

Original research article



The effect of chemotherapy type and timing among the other factors on patency of totally implantable vascular access devices in colorectal carcinoma

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Abstract

Purpose: Catheter-related complications are observed in infusion of chemotherapy, and these were encountered with targeted therapies. Our principle is to study non-mechanical effects of type and initiation time of chemotherapy among the other factors on patency of totally implantable vascular access devices (TIVAD) inserted in patients with colorectal carcinoma.

Methods: This is a one-center retrospective cohort study. We analyzed TIVAD related complications in 624 patients with colorectal carcinoma. The patients were categorized by chemotherapy type (non-target-directed chemotherapy agents (Group A), bevacizumab (Group B), and cetuximab (Group C)). Additionally, we divided the patients into groups by the time interval between TIVAD insertion and chemotherapy initiation. According to our study, a 3-day period was optimal. Therefore, we named the groups as within 3 days and beyond 3 days, and called this process 3 days cut-off. Age, gender, jugular-subclavian access, platelet count, INR, the types of chemotherapy, and the initiation time of chemotherapy were investigated by survival tests. We compared chemotherapy type groups both one-by-one and combined into one group.

Results: The TIVADs were removed due to the complications in 11 patients of Group A, 6 patients of Group B, and 3 patients of Group C. Only chemotherapy type was significant (p=0.011) in Cox regression test. A clear difference (p=0.010) was detected between the catheter patency of Group A and combination of Groups B and C, because of skin necrosis and thrombosis. Within 3 days of their first chemotherapy day, an important difference between Group A and Group C (p=0.013) was observed in the TIVAD patency. The same observation was made between Group A and Group B (p=0.007). Beyond this period, no major difference was detected (p=0.341).

Conclusion: A major effect on catheter patency was detected by using the target-directed chemotherapy agent within 3 days, which should be considered in target-directed chemotherapy.

Keywords

Vascular access devices, radiology, neoplasms, bevacizumab, cetuximab, colorectal cancer

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Introduction

The use of TIVADs became standard practice. ^{1,2} Infusion chemotherapy may lead to TIVAD-related complications, which are increasing due to usage of targeted chemotherapy. ³ The most common complications are infection and thrombosis, ranging from 4% to 15%. ³ Molecular targeted therapies involve various monoclonal antibody agents; cetuximab (anti-EGFR: epidermal growth factor receptor) and bevacizumab (anti-VEGF: vascular endothelial growth factor). ^{3–5} Cetuximab therapy may increase the wound complication risk, due to its inhibition of epithelial cell proliferation and angiogenesis, which are requirements for normal wound repair. ⁴ Also, bevacizumab therapy may delay wound healing and predispose to bleeding. ⁵

The objectives of this study are to examine non-mechanical effects (venous thrombosis, catheter occlusion, infection, bleeding, and skin necrosis/wound infection) of chemotherapy type and timing among the other factors (age, gender, access method (jugular or subclavian), international normalized ratio (INR), and platelet count) on the patency of TIVAD (the primary outcome measure is unplanned TIVAD removal due to non-mechanical complications), using ultrasonography (US) and fluoroscopy guidance in colorectal carcinoma patients.

Patients and methods

Patients and TIVADs

Between 2009 and 2017, TIVADs were inserted in 624 colorectal carcinoma patients: 241 of them were female, 383 were male, with a mean age of 57.8 ± 11.3 (range; 20–84) years. Our study was designed as retrospective study.

All of the patients had malignancies with or without metastases. Age, gender, access method (jugular or subclavian), INR, platelet count, the types of chemotherapy given to patients (bevacizumab, cetuximab, and other chemotherapy agents), and the time interval of chemotherapy between TIVAD insertion and chemotherapy initiation were recorded in our database. In this study, we assessed the resectability of colorectal cancer after radiological and surgical consultations. Metastatic patients with resectable and unresectable primary tumor were administered nontarget and target metastatic chemotherapy, respectively. The patients with unresectable primary tumor underwent a multidisciplinary evaluation of their clinical and laboratory features, right or left side primary, previous therapy, molecular genetic analysis, and allergy. According to this judgment, we selected either bevacizumab or cetuximab in targeted chemotherapy.

All of the used TIVADs (7–8 French silicone catheters) were designed as single titanium chamber. Platelet count, INR were assessed. We corrected the deficiencies in case of coagulopathy. No antibiotic prophylaxis was

administered. The exclusion criteria were active infections, uncorrected coagulopathy (platelet $< 30 \times 10^{-3} \, \mu/L$, INR > 1.8), and lack of informed consent by the patient or his/her legal representative.

Procedure technique

The TIVADs were placed into jugular or subclavian under US and fluoroscopy guidance. If the chest had hair, it was clipped. The area of chest was sterilized with a solution containing povidone-iodine 10% with 70% ethyl alcohol. We waited until the skin was dry before inserting a needle. Sedation was given to uncooperative patients.

We performed the intervention by the same method described in a previous study. 6 Central venous access was performed with an 18 Gauge Seldinger needle, and guide wire was moved forward into the vena cava superior. Then, a subcutaneous pocket was opened using scalpel and clamps. The TIVAD was tunneled with a trocar and was flushed with diluted heparin (100 IU/mL) before insertion. The TIVAD chamber was not sutured to fascia. The catheter was moved into superior vena cava -right atrium junction, by using a peel away sheath. The tip position of the catheter was confirmed by fluoroscopy. The incision was closed with 3-0 vicryl subcutaneous suture. The skin was sutured with polypropylene stitches (we used silk suture in the first 2 years), also a control chest X-ray was specifically taken 2h after in case of pendulous breast. We used non-heparinized 0.9% NaCl solution after each treatment and every month thereafter.

Ethics, complications, and statistics

This study was approved by the Ethical Committee of our institution (decision number: 2015-02/146). Informed consent was obtained from each patient. Following approval of the hospital board, the data were obtained from records and the patients were categorized according to whether by their last follow-up visit or death. Follow up period was accepted as the time elapsed from TIVAD placement to its removal or the last follow-up of the patient or death.

Complications were described and managed according to the guideline. Early and late complications were defined as those occurring before and after 30 days, respectively. Only non-mechanical complications (venous thrombosis, catheter occlusion (excluding TIVAD flip-over, catheter fracture, migration, kinking, distortion, and displacement), infection, bleeding, and skin necrosis/wound infection) were taken into account in this study.

Some patients underwent unplanned TIVAD removal due to non-mechanical complications. We called this situation an "event." If there was no event, the patency time was considered equal to the survival period but censored. Patients were classified due to chemotherapy type groups

Table I.	Comparison of	demographic features o	f patients among the chemotherapy type groups.	

Characteristics	Total	Non-target-directed (Group A)	Bevacizumab (Group B)	Cetuximab (Group C)	p-Value (95% CI)
Age (years)	57.7 ± 11.3	57.7 ± 11.5	57.5 ± 10.7	59.0 ± 10.1	0.812
Gender					
Women	241 (38.4%)	194 (39.8%)	37 (34.9%)	10 (33.3%)	0.539
Male	383 (61.1%)	294 (60.2%)	69 (65.1%)	20 (66.7%)	
Access vein					
Jugular	587 (93.6%)	459 (94.1%)	98 (92.5%)	30 (100%)	0.303
Subclavian	37 (5.9%)	29 (5.9%)	8 (7.5%)	0 (0%)	
Platelet count $\times 10^{-3} \mu/L$	295.7 ± 106.7	297.5 ± 106.8	284.4 ± 109.9	306.5 ± 92.9	0.443
International normalized ratio (INR)	1.001 ± 0.124	$\textbf{0.994} \pm \textbf{0.123}$	1.021 ± 0.124	1.050 ± 0.131	0.012
Living status					
Death	13 (2.1%)	9 (1.8%)	4 (3.8%)	0 (0%)	0.323
Live	611 (97.9%)	479 (98.2%)	102 (96.2%)	30 (100%)	
The patency time (days)	444.2 ± 385.6	474.1 ± 409.4	356.5 ± 264.1	267.5 ± 225.9	0.001
, ,	(1-1787)	(1-1787)	(1-1412)	(8-882)	
Groups' numbers	624	488	106	30	

Note. Numbers are mean \pm 2SD; number (percent); mean \pm 2SD (minimum—maximum). In order to evaluate the distribution of groups, p-value was obtained from Chi-square analysis for non-parametric variables and from independent-samples T test for parametric ones. No significant difference in demographic data was found among chemotherapy type groups except for patency time.

as follows: non-target-directed chemotherapy (Group A), bevacizumab (Group B), and cetuximab (Group C). Three days cut-off was also taken into account during classification. This 3-day cut-off does not mean duration of the drug cycle, but it represents the period between TIVAD placement and chemotherapy start. Age, gender, jugular-subclavian access, platelet count $\times 10^{-3} \, \mu/L$, INR, the type of chemotherapy (which creates Group A, Group B, and Group C), and the time interval of chemotherapy (which creates chemotherapy timing groups) were examined as variables.

The demographic features of the patients, were categorized by their chemotherapy type groups and chemotherapy interval time groups, and were analyzed. In order to evaluate the distribution of these groups, the p values were obtained from Chi-square test for non-parametric variables and from independent-samples T test for parametric ones. Similarly, the complications of Groups A, B, and C were also investigated. The patency periods of the TIVADs were analyzed by both univariate Kaplan-Meier survival analysis and multivariable Cox regression test. Additionally, by using the former test with Log rank (Mantel-Cox) comparisons over strata (both pooled and pairwise), for each stratum, and pairwise for each stratum, survival analysis was performed for groups and combination of groups in the categorical variable. Depending on the results of for Kaplan-Meier survival analysis, we compared Groups A, B, and C both one-by-one and combined into one group. In addition, Groups A, B, and C were stratified by 3 days cut-off for this analysis. Significance was established when p value was less than 0.05 with 95% confidence interval.

Results

No periprocedural complication was observed. About 132 days after the procedure, a late complication was seen in a patient who had jugular access (a 69-year-old male with skin necrosis and infection, related to bevacizumab use). The TIVAD was removed, and replaced after 3 months.

Table 1 shows demographic features of patients included in the study, categorized by their chemotherapy type groups. The mean follow-up period was 444.2 ± 385.6 days (1–1787 days). A total of 624 patients were enrolled. About 488 patients were administered chemotherapy as non-target-directed agents (Group A), remaining 136 patients as target-directed agents (106 patients of Group B, 30 patients of Group C). The mean platelet count was $295.7 \pm 106.7 \times 10^{-3} \,\mu/L$ and INR was 1.001 ± 0.124 .

Table 2 shows demographic features of patients categorized by their chemotherapy time interval. The number of patients given chemotherapy beyond 3 days detected as 60 patients of Group A, 11 patients of Group B, and 5 patients of Group C. In total, there was 16 patients of Groups B and C, which represents the groups given the target-directed agents.

There was no difference in the dose, time, and regimen of the cytotoxic agents used between target-directed drugs. We clarified the details of the characteristics of patients (metastatic or adjuvant, first-line or second-line chemotherapy). Adjuvant chemotherapy was given to 460 (73.7%) patients of Group A. Metastatic chemotherapy was administered to a total of 164 (26.3%) patients: 28 (4.5%) patients of Group A, 106 (17.0%) patients of Group

Table 2.	Comparison of	f demographic features o	of patients bet	ween the chemoth	erapy timing groups.

Characteristics	Total	Within 3 days	Beyond 3 days	p-Value (95% CI)
Age (years)	57.7 ± 11.3	57.7 ± 11.4	57.6 ± 10.9	0.943
Gender				
Women	241 (38.4%)	207 (37.8%)	34 (44.7%)	0.243
Male	383 (61.1%)	341 (62.2%)	42 (55.3%)	
Access vein				
Jugular	587 (93.6%)	518 (94.5%)	69 (90.8%)	0.196
Subclavian	37 (5.9%)	30 (5.5%)	7 (9.2%)	
Platelet count $\times 10^{-3} \mu/L$	295.7 ± 106.7	296.0 ± 107.5	293.3 ± 101.1	0.836
International normalized ratio (INR)	1.001 ± 0.124	1.000 ± 0.122	1.013 ± 0.138	0.373
Living status				
Death	13 (2.1%)	12 (2.2%)	I (I.3%)	0.617
Live	611 (97.9%)	536 (97.8%)	75 (98.7%)	
The patency time (days)	444.2 ± 385.6 (1–1787)	451.4 ± 382.5 (1–1787)	392.2 ± 406.0 (13–1729)	0.234
Groups' numbers	624	548	76	

Numbers are mean \pm 2SD; number (percent); mean \pm 2SD (minimum–maximum). Total patency days were 277,154 of total, 247,344 of the time intervals within 3 days, and 29,810 of beyond 3 days. In order to evaluate the distribution of groups, p value was obtained from Chi-square analysis for non-parametric variables and from independent-samples T test for parametric ones. No significant difference in demographic data was found between chemotherapy timing groups.

Table 3. Comparison of non-mechanical complications leading to TIVAD removal among the chemotherapy type groups.

Complication n (%)	Total	Non-target-	Bevacizumab	Cetuximab	p-Value
Rates per 100 catheter days		directed (Group A)	(Group B)	(Group)	(95% CI)
Venous thrombosis	5 (25%)	4 (20%)	0	I (5%)	0.180
	0.0018	0.00172		0.01245	
Catheter occlusion	9 (45%)	5 (25%)	2 (10%)	2 (10%)	0.035
	0.00324	0.00216	0.00529	0.02491	
Bleeding	2 (10%)	2 (10%)	0	0	0.766
_	0.00072	0.00086			
Skin necrosis (one with infection)	4 (20%)	0	4 (20%)	0	< 0.001
,	0.00144		0.01058		
Groups' numbers	20 (100%)	11 (55%)	6 (30%)	3 (15%)	
TIVAD removal rate	0.00721	0.00475	0.01587	0.03737	

Note. Total catheter patency days: 277,154 in total, 231,335 in Group A, 37,793 in Group B, and 8026 in Group C. In order to evaluate the distribution of groups, p value was obtained from Chi-square analysis for non-parametric variables and from independent-samples T-test for parametric ones. No significant difference in complications was found between among chemotherapy type groups.

B, and 30 (4.8%) patients of Group C. In metastatic chemotherapy, first-line chemotherapy was given to 27 patients of Group A, 106 patients of Group B, and 30 patients of Group C, 163 patients in total. Second-line chemotherapy was given to only a patient of Group A.

The mean retention time of the TIVADs for adjuvant chemotherapy and metastatic chemotherapy was found to be $487.40~(\pm 414.355)$ days and $322.87~(\pm 254.439)$ days, respectively (p < 0.001). After TIVAD placement, an adjuvant chemotherapy was given to 410 (89.1%) patients within 3 days and 50 (10.9%) patients beyond 3 days. Also, metastatic chemotherapy was given to 138 (84.1%) patients within 3 days and 26 (15.9%) patients beyond 3 days. No significant difference was observed between

metastatic and adjuvant chemotherapy within and beyond 3 days (p=0.094 at Chi-square test).

Table 3 shows non-mechanical complications leading to TIVAD removal. The catheters were taken out in 11 patients of Group A, 6 patients of Group B, and 3 patients of Group C. The TIVAD removal rate was calculated to be 0.00721 per 100 TIVAD days. In particular, for Groups A, B, and C the rate was 0.00475, 0.01587, and 0.03737, respectively. Additionally, the rates in case of thrombosis, venous thrombosis, catheter occlusion, bleeding, and skin necrosis were 0.00505, 0.0018, 0.00324, 0.00072, and 0.00144, respectively. Specifically, in Group A, the rates in case of thrombosis, venous thrombosis, catheter occlusion, and bleeding were 0.003890, 0.00172, 0.00216, and

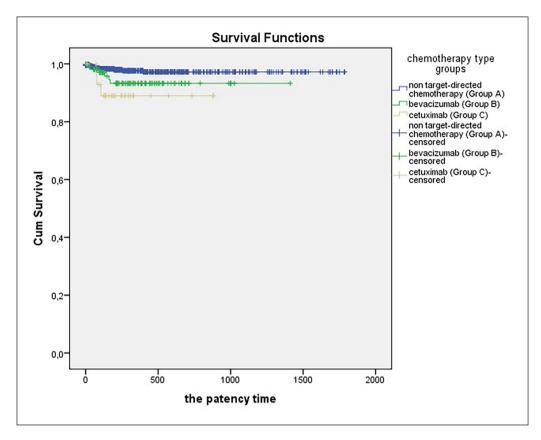


Figure 1. A clear difference (p = 0.013) in the TIVAD patency was detected among Groups A, B, and C. Test was pooled over strata.

0.00086, respectively. In Group B, the rates in case of thrombosis (only catheter occlusion) and skin necrosis were 0.00529 and 0.01058, respectively. In Group C, the rates in case of thrombosis, venous thrombosis, and catheter occlusion were 0.03737, 0.01245, and 0.02491, respectively.

The retention times of TIVADs were compared by univariate Kaplan-Meier survival analysis according to gender (p=0.578), access method (p=0.112), chemotherapy time interval (p=0.058), and chemotherapy type (p=0.013) (Figure 1). Furthermore, by using multivariable Cox regression test, we analyzed these parameters: age (p=0.599), gender (p=0.595), entry method (p=0.119), chemotherapy time interval (p=0.086), chemotherapy type (p=0.011), platelet count (p=0.729), and INR (p=0.228).

A clear difference (p=0.010) was detected between the catheter patency of Group A and combination of Groups B and C, because of skin necrosis and thrombosis. This difference was significant (p=0.002) within 3 days chemotherapy (Figure 2) whereas it was not the case beyond 3 days (p=0.894). Figure 3 describes that a significant difference in the catheter patency was observed within 3 days between Group A and Group C (p=0.013), also between Group A and Group B (p=0.007). Figure 4 demonstrates

that no major difference was detected beyond 3 days among Groups A, B, and C (p=0.341).

Discussion

The most common non-mechanical complications after implantation are thrombosis, catheter blockage, infection, and bleeding. ^{1–6} Moreover, catheter-related thrombosis is a serious complication (0.67%–5%).²

The catheter tip position was detected as the major reason for thrombosis. Other significant risk factors were gender and lung carcinoma.² The probability of thrombosis increased with carcinoma, chemotherapy, malposition of catheter tip in some series whereas Beckers et al.⁸ stated that risk factors were multiple placement attempts, ovarian cancer, and previous central venous catheter insertion. Nevertheless, Haggstrom et al.'s⁹ work explored rates of central venous catheter-related thrombosis in a general cancer population, observing increased rates in those with peripherally inserted central catheters or increased body mass index.

Recently, Nalluri et al.¹⁰ in their meta-analysis reported that bevacizumab increased the possibility of thromboembolism in carcinoma patients along with chemotherapy. Nevertheless, Scappaticci et al.¹¹ detected that the venous

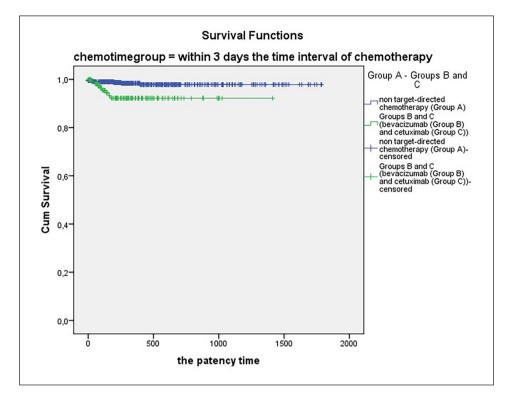


Figure 2. The difference in the TIVAD patency between Group A and a combination of Groups B and C was significant within 3 days (p=0.002). Strata was done within 3 days.

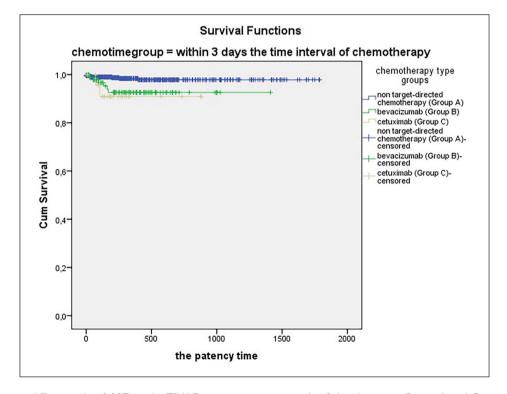


Figure 3. A major difference (p=0.007) in the TIVAD patency was seen within 3 days between Group A and Group C, and Group A and Group B. Within 3 days of their first chemotherapy day, an important difference between Group A and Group C (p=0.013) was observed in the TIVAD patency. The same observation was made between Group A and Group B (p=0.007). Strata in paired for each stratum was done within 3 days.

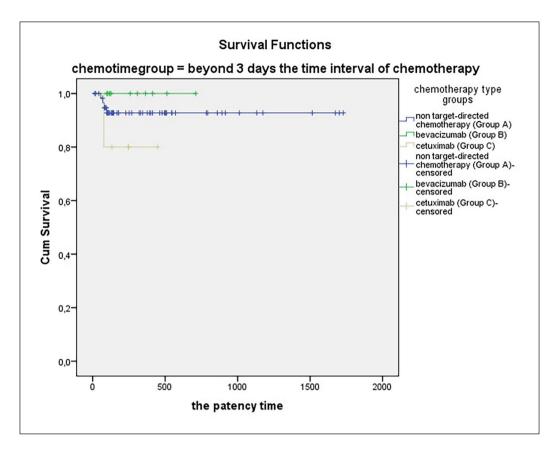


Figure 4. No major difference (p=0.341) in the TIVAD patency was seen among Group A, Group B, and Group C, according to chemotherapy initiation time beyond 3 days. The difference was not significant between Groups A and B (p=0.365), Groups A and C (p=0.313), and Groups B and C (p=0.138). Strata in paired for each stratum was done beyond 3 days.

thrombosis rate in metastatic cancer patients did not increase with the use of bevacizumab.

The infection rate varied from 2.6% to 9%.11 TIVAD pocket infection was reported to occur at a rate of 0.3% to 4.4%. 12 The series found that the TIVAD-related infection was significantly associated with advanced cancer stage, administration of palliative care immediately after implantation, and body surface area >1.71 m^{2.3,13,14} Blood product administration and parenteral nutrition were seen associated with early catheter-related infections. 13 Touré et al. 's 14 study highlighted that four risk factors (performance class, pancreatic carcinoma, parenteral nutrition management, and accumulative TIVAD procedures) were independently associated with infections. Although the risk of TIVAD infection was reportedly lower for subclavian vein access in some studies, there was not any significant difference between infections of jugular and subclavian access methods in a study.6

A rare catheter-related non-mechanical complication is necrosis of the skin.^{2,6} Wound dehiscence after TIVAD placement requires its removal.¹⁵ Target directed therapy may also lead to wound healing delay.^{3–5} The risk factor for wound healing complication related to bevacizumab

treatment is unidentified.¹⁶ It was reported that the absolute risk of wound dehiscence was 2.1% versus 0.5% when the TIVAD was placed during the previous week.⁵

It was found that the use of bevacizumab has affected the wound opening in Zawacki et al.'s¹⁵ and Kriegel et al.'s⁵ studies. The risk of wound opening increased with the use of chemotherapy within 10 days in Zawacki et al.'s¹⁵ study and within 7 days in Kriegel et al.'s⁵ study. On the other hand, Grenader et al.¹⁷ found that a TIVAD may safely be inserted a short time before or during bevacizumab treatment. Grenader et al.¹⁷ reported that bevacizumab therapy had no effect on the wound healing process whereas Erinjeri et al.¹⁸ reported that the risk of wound dehiscence was inversely proportional to the interval between bevacizumab administration and TIVAD placement, with significantly higher risk seen when the interval is less than 14 days.

Bleeding is another non-mechanical complication of TIVAD. Grenader et al.¹⁷ found that there were no instances of abnormal bleeding or infection in any of the patients during bevacizumab therapy. Biffi et al.¹⁹ stated that thromboprophylaxis had no significant effect on the risk of catheter-related thrombosis or bleeding. For this reason, we did not use any thromboprophylaxis for thrombosis or

bleeding in this study. We also think that thromboprophylaxis is not necessary for the placement of TIVAD.

Aseptic Non Touch Technique (ANTT) is necessary to decrease the TIVAD infection rate.²⁰ In order to use TIVAD in outpatient chemotherapy, double-checking must be performed, and the correct countermeasures must be taken.²¹ We followed these instructions, as well. In Shanghai expert consensus on TIVADs 2019: if there is no contraindication, it is recommended to routinely disinfect the skin with alcohol-containing disinfectants before the procedure.²² Povidone-iodine-ethanol, chlorhexidine-ethanol may be the best option at present. According to the Queensland GHD guideline²³, 2% alcoholic chlorhexidine or 10% povidone iodine with 70% alcohol is recommended to use for insertion site. We chose to use the latter for insertion site, and preferred the former for dressings.

In addition, we initially performed subclavian vein cannulation but mainly internal jugular vein under US-guidance. It is known that the US-guidance and confirmation of the catheter tip position by fluoroscopy reduce complications. 24 In our first 2 years, we performed subclavian vein cannulation, but we saw that it is more practical and less painful to use jugular vein access. Therefore, we used the latter method primarily, also we took into consideration the angle of the catheter which should be wider than 60° , as Kumar et al. 25 suggested.

Some studies^{1,26} have demonstrated that chemotherapy on the first day is safe, but this was not the case in target-directed therapy in our series.

Limitations of the study

This study has some restrictions. First, the series was retrospective and had heterogeneous distribution among the chemotherapy type groups (488 patients of Group A, 106 patients of Group B, and 30 patients of Group C). Second, the patients were not equally distributed between chemotherapy timing groups (548 within 3 days vs 76 beyond 3 days). Although these biases might have affected the study results, p values showed that no significant difference was found in demographic data between chemotherapy timing groups, and among chemotherapy type groups except for patency time. Third, although central venous access methods (jugular and subclavian) might have been an additional confounding factor, no significant difference was found in demographic data, complications, and patency between groups. There was no difference in univariate and multivariable survival analysis results. This observation shows that having two different cannulation methods does not affect the survival results. Moreover, this result is compatible with the literature. 6,26 Fourth, we chose to use heparinized 0.9% NaCl solution before insertion, but used 0.9% NaCl after each treatment and every month thereafter. In 2021, Wu et al.²⁷ suggested that there was no difference between 1/10 heparinized and non-heparinized NaCl solutions. Guidelines

for TIVAD recently prefer non-heparinized NaCl solution.^{22,23} Fifth, the cut-off period might be a questionable issue. According to our study, a 3-day period was optimal. This cut-off period was shorter than both 7 days cut-off in Krigel et al.'s5 and 10 days cut-off in Zawacki et al.'s15 studies. Erinjeri et al. reported that wound healing angiogenesis mediated by VEGF and produced by stimulated macrophages, takes place between 4 and 14 days. Therefore, VEGF inhibition by bevacizumab that could result in poor wound healing and dehiscence should be within the first 2 weeks. 18 Besides, new collagen fibers secreted by fibroblasts and myofibroblasts are present as early as 3 days after wounding, and myofibroblasts play a key role in wound contraction and healing.²⁸ To date, wound healing remains controversial. In the first 3 days, we think that target therapy can be harmful to wound healing. Therefore, the effect of the cut-off period length on catheter patency should be examined in prospective studies. Sixth, catheter occlusion, regardless of its cause, might be a mechanical complication. But we only accepted TIVAD flip-over, catheter fracture, migration, kinking, distortion, and displacement as mechanical complications. On the other hand, catheter tip thrombus deposition is caused by intravascular protein and cell deposition. Therefore, we considered it as a non-mechanical complication. This process begins almost immediately after catheter placement when albumin, lipoprotein, and fibrinogen create a protein sleeve around fresh intravascular catheters within 24h of placement.⁷

Conclusion

In the patients with colorectal carcinoma, we found that target-directed chemotherapy had a negative effect on the success of the TIVAD. While performing target-directed chemotherapy, a significant effect on TIVAD patency was seen by decreasing the period between TIVAD placement and chemotherapy start to 3 days. This period should be considered during target-directed chemotherapy.

Author's note

The corresponding author is affiliated to CIRSE.

Declaration of conflicting interests

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Ethical statement

Ankara Oncology Education and Research Hospital of Medicine Clinical Research Ethical Committee granted approval (decision number: 2015-02/146).

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References

- Ozdemir NY, Abali H, Oksüzoğlu B, et al. It appears to be safe to start chemotherapy on the day of implantation through subcutaneous venous port catheters in inpatient setting. Support Care Cancer 2009; 17: 399–403.
- 2. Caers J, Fontaine C, Vinh-Hung V, et al. Catheter tip position as a risk factor for thrombosis associated with the use of subcutaneous infusion ports. *Support Care Cancer* 2005; 13(5): 325–331.
- 3. Berardi R, Rinaldi S, Santini D, et al. Increased rates of local complication of central venous catheters in the targeted anticancer therapy era: a 2-year retrospective analysis. *Support Care Cancer* 2015; 23(5): 1295–1302.
- Dean NR, Sweeny L, Harari PM, et al. Wound healing following combined radiation and cetuximab therapy in head and neck cancer patients. *J Wound Care* 2011; 20: 166–170.
- Kriegel I, Cottu PH, Fourchotte V, et al. Wound healing and catheter thrombosis after implantable venous access device placement in 266 breast cancers treated with bevacizumab therapy. *Anticancer Drugs* 2011; 22: 1020–1023.
- Aribaş BK, Arda K, Aribaş Ö, et al. Comparison of subcutaneous central venous port via jugular and subclavian access in 347 patients at a single center. *Exp Ther Med* 2012; 4: 675–680.
- Walser EM. Venous access ports: indications, implantation technique, follow-up, and complications. *Cardiovasc Intervent Radiol* 2012; 35: 751–764.
- Beckers MM, Ruven HJ, Seldenrijk CA, et al. Risk of thrombosis and infections of central venous catheters and totally implanted access ports in patients treated for cancer. *Thromb Res* 2010; 125: 318–321.
- Haggstrom L, Parmar G and Brungs D. Central venous catheter thrombosis in cancer: a multi-centre retrospective study investigating risk factors and contemporary trends in management. Clin Med Insights Oncol 2020; 14: 1179554920953097.
- 10. Nalluri SR, Chu D, Keresztes R, et al. Risk of venous thromboembolism with the angiogenesis inhibitor bevacizumab in cancer patients: a meta-analysis. *JAMA* 2008; 300: 2277–2285.
- 11. Scappaticci FA, Skillings JR, Holden SN, et al. Arterial thromboembolic events in patients with metastatic carcinoma treated with chemotherapy and bevacizumab. *J Natl Cancer Inst* 2007; 99: 1232–1239.
- Cil BE, Canyiğit M, Peynircioğlu B, et al. Subcutaneous venous port implantation in adult patients: a single center experience. *Diagn Interv Radiol* 2006; 12: 93–98.
- 13. Chang YF, Lo AC, Tsai CH, et al. Higher complication risk of totally implantable venous access port systems in patients

- with advanced cancer a single institution retrospective analysis. *Palliat Med* 2013; 27: 185–191.
- Touré A, Vanhems P, Lombard-Bohas C, et al. Totally implantable central venous access port infections in patients with digestive cancer: incidence and risk factors. Am J Infect Control 2012; 40: 935–939.
- Zawacki WJ, Walker TG, DeVasher E, et al. Wound dehiscence or failure to heal following venous access port placement in patients receiving bevacizumab therapy. *J Vasc Interv Radiol* 2009; 20: 624–627.
- Scappaticci FA, Fehrenbacher L, Cartwright T, et al. Surgical wound healing complications in metastatic colorectal cancer patients treated with bevacizumab. *J Surg Oncol* 2005; 91: 173–180.
- Grenader T, Goldberg A, Verstandig A, et al. Indwelling central venous access port insertion during bevacizumabbased therapy. *Anticancer Drugs* 2010; 21(7): 704–707.
- Erinjeri JP, Fong AJ, Kemeny NE, et al. Timing of administration of bevacizumab chemotherapy affects wound healing after chest wall port placement. *Cancer* 2011; 117(6): 1296–1301.
- 19. Biffi R, Orsi F, Pozzi S, et al. Best choice of central venous insertion site for the prevention of catheter-related complications in adult patients who need cancer therapy: a randomized trial. *Ann Oncol* 2009; 20(5): 935–940.
- Gonda SJ and Li R. Principles of subcutaneous port placement. *Tech Vasc Interv Radiol* 2011; 14: 198–203.
- Inaba Y, Yamaura H, Sato Y, et al. Central venous access port-related complications in outpatient chemotherapy for colorectal cancer. *Jpn J Clin Oncol* 2007; 37: 951–954.
- Ding X, Ding F, Wang Y, et al. Shanghai expert consensus on totally implantable access ports 2019. *Journal of Interventional Medicine* 2019; 2: 141–145.
- Totally implantable central venous access ports. https:// www.health.qld.gov.au/__data/assets/pdf_file/0030/444 486/icare-port-guideline.pdf.
- Kim HC, Hur S and Jeon H. Malfunction of totally implantable central venous ports. *Iran J Radiol* 2017; 14: e13455.
- 25. Kumar C, Jha CK, Bichoo RA, et al. Wide angled 'V' is the perfect disposition of a TIVAD catheter when right internal jugular vein is cannulated to gain central access. *Gastroenterol Rep* 2019; 7: 374–375.
- Aribas BK, Tiken R, Aribas O, et al. Factors on patency periods of subcutaneous central venous port: long-term results of 1408 patients. *Iran J Radiol* 2017; 14: e36816.
- 27. Wu XH, Chen LC, Liu GL, et al. Heparin versus 0.9% saline solution to maintain patency of totally implanted venous access ports in cancer patients: a systematic review and meta-analysis. *Int J Nurs Pract* 2021; 27: e12913.
- Sorg H, Tilkorn DJ, Hager S, et al. Skin wound healing: an update on the current knowledge and concepts. *Eur Surg Res* 2017; 58: 81–94.