Safe use of Peripherally Inserted Central Catheters for chemotherapy of solid malignancies in adult patients: A 1-year monocentric, prospectively-assessed, unselected cohort of 482 patients

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Abstract

Introduction: Aim of this study was to analyze the overall complication and failure rates of Peripherally Inserted Central Catheters (PICCs), in a 1-year consecutive unselected cohort of 482 adult patients, affected by non-hematological malignancies undergoing chemotherapy.

Methods: Adult outpatients (aged 18–75 years), with an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, bearing solid tumors and candidates for intravenous chemotherapy were eligible for the study. Exclusion criteria were active infections, coagulopathy (defined as platelet count <50,000/μL and/or prothrombin time more than 18 s), life expectancy <6 months, or inability to give written informed consent. Devices were all implanted in an outpatients’ hospital facility, following predefined evidence-based institutional guidelines and protocols by a PICC-dedicated team at the European Institute of Oncology in Milan, Italy, during the 12-month period from January 1 to December 31, 2019.

Results: Five-hundred PICCs were implanted in a cohort of 482 patients during the time interval of this study. Thirty devices were overall removed (6.2%), 23 as a consequence of a complication occurred, and seven inadvertently. The inserted PICCs accounted for a total of 49,718 catheter days in situ, median duration was 85.5 days [interquartile range (IQR): 56–146]. Overall there were 42 (8.7%) complications, corresponding to 0.84 catheter-adverse events (CAE)/1000 PICC-days (95% CI: 0.61–1.14). There were N=13 (2.7%) thromboses, N=11 (2.3%) irreversible occlusions, N=7 (1.5%) accidental removals, N=5 (1.0%) infections [two Catheter Related Blood Stream Infection (CRBSI) and three exit site/local infection], N=3 (0.6%) ruptures and N=3 (0.6%) primary or secondary malpositions.

Conclusion: This large prospective study supports the increasing use of PICCs in adult oncology outpatients treated in specialized centers with chemotherapy for non-hematological malignancies. In this clinical setting, PICC failure occurred in 6% only of the inserted devices.

Keywords
Peripherally Inserted Central Catheters, ultrasound guidance, chemotherapy, complications, failures rates

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**Introduction**

Many cancer patients require central venous access for the safe deliverance of chemotherapeutic agents, transfusion of blood products, nutrition and the performance of laboratory tests. The choice of the device is usually made by the treating physician in cooperation with nursing staff, patients and their families on the basis of morbidity and longevity of various devices, patient characteristics, hospital availability, as well as personal experience. The Peripherally Inserted Central Catheters (PICCs) are gaining in popularity, as safely inserted through a peripheral vein offer an alternative for central vein access that is perceived easy to place, reliable, cost-effective, and with few serious complications when compared to Centrally Inserted Central Catheters (CICC) and TIVADs (Totally Implanted Vascular Access Devices), thus enhancing their use in different clinical settings.\(^1\)\(^-\)\(^4\) In spite of recognized benefits, PICCs are associated with a significant risk of complications and failures, including upper extremity deep veins thrombosis (UEDVT), local exit site and catheter-related bloodstream infection (CRBSI), and mechanical complications (especially occlusion and dislodgment causing a removal), raising concerns on their use, especially in oncology patients.\(^5\)\(^-\)\(^9\)

A recent, large retrospective multicenter study\(^10\) showed that use of PICCs for chemotherapy administration has to be considered a significant risk factor for infection, and prognosticator of higher risk of CRBSI. In the oncology setting, safety and efficacy of PICCs use have indeed limited evidence, mostly derived from retrospective series.\(^11\)\(^-\)\(^17\) Two Randomized Clinical trials (RCTs) exploring PICCs performance have been so far conducted against TIVADs (Totally Implanted Vascular Access Devices),\(^18\)\(^,\)\(^19\) giving limited evidence in favor of the latter, with possible biases in interpretation of obtained findings. Aim of this large, prospectively-assessed single-center study was to analyze the overall complication and failure rates of PICCs, in a 1-year, consecutive unselected cohort of 482 adult patients, affected by non-hematological malignancies undergoing chemotherapy. The frequency of each complication (i.e. UEDVT, irreversible occlusion, accidental removal, CRBSI, infection of the exit site and surrounding tissues, rupture and primary/secondary malposition) was investigated as a primary end point of the study. Cumulative Incidence Functions (CIF) according to the Fine and Gray’s regression analysis, and adverse event—free duration of the device were analyzed as secondary endpoint.

**Patients and methods**

**Study design and patients’ characteristics**

This study was conducted at the European Institute of Oncology – IRCCS in Milan, Italy. Before activation, it was approved by the relevant Institutional Review Board. Outpatients adults (aged 18–75 years), with an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, bearing solid tumors and candidates for intravenous chemotherapy (either adjuvant or palliative) were eligible for the study; exclusion criteria were active infections, coagulopathy (defined as platelet count <50,000/\(\mu\)L and/or prothrombin time more than 18 s), life expectancy <6 months, or inability to give written informed consent. PICCs placed in a consecutive series of 482 adult unselected outpatients, during the 12-month period from January 1, 2019 to December 31, 2019 were followed prospectively for device-related complications. They were recorded according to the timing of occurrence: early (intraoperative and post-implantation period to first use) and late complications (occurring after the first chemotherapy course given through the device). Follow-up continued until the device was removed, the patient died or the study was closed (January 31, 2020). Patients who died within the end of the study were retained in the analysis and were recorded as having no late complications, unless one was noted before death. The main tumor types were breast, followed by colorectal, lung, gastric, pancreatic, head and neck, gynecologic and sarcoma.

**PICC insertion, definitions, and maintenance**

Devices were all implanted in an outpatients’ facility with maximal barrier precautions, following predefined evidence-based institutional guidelines and protocols by a PICC-dedicated team. Preoperative evaluation included a clinical history, physical examination and ultrasonography exam of upper arm veins,\(^20\) all focused on possible anatomic pitfalls (upper limb edema, cervical or axillary adenopathy, asymptomatic vein thrombosis, presence of rotation flaps as part of head and neck reconstructive surgery). Vascular access history (side used, previous line infection or thrombosis), and history of chronic renal failure with a prevision of dialysis fistula were acquired. There was not a specific laterality, unless clinical contraindications occurred. All patients received a local anesthesia, without routine additional intravenous sedation; no prophylactic antibiotic dose was given. Percutaneous access was performed with real-time ultrasonography and micro-introducer technique at the upper mid-arm (Dawson’s green area), and catheter tip location at the atrio-caval junction/inferior third of the superior vena cava (SVC) was assessed by EKG intracavitary technique.\(^21\) No breaks in operative technique or instrument sterility were documented. Implanted PICCs were all open-ended, power-injectable thermoplastic polycarbonate-urethanes catheters of a single manufacturer. The size was 4 French (F) or 5 F, according to the vein diameter and respecting a vein to PICC ratio ≥ 3.\(^22\) Fixation to the skin was performed with sutureless device or a subcutaneous anchoring device, and dressed with chlorhexidine-impregnated transparent films. Prophylaxis of PICC-related UEDVT was not routinely adopted.
A PICC form was filled in by the operator after the procedure, and a dedicated pre-defined software registry was assembled to collect PICCs outcome at regular time intervals (every drug deliverance or at weekly intervals). It included duration of PICCs and occurrence of UEDVT, CRBSI, exit site infection, irreversible occlusion, catheter malposition, rupture or accidental removal.

Blood screening for bacteremia was not performed at regular intervals, since blood sampling for microbiology test was obtained when clinically suggested (unexplained fever and/or signs of sepsis). Criteria for the diagnosis of CRBSI were defined as a differential time to positivity (DTP) of 120 min or more from paired set of blood cultures drawn from the PICC and a peripheral vein, positive for the same microorganism. Intraluminal antibiotic lock therapy was routinely used in case of CoNS (Coagulase Negative Staphylococci) catheter related bacteremia, together with systemic sensitivity-tested antibiotic therapy. Catheter was removed in case of no regression of symptoms and/or persistence of positive blood culture within a week from start of treatment, or even earlier if symptoms were worsening. In case of CRBSI caused by Gram negative bacteria, S. aureus or fungi, PICC was immediately removed and proper antibiotic/antifungal treatment given.

Exit site/local infection was defined as induration, erythema, or tenderness and exudate at PICC exit site and/or surrounding tissues. No culture confirmation was required. Catheter was removed in case of no regression of symptoms and persistence of local infection within a week from start of treatment, which included daily dressing change and antibiotic therapy.

Thrombosis was diagnosed with ultrasound (US) color-Doppler when clinically suggested by the appearance of arm or facial swelling and/or pain. Patients with positive or dubious US scans underwent a neck–chest computerized tomography scan, with i.v. contrast medium administration to rule out pulmonary emboli. UEDVT patients were treated with low-weight molecular heparin (LWMH) 100 IU/kg body weight (b.w.) *bis in die* (b.i.d.). Catheter was removed in case of persistence or worsening of symptoms within 14 days, or when infected thrombus, late malposition of the catheter tip, or a complete occlusion (defined as inability to infuse normal saline solution, in spite of the manual pressure performed on the piston of a ≥10 mL syringe) were detected.

Catheter dislodgment and inadvertent removal were defined as an accidental partial or complete removal of the PICC by either the patient or the nursing staff. Partial dislodgment was initially treated with a J-wire aseptic attempt of repositioning, when technically feasible.

A specialized PICC team of oncology nurses took care of the devices in accordance with institutional protocols, routinely performed at every drug deliverance or at weekly intervals. It included redressing of the catheter exit site with skin disinfection with a 2% chlorhexidine gluconate and 70% isopropyl alcohol solution with aseptic technique, and stabilization of the catheter with a sutureless or subcutaneous anchoring devices. Check of patency, flushing and locking of PICCs with normal saline by pulsatile method before and after every i.v. drug deliverance or blood test performance were used.

Statistical analyses

Patients’ characteristics and outcome were summarized either by count and percent or mean, median, Standard Deviation (SD) and interquartile range (IQR) for categorical and continuous variables respectively. Complication-specific and overall Incidence Rate (IR) were calculated and tabulated as number of cases per 1000 PICC-days, alongside 95% Confidence Intervals using the Byar’s approximation of the exact Poisson distribution. Risk factors for the catheter-related adverse events – with at least five events observed during the study period – have been analyzed using the Fine and Gray’s extension of the Cox regression for competing risks, and results are presented as Hazard Ratios (HR) and 95% Confidence Intervals. All tests were two-tailed and considered significant at the 5% level. All analyses were done using SAS 9.4 (Cary, NC, USA).

Results

Table 1 lists patients’ baseline characteristics and PICCs outcomes. Five-hundred PICCs were implanted in a cohort of 482 patients during the time interval of this study. Thirty devices were overall removed, 23 as a consequence of a complication occurred, and seven inadvertently. Eighteen patients underwent a placement of a second PICC after removal of the first one, 10 preferred to receive a CICC/TIVAD, and two refused a new device. Inserted PICCs accounted for a total of 49,718 catheter days in situ, median duration was 85.5 days (IQR: 56–146). Three-hundred fifty three patients (73.2%) were female. Two-hundred nineteen (45.4%) patients were breast cancer cases, N = 293 (60.8%) PICCs were inserted in the left side and N = 445 (92.3%) into the basilic vein. At 1-year from insertion N = 128 (26.6%) PICCs were still in use. Four-hundred fifty-one patients (93.6%) were still alive at the end of the study. All patients but one received at least one cycle of chemotherapy through the device. Adequate follow-up was obtained in all cases and no drop-outs occurred. The majority of patients (60%) received palliative chemotherapy treatment.

We did not observe any PICC-related deaths in this series. Overall there were 42 (8.7%) complications (two early and 40 late), corresponding to 0.84 catheter-adverse events (CAE)/1000 PICC-days (95% CI: 0.61–1.14). There were N = 13 (2.7%) thrombosis, N = 11 (2.3%)
irreversible occlusions, \(N=7\) (1.5%) accidental removals, \(N=5\) (1.0%) infections (two CRBSI and three exit site/local infection), \(N=3\) (0.6%) ruptures and \(N=3\) (0.6%) primary or secondary malposition; their corresponding incidence rates and actions taken are showed in Table 2.

Primary malposition occurred as early complication in two patients, and as a late adverse event in one. All malpositions occurred in the brachio-cephalic contralateral vein, were corrected by interventional radiology techniques, and catheters rescued with no additional morbidity. The most frequently observed late complication was symptomatic UEDVT. It occurred in 13 cases (2.7%; 0.84 CAE/1000 PICC-days); all were treated with LWMH 100IU/kg b.w. b.i.d., and just one device had to be removed, as a consequence of infected thrombus. Time of development was 14 to 107 days after implantation. Eleven cases of irreversible occlusion were detected in this series (2.3%; 0.22 CAE/1000 PICC-days) and nine cases underwent a new implantation; two patients refused a re-implant. 3/189 occlusions occurred in the right side, and 8/293 in the left one. Nevertheless, HR for the left side resulted 1.59 (0.42–6.00, 95% CI), with a \(p=0.50\) (NS).
Accidental partial or complete removal occurred in seven cases (1.5%; 0.14 CAE/1000 PICC-days) and all were re-implanted.

Infectious complications were diagnosed in five cases (three exit site/local infections and two CRBSI = 1%; 0.10 CAE/1000 PICC-days). All had to be removed as a consequence of this complication, after failed initial attempt to resolve it, and delayed re-implant was done.

Finally, three cases of catheter rupture occurred (0.6%; 0.06 CAE/1000 PICC-days), and all were reimplanted.

Univariate analyses of the complication-specific risk factors for complications having at least five events are shown in Table 3. Age at implant, sex, cancer diagnosis, side and vein were not significantly associated with any complication-type, except the brachial versus basilic vein comparison for the irreversible occlusion.
events (secondary end point, including insertion complication, thrombosis, occlusion, infection, and mechanical problems) was higher for patients with a PICC compared with those with a PORT (HR = 2.7; 95% CI 1.6–4.6, p < 0.001), leading to the conclusion that this increased risk should be considered when choosing a vascular access device for chemotherapy, especially in patients with solid malignancy. The same Group eventually published a health economic evaluation based on the findings obtained by this trial, demonstrating that the cost from a healthcare perspective is higher in cancer patients receiving a PICC than those with a PORT. Some remarks can be done: first, vein-catheter diameter ratio was not routinely measured, and different devices were used in both groups, having possible different impact on thrombosis rate. In the PICCs recipients, a Bard 4Fr. Groshong NTX Clear VUE or the PowerPICC Solo® 2 Fr. polyurethane catheters were used. Valved catheters could have a different performance when compared to open-ended devices, at least in TIVADs. Moreover, a correct tip position of PICCs at Distal Superior Vena Cava (SVC)/Right Atrium (RA) is crucial for a good performance of the catheter and reduction of thrombosis risk. In this RCT approximately 90% of PICCs had a correct position of the tip (as documented by Table 2 and Supplemental Data of that article). In other words, 10% of primary malpositions occurred in the PICC arm of this study, whose impact on eventual thrombosis rate is unknown, for sure not negligible. A recent systematic review and metaanalysis including 15 studies, 5420 patients and 5914 PICCs, restricted the analysis to reports which included in their methods ultrasound guidance for venipuncture, catheter tip intraoperative location, and a catheter size selection strategy. The weighted frequency of PICCs-related deep vein thrombosis resulted 2.4% (95% CI = 1.5–3.3) and remained low in oncology patients (2.2%, 95% CI = 0.6–3.9). These data are similar to those obtained in our prospective study, where we respected all the three rules: ultrasound guidance, choice of the proper device diameter, with a vein to PICC ratio ≥3, and intraoperative verification of a correct catheter tip location. Authors concluded that a proper technique is crucial at the moment of peripherally inserted central catheter insertion, and PICC-related deep vein thrombosis rate appears to be low when evidence-based technical factors are taken into consideration during the insertion procedure. In the largest not randomized so far published monocentric study, dealing with 291 unselected and consecutive adult cancer patients undergoing active chemotherapy, Bertoglio et al. found in 2016 a PICC complication rate of 24.7%, with a 15% of PICCs prematurely removed as a consequence of that, compared with an overall complication rate of 8.7% and complication-related removal rate of 6.2% in our series. In the Bertoglio’s study, the inserted PICC-days accounted for a total of 35.710 catheter day (ours was 49,718 days), and the median length of observation was 119 days (range 1–365) compared with 96 days (range 2–377) of the present study, limited to a 1-year.
longitudinal study. Looking at categories of complications occurred, in our study symptomatic UEDVT was again the leading late complication, but not the first reason for failure (1 out of 13 cases), whereas it accounts for more than one-fourth of all failures in the Bertoglio’s study. Observed prevalence of UEDVT is consistent with those reported in large series of pooled oncological and non-oncological patients. Studies in which PICCs were implanted solely in cancer patients reported UEDVT rates ranging from 1% to 50%, thus reflecting different diagnostic criteria and tools, patients’ population inhomogeneity, concomitantly administered drugs selection, and probably other factors. Noteworthy, in our study, a significant amount (12 out of 13, 92.3%) of the PICC-UEDVT was rescued by the implementation of an early treatment with LMWH that allowed to continue their use until the end of treatment. Safety of this approach for up to 12 months has been confirmed by DALTECAN study. Finally, laterality of PICC placement still remains a controversial issue; according to a RCT31 the overall incidence of complications on the right side was 23% versus 34% on the left side, confirming the hypothesis that right-sided insertions led to fewer complications \( p=0.046 \). Conversely, symptomatic UEDVT did not vary significantly in another trial, and in our prospective study as well.

Five PICCs (1%) was removed in our series for infectious complications, and CRBSI was detected in two cases only, with an incidence ratio of 0.4% and a CAE ratio of 0.04/1000 Picc-days. This is consistent with a declining incidence in many reports, suggesting a “targeting zero” objective for TIVADs and PICCs as well. Number of lumens and use of PICC for chemotherapy emerged as significant risk factors for development of infectious complications in most studies. Our use of PICCs with a minimum number of lumens (99% single) was confirmed to be able to reduce complications and costs, as previously noted.\(^{29} \) The impact of chlorhexidine (CHG)-impregnated versus non-CHG impregnated PICCs on infectious risk is still unknown. A recent RCT did not find any differences in the development of bacteremias and UEDVT between the CHG and non-CHG groups.\(^{40} \)

Rates of accidental removal (1.5%) and catheter rupture (0.6%) are consistent with other reports from the literature. Noteworthy, the systematic adoption of a subcutaneous anchoring device in the second semester of our study period was able to nullify the accidental removal as a possible complication.\(^{41, 42} \)

Rate of failure for irreversible occlusion (2.3%) was not significantly associated with age at implant, sex, cancer diagnosis and side used, whereas the brachial vein resulted significantly more prone to this complication when compared to the basilic vein \( \text{HR}=4.46, 95\% \text{ CI: 1.36–147, } p=0.01 \), thus reinforcing the value of the latter as first-choice vein for PICCs implantation.

A very recent phase II randomized trial from Clatot et al.\(^{43} \) analyzed 253 patients with EBC (Early Breast Cancer) undergoing ACT (Adjuvant Chemotherapy) administered through a PICC or a TIVAD. Aim was to identify which device has a lower probability of catheter-related significant adverse events (CR-SAEs) within the 35 weeks after device implantation. Authors found 7.8% (10 events) with TIVADs versus 16.6% (21 events) with PICCs (hazard ratio \( [HR]=2.2 \) [1.03–4.62], \( p=0.036 \). Clear differences can be detected with our prospective study, either in composition of cohort population or in techniques/definitions used, dealing to some difficulties in full comparison of obtained findings.

Good results obtained in our series are probably due to a number of factors, including choice of a proper catheter to vein ratio, use of single-lumen PICCs, use of stabilizing devices and adoption of institutional evidence-based nursing protocols. To our knowledge, this is now the largest prospective monocentric study assessing the PICC performance in adult patients with solid tumors under active chemotherapy treatment. All consecutive and unslected cancer patients candidate to a PICC placement for chemotherapy were enrolled. All procedures and device’s maintenance were performed by the same staff, strictly following institutional protocols. Finally, an adequate follow-up was obtained in all patients, with no drop outs. Limitations include the monocentric feature of the study, conducted at a single cancer research center, thus limiting the possible application of obtained findings to other settings.

In conclusion, our large prospective study confirms safety and effectiveness of PICCs and supports their increasing use for long-term treatment of oncology patients candidate to chemotherapy of solid tumors. In specialized comprehensive cancer centers, PICC failure occurs in 6% only of them. More randomized trials are needed to reinforce the positive safety findings we obtained, and to investigate additional topics, like cost/effectiveness and impact on patients’ QoL (Quality of Life), especially for long term use of PICCs in this clinical setting.

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