodes included). Data was analyzed with Kaplan-Meier survival function and Cox regression.

**Result:** 320 patients with 356 CVAD episodes (165 TIVAD and 191 PICC) were analyzed. 200 patients were excluded (mainly because of that the CVAD was not inserted at SÄS or age <18 years). In the Total TIVAD CRI-group, 46 CRIs was found (1.04 CRI/1000 catheter-days) and 26 CRIs was found (1.77 CRI/1000 catheter-days) in the Total PICC CRI-group. In the Confirmed TIVAD CRI-group, 24 CRIs was found (0.5 CRI/1000 catheter-days) and 2 CRIs (0.13 CRI/1000 catheter-days) in the PICC group. A significantly lower risk of CRI in patients with PICC was found in the Confirmed CRI-group (Hazard Ratio=0.093, 95% Confidence

Interval=0.01-0.869,  $p=0.037$ ) but not in the Total CRI-group (Hazard Ratio=1.029, 95% Confidence Interval=0.438-2.157,  $p=0.945$ ).

**Conclusion:** In patients with solid tumors there was no significant difference in CRI-incidence between PICC and TIVAD. Patients with PICC had a significantly lower CRI-incidence in the Confirmed CRI-group, indicating that PICC might be a safer alternative. The CRI-incidence in both groups were equivalent with earlier studies. Further prospective studies are needed.

**Keywords:** Catheter-Related Infections, Central Venous Catheters, Peripherally Inserted Central Catheter, Totally Implantable Venous Access Device.

## Introduction

Catheter-Related Infection (CRI) is an important factor for morbidity in patients with a Central Venous Access Device (CVAD) and might even be life-threatening if the patient become septic. CVADs are afflicted with different CRI-incidence, which is important to know in oncological practice, since (1) the patients need a safe long term supply of chemotherapy, large volumes of fluids and circulatory surveillance, which a CVAD presents (1).

## Central Venous Access Device (CVAD)

All CVADs have the catheter tip placed in the vena cava superior, within proximity of the heart (2). Common intravenous accesses are listed in Table 1.

**Table 1.** Short facts about central catheters used for venous access. Modified from O'Grady (3).

Catheter type	Entry site	Usage	CRI-risk
Nontunneled Central Venous Catheter (CVC)	Inserted into subclavian or internal jugular vein	Short term <sup>^</sup>	High
Tunneled Central Venous Catheter (tCVC)	Inserted ca 10 cm subcutaneously before entering the central vein (1)	Long term <sup>*(2)</sup>	Low
Peripherally Inserted Central Venous Catheter (PICC)	Inserted via a peripheral vein	Intermediate-Long term <sup>*(4)</sup>	Low
Totally Implantable Central Venous Access Device (TIVAD)	A subcutaneous injection chamber with a catheter inserted in the subclavian or the internal jugular vein	Long term <sup>*(2)</sup>	Low

<sup>^</sup>Short term: Under 4 weeks. <sup>\*</sup>Long term: More than 4 weeks.

*CRI=Catheter-Related Infection*

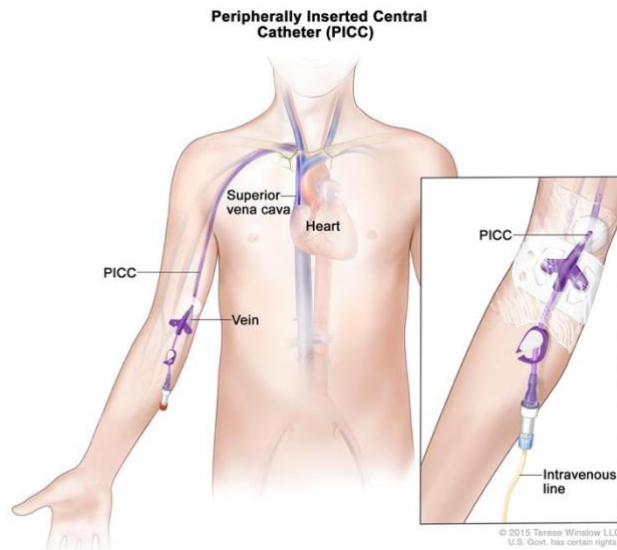
In oncological treatment, the most used CVADs are Totally Implantable Venous Access Device (TIVAD), Tunneled Central Venous Catheter (tCVC) and Peripherally Inserted Central Catheter (PICC), but data is not sufficient to recommend one specific type (5). Lately, PICC has become more frequently used, since it has fewer complications, costs less than other CVADs and the insertion is easier (1, 6). Oncology patients get infections easier since they have poor immune defense (7), partly because of chemotherapy and partly because of the disease. For this study to be as uniform as possible, the hematologic malignancies were excluded, since these patients often get intensive treatment of chemotherapy, which possibly could make them

more prone to get CRI. Hence, the focus of the study is on comparing CRI-incidence in PICC and TIVAD in patients with solid tumors.

### PICC

The PICC can be used for intermediate to long time (more than 4 weeks) (4). The insertion of a PICC is most often done under sterile procedures by a nurse

(1) with ultrasound guidance (4). The catheter is 20 cm or longer, depending on patient length (3).

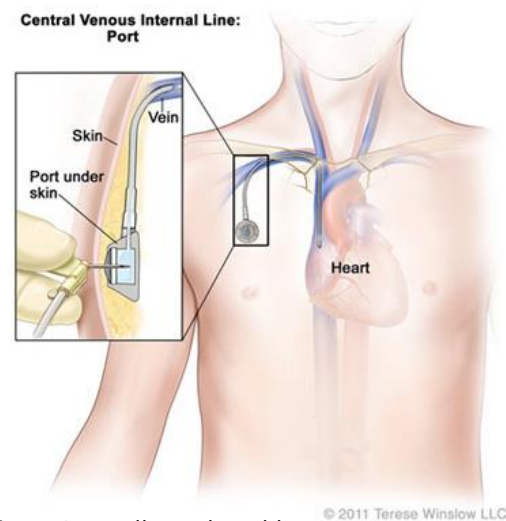


**Figure 1.** Peripherally Inserted Central Catheter inserted in a vein. Picture from (35).

### TIVAD

A TIVAD is for long-term (more than 4 weeks) usage (1, 8). The TIVAD has different terms in studies such as: port, port a cath (originally a name of a product, now used as a synonym for TIVAD), port-chamber catheter, Totally Implantable Venous Access Port System (TIVAPS) and Implantable Venous Access Device (IVAD).

The TIVAD consists of a chamber with a silicone membrane and an attached catheter (1). The chamber is implanted subcutaneously under sterile procedures (2). To access the venous blood, a port needle is injected into the implanted chamber (1). The needle needs to be changed at least every 5<sup>th</sup> day for inpatients and every 7<sup>th</sup> for outpatients (8).



**Figure 2.** Totally Implantable Venous Access Device inserted under the skin and in a vein. Port= Totally Implantable Venous Access Device Picture from (36).

## Complications

Patients with CVAD risk various complications, for example thrombosis, pneumothorax and CRI (1, 2), the latter is a common cause for premature catheter removal (9-12). Studies of PICC (11, 13, 14) show different complications (% of all episodes): Occlusion (2.4-44.3%), thrombosis (3.3-11.7%), CRI (3.2-6.9%) and migration (3.8-13.1%). One study showed that the most common complication in TIVAD is CRI (2.3%) and port expulsion (1.7%) (15). The results above are presented in percentage and not in CRIs per 1000 catheter-days (See definition below under the paragraph *Catheter-Related Infection - CRI-incidence*).

## Catheter-Related Infection (CRI)

### Definition

The definition of CRI differs among studies, which make them hard to compare. The most common definitions are Catheter-Related Blood Stream Infection (CRBSI) or Catheter-Line Associated Blood Stream Infection (CLABSI).

### *Catheter-Related Blood Stream Infection (CRBSI)*

There are different definitions of CRBSI (2, 16, 17) used which all include a positive blood culture. The Swedish guidelines use the following definition (2): 1. The same microorganism found in the catheter blood *or* at the catheter tip and in a peripheral vein *and* 2. Systemic inflammation symptoms, without any other source of the infection. (Criteria for systemic inflammation symptoms are found under the paragraph *Material and Methods - CRI definition*)

### *Catheter-Line Associated Blood Stream Infection (CLABSI)*

CLABSI is defined as a bloodstream infection in a central catheter that has been inserted longer than 48 hours, without any other source of infection (3). No confirming cultures are needed to classify the infection as CLABSI, but merely the lack of other focus for the infection than catheter-related. This definition could easily overvalue the incidence compared to CRBSI. In medical practice, CLABSI is more usable and CRBSI is more relevant at a scientific level.



### Local infection

A local infection includes redness with or without swelling and induration at the injection site and no signs of systemic inflammation or concomitant blood stream infection (2). This infection could lead to systemic inflammation and CRBSI, if not treated.

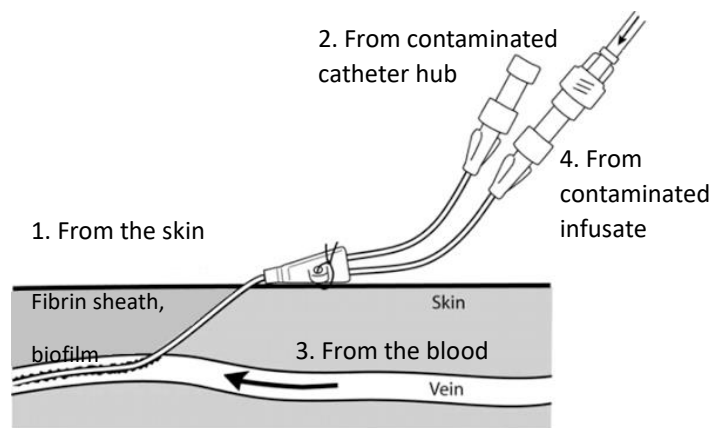
### Paired blood culture

The blood cultures taken shall be paired : Blood cultures from each lumen (if having more than one) of the CVAD and the peripheral blood are drawn at the same time and are measured by *time to positive blood culture* (To verify CRBSI, blood culture from the CVAD should be positive within 2 hours before the blood culture from the peripheral vein)(2) or by *quantity* (the ratio of concentration of microorganisms from the CVAD and peripheral blood is more than 3-5:1(18)). If one of these criteria is fulfilled, it is reasonable to assume that the infection originates from the CVAD (2).

### Pathogenesis

The source of CRI is microorganisms migrating to the catheter (19):

- 1) From the skin, along the outside of the catheter, to the tip,
- 2) Through the catheter, by contamination of the catheter hub,
- 3) From the blood to the catheter (hematogenous)
- 4) From contaminated infusate.



**Figure 3.** Origin of the Catheter-Related Infection  
Picture adapted from (37).

In long-term CVADs the most common source of infection is through the hub and in short-term CVADs from the skin (19). *Coagulase-negative staphylococci* or *Staphylococcus aureus* are the most common agents causing local infection (4). When the catheter is in place, a thin sheath of thrombin forms, in which microorganisms can adhere (19).

The bacteria can also adhere and aggregate on the catheter wall itself and form a biofilm. The adhesion is irreversible and the bacteria withstand antibiotic treatment. Hence the only way to cure an infection is to remove the CVAD. (20)

#### Prevention

In order to prevent CRI, one can focus on the ways CRI originates (See Figure 3):

1. The skin: CRI can be prevented by good hygiene routines and skin cleansing.
2. Contamination through the hub: CRI can be prevented by scrubbing the hub with alcohol (21).
3. The blood: CRI can be prevented by awareness of general sickness symptoms and treating other infections in the body.
4. The infusate: CRI can be prevented by using pre-filled syringes, when flushing the CVAD (22).

The importance of prevention is emphasized by both scientists and public authorities. Provonost (23) examined the prevention of CRBSI by showing that hygiene routines, avoiding unnecessary CVADs and femoral insertion reduced the CRBSIs from 0.62 to 0.34/1000 catheter-days in 18 months. Further, the Swedish Association of Local Authorities and Regions (24) has developed a bundle of measures for prevention of CRI, which stresses the points above and the importance of classifying the CRI adequately.

#### CRI-incidence

The incidence of CRI is preferably measured in CRI per 1000 catheter-days, which simplify the comparison between different CVADs, since they often are inserted for various time periods.

The comparison of CRI still is difficult, since studies often use different definitions of CRI.

The incidence of CLABSI in patients with PICC has shown to be 0.17-0.95 per 1000 catheter-days (11, 13) and the CRI-incidence 0.067-0.76 per 1000 catheter-days in TIVAD patients (25-27).

In 2006, Maki et al. (28) showed in a systematic review including 200 prospective studies (not only in oncology patients), that patients with TIVAD has the lowest incidence for CRBSI, with 0.1 CRBSI per 1000 catheter-days, while PICC had a CRBSI incidence of 1.0-2.1 per 1000 catheter-days.

Whether PICC is a safe long-term catheter choice has been debated (29, 30). Swedish Agency for Health Technology Assessment and Assessment of Social Services made an investigation of this in 2011, which was inconclusive due to too few high quality studies (1). The Swedish guidelines for central venous catheterization (2), from 2011, do not recommend PICC as a safe long term catheter choice. More recent studies indicate PICC to be a safe long term choice, regarding CRI (11, 13). There are few comparing studies of the CRI in patients with PICCs and TIVADs and some (29) focus only on complications and do not specifically look at CRI.

#### Situation at Södra Älvsborg Hospital

At Södra Älvsborg Hospital (SÄS), a secondary-level hospital in Western Sweden, which serves about 300 000 inhabitants, approximately 900 CVADs (CVC 67 %, PICC 20% and TIVAD 13 %) are inserted every year.

Specially trained nurses at the Department of Oncology insert all PICCs and all the personnel are trained to take care of CVADs. The nurses keep an own register (apart from registering complications in the medical record) of all complications related to the PICCs. This is not done for TIVADs.

TIVAD or PICC are both used as an intravenous access in oncology patients. The TIVAD might be difficult to get, because of low capacity at the operating theatre and the procedure must be scheduled a long time in advance compared to the PICC's insertion at the Department of Oncology.

During 2014, the incidence of CRI increased in patients with TIVAD. An unpublished study showed a CRI-incidence of 34% in 2014. No calculation for CRI per 1000 catheter-days was made. Consequently, the routines were revised.

According to SÄS guidelines (31), the use of CVAD shall be thoroughly documented, with emphasis to catheter complications.

### Medical relevance

It is important for the clinician to have knowledge about which of PICC or TIVAD is the safest long term central catheter regarding CRI.

### Aim

The aim of this study is to find whether PICC or TIVAD gives the lowest rate of CRI in patients with solid tumors.

Research question: Does the incidence of CRI differ in oncology patients with PICC or TIVAD treatment during the years 2015-2016 at SÄS?

## Material and Methods

### Study group

The study was a retrospective cohort study, conducted at Södra Älvsborg Hospital, in Västra Götaland, a region in south-west of Sweden. 560 medical records from oncological patients with either PICC or TIVAD, inserted at SÄS during January 2015 to December 2016, were analyzed. The medical records were reviewed for occurrence of CRI until CVAD removal or patient death. If none of the preceding occurred, the review lasted until the 3rd of August 2017.

Inclusion criteria: Patients  $\geq 18$  years of age, with a PICC or TIVAD inserted at SÄS due to their oncological disease. Solely care events given at SÄS were reviewed. In cases where patients were transferred to another hospital at some point during their catheter treatment, care events were only reviewed until the transfer date and not until catheter removal.

Exclusion criteria: Age < 18 years, CVADs not inserted at SÄS and hematologic malignancy or diagnoses other than malignancy as reason for CVAD treatment.

The patients were cared for at the Surgical or Medical Department. The PICCs were inserted by a special trained nurse in an examination room at the Department of Oncology and the TIVAD by an anesthesiologist in an operation theatre, with the continued care of the patient in respective department.

The data was collected from the CVAD-file (definition below, under the paragraph Documentation) registered in the medical record software system “Melior” and through a search in Melior, using the truncated terms: “infekt” (eng. infect), “hemm”, “hemsj” (truncated terms referring to home nursing) and “rodnad” (eng. redness).

#### CRI definition

The medical records were examined regarding CRI in accordance with the Swedish Society of Anesthesiology and Intensive Care’s (SFAI) definition (2), with some modification to make it more applicable for a retrospective study. The criteria for the different infection types are seen below.

**Local infection:** Redness with or without pus, induration or swelling at the injection site. No signs of Systemic Inflammatory Response Syndrome (SIRS). Absence of concomitant blood stream infection.

**TIVAD infection:** Local symptoms and a positive culture from the TIVAD injection chamber or the catheter tip. No signs of SIRS. Absence of concomitant blood stream infection.

**Catheter-tip infection (CTI):** Positive culture from the catheter tip. Signs of SIRS. Absence of concomitant blood stream infection. No other source of infection.

**Catheter-related blood stream infection (CRBSI):** The same microorganism is found in peripheral blood culture as in blood culture from PICC or TIVAD, or culture from the catheter tip. Signs of SIRS. No other source of infection.

**SIRS with unknown infection focus:** Signs of SIRS where the infection focus is unknown, but catheter-related focus can't be excluded. No positive blood culture.

**Systemic Inflammatory Response Syndrome (SIRS):**  $\geq 2$  of the following clinical findings: temperature  $> 38$  or  $< 36^{\circ}$  C, heart rate  $> 90$  beats/minute, respiratory rate  $> 20$  breaths/minute, B-leukocytes  $< 4 \cdot 10^9$  /liter or  $> 12 \cdot 10^9$  /liter.

**Fact box 1.** Definitions of Catheter-Related Infection.

*SIRS = Systemic Inflammatory Response Syndrome, TIVAD = Totally Implantable Venous Access Device,*

*PICC = Peripherally Inserted Central Catheter*

It is only possible to get one CRI per CVAD. If fulfilling a diagnosis with more severe criteria, the former is excluded. For example, if it is redness and swelling around the injection site (=local infection) and the catheter tip of the TIVAD has a positive culture (=TIVAD infection), it is classified as a TIVAD infection.

The medical records did not always include paired blood cultures and therefore the CRI-diagnose did included this in this study.

The CRI have also been categorized as either Confirmed or Uncertain:

**Confirmed CRI:** The physician diagnosed and treated the event as a CRI or when above criteria (See Fact box 1) were fulfilled and a positive culture (from the blood or the wound) were obtained.

**Uncertain CRI:** The medical records or diagnostics were faulty, making it difficult or impossible to classify the infections as catheter-related, but still not being able to exclude the possibility.

**Fact box 2.** Main groups of the Catheter-Related Infections

*CRI = Catheter-Related Infection*

Infections that were complicated to categorize were co-assessed with the study supervisor Maria Werner, a consultant in the infectious diseases and infection control. For example, one patient

with PICC had fever spikes without infection focus nor SIRS-symptoms at several times during a couple of months. After treatment, the PICC was removed and a culture was taken from the catheter tip, because of the previous fever spikes. At the time, the patient had no infection symptoms and the culture showed meagre of *Coagulase negative staphylococci*. This was judged to be a contamination, caused when the catheter was removed. Thus, this episode is not part of the CRI-analysis, since it is not an infection nor colonization, but shows the complexity of classifying infections with only the medical record as the source of information.

The date of infection was set to the first day when SIRS criteria or local infection criteria were met. In case the patient was treated for infection and discharged and then returned with infection symptoms again (no time limit was set), it was considered to be the same infection that had not properly healed. The date of infection was still set to the first day of the first episode and the last episode was not reported as a new infection.

### Variables

The examination protocol also included age, sex, diagnosis, catheter type, insertion date, reason for insertion, removal date, reason for removal, date of infection start, health care facility, chemotherapy, body mass index (BMI) and CVAD documentation compliance.

The diagnoses were categorized into cancer type groups: gastrointestinal cancer, gynecologic cancer, lung cancer, breast cancer and other malignancies (included peritoneal cancer, thyroid cancer, brain tumour, skin cancer, hypopharyngeal cancer, laryngeal cancer, liver cancer, neuroendocrine tumor (NET), kidney cancer, prostate cancer, testicular cancer, bladder cancer, oral cancer, sarcoma and cancer of unknown primary). In cases of disseminated cancer, the primary tumour determined the categorization of cancer type.

If the removal date was not documented or unclear and there was an uncertainty whether the CVAD was still in use, the review ended at the last seen notation of the CVAD. The same

procedure was used when the patient was transferred to another hospital, health care facility or went home with home health nursing.

BMI was registered in the protocol if measured one month prior to one month after insertion of the CVAD.

### CVAD-Documentation

A part of the study was to determine if the documentation in the digital medical records related to CVAD procedures had been made according to SÄS' guidelines (31), with the aim to validate the study data.

Every CVAD was obliged to have an own file, sorted in the correct place in the medical record. Furthermore, the documentation of the CVAD needed to include: indication, removal date, reason for removal, possible complications and have a separate connecting file for the treatment of the CVAD.

If the medical record included all the above conditions, it was classified as "adequate compliance" regarding present guidelines. If not, it was classified as "inadequate compliance". Concerning possible complications, the only complication that was considered during the review of the material was CRI. In the material, undocumented (as a complication in the CVAD-file) catheter-related thrombosis were found as a coincidence. Since thrombosis was not subject of this study more cases of thrombosis could have occurred without being documented in the CVAD-file.

### Statistical methods

470 CVADs divided into two groups of 235 CVADs each, were needed to achieve 80 % power with a significance level of 95 %.

All descriptive variables had their mean, median, range and percentage calculated when appropriate.



The number of catheter days was calculated as the difference between the removal date and the insertion date. To get CRI per 1000 catheter-days, the number of CRI were divided with the total sum of catheter-days in respective CVAD and multiplied by 1000. The total sum of catheter-days was calculated by summarizing the catheter-days until infection occurred and adding the rest of the non-infected CVADs' individual catheter-days.

Kaplan-Meier survival analysis for PICC and TIVAD were made, both for the Total CRI-group (Uncertain and Confirmed CRI) and the Confirmed CRI-group.

A Cox regression adjusted for age, sex, cancer type group and BMI was made. Statistical significance was set to  $p \leq 0,05$ .

All statistical calculations were performed with the computer program IBM SPSS Statistics 25.

## Ethics

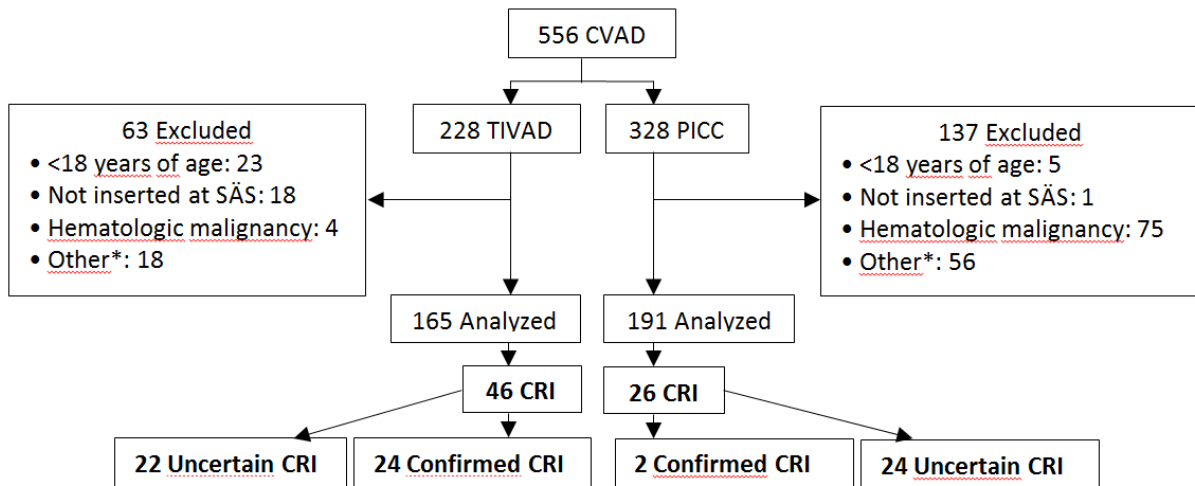
The study is a retrospective cohort study and therefore has no physical implications for the patients. The ethical consideration involves preservation of the patient's integrity. The patient secrecy is preserved by encrypting any digital documents containing personal data and no personal data is included in the report. Every patient is given a serial number, which is linked to the personal identity number using a code key, stored in paper form in a locked archive at the Department of Infectious Diseases, SÄS, until the year 2027.

The study has been approved by the Head Physician at SÄS, Jerker Isacson (See Appendix 1) and by the Consultants Ulf-Henrik Mellqvist at the Department of Oncology at SÄS and Nina Sjövall Widfelt at the Department of Anesthesiology at SÄS.

## Results

### Baseline data

556 CVAD episodes (328 PICC and 228 TIVAD) took part in the study. After exclusion, 356 CVAD episodes (165 TIVAD and 191 PICC) in 320 patients (242 women and 78 men) were analyzed (See Figure 4).



**Figure 4.** Flow chart of the study. Analyzed Catheter-Related Infections in bold.

\*Other: not treated at SÄS, duplicate, other diagnoses than malignancy and dummy document.

CVAD=Central Venous Access Device, TIVAD=Totally Implantable Venous Access Device, PICC=Peripherally Inserted Central Catheter, SÄS=Södra Älvsborg Hospital.

34 of the patients had two or three central catheters, of which 15 patients had both PICC and TIVAD. Only one central catheter was inserted at a time. Baseline characteristics of the CVAD episodes are shown in Table 2.

The total amount of catheter-days in the TIVAD group was 48 017 and 15 476 in the PICC group respectively (See Table 3). Reasons for removal of the CVADs are shown in Table 4.

**Table 2.** Baseline characteristics of the 356 analyzed CVAD episodes.

	<b>TIVAD</b> n=165	<b>PICC</b> n=191
Sex		
Female	113 (68.5%)	155 (81.2%)
Male	52 (31.5%)	36 (18.8%)
Age		
Mean; Median; [Range]	63.7; 65; [40-88]	59.7; 62; [23-84]
BMI		
Mean; Median; [Range]	24.8; 24.4; [13.8-36.4]	25.5; 24.8; [17.3-45.3]
Missing data	78 (47.3%)	52 (27.2%)
Malignancies		
Breast cancer	27 (16.4%)	107 (56.0%)
Gastrointestinal cancer	88 (53.3%)	25 (13.1%)
Lung cancer	11 (6.7%)	32 (16.8%)
Gynecologic cancer	23 (13.9%)	15 (7.9%)
Other malignancies	16 (9.7%)	12 (6.3%)
Chemotherapy	138 (83.6%)	156 (81.7%)
Health care facility <sup>^</sup>		
Home health nursing	26 (15.8%)	15 (7.9%)
Inpatient care	90 (54.5%)	171 (89.5%)
Unclear data*	49 (29.7%)	5 (2.6%)

<sup>^</sup>The health care facility that was involved in the treatment for the CVAD. \*Data was not clear whether the patient had home health nursing or not.  
*CVAD = Central Venous Access Device, TIVAD = Totally Implantable Venous Access Device, PICC = Peripherally Inserted Central Catheter, n = number, BMI = Body Mass Index*

**Table 3.** Comparison between catheter-days in all TIVAD and PICC patients and specifically with CRI.

	Entire group#		Total CRI-group <sup>^</sup>		Confirmed CRI-group	
	TIVAD	PICC	TIVAD	PICC	TIVAD	PICC
Sum catheter-days*	n=165	n=191	n=46	n=26	n=24	n=2
Per catheter						
Mean; Median; [Range]	48 017	15 476	7168	1363	2614	239
	291; 248; [2-918]	81; 68; [0-850]	156; 92; [2-825]	52; 20; [3-226]	109; 86; [14-399]	120; 120; [13-226]

#Patients with and without Catheter-Related Infection. <sup>^</sup>Confirmed Catheter-Related Infection and Uncertain Catheter-Related Infection.  
\*Sum catheter-days until removal or until infection (infection groups).  
*TIVAD = Totally Implantable Venous Access Device, PICC = Peripherally Inserted Central Catheter, CRI = Catheter-Related Infection, n= number*

**Table 4.** Reason for removal of Central Venous Access Device.

	TIVAD n=165	PICC n=191
Deceased	59 (35.8%)	27 (14.1%)
Not removed <sup>#</sup>	59 (35.8%)	0
Treatment completed	3 (1.8%)	90 (47.1%)
Change of CVAD-type	0	15 (7.8%)
Suspected CRI	26 (15.8%)	6 (3.1%)
Patient's wish	0	12 (6.3%)
Other complication <sup>*</sup>	7 (4.2%)	19 (10.0%)
Unclear if/when removed #	10 (6.1%)	9 (4.7%)
Other <sup>^</sup>	1 (0.6%)	13 (6.8%)

<sup>#</sup>Not removed until the end of the study. <sup>\*</sup>Other complication: malposition, malfunction or occlusion of the catheter. <sup>#</sup>Documentation of removal was faulty. <sup>^</sup>For example: CVAD dislodged, CVAD pulled out by patient and not documented removal reason.

TIVAD = Totally Implantable Venous Access Device, PICC = Peripherally Inserted Central Catheter, n= number, CVAD = Central Venous Access Device, CRI = Catheter-Related Infection

**Table 5.** Episodes of Catheter-Related Infection in TIVAD and PICC, divided into subcategories.

	TIVAD n=165		PICC n=191	
	CRI/1000 catheter-days		CRI/1000 catheter-days	
Catheter-related infections	46 (27.9%)	1.04	26 (13.6%)	1.77
Confirmed	24 (14.5%)	0.5	2 (1.0%)	0.13
Local infection	7		1	
TIVAD infection	16		0	
CRI	0		0	
CRBSI	1		1	
Uncertain	22 (13.3%)		24 (12.6%)	

TIVAD = Totally Implantable Venous Access Device, PICC = Peripherally Inserted Central Catheter, n = number, CRI = Catheter-Related Infection, CRBSI = Catheter-Related Blood Stream Infection

### Catheter-Related Infection (CRI)

There was a total of 46 episodes of CRI in the TIVAD group (27.9% of all episodes; 24 Confirmed and 22 Uncertain) and 26 episodes of CRI in the PICC group (13.6% of all episodes; 2 Confirmed and 24 Uncertain). Further subcategories of the Confirmed CRI are seen in Table 5.

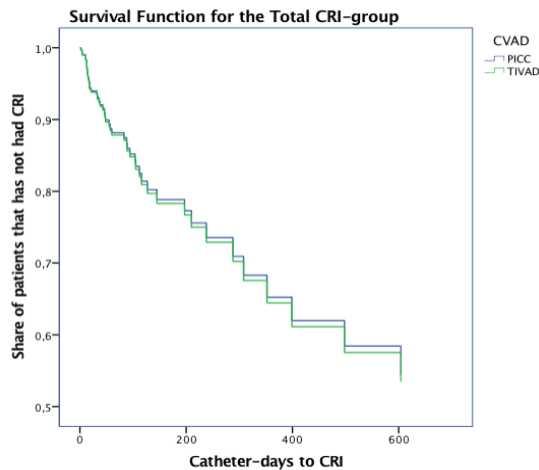
The number of catheter-days until CRI are shown in Table 3.

The total CRI rate in TIVAD were 1.04 per 1000 catheter-days and 0.5 per 1000 catheter-days in the Confirmed CRI-group. The same numbers for PICC were 1.77 in the Total CRI-group and 0.13 in the Confirmed CRI-group (See Table 5).

The Kaplan Meier survival function showed no significant difference in CRI-incidence between PICC and TIVAD.

There were two models of multivariate analysis of the CRI: Model 1, the Total CRI-group (Table 6) and Model 2, the Confirmed CRI-group (Table 7). Both models were adjusted for CVAD, sex, age, diagnose group and BMI. In Model 1, the Hazard Ratio (HR) for PICC was

1.03 (95 % Confidence Interval (CI): 0.44-2.16,  $p=0.95$ ), thus a 3% higher risk of getting a CRI if having PICC, but the difference was not significant. It was a significantly lower risk to get a CRI for a woman (HR=0.44, CI: 0.21-0.92,  $p= 0.03$ ) and a significantly higher risk to get a CRI for lung cancer patients (HR=7.34, CI: 1.38-38.96,  $p=0.02$ ) (See Figure 5 and Table 6).



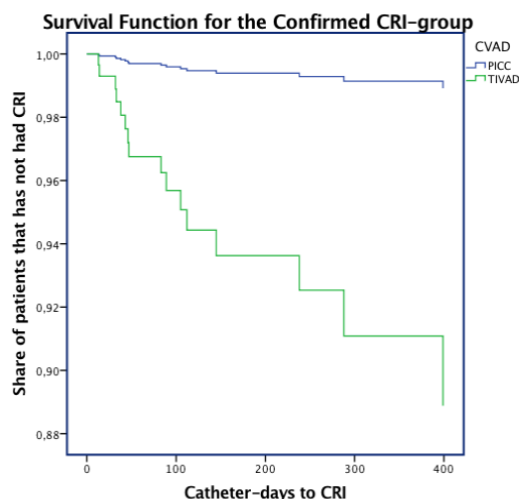
**Figure 5.** Kaplan-Meier survival function for the Total CRI-group, adjusted for CVAD, sex, age, diagnose group and BMI. CRI = Catheter-Related Infection, CVAD = Central Venous Access Device, PICC = Peripherally Inserted Central Catheter, TIVAD = Totally Implantable Venous Access Device

**Table 6.** Model 1: Cox regression for the Total Catheter-Related Infection-group.

	HR	95% CI	P-value
CVAD (PICC)	1.03	0.44 - 2.16	0.95
Sex (female)	0.44	0.21 - 0.92	0.03
Age	1.0	0.97 - 1.03	0.77
Diagnose group			
Other cancer (ref)			0.01
Breast cancer	1.60	0.25 - 10.27	0.62
GI cancer	2.57	0.58 - 11.31	0.21
Gynecological cancer	2.62	0.21 - 32.76	0.46
Lung cancer	7.34	1.38 - 38.96	0.02
BMI			
>30 (ref)			0.36
<18.5	0.39	0.04 - 3.48	0.40
18.5-24.9	1.72	0.69 - 4.28	0.24
25.0-29.9	1.33	0.52 - 3.40	0.55

HR = Hazard Ratio, CI = Confidence Interval, CVAD = Central Venous Access Device, PICC = Peripherally Inserted Central Catheter, ref = reference, GI = Gastrointestinal, BMI = Body Mass Index

Model 2 showed a 91% lower risk of getting a Confirmed CRI if having a PICC (HR=0.09, CI: 0.01-0.87,  $p=0.04$ ). None of the other variables were statistically significant (See Figure 6 and Table 7).



**Figure 6.** Kaplan-Meier survival function for the Confirmed CRI-group, adjusted for CVAD, sex, age, diagnose group and BMI. CRI = Catheter-Related Infection, CVAD = Central Venous Access Device, PICC = Peripherally Inserted Central Catheter, TIVAD = Totally Implantable Venous Access Device

**Table 7.** Model 2: Cox regression for the Confirmed Catheter-Related Infection-group.

	HR	95% CI	P-value
CVAD (PICC)	0.09	0.01 - 0.87	0.04
Sex (female)	0.52	0.16 - 1.69	0.28
Age	1.0	0.95 - 1.05	0.98
Diagnose group			
Other cancer (ref)			0.96
Breast cancer	1.44	0.07 - 28.50	0.81
GI cancer	1.85	0.20 - 16.94	0.59
Gynecological cancer	0	0	0.99
Lung cancer	2.51	0.15 - 42.68	0.53
BMI			
>30 (ref)			0.99
<18.5	0	0	0.99
18.5-24.9	0.86	0.19 - 3.93	0.84
25.0-29.9	1.02	0.22 - 4.76	0.98

HR = Hazard Ratio, CI = Confidence Interval, CVAD = Central Venous Access Device, PICC = Peripherally Inserted Central Catheter, ref = reference, GI = Gastrointestinal, BMI = Body Mass Index

## Compliance to guidelines for documentation

Criteria for adequate documentation of CVAD were met for 103 (62.4%) TIVADs and 147 (77.0%) PICCs. All Confirmed CRIs in PICC were documented under Complications in the CVAD-file and 91.7% (22 of 24) of the Confirmed CRIs in TIVAD (See Table 8).

## Discussion

The study shows that there is not a significant difference in the Total CRI-

incidence between PICC and TIVAD patients. This differ from previous conclusions (2, 3) which indicates that TIVAD is a safer choice than PICC, considering CRI.

Although, the analysis of the Confirmed CRI showed a significantly lower risk of CRI in PICC compared to TIVAD. The result is uncertain to rely on since the difference between the Confirmed CRI-group and the Total CRI-group is based on the Uncertain CRI-episodes. These episodes were infections that possibly, but not guaranteed, could be caused by the CVAD. Consisting either of true CRI-episodes with inferior diagnostics or other infections with inferior diagnostics. It is also important to note that some studies (11, 13) define CRI as CLABSI (defined as a positive blood culture and lack of other infection focus than the CVAD). Meaning that these CLABSIs might be misclassified. Considering the Uncertain episodes of CRI included in the Total CRI-group in this study, they do not have a confirming blood or wound culture nor a physician's confirming diagnosis, but merely a possibility to be catheter-related. They might be CRI, but could also be a neutropenic fever or another infection that the

<b>Table 8.</b> Compliance to guidelines for Central Venous Access Device-documentation at Södra Älvsborg Hospital.		
	<b>TIVAD</b> n=165	<b>PICC</b> n=191
Adequate documentation	103 (62.4%)	147 (77.0%)
Inadequate documentation#	62 (37.6%)	44 (23%)
Missing		
Indication	23	2
Removal date	10	21
Removal reason	11	19
Complication*	22	2
Wrong sorting of CVAD-file^	10	11
Missing Care-file	17	16
#When inadequate documentation, it is possible for each CVAD to have multiple inadequacies of the listed categories under Missing. *Only Confirmed Catheter-Related Infection was reviewed. ^The CVAD-file was not in the correct place in the medical record according to the guidelines. TIVAD=Totally Implantable Venous Access Device, PICC=Peripherally Inserted Central Catheter, n=number, CVAD=Central Venous Access Device		

diagnostics failed to find. Therefore, based on this study's result of the Confirmed CRI, it is possible that PICC might be an even better alternative than TIVAD, regarding CRI.

Furthermore, there was a significant difference between the Confirmed CRI-groups, that larger study groups as implied by the power analysis, were not needed. While in the Total CRI-group (including Uncertain CRI) no significant difference was found, which might depend on that the study group size did not fulfill the sizes of the power computed.

The study result is based on the follow-up time of the patients. Since 59 of the patients in the TIVAD-group (See Table 4) still had their TIVAD inserted at study completion and none in the PICC-group, the result is uncertain. If the remaining 59 patients with TIVAD had it inserted for 100 days more, it equals with 5900 more catheter-days, which could alter the result, but as we consider the risk of getting CRI to be the same every day it would not affect the result. To obtain an even more reliable result, only CVADs with follow-up until removal or the patient deceased should have been included in the study.

In addition, in 6.1% (n=10) of the episodes in TIVAD and 4.7% (n=9) in PICC the removal date was unknown (See Table 4) and the records were reviewed until the last notation of the CVAD, which could have given these CVADs a shorter catheter-time. Although, it was so few episodes that it probably does not have an implication on the result.

During the study, it emerged that TIVAD usually is chosen for patients in palliative care and PICC is usually chosen for patients with curative-intended treatment. A group with palliative care and one with curative-intended treatment cannot be considered equivalent groups, since palliative care probably is linked to a higher tendency to get infections.

Further, CRI can be categorized as early onset (the first 30 days (32)) or late onset, something that was not considered in this study. Early onset infection relates to the insertion and late onset relates to the treatment of the CVAD. In Table 3, the CRIs tend to occur late onset, in median

92 days in the Total CRI-group for TIVAD and 20 days for PICC. The catheter-time is longer in TIVAD in all groups, except in the Confirmed CRI-group, where the mean catheter-time is longer in PICC (120 days compared to 109 days), although, the PICC group consisted of only two episodes.

In the PICC and TIVAD groups there were 34 patients that appeared more than once, as they had been treated with more than one CVAD. These patients could get CRI in both of their CVADs, but would not be considered the same infection, since (20) the biofilm with attached bacteria are removed along with the catheter (20), hence, the CRI is treated (19). In addition, in occasions when PICC preceded TIVAD or vice versa, a possible CRI was considered unrelated since the CVADs are inserted at different places.

### Study population

#### Sex and age

The groups in Table 2, appear similar, both populations have a predominance of women, more distinct in the PICC-group (81% in PICC and 69% in TIVAD). This may be caused by the predominance of breast cancer in the PICC-group. Also, the lack of men could be caused by the fact that prostate cancer, the most common cancer in men, is not often treated with chemotherapy and consequently no CVAD is needed for the. Noticeable, is a greater range in age (23-84 years) in PICC patients compared to TIVAD patients (40-88 years), but the mean and median age were quite similar (PICC 59.7 and 62 years, TIVAD 63.7 and 65 years) indicating that there probably not was a greater difference in age.

#### BMI

We considered BMI under 18.5 a pseudo marker for a patient who might be in palliative care. Presumably, the incidence of CRI should have been increased in this group. The TIVAD group had more underweight patients and the PICC group had more obese patients, when looking at the range (Table 2). The multivariate analysis did not show a significant result for the group of patients with BMI under 18,5. Although, this group only consisted of 10 patients. There was



also a lot of BMI-data missing (almost 50% in the TIVAD-group and 30% in PICC-group), which means it is not possible to draw a conclusion from BMI. Low BMI might have had a bigger impact on the CRI-incidence if a larger sized group with complete data had been studied. One study (33) found obese patients to have an increased complication rate. No such results were found in this study.

#### Malignancies and chemotherapy

The malignancies in the different CVAD groups differed in numbers. This could indicate that the groups were not as similar as thought when starting the study. Each cancer type accompanies with its own burden of disease, neutropenia and chemotherapy. The chemotherapy itself might have had an impact on the result. Possibly, some type of chemotherapy facilitates CRI more than other chemotherapy, as Bertoglio et al. (13) found in their study.

#### Health care facility

Our hypothesis that home health nursing leads to more CRI (when the personnel might not have the same experience and training in taking care of CVADs) cannot be concluded, since there was a large decline in data, with almost 30% inconclusive data in the TIVAD-group. In the PICC group, only 7.9 % (n=15) of the patients had home health nursing, which might be a reason for the lower CRI-incidence in this group (See Table 2).

#### CRI

The CRIs were analyzed in two different groups: Confirmed CRI and Total CRI (including episodes of Uncertain CRI).

The CRI-incidence in the Confirmed CRI-group for TIVAD was 0.5 per 1000 catheter-days and for PICC 0.13 per 1000 catheter-days, which is comparable with earlier studies (11, 25-27).

Considering how the CRI originates, the tending of the CVAD is of utmost importance, since the most common contamination is through the hub (19). Depending on the skill of whom takes care of the treatment of the CVAD (personnel, patient or relative), contamination risk might

differ. Other factors, like type of treatment administrated through the CVAD (32), skin problems or amount of subcutaneous fat (when implanting a TIVAD) could differentiate the CRI-risk.

It only occurred two episodes of Confirmed CRI in the PICC-group. This might be because the PICC-group mainly consisted of breast cancer patients, who often do not have a great comorbidity. Furthermore, breast cancer patients are treated at the Department of Oncology, where the personnel have special training in taking care of PICCs. The fact that most of the patients (89.5%, n=171) were inpatients (meaning that the care of the CVAD was given at the hospital) also indicates better treatment of the PICC.

Looking at the TIVAD group, it occurred 24 Confirmed episodes of CRI. 26 patients (15.8%) had home health nursing, which might be associated with higher CRI-risk. There was an obscurity in almost 30% of the data, if all of these had home health nursing together it would constitute almost half of the TIVAD-episodes. In the PICC-group, only 7.9% had home health nursing and 2.6% were unclear data.

To further decrease the incidence of CRI in the TIVADs, an intervention could be made, with focus on education of both personnel and patients in hygiene routines and information about current CVAD guidelines. A TIVAD-team, a smaller group handling the care of the TIVADs, might be of great value.

Additional factors that previous work have found to be associated with a higher CRI-incidence is the CVAD material (19) and age less than 40 years (34). The CVAD-material were not considered in this study and might have had implications on the result, while the age was not related to a higher CRI-risk.

The multivariate analysis in the Total CRI-group also showed that women have a lower risk and lung cancer patients has a higher risk of getting CRI. One can speculate why women have

a lower risk of CRI: perhaps they seek medical care more often than men, they have better self-care or the hormonal difference is crucial. The subgroup of lung cancer patients has a high risk of CRI, although the result should be interpreted with care considering the large confidence interval (CI=1.38-38.96) (See Table 6). Further studies need to be made in order to find the reason for these indications.

#### Clinical documentation

The more adequacies in documentation for PICC (See Table 8) could be due to that all PICCs are inserted and many are managed by nurses at the Department of Oncology, a small and well-organized group. While patients with TIVAD has different responsible personnel, depending on which diagnosis the patient has got. The documentation might be missed more easily in the TIVAD group.

The fact that thrombosis occurred without being documented as a complication in the CVAD-file indicates that there may be more complications that fail to be documented.

#### Study limitations

First, there was a validation bias, since only one person reviewed the records. Consequently, CRIs could have been missed or misjudged. At the end of the study, knowledge and proficiency were acquired, thus the later CVAD episodes got a better assessment. Complex cases were co-assessed, making error less likely.

Second, being a retrospective medical record review, all information obtained originated from written medical records. The quality of the records differed and the possibility to classify infections were sometimes not optimum. In addition, the study was based on the diagnosis of CRI set up for the study and a part of the criteria was SIRS-symptoms. In Sweden, it is medical practice to diagnose infections with C-Reactive Protein (CRP), which is not included in the SIRS criteria. Making the CRI diagnose sometimes impossible to verify, when there only is

CRP and fever in the medical records. Also, there is a possibility that the clinicians use different definitions of CRI.

To find whether PICC or TIVAD is the safest regarding CRI, a Randomized Controlled Trial (RCT) is of interest. Only a few such studies have been done. One (29) was made in 2013, comparing the complications in PICC and TIVAD. TIVAD had less complications than PICC, but the study did not present specific statistics for CRI. A new RCT, focused on CRI, could possibly sort out whether there is a real difference in CRI-incidence between PICC and TIVAD.

Third, when reviewing a medical record by using truncated search terms, it relies on the personnel using the same terms to describe infection. If not, infections can be missed. The word infection might not have been used, but instead fever, tachypnea or antibiotics. To avoid this, the full length of the medical records needs to be read, which for this study was not manageable.

Fourth, there might be a selection bias, since it is possible that most of the patients with TIVAD are in palliative care. This is not consolidated, but if it is true the study groups are not equivalent.

Fifth, if the patients in the home health nursing are managing their CVADs themselves there might be an increase in the CRI-risk. Comparing inpatients with patients with self-care of the CVAD are not equivalent groups either.

## Conclusion

The study did not find a significant difference in CRI-incidence in the Total CRI-group, between PICC and TIVAD in patients with solid tumors, meaning that both catheters make a safe long-term CVAD choice. Possibly, PICC is an even safer alternative, when considering that in the Confirmed CRI-group a significantly lower risk for CRI in patients with PICC compared to TIVAD was shown. The incidence of Confirmed-CRI was low (0.05 for TIVAD and 0.13 for PICC) and equivalent with earlier studies.

The uncertainties of how many of the patients were in palliative care might have had implications on the result. Apart from this, the findings are interesting in a view of comparing two different CVADs, since many of the studies done are single CVAD studies.

The Uncertain CRIs (in the Total CRI-group) were characterized by inadequate diagnostics and documentation. Hence, the quality needs to improve to prevent these shortcomings.

Further prospective studies are of interest to compare the CRI-incidence in different CVADs the oncological population.

## Populärvetenskaplig sammanfattning

### Vilken kärlkateter ger lägst infektionsrisk hos cancerpatienter?

Kateterrelaterad infektion orsakar sjuklighet och kan ibland vara livshotande hos patienter med central kärlkateter. En central kärlkateter är en kateter som sätts i ett blodkärl nära hjärtat, vilket möjliggör kontinuerlig tillgång till blodbanan. Genom den kan man bland annat ge kärlretande läkemedel, stora volymer vätska och blod.

Antalet kateterrelaterade infektioner varierar mellan olika centrala kärlkatetrar, vilket är viktigt att veta inom vården så rätt kateter väljs vid rätt tillfälle. I cancervården används bland annat subkutan venport och perifert insatt central kateter (PICC). PICC kallas perifer för att den läggs via ett blodkärl i armen (istället för ett blodkärl nära hjärtat direkt) och löper sedan genom blodbanan och slutar precis i anslutning till hjärtat. Subkutan venport består av en dosa som opereras in under huden (subkutan = under huden) strax under nyckelbenet. Ifrån dosan går en kateter in i ett centralt blodkärl och slutar precis i anslutning till hjärtat. En nål sticks sedan i dosan då man vill få åtkomst till blodbanan.

Patienter som har en central kärlkateter kan drabbas av infektioner och det är även en vanlig orsak till att katetern tas ut tidigare än planerat. Att minska de kateterrelaterade infektionerna är viktigt. Ett sätt att göra det är att veta vilken kateter som ger lägst antal infektioner hos olika patientkategorier. Exempelvis används subkutan venport till patienter som behöver en central kärlkateter under lång tid, eftersom den anses vara förknippad med färre infektioner.

Syftet med studien var att ta reda på om det är någon skillnad i kateterrelaterad infektionsförekomst hos patienter med cancer (all cancer utom blodcancer), som har antingen en PICC eller en subkutan venport.

I studien analyserades 356 journaler tillhörande cancerpatienter med PICC eller subkutan venport.

Studien fann inte någon skillnad för cancerpatienter att få kateterrelaterad infektion om man hade subkutan venport eller PICC. Möjligen skulle PICC vara ett bättre alternativ, men infektionsdiagnostiken var för undermålig för att vara säker. Det var även osäkert hur många av patienterna som vårdades i livets slutskede, vilket kan inverka på resultatet. För att ytterligare utreda kateterrelaterade infektionsförekomsten och säkerställa resultatet krävs förbättrade studier.

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## Appendices

### Appendix 1 – Study approval



VÄSTRA  
GÖTALANDSREGIONEN  
SÖDRA ÄLVSBERGS SJUKHUS

1 (1)

Datum 2017-07-14  
Diarienummer SÄS 2017-00614

#### **Intyg avseende journalgranskning.**

Härmed intygar jag att Lisa Bjerling [REDACTED], Medicine studerande vid Göteborgs Universitet, har behörighet att granska journaler tillhörande patienter som har haft en PICC-line eller subkutan venport insatt på SÄS för att genomföra studien "Skiljer sig den kateterrelaterade infektionsincidensen hos onkologiska patienter mellan de med perifert insatt central kateter och subkutan venport på Södra Älvsborgs Sjukhus?". Undersökningen innefattar datainsamling från vårdtillfällen under åren 2015-2016 och utgör en del av sjukhusets systematiska kvalitetsarbete.

#### **Undersökningen pågår sommaren och höstterminen 2017 och är ett examensarbete som del i läkarexamen.**

Lisa Bjerling kommer att få tillgång till en arbetsplats på forskningsavdelningen /SÄS. Maria Werner, Överläkare, Vårdhygien/Infektionskliniken /Borås SÄS kommer att vara handledare.

Handledaren ansvarar för att Lisa har fått information och förstått gällande regler för sekretess, vilket är en förutsättning för behörigheten, samt att hon är införstådd med att loggranskning av journaler kommer att genomföras.

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