

Best choice of central venous insertion site for the prevention of catheter-related complications in adult patients who need cancer therapy: a randomized trial

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Background: Central venous access is extensively used in oncology, though practical information from randomized trials on the most convenient insertion modality and site is unavailable.

Methods: Four hundred and three 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 ultrasound (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.

Results: Four hundred and 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 0–1087). 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 ($P = 0.272$).

Conclusions: Central venous insertion modality and sites had no impact on either early or late complication rates, but US-guided subclavian insertion showed the lowest proportion of failures.

Key words: central venous ports, cephalic vein, chemotherapy, jugular vein, randomized trial, subclavian vein, surgical venous cut-down

introduction

Patients with cancer often require long-term central venous totally implantable access ports (TIAP) for repeated administration of chemotherapy and blood draw for testing [1, 2]. Approximately 15% of them experience access-related complications that are both hazardous and expensive to treat [3]. Subclavian venipuncture is the most popular route for transition and long-term central venous cannulation, although perioperative complications occur in up to 12% of the patients [4–6]. Percutaneous approach to the internal jugular vein is reported to be less prone to severe complications, but systematic information on this modality is scanty [7, 8]. Use of two-dimensional ultrasound (2D-US) guidance during internal

jugular catheterization has determined a reduction in the rates of unsuccessful cannulation, carotid artery puncture and hematoma formation when compared with anatomical landmark technique [9]. On the other hand, the risk of catheter-related infection was reported to be lower with subclavian than with jugular or femoral catheterization, at least in critically ill patients [4, 10–12]. Surgical cut-down of the cephalic vein at the deltoid-pectoralis groove is associated to minimal risk of severe early complications [13, 14], but its success rate has never been studied in a proper comparative investigation against percutaneously accessed veins.

Despite the wide use of TIAP in oncology, it is unknown whether one or the other central venous insertion site is less prone to complications since no randomized trial was carried out on this subject. Purpose of this prospective, three-arm randomized trial was to compare two different percutaneous routes of access to superior vena cava (subclavian and internal

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jugular) with a surgical cut-down access through the cephalic vein, evaluating early and late complications, including pneumothorax, clinically relevant bleeding, primary malposition, port-related bacteremia, pocket infections, late dislocation, fibrin sleeve formation, malfunction of the device, extravasation, clinically evident and silent venous thrombosis at anytime.

methods

patients

The trial was conducted during the 42-month period from 1 July 2003 to 31 December 2006, at the European Institute of Oncology in Milan, Italy. Before activation, it was approved by the relevant Ethics Committee. It was registered at Central Registry of Randomized Clinical Trials of the Italian Health Ministry. Hospitalized adults (aged 18–75), with an Eastern Cooperative Oncology Group performance status of zero to two, bearing solid tumors and candidate for i.v. chemotherapy were eligible for the study; exclusion criteria were active infections, coagulopathy (defined as platelet count <50 000/μl and/or prothrombin time >18 s), life expectancy <6 months or inability to give written informed consent.

ports and routes of access to central veins

Patients were randomly assigned to undergo implantation of a single type of port, constructed of titanium and silicone rubber, with a attached 6-F polyurethane catheter tubing (Bard Port™, Bard Inc., Salt Lake City, UT), through a percutaneous landmark access to internal jugular vein, a 2D-US-guided infraclavicular access to subclavian vein or a surgical cut-down access through the cephalic vein at deltoid–pectoralis groove. Generator of the assignment was separated from the executor; randomization was intraoperatively carried out by the data manager of the trial using a computer-assisted procedure and communicated to the operators.

insertion and maintenance of ports

Devices were implanted under local anesthesia in an operating room or in an angiographic suite, using maximal sterile barrier precautions. A confirmatory chest X-ray was always obtained after the placement. Data from the implantation and follow-up of these patients were entered into a software registry and analyzed by epidemiologists–biostatisticians (NR and DR). Follow-up continued on an outpatient basis at regular intervals of 15–21 days until the device was removed, the patient died or the study was closed (30 June 2007). The planned minimum follow-up period was 6 months for each patient. Power and color Doppler ultrasonography of internal jugular and subclavian veins was carried out at regular intervals (1 and 4 months after implant) or anytime when clinically suggested by the appearance of arm or facial swelling and/or pain. Patients with positive or dubious ultrasound (US) scans underwent a neck–chest computerized tomography scan, with i.v. contrast medium administration.

Implanted ports have been flushed with 20 ml of normal saline and then filled with sterile heparinized saline after each infusion of medication or blood withdrawal (5 ml of a solution containing 50 IU/ml). If the port remained unused for long periods of time, the heparin lock was changed once every 28 days.

Complications were recorded according to the timing of occurrence: early (intraoperative and postimplantation period to first use) and late complications (occurring after the first chemotherapy course given through the device). Patients who died within 6 months were retained in the analysis and were recorded as having no late complications unless one was noted before death. A trial profile, conforming to the Consolidated Standards of Reporting Trials guidelines, is shown in Figure 1.

statistical methods and sample size

The main end points for the comparison of the three central venous insertion sites were the percentage of patients with a complication in the perioperative setting and within 6 months of insertion, i.e. during chemotherapy treatment. From previous studies [1, 3], we anticipated that 3.2%–4.4% of patients at the European Institute of Oncology will experience an early complication as the consequence of the percutaneous placement of a central venous catheter and 1.8% will need a tube thoracostomy to treat a pneumothorax. Moreover, 2.4% of the patients will require the catheter to be removed for infection.

The sample size was calculated on the basis of the following assumptions. We anticipated a 5% of early complications for the percutaneous subclavian approach and assumed that the early complication rate for the other two arms is lower at 1%. At a 5% significance level, with a power of 80% and a two-sided test, 250 patients are required per arm. The two main contrasts were the comparison of (i) percutaneous subclavian to the cephalic surgical venous cut-down and (ii) internal jugular to the cephalic surgical venous cut-down.

An interim analysis was planned after half of the patients have been recruited. No formal stopping rule was defined; a repeated confidence interval (CI) analysis of the main contrasts for the exposure-adjusted incidence rate (EAIR) at 30 and 120 days and at the interim sample size has been adopted to aid early stopping decision. The EAIR difference CIs were calculated by the Wald method [15] with O'Brien–Fleming critical values [16]. Median duration of implant among insertion sites was compared using the log-rank test. The inverted Kaplan–Meier method was used to estimate the length of follow-up. Chi-square or Fisher's exact test was used for the comparison of groups where appropriate. Secondary analysis focused on the overall complication rates over the whole 6-month period of insertion of the catheter and the rates of specific perioperative and late complications and infections. Comparative analyses were completed on an intention-to-treat basis.

results

characteristics of patients and venous insertion sites

A total population of 465 patients has been considered for eligibility during the 42-month accrual period of the study. Main tumor types included breast cancer (~50% of the overall amount), colorectal, gastric, pancreatic, lung and sarcomas. The vast majority of the patients suffered from metastatic disease; the regimens of chemotherapy used were the following: vinorelbine–fluorouracil–cisplatin, vinorelbine–epirubicin–fluorouracil, epirubicin–cisplatin–fluorouracil, 5-fluorouracil (5-FU) continuous infusion + ledefolin, 5-FU continuous infusion + ledefolin + oxaliplatin, FOLFOX, FOLFIRI and ifosfamide continuous infusion.

A total of 403 patients were randomized (86.6%): 134 for internal jugular, 136 for subclavian and 133 for cephalic arm. Trial was closed before reaching the planned sample size after the results of the interim analysis since the differences of total late complications expressed as EAIRs were clinically insignificant: in favor of subclavian versus cephalic was 0.17% and in favor of internal jugular versus cephalic was 0.22% (Figure 2). The three groups of patients were similar with respect to characteristics (Table 1), with no significant differences in terms of underlying disease (breast cancer versus others, $P = 0.129$) and median duration of implant ($P = 0.813$). Complete data for late complications could be

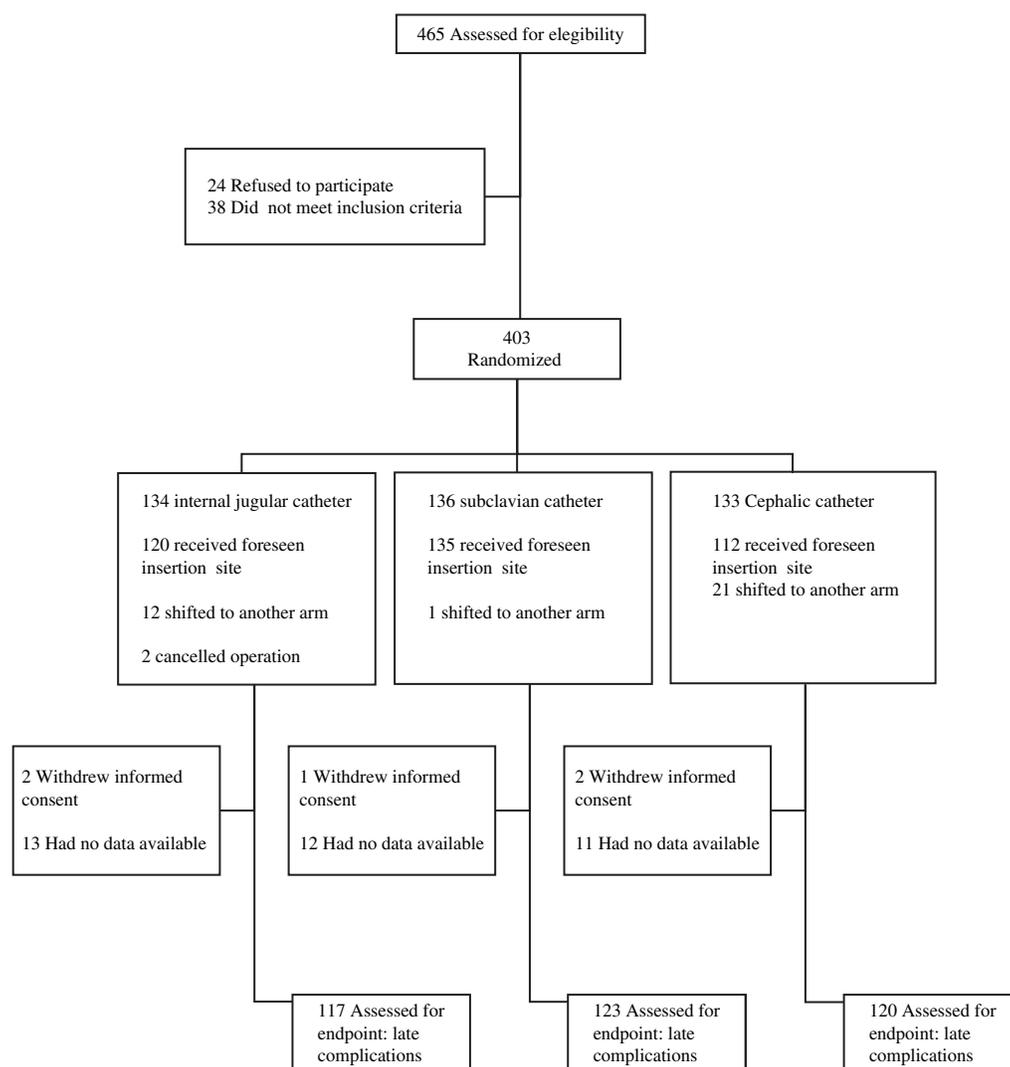


Figure 1. Trial profile conforming to the Consolidated Standards of Reporting Trials guidelines.

evaluated for 360 patients (89.3%; 117 internal jugular, 123 subclavian and 120 cephalic). The right side was used in 95, 95 and 90 patients, respectively, in the internal jugular, subclavian and cephalic groups. Twenty-one patients of cephalic group (15.8%) and 14 of internal jugular group (10.4%) had to be shifted to another arm ($P = 0.257$), as a consequence of failed attempts to place the catheter in agreement with the original arm of randomization, whereas just one case initially randomized to receive a 2D-US-guided subclavian catheter had to be shifted to cephalic arm (0.7%). 2D-US guidance to subclavian vein catheterization had significantly less failures compared with landmark access to internal jugular vein ($P = 0.001$) or cut-down surgical access to cephalic vein at deltoid-pectoralis groove ($P < 0.001$).

All the patients underwent at least one cycle of chemotherapy through the device. The median follow-up was 361 days [internal jugular group: 384 days (range 0–988), subclavian group: 360 days (range 0–666), cephalic group: 360 days (range 0–1087)], comprising a total of 30 890 days *in situ* for the internal jugular, 26 166 days for the subclavian and 28 458 days

for the cephalic group. There were no differences in the duration of observation between the three groups. A total of 113 patients in the internal jugular, 116 in the subclavian and 109 in the cephalic group were still alive at the closure of the study. There were no significant differences between the three groups in the numbers of patients who died within the minimum follow-up period of 6 months.

early complications

We did not observe any TIAP-related death in this series. There were no differences in the percentage of patients experiencing early complications between the three groups ($P = 0.132$). Zero patients of the internal jugular and zero patients of the subclavian [0% (95% CI 0.0% to 2.7%)] and two of the cephalic catheter group [1.5% (95% CI 0.1% to 5.3%)] had an early complication (2 of 401) (Table 2).

late complications

Twenty-one patients of the internal jugular [17.9% (95% CI 11.5% to 26.1%)], 16 patients of the subclavian [13.0% (95%

CI 7.6% to 20.2%)] and 21 patients of the cephalic catheter group [17.5% (95% CI 11.2% to 25.5%)] suffered from a late complication ($P = 0.612$) (Table 2). The percentages of patients

with infections in the internal jugular group were 0.8% (95% CI 0.0% to 4.7%), 2.4% (95% CI 0.0% to 4.7%) in the subclavian and 2.5% (95% CI 0.0% to 7.1%) in the cephalic catheter group ($P = 0.464$). As a consequence of infectious complications, the catheter had to be removed in one patient in the internal jugular group, in one patient in the subclavian and in two patients in the cephalic catheter group.

The incidence of catheter-associated venous thrombosis was globally 9.4% (95% CI 6.6% to 13.0%) in this series. Fifteen patients with internal jugular [12.8% (95% CI 7.3% to 20.3%)], eight patients with subclavian [6.5% (95% CI 2.8% to 12.4%)] and 11 of the cephalic catheter group [9.2% (95% CI 4.7% to 15.8%)] had thrombosis ($P = 0.272$). In 21 cases only (61.8%), there were clear clinical symptoms and signs of this complication. Pulmonary embolism was never found. Four cases required the removal of the catheter due to the concomitant dislocation of its tip from the superior vena cava to other veins.

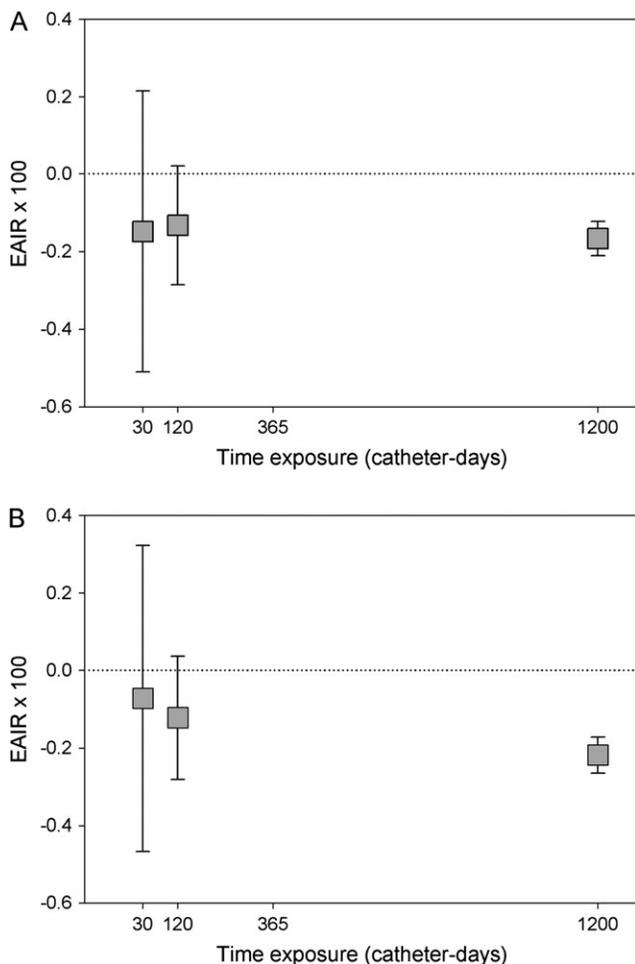


Figure 2. (A) Subclavian-cephalic and (B) internal jugular-cephalic total late complication exposure-adjusted incidence rate (EAIR) differences with 99% (O'Brien-Fleming) repeated confidence intervals.

discussion

This trial was aimed at clarifying which access, among those commonly used for TIAP implantation and administration of long-term chemotherapy (internal jugular, subclavian or cephalic), is associated with the lowest rate of complications, either early or late. A review and meta-analysis [17] of nonrandomized studies, mostly carried out in intensive care unit settings and published up to year 2000, reported that there were significantly more arterial punctures with jugular compared with subclavian access, but that there were significantly fewer malpositions with jugular access, with no difference in the incidence of hematoma, pneumothorax or vessel occlusion. The authors concluded that selection bias could not be ruled out. A recent randomized, multicenter trial of 750 severely ill, bed-bound adults requiring a first catheter insertion for renal replacement therapy showed that jugular venous catheterization access does not appear to reduce the risk of infection compared with femoral access, except among adults with a high body mass index, and may have a higher risk

Table 1. Characteristics of the patients

Characteristic	Internal jugular, n (%)	Subclavian, n (%)	Cephalic, n (%)	Total
No. of patients	134 (33.2)	136 (33.7)	133 (33.0)	403
Patient gender				
Female	104 (77.6)	108 (79.4)	101 (76.0)	313 (77.6)
Male	30 (22.4)	28 (20.6)	32 (24.0)	90 (22.4)
Age (years)				
Mean ± SD	53.4 ± 12.2	50.5 ± 12.0	52.1 ± 11.4	52.0 ± 11.9
Pathology				
Breast cancer	80 (59.7)	88 (64.7)	70 (52.6)	238 (60)
Others	54 (40.3)	48 (35.3)	63 (47.4)	165 (40)
Right side	95 (67.6)	95 (70.9)	90 (68.8)	280 (69.5)
Median duration of implant (range, days)	863 (0–988)	490 (0–666)	551 (0–1087)	596 (0–1087)
Alive at the end of the study	113 (84.3)	116 (85.3)	109 (81.9)	338 (83.9)
Patients with at least 6-month follow-up	117 (87.3)	123 (90.4)	120 (90.2)	360 (89.3)
Patients who died within 6-month follow-up period	9 (6.7)	9 (6.7)	8 (6.9)	26 (6.4)

SD, standard deviation.

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Table 2. Early and late complications in the experimental groups

Early complications	Internal jugular (n = 132), n (%)	Subclavian (n = 136), n (%)	Cephalic (n = 133), n (%)
Pneumothorax	0	0	1 (0.7)
Primary malposition	0	0	1 (0.7)
Total	0	0	2 (1.5)
Late complications	Internal jugular (n = 117) n (%)	Subclavian (n = 123) n (%)	Cephalic (n = 120) n (%)
Port-related bacteremia and/or pocket infection	1 (0.8)	3 (2.4)	3 (2.5)
Port removal	1	1	2
Migration/malposition	0	0	6 (5.0)
Port removal			2
Infiltration/extravasation	0	4 (3.2)	1 (0.8)
Venous thrombosis	15 (12.8)	8 (6.5)	11 (9.2)
Port removal			2
Fibrin sleeve	5 (4.3)	1 (0.8)	1 (0.8)
Total	21 (17.9)	16 (13.0)	21 (17.5)

of hematoma [18]. A review of the Cochrane Database of Systematic Reviews published in 2007 did not discover any randomized trials of subclavian versus jugular venous access, concluding that more evidence on whether the subclavian or the jugular access route is optimal was required [19]. Our report presents the first randomized evidence on this topic [20], showing that the proportion of patients with early complications is not influenced by the insertion site and technique used, but that insertion sites have different failure rates. The surgical exposure of the cephalic vein at deltoid-pectoralis groove is free of serious early complications, like pneumo- or hemothorax; the major pitfall is the inability to obtain a correct placement, as expressed in our series by 21 patients (15.7%) who had to be shifted from a cephalic access to another one, thus failed to have the catheter implanted as primarily foreseen. This is mainly due to the difficult identification and use of the cephalic vein, both characteristics not uncommon in patients who were preexposed to i.v. chemotherapies [21, 22].

Use of 2D-US guidance for subclavian cannulation did not change in our series the very low rate of early complication of internal jugular blind access (anatomical landmark technique). The role of US guidance in catheterization of central veins was investigated in randomized trials, also included in two meta-analyses [9, 23]. Taking into account 10 randomized trials investigating jugular vein catheterization with landmark methods or 2D-US technique, Hind et al. [23] concluded that the use of US reduced failure rate—both overall and on the first insertion attempt—and also placement-related complications when compared with landmark technique. Only one trial [24] investigated 2D-US for insertion of subclavian catheters and confirmed its superiority versus landmark method. In this and other trials [23–25], operators had limited experience in landmark methods, thus criticizable. Our monocentric trial, involving operators with proficiency in both procedures, confirms the previous evidence: 2D-US access to subclavian vein is associated with a failure in <1%, compared with 10.4%

and 15.7% of landmark-accessed internal jugular vein and surgically exposed cephalic vein, respectively.

The percentages of patients with late complications have resulted not significantly different among the three groups. In the literature, cross comparisons of infectious complications' rates are not reliable due to nonstandard definitions, dissimilar patient selection and lack of proper sample size in randomized trial [26]. A recent paper from Maki et al. [27] described a systematic analysis of >200 prospective studies for the risk of bloodstream infection associated with various types of intravascular devices. Surgically implanted long-term central venous devices (i.e. cuffed tunneled catheters and ports) were associated with less infections, defined as bloodstream infection per 1000 intravascular devices-days. Our data confirm that infectious morbidity related to TIAP is very low, irrespective of the access site used, as they are flushed less frequently, require no specific care at home and are less challenged by environmental or cutaneous contamination when not accessed. Close adherence to trial procedures and presence of a dedicated nursing staff helps to explain our findings [28].

The incidence of catheter-related venous thrombosis was quite low in this study (9.4%), with no significant differences among the trial arms. The association between cancer and venous thromboembolism arises as a consequence of cancer treatment and direct vessel trauma, as a result of long-term central venous catheter placement [29]. The incidence of symptomatic central catheter-related deep vein thrombosis in adults varies between 0.3% and 28.3%, whereas the incidence of venography-assessed cases ranges from 27% to 66% [30]. Thrombosis may cause several symptoms, be associated with loss of catheter function, with increased risk of infection, pulmonary embolism, postphlebotic syndrome of the upper extremity and greater costs [31]. In our trial, use of 2D-US guidance or surgical exposure of the cephalic vein was not associated with a significant reduction of catheter-related thrombotic events, although both techniques equally minimize direct and repeated trauma to vein wall. No thromboprophylaxis was used in this trial; recent meta-analyses in cancer patients with central venous devices showed that thromboprophylaxis has no significant effect on the risk of catheter-related thrombosis or bleeding. The use of primary thromboprophylaxis in cancer patients with central venous catheters while not causing any harm provides no benefit [32, 33].

In conclusion, our results illustrate that central venous access insertion site does not influence early or late occurrence of complications of venous ports connected to a standard open-ended catheter implanted in an experienced environment. 2D-US guidance to subclavian vein catheterization had significantly less failures compared with landmark access to internal jugular vein or cut-down surgical access to cephalic vein at deltoid-pectoralis groove. Cost, patients' quality of life and procedure compliance could be additional critical issues in the decision making about which insertion site has to be used and are currently matter of investigation [34]. While awaiting for further evidences, skilled operators may rely on their experience and on proper assessment of clinical setting and patients' characteristics when choosing the most appropriate venous access site for long-term drug administration.

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