

Vascular Access in Oncology Patients

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ABSTRACT Adequate vascular access is of paramount importance in oncology patients. It is important in the initial phase of surgical treatment or chemotherapy, as well as in the chronic management of advanced cancer and in the palliative care setting. We present an overview of the available vascular access devices and of the most relevant issues regarding insertion and management of vascular access. Particular emphasis is given to the use of ultrasound guidance as the preferred technique of insertion, which has dramatically decreased insertion-related complications. Vascular access management has considerably improved after the publication of effective guidelines for the appropriate nursing of the vascular device, which has reduced the risk of late complications, such as catheter-related bloodstream infection. However, many areas of clinical practice are still lacking an evidence-based background, such as the choice of the most appropriate vascular access device in each clinical situation, as well as prevention and treatment of thrombosis. We suggest an approach to the choice of the most appropriate vascular access device for the oncology patient, based on the literature available to date. (*CA Cancer J Clin* 2008;58:323–346.) © American Cancer Society, Inc., 2008.

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INTRODUCTION

The use of vascular access devices (VADs) is an integral aspect of health care for neonates, children, and adults and has moved beyond the acute care setting to chronic, long-term care. VADs have a paramount role throughout the management of the oncology patient, as they are needed in the initial phases for surgery or chemotherapy, in the advanced stages for chronic treatment, and in the last stages for palliative measures.

According to US data,¹ approximately 150 million intravenous catheters are purchased, and at least 5 million central venous catheters (CVCs) are inserted every year. It is difficult to estimate how many of these VADs are actually used for oncology patients. However, it is reasonable to assume that the proportion is high, as most surgery, chemotherapy, and radiotherapy protocols for the management of neoplastic disease require intravenous infusions, including even those for palliative care, for which a long-term VAD usually is the best route of administration.

Data from a study commissioned by the Food and Drug Administration in the 1990s² showed that the use of VADs is associated with a high complication rate (10% to 25% of all patients with VADs) and a morbidity of at least 10%; 52% of the reported complications were directly related to insufficient information (for nurses, patients, and other people dedicated to the care of the device) or inappropriate technique of VAD placement and nursing care.

In this review, we will summarize data indicating that at present, in 2008, technological developments; a new patient-oriented, cost-effective approach to the selection of procedures and techniques; and closer attention to the important issue of health practitioner education have decreased the complication rate, especially in the area of oncology and palliative care. In particular, the introduction of ultrasound guidance has dramatically decreased insertion-related complications, and the new, updated nursing guidelines related to VAD care have proved to be effective in reducing the risk of late complications, such as catheter-related bloodstream infection.

However, at least 2 issues are still reason for concern:

- (A) There is no evidence-based guide to the selection of the most appropriate VAD for each clinical situation, notwithstanding the broad range of VADs available, both in terms of features and performance. Moreover, there is little

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TABLE 1 Features, Advantages, and Disadvantages of Different Types of Vascular Access Devices

	Tip Position	Technical Feature	VAD Material	Expected Duration	Type of Use	Ideal Setting	Main Advantage	Main Disadvantage
Short-term VADs								
Short peripheral cannulas	Peripheral	Nontunneled	Teflon, silicone	72 to 96 hours	Continuous	Hospital	Low cost	Short duration
Short-term CVCs	Central	Nontunneled	Polyurethane	1 to 3 weeks	Continuous	Hospital	Low cost	High risk for CRBSI
Medium-term VADs								
Midline catheters	Peripheral	Nontunneled	Polyurethane, silicone	<2 to 3 months	Discontinuous	Hospital and/or outpatient	Low risk of CRBSI	Peripheral route
PICCs	Central	Nontunneled	Polyurethane, silicone	3 to 12 (?) months	Discontinuous	Hospital and/or outpatient	No risk at insertion	Low flow
Hohn	Central	Nontunneled	Silicone	<2 to 3 months	Discontinuous	Hospital and/or outpatient	Low risk of thrombosis	Risk of dislocation
Long-term VADs								
Tunneled catheters (Groshong, Hickman, Broviac)	Central	Tunneled	Polyurethane, silicone	Months to years	Discontinuous	Outpatient	Indefinite duration	High cost
Ports	Central	Totally implanted	Polyurethane, silicone	Months to years	Discontinuous	Outpatient	Indefinite duration	High cost

Abbreviations: CRBSI, catheter-related blood stream infection; CVC, central venous catheter; PICC, peripherally inserted central catheter; VAD, vascular access device.

guidance addressing the problem of the choice of the best VAD for the oncology patient—a consequence of the scarcity of randomized trials in this area. A few clear-cut indications come from the guidelines of the Registered Nurses’ Association of Ontario,³ from the guidelines of the British Committee for Standards in Haematology,⁴ and from the Standards for Infusion Therapy of the Royal College of Nursing (RCN)⁵ and of the Infusion Nurses Society (INS).⁶

(B) Patients and their families still currently play a minor role in the selection of VAD at the onset of treatment, notwithstanding the evidence showing that patient involvement is associated with greater patient satisfaction, fewer delays in therapy related to loss of vascular access, fewer device complications, preservation of peripheral veins, less nursing time spent attempting to gain vascular access, shorter hospital stays, fewer emergency room visits, and decreased infusion

therapy costs.⁷ However, most patients who require intravenous therapy for longer than 1 week are not routinely assessed for intermediate dwelling VADs. In addition, patient satisfaction about long-term VADs has rarely been addressed.^{8,9}

CLASSIFICATION AND FEATURES OF VENOUS VADS

Venous VADs can be classified as short-term, intermediate (medium-term), and long-term accesses. They can also be classified as central (when the tip of the catheter lies in the lower third of the superior vena cava [SVC], in the atrium, or in the upper portion of the inferior vena cava) or peripheral (in all the other instances). Table 1 summarizes features, advantages, and disadvantages of different types of VADs, which will be analyzed in this review. Central venous access is mandatory for a number of specific solutions for infusion, such as those containing vesicant drugs.

Short-term Venous VADs

Short-term peripheral venous VADs are usually 35- to 52-mm-long Teflon cannulas. They are the most commonly used VADs in daily clinical practice and are inserted into superficial veins of the arms of adult patients or into any superficial vein of children and neonates.

Short-term CVCs are nontunneled, 20- to 30-cm-long polyurethane catheters inserted into a central vein (subclavian, internal jugular, innominate, axillary, or femoral vein), preferably resorting to ultrasound guidance. They may have a single lumen or multiple lumens, and they should be used only for hospitalized patients.¹⁰ They are designed for continuous, short-term infusions (1 to 3 weeks).

Intermediate Venous VADs

Intermediate venous VADs are nontunneled, central venous devices specifically designed for prolonged intermittent use; they include midline catheters, peripherally inserted central catheters (PICCs), and Hohn catheters. Midline catheters are nontunneled, peripheral VADs inserted through a peripheral vein of the arm (antecubital, basilic, brachial, or cephalic vein), using either a “blind” technique or ultrasound guidance; they are 15- to 30-cm long and are usually made of silicone or second-third generation polyurethane. By definition, their tip is not “central,” ie, is not located in the SVC but in the axillary vein or in the subclavian vein. PICCs are nontunneled, central catheters inserted through a peripheral vein of the arm; they are 50- to 60-cm long and are usually made of silicone or second-third generation polyurethane. Hohn catheters are nontunneled, 20-cm long, centrally inserted silicone catheters.¹¹ Both PICCs and Hohn catheters can be used for prolonged continuous or intermittent infusion therapies (up to 3 months) both in hospitalized patients and in patients treated as outpatients, in a hospice, or at home.¹⁰ The use of PICCs is approved by the Food and Drug Administration for up to 12 months; although most PICCs may stay in place and in use for several months, there is growing evidence that their actual duration depends on many factors: type of material; technique of

insertion; stabilization of the VAD; patient compliance; and, most importantly, nurse competence in the maintenance of the device.

PICCs are usually inserted at the bedside by trained physicians or nurses either resorting to the “blind” technique via the antecubital vein or the cephalic vein or to ultrasound guidance via a deep vein in the midarm (basilic or brachial vein); they are available with one or more lumens. In the hematology-oncology setting, they are well suited for ambulatory or outpatient therapy¹² because they can be safely used even in patients with extremely low platelet counts or at high risk of hemorrhage.⁴

Materials (silicone versus polyurethane) may influence the risk of complications since some types of polyurethane may be associated with a higher incidence of thrombosis.¹³ Sometimes polyurethane PICCs may be preferable because they have thinner lumen walls and larger internal diameters; these features significantly increase flow rates and reduce the risk of breakage and complete rupture of the catheter. This may be an advantage in hematology patients, who often require blood and platelet infusions. On the other hand, pump-driven or low-flow intravenous infusions—as in chemotherapy treatments for solid tumors—can easily be delivered by either silicone or polyurethane PICCs; silicone is associated with better biocompatibility and durability than most types of polyurethane and thus seems more suitable for long-term use. In the United Kingdom, most chemotherapy treatments are delivered through PICCs, which are increasingly inserted using ultrasound guidance.

There is no evidence of significant advantages or disadvantages of PICCs over CVCs in hospitalized patients. A few studies suggest that PICCs may be preferable because they are associated with fewer mechanical complications at insertion, lower costs (since they are mainly inserted by nurses at the bedside), and a lower infection rate.^{1,11,14} The latter issue has recently been challenged,¹⁵ and it has been suggested that infection control and prevention programs should be consistently implemented whenever any type of VAD is used.¹⁶ However, it is accepted that placement in the antecubital fossa or at midarm carries the important advantage of moving the exit site of the catheter away from endotracheal,

oral, and nasal secretions.¹⁷ Moreover, ultrasound-guided placement of PICCs at midarm is associated with optimal nursing management of the exit site.¹⁸

Long-term VADs

Prolonged intravenous treatment (>3 months) requires a long-term venous VAD, such as a tunneled central catheter or a totally implanted port. Tunneled catheters are usually made of silicone rubber, with or without Dacron anchoring cuffs; the variety with the cuffs is strongly recommended, as it is more stable.¹⁹ The cuffs also induce an inflammatory reaction within the subcutaneous (SC) tunnel, leading to fibrosis and consequent catheter fixation, usually within 3 to 4 weeks after insertion. Tunneled catheters have been shown to be associated with lower infection rates than nontunneled catheters.^{16,20} Valved catheters have the advantage of not requiring heparin flushes but may need pressurized infusions for the administration of blood products and also tend to be more expensive. In a controlled trial, they were not superior to a traditional, open-ended device in terms of catheter efficacy and early and late complications.²¹ Thus, there is little evidence to support one type of catheter over another.

Totally implanted ports consist of a reservoir (usually made of titanium and/or plastic polymers) connected to a CVC (usually made of silicone), which may or may not be valved. Ports have lower reported rates of catheter-related bloodstream infections than both tunneled and nontunneled CVCs.¹⁶ Most ports have only one lumen, which makes them best suited for long-term intermittent chemotherapy, especially in patients with solid tumors. Double-lumen ports are used for specific purposes, as in patients undergoing bone marrow transplantation and in patients who require infusion of noncompatible medications and fluids, which necessitate a second intravenous access. Ports allow better bathing and swimming, which are restricted with external VAD, and they may appeal to patients concerned about the psychological implications of the presence of visible nonimplanted catheters. They are more expensive to purchase, insert, and remove, and they leave larger scars.

The choice between a tunneled catheter and a port depends on many factors, mainly related to patient compliance, experience of the nursing staff, and frequency of venous access. According to US Centers for Disease Control and Prevention (CDC) Guidelines,²² totally implantable access devices should be reserved for patients who require long-term, intermittent vascular access. A tunneled CVC is preferable for patients requiring continuous access. Thus, oncology patients who need chemotherapy treatment scheduled on a weekly or monthly basis should benefit from a totally implanted port, while those who need daily infusions of palliative treatment (analgesics, hydration, nutrition, etc.) should benefit from an external catheter.

Medium-term and long-term venous devices are both adequate for outpatients. The use of short-term CVCs for nonhospitalized patients should be discouraged, considering their high susceptibility to infection and the risk of obstruction of the device, dislocation, and catheter-related venous thrombosis.²²

PERIPHERAL VERSUS CENTRAL VENOUS ACCESS

According to Registered Nurses' Association of Ontario Guidelines,³ INS standards,⁴ and RCN standards,⁵ a central venous access is indicated in the following conditions: administration of solutions with pH <5 or pH >9; administration of drugs with osmolarity >600 mOsm/L⁴ or 500 mOsm/L³; parenteral nutrition with solutions containing ≥10% glucose or 5% amino acids because of their high osmolarity; administration of vesicant drugs or other drugs associated with vascular intimal damage; need for multiple-lumen intravenous treatment; need for dialysis or apheresis; need for central venous pressure monitoring; and venous access needed for more than 3 months.

Thus, in the oncology patient undergoing chemotherapy, the ideal venous access is central rather than peripheral since many antineoplastic drugs are notoriously vesicant. Despite the fact that many oncology units still deliver chemotherapy mainly by the peripheral route, it is commonly accepted that the infusion of vesicant drugs into a peripheral vein is potentially dangerous because it is associated with a high risk of extravasation,

infiltration, phlebitis, local tissue damage, and progressive loss of available peripheral veins. The INS standards for infusion therapy⁴ recommend a central venous access (including PICC) for the administration of boluses of vesicant medications; if a peripheral access is used, a new access site should be used for each administration, and its site should be documented to avoid repeated use. However, continuous infusion of vesicants should be performed exclusively by a central route.

On the other hand, when the oncologic patient is on a palliative care program, most of the infusions (analgesics, hydration, or nutrition) may be safely delivered by a peripheral route. However, peripheral parenteral nutrition (given through a short peripheral cannula or through a midline catheter) should be used only for a limited period of time and exclusively when the osmolarity of the nutrient solutions, which may contain lipids, does not exceed 800 mOsm/L. According to CDC guidelines,²² midline catheters should be preferred whenever intravenous therapy is expected to last more than 6 days; since this is the case for most intrahospital parenteral nutrition treatments, midline catheters are bound to play a major role in this setting. Also peripheral home parenteral nutrition should be given only via midline catheters since short cannulas carry a high risk of dislocation and infiltration.

CATHETER DESIGN AND MATERIALS

All central VADs may have single or multiple lumens and can be open-ended or valved. Multiple-lumen catheters are advantageous in patients undergoing stem cell transplantation or chemotherapy that involves the simultaneous infusion of a number of agents and blood products. Blood products may be administered concurrently with another drug/infusion through a dual-bore catheter. Although multiple-lumen catheters are generally associated with increased morbidity, particularly infections,^{23,24} in the hematology setting, the increased risk is likely to be offset by their convenience, thereby justifying their use. If total parenteral nutrition is being administered, a dedicated central route should be used exclusively for this purpose.¹⁷

VADs of small caliber should be employed to minimize the risk of catheter-related thrombosis

and/or subsequent venous stenosis.²⁵ This is particularly true for PICCs,²⁶ although it may be difficult to administer blood products or high-flow hydration with a very narrow lumen. When a totally implanted port is used, choosing a catheter caliber larger than 6 to 7 French does not carry significant advantages since the main limitation to flow is the caliber of the Huber needle used to access the port.

As regards the material, most central VADs are 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. Surface-active additives can be mixed with the polymer or added to the ends of the polymer chain to modify its surface properties, which can affect infection and thrombosis rates. Problems derived from the contact of blood with VADs are usually related to surface properties of the base catheter material. Surface treatment processes allow coupling or incorporation of substances to or into catheter materials. Coating with antimicrobials (silver, antiseptics, or antibiotics) may be a suitable way to prevent the development of catheter-associated infections, while coating with antithrombotic substances may prevent thrombosis. However, there are some controversial reports on the potential of adverse reactions due to silver- and antiseptic-coated catheters.²⁷

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). For catheter applications, polyether and polycarbonate soft segments are used. Polyurethanes with polycarbonate soft segments are more resistant to attack by biological enzymes and hydrolysis than those made of polyethers.

Material properties have some clinical implications that may influence catheter selection. The main biological issue for catheters is *hemocompatibility* and, to a lesser extent, compatibility with tissue contacted to access the vessel lumen. Hemocompatibility of a VAD refers to the ability of the device to carry out its intended function within flowing blood, with minimal interaction between device and blood that adversely affects device performance and without

inducing uncontrolled activation of cellular or plasma protein cascades. Hemocompatibility is a complex issue: depending on how it is defined, on the patient population, disease state, catheter entrance site, and other factors, one catheter material can be said to perform better or worse than another. For short-term applications, in general, there are no noticeable differences between polyurethane and silicone catheters. For longer-term applications, durability may be more important than biocompatibility.

Ease of insertion is influenced by catheter stiffness and wall thickness, as well as frictional properties of the catheter surface; in general, silicone catheters are more difficult to advance over guide wire than polyurethane catheters of similar size.

The risk of *mechanical phlebitis* is influenced by catheter stiffness and size. Given the same lumen size, silicone catheters are larger and potentially cause more mechanical phlebitis, but silicone is less stiff and, therefore, less traumatic to the vascular endothelium. Since silicone has lower tensile and burst strength than polyurethane catheters of equal dimensions, the wall thickness of silicone catheters is increased to provide adequate strength. Consequently, for the same catheter French size (outer diameter), silicone catheters have a smaller lumen and lower flow rate than polyurethane catheters. Flow is proportional to radius at the fourth power, so very small changes in inside diameter—especially of narrow catheters—have a very large effect on flow rates.

Infusate compatibility is a function of catheter composition and structure. Catheters are not attacked by drugs, but they are by the solvents necessary to put them into solution or to preserve them. In general, silicone is more compatible with infusates because it is cross-linked and hydrophobic. Alcohols, in particular, can permeate polyurethane catheters (especially those with polyether soft segments) and carry solubilized drugs with them.²⁸

The risk of *extravasation of infusates* is influenced by catheter stiffness, as stiffer catheters can damage the vessel. Silicone is less stiff than polyurethane.

Catheter occlusion caused by precipitates usually depends on the administration of incompatible infusates rather than on catheter material properties. Again, silicone catheters, having smaller

inner diameters, are more easily blocked by precipitates. However, polyurethane is more prone to degradation if alcohol or other solvents are used to dissolve the precipitate. The patency of the catheters is also related to their *kink-resistance* (the ability of the catheter to maintain an open lumen when it is bent): silicone catheters bend more easily, but kink with less applied force than polyurethane catheters. However, silicone catheters also recover more readily and are not permanently deformed as easily as are polyurethane catheters.

Clotting and thrombosis are influenced by the chemical as well as the physical properties of the material. Catheters with a rough surface are more thrombogenic than those with a smooth surface (radiopaque barium sulfate filler can have an influence). Some studies^{29,30} suggest that silicone may be less thrombogenic than some specific types of polyurethane. Polycarbonate-based polyurethane is more stable and less thrombogenic than polyether-based polyurethane.

Stability and durability are affected by the response of catheters to infusates (including solubilizing agents), disinfectants, and cleaning solutions, as well as by the biologic environment. Polyurethane is inherently stronger due to higher burst and tensile strength, but it is more susceptible to *in vivo* degradation and attack by solvents. Silicone is less prone to stress cracking than polyurethane because it is cross-linked.

Vascular damage is a function of catheter stiffness, especially of its tip. Thicker catheters are stiffer than thinner catheters. In general, silicone is softer and less traumatic than polyurethane.

With regard to *catheter maintenance requirements*, polyether polyurethanes are subject to degradation by alcohols and disinfectants, especially ointments in a PEG (polyethylene glycol) base. Silicone is more resistant to attack by cleaning and disinfecting agents but is more easily torn. Silicone is also more resistant to solvents in general because it is cross-linked. Silicone catheters may swell but don't break in most solvents, and their hydrophobicity limits the attack by water.

Radiopacity is a function of the amount of radiopaque material in the catheter. Smaller diameter catheters or catheters loaded with a lower concentration of radiopaque agent will have a dimmer fluoroscopic image. Radiopaque agents (ie, BaSO₄) weaken catheter materials.

Teflon, silicone, and polyurethane have been associated with fewer catheter-related infections than polyvinyl chloride or polyethylene. However, all available CVCs are made either of polyurethane or silicone, and there is no specific recommendation regarding materials for clinical practice.¹⁷

CHOICE OF THE VAD AND RISK OF INFECTION

The type and the design of the catheter itself may significantly affect the risk of catheter-related infection, as shown by Maki in an important systematic review of 200 prospective studies.¹⁶

Tunneling and Total Implantation

Tunneled catheters and totally implanted VADs are associated with a lower rate of infection since they are specifically protected from extraluminal contamination. On the other hand, tunneling and SC implantation require a minor surgical procedure, which is contraindicated in patients with low platelet counts or coagulation abnormalities.⁴

Coating with Antiseptic Drugs

Short-term CVCs coated with chlorhexidine/sulfadiazine or coated with rifampicin/minocycline have a significantly lower infection rate.¹⁶ In a recent systematic review and economic evaluation conducted by the Liverpool Reviews and Implementation Group,³¹ the authors conclude that rates of catheter-related bloodstream infection (CR-BSI) are significantly reduced by catheters coated with rifampicin/minocycline or internally and externally coated with chlorhexidine/silver sulfadiazine. Statistical significance was not seen with catheters only coated externally.

Thus, as suggested by Evidence-based Practice in Infection Control guidelines,¹⁷ the use of a VAD coated with an antimicrobial is to be considered for adult patients who require short-term central venous catheterization and who are at high risk for CR-BSI if the facility infection rates remain high despite the implementation of a comprehensive strategy to control them.

It is important to stress that most evidence in this area concerns short-term, nontunneled, central venous access. There is no evidence to support the use of PICCs or tunneled catheters coated with antiseptic drugs.

Multiple Versus Single Lumen

CVCs with *multiple lumens* may be associated with higher infection rates than single-lumen CVCs, as shown by several randomized controlled trials (RCTs) and stated by CDC guidelines²²; nonetheless, this contention has been questioned by recent papers. Two recent systematic reviews and quantitative meta-analyses have focused on the risk of CR-BSI and catheter colonization in multilumen catheters compared with single-lumen catheters. The first one concluded that multiple lumens are not a significant risk factor for increased CR-BSI or local catheter colonization compared with a single lumen.²³ The second one concluded that there is some evidence from 5 RCTs with data on 530 central VADs that for every 20 single-lumen catheters inserted, one CR-BSI will be avoided that would have occurred had multilumen catheters been used.³² Although further research is warranted, in the meantime it may be reasonable to recommend a single-lumen catheter unless multiple ports are essential for patient management. Moreover, if a multilumen catheter is used, one port should be identified and designated exclusively for parenteral nutrition because the interaction of parenteral nutrition solutions with drugs and solutions of different pH increases rates of thrombosis and, consequently, rates of infection. In addition, the larger lumen of double ports should be used for parenteral nutrition to reduce the tendency to obstruction.¹⁷ Of course, all lumens must be handled with the same meticulous attention to aseptic techniques.

Compared with central venous catheters, PICCs appear to be associated with a lower risk of infection, most probably because of the exit site on the arm, which is less prone to be contaminated by nasal and oral secretions¹; however, no RCTs have proven such contention to date.¹⁷ At present, it is reasonable to consider PICC insertion (a) in patients with tracheostomy; (b) in patients with severe anatomic abnormalities of neck and thorax, which may be associated with difficult positioning and nursing of a centrally placed CVC; and (c) in patients who need intravenous access for prolonged periods of time (months). On the other hand, PICCs are not advisable in patients with renal failure and impending need for dialysis, in whom preservation of

upper-extremity veins is needed for fistula or graft implantation. Anyway, the assumption that PICCs are safer than conventional CVCs with regard to the risk of infection is in question; the issue should be addressed by a larger, adequately powered RCT assessing peripheral vein thrombophlebitis, PICC-related thrombosis, and premature dislodgment, as well as CR-BSI.¹⁵

CATHETER PLACEMENT

Insertion Technique: State of the Art

Choice of Venous Access and Role of Ultrasound Guidance

With the exception of PICCs, all long-term catheters for oncology treatments require an access through tributary branches of the vena cava so that their tip is placed correctly in the central venous district.

PICCs are usually inserted at the antecubital site. The procedure is performed by a nurse or a physician, usually in a blind fashion. It is associated with a high risk of local phlebitis, patient discomfort, and venous thrombosis,³³ especially in patients with hematological malignancies³⁴; on the contrary, in our experience PICC insertion by ultrasound-guided venipuncture of deep veins at midarm is associated with a low risk of local complications and negligible patient discomfort.

The percutaneous approach to the subclavian or internal jugular vein currently is the most popular procedure for placing catheters in the SVC, both for short-term (no more than 6 to 8 weeks) and long-term use. Such venous approaches were made possible in the 1970s by the development of specific tools, like the Seldinger j-wire and the peel-away introducer-dilator, formerly not available. These technological instruments offer the option to avoid open surgical vein cannulation, which at that time was necessary for the placement of the silicone and polyurethane catheters required for long-term access. 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 or even bed-side procedure have made the superiority of percutaneous central vein access

quite obvious. The CDC recommends not to use routinely venous cut-down procedures as a method to insert catheters, even for long-term ones, because percutaneously placed catheters are associated with a lower infection rate than surgically implanted ones.²² However, in neonates and in children, not routinely but in selected cases, venous cut-down might be the safest choice.

Recognition of risk factors for difficult catheterization is 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. An alternative that may reduce the incidence of pneumothorax (the most frequent complication of central venous cannulation by subclavian route) is the preferential use of the internal jugular vein³⁵ for the percutaneous “blind” (based on anatomic landmarks) approach for central venous cannulation. Nonetheless, this may not always be possible due to anatomic abnormalities, dehydration, operator inexperience, or disease-related alterations; in such conditions, the operator may be forced to resort to subclavian venipuncture and expose the patient to the risk of pneumothorax. The issue, which is associated with additional costs, has been addressed by developing a number of imaging techniques to access the subclavian and/or internal jugular vein under guidance (simple Doppler, echo-color Doppler, digital venography, and others).

The only procedure that has been evaluated in RCTs, which have been pooled in 3 meta-analyses,^{36–38} is the ultrasound-guided placement of central venous access (technique adopted for both the subclavian and internal jugular vein). 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. During internal jugular venous catheterization, ultrasound guidance (both 2-dimensional [2D] ultrasound- and Doppler-guided methods) clearly reduces the number of complications, failures, and time required for insertion.³⁶ Conversely, its use for subclavian venous catheterization has yielded inconsistent results in a small number of trials^{36,39,40}; limited evidence favored 2D ultrasound guidance for subclavian vein procedures in adults (relative risk 0.14; 95% confidence interval, 0.04 to 0.57). The landmark Vascular Access

in Oncology Patients method was more successful than Doppler-guided cannulation for subclavian vein procedures (1.48; 1.03 to 2.14). An indirect comparison of relative risks suggested that 2D ultrasonography would be more successful than Doppler guidance for subclavian vein procedures in adults (0.09; 0.02 to 0.38).

The meta-analyses have shown that ultrasound guidance reduces complications relative to percutaneous accesses performed with the standard "landmark" technique, especially when the operators have little experience with the landmark method. In many studies the control arm (unguided percutaneous access) often had unusually high complication and unsuccessful rates (over 40%), whereas most prospective series report early complication rates for experienced operators usually under 5%.

National Institute for Clinical Excellence-UK made the following recommendations in 2002⁴¹:

- (A) 2D-imaging ultrasound guidance should be the preferred method when a CVC is inserted into the internal jugular vein of adults and children in "elective situations."
- (B) 2D-imaging ultrasound guidance should be considered in most clinical situations where CVC insertion is necessary, independently of the situation (elective or emergency procedure).
- (C) Everyone who uses 2D-imaging ultrasound guidance to insert CVCs should be appropriately trained so that they can use the technique competently.

The implementation of National Institute for Clinical Excellence-UK guidelines has been associated with a significant reduction in complication rates in a UK tertiary referral center.⁴²

Similar recommendations, based on the published data of RCT meta-analyses, have been made by several scientific societies.^{4,6,17} 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 nonemergent central vascular access procedures, including insertion of PICCs.

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,⁴³⁻⁴⁵ oncology,⁴⁶ pediatrics,⁴⁷ and dialysis,⁴⁸ leading to the conclusion that ultrasound guidance improves the success rate of vein cannulation, reducing the number of attempts, complications, and failures. 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.

Cost analysis is a key issue. Calculations should be precise and also include costs for ultrasound devices and operator training. Calvert et al³⁸ compared the economics of using 2D-ultrasound locating devices and more 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 pounds sterling (corresponding to about 20 USD) 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.³⁸

In conclusion, the present state of central venous long-term cannulation, especially for CVCs and ports used in oncology, remains quite controversial. These procedures are widespread, and most operators tend to rely on personal

TABLE 2 Frequency of Early Complications (Expressed in % of Cases), According to the Insertion Site, Using Anatomic Landmark Percutaneous Techniques*

	Internal Jugular	Subclavian	Femoral
Arterial puncture	6.3 to 9.4	3.1 to 4.9	9.0 to 15.0
Local bleeding	<0.1 to 2.2	1.2 to 2.1	3.8 to 4.4
Hemothorax	NA	0.4 to 0.6	NA
Pneumothorax	<0.1 to 0.2	1.5 to 3.1	NA
Total	6.3 to 11.8	6.2 to 10.7	12.8 to 19.4

*Adapted from Hamilton HC, Foxcroft DR.⁴⁹
Abbreviation: NA, not applicable.

experience and professional education when they choose an approach, the most important factor being their degree of familiarity with the various options. 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, and more studies are needed to address long-term benefits and cost-effectiveness. Adequately powered prospective RCTs are still lacking on several issues, especially late complications of central venous long-term accesses; for example, the impact of different techniques and access routes on infection and thrombosis rates in the oncology patient population is still unknown. No trial comparing the subclavian versus internal jugular vascular access in this patient population has been published so far, although an objective need for such a trial is clear.⁴⁹

Catheter Tip Position

The position of the catheter in the vascular system is a major determinant of CVC-related thrombosis, and tip position has emerged as the main independent prognostic factor for malfunction and reduced duration of the device. Placement of the catheter tip high in the SVC results in a higher incidence of thrombosis than low placement in the SVC or at the atriocaval junction.⁵⁰ Therefore, at least in oncology patients, the atriocaval junction appears to be the optimal position; hemodialysis could require full atrial positioning of the catheter tip, at least for cuffed devices.⁵¹ Thrombosis also seems to be more common when catheters are inserted entering the left subclavian vein. Many centers

systematically verify position by fluoroscopy after implantation; recently, an electrocardiography-derived method has been proposed as a radiation-free alternative, with initial encouraging results.⁵²

COMPLICATIONS OF CENTRAL VENOUS CATHETERS

The complications of CVCs can be classified into 2 main categories: (A) early (intraoperative and postimplantation period to first use) and (B) late complications.

Early Complications

Early complications are related to central venipuncture for catheter insertion. They include pneumothorax, hemothorax, primary malposition, arrhythmias, air embolism, and arterial perforation causing clinically relevant bleeding. Published rates of specific complications are highly dependent on patient selection and are based on series of several hundred patients⁵³; early complications occur in approximately 6.2% to 11.7% of patients (Table 2). Arterial puncture and hematoma are the most common mechanical complications during the insertion of CVCs, with similar rates for internal jugular and subclavian catheterization.⁵⁴

Pneumothorax continues to be reported in many prospective series, while no case of significant hemorrhage related to catheter placement has been reported recently in the literature.

Pneumothorax

Pneumothorax is described as the most frequent complication of percutaneous central venous cannulation. Its prevalence is 0.5% to 12%, depending on differences in clinical features,

access site, and operator experience; this last variable is considered by (almost) all authors as the key determinant of pneumothorax rate. Consequently, the operator learning curve (maybe up to 50 implants) has a major impact on complication rate and should be borne in mind when the complication prevalence is assessed: insertion of a catheter by a physician who has performed 50 or more catheterizations is half as likely to result in a mechanical complication as insertion by a physician who has performed fewer than 50 procedures.⁵⁵

With the ultrasound-guided approach, pneumothorax has become extremely rare. When it occurs, clinical presentation of iatrogenic pneumothorax complicating central venous access placement in cancer patients without severe underlying pulmonary disease is largely dependent on the size of the pleural space involved. Individuals with a small pneumothorax (one involving less than 30% of the hemithorax) are usually asymptomatic and may have a normal physical examination. The diagnosis of iatrogenic pneumothorax must always be confirmed by the identification of a thin, visceral pleural line, which is found to be displaced from the chest wall on a posterior-anterior chest x-ray performed with the patient in an upright position. A confirmatory x-ray is usually obtained after implantation, immediately after the procedure, or a few hours later, depending on the available facilities and on-site protocols. However, it has been suggested that postprocedural chest radiographs are not routinely required after image-guided (by fluoroscopy or ultrasound) central venous catheter insertion.^{56,57} A postprocedural chest radiograph can be performed on a case-by-case basis in symptomatic patients or when there is suspected inappropriate catheter tip position.

As there are anecdotal reports of delayed, severe pneumothorax not visible on earlier x-rays occurring hours and even days after the procedure, particularly in oncology patients, a delayed x-ray (at least 2 hours after implantation) should be preferred. Another chest x-ray should urgently be obtained for all patients carrying a central venous port who develop acute respiratory symptoms. An x-ray obtained during expiration may help in identifying a small apical pneumothorax;

however, the routine use of this imaging technique does not improve the diagnostic yield.⁵⁸ Treatment of iatrogenic pneumothorax aims at evacuating air from the pleural space and re-expanding the lung. Available therapeutic options include simple observation; aspiration with a catheter, with or without immediate removal of the catheter after pleural air is evacuated; and insertion of a chest tube or tube-thoracostomy.⁵⁹ The selection of the approach depends on the size of the pneumothorax, the severity of symptoms, and whether there is a persistent air leak or not. According to our own data and contributions in the literature, the first approach to a small asymptomatic pneumothorax (one involving less than 30% of the hemithorax) should be observation alone, with repeated chest x-rays and supplemental oxygen. The administration of oxygen is able to accelerate by a factor of 4 the reabsorption of air by the pleura, which occurs at the rate of 2% per day in patients breathing room air.⁶⁰ Most physicians hospitalize patients with a small pneumothorax, although patients who are likely to comply with treatment plans may be managed at home after 6 hours of observation and a new x-ray, provided that they have rapid access to an emergency service.⁶¹

A pneumothorax that is large (involving 30% of the hemithorax or more) or progressive may be drained by simple aspiration via a plastic intravenous catheter, thoracentesis catheter, or small-bore (7 to 14 French) catheter or by the insertion of a chest tube.⁶² Simple aspiration is successful in 70% of patients with moderate-sized primary spontaneous pneumothorax. No data are available in the medical literature regarding the success rate of this treatment in iatrogenic pneumothorax complicating a CVC placement. Iatrogenic pneumothorax may also be managed with a chest tube that is left in place for 1 or more days. The need for a chest tube is much more frequent in patients with severe emphysema, obstructive lung disease, or hyperinflation. Severe hypoxemia or hypotension may occur in patients with chronic obstructive pulmonary disease and be life-threatening. Also, hypercapnia occurs often, with values of partial pressure of arterial carbon dioxide exceeding 50 mmHg. Physicians should evaluate patients carefully, ruling out significant pulmonary disease

before scheduling a procedure for CVC implantation and taking alternative approaches into consideration (eg, venous cut-down, ultrasound guidance, or peripherally inserted CVCs).

LATE COMPLICATIONS

According to a general definition, late complications are events that occur after the perioperative period following catheter insertion.⁶³ In the oncology setting, events occurring after the first chemotherapy course given through the device can be considered late complications. They are mechanical complications (pinch off, fractures, dislodgement, or migration); extravasation injuries; infections (including phlebitis of the cannulated vessel); catheter and vein thrombosis/occlusion (including deep vein thrombosis, pulmonary embolism, or SVC syndrome).

The experience of one of the authors⁶⁴ in a large series of patients with totally implantable access ports connected to a Groshong catheter showed that the rate of late complications is low: catheter rupture and embolization 1.5% (0.063 episodes/1,000 days of use); venous thrombosis 1.5% (0.063 episodes/1,000 days of use); pocket infection 0.3% (0.012 episodes/1,000 days of use); port-related bacteremia 2.4% (0.101 episodes/1,000 days of use). In a retrospective study by Yildizeli et al,⁶⁵ long-term complications of catheter and port system placement occurred in 6.6% of cases, namely infection (2.2%), thrombosis (1.3%), extravasation (1.3%), and catheter fracture (1.8%).

Mechanical Complications

The obstruction of a CVC is usually due to intraluminal precipitation of lipid aggregates, drugs, clots, or contrast medium. It can be effectively prevented by appropriate nursing (ensuring continuous infusion of parenteral nutrition by intravenous pump; following appropriate protocols of flushing when the catheter is not in use or after blood withdrawal; avoiding routine use of the catheter for infusion of blood products, blood withdrawal, or infusion of contrast medium for radiological investigations; and avoiding direct contact between heparin and parenteral nutrition solution containing lipids). When the catheter lumen is obstructed, the most appropriate actions

are exchange over guidewire, removal (for nontunneled, short-term CVC), or an attempt at pharmacological disobstruction (for PICCs or long-term VADs). Disobstruction should always be performed using a 10 mL syringe (or larger) so as to avoid inappropriately high pressure, which may damage the catheter, and using the most adequate solution for the presumed type of obstruction (ethanol for lipid aggregates, urokinase or rTPA for clots, NaOH or HCl for drugs, and sodium bicarbonate for contrast medium).

Damage to the external part of the catheter may occur because of inappropriate nursing care of the catheter exit site (eg, using scissors changing the dressing, chemical damage to silicone due to inappropriate use of ether, chemical damage to polyurethanes due to inappropriate use of ethanol, etc.).^{5,6} Damage to PICCs and tunneled catheters is usually repaired with specific repair kits; for short-term, nontunneled CVCs, exchange over guide wire is more cost-effective.

Erosion or damage to the skin above the port is usually secondary to (A) errors during placement (choice of a port that is too large or positioning the port in an area that is too skinny because the absence of an adequate SC tissue will increase the chance of skin necrosis due to the presence of the VAD) or to (B) inappropriate nursing (ie, a Huber needle left in place for more than a week).

Dislocation of nontunneled catheters, both central and PICC, is usually secondary to inappropriate securing of the catheter at the time of insertion or to inadequate nursing of the catheter exit site. Catheter stabilization is used to preserve the integrity of the access device and to prevent catheter dislocation. CVCs are stabilized using a method that does not interfere with assessment and monitoring of the access site or impede vascular circulation or delivery of the prescribed therapy.⁶

Different products are used to stabilize catheters: manufactured catheter-stabilization devices, sterile tapes, and surgical strips. Whenever feasible, a manufactured catheter-stabilization device should be preferred. Stitches should not be used routinely, as they increase the risk of local thrombosis/phlebitis (in PICCs), as well as the risk of bloodstream infection (in CVCs) and the risk of dislocation and local infection of the exit site (in all devices).⁴

Dislocation of tunneled catheters should be prevented by positioning the cuff at least 2.5 cm inside the tunnel (or more, according to the manufacturer's instructions) and securing the catheter, preferably with a catheter-stabilization device, for at least 3 to 4 weeks.

The "pinch-off" syndrome is due to compression of a large-bore silicone catheter—tunneled or connected to an implantable port—between the clavicle and the first rib, typically secondary to "blind" percutaneous placement of the catheter in the subclavian vein via the infraclavicular route. Such compression may lead to malfunction, obstruction, damage, and even fracture of the catheter, with embolization in the lung vascular bed. It is a potentially severe complication, which is totally preventable simply by avoiding placement of silicone catheters via the infraclavicular "blind" venipuncture of the subclavian vein.

Tip migration is a complication of silicone long-term catheters. It is also defined as a secondary malposition, and it usually happens when an inappropriately short catheter (tip in the upper third of the SVC) dislocates because of increased thoracic pressures. It can be prevented by proper positioning of the tip of the catheter.

Evidence that the choice of the internal jugular vein is better than the subclavian vein for VAD placement comes from a recent prospective, nonrandomized, observational study in 1,201 patients.⁶⁶ Immediate complications were more frequent in the subclavian than in the internal jugular approach (respectively, 5.0% versus 1.5%; $P < .001$); catheter malposition (2.3% versus 0.2%), venous thrombosis (2.0% versus 0.6%), catheter malfunction (9.4% versus 4.3%), and long-term morbidity (15.8% versus 7.6%) were also significantly more frequent in the subclavian than in the internal jugular group.

Thus, most of the mechanical complications are dependent on technical aspects of VAD insertion (pinch-off syndrome, dislocation, tip migration, erosion above the reservoir, etc.) or on appropriateness of nursing (occlusion, dislocation, damage to the external tract of the VAD, erosion above the reservoir, etc.).

In particular, it appears that the cornerstones for effective prevention of insertion-related complications are (A) use of ultrasound guidance³⁵;

(B) choice of the internal jugular vein rather than the subclavian vein^{66,67}; (C) appropriate position of the tip of the catheter; (D) proper stabilization of the catheter (for external VADs); and (E) proper placement of the reservoir (for ports).

Extravasation Injuries

Central VADs have greatly reduced the incidence of extravasation injury, but this severe complication may still occur in cases of catheter malfunction, such as rupture or tear in the catheter or port septum, migration of the catheter into a smaller vein, perforation of the SVC wall, separation of the catheter from the reservoir, and improper placement of the needle into the port septum.⁶⁸ Extravasation injury has been reported to occur in 0.1% to 6.5% of cases.⁶⁹ Catheter occlusion, which may be due to a clot within the catheter lumen or to fibrin sheath formation, can be associated with extravasation because excessive force when flushing the catheter can rupture its connection to the septum.

Extravasation of chemotherapy drugs can result in significant tissue damage. Pain is the main warning sign. If pain suggests extravasation injury, drug infusion should be discontinued immediately, and the site should be aspirated for residual drug. In severe cases, tissue necrosis can occur. Depending on the site of extravasation, alteration in limb function and even mediastinal damage may occur.⁷⁰ The degree of tissue injury may be severe enough to necessitate surgical debridement.

Infections

Intravascular catheter-related infections are a major cause of morbidity and mortality in cancer patients. In the hospitalized population, bloodstream infections are the third most frequent type of nosocomial infection.⁷¹ A large European, multicenter, point-prevalence study reported that 71% of all sepsis patients had an intravenous line.⁷² Coagulase-negative staphylococci, *Staphylococcus aureus*, aerobic Gram-negative bacilli, and *Candida albicans* are the pathogens most commonly involved.

Infection prevention and control is a crucial aspect of the clinical care of patients carrying a vascular access. Cancer patients are especially susceptible to infections because of immunodepression, and they should therefore be carefully

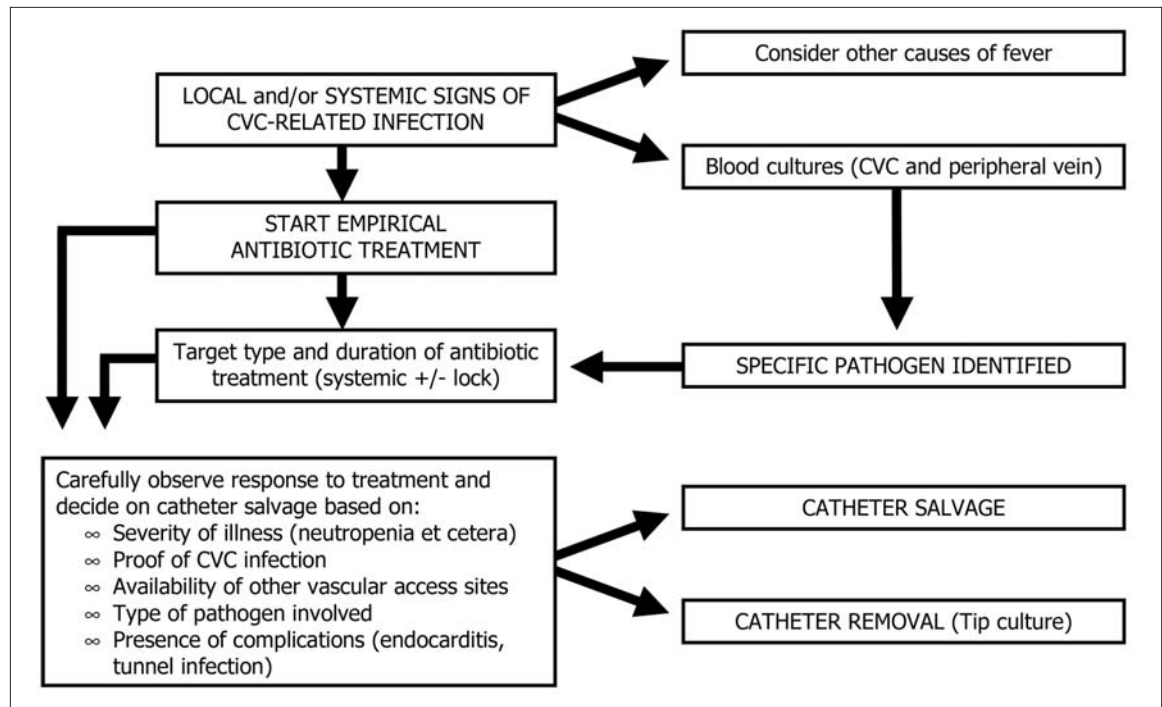


FIGURE 1 Management of Tunneled or Totally Implanted Central Venous Catheter-related Infection.

protected from this severe complication. Patient safety can be enhanced by incorporating guidelines^{17,73} into daily clinical practice.

Most catheter-related infections arise by 2 mechanisms: (A) infection of the exit site, followed by migration of the pathogen along the external catheter surface and (B) contamination of the catheter hub, leading to intraluminal colonization and consequent seeding of the pathogen into the circulation.

Because diagnosis is often clinical, and clinical diagnostic criteria are either insensitive or nonspecific, CVC-related infections are often overdiagnosed; this results in unnecessary and wasteful removal of the catheter.⁷⁴ Catheter-sparing diagnostic methods, such as differential quantitative blood cultures and differential time to positivity (DTTP), have 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 cut-off: 2 hours), this so-called DTTP can help to make the diagnosis of catheter-related infection.⁷²

Possible preventive strategies include skin antisepsis, maximum sterile barrier, use of

antimicrobial catheters, and antimicrobial catheter lock solutions. Management of catheter-related infections involves deciding on catheter removal, antimicrobial catheter lock solution, and the type and duration of systemic antimicrobial therapy (Figure 1). The type of catheter involved should also be taken into account. Empirical intravenous antimicrobial therapy should be initiated after samples for appropriate cultures have been obtained. In most cases of CVC-related bacteremia and fungemia, nontunneled CVCs should be removed. On the other hand, the decision to remove a tunneled catheter or implantable device should be based on several factors, such as the severity of the patient's illness and underlying condition (neutropenia, thrombocytopenia); proof that the VAD is infected; availability of other vascular access sites; assessment of the specific pathogen involved; and presence of complications, such as endocarditis, septic thrombosis, and tunnel infection.

When a catheter-related infection has been documented and a specific pathogen has been identified, systemic antimicrobial therapy should be targeted, and the use of antibiotic lock therapy should be considered. Specific guidelines on diagnosis, management, and prophylaxis of CVC-related infections are available.^{17,73,75}

McGee et al⁵³ have suggested that selection of the subclavian site appears to minimize the risk of infectious complications. However, while this statement is supported by an RCT comparing the infection rates associated with the selection of the subclavian or femoral vein,⁵⁴ no RCTs comparing the infection rates associated with internal jugular and subclavian vein cannulation are available. Moreover, a more recent nonrandomized study comparing the subclavian, internal jugular, and femoral sites in 657 intensive care patients (the largest sample size of all CVC studies conducted) showed that the overall incidence of CVC infection and colonization is low and does not differ both from a clinical and statistical standpoint among the 3 sites, provided that optimal insertion sites are selected, experienced operators insert the catheters, strict sterile techniques are adopted, and trained intensive care unit nursing staff perform catheter care.⁷⁶

Thrombosis

Catheter-related thrombosis, along with infection, is the most relevant complication in cancer patients who need long-term venous access.⁷⁷ To address this issue, the Italian Study Group for Long Term Central Venous Access promoted a nationwide consensus on catheter-related central venous thrombosis.⁷⁸ The problem of thrombosis is particularly relevant because the incidence of venous thromboembolism is markedly higher in patients with cancer than in patients without cancer,⁷⁹ 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. Indeed, cancer and chemotherapy are recognized risk factors for development of central venous thrombosis in patients with a CVC because of direct release of thrombogenic factors by neoplastic cells, decrease of antithrombotic natural factors induced by the tumor, and the procoagulant activity of many anticancer drugs.

In a systematic review,⁸⁰ 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. Although the thrombosis rate is high, only a third of the thrombosed CVCs become symptomatic. Nonetheless, CVC thrombosis can result in clinical symptoms, the loss of catheter function, a higher rate of infection, postphlebotic syndrome of the upper extremity, pulmonary embolism, and greater costs. However, using totally implantable access devices, we reported a low incidence of catheter-related symptomatic venous thrombosis: 1.06% (ie, 0.022/1,000 days of port use).⁸¹

Within 24 hours of CVC insertion, a fibrin sheath, always colonized by bacteria, forms around the catheter, but its presence does not predict subsequent thrombosis of the vessel in which the catheter is placed. Mechanisms of CVC-induced thrombosis include acute and chronic endothelial damage to the vein wall produced by an intravascular foreign body. 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. However, no RCTs in a long-term setting have investigated the relationships between insertion techniques (eg, percutaneous versus venous cut-down, ultrasound-guided versus anatomic landmark techniques) and central venous thrombosis rate.

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%.⁷⁸ 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. In addition, the risk of embolization during or immediately after

catheter removal has been reported.⁸² 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 hours 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/minute) 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 warfarin⁸³ or daily SC dose of LMWH,⁸⁴ more recent double-blind, placebo-controlled RCTs did not find any advantages for either of these prevention strategies.^{85–87}

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. However, 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,⁸⁸ 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%). The Italian Study Group for Long Term Central Venous Access⁷⁸ suggests considering prophylaxis with a single daily dose of LMWH (eg,

enoxaparin 100 IU/kg) in high-risk patients, including those who have a family history of thrombotic events or previously suffered from idiopathic venous thrombotic events.

With regard to the particular type of venous thrombosis (local or, more seldom, central), which may occasionally be associated with PICCs, it appears to be a multifactorial phenomenon influenced by caliber of the catheter, technique of placement (ultrasound-guided versus blind), cannulated vein (cephalic versus brachial versus basilica), position of the tip, stabilization technique (stabilization devices versus tape versus stitches), type of treatment, patient, and disease characteristics. PICC placement in the basilica vein or in a brachial vein at midarm by the ultrasound technique is recommended; catheters larger than 4 French are to be avoided.²⁶

Are Infections and Thrombotic Events Related?

Van Rooden et al⁸⁹ 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 2 or more positive subsequent CVC lock fluid cultures with identical micro-organisms, 71.4% developed thrombosis as compared with 3.3% in patients with negative or a single positive culture.

CATHETER MANAGEMENT

Catheter management is a critical issue in the care of cancer patients, and it is as important as catheter selection and placement. Venous access can be considered a routine matter, but it can carry serious complications, which can be maintained at a very low level if strict adherence to a regimented protocol of surgical technique and of catheter care is maintained.⁹⁰

In the early years of vascular access care,⁹¹ it was shown that the most significant way to reduce catheter-related infections was rigorous aseptic

nursing care, renewal of the dressings, and access to the catheter being the sole responsibility of specially trained nurses.

Nowadays, much nursing time is spent caring for patients receiving intravenous therapy. In several countries nursing care in vascular access is very advanced, as nurses select, insert, and remove both peripheral and central venous devices, but in all countries their role in assessing the patient's vascular access needs and in maintaining the access is crucial.^{92,93}

Many times patients and parents, rather than nurses, are caring for catheters. Therefore, VAD complication rates can be viewed in different perspectives. However, nursing care, regardless of the fact that the caregiver is the patient, a parent, or a nurse, should follow standard, high-quality procedures. Specific nursing aspects of vascular access care are beyond the scope of this review, but they are very important. We refer the reader to available nursing guidelines.⁶ We only summarize a few considerations on dressing technique, catheter flushing, and patient education.

Dressing Technique

Clinical management of VADs requires sterile technique because their correct maintenance increases the benefits to the patient and decreases the risk of serious complications.

It has been shown that wearing sterile gloves and disinfecting the skin with 2% chlorhexidine-based preparations reduce catheter-related infections most effectively.⁹⁴ Povidone-iodine or a 70% alcohol solution can be used alternatively in case of allergy to chlorhexidine. More recently,¹⁷ it has been suggested that the dressing of CVCs with the use of nonsterile gloves coupled to a no-touch technique is equivalent to the use of sterile gloves.

The port system is accessed using a special noncoring Huber needle, which avoids damage to the port and allows more than 2,000 punctures. The silicone port membrane needs to be punctured vertically in order to avoid bending the tip. During continuous use, access needles should be changed every 7 days, with caps and tubing changed every 2 days, but in patients treated with total parenteral nutrition, tubing is changed every day because of a greater potential for bacterial growth. VADs that are used intermittently should be accessed and flushed at least once a month.

Transparent polyurethane film is recommended for catheter-site insertion dressing by the CDC guidelines for the prevention of infections associated with intravascular catheters.²² It has proved to offer the advantages of excellent adhesion, firm support of the catheter, good tolerability, ease of application, and fewer replacements per catheter lifetime compared with standard gauze and tape dressings.⁹⁵ Regarding the risk of infection, recent guidelines¹⁷ suggest that transparent polyurethane films are also superior in preventing CVC-related infections.

There is no defined frequency for changing transparent dressings, but most facilities change the dressings weekly or sooner as needed. The dressing must be changed if it becomes wet, soiled, or loose. Patients who shower must protect the site to prevent any water from getting under the dressing.

A recent meta-analysis of 8 RCTs⁹⁶ found that chlorhexidine-impregnated dressing (a round patch with a slit that allows it to be fitted around the catheter and antimicrobial action that lasts for up to 7 days) is effective in reducing vascular and epidural catheter bacterial colonization and is also associated with a trend toward reduction in catheter-related bloodstream or central nervous system infections, suggesting the need for a large RCT to confirm whether chlorhexidine-impregnated dressing is cost-effective in preventing bacterial infections related to vascular and epidural catheters or not.

Catheter Flushing

Routine catheter flushing is the most common practice to maintain patency, reducing fibrin sheath and clot formation.⁶³ This is a common-sense practice as no studies are available in the literature. Flushing protocols vary by facility and type of VAD. In most cases flushing is carried out with 10 to 20 mL of normal saline, followed by 5 mL of heparin solution (10 U/mL for daily flushing or 100 U/mL in case of longer intervals). However, some catheters are designed to prevent the reflux of blood into the catheter through the presence of pressure-sensitive valves and can be flushed with normal saline only.

Saline flushing should be done with 10-mL or larger syringes to prevent excessive flushing force that can damage the catheter. Prefilled syringes

of smaller size are available with a traditional 10-mL syringe diameter; they generate a significantly lower pressure compared with traditional 3-mL syringes.

Flushing is recommended before and after administration of drugs, before and after transfusion of blood components, after obtaining blood specimens, and for device maintenance when not in use.

The only available publication on catheter flushing concerns catheter maintenance in patients who after completion of therapy retain their ports for extended periods of time.⁹⁷ Most manufacturers recommend heparin flushing of the port systems at 4-week intervals, but Kuo et al challenged this indication. They showed that patient compliance with monthly appointments is poor and that average intervals of accession among patients who had clotted catheters was 79 days versus 63 days for those without any difficulty in flushing. They concluded that monthly maintenance is excessive, inconvenient for the patients, and expensive, while clinical experience suggests that less frequent flushing could be safe and feasible.

Patient Education

Most long-term VADs are cared for by patients at home. Therefore, patient education is of utmost importance to reduce the occurrence of complications.

Patients and caregivers should understand the importance of thorough hand washing, of administering medications on time, and of routine assessment of the insertion site. Teaching aids include video tapes, information booklets, and hands-on practice using dummy devices and equipment. Reinforcement of information provided with lectures and written material by demonstration and practice has been found to achieve better retention of information.

Following adequate training, the nurse should establish whether the patient and/or family caregiver are ready to manage their vascular access at home. To do so, they should be able to describe the rationale and the risks and the benefits of the device, demonstrate care of the access to a level appropriate for their needs, list the signs and symptoms of catheter-related complications, and

state how to contact the hospital or health care professional if they have concerns.⁹⁸ In selected cases, it may be useful to arrange for a nurse to visit the patient at home in order to further reinforce the retention of training information.

PATIENT ISSUES: VASCULAR ACCESS AND QUALITY OF LIFE

Many patients suffering from solid tumors require long-term central venous access for safe, cyclic delivery of chemotherapeutic agents, transfusion of blood and blood products, and performance of laboratory tests. It is a common experience that venous integrity is quickly compromised by local trauma caused by the exposure to toxic effects of the antineoplastic drugs and repetitive cannulation and blood sampling so that an efficient peripheral venous access becomes progressively difficult to achieve and maintain over the period usually required to complete a chemotherapy program. Moreover, some oncology patients need an indefinite venous access for palliation and symptomatic therapies. In this specific clinical setting, totally implantable access ports are usually preferred to percutaneous tunneled catheters because they need no external dressing, do not interfere with patient activities (such as personal hygiene, swimming, and sexual life), require only monthly flushes of heparinized saline to keep the catheter patent, and have a relatively lower incidence of infection and malfunction. It is common practice to implant these devices at the beginning of the course of chemotherapy to avoid potential future venous access problems and failures; however, despite their extensive use, the pros and cons of this policy have been evaluated in only one RCT, particularly with respect to efficacy and cost-benefit ratio and its impact on patient quality of life.⁹⁹ 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.^{9,100}

Clinical trials to evaluate safety, costs, and quality of life of central venous ports have been basically open-label, single-arm, Phase II studies¹⁰¹⁻¹⁰³

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.^{104,105}

A paper from our group⁶⁴ has provided clinicians, health care planners, and funding agencies with data derived from a large prospective study on total cost of devices for long-term chemotherapy of solid tumors. Briefly, 333 port devices, amounting to a total of 79,178 days *in situ*, were placed during a 30-month period in 328 patients (5 patients underwent a second placement after removal of the first device), who were followed prospectively for a minimum of 180 days in order to detect device-related and overall complications. The average purchase cost of the devices was obtained from the hospital charges, based on the costs applied during the 30-month period of the study. Insertion and maintenance costs were estimated by obtaining the charges for an average port implant and subsequent use; costs of complication management were assessed analytically, providing the total amount of related costs when more than one case of a complication was observed. The *global cost* for each device was defined as the purchase cost plus the insertion cost plus the maintenance cost plus the cost of treating complications, if any. According to the obtained findings, the global cost per patient, treated for a 6-month period, was US \$1,971. Although these results cannot be easily extended to other institutions due to different staff policies, observed complication rates, and other factors, this single-center prospective study shows that ports are associated with high purchase and insertion charges, low complication rate, and low maintenance costs.

Bow and coworkers⁹⁹ have randomly allocated adults with solid tumors (mainly gynecologic malignancies) and beginning a course of intravenous chemotherapy at 2 university-affiliated Canadian hospitals to have venous access using a surgically implanted venous access port ($n = 59$) or using standard peripheral venous access ($n = 60$). Outcome measurements included port complications, access strategy failure, access-related anxiety and pain, quality of life (expressed by means of the Functional Living Index-Cancer, FLI-C, 21-item questionnaire), and costs. Port complication rates were low (0.23/1,000 days

of use); failure of the assigned venous-access strategy occurred in 16 (27%) of 60 controls, who had to cross over to receive central venous access to complete treatment. As expected, failure was correlated with significant access-related anxiety and pain according to the outcome of multiple linear regression. The analysis of quality of life was based on only 92 patients completing 6 cycles of chemotherapy; although no statistically significant differences were detected in the total FLI-C scores between the groups, a rise in the total scores over the course of the study was observed, which was consistent with a chemotherapy-induced effect. Cost was much higher in the ports group compared with controls ($2,178 \pm 271$ versus 530 ± 894 Canadian Dollars, $P < .0001$). This study has a number of limitations: first, in spite of stratification and randomization procedures, the small sample size caused an uneven distribution of diagnoses between the groups, which may have resulted in an imbalance of factors possibly affecting the frequency of venous accesses and quality-of-life measurements; second, serial quality-of-life data over 6 cycles of chemotherapy were available for analysis from only 92 subjects so that the study sample size had limited power to detect clinically important quality-of-life differences derived from each of the subscale scores; finally, ports were recommended for all venous accesses by the authors, but in reality they were used for only 39%—the remaining 61% of venous blood samples for laboratory tests were obtained by peripheral phlebotomy. This introduced a systematic negative bias obscuring the quality-of-life benefit related to port use.

Until quite recently fluorouracil (5-FU) monotherapy, usually modulated by folinic acid, used to be the one and only treatment option for metastatic colorectal cancer.¹⁰⁶ A significant issue for quality-of-life assessment in oncology patients was the recent introduction of oral agents, like capecitabine, in view of the claims that they mimic intravenous 5-FU, at least pharmacologically,¹⁰⁷ since open-tunneled Hickman lines or totally implantable access ports, which are necessary for prolonged 5-FU infusions, were found to be potentially risky devices. Randomized trials had previously demonstrated that 5-FU infusion was the optimal approach as response rate,

progression-free survival (or time to progression), and overall survival—as well as toxicity—were all significantly in favor of infusion over bolus administration.¹⁰⁸ Significantly less diarrhea, stomatitis, nausea and vomiting, alopecia, lethargy, and neutropenia (all with $P < .0001$) were seen with 5-FU infusion in a recent large multicenter trial.¹⁰⁹

Oral medicinal products were offered as an alternative to “unpleasant” intravenous 5-FU in a randomized trial by Twelves et al.¹¹⁰ The authors report on the preferences of “experienced” patients receiving capecitabine and the biweekly intravenous 5-FU regimen (LV5FU2), which was given according to either an outpatient or an in-patient regimen. Compared with the administration of intravenous 5-FU as an in-patient, patients preferred outpatient capecitabine. However, about 50% of those patients who preferred capecitabine as their favorite outpatient therapy later chose the outpatient intravenous 5-FU regimen with which to continue treatment; this was due to the fact that intravenous 5-FU was better tolerated than capecitabine. In addition, self-reported quality of life using the Functional Assessment of Cancer Therapy–Colorectal questionnaire was in favor of LV5FU2 (outpatient). An additional concern for patients who are already taking oral medication to control heart disease, hypertension, and/or diabetes might be to add 4 to 5 rather large tablets of capecitabine in the morning and another 4 to 5 in the evening.

In conclusion, the cost-effectiveness of central venous port use in the long-term treatment of oncology patients has not been fully established. Prospective RCTs comparing ports with repetitive peripheral venous accesses can be carried out exclusively in subjects with good peripheral vein status and undergoing intermittent bolus chemotherapy. Patients showing poor peripheral veins at the initial evaluation or scheduled to receive infusion chemotherapeutic regimens are usually candidates for port placement and cannot be enrolled in these randomized trials, thus limiting the feasibility of achieving conclusive evidence-based information. At this time, there is objective evidence that totally implantable port systems are a safe, effective strategy for long-term venous access and that their use has resulted in an association with a reduction in peripheral

access-related anxiety and pain. It is still unclear whether these benefits outweigh the overall costs of their purchase, implant, and use for the supportive care of an increasing number of cancer patients. During these times of economic restraint and limited health care resources, further well-designed and sufficiently powered RCTs are needed to answer the question.

HOW TO CHOOSE THE MOST APPROPRIATE VAD FOR THE ONCOLOGY PATIENT

Choosing the appropriate device for the cancer patient may be cumbersome. Therefore, we would like to summarize here the most useful indications from available guidelines and reviews. According to Registered Nurses' Association of Ontario Guidelines,³ INS Standards,⁶ and recommendations of the British Committee for Standards in Haematology,⁴ choosing the most appropriate type of vascular access device is the result of a collaborative process among nurse, patient, physician, and other members of the health care team, taking into account duration of prescribed therapy, anticipated supportive therapy, physical assessment, patient health history, support system and resources, patient-caregiver ability to care for the device, device availability, and patient preference. The use of a structured approach is strongly suggested in order to facilitate a comprehensive assessment and the development of a vascular access care plan before the initiation of therapy. All patients should receive clear and comprehensive verbal and written information explaining the risks, benefits, and care of the device.

Many issues about the choice of the device are still matters of investigation, and ongoing RCTs are expected to solve at least some of the controversies. Nevertheless, there is a general consensus on some issues in the following list:

1. Nontunneled central catheters are indicated for short-term in-hospital setting use when peripheral venous access is impractical or not indicated. Peripheral access (via a short cannula or a midline catheter) should be chosen only if the device will be used for nonvesicant drugs, nonhyperosmolar parenteral nutrition, and solutions with pH between 5 and 9.
2. Chemotherapy with vesicant drugs should be delivered by a central venous access in

order to reduce the risk of infusion-related complications (especially extravasation).

3. Tunneled CVCs are indicated for patients in whom long-term central venous access and intensive device use are anticipated. The repeated administration of chemotherapy, antibiotics, parenteral feeding, blood products, and frequent blood sampling are all conditions suggesting their preferential use.
4. Fully implanted catheters (ports) are more suitable for children and long-term use (more than 2 to 3 months) with less-frequent need for access, especially in patients receiving intermittent bolus chemotherapy for solid tumors.
5. PICCs are more suited for ambulatory or outpatient-based therapy when a medium-term use (3 months) is anticipated. Polyurethane PICCs allow easier infusion of blood products as greater flow rates are achieved because the thinner walls provide a larger internal diameter of the catheter. The risk of PICC-related venous thrombosis is reduced by avoiding PICCs with calibers >4 French and by preferring insertion via the ultrasound technique.
6. The number of lumens and diameter of catheters should be kept to the minimum.

FINAL REMARKS AND PROPOSALS FOR FUTURE INVESTIGATIONS

Over the last decade, many changes have occurred in oncology, with new chemotherapy combinations and more complex regimens becoming available. VADs are now widely used and have facilitated vascular access in this category of patients. Despite the availability of a variety of devices, each showing different features and performances, there are no definitive data from the literature for an evidence-based guide to the choice of the most appropriate device and insertion site, particularly in terms of the reduction of long-term complications. Important complications like thrombosis and infections are still associated with permanent CVCs in oncology, sometimes leading to VAD loss, significant morbidity, increased duration of hospitalization, and additional medical costs. Nowadays most VAD-related infections can be prevented. A number of measures have been implemented to reduce the risk of infections, including maximal barrier

precautions during catheter insertion, catheter-site maintenance, and hub handling. New technologies and materials will be available in the near future, needing appropriate trials.

Thrombosis still remains a major problem. When VAD-related deep vein thrombosis occurs, 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. It may be particularly troublesome in a patient who already has compromised venous access because of multiple courses of chemotherapy. 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. Future studies should be adequately powered and evaluate the effects of newer factor Xa inhibitors, such as pentasaccharide fondaparinux, or direct thrombin inhibitors, such as ximelegatran. Early trials suggest that the former is more effective for prophylaxis against venous thromboembolism and is associated with less bleeding than LMWH. The latter may be a more stable oral anticoagulant than warfarin, not being affected by diet or antibiotics. Clearly such agents would first have to undergo evaluation in large Phase III trials in this clinical setting.

Finally, more studies are needed to investigate the issue of patient satisfaction and quality of life and their relationships with the VAD adopted for long-term use, a topic rarely studied so far. Whereas patients and their families still currently play a minor role in the selection of a VAD at the onset of treatment, patient satisfaction should be a major issue in the clinical setting of cancer palliation.

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