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Safety and feasibility of 3-month interval access and flushing for maintenance of totally implantable central venous port system in colorectal cancer patients after completion of curative intended treatments

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Abstract

Patients with colorectal cancer (CRC) treated with curative intent surgery undergo continuous fluorouracil (5-FU) infusion-based chemotherapy using totally implantable central venous port system (TICVPS) in cases with high risk of recurrence. Approximately 30% of patients relapse after therapy completion, especially within 2 years. Hence, many patients with high risk CRC keep the TICVPS for 6 to 24 months after treatment with regular intervals of TICVPS flushing. However, little is known about the proper interval duration of the port. The aim of this study is to investigate whether a 3 months extended interval is safe and if port maintenance is feasible.

A retrospective cohort was compiled of patients with CRC who underwent curative intent surgery and perioperative chemotherapy using TICVPS between 2010 and 2017. The primary end point was TICVPS maintenance rate, including maintenance of TICVPS for at least 6 months, planned TICVPS removal after 6 months, and regaining the use of TICVPS at the time of recurrence.

A total of 214 patients with CRC underwent curative intent treatments during the study period. Among them, 60 patients were excluded, including 6 patients for early recurrence within 3 months and 54 patients with violation of flushing interval. Finally, 154 patients were analyzed. Mean flushing interval was 98.4 days (95% confidence interval [CI], 96.2–100.6; range, 60–120). In December 2018, 35 patients kept the TICVPS, 92 patients had planned removal, 25 patients reused the TICVPS, and 2 patients had to unexpectedly remove the TICVPS due to site infection and pain. Thus, the functional TICVPS maintenance rate was 98.8% (152/154). Thirty-eight patients relapsed, and 30 patients were treated with intravenous chemotherapy. Among them, 25 patients (83.3%) reused the maintained TICVPS without a reinsertion procedures.

Our study demonstrated that 3-month interval access and flushing is safe and feasible for maintaining TICVPS during surveillance of patients with CRC. An extended interval up to 3 months can be considered because it is compatible with CRC surveillance visit schedules.

Abbreviations: 5-FU = fluorouracil, CRC = colorectal cancer, ESMO = European Society for Medical Oncology, TICVPS = totally implantable central venous port system.

Keywords: central venous port, colorectal cancer, flushing, implantable, system, totally

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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1. Introduction

Colorectal cancer (CRC) is the third most common cancer type in the United States, and approximately 80% of patients initially diagnosed with CRC receive surgical treatment with curative intent.[1] CRC patients with high risk of recurrence who undergo curative intent surgical treatment are usually treated with adjuvant chemotherapy of a continuous fluorouracil (5-FU) infusion-based regimen for 6 months.[2] These continuous intravenous infusion regimens are mostly administered using totally implantable central venous port systems (TICVPS) because of difficulty providing IV access due to repetitive venipunctures, risk of chemotherapy extravasation, and increased application of home-pump systems.[3] Although TICVPS may have complications such as wound dehiscence and high financial cost for the initial insertion procedure, it provides long-term access compared with other forms of central venous devices.[4] It also allows patients to take part in social and leisure activities when not receiving therapy.[5]

However, after curative intent treatment, 20% to 30% of patients with high risk CRC develop recurrent disease.[6] Much of these recurrences occurred within 2 years,[7] so these patients are recommended to have surveillance visits every 3 to 6 months for 2 years after completing treatment.[8] Because of the ability to reuse within 2 years and the financial cost of reinsertion, some patients with CRC keep their TICVPS for 6 to 24 months even after completing adjuvant chemotherapy.

When TICVPS is not used, access and heparin flushing at regular intervals are essential for maintaining function and minimizing complications such as thrombosis and infection.[9] However, little is known about the proper flushing interval for TICVPS. Manufacturers recommend flushing of TICVPS every 4 weeks,[10] and the European Society for Medical Oncology (ESMO) guidelines also recommend access with normal saline and heparin flushing every 4 weeks with lack of scientific evidence.[11] Considering that surveillance visits are scheduled every 3 to 6 months for 2 years after completion of curative treatment for CRC, monthly flushing is inconvenient and results in poor compliance.[3] Thus, convenient catheter maintenance protocol should address the use of extended intervals compatible with the CRC surveillance schedule.

Some studies have been conducted to investigate safeties and usefulness of extended intervals and flushing methods, and a few have reported favorable results.[12–16] However, the previous studies have small sample sizes, varying types of cancer and disease status, or are limited by the study designs. Some of them compared median flushing intervals according to development of port-related complications,[13,16] the others investigated the safety of longer 6 to 8 weeks intervals compared with those of 4 weeks.[14,15] Previous studies were conducted on patients with gynecologic cancer[13,16] or other types of cancer.[14–16] In terms of disease status, most studies involved heterogeneous groups ranging from supportive care to the surveillance setting. Thus, there have been limitations in providing guidelines about appropriate flushing intervals in CRC patients with planned surveillance every 3 months.

The aim of this study is to investigate whether extended 3-month interval access and flushing are safe to maintain potency of TICVPS in patients with CRC undergoing surveillance. Additionally, this study assesses the feasibility of keeping TICVPS by examining recurrence and the rate of port re-use.

2. Materials and methods

2.1. Patients and data collection

The present study retrospectively reviewed data from CRC patients who underwent curative intent surgical treatment and perioperative chemotherapy using TICVPS from January 2010 to December 2017 at Pusan National University Yangsan Hospital (Yangsan, Republic of Korea). Three months interval access and flushing have been employed since 2010. Patients with CRC who were supposed to maintain TICVPS for at least 6 months after curative treatment were included in this study. Patients with two or more port insertions were only analyzed the first time. Exclusion criteria were as follows: patients who recurred and were treated with chemotherapy using a port within 3 months after completing adjuvant chemotherapy, immediate TICVPS removal with or without complications after treatment completion, or violation of flushing interval (a window period of 30 days was permitted). Patient data were collected from the electronic medical records, including baseline characteristics, clinical setting, and chemotherapy regimen. After completing curative treatment, the number and interval of heparin flushing instances were examined. We also reviewed TICVPS-related complications, cancer recurrence, and reuse of TICVPS. This study was approved by the Institutional Review Board, which waived the requirement for informed consent due to the retrospective design of this study.

2.2. Insertion of TICVPS

TICVPS was implanted by an experienced vascular surgeon using ultrasound-guided venous access and was placed in the internal jugular vein or subclavian vein of the upper extremities. A single type of TICVPS (Districath; Districlass Medical SA, Chaponnay, France) was used. TICVPS insertion procedures were performed in the operating room, and surgeons constantly monitored the electrocardiogram, oxygen saturation, and blood pressure of patients during the procedure. The catheter tip was located in the superior vena cava above the right atrium. Antibiotics (flomoxef sodium 2 g) were intravenously administered as prophylaxis prior to the procedure. After insertion, patients underwent chest x-ray to assess catheter location and wound site for any immediate complications.

2.3. Flushing and monitoring of TICVPS

When visiting outpatient clinics, each patient was interviewed regarding symptoms such as fever and pain; the TICVPS site was inspected and evaluated for edema or tenderness. Then, registered nurses with expertise in the field of oncologic nursing care assessed for occlusion and performed TICVPS flushing. Access and flushing were performed following standard sterile precautions and procedures by pulsating 10 cm^3 of normal saline followed by 5 mL of heparin flushing (heparin sodium, 250 IUs/mL 5).

In patients with symptoms such as swelling or pain at the port site or ipsilateral neck, the port was removed without additional work-up such as ultrasound or contrast-enhanced CT. The port was removed if there was a merely cumbersome or uncomfortable feeling because it was for unpredictable future relapse. The port was maintained in cases of blood regurgitation difficulties with fluid infusion possible, but it was removed in cases of definitive obstruction. No patients used anticoagulation therapy as port occlusion prophylaxis.

2.4. Statistics

Baseline demographics using descriptive statistics including medians, means, and ranges were summarized. The flushing interval was defined as the period between 2 consecutive flushings, and it was described as a median value and range based on all data from 154 patients. The primary end point was TICVPS maintenance rate, including maintenance of TICVPS for at least 6 months, planned TICVPS removal after 6 months, and regained use of TICVPS at the time of recurrence. Secondary endpoints were catheter life span, complication rate, and rate of successful port reuse. The TICVPS life span was defined as the time from last day of perioperative chemotherapy until the date of port removal. Successful reuse rate of ports was defined as the proportion of patients treated with the maintained port without any port-related problem among all patients with recurrence who underwent intravenous chemotherapy. Median follow-up duration was calculated according to the inverted Kaplan–Meier method. Statistical analyses were performed using SPSS version 19.0 (SPSS Inc. Chicago, IL).

3. Results

3.1. Patient characteristics

A total of 242 CRC patients underwent curative intent surgical treatment and initiated perioperative chemotherapy between January 2010 and December 2017. Among them, 14 patients were treated with oral agents or peripheral line, 8 patients were lost to follow-up, 1 patient died during adjuvant chemotherapy, 3 patients had their removed port due to complications during chemotherapy, and 2 patients had their ports removed without complication immediately after completing chemotherapy. A total of 214 patients completed adjuvant chemotherapy using a port and started surveillance with flushing every 3 months. However, 6 patients relapsed early within 3 months after completing chemotherapy and 54 patients with violation of flushing interval (51 patients, 4 months or more; 3 patients, 2 months or less) were excluded. Finally, the remaining 154 patients with 3-month interval access and flushing were analyzed (Fig. 1). The characteristics of the 154 patients are shown in Table 1. The median age of patients was 62 years (range, 36–76) and 78 (50.6%) patients were men. Disease stages were stage II (38, 24.7%), III (83, 53.9%), IV-synchronous (25, 16.2%), and IV-metachronous (8, 5.2%). The most common perioperative regimen was FOLFOX (129 patients, 83.8%), and bevacizumab was used in 13.6% of patients.

Table 1

Baseline patient characteristics.

Characteristic	Total (N = 154)	%
Age, years, median (range)	62 (36–76)	
Sex		
Male	78	50.6%
Female	76	49.4%
Primary cancer site		
Cecum, ascending	46	29.8%
Transverse	9	5.8%
Descending	8	5.2%
Sigmoid	62	40.3%
Rectosigmoid, rectum	29	18.8%
Stage		
II	38	24.7%
III	83	53.9%
IV—synchronous	25	16.2%
IV—metachronous	8	5.2%
Perioperative chemotherapy regimen		
FOLFOX or XELOX	135	87.7%
FOLFIRI	14	9.1%
Bevacizumab containing regimens	21	13.6%
Cetuximab containing regimens	6	3.9%
Others	5	3.2%

3.2. Outcomes of TICVPS using 3-month interval access and flushing

At December 2018, the median follow-up time was 41.2 months (interquartile range, 23.9–60.6), and a total of 101,448 catheter-days were analyzed. The median flushing interval was about 98.4 days (range, 60–120; 95% CI, 96.2–100.6), and 76.7% of patients performed flushing at intervals of 91 to 120 days. The median

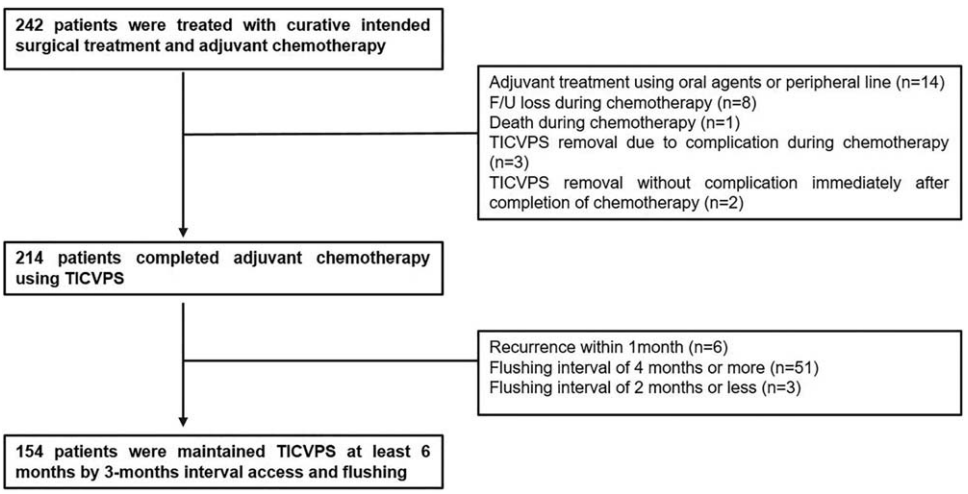

Figure 1. Study design flow chart. Flow chart shows how data were excluded from the review due to insufficient information on outcomes of interest. F/U = follow up; TICVPS = totally implantable central venous port system.

Table 2

Access and flushing status of TICVPS.

Characteristic	Total (N = 154)	%
Number of heparin flushing		
1–3	43	27.9%
4–6	72	46.8%
7–9	24	15.6%
≥10	15	9.7%
Median heparin flushing interval	98.4 days (95% CI, 96.2–100.6, range 60–120)	
Heparin flushing interval		
61–90	36	23.3%
91–120	118	76.7%

TICVPS = totally implantable central venous port system.

number of flushing instances was 5.27 (95% CI, 4.90–5.65), and 15 patients (9.7%) had flushing performed >10 times (Table 2).

In December 2018, 35 patients had maintained TICVPS, 92 patients had TICVPS removed after 6 months of surveillance as scheduled, 25 patients reused the maintained TICVPS at the time of recurrence, and 2 patients had unexpected removal due to TICVPS-associated complications. One patient underwent TICVPS removal due to catheter-associated infection and received intravenous antibiotics based on the results of catheter tip culture. Another patient had TICVPS removed due to pain at the insertion site. Thus, the TICVPS maintenance rate was 98.8% (152/154), and the TICVPS-associated complication rate was 0.02 per 1000 catheter-days. The median TICVPS life span was 588 days (range, 143–1820), and 147 patients (95.5%) had the TICVPS for >300 days (Table 3).

3.3. Treatment outcomes of CRC and feasibility of maintained TICVPS

Thirty-eight (24.7%) patients had relapsed at the time of analysis. Among them, 27 patients (71.1%) relapsed within 1 year. Treatment after cancer relapse is as follows: supportive care only or loss to follow-up (3 patients), metastasectomy or definitive radiation therapy without systemic chemotherapy (5 patients), metastasectomy plus perioperative intravenous chemotherapy (14 patients), and palliative intravenous chemotherapy (16 patients). Among 30 patients treated with intravenous chemotherapy, 26 patients reused the maintained TICVPS without reinsertion. Of the 4 patients who did not reuse the port, 3 had planned TICVPS removal before relapse, and the other removed the port due to site discomfort at 4 months of surveillance. Thus, the successful reuse rate of TICVPS was 86.7% (26/30) (Table 4).

Table 3

Outcomes of 3-month interval access and heparin flushing.

Characteristic	Total (N = 154)	%
Current status of TICVPS		
Keeping	35	22.7%
Planned removal	92	60%
Reused after recurrence	26	16.9%
Early removal due to port related complication	2	1.2%
TICVPS maintenance rate	152	98.8%
Median TIVCPS life span (days, 95% CI)	588.0 (95% CI, 610.3–707.20; 143–1820)	

TICVPS = totally implantable central venous port system.

Table 4

Treatment outcomes of CRC and reuse rate of TICVPS.

Characteristic	Number	%
Recurrence rate (N = 154)	38	24.7%
6 months recurrence rate	6	3.9%
12 months recurrence rate	27	17.5%
24 months recurrence rate	29	18.8%
Treatment at recurrence (N = 38)		
BSC or follow-up loss	3	7.9%
Metastasectomy or definitive radiation therapy	5	13.2%
Metastasectomy plus perioperative chemotherapy	14	36.8%
Palliative chemotherapy	16	42.1%
Successful reuse rate of maintained TICVPS (N = 30*)	26	86.7%

BSC = best supportive care, CRC = colorectal cancer, TICVPS = totally implantable central venous port system.

* Number of patients treated with intravenous chemotherapy using port at recurrence.

4. Discussion

The current study showed that 3-month interval access and heparin flushing of TICVPS had a 98.9% maintenance rate, indicating that TICVPS can be maintained for >6 months and reused at the time of relapse in CRC patients after completion of curative treatment. This study also showed that maintained TICVPS can be reused without any additional insertion procedure in 17% of all enrolled patients and in 87% of patients who had to undergo intravenous chemotherapy due to relapse. In summary, our results suggest that 3 months extended interval access and heparin flushing is safe and feasible in the surveillance setting for CRC patients. This procedure had a favorable maintenance rate, relatively high rate of reuse without complications, avoids procedure-related risk of reinsertion, and allows a 3 months visiting schedule. To our knowledge, this is first study to evaluate the role of 3 months extended intervals for maintenance of TICVPS in a homogenous surveillance setting of CRC patients.

Access and heparin flushing are considered the most important interventions to maintain TICVPS patency, prevent catheter occlusion, and minimize the risk of catheter-associated infection.[11] However, the best solution, irrigation volume, and flushing interval for TICVPS remain unknown.[12] Flushing interval is the most important and clinically meaningful of these factors, and many studies have shown that an extended interval is safe and convenient.[13–16] In a retrospective study, Kefeli et al[15] reported that extended interval flushing was safe, cost effective, and convenient to perform at 6-week intervals. Kuo et al[13] and Igantov et al[16] reported that 3-month intervals or more heparin flushing are safe in gynecologic cancer. In a prospective study regarding flushing interval, there was no difference in the degree of catheter thrombosis between 4 and 8 weeks.[14] However, these studies mainly investigated heterogeneous or gynecologic cancer patients, and no study has been conducted in the setting of surveillance after completion of adjuvant treatment. Considering the limitations of previous studies, our study population was homogeneously composed of CRC patients with 3 months visiting schedules.

This study showed port-related adverse events of 1.1%, which is favorable compared with 5% to 20% of port-related complications in the generalized setting[14,16] or 3.8% of symptomatic port-related thrombosis in CRC patients.[17] We presumed that patients of the current study show less cancer-associated thrombogenic risks than cancer patients undergoing active treatment because there was no evidence of disease and patients were not treated with chemotherapy, especially bevacizumab, which is reported to be

associated with thrombosis.[17,18] Most of all, this study is based on patients who had already completed 6 months of chemotherapy. For instance, patients who had ports removed due to trivial symptoms such as pain, thrombus, or infection during chemotherapy were excluded from the study. These findings are concordant with those of a previous study by Dal Molin et al,[19] which reported that late port-related complications developed at a relatively low rate in out-patients undergoing continuous flushing without any treatment compared with patients under active treatment. The purpose of this study was to evaluate an effective method for port maintenance in patients who already completed adjuvant chemotherapy. Our results can be adapted in clinical practice in cancer patients who have completed curative treatments.

Apart from flushing interval, there is no definite conclusion regarding whether to keep or remove TICVPS during surveillance period of CRC patients. In this study, 24.7% of enrolled patients had recurrence and 19.5% underwent intravenous chemotherapy at the time of relapse. International guidelines do not mention port maintenance itself. Decisions related to port maintenance might be made individually based on a patient's risk of recurrence rather than on uniform guidelines. For example, port maintenance may not be appropriate for stage II CRC, but it may be adopted in CRC patients with advanced stage disease, including stage III or stage IV. Curative treatment is now actively applied in advanced stage disease,[20] increasing the need for port maintenance.

This study has some limitations due to its retrospective design. First, this study was not conducted using a sample size calculation based on the hypothesis. However, 154 patients are relatively large compared with samples of previous studies. The sample size is considered sufficient to show 94% statistical power with a 4% incidence rate of definitive complications. Second, this study did not investigate "flushing the catheters with no venous blood return," which is a surrogate marker of catheter malfunction.[16,19] Nevertheless, we clearly identified potentially life-threatening or definitive complications. All 26 cases with maintained ports at the time of recurrence were able to reuse ports without any problem, which could alleviate concerns about the functional status of catheters.

Despite these limitations, the present study is the first analysis of a large and homogeneous population that shows the usefulness of the 3 months extended interval of access and flushing in surveillance of CRC patients. The extended interval is convenient because it is compatible with surveillance visit schedules for CRC. Further study should be conducted using clarified flushing methods, prospective controlled design, and more detailed self-reported questionnaires including patient satisfaction.

5. Conclusion

Our study demonstrated that 3-month interval access and flushing is safe and feasible in CRC patients. Extended intervals up to 3 months might be considered because they are compatible with CRC surveillance visit schedules and convenient for patients.

Author contributions

Conceptualization: Sang-Bo Oh, Kwonoh Park, Jae-Joon Kim, So-Yeon Oh, Ki-Sun Jung.
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Writing – review & editing: Sang-Bo Oh, Kwonoh Park.

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