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Original Article

Endovascular stenting for end-stage lung cancer patients with superior vena cava syndrome post first-line treatments − A single-center experience and literature review

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Abstract

Background: Superior vena cava (SVC) syndrome is a major complication that occurs when a growing lung malignancy compresses the SVC extrinsically. Current treatment options include radiotherapy or chemotherapy to shrink the tumor or endovascular stenting of the SVC to restore flow. Herein, we report a case series treated in a single institution to demonstrate the safety, effectiveness, and outcomes of salvage and primary stenting for malignant SVC obstruction.
Methods: A total of 12 male patients with malignant superior vena cava obstruction caused by lung cancer underwent SVC stenting from October 2009 to May 2015. Data were reviewed retrospectively, including demographic and clinical characteristics, procedural details, and outcomes.
Results: Seven patients had received radiotherapy prior to SVC stenting, while the other five patients received stenting as first-line therapy for SVC syndrome. Only one patient experienced initial symptomatic improvement after radiotherapy, and symptoms of SVC syndrome recurred one year later. Wallstents® (Boston Scientific, Natick MA, USA) were used in all patients. Preoperatively, the mean narrowest SVC diameter measured by CT was 2.16 mm (0−5.5 mm). Technical success was achieved in all patients without complications such as pulmonary embolism, rupture or bleeding. Postoperative mean narrowest SVC diameter measured by CT during follow-up was 11.17 mm (8−13.5 mm). Symptoms of SVC syndrome such as arm and face swelling and dyspnea improved within 1−5 days in all patients. After median follow-up duration of 11.5 months, only one patient presented recurrent SVC syndrome due to in-stent thrombosis two months after stenting.
Conclusion: Salvage SVC stenting remains a safe and effective treatment for patients with SVC obstruction after failure of radiotherapy and chemotherapy. Primary stenting may be considered at initial presentation of SVC syndrome to improve patients' quality of life.

Keywords: Lung neoplasm; Stent; Superior vena cava syndrome

1. Introduction

Superior vena cava (SVC) syndrome comprises a group of signs and symptoms secondary to SVC obstruction. Obstruction occurs when venous return from the SVC to the right atrium is compromised, mostly by a growing malignancy compressing the SVC extrinsically.[1−5] In the absence of adequate collaterals, the resulting elevated venous pressure in the upper body leads to edema of the head, neck, and upper extremities. Rarely, swelling of the larynx may cause life-threatening airway obstruction and cerebral edema, which can result in confusion and coma. While treatment of underlying malignant disease is paramount, it may be slow to alleviate the patient's discomfort. In some radiosensitive malignancies, radiotherapy may effectively reduce

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symptoms by reducing the tumor size,[3,6] but this process can take weeks to months and has a higher recurrence rate. The increasing technical and clinical success rate of SVC stenting makes it another option for salvage therapy after conventional radiochemotherapy has failed. In fact, Ganeshan et al. suggested that primary SVC stenting should be the first-line treatment to relieve the symptoms of SVC syndrome.[4] The aim of the present study was to review our SVC stenting experience retrospectively in order to validate the safety, effectiveness, and outcomes of salvage and primary stenting for malignant SVC obstruction.

2. Methods

2.1. Patients

The data of 12 patients with clinical symptoms of SVC obstruction who underwent SVC stenting in Taipei Veterans General Hospital between October 2009 and May 2015 were reviewed retrospectively, including chart review of indications, clinical characteristics, procedures, complications, and outcomes (Table 1). The Institutional Review Board of Taipei Veterans General Hospital approved the study protocol, and patients' informed consent was waived due to the retrospective nature of the study. All included patients had SVC syndrome caused by lung cancer, including adenocarcinoma, large cell carcinoma and small cell carcinoma. All the patients experienced swelling over their faces, neck and arms, which limited their range of motion and caused distended discomfort or even pain. Except for one patient who received chemotherapy during the month prior to SVC stenting, all other patients had received chemotherapy for at least two months prior to SVC stenting. Seven patients had received radiotherapy targeting the lesion adjacent to the SVC. Only one patient experienced symptom improvement after radiotherapy; however, symptoms of SVC syndrome recurred in that patient one year later and were not resolved by the second radiotherapy. All patients received chest CT scan follow-up at 3 months, 6 months and then yearly after the procedure.

Table 1
Patients' demographic and clinical characteristics.

Characteristic	Value
Age (years)	58.4 (37–76)
Gender	
Male	12
Female	0
Cause of superior vena cava syndrome	
Adenocarcinoma	6
Squamous cell carcinoma	1
Large cell carcinoma	2
Small cell lung cancer	3
Previous treatment	
Radiotherapy	7
Chemotherapy	12
Duration of superior vena cava syndrome since diagnosis (months)	20.3 (1–53)
Stenosis site	
SVC	10
SVC + Right internal jugular vein	1
SVC + Right internal jugular vein + Innominate vein	1
Thrombosis	5
Previous port-A insertion	2

2.2. Methods

Interventions were performed using local anesthesia in nine patients and general anesthesia in three patients. Right femoral venous access was used in 11 patients (Table 2). Each patient received 3000 IU heparin bolus prior to the procedure. After cavography was performed and the route was confirmed (Fig. 1A), a 0.035-in 180-cm Terumo wire (Radifocus®, Terumo, Tokyo, Japan) under support of a Glide catheter (Glidecath®, Terumo, Tokyo, Japan) was used to traverse the stenosis to the right internal jugular vein (RIJV) or right subclavian vein. Five patients had thrombosis within the SVC, and three with extensive thrombus burden needed thrombolytic therapy with urokinase 120,000 IU injections locally in the SVC. A 0.018-in guidewire was needed in an occasional patient with severely stenotic lesions. After crossing the lesion, the hydrophilic wire was replaced with Amplatz Super Stiff ™ Guidewire (Boston Scientific, Boston, MA, USA). Predilatation of SVC was usually not necessary unless the SVC was chronically occluded. In this case series, only three patients needed predilatation of SVC with a 10-mm-in-diameter balloon (Fig. 1B). Once the lesion was confirmed, the diameter of the proximal and distal end of the lesion was measured over the relatively healthy site. A Wallstent™ (Boston Scientific, Boston, MA, USA) was deployed across the lesion. Additional stents were used in cases in which a single stent could not safely bridge the lesion. The XXL™ balloon dilatation catheter (Boston Scientific, Boston, MA,

Table 2
Treatment characteristics of 12 patients receiving SVC stenting.

Procedure and outcomes	
Approach site	
Right internal jugular vein	1
Right common femoral vein	11
Anesthesia	
General anesthesia	3
Local anesthesia	9
Pre-dilatation	3
Post-dilatation	12
Thrombolytic therapy with urokinase	3
Number of stents	
1	9
2	2
3	1
Postoperative anti-thrombosis therapy	
Warfarin	2
Clopidogrel	10
Follow-up (months)	11.5 (0.3–17)
Symptoms relieved	12
6-Month primary patency rate	91.67%
6-Month secondary patency rate	100%
Pre-stenting SVC narrowest diameter (mm)	2.16 (0–5.5)
Post-stenting SVC narrowest diameter (mm)	11.17 (8–13.5)
Stent thrombosis	2
Total	1
Partial	1

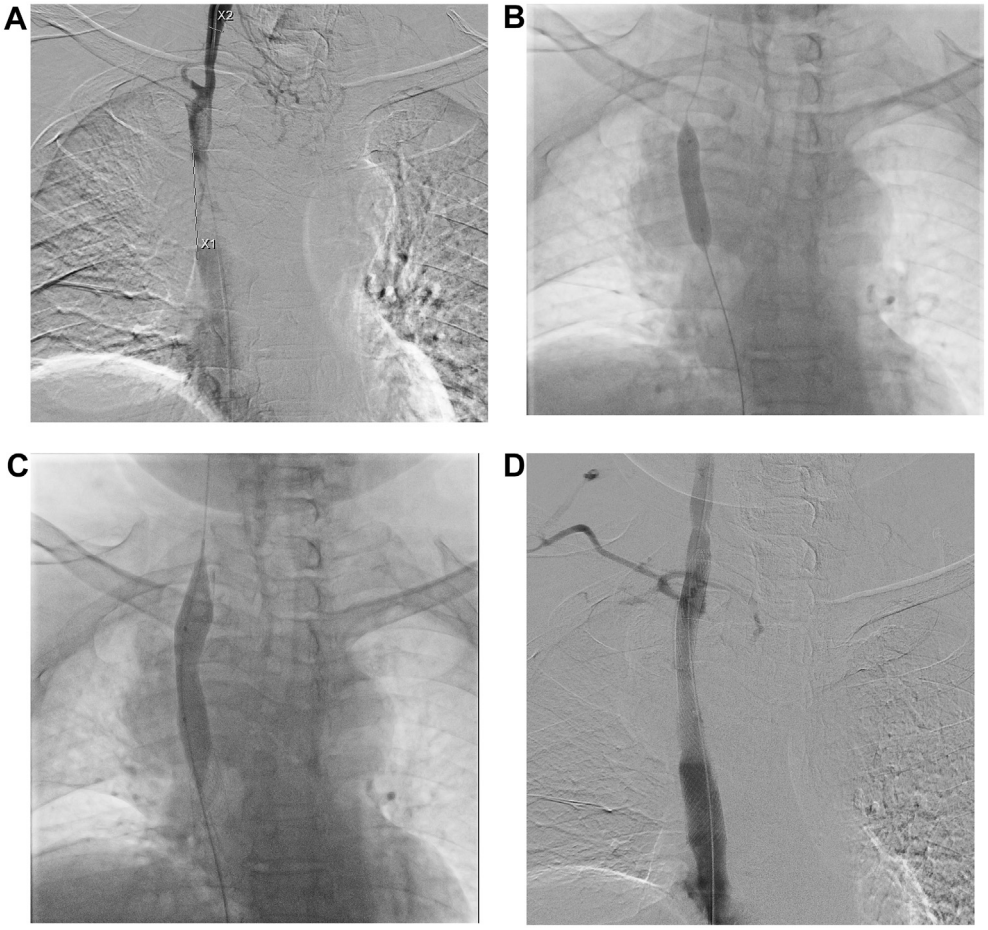

Fig. 1. (A) Nearly total occlusion of SVC with thrombus formation near internal jugular vein. (B) Predilatation of SVC with a 10 mm-in-diameter balloon. (C) Postdilatation after SVC stenting with an 18 mm-in-diameter balloon. (D) Final angiogram showed patency of SVC.

USA) was used for post-dilatation to expand the stent (Fig. 1C). Finally, completion venography was performed (Fig. 1D). After removing the wire and the sheath, the puncture wound was compressed to achieve hemostasis.

One patient with extensive preoperative obvious thrombus in the SVC received low-molecular-weight heparin injection bridging to warfarin therapy post-procedure. Another patient with profound thrombus required continuous infusion of urokinase at the rate of 20,000 IU per hour for one day; warfarin treatment was then given, and no in-stent thrombosis was noted during follow-up. The INR was maintained around 2. In the remaining nine cases, only clopidogrel was prescribed after stent insertion.

3. Results

Our technical success rate with this case series was 100%, without any complications. The technical success rate was 100% in that all patients experienced symptomatic relief within 1–5 days, including resolution of edema over the face, neck and arms (Fig. 2A and B). Due to the terminal stage of lung malignancy, the median follow-up duration was only 11.5 months (0.3–17 months). Preoperative mean SVC diameter as measured by CT scan was 2.16 mm (0–5.5 mm). Postoperative CT imaging showed patent SVC stents in 11 patients, and the mean narrowest diameter of SVC was 11.17 mm (8–13.5 mm). Two patients received 2 stents, and one patient received 1 stent insertion because the stent length wasn't long enough to cross the whole lesion. One patient experienced recurrent SVC syndrome due to in-stent thrombosis, with total occlusion at 2 months post-procedure, and was treated with thrombolytic therapy and balloon angioplasty. Another patient had partial thrombosis of the stent, which did not cause recurrent symptoms. Progressive cancer in another patient compressed the stent with significant narrowing of the lumen, but with no thrombosis and no recurrent symptoms. No further intervention was performed in these two asymptomatic patients. The 6-month primary patency rate was 91.67%, and the 6-month secondary patency rate was 100%. No major complications, such as SVC rupture, stent migration or pulmonary embolism occurred in any patient in this series.

4. Discussion

SVC syndrome is an extremely troublesome condition in end-stage lung cancer patients. Despite the increasing incidence

Fig. 2. (A) Patient experienced face swelling before the operation. (B) The swelling improved after SVC stent.

of central catheter-related thrombosis, the leading cause of SVC syndrome is malignancy, accounting for 65–80% of cases.[4,7–11] Among these cases, lung cancer is the most common, followed-by lymphoma and metastatic tumor.[8,10,12,13] In our experience with this case series, all patients had end-stage lung cancer and all received chemotherapy and/or targeted radiotherapy. SVC syndrome developed approximately 0.5–2 years after the initial diagnosis, either due to compression of metastatic lymph nodes or the tumor itself over the right upper lung. Eleven of our patients received chemotherapy for at least two months prior to stenting without relief of symptoms. All patients then required successful SVC stenting to obtain symptom relief. Seven patients had already received radiotherapy for SVC syndrome, with radiation doses ranging from 3000 cGy to 6600 cGy targeting the tumor base. In the present study, only one patient experienced symptom relief, as a result of radiotherapy 5000 cGy. However, face swelling recurred one year later, at which time the patient underwent a second course of radiotherapy 3200 cGy targeting the SVC but failed to improve. This patient also had extensive SVC thrombosis extending to the right internal jugular vein, innominate vein and bilateral subclavian vein. The patient received stent insertion one month after the second attempt at radiotherapy, and the symptoms improved.

Endovascular stenting for SVC syndrome has a high technical success rate, greater than 95% in some series.[11,14–17] The clinical success rate, as defined by symptoms remission, can be as high as 80%.[4,11,14–17] SVC stenting can usually be performed under local anesthesia, and the most crucial step in the procedure is to cross the stenotic lesion. In cases of near total occlusion, bi-directional cannulation (femoral vein and jugular vein approach) can be helpful. Pharmacological thrombolysis was performed in this series when necessary to reduce excessive thrombus burden and prevent complications of thromboembolism. Dosage of urokinase was determined according to each patient's weight and thrombus burden, while balancing the risks of bleeding and the severity of thrombosis individually. In cases of bilateral brachiocephalic vein thrombosis, restoring flow in one vein is usually sufficient to relieve symptoms on both sides.[1,4,14,18,19] This is likely explained by the fact that the collaterals would cross midline and drain the contralateral vein. Cannulation of both veins is not only time-consuming but is also technically difficult and not cost effective.[1,4,14,18] One of the patients in our series received balloon dilatation at the orifice of the innominate vein because the stenosis involved both veins.

Normal diameter of the SVC ranged from 18 to 22 mm in the present series. The mean diameter of the compressed SVC was 2.16 mm preoperatively and 11.17 mm postoperatively. Although the diameter of the SVC did not return to normal size after stenting due to persistent external tumor compression, the symptoms of dyspnea and swelling of the face and arms improved markedly in all patients.

Major complications after SVC stenting for SVC syndrome have been reported, but only rarely. Complications have included mainly SVC rupture, cardiac tamponade, pulmonary embolism and hemorrhage. Other minor complications such as puncture site hematoma, chest pain and hemoptysis have also been reported. Stent migration into the right atrium or even right ventricle is of particular concern.[4,14–16,19] This can be minimized by accurate measurement of vascular size, adequate oversizing of the stent and proper positioning of the stent at the stenosis site. None of these technical complications occurred in any patient in our series. The most common late complication following SVC stenting is in-stent restenosis or thrombosis, which has been found in 0–40% of patients.[4,14–16,19] Late in-stent thrombosis or restenosis can be a result of direct thrombus formation, extrinsic compression or direct invasion of the tumor. Since the aim of SVC stenting is to alleviate patients' discomfort, we only repeat intervention to the patient with symptom recurrence.

While there is no consensus in the literature regarding the effectiveness of anticoagulation therapy in preventing SVC stent thrombosis, anticoagulants or anti-platelet agents are generally prescribed for a period of 1−9 months post-operatively.[4,14,16,19,20] Currently, no large clinical trials are underway that compare antiplatelet agents vs. anticoagulants after SVC stenting. In our series, we chose clopidogrel because it exhibits higher potency in anti-platelet aggregation effect than aspirin and is recommended by the American College of Chest Physicians for patients undergoing peripheral vascular angioplasty.[21] We prescribed warfarin for patients who had significant thrombus in the SVC.

Just as there is no consensus regarding anticoagulation regimens, no agreed upon routine imaging follow-up protocol is found in the literature. Most patients in our series received regular surveillance CT scans to follow the primary lung neoplasm or to monitor the SVC to watch for recurrence of SVC syndrome. Once a diagnosis was confirmed which was compatible with the patient's symptoms, endovascular intervention was recommended, either by thrombolysis therapy, balloon dilatation or repeat stenting.

No prospective studies have compared the outcomes of stenting with those of chemotherapy and/or radiotherapy in SVC syndrome. To date, more and more studies have indicated that SVC stenting may be the most appropriate first-line therapy instead of being reserved for salvage treatment following radiotherapy or chemotherapy. Although our short-term results for SVC stenting are promising, the present study is not without limitations. First, this was a retrospective study with only a small number of patients. Secondly, due to the nature of end-stage lung cancer, the follow-up time is relatively short and the long-term patency rate is unknown. Finally, no objective scoring system or quality-of-life metrics is available to describe improvement in symptoms. Clinical success in this case series could only be confirmed by subjective description and clinical observation. Nevertheless, all patients in the present series were satisfied with the symptomatic relief after SVC stenting.

In conclusion, endovascular stenting is safe and effective for relieving malignant SVC obstruction in both primary and salvage stenting settings. Salvage SVC stenting remains an efficient treatment after failure of radiotherapy and chemotherapy. Results of this study suggest that primary SVC stenting may be considered as first-line therapy for SVC syndrome to provide an efficient and effective improvement of quality of life in patients with end-stage lung cancer.

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References

1. Nicholson AA, Ettles DF, Arnold A, Greenstone M, Dyet JF. Treatment of malignant vena cava obstruction: metal stents or radiation therapy. *J Vasc Interv Radiol* 1997;**8**:781−8.
2. Baker GL, Barnes HJ. Superior vena cava syndrome: etiology, diagnosis, and treatment. *Am J Crit Care* 1992;**1**:54−64.
3. Armstrong BA, Perez CA, Simpson JR, Hederman MA. Role of irradiation in the management of superior vena cava syndrome. *Int J Radiat Oncol Biol Phys* 1987;**13**:531−9.
4. Ganeshan A, Hon LQ, Warakaulle DR, Morgan R, Uberoi R. Superior vena caval stenting for SVC obstruction: current status. *Eur J Radiol* 2009;**71**:343−9.
5. Urban T, Lebeau B, Chastang C, Leclerc P, Botto MJ, Sauvaget J. Superior vena cava syndrome in small cell lung cancer. *Arch Intern Med* 1993;**153**:384−7.
6. Rodrigues CI, Njo KH, Karim AB. Hypofractionated radiation therapy in the treatment of superior vena cava syndrome. *Lung Cancer* 1993;**10**:221−8.
7. Parish JM, Marschke Jr RF, Dines DE, Lee RE. Etiologic considerations in superior vena cava syndrome. *Mayo Clin Proc* 1981;**56**:407−13.
8. Chen JC, Bongard F, Klein SR. A contemporary perspective on superior vena cava syndrome. *Am J Surg* 1990;**160**:207−11.
9. Rice TW, Rodriguez RM, Light RW. The superior vena cava syndrome: clinical characteristics and evolving etiology. *Medicine (Baltimore)* 2006;**85**:37−42.
10. Wilson LD, Detterbeck FC, Yahalom J. Superior vena cava syndrome with malignant causes. *N Engl J Med* 2007;**356**:1862−9.
11. Chatziioannou A, Alexopoulos T, Mourikis D, Dardoufas K, Katsenis S, Lazarou S, et al. Stent therapy for malignant superior vena cava syndrome: should be first line therapy or simple adjunct to radiotherapy. *Eur J Radiol* 2003;**47**:247−50.
12. Detterbeck FC, Parsons AM. Thymic tumors. *Ann Thorac Surg* 2004;**77**:1860−9.
13. Rice TW, Rodriguez RM, Barnette R, Light RW. Prevalence and characteristics of pleural effusions in superior vena cava syndrome. *Respirology* 2006;**11**:299−305.
14. Lanciego C, Pangua C, Chacón JI, Velasco J, Boy RC, Viana A, et al. Endovascular stenting as the first step in the overall management of malignant superior vena cava syndrome. *AJR Am J Roentgenol* 2009;**193**:549−58.
15. García Mónaco R, Bertonia H, Pallota G, Lastiri R, Varela M, Beveraggi EM, et al. Use of self-expanding vascular endoprostheses in superior vena cava syndrome. *Eur J Cardiothorac Surg* 2003;**24**:208−11.
16. de Gregorio Ariza M, Gamboa P, Gimeno MJ, Alfonso E, Mainar A, Medrano J, et al. Percutaneous treatment of superior vena cava syndrome using metallic stents. *Eur Radiol* 2003;**13**:853−62.
17. Nguyen NP, Borok TL, Welsh J, Vinh-Hung V. Safety and effectiveness of vascular endoprosthesis for malignant superior vena cava syndrome. *Thorax* 2009;**64**:174−8.
18. Dinkel HP, Mettke B, Schmid F, Baumgartner I, Triller J, Do DD. Endovascular treatment of malignant superior vena cava syndrome: is bilateral wallstent placement superior to unilateral placement? *J Endovasc Ther* 2003;**10**:788−97.
19. Jackson JE, Brooks DM. Stenting of superior vena caval obstruction. *Thorax* 1995;**50**:S31−6.
20. Warner P, Uberoi R. Superior vena cava stenting in the 21st century. *Postgrad Med J* 2013;**89**:224−30.
21. Alonso-Coello P, Bellmunt S, McGorrian C, Anand SS, Guzman R, Criqui MH, et al. Antithrombotic therapy in peripheral artery disease: antithrombotic therapy and prevention of thrombosis, 9th ed. American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* 2012;**141**(Suppl 2):e669S−90S.