Support Care Cancer (2014) 22:1705–1714
DOI 10.1007/s00520-014-2208-1

REVIEW ARTICLE

Totally implantable vascular access devices 30 years after the first procedure. What has changed and what is still unsolved?

Roberto Biffi · Adriana Toro · Simonetta Pozzi · Isidoro Di Carlo

Received: 6 June 2013 / Accepted: 9 March 2014 / Published online: 22 March 2014

Abstract The first placement of a totally implantable central venous access device (TIVAD) was performed in 1982 at the MD Anderson Cancer Center in Houston by John Niederhuber, using the cephalic vein—exposed by surgical cut-down—as route of access to central veins. After that, TIVADs proved to be safe and effective for repeated administration of drugs, blood, nutrients, and blood drawing for testing in many clinical settings, especially in the oncologic applications. They allow for administration of hyperosmolar solutions, extreme pH drugs, and vescicant chemotherapeutic agents, thus improving venous access reliability and overall patients' quality of life. Despite the availability of a variety of devices, each showing different features and performances, many issues are still unsolved. The aim of this review article is to point out what has changed since the first implant of a TIVAD, and what it is still matter of debate, thus needing more investigation. Topics analyzed here include materials, choice of the veins and techniques of implantation, role of ultrasound (US) guidance in central venous access, position of catheter tip assessment, TIVAD-related infection and thrombosis, and quality of life issues.

R. Biffi (✉) · S. Pozzi
Division of Abdomino-Pelvic and Minimally Invasive Surgery, European Institute of Oncology, Via G. Ripamonti 435, 20141 Milan, Italy
e-mail: roberto.biffi@ieo.it

A. Toro · I. Di Carlo
Department of Surgical Sciences, Organ Transplantation and Advanced Technologies, University of Catania, Cannizzaro Hospital, Catania, Italy

Keywords Central venous catheter · Totally implantable vascular access devices (TIVAD) · Ultrasound guidance · Catheter tip · Catheter-related bloodstream infection (CRBSI) · Central venous thrombosis

Introduction

The first placement of a totally implantable central venous access device (TIVAD) was performed in 1982 at the MD Anderson Cancer Center in Houston by John Niederhuber, using the cephalic vein—exposed by surgical cut-down—as route of access to central veins [1]. After this initial application, technique spread throughout the world, and long-term TIVADs proved to be safe and effective for repeated administration of drugs, blood, nutrients, and blood drawing for testing in many clinical settings. Their increasing use has been advocated for allowing the administration of hyperosmolar solutions, extreme pH drugs, vescicant chemotherapeutic agents, thus improving venous access reliability, reducing the discomfort and anxiety associated with repetitive venous access, and increasing the overall patients' quality of life. Over the last decades, many changes have occurred in this field, especially in the oncology setting, which is the most frequent application of these devices, with new chemotherapy combinations and more complex regimens becoming available. Despite the availability of a variety of devices, each showing different features and performances, many issues are still unsolved. The Aim of this review article is to point out what has changed since the first implant of a TIVAD in 1982, and what it is still matter of debate, thus needing more investigation. Topics analyzed here include materials, choice of the veins and techniques of implantation, role of ultrasound (US) guidance, position of catheter tip assessment, TIVAD-related infection and thrombosis, and quality of life issues.

Materials

Silicone versus polyurethanes

TIVADs consist of a reservoir [usually made of titanium and/or plastic polymers, developed to safely perform magnetic resonance imaging (MRI)], connected to a central venous catheter (CVC). Catheters are usually made of silicone or polyurethane, which have different features. Silicone rubber chemical structure is composed of adjacent polymer chains, cross-linked to each other. Its physical properties vary according to the degree of cross-linking. Polyurethanes are a class of materials with a broad spectrum of physical and chemical properties. Their commonality is the urethane linkage between "hard" and "soft" polymer chains (segments). New generation polyurethanes guarantee a minimal interaction between device and blood, thus showing a nice biocompatibility, previously attributed to silicone only. In spite of many reports from the literature, investigating ease of insertion, risk of mechanical phlebitis, infusate compatibility, stability, durability, and vascular damage, there is no currently conclusive evidence supporting an inherent superiority of a material over another. Teflon, silicone, and polyurethane have been associated with fewer catheter-related infections than polyvinyl chloride or polyethylene. However, all available catheters for long-term use are made either of polyurethane or silicone, and there is no specific recommendation regarding materials for clinical practice [2].

Catheter design

Valved catheters have the advantage of not requiring heparin flushes. Nevertheless, they may need pressurized infusions for the administration of blood products and are more expensive. In a controlled randomized trial, they were not superior to a traditional, open-ended device in terms of catheter efficacy and early and late complications [3].

Catheters coated with antiseptic drugs

Rates of catheter-related bloodstream infection (CRBSI) are significantly reduced by catheters coated with rifampicin/minocycline or internally and externally coated with chlorhexidine/silver sulfadiazine [4, 5]. The use of a CVC coated with an antimicrobial is therefore to be considered for adult patients who require short-term central venous catheterization and who are at high risk for CRBSI if the facility infection rates remain high despite the implementation of a comprehensive strategy to control them [6]. It is important to underline that most evidence in this area concerns short-term, non-tunneled central venous access. There is no evidence to support the use of TIVADs or long-term tunneled catheters coated with antiseptic drugs. In the near future, new materials will be available in this clinical setting, needing appropriate trials.

Power technology

The use of totally implantable venous access devices in radiology may be associated with complications such as occlusion of the system (because of the high density of contrast media), infection (if the port is not handled in aseptic conditions, using proper barrier protections), and mechanical complications due to the high-pressure administration of contrast by automatic injectors (so-called "power injectors"): extravasation of contrast medium into the soft tissues, subintimal venous or myocardial injection, or serious damage to the device itself (breakage of the external connections, dislocation of the non-coring needle, or breakage of the catheter). The latter problem—i.e., damage of the device from a *power injection*—is not an unjustified fear, but a reality. A warning by the U.S. Food and Drug Administration first issued in July 2004 [7] reported around 250 complications of this kind, referring to both TIVADs and CVC and peripherally inserted central catheter (PICC) systems, which occurred over a period of several years. In all cases, the damage occurred during the injection of contrast by means of "power injectors" for computed tomography (CT) or MRI procedures. In addition to the obvious loss of a vascular access and the need for repositioning a new device, in some cases, the breakage of the catheter may cause an extravasation of contrast into the patient's soft tissues, and/or an embolization of catheter fragments in the central venous or pulmonary arterial circulation (which may result in the need to retrieve them by interventional radiology). Typical mechanical damage includes breakage of the extension of the non-coring needle or its detachment from the needle, sudden expulsion of the non-coring needle from the silicone septum and thus from the port chamber, and breakage of the silicone portal septum. The more fragile the system is, even in one of its components, the lower the injection pressure at which mechanical damage may occur.

The availability of power-certified TIVADs has recently solved this problem; a final recommendation of a multidisciplinary international panel recently addressing this issue is that radiologic units using contrast infusion through venous ports should adopt specific protocols (or "bundles") for prevention of infective and mechanical complications and should implement an educational strategy including training courses for the healthcare personnel working with venous access devices [8].

Techniques, choice of the venous site, and use of ultrasound guidance for central venous access

Surgeons have traditionally implanted the TIVADs in the operating theater, using the cephalic vein isolated at deltoid–

pectoralis groove by cut-down technique to access central veins. In case of atrophy or inability to use the cephalic vein, it is possible to use external jugular, axillary, or internal jugular vein. When the patients present an occlusion of the superior vena cava, femoral or saphenous vein can be used [9, 10]. However, in the last decades, this procedure is being performed more commonly by the Seldinger's technique via a percutaneous approach. The percutaneous approach to the subclavian or internal jugular vein has become the most popular procedure for placing a CVC in the superior vena cava, both for short- and long-term use. The great flexibility of percutaneous cannulation, the short duration of the procedure in most situations, and the possibility to switch from a procedure that requires an operating theater to a less demanding (especially cost-wise) outpatient procedure have made the superiority of percutaneous central vein access quite obvious, reducing significantly the need for open cut-down procedures.

Recently, a modified Seldinger's technique was proposed, first described by Coit et al. [11] in 1988 and successfully applied in a subsequent randomized controlled trial [12]. It is a combination of open cannulation of the cephalic vein and the Seldinger's technique. The aim of this rescue technique is to avoid a percutaneous puncture of the subclavian vein and the risk of pneumothorax/hemothorax after a failed open access of the cephalic vein. Therefore, a guidewire and, if necessary, a dilator and peel away sheath is introduced into the dissected cephalic vein to overcome a narrow or strongly curved vessel.

Central venous cannulation can be an unsafe procedure: the National Confidential Enquiry into perioperative deaths has reported one death resulting from a procedure-induced pneumothorax. Recognition of risk factors for difficult catheterization is therefore essential, and all patients should be evaluated for conditions that might increase the difficulty of catheter insertion, such as skeletal deformity, presence of scars, obesity, or previous surgery at insertion site. The preferential use of the internal jugular vein for the percutaneous "blind" (based on anatomic landmarks) approach for central venous cannulation is not able to eliminate the risk of pneumothorax, especially when anatomic abnormalities, dehydration, inexperience, or disease-related alterations may force the operator to resort to subclavian venipuncture after failed attempts. Mechanical complications of CVC insertion without US guidance, such as arterial puncture and pneumothorax, are seen in up to 21 % of attempts, and up to 35 % of insertion attempts are not successful. Real-time sonography provides a means to safely direct the cannulating needle toward the internal jugular, axillary/subclavian, and femoral veins while avoiding puncture of the accompanying arteries and other organs. According to this technique, an ultrasound probe is used to locate the vein, and the introducer needle is guided through the skin and into the vessel. Although some investigators have suggested in the past the use of ultrasound for assistance of vascular access, it is now evident that the full benefits of ultrasound are obtained only when coupling the pre-procedural ultrasound assessment with a real-time ultrasound-guided venipuncture. Ultrasound does not obviate the need for anatomic knowledge, so surface anatomic landmarks remain necessary for orientation of both cannulating needles and the ultrasound probe itself. Given the superficial location of the central veins at the sites of venipuncture, a high frequency probe of at least 7.5 mHz creates optimal images. Higher probe frequencies are most suitable for superficial vessels, because higher image resolution enables the visualization of adjacent nerves and smaller arterial branches. They are ideal for guiding central venous cannulation in neonates and small children. Lower probe frequencies are required for imaging target vessels at a greater depth, including obese patients. Ultrasound equipment can be easily used within a sterile field. Needle guides which orient the needle within the field of view along the path of the ultrasound beam can facilitate venipuncture in some conditions, but they are not favored by many operators (including the authors of this paper), willing a complete maneuverability of the needle.

With respect to long-term use of TIVADs ports in oncology patients, we recently investigated the issue of which vein or technique, if any, is the best for accessing the central veins in a randomized three-arm trial [13]. Briefly, 403 patients eligible for receiving i.v. chemotherapy for solid tumors were randomly assigned to implantation of a single type of port (Bard Port, Bard Inc., Salt Lake City, UT), through a percutaneous landmark access to the internal jugular, a US-guided access to the subclavian, or a surgical cut-down access through the cephalic vein at the deltoid–pectoralis groove. Early and late complications were prospectively recorded until removal of the device, patient's death, or ending of the study. Four hundred one patients (99.9 %) were assessable: 132 with the internal jugular, 136 with the subclavian, and 133 with the cephalic vein access. The median follow-up was 356.5 days (range, 0–1,087). No differences were found for early complication rate in the three groups: internal jugular, 0 % [95 % confidence interval (CI) 0.0 to 2.7 %]; subclavian, 0 % (95 % CI 0.0 to 2.7 %); cephalic, 1.5 % (95 % CI 0.1 to 5.3 %). US-guided subclavian insertion site had significantly lower failures (e.g., failed attempts to place the catheter in agreement with the original arm of randomization, $P=0.001$). Infections occurred in one, three, and one patients (internal jugular, subclavian, and cephalic access, respectively, $P=0.464$), whereas venous thrombosis was observed in 15, 8, and 11 patients ($P=0.272$). We concluded that central venous insertion modality and sites had no impact on either early or late complication rates when performed by experienced operators, but US-guided subclavian insertion showed the lowest proportion of failures.

There is now compelling evidence that ultrasound-guided venipuncture (by real-time ultrasonography) is associated with a substantial benefit, and ultrasound support is therefore strongly recommended (Grade A) for all CVC insertion. The

US guidance has been evaluated in RCTs, which have been pooled in three meta-analyses [14–16]. In a 1996 meta-analysis of eight RCTs, US guidance was characterized by a lower rate of failure and complications and by a higher rate of success at the first attempt if compared to the landmark technique. In 2001, the Stanford Evidence Based Practice Center at the UCSF published the results of the project "Making Health Care Safer: A critical analysis of patient safety practices," identifying US guidance for CVC placement as 1 of 11 evidence-based clinical tools which should be enforced in clinical practice. National Institute for Clinical Excellence-UK made similar recommendations in 2002, and the implementation of National Institute for Clinical Excellence-UK guidelines has been associated with a significant reduction in complication rates in UK tertiary referral centers. Similar recommendations, based on the published data of RCT meta-analyses, have been made by several scientific societies. Most recently, the Association for Vascular Access has drafted a position statement on the use of real-time imaging for placement of central VADs (available at www.avainfo.org) advocating the use of ultrasound guidance for all non-emergent central vascular access procedures. Other prospective studies, some of which were RCTs, have addressed this issue in a number of settings, such as the intensive care unit, emergency room, oncology, pediatrics, and dialysis, leading to the conclusion that ultrasound guidance improves the success rate of vein cannulation, reducing the number of attempts, complications, and failures. A randomized study of US-guided versus blind catheterization of the internal jugular vein in critical care patients showed that US guidance was also associated with a decrease of catheter-related infections [17]. Finally, an international panel of experts recently provided evidence-based recommendations for the systematic use of ultrasound guidance for all vascular access [18].

Concerns have been expressed with respect to training, as the novel techniques should be incorporated into the ultrasound courses that are currently being set up for radiologists, anesthesiologists, and surgeons. Moreover, the landmark method would remain important for emergencies when ultrasound equipment and/or expertise might not be immediately available.

There is a lack of consensus for standards of training in ultrasound vascular cannulation. Although formal education and training are considered necessary, barriers to this goal are apparent, such as hardware deficiencies, insufficient instructor availability, and a perceived lack of time required to achieve certified competency [19]. Theoretical lessons on ultrasound physics, ultrasound anatomy, and hands-on-training on inanimate models could achieve standardization across medical centers.

Cost analysis is certainly a key issue. Calculations should be precise and also include costs for ultrasound devices and operator training. Calvert et al. [16] compared the economics of using 2D-ultrasound locating devices and traditional landmark methods for central venous cannulation. They reached the conclusions that the cost of using ultrasound for central venous cannulation was less than 10 lb sterling per procedure, and that the introduction of 2D ultrasound for central venous cannulation would save the United Kingdom–National Health Service money (£2,000 for every 1,000 procedures). However, some criticism derived from the incidence of arterial puncture that the authors used in their analysis. Based on experience and published data, a 12 % incidence of arterial puncture using the landmark approach was judged almost an order of magnitude too high. Using a significantly lower and more realistic arterial puncture incidence reduces the cost of the landmark technique and may change the cost-effectiveness calculation to the point where the ultrasound choice may no longer be dominant, meaning that while ultrasound is more effective, it also costs more. Finally, since the reference is internal jugular vein cannulation in the operating theater, the question of whether the results can be extrapolated to other central venous cannulations performed outside that setting was not addressed. While many RCTs have clearly shown that ultrasound guidance is superior to the landmark technique—at least in terms of immediate outcome—for internal jugular vein cannulation in a variety of clinical settings, doubts still persist for the subclavian insertion site. US guidance for subclavian venous catheterization has yielded inconsistent results in a small number of trials [20, 21]; limited evidence favored 2D ultrasound guidance for subclavian vein procedures in adults (relative risk 0.14; 95 % confidence interval, 0.04 to 0.57). A recent randomized trial in ICU patients [22] suggests that ultrasound-guided cannulation of the subclavian vein is superior to the landmark method in terms of average access time, number of attempts, frequency of artery puncture, hematoma, hemothorax, pneumothorax, brachial plexus, and phrenic nerve injury.

Quite obviously, a TIVAD implantation does not finish with catheter positioning in the superior vena cava, and to make a subcutaneous pocket for the port still represents a significant part of the entire procedure. According to some authors, as long as there will be a need to perform a skin incision to create the subcutaneous pocket, the surgical cut-down could be reasonably attempted and the cephalic vein used as preferred choice, having a range of possible alternatives in case of failure [23]. More studies are needed to address cost-effectiveness of this policy.

Position of catheter tip, its influence on late complications, and methods to assess it

The optimal position of the catheter tip and the definition of the best assessment technique of this position are still a matter of debate [24], in spite of their importance for avoiding

complications and maintaining functionality of long-term TIVADs. Once excluded, the branches of the superior vena cava (SVC) [25, 26] or the lower part of the right atrium (RA), where catheter tip can damage the vein or heart wall [27], the golden standard—at least for oncology patients receiving long-term treatments—seems to be the atriocaval junction, where the SVC merges into the RA. Unfortunately, precise localization of the junction between SVC and RA may be difficult to obtain on plain film radiograph. Tumors or mediastinal shifting may indeed obscure the recognition of these structures, and some thin catheters are not easily seen, particularly in obese patients. So, the precise location of catheter tip with respect to surrounding structures is often imprecise and subject to inter-observer variability. In the 1980s, FDA recommendations [28] and NAVAN statements [29] were driven by potentially fatal complications observed in patients with catheter tips deeply located in the RA. Atrial perforation, atrial thrombus formation—with eventual pulmonary embolism—and cardiac tamponade with exceptional cases of fatal outcome were reported. In adherence with these recommendations, tips of central catheters shifted outside the RA, even into the brachiocephalic veins, where they are associated with a significant incidence of catheter malfunction, venous thrombosis, and vessel's stenosis. Different findings were obtained by hemodialysis catheters: tip location in the right atrium allows better flow rates in both directions, without an increase in thrombus formation nor damage to the atrial wall. Consequently, guidelines from the National Kidney Foundation: Dialysis Outcomes Quality Initiatives [30] advised inserting catheter tips in the RA as preferential site. More recently, the European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines addressed the long-term delivery of hyperosmolar parenteral nutrition solutions. On the basis of grade A level of evidence, they recommended inserting central catheter tips in the lower third of the superior vena cava, at the atriocaval junction, or in the upper portion of the right atrium [31].

Instrumental assessment of catheter tip position is mandatory before releasing the device for use, as the risk of initial catheter malposition is quite high when evaluation rely only on anatomical landmarks, without other verification [32, 33]. The simplest method is a postoperative plain chest X-ray, but its interpretation can lack precision. Moreover, this policy is not advised for TIVADs, which require a new, costly procedure for postoperative correction of initial malposition. This led to the implementation of intraoperioperative checking techniques, among which fluoroscopy and more recently intravascular electrocardiogram, either using an ionic conducting solution or a metallic guidewire [34–36], are the most widely used. Fluoroscopy is currently the most used; patients receive only a small amount of radiation, but repeated exposure remains a concern for care providers. Further limitation is the need of an expensive equipment, not always available. This favored the use of an assessment method based on electrocardiography [intravascular electrocardiogram (IEG) technique]. Tracking the IEG "P-wave" changes during intravascular motion of the electrode allows to detect very precisely the junction between the SVC and the RA, but only in the presence of atrial contractions. Consequently, the absence of a clear P-wave on the surface ECG (for example, in case of atrial fibrillation) or catheter malposition in one of the affluent veins of the SVC precludes IEG changes and information about the intravascular electrode location may not be obtained.

Infectious complications and central venous catheter-related thrombosis

Important complications like thrombosis and infections are still associated with TIVADs, sometimes leading to device loss, significant morbidity, increased duration of hospitalization, and additional medical costs. Intravascular catheter-related infections are a major cause of morbidity and mortality, representing the third most frequent type of nosocomial infection [37]. Catheter-sparing diagnostic methods, such as differential quantitative blood cultures and differential time to positivity (DTTP), have recently emerged as reliable diagnostic techniques. Paired blood cultures (aerobic and anaerobic) from a peripheral vein and the central catheter should be obtained. If the culture from the central catheter turns positive before the peripheral sample (diagnostic cutoff, 2 h), this so-called DTTP can help to make the diagnosis of catheter-related infection [38].

Possible preventive strategies include skin antisepsis, maximum sterile barrier, use of antimicrobial catheters, and antimicrobial catheter lock solutions. It should be underlined that respect of sterility is of paramount importance in both the implant and management of a long-term central venous access. Prospective trials suggest that the risk of CRBSI may be reduced by using maximal sterile barriers, including a sterile gown and sterile gloves for the operator, and a large sterile drape for the insertion of central venous access devices. Full-barrier precautions during CVC insertion are recommended by most guidelines, and this practice has been adopted by most "bundles" of evidence-based interventions aiming to reduce CRBSI in multicenter prospective trials. Proper education and specific training of the staff is universally recommended as one of the most important and evidence-based strategies for reducing the risk of catheter-related infections (Grade A). There is now good evidence demonstrating that the risk of infection declines following the standardization of aseptic care and increases when the maintenance of intravascular catheters is undertaken by inexperienced healthcare workers. In addition, it has been proven that relatively simple education programs focused on training healthcare workers to

adhere to local evidence-based protocols may decrease the risk to patients of CRBSI. In a very important multicenter prospective study carried out in 108 ICUs, Provonost et al. [39] showed that the adoption of a bundle of a small number of evidence-based interventions (hand washing; full-barrier precautions during the insertion of central venous catheters; skin antisepsis with chlorhexidine; avoiding the femoral site if possible; removing unnecessary catheters as soon as possible) was highly effective in producing a clinically relevant (up to 66 %) and persistent reduction in the incidence of CRBSI.

Catheter-related thrombosis is particularly relevant because the incidence of venous thromboembolism is markedly higher in patients with cancer than in patients without cancer [40] as thrombosis is a direct consequence of tumor growth and host inflammatory responses and an indirect consequence of cancer treatment, venous stasis, and direct vessel trauma. In a systematic review [41], the incidence of symptomatic CVC-related deep vein thrombosis in adults varied between 0.3 and 28.3 %, whereas the incidence of venography-assessed cases (mostly asymptomatic) ranged from 27 to 66 %. Pulmonary embolism has been reported to occur in 15 to 25 % of patients with CVC-related vein thrombosis. Regarding the possible role of the insertion technique in inducing thrombosis, prospective nonrandomized studies have suggested a relationship between minimal insertion damage to the vein wall, as obtained with ultrasound guidance, and low rate of subsequent thrombotic events. Materials can also have an effect on thrombosis rates. Prospective trials have indicated an inherent superiority of silicone and second–third generation polyurethane over more rigid materials like polyvinylchloride, tetrafluoroethylene, and polyethylene. In addition, a lower diameter catheter and a single lumen might be protective against the risk of central venous thrombosis.

When thrombosis occurs, medical treatment or catheter removal are the possible options. Studies on the pharmacologic treatment of catheter-related thrombosis have focused on clinically overt thromboses, reporting a rate of successful catheter preservation ranging from 45.5 to 96 %. No clear advantages could be obtained by catheter removal after the thrombosis was established, and the clinical outcome did not seem to be influenced by this measure. The mandatory indications to catheter removal in case of thrombosis include infected thrombus, malposition of the tip (primary or secondary to migration), and irreversible occlusion of the lumen.

Thrombolytic drugs (urokinase or recombinant tissue plasminogen activator) should be used in acute symptomatic cases diagnosed fewer than 24 h after the first symptoms. Efficacy of systemic versus local thrombolysis is still a matter of debate, especially for large thrombi. Chronic symptomatic cases should be treated with a combination of low-molecular-weight heparin (LMWH) and then oral anticoagulants or with LMWH long-term alone, depending on the clinical setting. Compared with warfarin, LMWH exhibits a superior safety profile and more predictable antithrombotic effects and can usually be given once daily in a unit dose without the need for dose monitoring, but use in patients with renal failure (especially for glomerular filtration rate <30 mL/min) should be cautious because even low prophylactic doses of LMWH may accumulate and cause bleeding.

Although some early open-label trials suggested a benefit from oral, low-dose daily warfarin or daily SC dose of LMWH, more recent double-blind, placebo-controlled RCTs did not find any advantages for either of these prevention strategies [42–44], and the choice to start prophylaxis against venous thromboembolic events in all oncology patients bearing a CVC, either with LMWH or with minidose warfarin, remains unsupported by evidence-based medicine. More studies are needed to identify subsets of cancer patients who are at high risk of developing CVC thrombosis and may benefit from prophylactic systemic anticoagulation. Indeed, in a recent observational study [45] compared with patients with no treatment, continuous antithrombotic prophylaxis administered to patients who were older and had a history of venous thromboembolism, as well as more advanced cancer, did not prevent catheter-related thrombosis but significantly reduced systemic venous thromboembolism (8.2 versus 4 %) and mortality (44 versus 25 %).

van Rooden et al. [46] have shown a close association of CVC-related infection with thrombosis: they found that the risk of developing clinically manifest thrombosis increases substantially after an episode of CVC-related infection (relative risk, 17.6) and is enhanced by the severity of the infection. Comparing patients without catheter-related infections and patients with systemic catheter-related infection, the absolute risk of thrombosis increased from 2.5 to 57.1 %. Moreover, in patients having two or more positive subsequent CVC lock fluid cultures with identical microorganisms, 71.4 % developed thrombosis as compared with 3.3 % in patients with negative or a single positive culture.

In conclusion, most TIVAD-related infections can be nowadays prevented, and a number of measures have been implemented to reduce the risk of infections. Thrombosis still remains a major problem. Future prevention studies should aim to achieve a better understanding of the risk factors for thrombosis, contributing to a better definition of the patient population at risk; certain patient groups, including those with a hematologic malignancy undergoing intensive chemotherapy, as well as those with hereditary thrombophilia or with a history of unprovoked thrombosis, may have an elevated risk of developing this complication, making them reasonable candidates for prophylaxis. Currently, available prophylactic agents are not optimal for the prevention of thrombosis, especially in the cancer patient, and future studies should be adequately powered and evaluate the effects of newer anticoagulant agents like factor Xa or direct thrombin inhibitors.

Quality of life issues

Many patients suffering from solid tumors require long-term TIVADs for safe, cyclic delivery of chemotherapeutic agents, transfusion of blood and blood products, and performance of laboratory tests. Descriptive and prospective nonrandomized trials have reported a number of patient benefits, including no need for additional peripheral venipunctures, greater convenience, and arms left free for activities of daily living, whereas patients generally disliked the visibility of ports and complained about site soreness [47, 48]. Clinical trials to evaluate safety, costs, and quality of life of central venous ports have been basically open-label, single-arm, phase II studies or comparative studies with externalized tunneled systems; they have provided little information on quality of life and global costs, especially when only prospective data are taken into consideration. Assessments of quality and satisfaction of care have focused on patients' satisfaction with physicians or the health care system [49, 50], while research on the specific topic of impact of TIVAD on patients' satisfaction and QoL has been very limited [51–54], and results must be interpreted with caution, as the cited studies are nonrandomized. Moreover, evaluation of QoL in these studies was performed at port removal, using an auto-questionnaire with items concerning interference of the implanted port with daily life, using a single visual analog scale.

A well-functioning TIVAD that will remain in situ for the time needed is highly desirable in the management of patients undergoing long-term chemotherapy. An important factor in the overall assessment of long-term TIVAD is the rate of early and late complications, as the occurrence of TIVAD-related complication, especially when it is cause of the loss of the device, is surely able to have a negative impact on patients' QoL. A critical analysis of the literature shows very low rates of complications related to implantation and use of TIVAD in oncology patients undergoing long-term chemotherapy. Moreover, we already demonstrated by means of a randomized three-arm trial that central venous insertion modality and sites had no impact on either early or late complication rates [13], so we can exclude complications' rate as a factor able to

Table 1 Most relevant improvements and unsolved questions in the field of TIVADs implantation and use

Issue	Improvements	Unsolved questions
Materials	New generation polyurethans, showing higher biocompatibility and stability. Power certification of most TIVADs, able to avoid potential damage occurring during the injection of contrast by means of "power injectors."	Unavailability of TIVADs coated with antiseptic drugs for long-term prevention of infectious complications.
Technique	Systematic use of real-time two-dimensional US guidance for safe and cost-effective implantation of every central venous device. Development of reliable techniques for fuoro-free catheter tip position assessment, like intravascular EKG.	Three-dimensional multiplanar and volume-rendered US devices, allowing the simultaneous view of the anatomical structures in 3 orthogonal planes. Prototypes already available.
Infectious complications	Availability of reliable, catheter-sparing diagnostic methods, such as differential quantitative blood cultures and differential time to positivity (DTTP). Availability of "bundles" of evidence-based interventions able to reduce infectious complications in randomized trials.	Development and successful cost-effective testing of pharmacological agents able to prevent infectious complications in the long-term setting. Some drugs in the pipeline at present time, needing appropriately powered trials.
Catheter-related thrombosis	Evidence of a correct technique of implantation and catheter tip position in reducing the incidence of this still relevant complication.	Currently available prophylactic agents are not optimal for the prevention of thrombosis, especially in the cancer patient. A better definition of the patient population at risk should be obtained, including those with a hematologic malignancy undergoing intensive chemotherapy, as well as those with hereditary thrombophilia or with a history of unprovoked thrombosis.
Quality of life assessment	Availability of validated questionnaires able to investigate quality of life and anxiety-depression in oncology patients bearing a TIVAD.	Patient satisfaction and quality of life, and their relationships with the device adopted for long-term use, need further investigation. Patients and their families still currently play a minor role in the selection of a device, whereas patient satisfaction should be a major issue in the clinical setting of cancer palliation.

seriously affect QoL and/or patients' satisfaction or psychological distress in our experience. Based on these considerations, we performed a randomized trial to compare two different percutaneous routes of access to superior vena cava (subclavian and internal jugular) with a surgical cut-down access through the cephalic vein, evaluating patients' psychological distress and quality of life at regular intervals by means of specific and validated questionnaires. Briefly, 403 patients eligible for receiving intravenous chemotherapy for solid tumors were randomly assigned to implantation of a single type of TIVAD, either through a percutaneous landmark access to the internal jugular or an ultrasound-guided access to the subclavian or a surgical cut-down access through the cephalic vein at the deltoid–pectoralis groove. Patients' QoL and psychological distress were investigated at regular intervals by means of EORTC QLQ-C30 and Hospital Anxiety and Depression Scale (HADS) questionnaires, using univariate and multivariate repeated measure linear mixed models. A post hoc analysis investigated the impact of type of administered chemotherapy (adjuvant versus palliative). Three hundred eighty-four patients (95.2 %) were evaluable, 126 with the internal jugular, 132 with the subclavian, and 126 with the cephalic vein access. The median follow-up was 361 days (range, 0–1,087). Mean score changes for the items of the EORTC QLQ-C30 scales were significantly associated with type of administered chemotherapy only ($P<0.001$), and not with implantation site. Frequency distribution of patients with depression and anxiety score greater than 10 at HADS was not significantly different, with respect either to type of administered chemotherapy or TIVAD implantation site. Our report presents the first randomized evidence on this topic, showing that QoL assessed by EORTC QLQ-C30 and level of anxiety and depression expressed by HADS are not influenced by the TIVAD insertion site and technique used. QoL resulted globally poorer in patients undergoing palliative therapies, when compared to those receiving adjuvant treatments [55]. While awaiting for further evidences, a proper assessment of clinical setting and patients' characteristics, and good cooperation and communication between clinicians and patients, incorporating reported evidence, may form a good basis for optimal clinically relevant decisions.

Table 1 summarizes most relevant improvements and unsolved issues in the field of TIVADs use, across the 30 years of their clinical application.

Closing remarks

After their initial application in 1982, TIVADs spread throughout the world, facilitating a repeated and safe vascular access in a number of patients' categories, in many clinical settings. Systematic use of real-time two-dimensional US guidance proved to be safe and cost-effective for TIVAD implantation, significantly reducing the rate of procedural complications and related costs. New devices, allowing the simultaneous view of the anatomical structures in three orthogonal planes, will be soon available. Finally, reliable techniques for fuoro-free catheter tip position assessment, like intravascular EKG, have been successfully developed and tested.

Complications like thrombosis and infections are still associated with these devices, sometimes leading to their loss, significant morbidity, increased duration of hospitalization, and additional medical costs. A number of measures have been implemented to successfully reduce the risk of infections, including maximal barrier precautions during catheter insertion, catheter site maintenance, and hub handling. Thrombosis still remains a major problem, as it seriously complicates the clinical management of the patient because of the need for anticoagulant treatment and sometimes the need to achieve another central line. Future prevention studies should aim to achieve a better understanding of the risk factors for thrombosis, contributing to a better definition of the patient population at risk; as currently available prophylactic agents are not optimal for the prevention of thrombosis, especially in the cancer patient, future studies should be adequately powered and evaluate the effects of newer factor Xa or direct thrombin inhibitors.

Conflict of interest We here declare we have full control of all primary data, and we agree to allow the Journal to review them if requested.

References

1. Niederhuber JE, Ensminger W, Gyves JW et al (1982) Totally implanted venous and arterial access system to replace external catheters in cancer treatment. Surgery 92:706–712
2. Pratt RJ, Pellowe CM, Wilson JA et al (2007) epic2: national evidence-based guidelines for preventing healthcare-associated infections in NHS hospitals in England. J Hosp Infect 65(suppl):S1–S64
3. Biffi R, De Braud F, Orsi F et al (2001) A randomized, prospective trial of central venous ports connected to standard open-ended or Groshong catheters in adult oncology patients. Cancer 92(5):1204–1212
4. Maki DG, Kluger DM, Cornich CJ (2006) The risk of bloodstream infection in adults with different intravascular devices: a systematic review of 200 published prospective studies. Mayo Clin Proc 81: 1159–1171
5. Hockenhull JC, Dwan K, Boland A et al (2008) The clinical effectiveness and cost effectiveness of central venous catheters treated with anti-infective agents in preventing bloodstream infections: a systematic review and economic evaluation. Health Technol Assess 12:1–154
6. O'Grady NP, Alexander M, Burns LA et al (2011) Guidelines for the prevention of intravascular catheter-related infections. Clin Infect Dis 52:162–193
7. Center for Devices and Radiological Health. Reminders from FDA regarding ruptured vascular access devices from power injection,

July 7 - 2004. Available at: www.fda.gov/cdrh/medicaldevicesafety/tipsarticles/reminder-rvad.html
8. Bonciarelli G, Batacchi S, Biffi R et al (2011) GAVeCeLT consensus statement on the correct use of totally implantable venous access devices for diagnostic radiology procedures. J Vasc Access 12:292–305
9. Di Carlo I, Toro A (2011) Choice of venous sites. Surgical implant/technique. In: Di Carlo I, Biffi R (eds) Totally implantable venous access devices. Springer-Verlag, Italia, pp 43–54
10. Toro A, Mannino M, Cappello G et al (2012) Totally implanted venous access devices implanted in saphenous vein. Relation between the reservoir site and comfort/discomfort of the patients. Ann Vasc Surg 26(8):1127.e9–1127.e13
11. Coit DG, Turnbull AD (1988) A safe technique for the placement of implantable vascular access devices in patients with thrombocytopenia. Surg Gynecol Obstet 167:429–431
12. Knebel P, Fischer L, Huesing J et al (2009) Randomized clinical trial of a modified Seldinger technique for open central venous cannulation for implantable access devices. Br J Surg 96:159–165
13. Biffi R, Orsi F, Pozzi S et al (2009) Best choice of central venous insertion site for the prevention of catheter-related complications in adult patients who need cancer therapy: a randomized trial. Ann Oncol 20:935–940
14. Randolph AG, Cook DJ, Gonzales CA, Pribble CG (1996) Ultrasound guidance for placement of central venous catheters: a meta-analysis of the literature. Crit Care Med 24:2053–2058
15. Hind D, Calvert N, McWilliams R et al (2003) Ultrasonic locating devices for central venous cannulation: meta-analysis. BMJ 327: 361–367
16. Calvert N, Hind D, McWilliams R et al (2004) Ultrasound for central venous cannulation: economic evaluation of cost-effectiveness. Anaesthesia 59:1116–1120
17. Karakitsos D, Labropoulos N, De Groot E et al (2006) Real-time ultrasound-guided catheterisation of the internal jugular vein: a prospective comparison with the landmark technique in critical care patients. Crit Care 10:R162
18. Lamperti M, Bodenham AR, Pittiruti M et al (2012) International evidence-based recommendations on ultrasound-guided vascular access. Intensive Care Med 38:1105–1117
19. Barsuk JH, McGaghie WC, Cohen ER (2009) Simulation-based mastery learning program reduces complications during central venous catheter insertion in a medical intensive care unit. Crit Care Med 37:2697–2701
20. Lefrant JY, Cuvillon P, Bénézet JF et al (1998) Pulsed Doppler ultrasonography guidance for catheterization of the subclavian vein: a randomized study. Anesthesiology 88:1195–1201
21. Bold RJ, Winchester DJ, Madary AR et al (1998) Prospective, randomized trial of Doppler-assisted subclavian vein catheterization. Arch Surg 133:1089–1093
22. Fragou M, Gravvanis A, Dimitriou V et al (2011) Real-time ultrasound-guided subclavian vein cannulation versus the landmark method in critical care patients: a prospective randomized study. Crit Care Med 39:1607–1612
23. Di Carlo I, Toro A (2012) Skin incision to implant the port: could be this the real reason to prefer the surgical cut down to implant a totally implantable venous access device? Ann Surg 255:e9
24. Nakazawa N (2010) Challenges in the accurate identification of the ideal catheter tip location. JAVA 15:196–200
25. Cadman A, Lawrence JA, Fitzsimmons L et al (2004) To clot or not to clot? That is the question in central venous catheters. Clin Radiol 59:349–355
26. Caers J, Fontaine C, Vinh-Hung V et al (2005) Catheter tip position as a risk factor for thrombosis associated with the use of subcutaneous infusion ports. Support Care Cancer 13:325–331
27. Korones DN, Buzzard CJ, Asselin BL, Harris JP (1996) Right atrial thrombi in children with cancer and indwelling catheters. J Pediatr 128:841–846
28. Food and Drug Administration Task Force (1989) Precautions necessary with central venous catheters. FDA Drug Bulletin, 15-16
29. National Association of Vascular Access Networks (1998) NAVAN position statement. J Vasc Access Devices 3:8–10
30. (2001) National Kidney Foundation K/DOQI clinical practice guidelines for vascular access. Am J Kidney Dis 37(Suppl 1):S137-S181
31. Pittiruti M, Hamilton H, Biffi R et al (2009) ESPEN guidelines on parenteral nutrition: central venous catheters (access, care, diagnosis and therapy of complications). Clin Nutr 28:365–377
32. Stas M, Willems R (2011) Verifying catheter tip position: fluoroscopy vs intravasal electrogram. In: Di Carlo I, Biffi R (eds) Totally implantable venous access devices. Springer-Verlag, Italia, pp 93–104
33. Fricke BL, Racadio JM, Duckworth T et al (2005) Placement of peripherally inserted central catheters without fluoroscopy in children: initial catheter tip position. Radiology 234:887–892
34. Neubauer AP (1995) Percutaneous central iv access in the neonate: experience with 535 silastic catheters. Acta Paediatr 84:756–760
35. Pawlik MT, Kutz N, Keyl C et al (2004) Central venous catheter placement: comparison of the intravascular guidewire and the fluid column electrocardiograms. Eur J Anaesthesiol 21:594–599
36. Stas M, Mulier S, Pattyn P et al (2001) Peroperative intravasal electrographic control of catheter tip position in access ports placed by venous cut-down technique. Eur J Surg Oncol 27:316–320
37. Richards MJ, Edwards JR, Culver DH et al (2000) Nosocomial infections in combined medical surgical intensive care units in the United States. Infect Control Hosp Epidemiol 21:510–515
38. Raad I, Hanna H, Maki D (2007) Intravascular catheter-related infections: advances in diagnosis, prevention, and management. Lancet Infect Dis 7:645–657
39. Provonost P, Needham D, Berenholtz S et al (2006) An intervention to decrease catheter-related bloodstream infections in the ICU. N Engl J Med 355:2725–2732
40. Kuter DJ (2004) Thrombotic complications of central venous catheters in cancer patients. Oncologist 9:207–216
41. Verso M, Agnelli G (2003) Venous thromboembolism associated with long-term use of central venous catheters in cancer patients. J Clin Oncol 21:3665–3675
42. Karthaus M, Kretzschmar A, Kröning H et al (2006) Dalteparin for prevention of catheter-related complications in cancer patients with central venous catheters: final results of a double-blind, placebo-controlled phase III trial. Ann Oncol 17:289–296
43. Chan A, Iannucci A, Dager WE (2007) Systemic anticoagulant prophylaxis for central catheter associated venous thrombosis in cancer patients. Ann Pharmacother 41:635–641
44. Agnelli G, Verso M (2006) Therapy insight: venous catheter-related thrombosis in cancer patients. Nat Clin Pract Oncol 3:214–222
45. Fagnani D, Franchi R, Porta C et al (2007) Thrombosis-related complications and mortality in cancer patients with central venous devices: an observational study on the effect of antithrombotic prophylaxis. Ann Oncol 18:551–555
46. van Rooden CJ, Schippers EF, Barge RM et al (2005) Infectious complications of central venous catheters increase the risk of catheter-related thrombosis in hematology patients: a prospective study. J Clin Oncol 23:2655–2660
47. Goossens GA, Vrebos M, Stas M et al (2005) Central vascular access devices in oncology and hematology considered from a different point of view: how do patients experience their vascular access ports? J Infus Nurs 28:61–67
48. Chenecky C (2001) Satisfaction versus dissatisfaction with venous access devices in outpatient oncology: a pilot study. Oncol Nurs Forum 28:1613–1616
49. Landen CN, Younger NO, Sharp BAC, Underwood PB (2003) Cancer patients' satisfaction with physicians: Princess Margaret Hospital satisfaction with doctor questionnaire results. Am J Obstet Gynecol 188:1177–1179

50. Ayanian JZ, Zaslavsky AM, Guadagnoli E et al (2005) Patients' perception of quality of care for colorectal cancer by race, ethnicity, and language. J Clin Oncol 23:6576–6586
51. Johansson E, Engervall P, Bjorvell H et al (2009) Patients' perceptions of having a central venous catheter or a totally implantable subcutaneous port system—results from a randomized study in acute leukaemia. Support Care Cancer 17:137–143
52. Ignatov A, Hoffman O, Smith B et al (2009) An 11-year retrospective study of totally implantanted central venous access ports: complications and patient satisfaction. Eur J Surg Oncol 35:241–246
53. Marcy PY, Magné N, Castadot P et al (2005) Radiological and surgical placement of port devices: a 4-year institutional analysis of procedure performance, quality of life and cost in breast cancer patients. Breast Cancer Res Treat 92:61–67
54. Marcy PY, Magné N, Castadot P et al (2007) Is radiologic placement of an arm port mandatory in oncology patients? Analysis of a large Bi-institutional experience. Cancer 110:2331–2338
55. Biffi R, Orsi F, Pozzi S et al (2011) No impact of central venous insertion site on oncology patients' quality of life and psychological distress. A randomized three-arm trial. Support Care Cancer 19: 1573–1580