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

3

4 Amaury Bailleul, MD<sup>1</sup> ; Jean-Pierre Fulgencio, MD, PhD<sup>1</sup>; Sophie Vimont, PharmD, PhD<sup>2,3</sup> ;  
5 Cécile Mordelet, anesthetic nurse<sup>1</sup> ; Benoit Ray, anesthetic nurse<sup>1</sup> ; Ludovic Lassel, MD<sup>4</sup> ;  
6 Nathanaël Lapidus, MD, PhD<sup>5</sup> ; Christophe Quesnel, MD, PhD<sup>1</sup> ; and Marc Garnier, MD,  
7 PhD<sup>1,6,\*</sup>.

8

9 <sup>1</sup> Sorbonne Université, AP-HP, GRC29, DMU DREAM, Hôpital Tenon, Service d'Anesthésie-  
10 Réanimation et Médecine Périopératoire – 4 rue de la Chine, 75020 Paris, France

11 <sup>2</sup> Département de Bactériologie, Hôpital Saint-Antoine, AP-HP, Sorbonne Université, - 184 rue  
12 du Faubourg Saint-Antoine, 75012 Paris, France

13 <sup>3</sup> Sorbonne Université, INSERM UMR S\_1155, Hôpital Tenon, Paris, France

14 <sup>4</sup> Sorbonne Université, AP-HP, DMU 3ID, Hôpital Tenon, Service des Maladies Infectieuses  
15 et Tropicales – 4 rue de la Chine, 75020 Paris, France

<sup>5</sup> Sorbonne Université, Inserm, Institut Pierre Louis d'Epidémiologie et de Santé Publique, AP-  
HP, Saint-Antoine Hospital, Public Health Department, 75012, Paris, France

16 <sup>6</sup> Université Clermont-Auvergne, CHU de Clermont-Ferrand, Service d'Anesthésie-  
17 Réanimation et Médecine Périopératoire, 58 rue Montalembert, 63000 Clermont-Ferrand,  
18 France

19

20 \* Corresponding author:

21 Dr Marc Garnier

22 Postal address: CHU de Clermont-Ferrand, Service d'Anesthésie-Réanimation et Médecine  
23 Périopératoire, 58 rue Montalembert, 63000 Clermont-Ferrand, France

24 Email: mgarnier@chu-clermontferrand.fr

25 Phone: +33 (0) 473751590

26 ORCID: 0000-0002-5716-4239

27

28 **Authors' contributions**

29 All authors contributed to the study conception and design. Data collection was performed by  
30 A. Bailleul, JP Fulgencio and S. Vimont. Data interpretation and analysis was performed by A.  
31 Bailleul, M. Garnier et N. Lapidus. The first draft of the manuscript was written by A. Bailleul  
32 and M. Garnier. Review and editing of the manuscript were performed by M. Garnier. All  
33 authors commented on previous versions of the manuscript. All authors read and approved the  
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37

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38 **ABSTRACT**

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

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

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

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

60

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

62 Port

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63 **1. INTRODUCTION**

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

69 The implantation of TIVAP is accompanied by complications of varying severity. The most  
70 frequent complication is TIVAP-related infection (TIVAP-RI), associated with over-morbidity  
71 and mortality [3]. Its incidence rate has been estimated between 0.02 and 0.35 infections/1000  
72 catheter-days, corresponding to the contamination of 2% to 14% of all TIVAP inserted [4–9].  
73 This wide range is explained by the heterogeneity of the populations studied (*e.g.* adult *vs.*  
74 pediatric patients, hematological malignancies *vs.* non-cancer patients, etc.), the diagnostic  
75 criteria of infection used (*i.e.* clinically suspected *vs.* blood culture documented *vs.* port culture  
76 proven infection), and the length of patient follow-up [10]. Nevertheless, TIVAP-RI rates seem  
77 stable over the last 20 years [11–13]. To date, risk factors for TIVAP-RI have been primarily  
78 assessed in retrospective studies, which included patients in whom the TIVAP was inserted  
79 before the 2010's [6,8,14–19]. The most commonly reported risk factors are hematological  
80 malignancies, late-stage cancer and younger age [11], which are non-modifiable risk factors.  
81 However, some technical advances and updated hygiene rules, such as systematic location of  
82 the vein by ultrasound and skin antiseptics with 2% chlorhexidine in alcohol, have recently  
83 changed insertion procedures [20]. Finally, while the outcome of patients who experienced a  
84 TIVAP-RI appeared unfavorable [9,21], the specific effect of TIVAP-RI comparatively to other  
85 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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89 **2. MATERIAL AND METHODS**

90 **2.1 Study design**

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

96

97 **2.2 Ethics**

98 This study was approved by the French society of anesthesiology and critical care medicine  
99 ethics committee (CERAR - IRB #00010254-2020-194), and performed in accordance with the  
100 1964 Helsinki declaration and its later amendments. Due to the non-interventional design of the  
101 study, patients' written consent was waived by the ethical committee [22]. Thus, written  
102 information was delivered to patients before TIVAP placement.

103

104 **2.3 Patients**

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



114

## 115 **2.4 Technical procedures**

116 TIVAP were all inserted in our dedicated technical platform. The healthcare professional team  
117 was composed of 3 anesthesiologists and 2 anesthetic nurses specifically trained in TIVAP  
118 placement. Only the percutaneous technique was used. The preferred site of catheterization was  
119 the right internal jugular vein. All the practitioners used a common protocol that followed the  
120 most recent national guidelines [23], including notably systematically ultrasound-guided vein  
121 puncture (Mindray TE7, 11 MHz linear probe), use of sterile gown, and skin antisepsis with  
122 2% chlorhexidine in alcohol. The correct position of the catheter was confirmed with an image  
123 intensifier during the procedure. Two types of TIVAP were sequentially implanted in  
124 accordance with public market rules, both composed of a silicone catheter connected to a  
125 titanium/polyoxymethylene chamber with a silicone membrane (Heliosite<sup>®</sup>, Vygon SAS,  
126 Ecoen, France; Polysite<sup>®</sup>, Perouse Médical, Ivry, France). If the device was intended to be  
127 used within the first 48 hours after insertion, a Huber needle was sterilely inserted by the  
128 operator at the end of the procedure; conversely, a healing time of at least 7 days was  
129 recommended before use.

130

## 131 **2.5 Microbiology**

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

139 TIVAP. 1 mL of sterile water was injected in the port on one hand, and in the catheter on the  
140 other hand, vortexed and 100 µL of both rinsing fluids were inoculated on horse blood agar  
141 plates, and incubated at 37°C for 48h. Positivity threshold was 10<sup>3</sup> cfu/mL [25].

142

## 143 2.6 Definition of TIVAP-related infection

144 In our center, all patients with suspected TIVAP-RI are referred to us either directly to the  
145 TIVAP platform or after a consultation with the attending oncologist. To ensure that no  
146 infection was missed, the notion of a TIVAP-RI was checked in patients' computerized medical  
147 records, which includes the microbiological results, one year after insertion. Definition of  
148 definite TIVAP-RI was adapted from the Infectious Diseases Society of America guidelines  
149 [26], as one of the following conditions:

150 - The presence of local signs of infection (inflammation or purulence of the tunnel or the  
151 pocket), associated with a positive culture of the TIVAP;  
152 - Or the presence of a bacteremia or fungemia without any apparent source for bloodstream  
153 infection apart from the TIVAP, associated with at least one of the following criteria:

- 154 i. The same micro-organism is isolated from a peripheral blood sample and the culture of the  
155 TIVAP;  
156 ii. Differential time to positivity: growth of the same micro-organism(s) (except *S. aureus*  
157 and *Candida* for which differential time to positivity is not validated) in a culture of blood  
158 obtained through a TIVAP is detected by an automated blood culture system at least 2h  
159 earlier than a culture of simultaneously drawn peripheral blood of equal volume;  
160 iii. Positive culture of the catheter or port, with partial or total regression of general infectious  
161 signs within 48 hours of TIVAP removal.

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

165

## 166 **2.7 Data collection** (*see the additional method file for detailed list of data collected*)

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

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

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

180

## 181 **2.8 Statistical Analysis**

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

187 covariates deemed clinically relevant were included in the model without univariate screening  
188 [27]: age, World Health Organization (WHO) Performance Status (PS), antineoplastic  
189 chemotherapy received in the month before TIVAP placement, radiotherapy of the chest wall  
190 homolateral to the site of TIVAP insertion, difficult insertion assessed by the need for more  
191 than 2 venipunctures, use of the new TIVAP within the first week of insertion, and need for an  
192 early re-intervention. The same approach was used to identify factors associated with 1-year  
193 mortality, including the following variables into the model: age, sex, body mass index (BMI),  
194 WHO PS, diabetes, location of the tumor, metastatic stage of the tumor, antineoplastic  
195 chemotherapy received in the month before TIVAP placement, TIVAP-RI, use of the new  
196 TIVAP within the first week of insertion, and need for an early re-intervention. Results of the  
197 multivariate models are reported as odds ratios (OR) with their 95% confidence intervals (95%  
198 CI). All tests were two-tailed and p values below 0.05 were considered significant. Statistical  
199 analysis was performed using R version 4.0.3 (R foundation for statistical computing, Vienna,  
200 Austria).

201 **3. RESULTS**

202 **3.1 Inclusions and patients' characteristics**

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

206 The demographic characteristics of the patients included are summarized in **Table 1**. Briefly,  
207 618 (60.9%) patients were women. TIVAP were inserted in an ambulatory setting in 823  
208 (81.2%) patients. Patients suffered predominantly from breast tumors (n=276; 27.2%), followed  
209 by digestive and lung tumors (n=224 and 223, respectively; 22%). Five hundred and nineteen  
210 (51%) patients suffered from metastatic tumors. The internal jugular vein (n=598; 59%) and  
211 the jugulo-subclavian junction (n=319; 31.5%) were the two main sites of venipuncture (**Table**  
212 **1**). The time from TIVAP placement to first use was 7 [3-11] days.

213  
214 **3.2 TIVAP-related infections**

215 *3.2.1 Epidemiology*

216 Forty-eight (4.7%) patients presented a TIVAP-RI, 90 [40-226] days after insertion, among  
217 which seven were early infections. TIVAP-RI were diagnosed by the presence of local signs  
218 and positive culture of the TIVAP in 11 patients, bacteremia associated with differential time  
219 to positivity in 25 patients, and bacteremia with positive culture of the TIVAP followed by  
220 regression of infectious signs after its removal in 12 patients. Only 11 (22.9%) patients  
221 presented local signs of infection. Gram-positive cocci were predominantly isolated (n=26;  
222 50.9%), followed by Gram-negative bacilli (n=21; 41.2%), and *Candida* species (n=4; 7.8%)  
223 (**Table 2**). Three infections were due to two micro-organisms. Six out of the seven early  
224 TIVAP-RI were due to *Staphylococcus sp.*, including four *S. aureus*.

225

### 226 3.2.2 Therapeutic management

227 An empirical antimicrobial therapy was initiated in 27 (56.3%) patients, and was effective in  
228 22 (81.5%) out of these 27 cases. A definite antimicrobial therapy was initiated after the results  
229 of the antibiogram were available in 18 (37.5%) patients, while 3 (6.3%) patients did not receive  
230 systemic antibiotic. These three patients were treated by TIVAP removal and local care. An  
231 antibiotic lock was used in 19 (39.6%) patients, and was a success in 11 cases. Contaminated  
232 TIVAP were removed in 37 (77.1%) patients. TIVAP was removed from the outset in 29  
233 patients, due to the isolation of *S. aureus* (n=5), *Candida sp* (n=4) or *P. aeruginosa* (n=3), to  
234 the presence of important local signs (n=10) or systemic signs (n=7), 2 [1-4] days after TIVAP-  
235 RI suspicion. The eight remaining devices were removed after the failure of the conservative  
236 treatment. The microbiological culture was positive for 23 of the 37 (62.2%) removed TIVAP.  
237 Two patients presented a severe complication of their TIVAP-RI: one had an endocarditis on  
238 aortic prosthetic valve due to *Staphylococcus epidermidis* that required surgical valve  
239 replacement, and one with TIVAP-RI due to *Candida albicans* had a mycotic aneurysm of the  
240 pulmonary artery that required urgent pneumonectomy for life-threatening hemoptysis.

241

### 242 3.2.3 Risk factors of TIVAP-RI

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

248

### 249 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  $\geq 3$  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],  $P = 0.22$ ).

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261 **4. DISCUSSION**

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

268

269 **4.1 Epidemiology of TIVAP-RI**

270 The incidence of TIVAP-RI observed in our study is among the lowest reported in the literature  
271 [4–8]. The non-inclusion of some patients deemed at risk of TIVAP-RI, such as patients  
272 suffering from hematological malignancies or pediatric patients [15,19,28], not managed in our  
273 center, may have contributed to this low incidence. Nevertheless, our expert technical platform  
274 dedicated to TIVAP insertions, with trained practitioners using updated protocols, has also  
275 probably contributed to reducing TIVAP-RI incidence.

276 Several clinical and microbiological features of TIVAP-RI are similar between our study and  
277 others. Less than one-third of patients presented local infectious signs, as also reported by Vidal  
278 *et al.* [21]. The microbiological distribution was close to those previously reported, with  
279 Staphylococci and Gram-negative bacilli (GNB) representing each about 40% of the isolated  
280 micro-organisms, while yeasts accounted for less than 10% of cases in patients with solid tumor  
281 [9,21].

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



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

289

#### 290 **4.2 Risk factors of TIVAP-RI**

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

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

304 Administration of antineoplastic chemotherapy in the month before TIVAP placement was  
305 associated with a doubling of the risk of TIVAP-RI. As neutropenia below 1000/mm<sup>3</sup> was a  
306 contraindication for TIVAP placement, another mechanism of antineoplastic chemotherapy-  
307 induced immunosuppression is probably involved. To our knowledge, this is the first report of  
308 this risk factor. Interestingly, it is a modifiable risk factor. Indeed, in the majority of cases,  
309 TIVAP placement may be planned before the first dose of antineoplastic chemotherapy, to  
310 avoid its initiation via a peripheral venous access.

311 Finally, radiation therapy of the chest wall homolateral to the site of insertion was associated  
312 with TIVAP-RI. TIVAP placement in an area that has been or will be irradiated is discouraged  
313 by French guidelines [2]. However, this recommendation was not supported by clinical data,  
314 even if it is known that radiotherapy weakens the skin barrier [31] and impairs wound healing  
315 [32]. Our results provide new evidence that reinforces the recommendations.

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

326

### 327 **4.3 Prognostic impact of TIVAP-RI**

328 To our knowledge, no study has specifically evaluated the influence of TIVAP-RI on long-term  
329 mortality. Some studies reported three-month and one-year mortality after TIVAP-RI as high  
330 as 45% and 54% [9,21], but without assessing the specific effect of the infection of the device.

331 At first glance, one-year mortality of patients with TIVAP-RI appeared to be higher than that  
332 of their counterparts in our cohort (44% vs. 27.5%). However, after adjustment for variables  
333 affecting the mortality of cancer patients, TIVAP-RI was not associated with poor prognosis.  
334 Hence, TIVAP-RI may be more a marker of frailty than a factor contributing in itself to death.

335

336 **4.4 Limitations**

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

351 **5. CONCLUSION**

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

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361 **Competing interests**

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363

364 **Data availability**

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

366

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

Characteristics	All TIVAP (n = 1014)	No TIVAP- related infection (n = 966)	TIVAP-related infection (n = 48)	P value
<b>Demographics</b>				
Age, years	63 [52–71]	63 [53–71]	56 [46–64]	< 0.001
Female sex, n (%)	618 (60.9%)	591 (61.2%)	27 (56.3%)	0.55
Body Mass Index, kg/m <sup>2</sup>	24.2 [21.2–27.8]	24.2 [21.2–27.8]	23.6 [20.4–26.5]	0.51
Ambulatory care, n (%)	823 (81.2%)	791 (81.9%)	32 (66.7%)	0.05
WHO PS ≥ 1, n (%)	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, n (%)	111 (10.9%)	106 (11.0%)	5 (10.4%)	0.99
HIV infection, n (%)	13 (1.3%)	12 (1.2%)	1 (2.1%)	0.47
including AIDS stage, n (%)	3 (0.3%)	2 (0.2%)	1 (2.1%)	-
<b>Tumor characteristics, n (%)</b>				
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
<b>Insertion technical features, n (%)</b>				
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 <sup>a</sup>	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%)	
Jugulo-subclavian junction	319 (31.5%)	310 (32.1%)	9 (18.8%)	
Subclavian vein	91 (9.0%)	86 (8.9%)	5 (10.4%)	0.24
Femoral vein	5 (0.5%)	5 (0.5%)	0 (0%)	
External jugular vein	1 (0.1%)	1 (0.1%)	0 (0%)	
Insertion on the right side	814 (80.3%)	776 (80.3%)	38 (79.2%)	0.85
Early re-intervention <sup>b</sup>	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
<b>Biological data at TIVAP insertion</b>				
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

<sup>a</sup> 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.

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

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

Characteristics	TIVAP-related infection (n = 48)
<b><i>Clinical</i></b>	
Presence of local signs, n (%)	11 (22.9%)
Early infections <sup>a</sup> , n (%)	7 (14.6%)
Need for intensive care unit admission, n (%)	2 (4.2%)
Deceased < 1 year after implantation, n (%)	21 (44%)
<b><i>Microbiological, n (%)</i></b>	
Isolated micro-organisms <sup>b</sup>	
Gram positive cocci, n (%)	26 (51%)
<i>Coagulase negative Staphylococci</i> <sup>c</sup>	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> <sup>d</sup>	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 <sup>e</sup>	23 (62.2%)
<b><i>Therapeutic management</i></b>	
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.*

<sup>a</sup> < 1 month following TIVAP insertion

<sup>b</sup> n=51; 3 infections were due to 2 micro-organisms

<sup>c</sup> including *S. epidermidis* (n=12), *S. haemolyticus* (n=2), *S. hominis* (n=1), *S. schleiferi* (n=1) and *S. capitis* (n=1)

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

<sup>e</sup> among the 37 devices removed

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

484

<b>Factor</b>	<b>Odds ratio</b>	<b>95% Confidence Interval</b>	<b>P value</b>
Age, <i>per ten years</i>	0.67	0.53–0.83	<0.001
WHO Performance Status $\geq 1$	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 $\leq 7$ days	1.48	0.80–2.81	0.22
Need for early re-intervention	0.47	0.03–2.37	0.47

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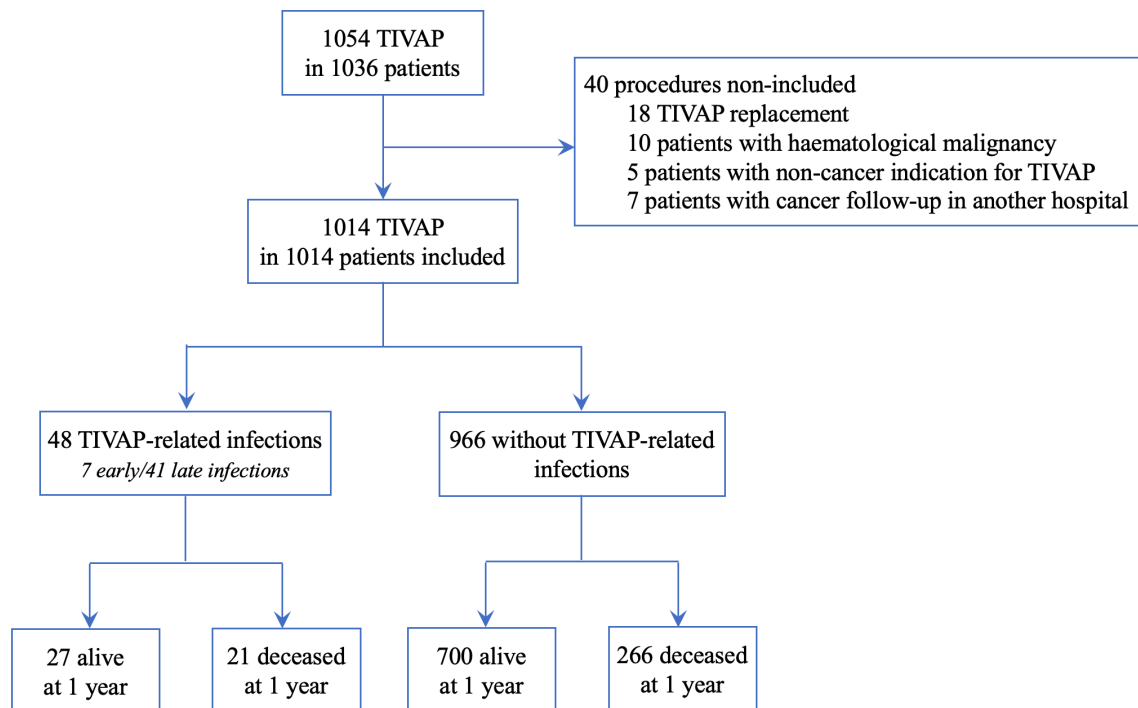
485 **Table 4.** Factors associated with mortality 1-year after TIVAP insertion in multivariate analysis

Factors	Odds ratio	95% Confidence Interval	P value
Age, per ten years	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 <sup>2</sup>	1.13	0.63–2.02	0.67
WHO Performance Status (PS)			
WHO PS 0	1 (ref)		
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 (ref)		
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



Accer