period that epinephrine is sufficiently effective [10]. Finally, we performed celiac and/or superior mesenteric arteriography to evaluate whether the pseudoaneurysm had been sufficiently embolized. In all cases, abdominal CT was obtained within 7 days after embolization. In two cases (patients 1 and 4), follow-up contrast-enhanced CT was not performed, because one of them could not be contacted approximately 1 month after the procedure, and the other died of cerebral hemorrhage 3 weeks postprocedure. The others underwent follow-up CT once every 6 months.

We evaluated the technical success of the embolization procedure, complications, and clinical course after embolization.

Results

The results for each patient are summarized in Table 1. The volume of injected glue was smaller than the volume of the sac in all cases. The pseudoaneurysm was completely filled with NBCA, and the proximal and distal sides of the parent artery were embolized, as shown on arteriography performed immediately after embolization in all cases. In three cases with embolization of the splenic artery, postprocedural arteriography demonstrated collateral flow to the spleen via the gastroepiploic artery. After the procedure, melena resolved and anemia improved in all cases. Abdominal CT performed within 7 days after the procedure revealed an accumulation of the mixture of NBCA and lipiodol within the pseudoaneurysm in all cases, and small splenic infarction and very small deposits of migrated NBCA were detected in two cases. In two follow-up cases, the patients had not experienced rerupture of the pseudoaneurysm for more than 2 years after the procedure, and NBCA remained on CT at more than 25 months postprocedure. In one of them, the splenic infarction was scarred.

There were no significant procedure-related complications. As a minor complication, besides the small splenic infarction mentioned earlier, the systolic blood pressure increased by approximately 20 mmHg for approximately 10 min after the injection of the diluted epinephrine in all patients, but no one showed significant symptoms related to the increased blood pressure. In all cases, after the embolization, transient abdominal pain and slight epigastralgia occurred for a few days, but there was no clinical evidence of worsening of the pancreatitis.

Discussion

Pseudoaneurysm rupture is a rare complication of chronic pancreatitis, but it is one of the most critical complications. Bergert et al. [6] reported severe hemorrhagic complications in 36 patients from a series of 541 patients with chronic pancreatitis. A diagnosis of hemosuccus pancreaticus is made on the basis of ultrasonography or CT, which is performed to detect pancreatic pseudoaneurysms of the peripancreatic arteries. When a pseudoaneurysm is detected, additionally, angiography is useful not only to detect the bleeding artery but also to stop the bleeding with endovascular therapy. The splenic artery and its branches are the most common sites of bleeding (45%), followed by the gastroduodenal (17%) and pancreaticoduodenal (16%) arteries [11].

Treatments for hemosuccus pancreaticus include surgical resection of the pseudoaneurysm and the ligation of bleeding arteries, as well as endovascular procedures. In recent reports, the success rates of embolization for visceral pseudoaneurysms are 63–100% [12], and the morbidity and mortality rates are low [9, 13]. In contrast, open surgery is indicated when a patient's vital signs are unstable, bleeding is not controlled, or endovascular therapy has failed, because it is much more time-consuming and it has a significantly higher risk of mortality, up to 37% [14]. Udd et al. [5] concluded that all hemodynamically stable patients should undergo prompt initial angiographic evaluation and embolization if possible. As another endovascular procedure, stent-graft implantation has been proposed [15]. However, we consider that it often is difficult to deliver the stent-graft over the pseudoaneurysm because of the vascular size and tortuosities of the parent artery. In addition, we cannot use a commercially available stent-graft for abdominal visceral arteries in our country.

As an endovascular therapeutic method for pseudoaneurysms, embolization of both the distal and proximal segments of the parent artery with microcoils is mostly reported [1–7, 11, 16]. It has been reported that, in general, packing the pseudoaneurysm sac with metallic coils should be avoided, because the wall of pseudoaneurysm is so fragile that it can be ruptured by the extension of coils [15, 16]. However, Loffloy et al. [9, 17] reported the usefulness of sac packing with detachable coils for pseudoaneurysm. Recently, they reported 3D sac packing for pseudoaneurysms in 16 cases; the success rate was 100% (16/16), no technical complication occurred, and there was one case of secondary rupture (6.3%, 1/16) [17]. Considering the favorable results in these reports, we believe that packing the pseudoaneurysm sac could be acceptable.

As an embolization material, fibered coils are mostly used [1–7, 12, 16], and reabsorbable embolic agents, such as gelatin-sponge, are used in some cases [18]. Recently, in some reports, NBCA was used for endovascular management of the pseudoaneurysm: embolizing the parent artery, intra-aneurysmal glue embolization (packing), and both [8, 9, 12, 13, 16, 19–21]. Song et al. [21] reported that

embolization with NBCA is a safe and effective technique for pseudoaneurysms at various locations. The study by Izaki et al. [12] shows that NBCA embolization is feasible and effective for pseudoaneurysm that occurred as a complication of pancreatitis. Furthermore, Will et al. [22] reported the direct ultrasound-guided injection of NBCA into the pseudoaneurysm sac in hemosuccus pancreaticus. Therefore, we considered that the combination of packing and isolation of pseudoaneurysm with NBCA is feasible.

NBCA is a liquid and permanent adhesive material that can be injected through a catheter with a narrow lumen because of its low viscosity [23]. However, there are some technical difficulties in using NBCA, such as its rapid polymerization and precise positioning of the delivery microcatheter, and so proficient skills and experience are required for embolization with NBCA [24]. Furthermore, the injection of NBCA into the pseudoaneurysm without blood flow control causes the overflow and reflux of NBCA to the parent artery and it results in undesirable complications. Therefore, the flow control is necessary for embolizing pseudoaneurysms safely.

Generally, an occlusion-balloon is used for the control of flow. However, in pancreatitis, there is a risk of vascular perforation by the balloon, because the vascular wall is damaged and fragile due to pancreatic enzymes. Katsumori et al. [25] reported a case of perforation of the splenic artery caused by a balloon in severe acute pancreatitis. They suggested that pancreatitis makes the vascular wall so fragile that it can be ruptured easily with balloon inflation. Therefore, we did not select the balloon. As a method to control blood flow, we adopted the injection of diluted epinephrine before embolization. In the 1960s, many authors reported the usefulness of epinephrine in diagnostic angiography for gastrointestinal tumors and preventing radiation nephritis in renal tumors [10, 26]. One of the effects of epinephrine is strongly contracting blood vessels by binding to the alpha-1 adrenergic receptor of smooth muscle. A selective arterial infusion of epinephrine causes local vasoconstriction; however, it causes almost no constriction of vessels, which are lacking the alpha-1 adrenergic receptor, like tumor vessels [10, 26]. The infusion of diluted epinephrine through the selective cannulated microcatheter, enough to overflow from the pseudoaneurysm, causes vasoconstriction of the proximal and distal segments of the parent artery. This makes it straightforward to embolize the pseudoaneurysm using NBCA without being concerned with overflow. Furthermore, this method makes it possible to embolize the localized artery and to avoid embolizing arteries that are not to be occluded. Therefore, this method makes it possible to embolize the pseudoaneurysm and segment of the parent artery proximal and distal to the pseudoaneurysm safely at the same time without migration of NBCA causing undesirable visceral infarction. We consider that our method makes it straightforward to embolize a pseudoaneurysm sac with NBCA. Because one of the other important effects of epinephrine is increasing the blood pressure by increasing peripheral resistance via α_1 receptor-dependent vasoconstriction and increasing cardiac output via its binding to β_1 receptors, the IV injection of high-dose epinephrine into a healthy person results in acute hypertension, which damages many organs. In our case, the quantity of injected epinephrine was too small to cause severe hypertension, and the diluted epinephrine was injected into a local artery. Furthermore, the half life of epinephrine is short (approximately 2 min) so we considered that the injection of diluted epinephrine never significantly affected the blood pressure. In fact, in all our cases, the systolic blood pressure increased only by 20 mmHg for approximately 10 min, and they had no symptoms.

As a complication of embolization for hemosuccus pancreaticus, worsening of chronic pancreatitis and splenic infarction were reported [19] because of a decreasing blood supply to the pancreas or spleen or the migration of the embolic material. In our two cases, very small splenic infarction was detected on CT due to migration of NBCA. In these cases, flow in the splenic artery was high, so we considered that our technique was useful to prevent significant infarction. In our cases, transient abdominal pain and slight epigastralgia occurred for a few days after TAE, but no significant procedure-related complications occurred.

In summary, hemosuccus pancreaticus is gastrointestinal bleeding via the pancreatic duct and duodenal papilla, mostly due to pseudoaneurysm rupture. In this report, we presented cases of hemosuccus pancreaticus causing melena and significant anemia, and we succeeded in TAE of the pseudoaneurysm with NBCA under blood flow control by the injection of diluted epinephrine, without significant complications. This new flow control method has the possibility to reduce the difficulty and risk of using liquid embolic materials, such as NBCA, in emergent endovascular treatments for the perforation of an aneurysm or a pseudoaneurysm. Further investigation with larger numbers of subjects and long-term follow-up results using this method are required to define ideal indications, the technical conditions, and the appropriate volume of epinephrine to inject.

Conflict of interest The authors declare that they have no conflicts of interest.

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Use of N-Butyl-2-Cyanoacrylate for Transcatheter Arterial Embolization of Renal Arteries in Patients with Polycystic Kidney Disease

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Most patients with autosomal-dominant polycystic kidney disease (ADPKD) have chronic renal failure and show increasing renal size inversely proportional to their renal function. Kidneys sizes in patients with ADPKD usually continue to increase, even after hemodialysis begins. Sclerotherapy of renal cysts, surgical or laparoscopic fenestration, and nephrectomy have been used to reduce the size of these kidneys (1,2). In 1999, Ubara et al (3) reported their use of coil embolization of renal arteries to reduce kidney size. This less invasive approach can relieve symptoms and avoid the morbidity and mortality associated with open surgery (4,5). After embolization experience increased, the problem of recanalization became evident. To overcome this problem, we performed renal artery embolization by using a mixture of N-butyl-2-cyanoacrylate (NBCA; B. Braun, Melsungen, Germany) and iodized oil (Lipiodol Ultra-Fluid; Terumo, Tokyo, Japan) as a pilot study to evaluate its effectiveness and safety.

Three dialysis-dependent patients with anuria (two women and one man; age range, 61–66 y; mean age, 63 y) with enlarged renal cysts as a result of ADPKD presented with various symptoms, including loss of appetite, nausea, constipation, and abdominal distension. Our institutional review board does not require approval for this type of retrospective study. In two patients, both renal arteries were embolized; in the other patient, only one renal artery was embolized because only one kidney was enlarged (**Table**, **Fig 1**).

Computed tomography (CT) was used to calculate renal sizes before embolization, within 1 week after embolization, and 12 months after embolization according to the formula for an ellipsoid: $a \times b \times c \times (\pi/6)$, where a is the maximum length of the kidney and b and c are the maximum widths in the two transverse dimensions. The abdominal circumference was specifically measured at the umbilicus because the maximal abdominal circumference may not be an accurate index of the renal volume in patients with hepatomegaly.

During angiography, the main renal arteries and branches were extremely narrowed and stretched, and the injected contrast material was easily refluxed into the aorta (**Fig 2a**). A microcatheter (Progreat; Terumo) was introduced coaxially into a segmental renal artery as peripherally as possible. To embolize arcuate or interlobular arteries, which were smaller in caliber than the microcatheter, we injected a 1:9 diluted mixture of NBCA and Lipiodol while withdrawing the catheter from distal to proximal portions. The microcatheter was flushed thoroughly with Lipiodol immediately after removal and was reused for repeated glue injections, allowing the entire procedure to be completed with one microcatheter. This procedure was repeated to fill each renal artery (**Figures 2b and 2c**). The mean procedure time was 86 minutes, with times ranging from 80 to 100 minutes. Pain was well controlled with epidural anesthesia. For a few days after embolization, patients experienced slight abdominal and back pain and low-grade fever, but the symptoms were relieved with nonsteroidal antiinflammatory drugs alone. There were no other definite side effects or major complications. Follow-up CT showed the renal artery branches well filled with NBCA/Lipiodol mixture on noncontrast images. There was no renal parenchymal enhancement on contrast-enhanced CT within 1 week after embolization.

In all cases, symptoms notably improved by approximately 5–6 months after the procedure. For example, patients were able to straighten up and turn their bodies easily, which had been difficult before treatment, especially in the morning. At 1 year, mean renal size on CT decreased from 3,145 cm^3 to 1,716 cm^3, a decrease of 45.9% versus before embolization (**Table**). In addition, the mean maximum upper-abdominal circumference decreased from 95 cm to 76 cm.

According to the report of Ubara et al involving 64 patients (4), renal size decreased 53.4% ± 11.6 versus before embolization at 12 months after treatment. Recanalization was reported in three of 12 patients (25%) who underwent embolization of the renal arteries with coils and in two of 10 patients (20%) who underwent embolization with microcoils only. Subsequently, gelatin sponge was added to microcoils to reduce the rate of

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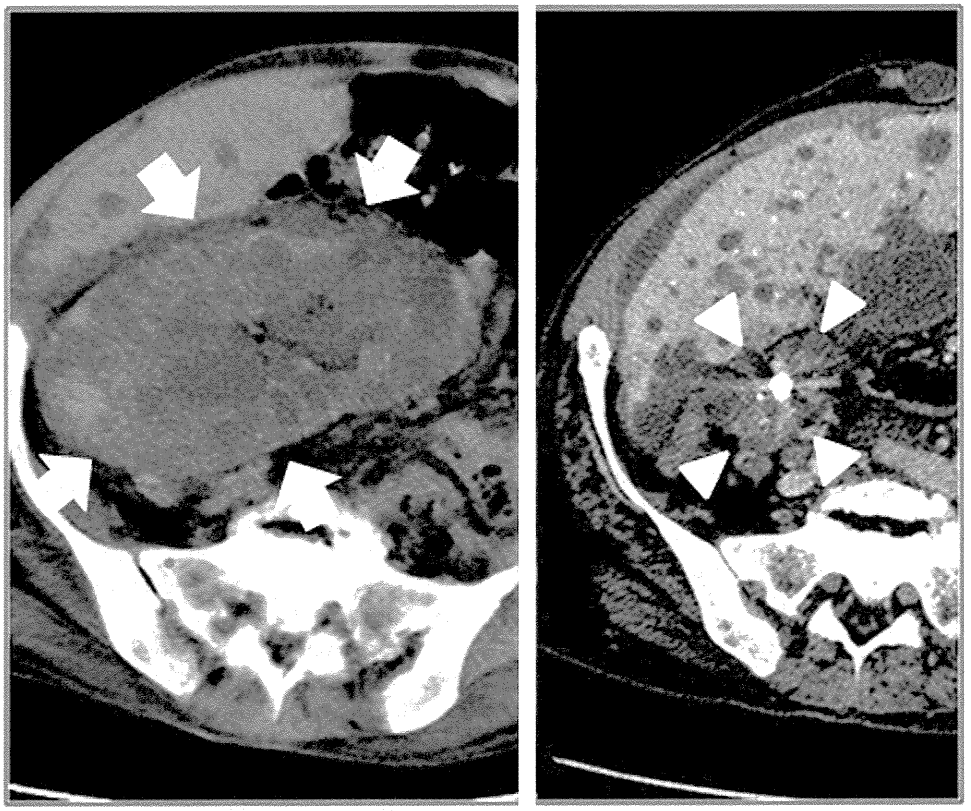
Table. Characteristics of Patients with Enlarged Kidneys and Findings 12 Months after Treatment

Pt. No./Sex/Age (y)	Dialysis Duration (y)	Height (cm)	Hospitalization (day)	Abdominal Circumference (cm)	
				Pre	Post
1/F/61	6	140	8	102	77
2/F/62	2	150	8	94	80
3/M/66	16	172	5	90	72

Note.—Each of the three patients showed improvement of symptoms (appetite loss, nausea, constipation, and abdominal distension) at 12 months after the procedure. NA = not applicable.
* Renal size calculated as maximum length and width in the two transverse dimensions.
† Only the patient's right kidney was enlarged, so treatment of the left kidney was unnecessary.



a. b.

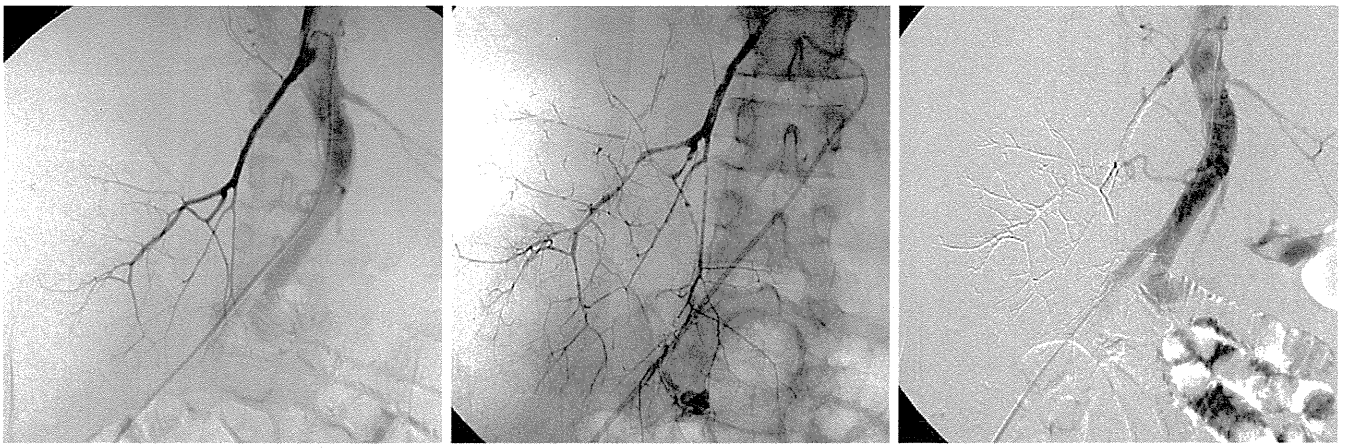
Figure 1. Images from a 62-year-old female patient with ADPKD (patient 2). **(a)** CT before embolization shows a markedly enlarged right kidney with renal cysts (arrows). Note that the abdomen is distended and the gastrointestinal tract is compressed by the enlarged right kidney. **(b)** On abdominal CT 12 months after embolization, the kidney size has decreased 7.5% compared with its size before embolization (arrowheads).

recanalization (4); however, the temporary nature of gelatin sponge leaves a risk of recanalization. Other reported materials include polyvinyl alcohol particles, absolute ethanol, and NBCA (6). Because polyvinyl alcohol particles can cause occlusion of the microcatheter (6), we chose NBCA in the present series. The use of absolute ethanol has several advantages, but it cannot be monitored fluoroscopically, and the use of a balloon is recommended to avoid aortic reflux (7,8). In the cases described here, the renal arteries were too narrow for the use of a balloon.

By adding Lipiodol to NBCA in a very dilute mixture, it can be visualized fluoroscopically and its polymerizing time can be suitably regulated (9–11), in contrast to the typical dilution ratios of Lipiodol to NBCA of 2:1 (10) to 6:1 (11).

In the present cases, kidney size decreased by 7.5%–75%, which compares favorably with the 53.4% ± 11.6 decrease reported by Ubara et al (4,5). The most mark-

Renal Size on CT (cm^3)*					
Left			Right		
Pre	Post	Difference (%)	Pre	Post	Difference (%)
4,836 (30 × 14 × 22)	3,663 (25 × 20 × 14)	75	5,765 (27 × 17 × 24)	2,826 (20 × 18 × 15)	49
NA†	—	—	967 (16.5 × 14 × 8)	73 (9.3 × 5 × 3)	7.5
2,286 (26 × 14 × 12)	1,036 (22 × 10 × 9)	45	1,871 (25 × 13 × 11)	984 (19 × 11 × 9)	53



a. b. c.

Figure 2. **(a)** On selective right renal angiography in patient 2, the right renal arterial branches are stretched and narrowed by markedly enlarged cysts. Most of the injected contrast material (only 5 mL) has refluxed into the aorta. **(b)** After the procedure, all renal branches were filled with NBCA/Lipiodol mixture, and small peripheral branches could be visualized fluoroscopically, even though they could not be visualized on angiography. **(c)** Postprocedural aortography shows complete occlusion of the right renal artery without any collateral supply.

edly decreased kidney size was that of the right kidney in patient 2 (**Table, Fig 1**), and the least decreased kidney size was that of the left kidney in patient 1 (**Table**). The marked difference in size decrease between these two cases may reflect an inadequate volume of NBCA/Lipiodol mixture: the left kidney in patient 1 was five times larger than the right kidney in patient 2, and the volumes of injected NBCA/Lipiodol mixture were nearly the same. However, the largest kidney in the cases described here showed a favorable size decrease after embolization with the same volume of NBCA/Lipiodol; therefore, the injected amounts may not be the sole explanation.

In summary, the present report suggests that NBCA is an acceptable and effective embolic agent for embolization of renal arteries of enlarged kidneys in patients with symptomatic ADPKD.

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● 特別寄稿 ●

医師主導の多施設共同臨床試験におけるUMINインターネット症例登録センター（UMIN-INDICE）の活用: 日本腫瘍IVR研究グループ（Japan Interventional Radiology in Oncology Study Group: JIVROSG）での評価

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Shared Web-Based Data Center for Multi-Institutional Clinical Trials: Evaluation of UMIN-INDICE (University Hospital Medical Information Network-Internet Data and Information Center for Medical Research) in Clinical Trials of JIVROSG (Japan Interventional Radiology in Oncology Study Group): Miyuki Sone[*1], Yasuaki Arai[*2], Takahiro Kiuchi[*3], Hirono Ishikawa[*3], Noriaki Aoki[*3], Yoshitaka Inaba[*4], Tetsuya Yoshioka[*5], Takeshi Aramaki[*6], Takeshi Kobayashi[*7], Toshiyuki Matsuoka[*8], Hiroshi Anai[*9], Noboru Tanigawa[*10], Keigo Osuga[*11], Yoshito Takeuchi[*2], Takushi Okusaka[*2], Susumu Kanazawa[13], Osamu Matsui[*14] and Keigo Endo[*15] (*[1]*Iwate Medical University*, *[2]*National Cancer Center*, *[3]*The University of Tokyo*, *[4]*Aichi Cancer Center*, *[5]*Narumi Hospital*, *[6]*Shizuoka Cancer Center*, *[7]*Ishikawa Prefectural Central Hospital*, *[8]*Osaka City University*, *[9]*Nara Medical University*, *[10]*Kansai Medical University*, *[11]*Osaka University*, *[12]*Okayama University*, *[13]*Kanazawa University*, *[14]*Gunma University*)

Summary

A patient registration system is mandatory for establishing the scientific credibility of the multi-center clinical trials. The Japan Interventional Radiology in Oncology Study Group (JIVROSG) was organized in 2002 to establish evidence supporting the procedures used in interventional radiology. The Internet Data and Information Center for Medical Research (INDICE), provided by the University Hospital Medical Information Network (UMIN), has been utilized for patient registration in the clinical trials of JIVROSG. In this study, the safety and efficacy of UMIN-INDICE were evaluated. From 2002 to 2010, 18 clinical trials, including one international trial, were conducted. A total of 736 patients were enrolled from 51 institutions. No significant trouble was encountered during this period. A questionnaire survey demonstrated that 90% of participating researchers could use this system without difficulties. UMIN-INDICE may contribute to promoting clinical trials as an infrastructure of multicenter studies. **Key words**: Clinical trials, Internet, Data center, Infrastructure (*Recevied May 31, 2011/Accepted Aug. 3, 2011*)

要旨 前向き研究として行われる臨床試験においては，研究の科学的信頼性を担保するために症例の事前登録が必須である。日本腫瘍IVR研究グループ（Japan Interventional Radiology in Oncology Study Group: JIVROSG）は，画像ガイド下に経皮的治療を行うinterventional radiology（IVR）のがん治療におけるエビデンスを確立することを目的に2002年に発足した多施設共同臨床試験組織であり，開始当初より大学病院医療情報ネットワーク（University hospital Medical Information Net

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work: UMIN）が提供する共同利用型のインターネット・データセンター（Internet Data and Information Center for Medical Research: INDICE）を用いて症例登録を行ってきた。本研究では，UMIN-INDICEの安全性と有用性をJIVROSGにおける運用実績に基づき検証した。2002～2010年の間に行われた27本の臨床試験において，85施設から736症例が登録され，研究遂行に支障を来す運用トラブルやセキュリティに関連するトラブルはみられなかった。また，研究者を対象に行ったアンケート調査では，90%という高い頻度で「UMIN-INDICEを用いた症例登録は容易ないしは比較的容易」との回答であった。UMIN-INDICEは多施設共同臨床試験における症例登録システムとして安全性が高く，かつ研究者にとって有用であり，臨床研究のインフラストラクチャーとしてエビデンス生成に寄与すると考えられた。

はじめに

臨床試験におけるインフラストラクチャーは，多施設共同臨床研究を遂行する上で最も重要な要件の一つである。しかし，研究者主導の場合，データセンターなどのインフラストラクチャー構築は容易ではなく，臨床研究推進の障壁の一つとなっている。

日本腫瘍IVR研究グループ（Japan Interventional Radiology in Oncology Study Group: JIVROSG）は，画像ガイド下に経皮的治療を行うinterventional radiology（IVR）のがん治療におけるエビデンスを確立することを目的として，2002年に発足した[1]。JIVROSGでは活動開始当初より，研究遂行のためには昼夜を問わず症例登録が可能なシステムを用いることが必要と考え，大学病院医療情報ネットワーク（University Hospital Medical Information Network: UMIN）が提供するインターネット・データセンターINDICE（Internet Data and Information Center for Medical Research）を利用してきた。

インターネットを利用した症例登録システムやデータセンターの有用性，利便性は過去にも報告されているが，一つのプロジェクトのために独自に構築したものが多い[2-4]。一方，UMIN-INDICEは共同利用型のデータセンターであり，多数の研究に実績をもつ信頼性の高いシステムを安価に利用することが可能である[5]。本研究の目的は，複数の研究を随時施行する多施設共同研究組織において，共同利用型のインターネット・データセンターを利用することの安全性ならびに有用性を評価することである。

Ⅰ．対象・方法

1．JIVROSGの概要

JIVROSGは公的競争的研究費を経済的基盤として，研究者主導による臨床試験を行っている多施設共同研究組織である。2011年1月の時点で85施設が参加し，これまでに27試験を実施し，海外施設との共同試験も行った。主要構成メンバーはIVRを専門とする放射線科医であるが，これに若干名の内科，外科，整形外科，産婦人科医なども含まれている。

2．UMIN-INDICEの概要

UMIN-INDICEは研究者主導の臨床試験におけるインフラストラクチャーを提供している。症例登録と割り付け，データ収集，ホームページ・サービス，メーリングシステムからなり，2000年に運用が開始された。症例登録システムは，UMINの基本システムを基に研究プロトコールごとにカスタマイズする形で開発されるため，研究グループがサーバなどのハードやソフトウエアを購入する必要はない。システムはパスワードで保護されたウェブサイト上に構築され，サーバの保守作業の時以外は24時間365日，登録が可能である。IDはUMINの他のコンテンツと共通のものが使用され，パスワードは共通のものに加えて研究グループ固有のものが発行される[6]。ソフトウエアの開発にはおおよそ2～6か月を要し，費用は当該研究依頼者がUMINに支払う形となっている。

UMIN-INDICEのサーバの管理・保守は専門の技術者により無休で運営されており，物理的侵入対策としてセンター入室者の指紋による個人認証，カメラによる入退室監視を施行している。また，ネットワーク侵入対策として，ファイアウォールの二重設置，侵入検知システム，通信の暗号化を行い，さらにデータは毎日バックアップされ遠隔保存も行われている。

3．JIVROSGでの臨床試験運用の実際

研究に参加する担当医は，インターネットを介してJIVROSGの研究者のみがアクセスできる研究者限定ページ[6]にログインし，該当する試験の症例登録ページを選択する（図1）。必要項目を記入すると症例選択規準がシステムにより確認され，登録番号およびランダム化比較試験の割り付けが決定される（図2，3）。割り付け・登録が完了すると研究グループ担当者へ登録番号と施設のみを記載したE-mailが送付される。インターネットを介して行うのは症例登録のみであり，これ以降のデータ収集はcase report form（CRF）をJIVROSGのデータセンターにFAXで送信して行う。症例登録に関する質問やトラブルの相談がある場合には，JIVROSGのUMIN担当医師に連絡し，必要に応じてUMINにも連絡をとり対処する。

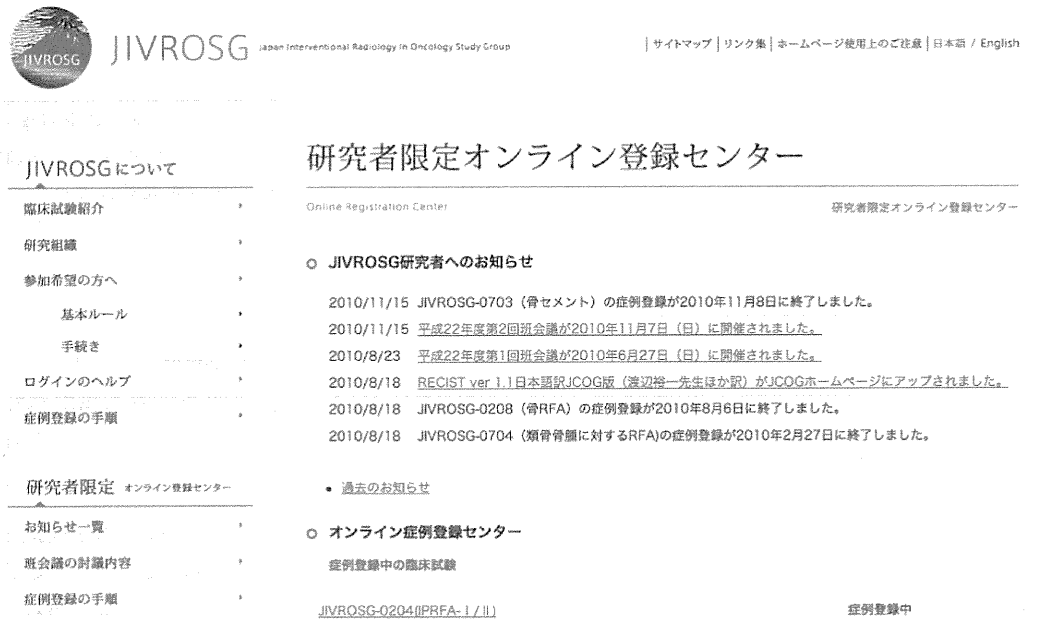

図 1　JIVROSGの研究者限定ページ（http://jivrosg.umin.jp/）

◇適格条件チェックリスト

1	総胆管を主座とする根治術不能悪性胆道閉塞を有す症例	⊙Yes ○No
2	チューブによる内外瘻化が完了している症例	⊙Yes ○No
3	P.S.（ECOG）：0，1，2	⊙Yes ○No
4	血清ビリルビン値 5．0mg/dl 以下	⊙Yes ○No
5	主要臓器（骨髄、心、肝、肺、腎など）機能が保持されている症例 1) 白血球数 >= 3，000 2) 血小板数 >= 50，000 3) プロトロンビン時間 >= 50% 4) 血清 Cr <= 2．0mg/dl 5) Normal EKG （ただし、臨床的に問題とならない不整脈、虚血性変化は適格）	1) ⊙Yes ○No 2) ⊙Yes ○No 3) ⊙Yes ○No 4) ⊙Yes ○No 5) ⊙Yes ○No
6	4週間以上の生存が見込める	⊙Yes ○No
7	患者本人から文書による同意が得られている	⊙Yes ○No

◇除外条件チェックリスト

1	胆管空腸吻合術後再発、肝細胞癌、十二指腸癌、癌性腹膜炎、粘液産性腫瘍症例ではない	⊙Yes ○No
2	ファーター乳頭部より肛門側の腸管に通過障害がない	⊙Yes ○No

図 2　UMIN-INDICEの症例登録画面

4．運用実績の検討

UMIN-INDICEを用いたJIVROSG臨床試験における登録の症例数と，登録に伴うトラブルの有無および種類について検討した。

5．システムの安全性と安定性の検討

症例登録システムのトラブルや個人情報漏洩の有無について検討した。

6．ユーザの利便性の検討

研究者に対して，システムの利便性および満足度についてのアンケート調査を行った。対象は，JIVROSG開始当初より参加し，症例登録経験をもつ研究者41名である。質問票を郵送し，回答をFAXにて回収した。質問票は，回答者の特徴，JIVROSGにおける症例登録の経験，利便性（5段階評価），他の研究への参加経験がある場合はそれとの比較（5段階評価）で構成した。

Ⅱ．結　果

1．運用実績

2003年2月～2010年7月までに27の臨床研究がJIVROSGにて施行され，このうち18試験でUMIN-INDICEを用いた症例登録が行われた。UMIN-INDICEを用いなかったのは，後ろ向き研究と別の症例登録シス

登録完了

ベア・ステント（A群）

へ割り付けされました

割り付け結果	
症例登録番号	BS-047
割付番号	A-025
割付群	ベア・ステント (対照群)
カルテ番号	000-0000
生年月日	昭和30年03月03日
登録時点の年齢	55
登録日時	2010/08/15 17:07:52

図 3 UMIN-INDICE の登録・割り付け終了画面（テスト登録用）

表 2 UMIN-INDICE における登録の難易度（n=30）

	人数（%）
登録回数	
1	3（10）
2～10	21（70）
11～20	3（10）
20<	3（10）
症例登録システムへのログオン	
容易	11（36）
比較的容易	15（50）
どちらでもない	2（7）
比較的困難	2（7）
困難	0（0）
症例登録	
容易	13（43）
比較的容易	14（47）
どちらでもない	2（7）
比較的困難	1（3）
困難	0（0）

テムが使用された前向き研究である。51 施設（うち海外 9 施設）から総数 736 症例の登録が行われた。

登録に伴うトラブルとして，研究者のパスワード紛失または未取得による事務局での代理登録が 5 回，第 I 相試験での登録一時停止の際の周知不備が 1 回みられた。これらのトラブルは電話または電子メールで 2 日以内に対処され，治療の遅延や症例登録の中止はみられなかった。

2．システムの安全性と安定性

UMIN-INDICE のシステムに起因する登録不能やデータ消失などのトラブルはみられなかった。ランダム化比較試験において，センターでのランダム化に関連するトラブルはみられなかった。また，個人情報漏洩が危惧されるトラブルはみられなかった。

表 1 アンケート回答者の背景（n=30）

特徴	人数（%）
性別	
男性	28（93）
女性	2（7）
年齢（歳）	
20～29	0（0）
30～39	14（47）
40～49	13（43）
50～59	3（10）
パソコン使用年数	
<1	0（0）
−5	2（7）
−10	5（16）
10<	23（77）
インターネット使用年数	
<1	0（0）
−5	4（13）
−10	14（47）
10<	12（40）

表 3 UMIN-INDICE の利便性についての満足度（n=30）

満足度	人数（%）
満足	15（50）
やや満足	12（40）
どちらでもない	3（10）
やや不満足	0（0）
不満足	0（0）

3．ユーザの利便性に関するアンケート結果

該当する 41 名のうち，30 名（73%）から回答が得られた。93%が男性であり，30 歳台，40 歳台が 90%を占めた。パソコン使用歴は 10 年以上が 93%，インターネット使用歴は 10 年以上が 87%であった（表 1）。

登録サイトへのログオンについては，「容易」または「比較的容易」の回答が 86%，症例登録については，「容易」または「比較的容易」の回答が 90%であった（表 2）。UMIN-INDICE の利便性については，「満足」ないし「やや満足」が 90%であった（表 3）。他の共同研究に参加経験のある 17 名によると，他の研究での症例登録方法で最も多いのは FAX（82%）であった。17 名中 15 名（88%）が，「他の方法よりも UMIN-INDICE のほうがよい」と回答した。

Ⅲ．考　察

エビデンスを創るために前向き研究として行われる臨床試験において，症例の事前登録は研究の科学的信頼性を担保するために必須である[5,7]。複数の試験を行う多施設共同研究グループにおいては，グループ内に設置した

データセンターの業務の一つとして患者登録システムを運営することが多く，かつてはFAXや電話がその手段であった。近年，インターネットの普及に伴い，インターネットを用いた症例登録が増加している[2-4]。症例登録にインターネットを用いることの利点として，症例適格性のチェックと症例番号の発行が即時完了できること，24時間いつでも症例登録が行えることがあげられる。特に時間帯の制限がないことは，多忙な日常診療と並行して行われる臨床研究において大きな利点である。われわれの検討では，700例を超える症例すべてで症例登録が問題なく完遂されており，UMIN-INDICEの実行可能性ならびに有効性は極めて高いと考えられた。

研究者主導でインターネットを用いた研究基盤を構築するには，自前のサーバを立ち上げてデータセンターを構築する方法と，企業に依頼して構築する方法，公的データセンターを利用する方法がある。自前のシステム構築には，ソフトウエアの開発とシステム維持に手間やコストがかかり，研究資金や人的資源が限定される研究者主導のグループでは実現困難なことが多い。企業に依頼する場合は，研究グループの手間は節減されるが，ソフトウエアの開発に要する時間は大幅に減少するとは限らず，また，一般に開発および維持のコストは高額であり，研究資金が恒常的に確保されないと使用は難しい。国内には国営の公的データセンターは存在しないが，UMIN-INDICEはこれに近い位置付けであり，データセンター用の情報システムおよびその運用管理を種々の研究グループが共同利用する形態をとっている[5]。この結果，研究グループが自前でサーバを用意する必要はなく，運用コストは大幅に削減される。UMIN-INDICEは2000～2010年に159のプロジェクトで利用され，登録された症例の合計は107万例を超えており[8]，このような運用管理の集中化が結果として信頼性とセキュリティならびにユーザの利便性の向上につながっている[5]。われわれの経験においても，UMIN-INDICEの利便性と信頼性が再確認された。一方，UMIN-INDICEは，データセンター機能のすべてを提供しているわけではない。データセンターに必要な人材のうち情報処理専門家，システムエンジニア，プログラマー，オペレーターを擁しているが，研究計画の作成やデータの品質管理にかかわる生物統計学者やデータマネージャーは含まれていない。このため，生物統計学者およびデータマネージャーは，研究グループごとに依頼する必要がある。

UMIN-INDICEの利便性については，われわれの検討においては高いと考えられた。理由として，同じシステムを用いることにより操作法の習得が1回で済むことと，パスワードが共通で管理が容易であることがあげられる。したがって，複数の臨床試験を行うJIVROSGのような研究グループにおいては，特に有用性が高いと考えられる。ユーザの利便性を考えるに当たっては，インターネット環境が近年急速に整備されたことも重要な要素である。マイナーなトラブルとしてパスワードの紛失があったが，研究グループ内での連絡先および対処法を明確にしておくことで迅速に対応でき，登録不能のトラブルはみられなかった。

本研究の限界として，他の症例登録法との直接比較を行っていない点があげられる。しかし，JIVROSGでは他の多施設共同研究への参加経験がない研究者が多数を占めており，そのような初心者にとっても使用しやすいシステムであることが示された点は意味があると考えられる。

結論として，複数の臨床研究を行う多施設共同研究組織であるJIVROSGにおいて，共同利用型のUMIN-INDICEは症例登録システムとして有用かつ安全性が高く，臨床研究のインフラストラクチャーとしてエビデンス生成に寄与すると考えられた。

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ORIGINAL ARTICLE

Central venous port-related infection in patients with malignant tumors: An observational study

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Abstract

Purpose. We evaluated the characteristics of central venous port (CVP)-related infection with microbiological assessments in patients with malignant tumors.

Materials and methods. In a prospective setting, patients with CVP for the treatment of malignant tumors were enrolled in this study. The incidence of CVP-related infection during three months was determined. Microbiological surveillance from skin swab was performed before and after CVP placement.

Results. Fifty-nine patients were enrolled in this study, and 60 CVPs were implanted. Thirty-six (61%) patients had head and neck malignancies. Access route was subclavian vein in 43 (71.7%) CVPs and forearm vein in 17 (28.3%). CVP-related infection was observed in three (5.1%) patients: port-pocket infection in one and probable CVP-related infection in two patients, respectively. No definitive CVP-related bloodstream infection was observed. Before the placement of CVP, colonization at the insertion site was observed in ten subclavian CVP patients, while no colonization was observed in the forearm CVP patients. At 1 and 4 weeks, detection rates of colonization were also higher in subclavian CVP patients. No definitive relationship was demonstrated between skin colonization and clinical development of CVP-related infection.

Conclusion. The rate of CVP-related infection in this prospective evaluation in patients with malignant tumors was comparable to previous studies. Colonization of the skin was more prominent in the subclavian site than in the forearm site. Although skin colonization was not proven to be a risk factor of infection, these results may draw attention to the adequate maintenance of CVP. (Trial registration: UMIN000003664).

Key words: *Central venous catheter, infection, venous port system*

Introduction

Central venous catheter (CVC)-related infection has been a frequent cause of hospital-acquired infection in patients with malignant tumors (1). Infection may lead to treatment delay and increase in patient morbidity and mortality. The reported incidence of CVC-related infections in patients with malignant tumor ranges from 7% to 19% (1,2).

The central venous port (CVP), a completely implantable device that enables repeated and long-term central venous access, was developed in the 1980s. During the past decade, the CVP has grown in importance in clinical practice in oncology for both emerging anticancer treatments and advances in supportive care. The CVP may have an advantage over the CVC in reducing the likelihood of contamination of the device by extraneous pathogens. However, infection remains a major problem in cancer patients who have undergone CVP implantation. The incidence of CVP-related infection varies between 0.9 and 10.1% (3–10). Most of the studies were retrospective investigations, and limited information regarding infection is available from prospective studies (5,7). Moreover, the

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indigenous bacterial flora of the overlying skin of the port may be associated with infectious adverse events (AEs); however, no data are available for this topic. The aim of this study was to evaluate the characteristics of CVP-related infections with microbiological assessments in patients with malignant tumors.

Materials and methods

Study design and patients

This study was a single-institute, prospective observational study on infectious AEs in patients with a central venous port system (CVP). The Institutional Review Board approved the study protocol before the initiation of patient enrollment. Between January 2010 and July 2010, eligible patients were included in this study and were prospectively observed for the study outcomes. Criteria for patient eligibility were as follows: hospitalized patient; 18 years old or older; indication for implantation of CVP for the treatment of a malignant tumor; follow-up was available at our institution; and written informed consent was obtained. Exclusion criteria included the following: pre-existing CVP, active inflammatory disease, and uncontrollable co-morbid diseases. All patients were informed of the complications and benefits of both chest port and arm port, and selected to the implantation site.

Placement procedure of CVP

All CVPs were implanted via forearm or subclavian veins in the angiography suite by interventional radiologists or in the operating room by surgeons. Prophylactic antibiotics were not used. Maximal sterile barrier precautions using sterile gloves, gown, cap, mask, and a large drape were obtained throughout the procedure. We used 10% povidone-iodine for the sterilization. All venipunctures were made with an 18-G indwelling needle after subcutaneous administration of local anesthetic.

For the forearm approach, either the ulnar or radial antecubital vein was punctured. The ulnar vein was used when possible; however, the radial vein was accessed when the ulnar vein was narrow upon visual examination. Venography was not performed when selecting the vein to access. The forearm CVP was to be inserted on the opposite side of the dominant arm except in patients with only small-caliber veins on this side. A 5-Fr heparin-coated open-ended polyurethane catheter (Anthron PU; Toray Medical, Tokyo, Japan) was inserted over the guide wire, and the tip was placed at the level of junction of the superior vena cava and right atrium. After subcutaneous administration of local anesthetic, a pocket was created by making a 2–3-cm incision 1–3 cm peripheral to the venipuncture site.

For the subclavian approach, a 5-Fr heparin-coated polyurethane catheter (same catheter used in the forearm approach) or an 8-Fr valved silicone catheter (Groshong catheter; Bard Access Systems, Salt Lake City, UT, USA) was inserted over the guide wire, and the tip was placed at the level of the junction of the superior vena cava and right atrium. A pocket was created by making a 4–5-cm incision in the ipsilateral chest wall approximately 2 cm from the puncture site.

Implantation procedures, access routes, guiding method, and required time were recorded using dedicated case report forms.

Maintenance of CVP

We did not have uniform hospital guidelines for the maintenance of CVP at the time of this investigation. In general, a port was punctured with a non-coring needle following sterilization with 10% povidone-iodine. A semipermeable transparent dressing was used to cover the needle and was fixed with adhesive tape. Needle insertion was performed when intravenous drip infusion was required. In patients with continuous or multiple infusion, a needle and an infusion line were exchanged every week. A total of 10 mL of 10% heparinized saline (100 IU/mL) was administered to lock the system before removal of the needle.

Microbiological surveillance

We undertook microbiological surveillance at three time points: on the day of the placement of the CVP, 5–7 days after the placement, and 4 weeks after the placement. On the day of the placement of the CVP, two samples were obtained with a skin swab from an area about 4 cm in diameter at the insertion site of CVP before sterilization, and just after the CVP placement in a sterilized condition. At 5–7 days and 4 weeks after the placement, skin swabs were taken from the same area without sterilization. Microorganisms were identified with Gram-stained smear examination. After searching 1000 fields per smear, samples were categorized using a five-grade scale: 0, ±, 1+, 2+, and 3+. We performed a qualitative analysis as follows: negative colonization, 0 or ±; positive colonization, 1+, 2+, or 3+. During episodes of fever (body temperature > 38.5°C) without any contributing sources other than the CVP, blood cultures were drawn from at least two sites: one via the CVP and the other by standard venipuncture. For

Table I. Definitions of the different types of CVP-related infection.

Definition
CVP-related bloodstream infection
Defined as a combination of
1) Clinical features of infection, fever, and chills
2) Isolation of the same organism from the catheter tip and peripheral blood cultures
3) No other infectious focus explaining the positive blood culture result
Port-pocket infection
1) Purulent discharge from the port pocket or other suspicious symptoms such as erythema, induration, or pain in the region of the port pocket
2) Isolation of the same organism from the catheter tip and from pus, with or without positive peripheral blood cultures
Probable CVP-related infection
Defined as a combination of
1) Clinical features of infection, fever, and chills
2) Resolution of clinical sepsis after catheter removal
3) Absence of any other infectious focus
One of the following criteria was included:
a) Isolation of the organism from the peripheral blood cultures, but the catheter-tip culture was negative
b) Isolation of the same organism from peripheral blood cultures at a different time when fever and chills followed port flush, but the catheter-tip culture was negative
c) Blood cultures were negative or not performed

CVP = central venous port.

cases of infectious signs around the port pocket, swab cultures were taken from either overlying skin or inside the pocket when removal was performed. Catheter-tip cultures were performed in patients with removal of CVP for the suspicion of CVP-related infections.

Study outcomes

The main outcome measure was the incidence of CVP-related infection at 3 months after implantation of the system. According to the Centers for Disease Control and Prevention (CDC) guidelines for the prevention of CVC-related infections (11) and previous studies (12–14) regarding CVP-related infections, CVP-related infection was classified into three categories: CVP-related bloodstream infection, port-pocket infection, and probable CVP-related infection (Table I). The follow-up period was set at 3 months because the reported median time-to-infection ranged from 27 to 119 days in previous studies (4,15,16). The presence of the symptoms and signs of infection were routinely checked daily by the nursing staff, attending physicians, or the authors until discharge. Discharged patients were seen weekly or biweekly by attending physicians or the authors. The presence or absence of infection was recorded on a case report form of this study.

Secondary outcomes included technical success of CVP placement, types, and rates of non-infectious AEs, presence or absence of colonization and types of micro-organisms from skin swab cultures, and rates and reasons of CVP removal. Non-infectious AEs were categorized according to the Common Terminology Criteria for Adverse Events (CTCAE) v4.0 and reported if grade 2 or greater AEs were encountered. In patients with grade 2 or greater AEs before CVP placement, relevant AEs were recorded when the worsening of the grade was observed.

Statistical considerations

Demographic and baseline variables were summarized by descriptive statistics. Incidences for each category of CVP-related infection were calculated as the number of first events over the number of patients at baseline. SPSS software, version 17 (SPSS, Chicago, IL, USA) was used for all analyses.

The sample size was considered 'more is better' regarding the nature of the observational study of frequency; however, we calculated the minimum required sample size in view of the feasibility of the study. We anticipated a 2.4% rate of CVP-related infection based on the median incidence from the literature. Calculating with a confidence interval of 95% and an interval estimation of 0.10, the minimum required sample was determined to be 55 (17). Thus, we set a sample size of 60 considering dropouts from the follow-up.

Results

Patient and treatment characteristics

Fifty-nine patients were enrolled in this study, and 60 CVPs were implanted: 58 patients had one CVP placement and 1 patient had two. Patient and treatment characteristics are reported in Tables II and III, respectively. Approximately two-thirds of the study population had head and neck malignancies. Forty-three (72.9%) patients underwent either chemotherapy or chemoradiotherapy as anticancer treatments. In all patients, planned follow-up was completed, and the intention-to-treat analysis was performed.

Table II. Baseline characteristics of patients (n = 59).

Characteristic	No. of patients (%)
Age, years	
Median	62
Range	24–85
Gender	
Male	41 (69.5)
Female	18 (30.5)
Primary tumor site	
Head and neck	36 (61.0)
Hematological	15 (25.4)
Gastrointestinal	4 (6.8)
Breast	3 (5.1)
Lung	1 (1.7)
Host risk factor	
Diabetes	3 (5.1)
Leukopenia[a]	5 (8.5)
Therapeutic risk factor	
Urinary catheter	0 (0)
Tracheostomy	9 (15.3)
Chest drainage tube	1 (1.7)
Prior antibiotics	10 (16.9)
Steroid use	4 (6.8)
Mean laboratory values	
Albumin, g/dL	3.5
Hemoglobin, g/dL	8.3

[a]WBC < 3000 μL.

Implantation of CVP

Technical success of CVP placement was achieved in all patients (100%). Details of the placement procedure are shown in Table IV. The access route was the subclavian vein in 43 (71.7%) CVPs, and 36 (60%) CVPs were placed by interventional radiologists in the angiography suite. All forearm CVP placements were performed by interventional radiologists.

Table III. Treatment characteristics.

Treatment	No. of patients (%)
Chemoradiotherapy	32 (54.2)
Chemotherapy alone	11 (18.6)
Radiotherapy alone	0 (0)
Stem cell transplantation	1 (1.7)
Surgery	20 (33.9)
Palliative treatments	8 (13.6)

Periprocedural AEs are addressed in the following section of non-infectious AEs.

The cumulative port access period was 2038 days (range 0–90 days, median 32.5 days), and port puncture occurred 263 times (range 0–20, median 4). In three patients, CVP was not used during the study period due to the alteration of the treatment from systemic chemotherapy to oral chemotherapy or the extension of parenteral nutrition.

CVP-related infection and colonization

CVP-related infection was observed in three patients (5.1%): port-pocket infection was observed in one patient (1.7%), and probable CVP-related infection was found in two patients (3.4%). Summaries of the characteristics of patients and infection are listed in Tables V and VI, respectively. All patients had head and neck malignancies. In two patients,

Table IV. Details of CVP placement.

Parameter	No. of patients (%)
Insertion site	
Subclavian	43 (71.7)
Forearm	17 (28.3)
Side	
Right	38 (63.3)
Left	22 (36.7)
Procedure place	
Operating room	7 (11.7)
Angiography suite	53 (88.3)
Guiding method	
Ultrasound and fluoroscopy	36 (60.0)
External landmark	24 (40.0)
Type of catheter	
Open-ended	57 (95.0)
Valved	3 (5.0)
Procedure time, minutes	
10–30	36 (60.0)
31–45	16 (26.7)
46–60	8 (13.3)
Operator experience, cases	
<10	11 (18.3)
10–50	10 (16.7)
51–100	28 (46.7)
101–200	9 (15.0)
>200	2 (3.3)

The denominator for the percentage is the total number of procedures (n = 60).

Table VI. Summary of CVP-related infection: characteristics of infection (n = 3).

Patient	Type	Onset, days	Micro-organism in the insertion site on surveillance			Micro-organisms at removal of CVP		
			Pre-CVP placement	1 week	4 weeks	Port pocket	Catheter tip	Peripheral blood
1	Port-pocket infection	66	Negative	Negative	*Corynebacterium*	*S. aureus*	*S. aureus*	Negative
2	Probable CVP-related infection	94	CNS, *Corynebacterium*	*Corynebacterium*	Negative	Negative	Negative	Negative
3	Probable CVP-related infection	69	Negative	Negative	Negative	Negative	Negative	MRSA

CNS = coagulase-negative staphylococci; *S. aureus* = *Staphylococcus aureus*; MRSA = methicillin-resistant *Staphylococcus aureus*.

definitive CVP-related culture findings were not observed; however, fever and chills were observed following the flush of a port and categorized as probable CVP-related infection. The port access periods of the patients were 60, 80, and 45 days, and the number of port punctures were 8, 10, and 5 times, respectively. These three patients were successfully treated with the removal of CVP and the administration of antibiotics. No definitive CVP-related bloodstream infection was observed in this study.

Colonization at the insertion site of CVP was observed only in ten subclavian port patients (Table VII) before sterilization on the day of CVP placement. After sterilization, only one patient showed colonization (Table VII). At baseline, indigenous skin bacteria (i.e. *Staphylococcus aureus* and coagulase-negative staphylococci) were the frequently detected micro-organisms (18.6%). At 1 and 4 weeks after placement, detection rates of all micro-organisms were also higher in subclavian CVP patients than in forearm CVP patients. Colonization at 1 and 4 weeks was observed in 10 head and neck cancer patients out of a total of 11 patients.

Non-infectious AEs

Table VIII lists non-infectious AEs that occurred during and after CVP placement. During the placement procedure, we did not encounter severe AEs. Three patients developed hematoma at the port pocket, which was treated with compression and needle drainage but did not require continuous drainage or further hemostatic treatments. Five patients experienced non-infectious postprocedural AEs. Phlebitis and system occlusion were observed in forearm port patients, and venous thrombosis and pulmonary thromboembolism were observed in a subclavian port patient. All instances of phlebitis were recorded within 1 week after insertion. In patients with system occlusion, recanalization was successfully performed by injecting a mixture of 60,000 IU urokinase and 5,000 IU heparin through a port. In one patient with venous thrombosis and pulmonary thromboembolism, we removed the CVP immediately after the diagnosis and treated the patient with anticoagulants. We did not observe any CVP-related death in this study.

Removal of CVP

We removed the CVP in seven patients (11.7%). Emergency removal for AE was needed in five patients (8.3%). In the emergency patients, the median time-to-removal was 65 days (range 34–94 days) (Table IX).

Table V. Summary of CVP-related infection: characteristics of patients ($n = 3$).

	Age	Sex	Primary tumor site	Risk factor	Laboratory data (lowest values)			Insertion site	Treatment characteristics	Insertion site	Type of catheter
					Albumin, g/dL	Hemoglobin, g/dL	Lymphocyte/μL				
1	74	M	Gingiva	Tracheostomy	1.9	7.3	350	Subclavian	Chemoradiotherapy	Subclavian	Open-ended
2	70	M	Mandible	None	2.5	8.1	220	Subclavian	Chemoradiotherapy	Subclavian	Open-ended
3	62	M	Larynx	Steroids, prior antibiotics	2.7	10.1	360	Forearm	Chemoradiotherapy	Forearm	Open-ended

Discussion

The incidence of CVP-related infection in the literature varies between 0.9 and 10.1% (3–10), and most of the studies were retrospective investigations. In this prospective study, 3 out of 59 patients (5%) presented CVP-related infection. At the surveillance of the overlying skin of the port, the subclavian site was associated with a higher incidence of colonization than the forearm site, both before implantation (23.3% versus 0%) and at 1 week (18.6% versus 5.9%) and 4 weeks after implantation (20.9% versus 11.8%). However, no definitive relation was observed between the presence of colonization and the development of infection.

According to the guidelines from the CDC (11), the density of skin flora at the catheter insertion site is a major risk factor for catheter-related bloodstream infections of CVC. The subclavian site is preferred instead of a jugular or femoral site to reduce the risk for infection because of a lower density of skin flora (18–20). In the setting of CVP, skin flora may also contribute to infection because repeated puncture is performed through the overlying skin of the port, although no data are available from the literature. In our study, more colonization was observed at the subclavian site than at the forearm site. Sadoyama et al. demonstrated that more colonization was observed at the subclavian site than at the jugular site in patients with CVCs at the intensive care unit (21). The subclavian site may be more vulnerable to skin flora than previously recognized; however, no definitive relevance with clinical infection was demonstrated in our study.

The incidence of CVP-related infection of 5% in our study is consistent with that reported in other studies (3,7,22–24). In our study, all cases of infection were observed in head and neck cancer patients. We could not eliminate selection bias. Because of the referral pattern, two-thirds of our cohort constituted head and neck cancer patients. Previous studies revealed an infection rate of 8.0%–8.4% in head and neck cancer patients (25,26), and this population may be at risk of CVP-related infection. Hematologic malignancies may also be a risk factor for infection because of intensive chemotherapies resulting in neutropenia. In our study, however, no infection was observed in patients with hematologic malignancy. Moreover, regarding the incidence of CVP-related infection, adequate diagnosis and classification are important because the reported diagnostic criteria of infection varied among studies (3,5,24) and may result in uncertainty in comparison. In our study, evaluation of infection was performed with rigorous methods to obtain reliable results.

Table VII. Colonization at the insertion site of subclavian and forearm CVPs (n = 59).

	Subclavian: No. of patients (%)				Forearm: No. of patients (%)			
	On the day of placement		1 week	4 weeks	On the day of placement		1 week	4 weeks
	Pre-sterilization	Post-sterilization			Pre-sterilization	Post-sterilization		
Gram-positive cocci	10 (23.3)	1 (2.3)	8 (18.6)	8 (18.6)	0	0	1 (5.9)	2 (11.8)
Staphylococcus aureus	0	0	1 (2.3)	0	0	0	1 (5.9)	0
CNS	8 (18.6)	1 (2.3)	5	6	0	0	0	2 (11.8)
Enterococci	0	0	0	0	0	0	0	0
Other cocci	2 (4.7)	0	2 (4.7)	2 (4.7)	0	0	0	0
Gram-negative bacilli	0	0	0	1 (2.3)	0	0	0	0
Yeasts	0	0	0	0	0	0	0	0
Others	0	0	0	0	0	0	0	0
Total	10 (23.3)	1 (2.3)	8 (18.6)	9 (20.9)	0	0	1 (5.9)	2 (11.8)

CNS = coagulase-negative staphylococci.

Various factors may contribute to the development of infection. Possible factors include the general status of the patients, therapeutic regimen, materials making up the catheter, placement procedures, and maintenance procedures. Maintenance of CVPs differs from that of other long-term venous devices such as CVCs. A reservoir in a port enables the CVP to be completely implanted under the skin and may reduce the risk of infection. However, multiple and somewhat complicated maintenance procedures are required for CVPs, which may increase the risk of contamination. Factors associated with the risk of infection at maintenance include the timing and duration of needle insertion, aseptic techniques, dressing, management of lines and hubs, and the use of prophylactics for venous thrombosis. Although definitive evidence is not established for each of these factors, sensible measures against these issues are mandatory. We have been developing a uniform protocol for the maintenance of CVP in our hospital. In particular, review and revision of the management of subclavian CVP are considered important based on the microbiological results of this study.

Table VIII. Non-infectious AEs.

AE	No. (%)
Periprocedural	
Pneumothorax	0 (0)
Arterial puncture	0 (0)
Hematoma	3 (5.1)
Total	3 (5.1)
Postprocedural	
Phlebitis	3 (5.1)
Fibrin sheath	0 (0)
System occlusion	1 (1.7)
Subcutaneous extravasation	0 (0)
Venous thrombosis	1 (1.7)
Pulmonary thromboembolism	1 (1.7)
Catheter detachment	0 (0)
Total	6 (10.1)

According to a review by Vescia et al. (27), removal of the CVP is not routinely recommended in patients with CVP-related infections. The CVP must be removed for patients with instability, systemic complications from infection, signs of port-pocket infection, persistent sepsis or relapse of infection after antibiotic treatment, or the detection of certain micro-organisms resistant to antimicrobial treatments with catheter salvage (e.g. *S. aureus* or *Candida* species). In the guidelines for CVCs, prophylactic antimicrobial therapy is not recommended (11). The efficacy of antibiotic lock of the CVP with a high-dose solution of antibiotics for treatment and prevention of infection remains controversial and is not routinely recommended (28–30). In our study, all three patients underwent catheter removal (port-pocket infection in one patient and unstable patient condition in two patients), and the patients recovered after the removal.

Several limitations of our study warrant comments. First, the cohort size was small, and the observational period was not long. The number of patients with infection of three is not sufficient to perform statistical analyses for risk factors of infection. Second, the patients were not

Table IX. Removal of CVP.

Parameter	No. of patients (%)
Removal of CVP	7 (11.7)
Indication for removal:	
Infection (total)	3 (5.1)
CVP-related bloodstream infection	0 (0)
Port-pocket infection	1 (1.7)
Probable CVP-related infection	2 (3.4)
Catheter occlusion	0 (0)
Pulmonary thromboembolism	1 (1.7)
Wound disruption	1 (1.7)
No longer needed	2 (3.4)
Median dwell time, days (range)	66 (34–103)

The denominator for the percentage is the total number of patients (n = 59).

adjusted regarding the tumor type or other factors because of the limitation of a single-arm observational study. Third, uninvestigated confounding factors may contribute to infection. Maintenance of CVP during the follow-up period certainly is the main uninvestigated confounding factor in this study. Optimization of the maintenance protocol is needed in future studies.

In conclusion, the rate of CVP-related infection in this prospective evaluation in patients with malignant tumors was comparable to that reported in previous studies. Colonization of the skin was more prominent in the subclavian site than in the forearm site. Although skin colonization was not proven to be a risk factor for infection, these findings serve to draw attention to the adequate maintenance of CVP.

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