

Title page:

Title: The central vein access port and catheter in outpatient chemotherapy for colorectal cancer: A retrospective study of 101 patients.

Hiroshi Sawayama, Naoko Hayashi, Masayuki Watanabe, Hiroshi Takamori, Toru Beppu and Hideo Baba

Department of Gastroenterological Surgery Graduate School of Medical Sciences,
Kumamoto University, Kumamoto, Japan

Request for reprints: Prof. Hideo Baba, Department of Gastroenterological Surgery, Graduate School of Medical Sciences, Kumamoto University, Honjo 1-1-1, Kumamoto 860-8556, Japan. Phone: +81-96-373-5587; Fax: +81-96-373-4378; E-mail address: hdobaba@kumamoto-u.ac.jp

Short title: CV-port and catheter complications

Article type: Original article

A summary of this study was presented at the 108th Annual Meeting of the Japan Surgical Society in 2008 and the 46th Annual Meeting of the Japan Society of Clinical Oncology in 2008.

Abstract

Background: The central venous access port (CV-port) system was examined in a series of colorectal cancer (CRC) patients. **Methods:** One hundred and one CRC patients underwent chemotherapy with the FOLFOX or FOLFIRI regimen. The complications of the CV-port system were retrospectively assessed. **Results:** A total of 101 patients had the CV-port system placed. The patients received a total of 1035 courses of these regimens. Eight complications occurred in the 101 patients (7.9%). The complications included three instances of catheter rupture, two thrombotic events around the catheter, and three infections at the site of the port or catheter. The complications were identified after a median of 9 courses (range 6–16) and 135 days after the placement of the CV-port system. Sixty-six of the 101 patients switched their regimen from FOLFOX to another regimen, and 4 of these 66 patients (6.1%) experienced complications associated with the CV-port system. There were 25 subjects who were admitted to the hospital emergency wing during the chemotherapeutic regimens, and 4 of these patients (16%) had complications associated with the CV-port system. **Conclusions:** The complications of the CV-port system occurred at a defined rate, therefore the early diagnosis and the appropriate treatment to address these complications is crucial.

Key words: Colorectal cancer, outpatient chemotherapy, central venous access port, complication, pinch off

Text

Introduction:

Completely implantable port systems were first introduced in the early 1980s. A variety of anticancer agents have been administered while using the devices without difficulty, and the patient acceptance of this system is excellent.¹ Late complications may occur, including catheter rupture and embolization, venous thrombosis, pocket infection, and port-related bacteremia. However, these devices have a long working life and a low rate of patient complications, and are of great value to patients who require long-term or cyclic intravenous treatments.² These data support the increasing use in current oncologic medical practices. The gastrointestinal division originally used the CV-port system, either for administering chemotherapy to patients with gastric cancer, to provide nourishment to patients with short bowel syndrome, or for the treatment of patients with other conditions. The CV-port system has been extensively used since its introduction in CRC patients receiving the FOLFOX or FOLFIRI + bevacizumab³ chemotherapy.

Methods:

Patients and chemotherapeutic regimens

One hundred and three CRC patients underwent FOLFOX or FOLFIRI chemotherapy between April 2005 and March 2008 at our institution. One hundred and one of the 103 patients (98%) underwent CV-port system placement. Two patients could not receive the CV-port, because one patient had a mechanical valve, and the other patient experienced difficulty in the placement of the CV-port. The 101 remaining patients (range: 27–82 years of age, with a median age of 62 years) underwent chemotherapy for unresectable metastatic CRC, and also underwent adjuvant chemotherapy following hepatectomy. The regimens consisted of the modified FOLFOX-6 (m-FOLFOX 6), FOLFOX-4, or FOLFIRI regimens. The regimens consisted of a continuous infusion of 5-FU using a portable disposable pump, which was manufactured by Baxter.

Ports and routes of access to the central vein and maintenance of ports

CV-ports were placed by surgeons in the CRC patients. An indwelling catheter was inserted from the right subclavian vein at the lateral side using diagnostic imaging guidance and fluoroscopy to confirm that the catheter was placed in the superior vena cava. The ports were placed at the jugular vein or the inguinal vein if the surgeon

experienced difficulty placing it in the subclavian vein. All 101 patients had a single lumen Groshong 8-Fr catheter and an MRI-Port (C.R. Bard, Inc) implanted. The first 1 or 2 courses of the regimen were administered while the patients were hospitalized in order to monitor any adverse events. The CV-port was put in place, and the patients were educated about the chemotherapy. After 1 or 2 courses of chemotherapy in the hospital, the patients underwent chemotherapy every two weeks as outpatients. Their ports were punctured by a doctor with a Huber-pointed needle. The doctor confirmed whether there was redness, swelling, or pain around the port, and confirmed that the natural drip was smooth before the patient was connected to the pump. The state of the catheter was regularly checked with chest X-rays every three months. The needle was removed without a saline flush after chemotherapy by the patients themselves or their family doctor.

The frequency and types of complications involving CV-ports and catheters were retrospectively evaluated. We also examined the instances of emergency hospital outpatient admission during chemotherapy and the reasons for changing to other regimens. The purpose of the present study was to demonstrate the placement methods and maintenance of the central venous access port (CV-port) system for preventing and identifying late complications.

Results:

A total of 101 patients underwent the FOLFOX regimen, and a total of 750 courses were administered (median, 8 courses per patient). Forty of the 101 patients also received the FOLFIRI regimen, and a total of 270 courses were administered (median, 6 courses). An overall total of 1035 courses were administered (median: 10). Eight patients had central vein access port and catheter complications (7.9%). The complications associated with the central vein access port and catheter occurred at a median of 9 courses (range, 6–16) and at a median time of 135 days after putting the CV-port system in place (Table 1).

The incidents involved catheter pinch-off syndrome and fracture of the catheter (n=1, Fig. 1), thrombosis around the catheter (n=2, Fig. 2, Fig. 3), the connection portion of the port and catheter coming off (n=1, Fig. 4), the flexure of the catheter (n=1, Fig. 5), and the infection of the site of the port or catheter (n=3) (Table 2).

Sixty-six of the 101 patients changed their regimen from FOLFOX to other regimens. Thirty-seven subjects were switched because of progressive disease (56.1%), 22 patients switched due to an adverse event (33.3%), and 4 patients were switched

because of complications associated with the CV port system (6.1%). The adverse events included peripheral neuropathy in 13 patients (19.7%), allergy in 5 patients (7.6%), and myelosuppression, interstitial pneumonia, and one patient's request (Table 3).

There were 25 patients admitted to the emergency department during the FOLFOX or FOLFIRI chemotherapeutic regimen, and 3 of 25 patients (12.5%) had adverse effects including pyrexia with neutropenia, severe anorexia, and acute exacerbation of interstitial pneumonia. However, 4 subjects (16.7%) required an emergency hospital admission due to complications associated with the CV-port system (Table 4).

Discussion:

FOLFOX or FOLFIRI regimen administration with a continuous infusion of 5-FU may be switched to combination chemotherapies with an oral anticancer drug, such as S-1 or capecitabine, L-OHP or CPT-11 (IRIS, XELOX, etc.).⁴⁻⁶ However, the FOLFOX and FOLFIRI regimens are administered to CRC patients because there is a large amount of evidence indicating the efficacy, safety, and feasibility of these regimens.

Complications have been associated with the long-term placement of a CV-port and catheter.⁷⁻¹⁰ The current series demonstrated complications in 8 of 101 patients (7.9%). The frequency of complications occurring in association with the CV-port system during the chemotherapeutic treatment of outpatients in the present study were consistent with past reports. Several CRC patients required hospitalization for complications associated with the catheter. Furthermore, the complications of the CV-port and catheter caused some patients to change to another regimen (6.1%) or to require emergency treatment (16.7%). Outpatient chemotherapy was safely performed for the majority of cases in our hospital. However, some issues remained, such as the occurrence of complications associated with the CV-port system, which led to changes to either another treatment regimen or to emergency hospital admission. These complications associated with the port and catheter included three instances of catheter rupture and embolisation, venous thrombosis, and infection. We herein discuss the

placement methods, the appropriate maintenance of CV ports, and the measures taken to address these complications when they occur.

Catheter rupture and embolisation

Pinch-off syndrome (POS) occurs when the CV access devices placed via the subclavian vein become obstructed due to thrombosis, impingement against a vein wall, or compression between the clavicle and the first rib. Luminal narrowing and complete catheter fracture occur in approximately 1% of catheter placements.¹¹ One case of catheter pinch-off was experienced at our institution during the study period. The patient did not report an active exercise history, but the subject had a small physique, weighed 45 kilos and was 145 cm in height. A catheter tip measuring 5 cm in length caused an embolus to a pulmonary artery. The catheter was withdrawn with a snare from the right inguinal vein by a radiologist. A puncture point is important to avoid pinch-off points. The catheter should be preferentially placed on the lateral side of the subclavian vein or in the internal jugular vein to avoid a pinch-off point.¹² Peripheral arm ports have been implanted in some CRC patients with no incidences of catheter POS.¹³ The supraclavicular technique provides the best results with regard to the percutaneous introduction of large bore central venous catheters.¹⁴ At our institution, the most general approach from the right subclavian vein is the first choice of a puncture. There are no reports of cases that have an increased tendency to have pinch-offs, but we perform a puncture from another portion; namely the right supraclavicular vein or left subclavian vein, not the right subclavian vein, due to the fact that patients who actively exercise or have a small physique may experience POS.

Port connector rupture is usually due to the method used to place the CV-port device. The method for connecting a port and catheter varies with the CV-port device, and the surgeon must confirm the type of CV-port device and the method used to ensure a proper connection.

Venous thrombosis

Catheter-related central venous thrombosis (CRCVT) occurs at a rate of 12–66%.^{15, 16} In a prospective study, CRCVT was observed in 63/95 (66%) patients; however, it was symptomatic in only 4/63 (6%) of these patients.¹⁵ There is no prognostic marker for venous thrombotic complications.¹⁶ Three recent clinical trials investigated the effects of prophylactic anticoagulation with either low molecular

weight-heparin or -warfarin in cancer patients who had central venous devices.¹⁷⁻¹⁹ However, these studies did not support the routine use of prophylactic anticoagulation in cancer patients with venous catheters to prevent catheter-induced thrombosis. Based on these results, routine anticoagulation is not recommended.²⁰ Anticoagulant administration just after the placement of the CV-port system is not used in our hospital. Two thrombosis cases were detected at our institution during the study period. These patients were diagnosed by injecting contrast media from the port and median vein on the port insertion side. The IRIS regimen (a combination therapy of the oral anticancer drug S-1 and irinotecan) was administered for the current patient series when the CV-port could not be replaced due to thrombosis. In the present study, thrombosis improved after the administration of anticoagulant therapy. Both patients had the CV-port system put in place again, and the FOLFOX regimen was restarted.

Infection

A diagnosis of a catheter-related infection might be difficult in the absence of local signs of inflammation.²¹ Routine device removal is not recommended for most patients. Empirical antibiotics are administered when the patient presents with sepsis or septic shock. Port systems must be removed in case of a persistent relapse of infection after antibiotic treatment, at signs of port or catheter tunnel infection, for unstable patients, or after the development of systemic complications.^{22, 23} However, CRC patients undergoing perioperative chemotherapy have had highly invasive surgery and the general opinion is that these guidelines do not apply to most of these patients. A high fever after CRC resection is usually due to an infection at the surgical site or an infection of the CV-port system. In our hospital, we experienced a case which demonstrated complications associated with a biliary fistula after hepatectomy who continued to have a high fever after antibiotic treatment. The CV-port system was withdrawn, but no bacteria was detected on the catheter. However, we thought that the CV-port system should be withdrawn in such a case, contrary to popular opinion.

In conclusion, the management of the CV-port system is an important factor in the administration of chemotherapy to outpatients with colorectal cancer. We have described proper CV-port system placement and summarized a recent report about the tendencies of port complications in the Discussion section. We have also explained measures that were used to treat the complications in our experimental cases. The

chemotherapeutic treatment of outpatients with the CV-port system is therefore best performed when the physicians are aware of these complications and how to best treat patients for CV-port complications without compromising their anti-cancer treatment.

References:

1. Niederhuber JE, Ensminger W, Gyves JW, Liepman M, Doan K, Cozzi E. Totally implanted venous and arterial access system to replace external catheters in cancer treatment. *Surgery* 1982; 92: 706-12
2. Torramade JR, Cienfuegos JA, Hernandez JL, Pardo F, Benito C, Gonzalez J, et al. The complications of central venous access systems: a study of 218 patients. *Eur J Surg* 1993; 159: 323-7
3. Konno H, Yamamoto M, Ohta M. Recent concepts of antiangiogenic therapy. *Surg Today* 2010; 40: 494-500
4. Cassidy J, Clarke S, Diaz-Rubio E, Scheithauer W, Figer A, Wong R, et al. Randomized phase III study of capecitabine plus oxaliplatin compared with fluorouracil/folinic acid plus oxaliplatin as first-line therapy for metastatic colorectal cancer. *J Clin Oncol* 2008; 26: 2006-12
5. Tsunoda A, Yasuda N, Nakao K, Narita K, Watanabe M, Matsui N, et al. Phase II study of S-1 combined with irinotecan (CPT-11) in patients with advanced colorectal cancer. *Oncology* 2009; 77: 192-6
6. Ishida H, Miyake Y, Fukunaga M, Watanabe Y, Kato T, Takemoto H, et al. A feasibility study of UFT/LV and irinotecan (TEGAFIRI) in advanced or metastatic colorectal cancer: Osaka Gastrointestinal Cancer Chemotherapy Study Group (OGSG) PROG 0304. *Jpn J Clin Oncol* 2009; 39: 601-5
7. Biffi R, de Braud F, Orsi F, Pozzi S, Mauri S, Goldhirsch A, et al. Totally implantable central venous access ports for long-term chemotherapy. A prospective study analyzing complications and costs of 333 devices with a minimum follow-up of 180 days. *Ann Oncol* 1998; 9: 767-73
8. Charvat J, Linke Z, Horaekova M, Prausova J. Implantation of central venous ports with catheter insertion via the right internal jugular vein in oncology patients: single center experience. *Support Care Cancer* 2006; 14: 1162-5
9. Yip D, Funaki B. Subcutaneous chest ports via the internal jugular vein. A retrospective study of 117 oncology patients. *Acta Radiol* 2002; 43: 371-5

10. Funaki B, Szymiski GX, Hackworth CA, Rosenblum JD, Burke R, Chang T, et al. Radiologic placement of subcutaneous infusion chest ports for long-term central venous access. *AJR Am J Roentgenol* 1997; 169: 1431-4
11. Hinke DH, Zandt-Stastny DA, Goodman LR, Quebbeman EJ, Krzywda EA, Andris DA. Pinch-off syndrome: a complication of implantable subclavian venous access devices. *Radiology* 1990; 177: 353-6
12. Andris DA, Krzywda EA, Schulte W, Ausman R, Quebbeman EJ. Pinch-off syndrome: a rare etiology for central venous catheter occlusion. *JPEN J Parenter Enteral Nutr* 1994; 18: 531-3
13. Kawamura J, Nagayama S, Nomura A, Itami A, Okabe H, Sato S, et al. Long-term outcomes of peripheral arm ports implanted in patients with colorectal cancer. *Int J Clin Oncol* 2008; 13: 349-54
14. Fazeny-Dorner B, Wenzel C, Berzlanovich A, Sunder-Plassmann G, Greinix H, Marosi C, et al. Central venous catheter pinch-off and fracture: recognition, prevention and management. *Bone Marrow Transplant* 2003; 31: 927-30
15. De Cicco M, Matovic M, Balestreri L, Panarello G, Fantin D, Morassut S, et al. Central venous thrombosis: an early and frequent complication in cancer patients bearing long-term silastic catheter. A prospective study. *Thromb Res* 1997; 86: 101-13
16. Cortelezzi A, Moia M, Falanga A, Pogliani EM, Agnelli G, Bonizzoni E, et al. Incidence of thrombotic complications in patients with haematological malignancies with central venous catheters: a prospective multicentre study. *Br J Haematol* 2005; 129: 811-7
17. Verso M, Agnelli G, Bertoglio S, Di Somma FC, Paoletti F, Ageno W, et al. Enoxaparin for the prevention of venous thromboembolism associated with central vein catheter: a double-blind, placebo-controlled, randomized study in cancer patients. *J Clin Oncol* 2005; 23: 4057-62
18. Couban S, Goodyear M, Burnell M, Dolan S, Wasi P, Barnes D, et al. Randomized placebo-controlled study of low-dose warfarin for the prevention of

central venous catheter-associated thrombosis in patients with cancer. *J Clin Oncol* 2005; 23: 4063-9

19. Karthaus M, Kretzschmar A, Kroning H, Biakhov M, Irwin D, Marschner N, et al. Dalteparin for prevention of catheter-related complications in cancer patients with central venous catheters: final results of a double-blind, placebo-controlled phase III trial. *Ann Oncol* 2006; 17: 289-96
20. Vescia S, Baumgartner AK, Jacobs VR, Kiechle-Bahat M, Rody A, Loibl S, et al. Management of venous port systems in oncology: a review of current evidence. *Ann Oncol* 2008; 19: 9-15
21. Bouza E, Burillo A, Munoz P. Catheter-related infections: diagnosis and intravascular treatment. *Clin Microbiol Infect* 2002; 8: 265-74
22. Ouriel K. Preventing complications of central venous catheterization. *N Engl J Med* 2003; 348: 2684-6; author reply 2684-6
23. Kovacevich DS, Papke LF. Guidelines for the prevention of intravascular catheter-related infections: Centers for Disease Control and Prevention. *Nutr Clin Pract* 2003; 18: 95-6

Tables:

Table 1. Complications of the CV-port and catheter

	Total patients	Patients with complications
Number of patients	101	8
Sex, male / female	66 / 35	6 / 2
Age, median (range)	62 (27–82)	69 (65–81)
Courses of chemotherapy		
median (range)	10 (1–25)	9 (6–16)

Table 2. Summary of complications of CV-ports or catheters, excluding 3 patients with a catheter infection

Age / sex	Chief complaint	Complication	Treatment
71 / F (9)	Pain around the port	Pinch off syndrome Fracture of the catheter	Extraction of the catheter by interventional radiology Change to IRIS regimen
68 / M (5)	Pain around the port	Thrombosis Fibrin sheath formation	Extraction of the catheter Change to IRIS regimen
62/M (9)	Right neck pain	Thrombosis, dislocation rt. internal jugular vein	Extraction of the catheter Anticoagulant and change to the IRIS regimen
73/M (11)	Swelling around port	Port connector rupture connection portion coming off	Extraction of the catheter by interventional radiology, catheter replacement
81/M (13)	Poor infusion	Flexure of the catheter bent in subcutis	Repositioning: stretch the catheter out

(Courses of chemotherapy)

Table 3. Reasons for changing from the FOLFOX regimen to another regimen.

Reason n=66	Number	Percent	Age, median	Sex, M / F	Courses of chemotherapy
Progressive disease	37	56.1%	61	24 / 13	8
Adverse events	22	33.3%			
Peripheral neuropathy	13	19.7%	63	10 / 3	10
Allergy	5	7.6%	55	2 / 3	10
Myelosuppression	2	3.0%	58	2 / 1	4
Interstitial pneumonia	1	1.5%	75	1 / 0	8
Patient's request	1	1.5%	44	0 / 1	2
Complication of CV port system	4	6.1%	69	3 / 1	12
Others	3	4.5%	61	2 / 1	10

Table 4. Emergency hospital admissions during FOLFOX or FOLFIRI chemotherapy.

Reason (n=25)	Number	Percent
Progressive disease	9	36%
Adverse events	3	12%
Peripheral neuropathy	0	0%
Allergy	0	0%
Myelosuppression	0	0%
Interstitial pneumonia	1	4%
Pyrexia with the neutropenia	1	4%
Severe anorexia	1	4%
Complication of CV port system	4	16%
Surgical site infection	2	8%
Others	7	28%

Figure Legends:

Fig. 1. Pinch-off syndrome and fracture of the catheter. The catheter was transected between the clavicle and the first rib, and the tip of the catheter was wedged into the pulmonary artery.

Fig. 2. A case of thrombosis around the site of the catheter (fibrin-sheath formation). A: Contrast medium was injected from the bilateral median veins; however, the contrasting effect was not seen in the right subclavian vein, and it was concluded that a collateral pathway had developed. B: There was no outflow of contrast media from the catheter tip, and a light contrasting effect was observed around the catheter.

Fig. 3. The cases of thrombosis in the internal jugular vein. A: The tip of the catheter was detected in an internal jugular vein and there was thrombosis around the catheter, as observed on the contrasting CT. B: Thrombosis in the internal jugular vein improved after five months of warfarin treatment.

Fig. 4. Port connector rupture, connection portion coming off. The catheter was not fractured, and the rupture was judged to be caused by the catheter separating from the port connector.

Fig. 5. Flexure and obstruction of the catheter. The catheter was bent in the subcutis, not in the subclavian vein, and was therefore manually repositioned.