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ORIGINAL ARTICLE

Evaluation of stent placement for vena cava syndrome: phase II trial and phase III randomized controlled trial

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Abstract

Purpose Vena cava syndrome (VCS) from stenosis of the superior vena cava or inferior vena cava caused by compression from a malignant tumor is one of the typical clinical conditions in patients with advanced stage malignant disease. VCS is difficult to manage and painful, reducing patients' quality of life. Although several reports have investigated stent placement for VCS, this treatment has never been established as the standard because of the lack of evidence of the safety and efficacy. We conducted a phase II trial and a phase III randomized controlled trial to clarify the role of stent placement in managing patients with VCS.

Methods In the phase II trial, 28 eligible patients were treated with stent placement. The efficacy of stent placement for VCS was evaluated based on the reduction of patients' symptom scores during 14 days following treatment. Technical success, technical feasibility, overall survival, recurrence of symptoms, and adverse events were evaluated. In the phase III trial, 32 patients were enrolled and randomly assigned to the test ($n = 16$) and control groups ($n = 16$). The area under the symptom score curve was compared between the groups. The EQ-5D, SF-8, and adverse events were evaluated until discontinuation of the protocol treatment or 28 days after enrollment.

Results In the phase II trial, the median patients' symptom scores significantly decreased from 10.50 before the procedure to 3.00 after the procedure. Technical success and technical feasibility rates were 96.4% and 100%, respectively. The incidence of treatment-related grade 3 or higher adverse events was 14.3%. In the phase III trial, significant superiority of stent placement was observed in the test, compared to that in the control, group. There was no significant difference in most other evaluations between the groups.

Conclusions Stent placement significantly improved the symptoms of VCS; thus, it might be accepted as the standard treatment to manage the symptoms of VCS.

Trial registration: JIVROSG-0402, JIVROSG-0807

Keywords Vena cava syndrome · Stent placement · Symptom palliation · Randomized controlled trial · Quality of life

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Introduction

Stenosis of the superior vena cava (SVC) or inferior vena cava (IVC) caused by compression from a malignant tumor is one of the typical clinical conditions occurring in patients with advanced stage malignant disease [1–3]. SVC syndrome causes symptoms of upper limb and facial edema and serious conditions and is an oncologic emergency [2, 4, 5]. Stenosis of the IVC causes edema of the lower limbs and sometimes ascites [3, 6, 7]. Brountzos et al. reported that the clinical condition caused by stenosis of the IVC is similar to that of SVC syndrome [6]. They described the symptoms caused by stenosis of the IVC as IVC syndrome, and SVC syndrome and IVC syndrome were described generically as vena cava syndrome (VCS).

VCS sometimes improves with development of the collateral pathway; however, its symptoms are usually progressive. VCS can be controlled only when the tumor is hypersensitive to chemotherapy or radiation therapy; unless improvement is impossible because surgical treatment is not indicated, the patient has a poor performance status, or medical treatments cannot maintain their effect. When VCS occurs in advanced stage cancer, it is difficult to manage and painful, reducing patients' quality of life (QOL).

Stent placement for VCS was initially reported by Charnsangavej et al. in 1986, and there have been several reports of clinical practices [1, 2, 7–10]. However, with the lack of evidence and prospective study, this treatment has never been established as the standard. Hence, we conducted a phase II trial and phase III randomized controlled trial to clarify the role of stent placement in managing patients with VCS.

Patients and methods

Phase II clinical trial (JIVROSG-0402)

Study design and patients

This prospective multi-institutional, single-arm phase II study aimed to evaluate the efficacy and safety of stent placement for VCS. The primary endpoint was the clinical effectiveness of stent placement for VCS, and secondary endpoints were the frequency and grade of adverse events, technical success rate, and feasibility. This trial was approved by the Japanese Society of Interventional Radiology and ethics committee at each participating institution, and registered in the UMIN clinical trial registry system (C000000050, www.umin.ac.jp/ctr/index.htm).

Patients with symptoms of VCS, vena cava stenosis caused by compression of a malignant tumor confirmed by contrast-enhanced computed tomography, uncontrollable symptoms with medical treatment, an Eastern Cooperative Oncology Group performance status of 0–3, adequate organ function (hemoglobin level ≥ 8.0 g/dl, white blood cell count ≥ 3000/mm^3, serum bilirubin level ≤ 3.0 mg/dl, serum creatinine level ≤ 2.0 mg/dl), normal electrocardiogram, life expectancy ≥ 4 weeks, and written informed consent were eligible. Key exclusion criteria were controllable symptoms with standard treatments, symptoms caused by an intravenous tumor, severe cardiac dysfunction, overlaps of SVC and IVC stenosis, active inflammation or active bleeding, and pregnancy.

Techniques

All procedures were performed under local anesthesia with intravenous analgesics. Prophylactic intravenous antibiotics were administered between days − 1 and 3. Venous stenosis was confirmed by digital subtraction venography (DSV), the stenosis was broken down with a guide wire and angiographic catheter, and then, a stent delivery system was inserted beyond the stenotic site. Metallic bare stents were placed across the stenotic site. The stent was chosen by the operator from commercially available ones approved in Japan for biliary or tracheal obstruction. Balloon dilatation was performed as needed. Subsequently, DSV was performed to confirm improvement of stenosis. The pressure gradient across the stenotic site was measured before and after stent placement. Lastly, the catheter and a guide wire were removed. Pre-balloon or post-balloon dilatations were permitted. Low-dose catecholamine was continually administered until the next morning to increase renal serum circulation.

Evaluation

There is no established evaluation criterion of the clinical effectiveness of treatment for VCS. Therefore, we used a patients' symptom score measured by selected items from CTCAE version 3 [11] that correlated with the symptoms of VCS (Table 1). Patient's symptom score was calculated by the grading scale sum of each item before the procedure and on day 1 and weeks 1, 2, 3, and 4 after the procedure. "Effective" was defined when the patient's symptom score decreased to 50% or less for more than 14 days compared to that before the procedure; all other instances were considered "ineffective." "Time to response" was defined as days from the procedure to the time when the patient's symptom score decreased to less than 50% compared with that before the procedure. "Technical success" was defined as the significant decrease of congestion of blood stream or the collateral vessels detected by DSV; all other cases were considered "not successful." Rates of effectiveness and technical success were based on the total number of enrolled cases. Technical feasibility was calculated with the number of patients who received stent placement of the total enrolled number of patients. Overall

Table 1 Evaluated symptoms in phase II trial and questionnaires in phase III trial

	Evaluated symptoms in phase II trial	Questionnaires in phase III trial
SVCS	1. Facial and cervical edema	1. Do you suffer swelling of face and neck?
	2. Upper limb edema	2. Do you suffer swelling of upper limbs, shoulders or chest wall?
	3. Chest wall swelling	
	4. Dilatation of thoracic subcutaneous veins	3. Do you suffer dyspnea with difficulty in lying your body down?
	5. Pleural effusion	4. Do you have headache, heaviness of the head, or excessive sleepiness?
	6. Pericardial effusion	
	7. Dyspnea	
	8. Laryngeal edema	
	9. Blurred vision	
	10. Proptosis	
	11. Hearing disorder	
	12. Tinnitus	
	13. Headache	
	14. Sleepiness	
IVCS	1. Lower limb edema	1. Do you suffer swelling of lower limbs?
	2. Genital edema	2. Do you suffer abdominal wall swelling?
	3. Abdominal wall swelling	3. Do you suffer swelling of genital or buttocks?
	4. Dilatation of abdominal subcutaneous veins	4. Do you suffer difficulty in walking, urination, or defecation?
	5. Ascites	

SVCS, superior vena cava syndrome; *IVCS*, inferior vena cava syndrome

survival in all enrolled patients and the rate of recurrence of symptoms were observed. Adverse events were evaluated with the CTCAE version 3 until 4 weeks post-procedure.

Statistical analysis

With the threshold response rate of 30% and expected response rate of 60%, $\alpha = 0.050$, $\beta = 0.10$, the number of patients required for enrollment was 28. For statistical analysis, SAS version 9.3 (SAS Institute Co., Ltd.) was used. Interim analysis was conducted when 15 cases were enrolled, and the trial was terminated when the possibility of the threshold response rate of 30% was rejected with three or fewer effective cases.

Phase III randomized controlled trial (JIVROSG-0807)

Study design and patients

Based on our phase II trial results, a phase III randomized controlled trial was conducted to evaluate the superiority of stent placement for malignant VCS with respect to other treatments by multi-institutional randomized controlled trials. This clinical trial was approved by the Japanese Society of Interventional Radiology and ethics committee at each participating institution, and registered in the UMIN clinical trial registry system (UMIN000003579).

Patients with symptoms of VCS caused by compression from a malignant tumor confirmed by contrast-enhanced computer tomography, uncontrollable symptoms with standard treatments, palliative prognostic index [12, 13] of 6 or less, and written informed consent were eligible. Key exclusion criteria were unacceptable organ function (platelet count < 50,000/mm^3, serum creatinine level ≥ 2.0 mg/dl, serum total bilirubin level ≥ 3.0 mg/dl), severe cardiac malfunction, overlaps of SVC and IVC stenosis, active inflammation or active bleeding, and pregnancy.

Eligible patients were randomly allocated 1:1 to the stent placement group (test group) and control group using the minimization method with allocation adjustment factors (institution and narrowing site of the vena cava [the SVC or IVC]). The treatment protocol for the test group was stent placement. The treatment protocol for the control was any kind of treatment, except stent placement. Termination of the treatment protocol was granted if the patient desired to withdraw or the physician deemed withdrawal necessary because of adverse events. Treatments after termination were not regulated. The primary endpoint was the area under the curve (AUC) of the symptom score curve depicted by the symptom scores until 4 weeks after registration or until termination of the treatment protocol. Secondary endpoints were improvement in scores of the EQ-5D and SF-8, adverse events, and survival time.

Evaluation

The questionnaire was used to evaluate symptoms of SVC and IVC syndromes based on the phase II trial results (Table 1). Each question item was classified into four stages of "not at all" (4 points), "a little" (3 points), "strong" (2 points), and "very strong" (1 point), and evaluated 14 times every other day from days 0 (day of enrollment) to 28, creating the total point. The AUC of the symptom score curve was calculated from the measured symptom scores [14].

To evaluate comprehensive QOL, the EQ-5D (Japanese version EuroQOL) (8.1.6) [15] and SF-8 (Japanese version, acute 1-week version) (8.1.7.) [16] were used. Evaluations were conducted twice before enrollment, and once per week between days 0 and 28. The symptomatic data collection from patients was performed by independent investigating members of this trial. When treatment was terminated within 4 weeks from enrollment, data after termination were not combined for each AUC. Adverse events were evaluated with the CTCAE version 3.0 [11]. Adverse events were evaluated when the grade increased to 1 or more compared to that before registration.

Statistical analysis

Based on the phase II trial results, the difference in AUC of the symptom score curve was estimated to be 40 and the SD as 40, and the two-sided significance level was set at 10%. Therefore, we required 16 patients per group and 32 patients overall to ensure 80% power.

Superiority between the two groups was assessed with the Wilcoxon rank-sum test in a full analysis set (FAS). For a comprehensive QOL improvement analysis, AUCs of the EQ-5D and SF-8 were used with the stratified Wilcoxon rank-sum test. In calculating the survival time, the Kaplan-Meier method and Brookmeyer and Crowley method in FAS were used, and for the inter-group comparison, the stratified log-rank test with stratification of the site of vena cava stenosis was used. The Fisher exact test was used for inter-group comparison of adverse event incidence rates in the safety analysis population. SAS versions 9.2 and 9.3 (SAS Institute Co., Ltd.) were used for statistical analyses.

Results

Phase II clinical trial

Patient population

Twenty-eight patients were enrolled between October 2005 and October 2008. All patients were eligible (Table 2). The study was not terminated based on the interim analysis. Nineteen of 28 patients were treated effectively, resulting in a clinical effectiveness rate of 67.9% (95% confidence interval [CI] 47.6–84.1%). The median patient's symptom score significantly decreased from 10.50 (range 0–26) before procedure to 3.00 (range 0–26) after procedure ($P < 0.0001$). In the SVC and IVC syndrome groups, the median patients' symptom score decreased significantly. The median time of response in the 19 effectively treated patients was 1 day (range 1–12 days, mean 3.42 days, standard deviation [SD] 3.22).

Adverse events

Five patients died within 30 days after the procedure (disease progression, three; procedure-related pulmonary thromboembolism, two). Grade 3 hypotension and low back pain were observed in one patient each (Table 4). Grade 2 stent occlusion caused by thrombosis, hypoalbuminemia, anorexia, platelet depression, and restlessness was observed (one case each). Stent occlusion occurred in one patient with symptom recurrence. The incidence of treatment-related grade 3 or higher adverse events was 14.3% (95% CI 1.3–27.3%).

Technical success rate and feasibility

Among 28 patients, significant improvement of venous stasis detected by postoperative DSV was observed in 27 patients (96.4%), and a significant decrease of collateral vessels was seen in 24 (85.7%), resulting in a technical success rate of 96.4% (27/28) (Fig. 1). Stent placement was completed in all patients, resulting in technical feasibility of 100%.

Phase III randomized controlled trial

Patient population

Between October 2009 and March 2013, 32 patients were enrolled and randomly assigned to the test ($n = 16$) and control groups ($n = 16$) (Table 2). All patients were eligible for evaluation of the primary and secondary endpoints. Stent placement was completed in all patients of the test group (Table 3). In the 16 patients of the control group, anticoagulant therapies ($n = 14$), administration of diuretics ($n = 8$), administration of albumin ($n = 2$), physical therapies ($n = 2$), chemotherapy ($n = 4$), and radiation therapy for SVC syndrome ($n = 4$) were performed (including duplication). Discontinuation of the treatment protocol occurred in 27 of 32 patients; the reason was death in 14 cases of the test group. In the control group, the treatment protocol was terminated in 13 cases because of the patients' desire ($n = 10$) and death ($n = 3$). Ten patients of the control group for whom the treatment protocol was terminated received stent placement.

Table 2 Patient characteristics

	Phase II	Phase III		
	Number (%)	VCS group Number (%)	Control group Number (%)	*P* value
Number of enrolled patients	28	16	16	0.1866
Age; median (range)	61 (29–91)	63 (42–75)	57 (38–78)	0.1866
Gender				
Male	16 (57.1%)	10 (62.5%)	7 (43.8%)	0.4795
Female	12 (42.9%)	6 (37.5%)	9 (56.3%)	
Performance status (ECOG)				
0	1 (3.6%)	0	1 (6.3)	
1	11 (39.3%)	4 (25.0)	9 (56.3)	
2	10 (35.7%)	9 (56.3)	3 (18.8)	
3	6 (21.4%)	3 (18.8)	2 (12.5)	
4	0	0	1 (6.3)	
Palliative Prognostic Index				
Mean ± SD		3.53 ± 1.34	2.69 ± 1.54	0.12
Primary disease				
Lung cancer	13 (46.4%)	8 (50.0%)	5 (31.3%)	
Colorectal cancer	5 (17.9%)	4 (25.0%)	2 (12.5%)	
Breast cancer	2 (7.1%)	0	3 (18.8%)	
Esophageal cancer	0	0	2 (12.5%)	
Others*	8 (28.6%)	4 (25.0%)	4 (25.3%)	
Stenotic portion				
SVC	16 (57.1%)	9 (56.3%)	9 (56.3%)	1.0000
IVC	12 (42.9%)	7 (43.8%)	7 (43.8%)	
Combination of RT				
In SVC syndrome	11/16 (68.8%)	2/16 (12.5%)	3/16 (18.8%)	
In IVC syndrome	0/12 (0.0%)	0/16 (0%)	0/16 (0%)	
Symptoms (mean ± SD)				
QA of symptom		16 ± 9.06	16 ± 9.28	0.78
EQ-5D		0.39 ± 0.28	0.43 ± 0.26	0.62
SF-8 (physical score)		30.2 ± 7.8	31.2 ± 7.6	0.71
SF-8 (mental score)		41.4 ± 8.9	41.8 ± 7.9	0.82

SVC, superior vena cava; *IVC*, inferior vena cava; *ECOG*, Eastern Cooperative Oncology Group score; *QA*, quantitative analysis; *RT*, radiotherapy

*Other primary diseases were hepatocellular carcinoma ($n = 1$), gastric cancer ($n = 1$), malignant lymphoma ($n = 1$), liposarcoma ($n = 1$), prostatic cancer ($n = 1$), melanoma ($n = 1$), malignant fibrous histiocytoma ($n = 1$), and thymic cancer ($n = 1$) in phase II. In phase III, hepatic neuroendocrine cancer ($n = 1$), renal cellular carcinoma ($n = 1$), liposarcoma ($n = 1$), and pancreatic cancer ($n = 1$) were included in VSC group, and melanoma ($n = 1$), pleural synovial sarcoma ($n = 1$), intrahepatic bile duct cancer ($n = 1$), and pancreatic cancer ($n = 1$) in control group

Effectiveness

The test group was significantly superior to the control ($P < 0.0001$) (Table 3). A significant difference was observed between the groups in the stratified analysis regarding the site of vena cava stenosis. Significant superiority of stent placement was not observed, except in the SF-8 physical summary score in cases of IVC syndrome ($P = 0.0455$).

Adverse events

Eight patients died within 30 days after enrollment due to disease progression. Grade 4 aspartate aminotransferase elevation and serum bilirubin elevation were observed in the test group, although the causal relationship with treatment was considered unrelated. Seventy-seven adverse events and 19 adverse events were reported in the test and control groups,

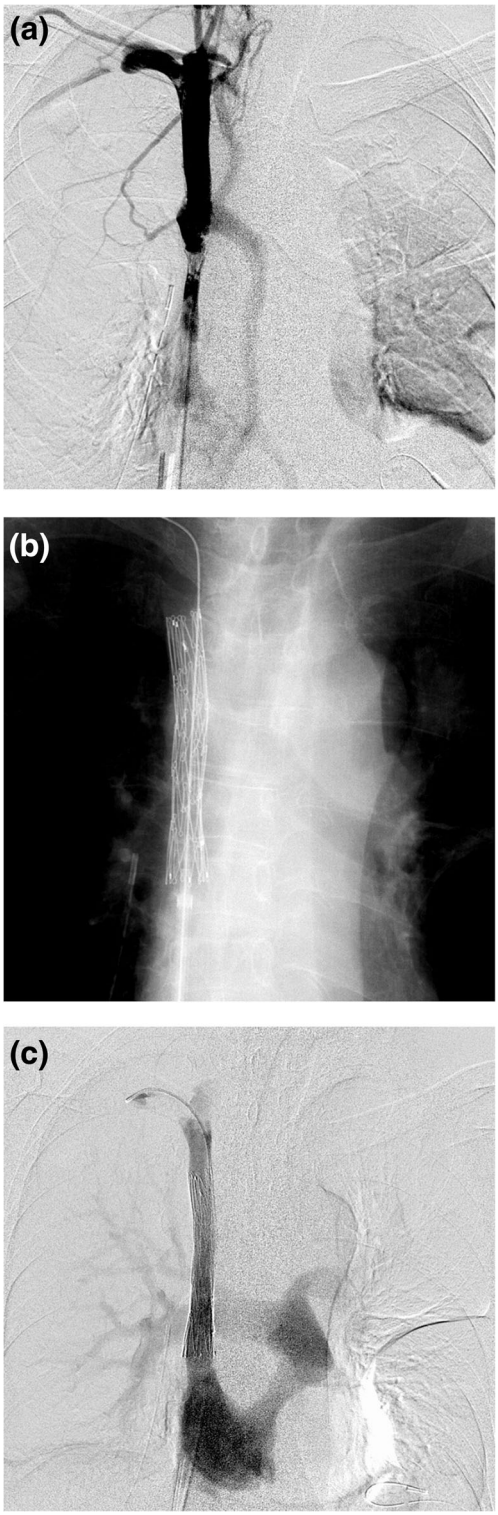

Fig. 1 A 62-year-old female with superior vena cava syndrome caused by lung cancer. **a** Venography shows severe stenosis of the superior vena cava and retrograde visualization of collateral veins such as the azygos vein. **b** Spiral Z stent (14 mm in distal diameter, 20 mm in proximal diameter, and 80 mm in length) was placed across the stenotic site of the superior vena cava. **c** Venography after stent placement demonstrates the significant improvement of flow in the superior vena cava and disappearance of collateral veins

respectively (Table 4), but there was no significant difference ($P = 0.1012$).

Survival

Median survival times were 67.0 days (range 16–639 days, 95% CI 24.0–232.0) and 93.0 days (range 18–1002 days, 95% CI 32.0–189.0) in the test and control groups, respectively. The Cox hazard ratio stratified by the site of vena cava stenosis in both groups was 1.047 (95% CI 0.471–2.328); no significant difference was observed according to the stratified log-rank test ($P = 0.9110$).

Discussion

The ratio of patients with SVC or IVC syndrome was well-balanced in both trials; so, we determined that there was no serious problem in evaluating the trial results. It took 7 years and 5 months to perform both trials. Stent placement is not a major invasive treatment like surgical treatment; however, it is invasive for patients, especially those with advanced stage cancer. We considered the main reason that we needed a long period for enrollment was the difficulty of performing trials of invasive treatment in the palliative care setting. During this study period, there was no progress in treatment for VCS.

In the phase III randomized controlled trial, the total symptom score significantly improved in the stent placement group compared with that in the control. This result was observed in patients with both SVC syndrome and IVC syndrome, and it was revealed that stent placement contributes to the improvement of symptoms caused by VCS. Yet, in the comprehensive QOL evaluation, significant improvement of the SF-8 physical summary score was observed only in the patients with IVC syndrome, and there was no difference of survival between the two groups. These results indicate the limit of stent placement for VCS. That is, stent placement can improve the symptoms caused by VCS, although it does not necessarily improve the comprehensive QOL or prolong survival.

The main weakness of this study is that there was no established evaluation criterion of clinical effectiveness for the treatment of VCS. Therefore, in the phase II trial, we used the patient's symptom score. Additionally, in the phase III randomized controlled trial, we used the AUC of symptom score curve for SVC and IVC syndromes. The evaluation method using the AUC of QOL curve has been previously reported in a clinical trial of palliative care [14]. We understand these methods for evaluation are not ideal and not suitable for comparison with previous studies; however, given the lack of evidence of patient-reported outcomes in this field, presently we believe that it is acceptable to evaluate the

Table 3 Procedure of vena cava stenting and change in symptoms

	Phase II	Phase III		
	Number (%)	VCS group Number (%)	Control group Number (%)	*P* value
Number of cases	28	16	16	
Accomplished stenting	27 (96.4%)	16 (100%)	–	
Mean operation time				
Mean ± SD (minutes)	70 ± 39.4			
Accessed vein				
Femoral vein	19 (67.9%)			
Jugular vein	6 (21.4%)			
Femoral and jugular veins	3 (10.7%)			
Mean pressure gradient across stenosis (mmHg)	▼13.9 ± 7.86	▼9.35 ± 4.91	–	
AUC of symptom		Mean ± SD	Mean ± SD	
SVC		79.7 ± 63.7 ($n = 9$)	1.0 ± 17.1 ($n = 9$)	0.0009*
IVC		91.6 ± 42.3 ($n = 7$)	21.7 ± 39.6 ($n = 7$)	0.018
Overall		84.9 ± 54.0‡	10.0 ± 30.0‡	< 0.0001†

AUC, area under the curve; *SVC*, superior vena cava; *IVC*, inferior vena cava

*Wilcoxon rank sum test

†Stratified Wilcoxon rank sum test adjusted for the SVC/IVC

‡Overall mean and SD was calculated without adjustment for the SVC/IVC

change of subjective symptoms objectively in special clinical conditions such as VCS.

Regarding patient selection, eligibility criteria were less strict in the phase III randomized controlled trial than those in the phase II trial. Because complicated symptoms coexist in patients of the palliative care setting, we thought narrowed eligibility criteria were unsuitable for generalizability of the results to general clinical practices. In order to maintain the

Table 4 Adverse events

	Phase II*	Phase III**	
	$N = 28$	VCS group $N = 16$	Control group $N = 16$
Grade 3	Hypotension (1), lumbago(1)	Hypoxia (4), dyspnea (4), ALT increased (2), AST increased (2), ALP increased (2), bilirubin increased (2), pneumonia (2), gastrointestinal bleeding (2), platelet count decreased (1), nausea (1), thrombosis (1), hyperglycemia (1), somnolence (1), confusion (1), anorexia (1), hypoalbuminemia (1), pulmonary edema (1), paralytic ileus (1), vomiting, pain (lower extremity) (1), lumbago (1), epigastralgia (1), headache (1), hyponatremia (1), edema (head and neck) (1), edema (extremities) (1)	Dyspnea (3), hypoxia (2), AST increased (1), bilirubin increased (1), pneumonia, hyponatremia (1), edema (head and neck) (1), hypotension (1), fatigue (1)
Grade 4	Pulmonary thromboembolism (2)	Dyspnea (1), AST increased (1), bilirubin increased (1), hyponatremia (1), hypotension (1), fatigue (1)	Edema (extremities) (1)

AST, aspartate aminotransferase; *ALT*, alanine aminotransferase; *ALP*, alkaline phosphatase

*Adverse events grade 3 or above related to vena cava stent placement (adverse reaction) are listed

**Adverse events grade 3 or above after vena cava stent placement are listed

safety of stent placement, we added some conditions in the exclusion criteria to prevent pulmonary thromboembolism and heart failure caused by the increase of venous return.

Considering that there has been no standard treatment for improving symptoms caused by VCS, it is extremely important that this study showed the advantage of stent placement for the improvement of symptoms caused by VCS. Although the prolongation of survival may be proven with a new randomized controlled trial of selected patients such as those with SVC syndrome, this seems difficult to achieve.

Conclusions

Stent placement significantly improved the symptoms of VCS. Although the power was limited in improving the comprehensive QOL scores and prolonging survival time, stent placement might be accepted as the standard treatment to manage the symptoms of VCS.

Compliance with ethical standards

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

Ethical approval All procedures performed in this study which involved human participants were in accordance with the ethical standards of the institutional national research committee and with the 1964 Helsinki declaration and its later amendments are comparable ethical standards.

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