

Can Peripherally Inserted Central Catheters Be Safely Placed in Patients with Cancer Receiving Chemotherapy? A Retrospective Study of Almost 400,000 Catheter-Days

SARA CAMPAGNA,^a SILVIA GONELLA,^c PAOLA BERCHIALLA,^b GIACOMO MORANO,^d CARLA RIGO,^e PIETRO ANTONIO ZERLA,^f RAFFAELLA FUZZI,^g GIANVITO CORONA,^h SILVANA STORTO,^d VALERIO DIMONTE,^{a,c} BAUDOLINO MUSSA^c

Departments of ^aPublic Health and Pediatrics and ^bClinical and Biological Sciences, University of Torino, Torino, Italy; ^cAzienda Ospedaliero Universitaria Città della Salute e della Scienza di Torino, Torino, Italy; ^dAzienda Policlinico Umberto I, Rome, Italy; ^eAzienda Ospedaliero Universitaria Maggiore della Carità, Novara, Italy; ^fAzienda Socio Sanitaria Territoriale Melegnano e della Martesana, Vizzolo Predabissi, Italy; ^gAzienda Unità Sanitaria Locale Romagna sede di Forlì, Forlì, Italy; ^hAzienda Sanitaria Provinciale Potenza, Potenza, Italy

Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Complications • Hematologic neoplasms • Medical oncology • Peripheral catheterization • Patient safety • Vascular access devices

ABSTRACT

Background. Peripherally inserted central catheters (PICCs) are central venous catheters (CVCs) that are commonly used in onco-hematologic settings for chemotherapy administration. As there is insufficient evidence to recommend a specific CVC for chemotherapy administration, we aimed to ascertain PICC-related adverse events (AEs) and identify independent predictors of PICC removal in patients with cancer receiving chemotherapy.

Materials and Methods. Information on adult patients with cancer with a PICC inserted for chemotherapy administration between September 2007 and December 2014 was extracted from six hospital databases. The primary outcome was PICC removal due to PICC-related AEs (occlusion, infection, or symptomatic thrombosis). Independent predictors of PICC

removal were identified using a multivariate Cox regression model.

Results. Among the 2,477 included patients, 419 PICC-related AEs (16.9%; 1.09 AEs per 1,000 PICC-days) were reported. AEs increased when PICC was inserted at the brachial site (hazard ratio [HR], 1.37; 95% confidence interval [CI], 1.02–1.84) and with open systems (HR, 1.89; 95% CI, 1.24–2.88) and decreased in older men (HR, 0.63; 95% CI, 0.49–0.81).

Conclusion. Use of PICC for chemotherapy administration was associated with a low all-AEs rate. The basilic vein was the safer site, and valved systems had fewer AEs than open systems. More research is needed to explore the interaction between AEs, sex, and age. *The Oncologist* 2019;24:1–7

Implications for Practice: These findings provide clinicians with evidence that peripherally inserted central catheters (PICCs) are safe for chemotherapy administration. They also suggest that clinicians should limit the use of open systems when long chemotherapy regimens are scheduled. Moreover, alternatives to PICCs should be considered when administering chemotherapy to young men.

INTRODUCTION

Choosing the appropriate vascular access device for an oncology patient is a collaborative process involving the physician, patient, nurses, and other members of the health care team [1]. The selection of either a peripheral catheter or central venous catheter (CVC) is the first decision in vascular access planning, and some validated tools can help health care professionals identify patients that are candidates for CVCs [2].

In patients with cancer, CVCs are used throughout the course of their illness. In initial phases, CVCs can be used for neoadjuvant chemotherapy or postsurgery adjuvant therapy; in advanced and final phases, CVCs can be used for palliative and supportive care [3]. However, there is insufficient evidence to recommend a specific type of CVC or insertion site for chemotherapy administration [4]. The choice largely

Correspondence: Silvia Gonella, M.Sc., Azienda Ospedaliero Universitario Città della Salute e della Scienza di Torino, Corso Bramante 88-90, 10126, Torino, Italy. Telephone: 39-011-0915831; e-mail: silvia.gonella@unito.it Received May 9, 2018; accepted for publication November 21, 2018. <http://dx.doi.org/10.1634/theoncologist.2018-0281>

depends on the type of treatment, the number of drugs administered together with the expected duration of treatment, the patient's preferences and ability to care for the device, the global cost of insertion, and the clinical experience of the provider [3, 5].

The use of peripherally inserted central catheters (PICCs) has steadily gained popularity over traditional CVCs in all fields of clinical practice, including in onco-hematologic settings. This may be due to the perception that PICC insertion is an easy procedure that can be performed by trained nurses at the patient's bedside without the need of an operating room, thus saving money and reducing delays in treatment administration [6]. Moreover, when inserted in a peripheral vein, PICCs are associated with fewer adverse events (AEs) than traditional CVCs while providing the benefit of a central tip location for high-flow infusion, high-pressure injection, and any osmolarity solutions [7].

Despite these benefits, bloodstream infections (BSIs) occurred as frequently in hospitalized patients with PICCs as in patients with other CVCs [8]. In addition, the risk of deep vein thrombosis and mechanical AEs is increased in patients with PICCs [9], and in critically ill patients or patients with cancer, the risk of PICC-associated thrombosis grows dramatically [9]. Any such AE creates problems for treatment and could potentially result in CVC removal, causing delayed intravenous infusion and increased costs [10]. Therefore, there continues to be concern about the potential risk of using PICCs for chemotherapy administration in patients with cancer, as they usually require prolonged intravenous therapies, are immunocompromized, and are prone to prothrombotic events. Moreover, patients may perceive a PICC as a constraint to their daily activities because of the presence of a foreign body at the superior midarm, and thus may prefer other CVCs [11].

Information regarding PICC safety in patients with cancer receiving chemotherapy is scarce. To our knowledge, the few existing studies on this topic had short observation periods and included only homogeneous populations of patients with malignant tumors (i.e., solid neoplasms [12–14] or hematological malignancies [15–17]), and the majority addressed only thrombosis or BSI [12, 18–21], making their reports on PICC safety difficult to generalize to all patients with cancer. Indeed, a clinician's choice of CVC for chemotherapy administration should be rooted in strong evidence. Therefore, in order to guide clinical practice and ensure patient safety, this study aimed to ascertain PICC-related AEs and identify independent predictors of PICC removal in a large sample of patients with oncologic or hematologic malignancies undergoing chemotherapy.

MATERIALS AND METHODS

Study Design and Setting

This was a multicenter retrospective study. All public Italian hospitals that (a) adopted the Safe Insertion Protocol of PICCs [22], (b) inserted >1,000 PICCs per year, and (c) offered specific training to the staff for inserting and managing PICCs were invited to participate to the study. Among 12 eligible hospitals, 2 declined participation and 4 provided information

limited to PICC insertion and were therefore excluded. Thus, six hospitals finally participated in the study on a voluntary basis. All adult patients with cancer (inpatients and outpatients; $n = 3,490$) with a PICC inserted for chemotherapy administration between September 2007 and December 2014 were eligible for inclusion. We excluded those who had no PICC removal date reported ($n = 1,013$; 29%).

PICC Insertion and Maintenance

All hospitals had policies and specific staff intended to ensure that the best insertion practices were followed [22].

The PICCs used in this study were manufactured by Bard (Covington, GA) and Medcomp (Harleysville, PA). They were mainly 4 French (Fr) in diameter and 25–55 cm in length. Hospitals used both valved-system and open-system PICCs, with the latter usually being employed when patients needed repeated high-pressure injections (e.g., contrast agent for computed axial tomography) or high-osmolarity infusions (e.g., blood products, parenteral nutrition).

After the PICC was inserted, a sterile 5 × 5 cm gauze dressing was positioned and held in place with a transparent dressing (Tegaderm 3M IV3000, Smith & Nephew; Agrate Brianza, Italy). The dressing was changed the day after insertion using transparent dressing only unless there was evidence of hematic or serous material. Thereafter, transparent dressings were changed every 7 days, and gauze plus transparent dressings were changed every 48 hours. PICCs were anchored with an adhesive-based sutureless fixation device (e.g., StatLock). All PICCs were assessed for patency and flushed with 10 mL of 0.9% saline solution at the time of insertion. PICC tip location at the distal third of the superior vena cava was confirmed by chest x-ray within 6 hours, and PICCs were repositioned when the tip was not at the appropriate location. Staff nurses inspected the intravenous sites once per shift for signs of mechanical or infectious AEs. Devices were cared for by staff nurses in accordance with institutional protocols.

Data Collection

Information was taken from six hospital databases on PICCs. Each hospital adopted a specific database using Excel as a quality monitoring. According to hospital policy, data on patient characteristics, PICC characteristics, and cause of PICC removal are routinely collected and entered into a database by the PICC insertion team. These data include (a) patients' sex, age, and underlying disease (oncologic malignancy, hematologic malignancy, or other); (b) PICC insertion site (side and vein used), dwell time (calculated as the difference between the insertion and the removal dates), PICC system (open or valved, i.e., a distal valve that prevents backflow of blood when the PICC is not in use); and (c) cause of PICC removal: PICC-related AEs (occlusion, exit-site infection, or symptomatic thrombosis) or other reason (accidental removal, termination of therapy, natural device expiration, or death of the patient).

Study Endpoints and Definitions

The primary study endpoint was PICC removal due to PICC-related AEs. Because PICC-related AEs represented a composite of AEs, a composite rate was used to provide an overall understanding of PICC safety. The composite measure was

defined as the number of AEs per PICC-days (i.e., the time period during which a PICC was in place) and was presented as per 100 PICCs (%) and per 1,000 PICC-days. The latter was generated by dividing AEs by the number of days the PICC was inserted and then multiplied by 1,000. A rate per 1,000 PICC-days allows for more meaningful estimates of risk when catheters have different dwell times and is a standardized measure that allows us to compare results across studies [23].

The frequency of each AE (i.e., occlusion, exit-site infection, or symptomatic thrombosis) was reported as a secondary outcome.

Chemotherapy was defined as the use of intravenous chemotherapy prescribed by oncologists in accordance with institutional protocols of neoadjuvant, adjuvant, or palliative chemotherapy for different types and stages of tumors.

Occlusion was defined as the complete inability to flush, infuse, or aspirate (i.e., complete occlusion); resistance with flushing and aspiration or sluggish infusion (i.e., partial occlusion); or the ability to flush and infuse but not aspirate (i.e., persistent withdrawal occlusion) [24].

Exit-site infection was defined as the presence of purulent discharge with erythema and/or tenderness close to the PICC exit site.

Symptomatic thrombosis was defined as lack of flow or nonpulsatile and nonphasic flow associated with lack of compressibility of the veins, edema, and erythema of the cannulated arm and was confirmed by ultrasound.

Accidental removal was defined as an unplanned removal of the catheter either by the patient or the staff.

Data Analysis

Each patient was included in the study only once. Continuous variables were expressed as median and interquartile range (IQR), whereas categorical variables were shown as sums and percentages. The primary outcome measure (PICC removal due to AE) was considered a categorical variable (PICC removal due to AEs and PICC removal due to other reasons). As appropriate, the chi square, Fisher's test, and the Mann-Whitney *U* test were used to test for associations between the variables measured and the rate of AEs. Moreover, univariate and multivariate Cox regressions models were adopted to identify independent predictors of PICC-related AEs. Hazard ratios (HRs) with 95% confidence intervals (CIs) were computed for each recorded variable. In the multivariate analysis, a stepwise selection procedure was followed. Variables considered in the univariate analysis were entered and interactions were assessed using the Wald test. The best fitting model was chosen according to the Akaike information criterion, which was applied in a backward manner. The proportional hazard assumptions to adopt Cox regression were verified using Schoenfeld residuals.

Analyses were performed using R v. 3.3.3 statistical software [25], and the significance level was set at $p < .05$.

Ethics

These data were routinely recorded during daily clinical practice as a quality assurance measure and to explore improvements in the quality of services; therefore, ethics committee approval was not required.

RESULTS

Patient Profile and PICC Characteristics

During the 7-year study period, 2,477 adult patients with cancer had a documented PICC removal. The analyzed PICCs accounted for a total of 385,899 PICC-days. Half the patients had a PICC in place for no more than 135 days; 55.6% of the patients used a PICC for more than 4 months.

The majority of the study sample was female (64.3%), and the median age of the sample was 60 years (IQR, 47–69). Over 70% of patients had an oncologic malignancy, and about 28% suffered from a hematologic malignancy. Most PICCs had valved systems (86.4%) and were inserted in the right side (73.4%) and into the basilic vein (74.5%). The median dwell time was 135 days (IQR, 73–203; Table 1).

AEs were more frequent in younger patients ($p = .04$), in patients with hematologic malignancies ($p < .001$), in patients with an open-system PICC ($p = .003$), and in patients whose brachial vein was accessed ($p = .01$). Patients with PICC removal due to AEs had a shorter dwell time than those with removal for other reasons, namely overall (median, 87 days IQR [29–168] vs. 141 days IQR [84–210], $p < .001$), when an open-system PICC was inserted (median 69 days IQR [38–131] vs. 118 days IQR [63–167], $p < .001$), and when a valved-system PICC was inserted (median 93 days IQR [29–180] vs. 149 days IQR [89–178], $p < .001$; Table 1).

Reasons for PICC Removal

Most PICCs ($n = 2,058$, 83.1%) were removed for reasons other than AEs. There were 1,640 (66.2%) removals due to termination of therapy, 379 (15.3%) due to patient death, and 38 (1.5%) due to accidents. Only one PICC removal was due to the device reaching its expiration date. Symptomatic thrombosis (odds ratio [OR], 1.35; $p = .29$) and accidental removals (OR, 1.02; $p = .95$) were more frequent when the PICC was inserted on the right side compared with the left side, whereas exit-site infection decreased when the right side was accessed (OR, 1.35; $p = .29$). In all, the 419 AEs reported accounted for 16.9% of PICC removal, corresponding to an all-AEs rate of 1.09 per 1,000 PICC-days (Table 2). Individual AEs experienced by patients and time elapsed between PICC insertion and the onset of each AE are shown in Table 2.

Median time to onset of occlusion was 92 days, and 220 of 281 (78%) patients were diagnosed within 30 days of PICC insertion. Within 7 days of PICC insertion, 1.3% of patients developed exit-site infections. Corresponding values for 7–30 days of PICC insertion and >30 days after PICC insertion were 26.6% and 71.3%, respectively. The median time to onset of symptomatic thrombosis was 73 days, and 19 of these 58 cases (32.8%) were diagnosed within 30 days of PICC insertion.

Predictors of PICC-Related Adverse Effects

The multivariate Cox proportional hazard regression model detected an interaction between age and sex. In older men, the risk of AEs decreased by 37% (HR, 0.63; 95% CI, 0.49–0.81) compared with those who were 22 years younger. In women, no significant interaction between age and sex emerged. Patients with PICCs inserted in the brachial vein were almost 40% more likely to develop PICC-related

Table 1. Patient and PICC characteristics according to reason for PICC removal: Bivariate analysis

Variables	All patients (n = 2,477)	PICC removal because of AEs ^a (n = 419)	PICC removal for other reasons (n = 2,058)	p value
Patient characteristics				
Female sex (n = 2,169), n (%)	1,375 (63.4)	227 (59.3)	1,148 (64.3)	.074
Age, years (median [IQR]) (n = 1,537)	60 (47–69)	58 (45–67)	60 (48–70)	.04
Main underlying disease (n = 2,477), n (%)				<.001
Oncologic malignancy	1,760 (71.1)	258 (61.6)	1,502 (73.0)	
Hematologic malignancy	717 (28.9)	161 (38.4)	556 (27.0)	
PICC characteristic				
PICC system, (n = 2,321), n (%)				.003
Open	315 (13.6)	72 (18.3)	243 (12.6)	
Valved	2,006 (86.4)	321 (81.7)	1,685 (87.4)	
Insertion on left side (n = 2,465), n (%)	656 (26.6)	110 (26.5)	546 (26.6)	.99
Accessed vein (n = 2,469), n (%)				.01
Basilic	1,840 (74.5)	285 (68.7)	1,555 (75.7)	
Brachial	620 (25.1)	128 (30.8)	492 (24.0)	
Cephalic	9 (0.4)	2 (0.5)	7 (0.3)	
Median dwell time (n = 2,457), n (IQR), d	135 (73–203)	87 (29–168)	141 (84–210)	<.001
Open system	110 (52–162)	69 (38–131)	118 (63–167)	<.001
Valved system	142 (79–213)	93 (29–180)	149 (89–178)	<.001

^aAEs were defined as one or more of the following: occlusion, exit-site infection, or symptomatic thrombosis. Abbreviations: AEs, adverse events; IQR, interquartile range; PICC, peripherally inserted central catheter.

Table 2. Individual AEs (n = 419)

AE	n	Number of complications per 1,000 PICC-days	Time elapsed between PICC insertion and onset of AE, median (IQR), d
Occlusion ^a	281	0.73	92 (35–172)
Exit-site infection ^b	80	0.21	66 (29–148)
Symptomatic thrombosis ^c	58	0.15	73 (21–163)
All AEs ^d	419	1.09	87 (29–168)

^aDefined as the complete inability to flush, infuse, or aspirate (i.e., complete occlusion); resistance with flushing and aspiration or sluggish infusion (i.e., partial occlusion); or the ability to flush and infuse but not aspirate (i.e., persistent withdrawal occlusion) [24].

^bDefined as presence of purulent discharge with erythema and/or tenderness close to the PICC exit site.

^cDefined as the lack of flow or nonpulsatile and nonphasic flow, associated with lack of compressibility of the veins, edema, and erythema of the cannulated arm, and was confirmed by ultrasound.

^dConsisting of a composite of AEs (occlusion, exit-site infection, or symptomatic thrombosis).

Abbreviations: AEs, adverse events; IQR, interquartile range; PICC, peripherally inserted central catheter.

AEs compared with those with PICCs inserted in the basilic vein (HR, 1.37; 95% CI, 1.02–1.84). Patients who had an open-system PICC inserted were 90% more likely to experience PICC-related AEs (HR, 1.89; 95% CI, 1.24–2.88) compared with those with a valved-system PICC (Table 3).

DISCUSSION

This study described the overall rate of PICC-related AEs in patients with oncologic and hematologic malignancies

undergoing chemotherapy and the time elapsed between PICC insertion and the onset of each AE. To our knowledge, this is the largest study assessing the overall risk of PICC removal due to AEs in patients under active chemotherapy treatment and the first paper that considered both solid tumors and hematological malignancies, thus allowing results to be applied to all patients with cancer.

The main finding of this study was that PICCs can be safely used in the medium to long term for patients with cancer who receive chemotherapy, with a low incidence of major AEs such as infection and thrombosis. We found an overall PICC-related AE rate (1.09 per 1,000 catheter-days) that was in line with previous studies conducted in the cancer context, in which the all-AEs rate ranged from 0.85 to 1.23 per 1,000 catheter-days [12, 13].

Looking at each AE individually, occlusion, which is usually considered a minor complication [17], was the most common reason for PICC removal, accounting for about two-thirds of all removals. However, our occlusion rate was far lower (0.73 vs. 11.10–20.43 per 1,000 catheter-days) than those reported in previous studies [15, 17], with a median time between PICC insertion and the onset of occlusion that overlapped previous findings in the literature [13]. This may be due to a lower number of hematological malignancies, which are largely recognized to be thrombogenic [26].

Rates of PICC removal due to exit-site infection (3.2% with a ratio of 0.21 per 1,000 PICC-days) were in agreement with previous literature [12] (2.2% with a ratio of 0.11 per 1,000 PICC-days), although rates for PICC removal due to exit-site infection as high as 1.46 per 1,000 catheter-days have been registered [13].

Table 3. Predictors of PICC-related AEs^a: Univariate and multivariate Cox regressions

Variables	Univariate Cox regression, HR (95% CI)	Multivariate Cox regression, HR (95% CI)
Male sex	1.47 (1.19–1.80)	1.25 (0.96–1.64)
Age, yr	0.80 (0.68–0.95)	
Older vs. younger men ^b		0.63 (0.49–0.81)
Older vs. younger women ^b		1.04 (0.82–1.33)
Accessed vein		
Basilic	§	§
Brachial	1.48 (1.20–1.83)	1.37 (1.02–1.84)
Cephalic	1.39 (0.35–5.59)	5.74 (0.84–39.34)
Insertion location, left vs. right	0.96 (0.77–1.20)	
PICC system, open vs. valved	1.99 (1.54–2.59)	1.89 (1.24–2.88)

^aAEs were defined as one or more of the following: occlusion, infection, or symptomatic thrombosis.

^bDifference in age of 22 years.

[§]Reference group.

Abbreviations: AE, adverse event; CI, confidence interval; HR, hazard ratio; PICC, peripherally inserted central catheter.

Differently from previous authors [13], in this study, PICC-related symptomatic thrombosis was the AE with the lowest incidence (0.15 per 1,000 PICC-days). This can be explained by the consistent choice of deep veins of the upper midarm (mainly the basilic vein) with an appropriate vessel-to-catheter ratio (at least 3:1) [22] and the prevalent use of a PICC with a small diameter. In Bertoglio's study, almost 75% of PICCs were 5 Fr in diameter, and symptomatic thrombosis accounted for more than one-fourth of all removals, whereas the majority of our patients had a 4-Fr PICC. Generally, when 4-Fr PICCs are adopted, thrombosis-related removals range from 0.01 [27] to 0.05 per 1,000 PICC-days [12]. Our thrombosis rate was slightly higher than that in the aforementioned studies, likely because we also included patients with hematological malignancies, who are at higher risk of thrombotic events [15–17]. Finally, regular control of the position of the PICC tip, with repositioning performed when the tip was not at the distal third of the superior vena cava, may have decreased the incidence of thrombosis. Indeed, a patient-level data meta-analysis on 5,636 patients with cancer found that the risk of thrombosis increased by 92% when catheters were malpositioned [28].

Our findings suggest the need to improve PICC maintenance, because almost 80% of the occlusions were diagnosed within 30 days of PICC insertion and thereby were likely caused by missed or incorrect flushing practices. Similarly, over 70% of exit-site infections arose after 30 days of PICC insertion, with a median dwell time before their occurrence of 66 days, suggesting that infections were related to postinsertion care rather than PICC insertion. Therefore, health care institutions should promote the implementation of care protocols for CVCs, including education programs

for nursing staff that handles these devices daily. A re-education course for nurses on PICC-associated knowledge, infection control practices, and PICC aftercare was indeed found to significantly reduce both infective and noninfective AEs in adult patients with cancer [29].

Consistent with the literature [13, 27, 30, 31], the basilic vein was most often used. The cephalic and brachial veins were cannulated in only one-fourth of patients. When the basilic vein is cannulated, the procedure is more likely to be successful and there are fewer AEs [32]. The basilic vein covers a greater distance from arterial and nervous structures compared with the brachial vein, thus reducing the likelihood of involuntary injury. Moreover, the basilic vein has a larger diameter than the brachial and cephalic veins. According to our findings, it would seem that accessing the brachial vein increases the risk of AEs. Unexpectedly, we found that men had a lower risk of AEs with increasing age. We may hypothesize that this difference is related to the type of tumor and related chemotherapy. The most frequent neoplasm among young men is the germ cell tumor, which is treated with cisplatin-based chemotherapy, with a high risk of thromboembolic events [33]. Finally, we found that open-system PICCs conferred a higher risk of AEs than valved-system PICCs. Open-system PICCs do not have a distal valve that prevents the backflow of blood when the catheter is not in use; thus, poor flushing practices in these devices can promote thrombosis. Moreover, open-system PICCs have a larger distal diameter than conventional PICCs, and are thus predisposed to venous stasis [34, 35], which can lead to an increased risk of thrombosis [36, 37]. In addition, previous authors found that open-system PICCs lead to a greater risk of infection [37] because of the rough polyurethane surface, which facilitates biofilm formation over the PICC line and migration of microorganisms into the intravascular space [38].

Limitations

Our study presented several limitations. It is retrospective in nature with problems of incomplete documentation. Relevant factors that may contribute to PICC-related AEs, such as the number of lumens, length of hospital stay, comorbidities (i.e., obesity, diabetes, malnourishment, hypercoagulability status), surgery, use of erythropoiesis-stimulating agents, chemotherapy regimen, and flushing practices, were not collected [19, 30, 37]. The diagnosis of PICC-associated thrombosis was exclusively clinical, based on symptoms such as lack of compressibility of the veins, edema, and erythema. Ultrasound imaging was performed only when PICC-associated thrombosis was suspected because of clinical manifestations. Therefore, we may have underestimated the true thrombosis rate, which has been reported to affect almost half of patients with cancer [31]. However, our decision to look for only symptomatic thrombosis was based on the consideration that the clinical significance of asymptomatic central catheter thrombosis is still debated, regular screening with objective tests is generally not recommended, and thereby the relevance of their underdetection is still unclear [39]. However, this was a multicenter study that enrolled a large sample of both inpatients and outpatients and included solid tumors and hematological malignancies, thus allowing us to generalize the findings to all

patients with cancer. Finally, to our knowledge, this study had the longest observation time in a cancer setting, exceeding previous studies by more than fivefold.

CONCLUSION

The low all-AEs rate we observed across different hospitals suggested that PICC insertion by a trained team of nurses would likely result in optimal medium- to long-term outcomes. Thus, PICCs emerged as a safe and long-lasting central venous access device in hospitalized and nonhospitalized patients with cancer receiving chemotherapy.

Despite several limitations, our study confirmed the basilic vein as the site of choice for inserting a PICC. Moreover, our findings suggested that the decision regarding the type of catheter to be placed should be carefully considered. Health care professionals responsible for insertion should weigh the risks and benefits of each device. Indeed, PICCs may not be the best catheter for young men receiving chemotherapy, and alternatives to open-system PICCs should be explored for longer durations of intravascular access. Although open-system PICCs have many advantages (e.g., high-flow infusion, high-pressure injection of contrast media), their use should be

limited whenever possible when long chemotherapy regimens are scheduled.

AUTHOR CONTRIBUTIONS

Conception/design: Sara Campagna, Silvia Gonella, Valerio Dimonte
Provision of study material or patients: Giacomo Morano, Carla Rigo, Pietro Antonio Zerla, Raffaella Fuzzi, Gianvito Corona, Silvana Storto, Baudolino Mussa
Collection and/or assembly of data: Giacomo Morano, Carla Rigo, Pietro Antonio Zerla, Raffaella Fuzzi, Gianvito Corona, Silvana Storto, Baudolino Mussa
Data analysis and interpretation: Sara Campagna, Silvia Gonella, Paola Berchiolla, Baudolino Mussa
Manuscript writing: Sara Campagna, Silvia Gonella
Final approval of manuscript: Sara Campagna, Silvia Gonella, Paola Berchiolla, Giacomo Morano, Carla Rigo, Pietro Antonio Zerla, Raffaella Fuzzi, Gianvito Corona, Silvana Storto, Valerio Dimonte, Baudolino Mussa
Review of manuscript: Sara Campagna, Silvia Gonella, Paola Berchiolla, Giacomo Morano, Carla Rigo, Pietro Antonio Zerla, Raffaella Fuzzi, Gianvito Corona, Silvana Storto, Valerio Dimonte, Baudolino Mussa

DISCLOSURES

Baudolino Mussa: Bard (SAB-Board of Directors). The other authors indicated no financial relationships.

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