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ORIGINAL ARTICLE

Prospective observational study on the complications and tolerability of a peripherally inserted central catheter (PICC) in neuro-oncological patients

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Abstract

Purpose The use of central venous catheters with peripheral insertion (PICC) has increased rapidly in recent years, particularly in cancer patients. The benefits provided may occasionally be affected by relevant complications, such as infections and thrombotic events, especially in neuro-oncological patients. To date, the risk of PICC-related complications in this subset of patients is unknown, as is tolerability. As a primary objective, this study aimed to collect complications related to PICCs in primary neuro-oncological patients. As a secondary objective, the study aimed to evaluate PICC tolerability.

Methods Neuro-oncological patients with PICCs that were placed as part of normal clinical practice at IRCCS Neurologico C. Besta were consecutively enrolled in the study. PICC-related complications were recorded immediately (during the procedure), early (within 1 week after PICC insertion), and late (1–3-5 months after PICC placement). At the same time points, all patients were also evaluated for tolerability through interviews with semi-structured, open-ended questions.

Results Sixty patients were enrolled (41 males and 19 females, with a median age of 56.2 years). Excluding loss to follow-up, 33/49 patients developed at least one complication related to the PICC. Immediate complications mainly included hematoma (8), accidental arterial puncture (4), and primary malpositioning (3). Regarding early and late complications, 3 device-related infections, 8 thrombotic events, and 20 mechanical complications were registered. Semi-structured interviews revealed an overall positive experience with the device. The most negative impact was on hygiene habits, with 34 patients becoming caregiver-dependent. Over time, almost all patients became used to the device and perceived greater security during chemotherapy. A strongly negative issue was the difficulty of relying on competently trained healthcare personnel in outpatient setting.

Conclusion The results showed a nonnegligible increased thromboembolic risk in neuro-oncological patients with PICCs, almost double that in historical oncological populations. It is essential to extend the study to a greater number of patients to achieve reliable results and to identify patients at high risk. The device seems to be positively accepted by the majority of patients, without affecting activities of daily living.

Keywords Peripherally inserted central catheter (PICC) · High-grade glioma · Catheter-related bloodstream infection (CRBSI) · Catheter-related thromboembolism

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Introduction

The use of a central venous catheter (CVC), particularly a peripherally inserted central catheter (PICC), has increased rapidly in recent years in cancer patients for multiple reasons. First, they are strongly recommended by "Guidelines for the Prevention of Intravascular Catheter -Related – CDC" for intravenous therapy longer than 6 days, they are particularly indicated for patients receiving intravenous vesicant chemotherapy agents, and last but not least, they are easy to implant without requiring surgical procedures [1–3].

However, PICCs may occasionally be affected by serious complications, such as infection and thrombosis, which are also clinically relevant, especially in patients with hypercoagulability such as oncological patients but even more so in neuro-oncological patients who have a much higher thrombotic risk by default [4–6].

In this subgroup of patients, the incidence of venous thromboembolism (VTE) ranges between 10.7% 9–12 months after diagnosis and 22.9% after 12–15 months [7]. The mechanism of VTE development is multifactorial, and neuro-oncological patients have many risk factors, including histologic diagnosis of glioblastoma (due to possible intraluminal thrombosis) and the entity of surgery (subtotal resection versus total resection) as well as large tumor size (high levels of procoagulant factors, use of high-dose steroids and high probability of motor deficit), lengthy surgery (operative time more than 4 h), old age (procoagulant factors increase with age), chemotherapy (it reduces fibrinolytic activity), radiotherapy, and steroids [4–6]. Although high-grade glioma patients have a much higher thrombotic risk, also several studies indicate a higher VTE risk in patients with aggressive non-Hodgkin lymphomas localized in the central nervous system. Honhaus et al. reported that primary central nervous system lymphoma (PCNSL) patients had the highest VTE rate (27.2%) [8]. Also, Mahajan et al., in their retrospective study based on 992 patients with a PCNSL, found that the incidence of VTE was over 14% in this large population-based study [9].

Data exist about the safety of the device in oncological patients but not in neuro-oncological patients.

Considering the lack of information about the safety and tolerability of the device, as well as the short life expectancy of the target population, it is important to understand the real risk/benefit ratio of PICCs in patients with brain tumors.

Hence, we conducted a prospective observational study on the complications and tolerability of the PICC in neuro-oncological patients.

Patients and methods

Adult patients with a primary brain tumor, regardless of therapy or stage of disease, were consecutively enrolled. As per the daily clinical practice in our institute, the patient candidates for intravenous chemotherapy were assigned to undergo PICC insertion. The time of accrual ranged from February 2018 to March 2019. Clinical data (Karnofsky Performance Status and Eastern Cooperative Oncology Group Performance Status) were registered.

The exclusion criteria mainly concerned contraindications to PICC placement, such as known coagulopathies (platelet count $< 20{,}000/mm^3$ or an international normalized ratio (INR) > 2), hemiplegia, local contraindications, and the presence of cognitive disorders that could have interfered with adequate compliance with the study, at the discretion of the investigators, or a Mini-Mental State Examination score ≤ 25. The primary objective of the study was to evaluate the immediate (during the procedure), early (within 1 week after PICC insertion), and late (from 1, 3, and 5 months after placement) PICC-related complications in neuro-oncological patients. As a secondary objective, the study aimed to evaluate device tolerability through semi-structured interviews with open-ended questions.

Written informed consent was obtained from all enrolled patients. The study was approved by the Ethics Committee of IRCCS Neurological Carlo Besta.

The nonvalved, single-lumen, silicone/polyurethane PICC was placed by trained nurses and anesthetists through a standardized methodology: the PICC was placed using ultrasound guidance with a rigorous aseptic technique in a tip target position, between the superior vena cava and the right atrium, confirmed in most instances by an intracavitary electrocardiogram (IC-ECG); in the event of a nonexhaustive ECG signal, chest radiography was performed immediately after PICC placement. The devices were fixed by StatLock®, a sutureless skin adhesion system. In all cases, a transparent dressing was applied and changed every 7–10 days. The PICC was routinely flushed using a rapid push-stop action with 10–20 ml of 0.9% sodium chloride once a week and after every use.

An informative brochure with a brief device description and information on the behavior to adopt in daily life and guidelines to follow during the medication procedure as well as a diary for registration of all useful information about the PICC (catheter information, dressing change, adverse events) was delivered to all enrolled patients.

Immediate, early, and late complications were assessed by a physician and a nurse 1–5 months after placement and were classified as follows:

(a) Hematoma, evaluated according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0
(b) Local pain, assessed with the numerical rating scale (NRS) (0 = no pain, 10 = worst possible pain)
(c) Presence of fibrin flap or "tail" on the catheter tip
(d) Site infections evaluated with both visual inflammation scale Visual Exit-site score (0 = healthy skin, 3 =

presence of hyperemia, secretions, or pus) and CTCAE version 5.0

(e) Catheter-related bloodstream infection (CRBSI), diagnosed through the paired blood culture method defined as at least one blood sample drawn from a central vein catheter and at least one blood sample drawn by peripheral venipuncture

(f) Presence of symptomatic thrombi evaluated through eco-color Doppler

(g) Presence of symptomatic pulmonary embolism assessed by spiral thorax tomography

Patient satisfaction was evaluated using a semi-structured interview performed immediately after PICC insertion and 1, 3, and 5 months after placement, investigating the following:

1. Pain perceived during PICC placement using the NRS scale (0 = no pain, 10 = worst possible pain)
2. Home-territory management
3. Discomfort during daily life
4. Emotional impact
5. Overall satisfaction considering all advantages and disadvantages of the PICC ("Not at all Satisfied," "Partly Satisfied," "Satisfied," and "Very Satisfied")

Statistical analysis

A description of the participant characteristics at baseline was provided in terms of absolute number and percentages for categorical data and means with standard deviations (SDs) and medians with value ranges for continuous data. The 95% confidence interval (CI) of the proportion of patients with immediate, early, and late PICC-related complications was computed using the exact binomial method. Time to complication was analyzed using survival analysis techniques based on the Kaplan-Meier method. Fisher exact and Mann-Whitney tests were used to assess the association between serious PICC complications (CRBSI and thrombosis) and body mass index (BMI) (categorized as preobesity to obesity vs normal weight) and the use of corticosteroids administered at the time of PICC placement. The level of significance was set at < 0.05.

Results

Safety

Between February 2018 and March 2019, sixty neuro-oncological patients (41 males and 19 females) were consecutively enrolled in the study. Only two patients were excluded due to the presence of severe hemiplegia.

In 8 patients, the PICC was inserted twice during the study period due to dislocation, for a total of 68 PICCs inserted.

The median age was 56 years (range 25–80), the median KPS was 80 (range 70–100), and the median ECOG was 1 (range 0–2). Further characteristics are summarized in Table 1.

The most frequent histology was represented by glioblastoma ($n = 34$), followed by anaplastic astrocytoma (10), primary central nervous system lymphoma (PCNSL) (8), grade II glioma (7), and medulloblastoma (1).

Overall, 23.3% of patients were diagnosed initially, 53.3% of patients were diagnosed at the first recurrence, and the remaining patients were diagnosed at the second or third recurrence.

The intravenous chemotherapeutic agents administered were fotemustine ($n = 34$), depatuxizumab mafodotin (8), vincristine (7), high-dose methotrexate with vincristine (6), platinum-based chemotherapy (3), and bevacizumab (2).

In 7 patients treated with vincristine, procarbazine, and lomustine were orally administered concomitantly; in 6 patients treated with high-dose methotrexate and vincristine, procarbazine was also orally administered.

The devices were most commonly inserted in the right basilic vein and right brachial vein (85%).

In 83.3% of patients, the PICC was inserted the same day (or the day before) chemotherapy was started. In all other

Table 1 Baseline patient characteristics

Number of patients	60
Age	
Mean ± SD	56.2 ± 12.1
Median (range)	55 (25–80)
Sex, *N* (%)	
Males	41 (68.3%)
Females	19 (31.7%)
Histologic diagnosis, *N* (%)	
Glioblastoma	34 (56.7%)
Anaplastic astrocytoma	10 (16.7%)
Primary central nervous system lymphoma	8 (13.3%)
Grade II glioma	7 (11.7%)
Medulloblastoma	1 (1.7%)
Stage, *N* (%)	
First diagnosis	14 (23.3%)
First recurrence	32 (53.3%)
Second recurrence	10 (16.7%)
Third-fourth recurrence	4 (6.7%)
ECOG	
Mean ± SD	0.8 ± 0.8
Median (range)	1 (0–2)
KPS	
Mean ± SD	83.1 ± 9.8
Median (range)	80 (70–100)

cases, the device was inserted at the second (9.7%) or third infusion (6%). The PICC was exclusively used for chemotherapy infusion and blood exams.

Four patients, with mild motor impairment but independent walking, were receiving prophylactic low molecular weight heparin (LMWH). Only two patients received a higher dose of LMWH due to previous pulmonary embolism.

All patients were followed for a median period of 3 months (range 1–5). The dropout rate due to death related to disease progression ($n = 7$) or loss to follow-up (4) was 18.3% ($n = 11$).

All the registered complications are summarized in Table 2. Excluding loss to follow-up ($n = 11$), 67.3% (95% CI, 52.5%–80.1%) ($n = 33/49$) of patients developed at least one complication related to the PICC within a median time of 27 days (range 0–150) after PICC implantation (Fig. 1). Immediate complications included 8 exit-site grade 1 hematomas, 4 accidental arterial punctures, and 3 instances of primary malpositioning that required up to 3 insertion attempts. Early and late complications comprised 20 mechanical complications, including dislocation of the catheter (with 2 accidental self-removals) and occlusion, 3 CRBSIs, and 8 device-related thromboembolic events.

Among the early and late complications, catheter-related thromboembolism and CRBSI were the most relevant events registered. Among the former, 8 patients developed thrombotic events (16.3%), of which two developed massive pulmonary embolism. In all patients, the PICC was promptly removed, and the patient was treated with a high dose of LMWH.

Table 2 Overall PICC-related complications. The sum of all complications exceeds the total because a patient could have more than one complication

	N
Subjects with at least one complication	33/49 (67.3%)
Immediate complications	
Hematoma	8 (16.3%)
Accidental arterial puncture	4 (8.2%)
Primary malpositioning	3 (6.1%)
PICC-associated bloodstream infections	3 (6.1%)
PICC-related thrombosis	8 (16.3%)
Pulmonary embolism	2 (4.1%)
Mechanical complications	
Dislocation of the catheter	12 (24.5%)
Occlusion	8 (16.3%)
Causes of removal	
Serious PICC-related complications	11 (22.4%)
Issues related to PICC line management	3 (6.1%)
Death	8 (16.3%)

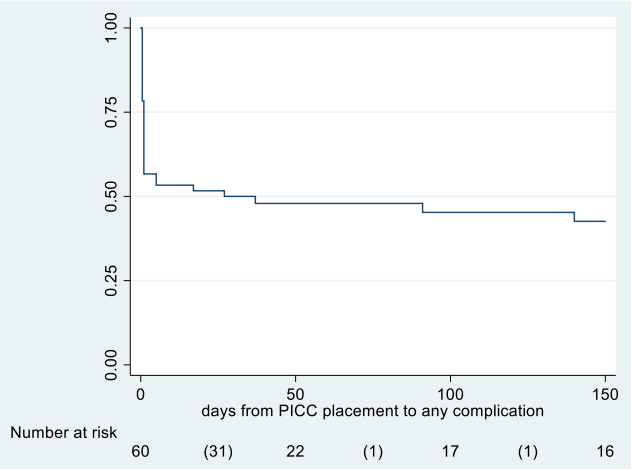

Fig. 1 PICC complication-free survival

Concerning CRBSI, 3 immunocompetent patients (6.1%) developed symptoms of bacterial infection at 1, 36, and 113 days after PICC insertion: all resulted in gram-positive bacteria-positive catheter tip cultures (*Staphylococcus epidermidis*, *Staphylococcus aureus*, and *Enterococcus faecium*). In all cases, the PICCs were rapidly removed and treated with adequate antibiotic therapy with prompt resolution of symptoms.

To determine the association between PICC-related thrombosis/CRBSI and BMI and the use of corticosteroids, univariate analyses were conducted. Concerning steroids, we found higher doses of steroids among patients who developed CRBSI or thrombosis compared to those who did not develop any CRBSI or thrombosis (mean ± SD, median [range] of 4.3 ± 2.7, 4 [0–8] vs 2.9 ± 3.5, 2 [0–12], respectively), although there was an absence of a significant association ($p = 0.09$, Mann-Whitney test) (Fig. 2). Concerning BMI, the data showed a trend towards a risk of developing CRBSI or thrombosis of 37.5% in overweight/obese patients compared to 21.7% in normal-weight patients ($p = 0.31$, Fisher exact test).

Subjective tolerability

Patients were interviewed through semi-structured, open-ended questions; the main themes investigated by the questionnaire were implantation, management, activities of daily living, emotional impact, and overall satisfaction. Implantation was generally nontraumatic, with 40/60 patients describing the procedure as slightly painful (mean NRS score 4) or not painful. At home, 43 subjects experienced both difficulty relying on qualified nursing and access to the specific material for device management, obligating patients to refer to our institution for the PICC line dressing change. During daily life, 34 patients experienced limitations in hygiene and self-care, becoming caregiver-dependent mainly during the first month. Over time, patients became familiar with the device

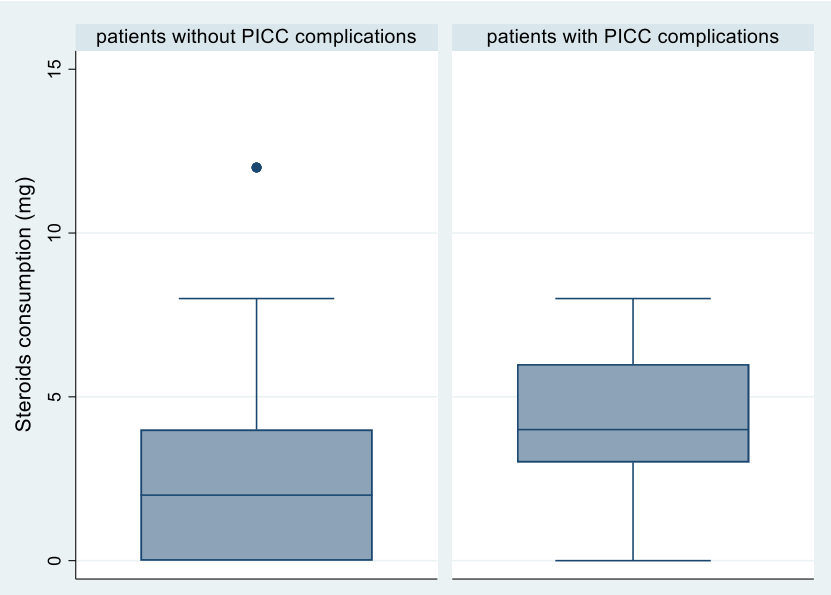

Fig. 2 Box plots of steroid consumption at the time of PICC placement among patients with and without PICC complications

but without achieving complete adaptation. However, social/work activities were not specifically affected, although younger people (< 40 years old) reported acting with "care and caution" in relation to the PICC. Regarding the emotional impact, the data showed that the PICC did not influence or solicit memory of disease in 44 patients during the 3 assessments. Three months after PICC implantation, 34 patients reported that the PICC was useful and safe. Venipuncture reduction was the greater perceived advantage. Overall, the experience was positive in more than 90% of patients, affirming their being "satisfied" based on a ranking of "Not at all Satisfied," "Partly Satisfied," "Satisfied," and "Very Satisfied."

Discussion

The present study evaluated the complications and tolerability of PICC in a neuro-oncological population through a prospective observational study. In recent years, studies have drawn attention to the risk of thrombosis and CRBSI related to PICCs in cancer patients. Among these studies, Chopra and Kramer reported in their systematic review and meta-analysis an incidence of DVT of 6.7% [10] and an infection of 5.5% [11] associated with PICCs.

To the best of our knowledge, no data are available on neuro-oncological patients.

In our study, the overall complication rate (of any type) was 67.3%. Of these, approximately 40.8% could be classified as "minor" complications: hematoma and pain occurred within 1 week after PICC placement with spontaneous resolution, and dislocations (approximately 24%) were recorded between the 3rd and 5th month that required repositioning when catheter leakage was > 4 cm to avoid potential extraluminal contamination.

"Serious" complications included CRBSI (6.1%) and thrombotic events (16.3%). We observed a CRBSI rate consistent with that previously reported in the literature, while in our study, thrombotic events were almost double those in the literature (16.3% vs 6.7%) [10, 11]. The highest rate of thromboembolic events recorded seemed to reflect the well-known risk of neuro-oncological patients developing thromboembolic events [4–6]. Only symptomatic thromboses were detected and confirmed through echocolordoppler; two cases of distal thrombosis were further complicated by vena cava syndrome and massive pulmonary embolism, confirmed through spiral thorax CT scan, which required immediate hospitalization of the patient with a consequent delay in chemotherapy administration. None of the events was fatal. In an attempt to find a possible link between the onset of thrombotic events and a specific administered chemotherapy schedule, no correlation emerged. Compared to nitrosureas, other chemotherapeutic agents, such as alkylating and antiangiogenic drugs, often produce vessel damage, increasing the thromboembolic risk; however, in our study, a smaller number of events was recorded in this subset of patients (5 patients treated with fotemustine vs 3 patients treated with other chemotherapeutic agents) [12].

A total of 6/8 patients who developed thrombotic complications had already undergone at least one line of chemotherapy before PICC placement, suggesting this condition as a possible risk factor for the onset of the event and that it should be considered in patient selection. Moreover, two patients with PICC thrombosis had primary malposition, with two or more failed attempts, which significantly lengthened the

duration of the procedure. Repeated venipuncture could damage the vascular endothelium, contributing to the onset of thrombotic complications.

Concerning PICC-related infections, we observed that higher doses of steroids seemed to be a possible risk factor for CRBSI, although such an association was not statistically significant ($p = 0.09$). Two patients with sepsis had serous material leakage from PICC insertion from the day after placement. Prevention and control of infection are the basis of clinical care, even more so in oncological patients with long-term venous access, who should be rigorously protected from complications. Nevertheless, a "near zero infection rate" seems to be no longer impossible: technological innovations, ultrasound-guided venipuncture, latest-generation materials, sutureless devices, strict hand-washing policies, and training for nurses and clinicians have made it possible to reduce infection rates considerably [13]. In 2006, Tian et al. demonstrated how awareness-raising interventions could reduce PICC complications by over 50% ($p = 0.0004$) [14]. Similarly, in the 2000s, Marmel et al. showed that the presence of a specialized nursing team reduced the percentage of CVC infections [15].

Education and training for all health practitioner is the essential prerogative to perform PICC placement in order to develop and increase knowledge and ability in the whole process management from placement to removal. For this reasons, in our study, all nurses and physicians were appropriately trained in order to upgrade their skills and, at the same time, to guarantee a safe and secure insertion. In fact, in our study, no correlation between the high frequency of complications and the health practitioner training was found.

Among the identification of independent risk factors for complications, the role of a BMI > 25 is now emerging in the literature and is likely associated with a higher rate of adverse events in patients with PICCs [16]. In our study, no role for BMI was confirmed; one possible reason could be the limited number of patients.

Many issues regarding the prevention of adverse events will probably remain unresolved about the role of anticoagulant prophylaxis in the prevention of device-related thromboembolic events. Indeed, the role of antithrombotic prophylaxis in cancer patients, and even more so in the neuro-oncology field, is controversial due to the biggest risk of intracranial hemorrhage; therefore, the potential benefit of prophylactic anticoagulation should be weighed against bleeding complications [17]. Currently, in the literature, a very limited number of studies, mostly retrospective and not always focused on oncological populations, have evaluated this aspect. In their retrospective studies, King and Marnejon failed to demonstrate the protective role of low molecular weight heparin and unfractionated heparin against PICC-related thrombotic events [18, 19]. Likewise, a recent meta-analysis evaluating both the role of heparin and warfarin in cancer patients with CVCs failed to demonstrate the ability to reduce device-related thromboembolic events [20]. Venous thrombosis-related vascular catheters are complex devices involving a series of unchangeable processes, such as the intrinsic variability of each human being, each patient's thrombophilic tendency, and the type of illness. Because of these aspects, thrombosis will remain only a partially preventable event. Although the limited number of patients treated with LMWH in our study does not allow to draw significant conclusions, no thromboembolic events were recorded in this soubgroup of patients.

This study also investigated, similar to only a few others in the literature, device tolerability from the patient's point of view, describing their experience of using the PICC [21, 22]. More than 90% of patients had satisfying experiences with the device. In interviews, patients revealed that the most positive aspect of a permanent intravenous device was certainly venipuncture reduction during chemotherapy treatments with consequent minor trauma and improvement in their quality of life. Of course, many disadvantages emerged. First, almost all patients experienced a self-care restriction because the PICC was inserted in the dominant arm in 85% of subjects. The most negative impact was on hygiene, which required the support of familial caregivers who provided some level of care, especially for older patients. Patients felt greater dependence on caregivers, which was likely the most important stress factor after disease.

Another negative aspect was catheter management. In most patients, the device potential was underused (i.e., it was not used to collect blood samples or to administer contrast agents during magnetic resonance imaging), probably due to a lack of knowledge about the device or flushing management. For this reason, it should be noted that in 3 patients, the PICC was removed due to the failure of device management by competent health practitioners. The patients underwent Port-a-Cath implantation.

Surprisingly, the impact of the permanent device on the emotive sphere mostly had no role on solicited memory of disease. Although disadvantageous, patients progressively comprehended the utility and benefits of the device.

Conclusion

Even considering the limitations of the study, including the small sample size and the detection of only symptomatic PICC-related thrombosis, the results showed a nonnegligible increased thromboembolic risk in neuro-oncological patients with PICCs, almost double that of the general oncology population. The poor prognosis at recurrence might suggest a not well balanced risk/benefit ratio between safe chemotherapeutic infusion and PICC-related complications. For these reasons, behind guidelines and recommendation on the use of a

central venous catheter during chemotherapies, an accurate history of patients as well as careful review of therapeutic treatments administered appear to be crucial to the early identification of risk factors that could farther negatively influence the outcome. However, it is essential to extend the study to a greater number of patients to achieve reliable results and identify the patient population considered to be at high risk. The data obtained will allow the implementation of corrective actions to reduce specific complications. Regarding tolerability, the device seemed to be positively accepted by the majority of interviewed patients, even if self-care habits were often affected because the device represented an obstacle to patient independence in almost all cases. However, relevant knowledge gaps still remain, including the real need to treat neuro-oncological patients with PICCs with routine pharmacological venous thrombosis prophylaxis as well as the early identification of independent risk factors, such as the role of obesity, in the development of thrombotic events.

Compliance with ethical standards

All human studies have been approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. All participants gave their informed consent prior to their inclusion in the study.

Conflict of interest The authors declare that they have no conflict of interest.

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