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► To cite this version:

Amaury Bailleul, Jean-Pierre Fulgencio, Sophie Vimont, Cécile Mordelet, Benoit Ray, et al.. Risk factors and prognostic significance of infection of totally implantable vascular access port in solid tumor patients: a prospective cohort study. *Infectious Diseases Now*, inPress, pp.104766. 10.1016/j.idnow.2023.104766 . hal-04178470

HAL Id: hal-04178470

<https://hal.science/hal-04178470>

Submitted on 8 Aug 2023

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**Risk factors and prognostic significance of infection of totally implantable
vascular access port in solid tumor patients: a prospective cohort study**

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Authors' contributions

All authors contributed to the study conception and design. Data collection was performed by A. Bailleul, JP Fulgencio and S. Vimont. Data interpretation and analysis was performed by A. Bailleul, M. Garnier et N. Lapidus. The first draft of the manuscript was written by A. Bailleul and M. Garnier. Review and editing of the manuscript were performed by M. Garnier. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Word count: manuscript: 3364 words ; abstract: 239 words.

ABSTRACT

Objectives. Totally implantable venous access ports (TIVAP) are devices mainly used to deliver antineoplastic chemotherapies, whose insertion may be complicated by TIVAP-related infection (TIVAP-RI). This study aims to provide data on the risk factors of TIVAP-RI and its influence on patients' prognosis.

Patients and methods. Prospective observational study including adult patients with solid tumors, in whom a TIVAP was inserted to deliver antineoplastic chemotherapy between January 2018 and October 2019. Factors associated with TIVAP-RI and one-year mortality were determined using multiple logistic regressions.

Results. 1014 patients were included, among whom 48 (4.7%) presented a TIVAP-RI. Gram-positive cocci and Gram-negative bacilli represented 51% and 41% of the pathogens isolated, respectively. Younger age (odds ratio [OR] 0.67; 95% Confidence Interval [0.53–0.83] per 10-year increase), WHO performance status ≥ 1 (OR 3.24 [1.52–7.79]), chemotherapy administration in the month before TIVAP placement (OR 2.26 [1.17–4.26]), and radiation therapy of the homolateral chest wall (OR 3.28 [1.51–6.67]) were independently associated with TIVAP-RI occurrence. During the year following TIVAP insertion, 287 (28%) patients died. TIVAP-RI was not associated with one-year mortality (OR 1.56 [0.75 - 3.19]).

Conclusion. TIVAP insertion in adult patients with solid tumors is associated with a low infection rate, that did not influence one-year mortality. In addition to young age and impaired health status, TIVAP insertion in the month following the initiation of the antineoplastic chemotherapy and in an irradiated area, are two newly reported preventable TIVAP-RI risk factors.

61 **Keywords:** infection, mortality, risk factors, solid tumor, Totally Implantable Vascular Access

62 Port

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1. INTRODUCTION

A totally-implantable-venous-access-port (TIVAP) is a device used for the administration of drugs that cannot be administered through a peripheral vein, or for prolonged intravenous administration of antibiotics, vasodilator treatment, parenteral nutrition, etc. TIVAP remains the reference intravenous access to deliver systemic antineoplastic chemotherapies [1], whose venotoxicity does not allow their repeated peripheral administration [2].

The implantation of TIVAP is accompanied by complications of varying severity. The most frequent complication is TIVAP-related infection (TIVAP-RI), associated with over-morbidity and mortality [3]. Its incidence rate has been estimated between 0.02 and 0.35 infections/1000 catheter-days, corresponding to the contamination of 2% to 14% of all TIVAP inserted [4–9]. This wide range is explained by the heterogeneity of the populations studied (*e.g.* adult vs. pediatric patients, hematological malignancies vs. non-cancer patients, etc.), the diagnostic criteria of infection used (*i.e.* clinically suspected vs. blood culture documented vs. port culture proven infection), and the length of patient follow-up [10]. Nevertheless, TIVAP-RI rates seem stable over the last 20 years [11–13]. To date, risk factors for TIVAP-RI have been primarily assessed in retrospective studies, which included patients in whom the TIVAP was inserted before the 2010's [6,8,14–19]. The most commonly reported risk factors are hematological malignancies, late-stage cancer and younger age [11], which are non-modifiable risk factors. However, some technical advances and updated hygiene rules, such as systematic location of the vein by ultrasound and skin antisepsis with 2% chlorhexidine in alcohol, have recently changed insertion procedures [20]. Finally, while the outcome of patients who experienced a TIVAP-RI appeared unfavorable [9,21], the specific effect of TIVAP-RI comparatively to other prognostic factors remains to be clarified.

86 The aim of this study was to update current knowledge on risk factors of TIVAP-RI and
87 evaluate the effect of TIVAP-RI on one-year mortality in patients treated with antineoplastic
88 chemotherapy for solid tumor.

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2. MATERIAL AND METHODS

2.1 Study design

This is an observational prospective study, part of a local prospective registry of all TIVAP insertion procedures performed at Tenon University Hospital (Assistance Publique – Hôpitaux de Paris, Paris, France; a 550-bed tertiary public hospital specialized in medical and surgical cancer care). This manuscript adheres to the STROBE guidelines. The STROBE checklist is provided as *Supplementary Material*.

2.2 Ethics

This study was approved by the French society of anesthesiology and critical care medicine ethics committee (CERAR - IRB #00010254-2020-194), and performed in accordance with the 1964 Helsinki declaration and its later amendments. Due to the non-interventional design of the study, patients' written consent was waived by the ethical committee [22]. Thus, written information was delivered to patients before TIVAP placement.

2.3 Patients

All the patients aged ≥ 18 years-old who had TIVAP insertion between January 1, 2018 and October 31, 2019 were eligible for the study. Non-inclusion criteria were: patients with hematological malignancies, insertions for other indications than administration of antineoplastic chemotherapy, patient's follow-up planned outside our hospital group, and TIVAP replacement in a patient already included in the study. Hematological malignancies and other indications of insertion than administration of chemotherapy were not included due to their low proportions in our center (1% and 0,3% respectively), which would have added heterogeneity without representing subgroups large enough to draw conclusions. All the other patients were included.

2.4 Technical procedures

TIVAP were all inserted in our dedicated technical platform. The healthcare professional team was composed of 3 anesthesiologists and 2 anesthetic nurses specifically trained in TIVAP placement. Only the percutaneous technique was used. The preferred site of catheterization was the right internal jugular vein. All the practitioners used a common protocol that followed the most recent national guidelines [23], including notably systematically ultrasound-guided vein puncture (Mindray TE7, 11 MHz linear probe), use of sterile gown, and skin antisepsis with 2% chlorhexidine in alcohol. The correct position of the catheter was confirmed with an image intensifier during the procedure. Two types of TIVAP were sequentially implanted in accordance with public market rules, both composed of a silicone catheter connected to a titanium/polyoxymethylene chamber with a silicone membrane (Heliosite[®], Vygon SAS, Ecouen, France; Polysite[®], Perouse Médical, Ivry, France). If the device was intended to be used within the first 48 hours after insertion, a Huber needle was sterilely inserted by the operator at the end of the procedure; conversely, a healing time of at least 7 days was recommended before use.

2.5 Microbiology

Blood cultures. In case of suspicion of TIVAP-RI, 5 to 10 mL of blood were sampled at the same time from a peripheral vein and the TIVAP in BACT/ALERT[®] bottles (bioMérieux, Marcy-l'Etoile, France), and then incubated in an automated blood culture BACT/ALERT[®] Virtuo[®] system (bioMérieux). In case of positivity, Gram staining and culture on medium adapted to the type of bacteria found were performed. Identification by mass spectrometry (MALDI-TOF, Bruker Daltonics, Bremen, Germany) on a 18h-subculture and an antibiogram were systematically performed according to CASFM/EUCAST guidelines [24].

TIVAP. 1 mL of sterile water was injected in the port on one hand, and in the catheter on the other hand, vortexed and 100 µL of both rinsing fluids were inoculated on horse blood agar plates, and incubated at 37°C for 48h. Positivity threshold was 10³ cfu/mL [25].

2.6 Definition of TIVAP-related infection

In our center, all patients with suspected TIVAP-RI are referred to us either directly to the TIVAP platform or after a consultation with the attending oncologist. To ensure that no infection was missed, the notion of a TIVAP-RI was checked in patients' computerized medical records, which includes the microbiological results, one year after insertion. Definition of definite TIVAP-RI was adapted from the Infectious Diseases Society of America guidelines [26], as one of the following conditions:

- The presence of local signs of infection (inflammation or purulence of the tunnel or the pocket), associated with a positive culture of the TIVAP;
- Or the presence of a bacteremia or fungemia without any apparent source for bloodstream infection apart from the TIVAP, associated with at least one of the following criteria:
 - i. The same micro-organism is isolated from a peripheral blood sample and the culture of the TIVAP;
 - ii. Differential time to positivity: growth of the same micro-organism(s) (except *S. aureus* and *Candida* for which differential time to positivity is not validated) in a culture of blood obtained through a TIVAP is detected by an automated blood culture system at least 2h earlier than a culture of simultaneously drawn peripheral blood of equal volume;
 - iii. Positive culture of the catheter or port, with partial or total regression of general infectious signs within 48 hours of TIVAP removal.

The date of TIVAP-RI was the date of the first clinical signs or first positive blood culture in the absence of clinical sign. An infection that occurred during the first month following TIVAP insertion was considered an “early” TIVAP-RI.

2.7 Data collection (*see the additional method file for detailed list of data collected*)

General demographic characteristics, cancer characteristics, and patient comorbidities previously associated with TIVAP-RI were prospectively collected. The main hematological data at the time of device placement were also collected, as well as some technical features regarding the insertion procedure.

When a TIVAP-RI occurred, the main data regarding the infection and its management were collected. Notably, we carefully assessed the success of the antimicrobial treatment (systemic antibiotics and/or lock therapy conducted in accordance with our institutional protocol [*additional method file*]), defined as the resolution of local and/or systemic signs of infection and negativity of at least two pairs of blood cultures incubated for at least 5 days, with no recurrence of TIVAP-RI due to the same germ within one month of the last negative blood culture.

Finally, vital status at one year was collected from the patient’s electronic medical file and/or the French national death register.

2.8 Statistical Analysis

Distributions are reported as median [25th-75th percentile] for continuous variables and count (proportions) for qualitative ones. Distributions among patients with and without TIVAP-RI were compared using Mann-Whitney-Wilcoxon tests, and chi-square or Fisher exact tests – as appropriate – for continuous and qualitative variables, respectively. To determine factors associated with TIVAP-RI, we performed a multiple logistic regression. The following baseline

covariates deemed clinically relevant were included in the model without univariate screening [27]: age, World Health Organization (WHO) Performance Status (PS), antineoplastic chemotherapy received in the month before TIVAP placement, radiotherapy of the chest wall homolateral to the site of TIVAP insertion, difficult insertion assessed by the need for more than 2 venipunctures, use of the new TIVAP within the first week of insertion, and need for an early re-intervention. The same approach was used to identify factors associated with 1-year mortality, including the following variables into the model: age, sex, body mass index (BMI), WHO PS, diabetes, location of the tumor, metastatic stage of the tumor, antineoplastic chemotherapy received in the month before TIVAP placement, TIVAP-RI, use of the new TIVAP within the first week of insertion, and need for an early re-intervention. Results of the multivariate models are reported as odds ratios (OR) with their 95% confidence intervals (95% CI). All tests were two-tailed and p values below 0.05 were considered significant. Statistical analysis was performed using R version 4.0.3 (R foundation for statistical computing, Vienna, Austria).

3. RESULTS

3.1 Inclusions and patients' characteristics

During the inclusion period, 1054 TIVAP were placed in 1036 patients, among which 40 procedures were not included (**Figure 1**). Finally, 1014 TIVAP insertions in 1014 patients were included in the study, among whom 48 presented a TIVAP-RI.

The demographic characteristics of the patients included are summarized in **Table 1**. Briefly, 618 (60.9%) patients were women. TIVAP were inserted in an ambulatory setting in 823 (81.2%) patients. Patients suffered predominantly from breast tumors (n=276; 27.2%), followed by digestive and lung tumors (n=224 and 223, respectively; 22%). Five hundred and nineteen (51%) patients suffered from metastatic tumors. The internal jugular vein (n=598; 59%) and the jugulo-subclavian junction (n=319; 31.5%) were the two main sites of venipuncture (**Table 1**). The time from TIVAP placement to first use was 7 [3-11] days.

3.2 TIVAP-related infections

3.2.1 Epidemiology

Forty-eight (4.7%) patients presented a TIVAP-RI, 90 [40-226] days after insertion, among which seven were early infections. TIVAP-RI were diagnosed by the presence of local signs and positive culture of the TIVAP in 11 patients, bacteremia associated with differential time to positivity in 25 patients, and bacteremia with positive culture of the TIVAP followed by regression of infectious signs after its removal in 12 patients. Only 11 (22.9%) patients presented local signs of infection. Gram-positive cocci were predominantly isolated (n=26; 50.9%), followed by Gram-negative bacilli (n=21; 41.2%), and *Candida* species (n=4; 7.8%) (**Table 2**). Three infections were due to two micro-organisms. Six out of the seven early TIVAP-RI were due to *Staphylococcus* sp., including four *S. aureus*.

3.2.2 Therapeutic management

An empirical antimicrobial therapy was initiated in 27 (56.3%) patients, and was effective in 22 (81.5%) out of these 27 cases. A definite antimicrobial therapy was initiated after the results of the antibiogram were available in 18 (37.5%) patients, while 3 (6.3%) patients did not receive systemic antibiotic. These three patients were treated by TIVAP removal and local care. An antibiotic lock was used in 19 (39.6%) patients, and was a success in 11 cases. Contaminated TIVAP were removed in 37 (77.1%) patients. TIVAP was removed from the outset in 29 patients, due to the isolation of *S. aureus* (n=5), *Candida sp* (n=4) or *P. aeruginosa* (n=3), to the presence of important local signs (n=10) or systemic signs (n=7), 2 [1-4] days after TIVAP-RI suspicion. The eight remaining devices were removed after the failure of the conservative treatment. The microbiological culture was positive for 23 of the 37 (62.2%) removed TIVAP. Two patients presented a severe complication of their TIVAP-RI: one had an endocarditis on aortic prosthetic valve due to *Staphylococcus epidermidis* that required surgical valve replacement, and one with TIVAP-RI due to *Candida albicans* had a mycotic aneurysm of the pulmonary artery that required urgent pneumonectomy for life-threatening hemoptysis.

3.2.3 Risk factors of TIVAP-RI

The multivariate analysis aiming to determine variables associated with TIVAP-RI identified the following factors: younger age (OR 0.67 [0.53–0.83] per 10-year increase, $P < 0.001$), WHO PS ≥ 1 (OR 3.24 [1.52–7.79], $P = 0.004$), antineoplastic chemotherapy in the month before TIVAP placement (OR 2.26 [1.17–4.26], $P = 0.012$), and radiation therapy of the chest wall homolateral to the site of TIVAP insertion (OR 3.28 [1.51–6.67], $p = 0.002$) (**Table 3**).

3.2.4 Influence of TIVAP-RI on patient prognosis

250 During the year following TIVAP insertion, 287 (28.3%) patients died, 155 days [70-244] days
251 after TIVAP insertion, among whom 266 (27.5%) patients without TIVAP-RI and 21 (43.8%)
252 patients with TIVAP-RI. No death occurred in the immediate aftermath of a TIVAP-RI.
253 After adjustment, variables associated with one-year mortality were: elevated WHO PS (OR
254 2.94 [1.87–4.74], 10.9 [6.13–19.7], 28.2 [10.9–84.0] for PS 1, 2 and ≥ 3 compared to PS 0
255 respectively, $P < 0.001$ for all); a digestive (OR 3.85 [2.03–7.56], $P < 0.001$), lung (OR 6.27
256 [3.26–12.5], $P < 0.001$), or gynecological (OR 2.21 [1.08–4.60], $P = 0.03$) cancer (compared to
257 breast cancer); a metastatic stage cancer (OR 2.06 [1.44–2.97], $P < 0.001$); and antineoplastic
258 chemotherapy administration in the month before TIVAP placement (OR 1.64 [1.07–2.49],
259 $P = 0.02$) (**Table 4**). TIVAP-related infection was not independently associated with one-year
260 mortality (OR 1.56 [0.75 - 3.19], $P = 0.22$).

4. DISCUSSION

Our results may be summarized as follows: i. in patients with solid tumors in whom a TIVAP was placed to administer antineoplastic chemotherapy, the incidence of TIVAP-RI was approximately 5%, with a large majority of late infections; ii. risk factors for TIVAP-RI were younger age, elevated WHO PS, antineoplastic chemotherapy administration in the month before TIVAP placement, and radiation therapy of the chest wall homolateral to the site of insertion; iii. TIVAP-RI was not associated with 1-year mortality.

4.1 Epidemiology of TIVAP-RI

The incidence of TIVAP-RI observed in our study is among the lowest reported in the literature [4–8]. The non-inclusion of some patients deemed at risk of TIVAP-RI, such as patients suffering from hematological malignancies or pediatric patients [15,19,28], not managed in our center, may have contributed to this low incidence. Nevertheless, our expert technical platform dedicated to TIVAP insertions, with trained practitioners using updated protocols, has also probably contributed to reducing TIVAP-RI incidence.

Several clinical and microbiological features of TIVAP-RI are similar between our study and others. Less than one-third of patients presented local infectious signs, as also reported by Vidal *et al.* [21]. The microbiological distribution was close to those previously reported, with Staphylococci and Gram-negative bacilli (GNB) representing each about 40% of the isolated micro-organisms, while yeasts accounted for less than 10% of cases in patients with solid tumor [9,21].

Despite effective systemic and/or lock antimicrobial therapies, conservative treatment was successful in only 58% of cases. This underlines the imperfect effectiveness of conservative treatment, even if a lock therapy was used. TIVAP-RI due to *S. aureus* and yeasts remain formal indications for systematic device removal, while it is still debated for *P. aeruginosa* [26,29]. In

other cases, while conservative treatment may be chosen as first line strategy, in particular in patients without significant systemic repercussion, it involves close patient monitoring and case-by-case discussion on the benefit-risk balance of TIVAP maintenance.

4.2 Risk factors of TIVAP-RI

Four factors were independently associated with TIVAP-RI in our study. Younger age was associated with a 30% increased risk for each decade less. An increased incidence in young adult patients has been previously reported [8,14], but without determining the specific effect of young age and type of cancer (*i.e.* hematological malignancy or solid tumor). Thus, our study is the first to report an association of young age with TIVAP-RI in patients with solid tumors. This may be explained by a particular sensitivity of young patients to TIVAP-RI and/or by confounding factors such as the use of more aggressive antineoplastic chemotherapy regimens than in an elderly population.

Impaired general condition was also associated with TIVAP-RI, assessed by the WHO PS in this study or the Karnofsky index in others [30]. This may be explained by factors such as cancer progression or undernutrition, which impact both patient's health and immune status, thereby increasing the risk of infection [30]. Impaired health condition also leads to more frequent hospitalizations, exposing to TIVAP healthcare-associated infections [6,7].

Administration of antineoplastic chemotherapy in the month before TIVAP placement was associated with a doubling of the risk of TIVAP-RI. As neutropenia below 1000/mm³ was a contraindication for TIVAP placement, another mechanism of antineoplastic chemotherapy-induced immunosuppression is probably involved. To our knowledge, this is the first report of this risk factor. Interestingly, it is a modifiable risk factor. Indeed, in the majority of cases, TIVAP placement may be planned before the first dose of antineoplastic chemotherapy, to avoid its initiation via a peripheral venous access.

Finally, radiation therapy of the chest wall homolateral to the site of insertion was associated with TIVAP-RI. TIVAP placement in an area that has been or will be irradiated is discouraged by French guidelines [2]. However, this recommendation was not supported by clinical data, even if it is known that radiotherapy weakens the skin barrier [31] and impairs wound healing [32]. Our results provide new evidence that reinforces the recommendations.

Conversely to previous reports [11,15], a large number of vein punctures or an early re-intervention on the TIVAP were not associated with infection. The improved technical skills of the professionals operating on our TIVAP-dedicated platform and systematic ultrasound guidance for venipuncture probably contributed to lower the infectious risk related to the insertion procedure. Similarly, TIVAP use within the first week after its placement was not associated with infection, whereas it has been reported that incomplete wound healing when the Huber needle is inserted into the chamber favors infection [28,33]. This is probably explained by the fact that if the TIVAP was intended to be used in the first days after insertion, the Huber needle was sterilely inserted by the operator at the end of procedure avoiding further manipulations.

4.3 Prognostic impact of TIVAP-RI

To our knowledge, no study has specifically evaluated the influence of TIVAP-RI on long-term mortality. Some studies reported three-month and one-year mortality after TIVAP-RI as high as 45% and 54% [9,21], but without assessing the specific effect of the infection of the device. At first glance, one-year mortality of patients with TIVAP-RI appeared to be higher than that of their counterparts in our cohort (44% vs. 27.5%). However, after adjustment for variables affecting the mortality of cancer patients, TIVAP-RI was not associated with poor prognosis. Hence, TIVAP-RI may be more a marker of frailty than a factor contributing in itself to death.

4.4 Limitations

First, due to the observational design and despite the use of multivariate analyses to control confounders, residual confounding factors cannot be ruled out. Second, even if it is reassuring to show that we reported epidemiological and microbiological features in agreement with previous studies, it can be argued that the monocentric design limits the external validity of our study. We acknowledge that our findings are only generalizable to adult patients suffering from solid tumors. Third, the number of patients having presented a TIVAP-RI may appear as relatively low. However, it is pleasing to note that this number was observed during the follow-up of more than 1000 patients over one year, which constitutes one of the largest available cohorts [9]. Although this limited the number of factors that could be included in the risk factor analysis, the large size of the whole cohort allowed a comprehensive number of variables to be included in the prognostic analysis. Finally, we acknowledge that we were unable to collect all the elements that have already been described as risk factors for TIVAP-RI, such as the administration of parenteral nutrition or blood products via the device, as this would have required to check every daily hospital and outpatient prescriptions for the entire cohort.

5. CONCLUSION

TIVAP insertion in adult patients with solid tumors was associated with a 5% infection rate, that did not influence one-year mortality. We confirmed that young age and impaired health status represent risk factors of TIVAP-RI, as well as two new avoidable situations: TIVAP insertion in the month following the initiation of the antineoplastic chemotherapy and in an area that has been or is planned to be irradiated.

Accepted manuscript

357 **STATEMENTS AND DECLARATIONS**

358 **Funding**

359 This study has not been funded by any external source.

360

361 **Competing interests**

362 The authors have no relevant financial or non-financial interests to disclose.

363

364 **Data availability**

365 Data are available from the corresponding author upon reasonable request.

366

367 **Acknowledgments**

368 The authors acknowledge all the physicians from the referring departments for their help in
369 filling in the missing data.

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Accepted manuscript

479 **Table 1.** Demographic and clinical characteristics of the included population

Characteristics	All TIVAP (<i>n</i> = 1014)	No TIVAP- related infection (<i>n</i> = 966)	TIVAP-related infection (<i>n</i> = 48)	P value
Demographics				
Age, years	63 [52–71]	63 [53–71]	56 [46–64]	< 0.001
Female sex, <i>n</i> (%)	618 (60.9%)	591 (61.2%)	27 (56.3%)	0.55
Body Mass Index, <i>kg/m</i> ²	24.2 [21.2–27.8]	24.2 [21.2–27.8]	23.6 [20.4–26.5]	0.51
Ambulatory care, <i>n</i> (%)	823 (81.2%)	791 (81.9%)	32 (66.7%)	0.05
WHO PS ≥ 1, <i>n</i> (%)	651 (64.2%)	611 (63.3%)	40 (83.3%)	0.005
0	363 (35.8%)	355 (36.7%)	8 (16.7%)	-
1	491 (48.4%)	463 (47.9%)	28 (58.3%)	-
2	120 (11.8%)	111 (11.5%)	9 (18.8%)	-
3	37 (3.6%)	34 (3.5%)	3 (6.3%)	-
4	3 (0.3%)	3 (0.3%)	0 (0%)	-
Diabetes, <i>n</i> (%)	111 (10.9%)	106 (11.0%)	5 (10.4%)	0.99
HIV infection, <i>n</i> (%)	13 (1.3%)	12 (1.2%)	1 (2.1%)	0.47
including AIDS stage, <i>n</i> (%)	3 (0.3%)	2 (0.2%)	1 (2.1%)	-
Tumor characteristics, <i>n</i> (%)				
Cancer location				
Breast	276 (27.2%)	267 (27.6%)	9 (18.8%)	0.12
Digestive tract	224 (22.1%)	217 (22.5%)	7 (14.6%)	
Lung	223 (22.0%)	207 (21.4%)	16 (33.3%)	
Gynecological (pelvic)	119 (11.7%)	115 (11.9%)	4 (8.3%)	
Other	172 (17.0%)	167 (17.3%)	5 (10.4%)	
Metastatic tumor	519 (51.2%)	492 (50.9%)	27 (56.3%)	0.55
Antineoplastic chemotherapy in the month prior to TIVAP insertion	191 (18.8%)	174 (18.0%)	17 (35.4%)	0.007
Radiotherapy of the chest wall homolateral to the device	98 (9.7%)	87 (9.0%)	11 (22.9%)	0.004
Insertion technical features, <i>n</i> (%)				
Insertion by an anesthesiologist	399 (39.3%)	377 (39.0%)	22 (45.8%)	0.37
Presence of at least 1 risk factors for difficult insertion ^a	89 (8.8%)	87 (9.0%)	2 (4.2%)	0.43
More than 2 venipunctures	40 (3.9%)	38 (3.9%)	2 (4.2%)	0.71

Site of insertion				
Internal jugular vein	598 (59.0%)	564 (58.4%)	34 (70.8%)	0.24
Jugulo-subclavian junction	319 (31.5%)	310 (32.1%)	9 (18.8%)	
Subclavian vein	91 (9.0%)	86 (8.9%)	5 (10.4%)	
Femoral vein	5 (0.5%)	5 (0.5%)	0 (0%)	
External jugular vein	1 (0.1%)	1 (0.1%)	0 (0%)	0.85
Insertion on the right side	814 (80.3%)	776 (80.3%)	38 (79.2%)	
Early re-intervention ^b	37 (3.6%)	36 (3.7%)	1 (2.1%)	0.99
Wound closure of the chamber pocket				
with biological glue	584 (57.6%)	557 (57.7%)	27 (56.3%)	0.88
with surgical strips	430 (42.4%)	409 (42.3%)	21 (43.8%)	
use of intradermal overlock	138 (13.6%)	124 (12.8%)	14 (29.2%)	0.004
Huber needle placed at the end of the procedure	151 (14.9%)	140 (14.5%)	11 (22.9%)	0.14
Time to use less than 8 days	559 (55.1%)	528 (54.7%)	31 (64.6%)	0.18
Biological data at TIVAP insertion				
Prothrombin time, %	98 [88–100]	98 [88–100]	94 [84–100]	0.22
Platelets, G/L	282 [223–354]	279 [223–352]	292 [229–387]	0.34
Leukocytes, G/L	7.3 [5.7–9.6]	7.3 [5.7–9.4]	8.0 [6.4–12.0]	0.07

WHO: World Human Organization; PS: performance status; HIV: Human Immunodeficiency Virus; AIDS: Acquired Immuno-Deficiency Syndrome

^a risk factors for difficult TIVAP insertion: cervical pathology, small size of the vein, other medical device already implanted in upper cave territory, situs inversus, subcutaneous emphysema.

^b early reintervention was defined as reintervention within 48h of TIVAP insertion due to malposition of the catheter or malfunction of the chamber.

Table 2. Clinical, microbiological and therapeutic characteristics of patients with TIVAP-related infections.

Characteristics	TIVAP-related infection (n = 48)
Clinical	
Presence of local signs, n (%)	11 (22.9%)
Early infections ^a , n (%)	7 (14.6%)
Need for intensive care unit admission, n (%)	2 (4.2%)
Deceased < 1 year after implantation, n (%)	21 (44%)
Microbiological, n (%)	
Isolated micro-organisms ^b	
Gram positive cocci, n (%)	26 (51%)
<i>Coagulase negative Staphylococci</i> ^c	19
<i>Staphylococcus aureus</i>	5
<i>Enterococcus faecalis</i>	1
<i>Enterococcus faecium</i>	1
Gram negative bacilli, n (%)	21 (41%)
<i>Enterobacteriaceae</i> ^d	12
<i>Pseudomonas aeruginosa</i>	4
<i>Stenotrophomonas maltophilia</i>	4
<i>Acinetobacter baumannii</i>	1
Yeasts, n (%)	4 (8%)
<i>Candida albicans</i>	2
<i>Candida parapsilosis</i>	1
<i>Candida glabrata</i>	1
Polymicrobial infection	3 (6.3%)
Multidrug resistant bacteria, n (%)	
Methicillin-resistant coagulase negative <i>Staphylococci</i>	11/19 (57.9%)
Methicillin-resistant <i>Staphylococcus aureus</i>	0/5 (0%)
ESBL-producing <i>Enterobacteriaceae</i>	5/12 (41.7%)
Positive culture of the TIVAP ^e	23 (62.2%)
Therapeutic management	
Antimicrobial therapy, n (%)	45 (93.8%)
Initiation of an empirical therapy	27 (56.3%)
among which effective empirical therapy	22 (81.5%)
Definite therapy adapted to the antibiogram from the outset	18 (37.5%)
No systemic antimicrobial therapy	3 (6.3%)

Duration of definite systemic anti-microbial therapy, <i>days</i>	11 [7–15]
Use of an antimicrobial lock, <i>n (%)</i>	19 (39.6%)
among which effective lock therapy	18 (94.7%)
TIVAP removal, <i>n (%)</i>	37 (77.1%)
Time from diagnosis to TIVAP removal, <i>days</i>	2 [1–4]

ESBL: Extended Spectrum Beta-Lactamase, TIVAP: totally implantable venous access port.

^a < 1 month following TIVAP insertion

^b n=51; 3 infections were due to 2 micro-organisms

^c including *S. epidermidis* (n=12), *S. haemolyticus* (n=2), *S. hominis* (n=1), *S. schleiferi* (n=1) and *S. capitis* (n=1)

^d including *K. pneumoniae* (n=5), *E. cloacae* (n=3), *E. coli* (n=2), *E. aerogenes* (n=1) and *S. marcescens* (n=1)

^e among the 37 devices removed

483 **Table 3.** Factors associated with a TIVAP-related infection in multivariate analysis

484

Factor	Odds ratio	95% Confidence Interval	P value
Age, <i>per ten years</i>	0.67	0.53–0.83	<0.001
WHO Performance Status ≥ 1	3.24	1.52–7.79	0.004
Antineoplastic chemotherapy during the month before TIVAP insertion	2.26	1.17–4.26	0.012
Previous radiation therapy of the chest wall homolateral to the site of TIVAP insertion	3.28	1.51–6.67	0.002
Number of punctures > 2	1.23	0.19–4.50	0.78
Time to use ≤ 7 days	1.48	0.80–2.81	0.22
Need for early re-intervention	0.47	0.03–2.37	0.47

485 **Table 4.** Factors associated with mortality 1-year after TIVAP insertion in multivariate analysis

Factors	Odds ratio	95% Confidence Interval	P value
Age, <i>per ten years</i>	1.08	0.94–1.24	0.27
Female sex	1.09	0.73–1.61	0.68
Antineoplastic chemotherapy during the month before TIVAP insertion	1.64	1.07–2.49	0.02
BMI < 18,5 kg/m ²	1.13	0.63–2.02	0.67
WHO Performance Status (PS)			
WHO PS 0	1 (<i>ref</i>)		
WHO PS 1	2.94	1.87–4.74	< 0.001
WHO PS 2	10.9	6.13–19.7	< 0.001
WHO PS ≥ 3	28.2	10.9–84.0	< 0.001
Diabetes	0.95	0.56–1.59	0.84
Cancer location			
Breast	1 (<i>ref</i>)		
Digestive	3.85	2.03–7.56	< 0.001
Lung	6.27	3.26–12.5	< 0.001
Gynecological (pelvic)	2.21	1.08–4.60	0.03
Others	3.35	1.66–6.91	< 0.001
Metastasis stage	2.06	1.44–2.97	< 0.001
Need for early re-intervention on the TIVAP	1.66	0.67–3.93	0.26
Time to use ≤ 7 days	1.03	0.73–1.44	0.88
TIVAP-related infection	1.56	0.75–3.19	0.22

486

487 **FIGURE CAPTION**

488 **Fig. 1** Flow chart for cohort recruitment including details on inclusion and non-inclusion
489 criteria and TIVAP-related infections

