Aus der Universitätsklinik und Poliklinik für Diagnostische Radiologie
an der Martin-Luther-Universität Halle-Wittenberg
(Direktor: Prof. Dr. med. R.P.Spielmann)

und
der Zentralklinik Bad Berka GmbH
Akademisches Lehrkrankenhaus des Universitätsklinikums Jena
(Direktor: Prof. Dr. med. W. Karzai)

Tumor-related Superior Vena Cava Syndrome- Symptomatic Therapy by Stent Placement in the Superior Vena Cava. Evaluation of a Patient Group of the Zentralklinik Bad Berka GmbH 1996 – 2009

Dissertation
zur Erlangung des akademischen Grades
Doktor der Medizin (Dr. med.)

vorgelegt
der Medizinischen Fakultät
des Universitätsklinikums Halle (Saale)

von Noha Antakia
geboren am: 13.04.1976 in Alexandria

Betreuer: Dr. med. habil. Hans-Jürgen Strauß

Gutachter: PD H.-J. Strauß (Bad Berka/ Jena)
Prof. R. Spielmann
PD R. Aschenbach (Jena)

16.02.2016

18.05.2017

To my loving family

Referat

Aim of the study is evaluation of the effectiveness and possible complications of superior vena cava stenting in malignant SVCS as a palliative measure and reaching a recommendation for these interventions.

Materials and Methods:

In the Zentralklinik Bad Berka SVC stenting in 95 patients (76 men, 19 women) with malignant SVCS (35 SCLC, 51 NSCLC, 9 extra pulmonary tumors with mediastinal metastasis) was performed. Self-expandable stents (91 Memotherm stent, 6 Wall stent, 18 Sinus-XL stent und 5 Gianturco-Z stent), were used. Before stenting diagnostic imaging using MSCT and phlebography was done. Stent implantation was performed through the trans-femoral venous route under ECG monitoring.

Results:

Stenting was abandoned in 2 patients because of cardiac complications. In 93 patients were 120 stents implanted. Patency of the venous drainage till the time of death was noted in 70.6% of cases, re-occurrence of SVCS was found in 18,9% patients and in the remaining 8,4% we did not have any follow-up data. The survival rate was determined by the underlying malignancy and ranged between 251 and 269 days with a median of 152 days.

Some factors proved to have no effect on the patency rate, such as post procedural heparinization and the type of stent used. Complications were rare and consisted of 2 asymptomatic partial stent migration in den right atrium, 1 intermediate arrhythmia, early re-closure in 7 cases und late re-closure in 8 cases. In three cases of re-obstruction a second intervention and new stent implantation secured a patent venous drainage.

Stent implantation is clinically effective and accompanied with only small risk. The indication for stenting in malignant SVCS should be decided interdisciplinary case by case also with considering other options of treatment.

Antakia, Noha: Tumor-related Superior Vena Cava Syndrome-Symptomatic Therapy by Stent Placement in the Superior Vena Cava. Evaluation of a Patient Group of the Zentralklinik Bad Berka GmbH 1996–2009, Halle(Saale), Univ., Med. Fak., Diss., 63 pages, 2016

List of Contents

List of Abbreviations

Ca	Cancer
CT	Computed tomography
F	French
IU	International Unit
IVC	Inferior Vena Cava
LMWH	Low Molecular Weight Heparin
mm	millimeter
MRI	Magnetic Resonance Imaging
n	number
NSCLC	Non-Small Cell Lung Cancer
OP	Operation
pts	patients
rt-PA	recombinant Tissue Plasminogen Activator
SCLC	Small Cell Lung Cancer
SD	Standard Deviation
SVC	Superior Vena Cava
SVCO	Superior Vena Cava Obstruction
SVCS	Superior Vena Cava Stenosis

1 Introduction

1.1 Definition and Incidence of Superior Vena Cava Syndrome

Superior vena cava syndrome (SVCS) is a set of symptoms including swelling of the head, neck and upper extremities that result when blood flow from the superior vena cava (SVC) to the heart is blocked. It is observed in any condition that leads to obstruction of blood flow through the SVC. This obstruction can be caused by invasion or external compression of the SVC by adjacent pathologic processes involving the right lung, lymph nodes and other mediastinal structures, or by thrombosis within the SVC. In some cases, both external compression and thrombosis can coexist. Furthermore SVCS can manifest clinically as a medical emergency (Cheng, 2009).

Superior vena cava syndrome was first described by William Hunter in 1757 in a patient with syphilitic aortic aneurysm. In 1954 Schechter (Schechter, 1954) described the syndrome in 274 cases, 40% of whom were due to syphilitic aortic aneurysm or tuberculous mediastinitis. With the introduction of effective antibiotic treatment, such etiologies have markedly decreased in incidence with neoplastic cases currently taking the upper hand and representing the most common etiology of superior vena cava syndrome especially with the increasing incidence of lung malignancies. Currently malignancy is responsible for up to 60% of cases of superior vena cava syndrome (Rice et al., 2006).

In the United States, the incidence of superior vena cava syndrome is estimated to be about 1500 cases per year (Wilson et al., 2007). According to Rowell et al. (Rowell and Gleeson, 2002), 3–4% of patients with bronchogenic cancer will develop superior vena cava syndrome.

1.2 Etiology of Superior Vena Cava Syndrome

A wide spectrum of diseases can cause obstruction of the superior vena cava. The obstruction can be due to external compression, invasion, or thrombosis. During the first part of the 20th century, benign causes accounted for more than half of all cases of superior vena cava obstruction. Currently malignancy is the main etiology (Dempke et al., 1999), usually caused by extrinsic compression and less commonly by invasion of the superior vena cava (Kim et al., 2013). Another common cause in recent years is intravascular thrombosis associated with the use of intravascular devices such as catheters and pacemakers' wires (Rice et al., 2006).

Since a growing majority of contemporary cases of superior vena cava syndrome are due to a combination of etiologies, it is helpful to consider pathologic mechanisms that often coexist to predispose to vascular obstruction in this particular anatomic location. In these cases, superior vena cava syndrome can be attributed to at least one or more of the following 3 pathologic mechanisms: compromised vessel anatomy, compromised vessel wall integrity, and compromised venous blood flow. Both common and rare conditions that are associated with SVC syndrome fall into one or more of these categories (Cheng, 2009).

1.2.1 Compromised Vessel Anatomy

Extrinsic compression from a mediastinal mass is a classic cause of superior vena cava syndrome. Although this is often due to malignancy, less commonly occurring non-malignant masses include goiter, sarcoid, aspergilloma, and large ascending aortic aneurysms. Other benign causes include cystic fibrosis, pulmonary artery dilation, pleural or pericardial effusion, congenital cardiovascular disease such as absent superior vena cava or conditions post-cardiovascular surgery in children with severe congenital cardiac abnormalities (Cheng, 2009). Amongst intrathoracic malignancies, which constitutes the main etiology, non–small-cell lung cancer account for about 50% of malignant causes, and the incidence is more with squamous cell lung carcinoma (10%) than non-squamous cell lung carcinoma (1,7%).

Small-cell lung cancer represent 22% of malignant causes, Lymphoma about 12%, Metastatic cancer about 9%, Germ-cell cancer about 3%, Thymoma about 2%, Mesothelioma about 1% and other cancers account for about 1% of malignant cases (Wilson et al., 2007).

1.2.2 Compromised Vessel Wall Integrity

A compromised SVC vessel wall integrity is an increasingly important contributor to SVC syndrome. This is often due to the presence of an intravascular device, such as an indwelling catheter, wire component of a pacemaker, internal defibrillator or Port catheter (Park et al., 2013). The tip of an indwelling catheter or lead can irritate the venous endothelium and lead to reactive inflammation, fibrosis, and stenosis (Khanna et al., 1993; Kitamura et al., 1996; Goudevenos et al., 1989; Bakken et al., 2007). Still the incidence of such a complication is reported to be very low according to Goudevenos et al. (Goudevenos et al., 1989), Chamorro et al. (Chamorro et al., 1978) and Bolad et al. (Bolad et al., 2005) who reported this complication in one out of 3,100

patients, four out of 1,000 patients and three out of 3,050 patients respectively after transvenous pacemaker implantation.

Another common cause of superior vena cava fibrosis is mediastinitis following radiotherapy to the chest (Rice et al., 2006; Mehta and Koo, 2014). Fibrosing mediastinitis caused by infections such as tuberculosis, syphilis, and histoplasmosis as well as other fungal microorganisms (Mackie et al., 2007), Klebsiella and Nocardia followed by superior vena cava syndrome have been reported as case reports in literature (Kim et al., 1997; Abdelkafi et al., 1997). Classic vasculitis of the superior vena cava e.g. in association with Behcet's disease can also present with superior vena cava syndrome. In these cases severe inflammation may or may not involve concurrent thrombosis of the vena cava (de Paiva et al., 2007). Vascular malignancies that can involve the SVC, such as leiomyosarcomas or angiotropic large cell lymphoma (Savarese et al., 2000) or iatrogenic trauma to the superior vena cava e.g. after elective mediastinoscopy (Power et al., 1997), are extremely rare.

1.2.3 Compromised Venous Flow

Compromised venous blood flow could result from occlusive or near occlusive venous thrombus. Many cases of superior vena cava thrombus occur in the setting of a hypercoagulable state, such as underlying malignancy. A contributing factor is the presence of an intravascular device such as a catheter or pacemaker/defibrillator wire. In fact, intravascular thrombosis occurs in up to 45% of patients with an indwelling catheter together with a concurrent chronic inflammatory or a malignant disease status (Rice et al., 2006). Less common conditions that can compromise venous flow include those manifesting with right atrial mass effect such as right atrial myxoma, leiomyosarcoma or metastases (Cheng, 2009).

There is a considerable overlap between the different mechanisms for example a malignant tumor might cause compression of the superior vena cava, and further progression will include direct invasion of the vessel wall and intravascular invasion which will lead to compromised venous flow and thrombosis.

1.3 Signs and Symptoms of Superior Vena Cava Syndrome

The major collateral pathways seen with SVC or inferior vena cava (IVC) obstruction are well described and include the azygos, hemiazygos, internal and external mammary, lateral thoracic, and vertebral pathways (Stanford and Doty, 1986). It generally takes several weeks for the venous collaterals to dilate sufficiently to accommodate the blood flow of the superior vena cava (Kim et al., 1993; Trigaux and Van Beers, 1990). In humans with obstruction of the superior vena cava, the cervical venous pressure is usually increased to 20 - 40 mm Hg (normal range, 2 - 8 mm Hg) (Gonzalez-Fajardo et al., 1994; Mineo et al., 1999; Ahmann, 1984). The severity of symptoms depends on the degree and location of the SVC obstruction, and also on the speed of onset as well as the development of collaterals (Plekker et al., 2008). For example, in those with a rapidly invading malignancy, superior vena cava obstruction will occur before the development of any collateral and thus symptoms will present acutely.

The superior vena cava syndrome is characterized by venous congestion of the upper extremities, head and neck in most of the patients. Signs include: dilatation of the neck, arm and chest wall veins; edema of the upper body, extremities, neck and face; cyanosis and engorged conjunctiva. Symptoms include cough, hemoptysis, dysphagia, chest pain and dyspnea. In cases of gradual superior vena cava obstruction, symptoms often appear slowly and are not noticed by the patient. However severe dyspnea often makes the patient seek medical advice (Kretschmer and Schneider, 1992). The dyspnea is usually aggravated by bending forward and in supine position, and thus the patient usually opts for an upright position at night (Witt et al., 1997). Oedema of the glottis is a life-threatening effect of the venous congestion (Okay and Bryk., 1969). Chest pain, cough, and a sense of head fullness are among the presenting symptoms in gradually developing superior vena cava obstruction (Eren et al., 2006).

Acute compression of the SVC increases the cerebral venous blood pressure and lack of adequate decompression can cause encephalopathy (wet brain syndrome) (Stanford and Doty, 1986). Thus the main presenting symptoms in this case will be in the form of neurological symptoms such as changes in the mental status, vertigo, syncope or seizures (Parish et al., 1981; Nieto and Doty, 1986). These patients have rather poor prognosis and require emergency intervention to decompress the SVC.

1.4 Classification of Superior Vena Cava Syndrome

In 1987 Stanford et al. (Stanford et al., 1987) (Figure 1) proposed a grading system for SVC obstruction based on venographic findings. They described four different grades of obstruction based on the degree of stenosis and direction of flow in the azygos vein:

Grade 1 Up to 90% stenosis of SVC with patency of the azygos vein (1a)

Grade 2 90-100% of SVC with patency of the azygos vein and antegrade blood flow through the azygos vein (1b)

Grade 3 90-100% of SVC with patency of the azygos vein and retrograde blood flow through the azygos vein (1c)

Grade 4 Complete obstruction/occlusion of SVC and one or more of its tributaries including the azygos vein (1d)

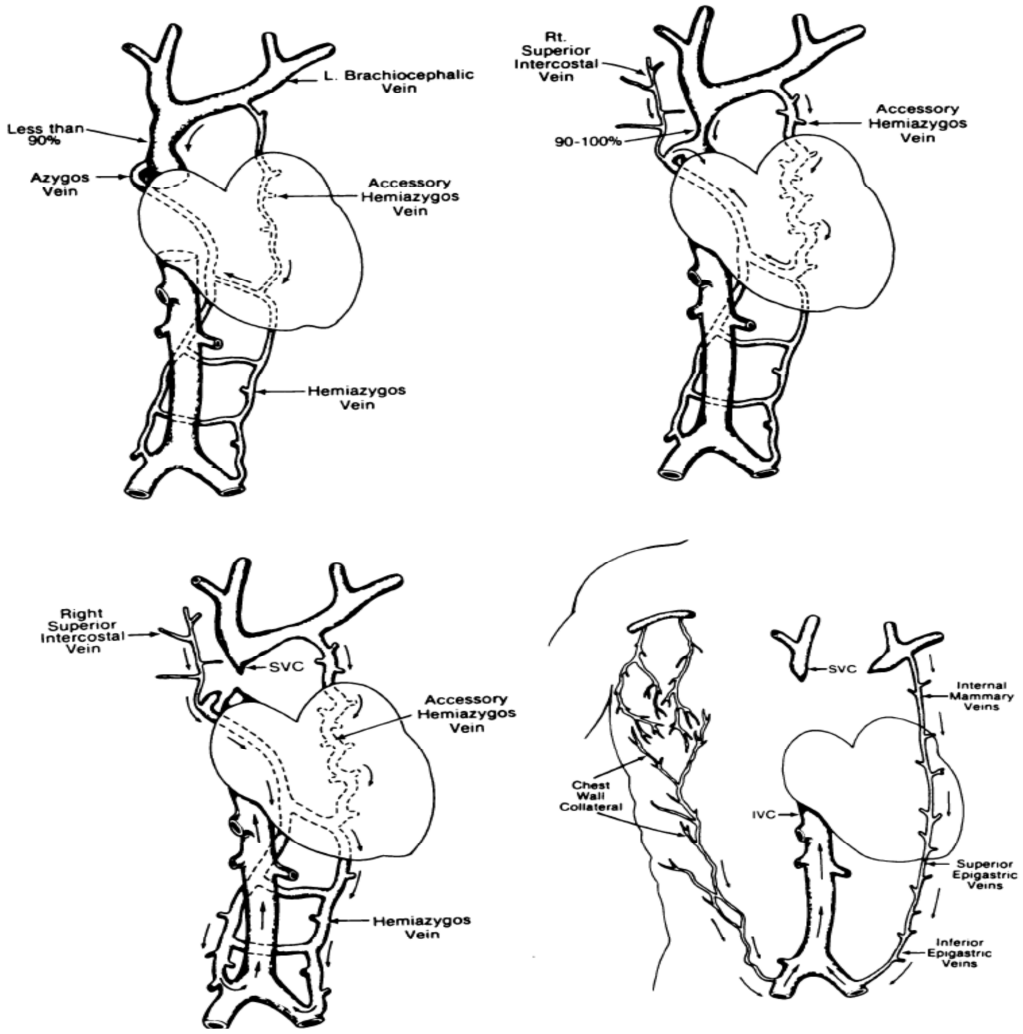


Figure 1a-d Classification of SVC obstruction according to Stanford et al. (Stanford et al., 1987)

Furthermore they described a correlation between this classification and patients' clinical course associated with bad outcome in Type III and IV. The clinical severity of superior vena cava obstruction symptoms can be graded based on a scoring system proposed by Kishi et al. (Kishi et al., 1993) in 1993.

In 2008 Yu et al. (Yu et al., 2008) proposed a new classification system for patients with superior vena cava obstruction based on categorizing the patients according to the severity of symptoms into 6 categories; asymptomatic, mild, moderate, severe, life-threatening, and fatal symptoms. They proposed this new system aiming to use it in future studies to provide a common language to describe patients' condition and thereby help define the role of intervention required. Their schema was patterned on the Common Terminology Criteria for Adverse Events (CTCAE) v3.0 of the National Institutes of Health, which does not address the superior vena cava syndrome, although it does include a category of edema of the head and neck (Yu et al., 2008).

1.5 Diagnosis of Superior Vena Cava Syndrome

The diagnosis of superior vena cava obstruction is usually made clinically in the first instance with the presence of neck swelling and distended veins over the chest being the most constant features. There may also be swelling of one or both arms (Rosenbloom, 1949). History taking should include the duration of symptoms, previous diagnoses of malignant conditions, and previous intravascular procedures. The severity of symptoms is important in determining the urgency of intervention (Wilson et al., 2007).

Imaging is vital when assessing and planning treatment of superior vena cava obstruction and is often used to confirm the clinical suspicion of this condition. Non-invasive investigations are recommended as an initial assessment, although direct visualization of the venous obstruction by selective venography remains the gold standard, especially for the interventional therapy (Ganeshan et al., 2009). Non-invasive diagnostic procedures include chest X-ray, computed tomography (CT), radionuclide studies, Doppler flow studies and magnetic resonance imaging (MRI) (Witt et al., 1997).

The initial chest x-ray is helpful but not specific. The most common abnormal findings noted are widening of the upper mediastinum, followed by right upper lobe mass, pleural effusion, and right hilar mass (Dempke et al, 1999; Bechtold et al., 1985).

However it is important to remember that chest X-ray might be normal in up to 16% of cases (Parish et al., 1981).

CT imaging is commonly used in diagnosing superior vena cava obstruction due to its increased availability, short acquisition time and reduced breathing and cardiac motion artifacts. Multi-detector row CT (MDCT) provides high quality images that are equal or superior to conventional venography (Bechtold et al., 1985; Eren et al., 2006). Contrast enhanced MDCT is now able to accurately identify the site of occlusion or stenosis and the presence of associated intravascular thrombus (Ganeshan et al., 2009).

Initially both the site and size of the mass behind the obstruction is detected. To verify the diagnosis of SVCO based on CT-contrast studies, two criteria need to be met: absent or reduced enhancement of the vein below the level of obstruction and presence of collateral circulation (Eren et al., 2006). The presence of dilated collateral vessels is highly suggestive of superior vena cava obstruction, with a sensitivity of 96% and specificity of 92% (Kim et al., 1993; Bechtold et al., 1985; Eren et al., 2006). The use of multi-plane and 3D reconstruction with large available numbers of planes and projections makes the detection of focal stenosis, the appreciation of the relationship of great vessels to each other and the extent of collateral formation much easier (Ganeshan et al., 2009). Chen et al. (Chen et al., 1990) reported that in 45 cases of superior vena cava syndrome, both angiogram of the superior vena cava and CT imaging using IV contrast were 100% accurate in making the diagnosis. Furthermore, impending superior vena cava obstruction may be apparent from CT or MRI prior to the development of symptoms (Bechtold et al., 1985).

Ultrasonography of the neck, subclavian, and brachial veins can identify the presence of thrombus, which should initiate urgent anticoagulation if this has not already been done and no contraindications exist (Cheng, 2009). Magnetic resonance venography is an alternative investigation to CT that is increasingly being used. It has 100% sensitivity, specificity, and accuracy to assess large central veins (Lin et al., 2005; Thornton et al., 1999). Furthermore MRI may be useful for patients who cannot tolerate the iodine containing contrast medium (Wilson et al., 2007).

1.6 Current Concepts in the Management of Superior Vena Cava Syndrome

The choice of therapy of the SVCO depends on the etiology. In malignant etiologies, a curative treatment is seldom possible. Symptomatic and palliative treatment take the upper hand.

Radiotherapy and chemotherapy were standards in the management of malignant SVCS. However, both therapies may not be possible under certain conditions, especially when the cumulative maximum dosage has been reached in previous treatments. In addition, it may take several weeks before either intervention shows a clinical effect (Uberoi, 2006).

Chemotherapy is more successful in SCLC than NSCLC, however it does not give an immediate impact. Radiotherapy depends on the radio-sensitivity of the tumor cells and may be accompanied with delayed results and potentially intermediate worsening of symptoms.

Medical treatment in the form of sedatives or analgesics as well as physiotherapy in the form of positioning or oxygen therapy do not improve the lifestyle much, whereas these therapeutic modules are resorted to in end-stage cancer.

In recent years, percutaneous stent or stent graft implantation gained more acceptance and significance due to the rapid relief of symptoms (Fagedet et al., 2013), lower invasiveness as well as low complication rate. This method was first described in 1986 by Charnsangavej C. et al. (Charnsangavej et al., 1986).

Surgical treatment strategies for SVC syndrome include (partial) tumor resection, thrombectomy and or bypass grafting. Operative intervention is rarely done due to high postoperative mortality rates of more than 5% (Warner et al., 2013) and is only preferred in cases when there is potential for curative resection or in cases of failed intravascular stenting (De Raet et al., 2012).

2 Aim of the Study

The study aimed to assess the applicability and effectiveness of SVC stenting in the management of superior vena cava syndrome in cancer patients. We tried to define the role of SVC stenting as a palliative measure in the treatment of SVCS in cancer patients according to the clinical patency of the stent in relation to the patient's symptoms and also the stent patency shown in the control CT.

Stent patency rate was estimated. Short- and long-term complications of SVC stenting, as well as the frequency of their occurrence were also reported.

3 Materials and Methods

3.1 Patients

The study included 95 cases with superior vena cava obstruction due to histologically confirmed malignant tumors as the underlying cause of obstruction. SVC stenting was performed in the time interval between 05/1996 and 11/2009, but the highest frequency of stent implantations was in the period from 05/1997 till 12/1999 (Figure 2).

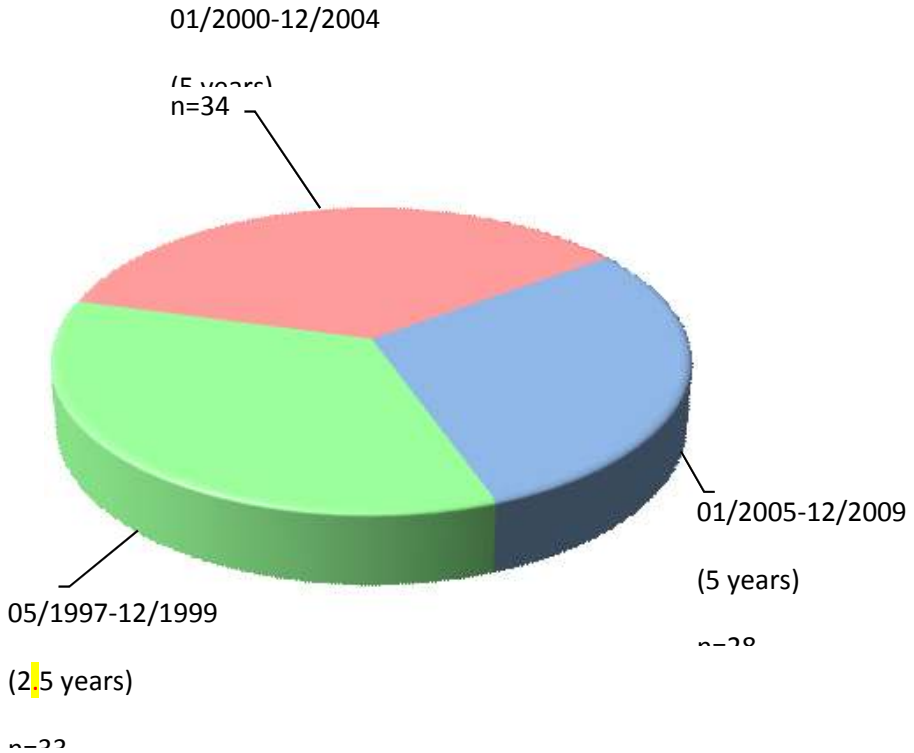


Figure 2. Distribution of studied cases according to stenting date

Our study is retrospective, done on symptomatic patients, hence there was no control group. The study group included 19 females aging between 43 – 76 years with a median of 58 years, and 76 males aging between 43-86 years with a median of 61.5 years.

Table 1. Demographic data of studied cases (n = 95)

Sex	Male	Female
N	76	19
%	80.0	20.0
Male/ female ratio	4 : 1	
Age (yrs)		
Range	43.0 – 86.0	43.0 – 76.0
Mean ± SD	61.58 ± 9.76	58.26 ± 8.89
Median	61.5	58.0

All patients were referred to our center from different practitioners, hospitals or oncology centers. All patients had radiologically proven superior vena cava obstruction and the majority had accompanied symptoms and signs.

For all 95 cases, a stenting procedure was intended, but was interrupted in 2 cases in which difficulties or complications occurred during the procedure. In the majority of cases, our approach was primary stent insertion except in one case in which we inserted a secondary stent to relieve obstruction in the primary stent which was inserted in another hospital.

3.2 Underlying Tumor Conditions

The studied group presented with the following malignant tumors:

- 35 small cell lung cancer (SCLC)
- 51 non small cell lung cancer (NSCLC)
- 9 Lymph node metastasis from an extra pulmonary primary tumor

The 9 extrapulmonary malignancies included:

- 5 thymus cancer
- 1 cancer of the cervix
- 1 mediastinal angiosarcoma
- 1 cancer of the caecum
- 1 breast cancer

All the cases were studied retrospectively and the following data were collected:

- Type of the primary tumor causing the obstruction
- Tumor grading mainly for NSCLC according to the TNM classification
- Tumor staging for all tumor types
- Time interval between diagnosis and stent insertion
- History of any earlier treatment for the underlying tumor condition

3.3 Confirmation of the Diagnosis of Superior Vena Cava Obstruction

Clinical signs of superior vena cava obstruction were observed in all patients.
SVC syndrome was visualized radiologically using computed tomography of the chest with intravenous contrast agent (Scanner: Somatom Sensation, Siemens Erlangen, Germany) as well as using phlebography of the SVC. In the majority of cases, phlebography was done in conjunction with the stent implantation procedure via the transfemoral route. And rarely a separate phlebography via the arm veins without intervention was performed.

3.4 Procedure and Materials

3.4.1 Patients Preparation for the Implantation

Pre-interventional patient education about the procedure, possible complications and alternative therapeutic measures was done. As all stents, excluding the Gianturco-Z stent and the Sinus XL stent, were used without official approval from the manufacturer for the venous implantation, however patient consent specifically for this “off label” use was obtained.

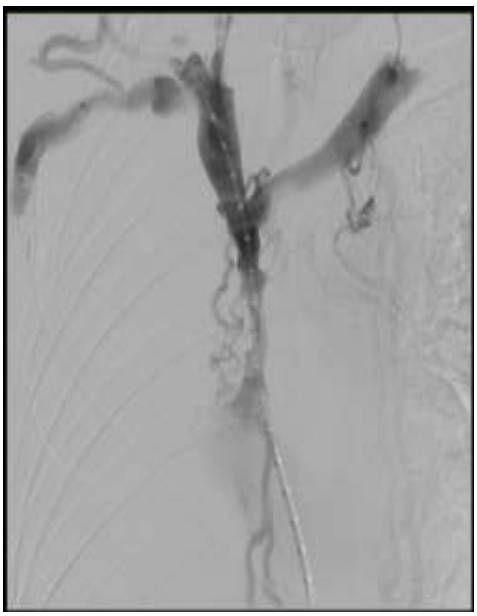
Before the interventional procedure, the following blood parameters were assessed:

- Coagulation time
- Serum creatinine
- Thyroid stimulating hormone

3.4.2 Procedure

Stenting was performed till April 2008 using an AXIOM Artis dBA angiography system (Siemens Erlangen, Germany) and later using the Artis zee (also Siemens). The procedure was performed under sterile conditions using local anesthesia of the groin before puncture of the femoral vein. Access through the right femoral vein was more common than through the left femoral vein. Heparinization with 5000 IU before the procedure, heart rate monitoring and electrocardiography during the procedure were performed.

The obstruction could usually be passed through using a combination of selective catheters, e.g. vertebral catheter 5F and hydrophilic guide-wire (Terumo Corp. Tokyo, Japan). Once the wire was passed through the lesion, the hydrophilic guide-wire was exchanged for a 260 cm long stiff guide-wire (Fa. Terumo, Japan) and a 5F-measuring catheter (Fa. Boston Scientific, USA) for the phlebography (15-20 ml contrast medium introduced with a flow of 12 ml/sec) from the left brachiocephalic trunk or the right jugular vein to estimate the length and degree of stenosis, width of the SVC and brachiocephalic veins to define landing zones for stents and exclude thrombosis in order to choose the appropriate stent. (Figure 3).



We then changed to a 10F-sheath (Terumo, Japan) and introduced the stent carrying catheter. After that the stent was introduced in the stenosis and then it was deployed. In case of extreme obstruction, pre-stenting dilatation was indicated. For this we used a 6-8 mm balloon-catheter (ev3 Endovascular, Inc., MN, Plymouth, USA), which was necessary in approximately one fifth of patients.

Figure 3. (W. R. 20.05.2009) Venography image following wire passage through the SVC stenosis using the measuring catheter

After stent deployment in more than 50% of the patients, the stent was dilated using an 8-12 mm balloon catheter to overcome a residual obstruction and to assist full stent expansion aiming to improve the venous backflow (Figure 4a-b).

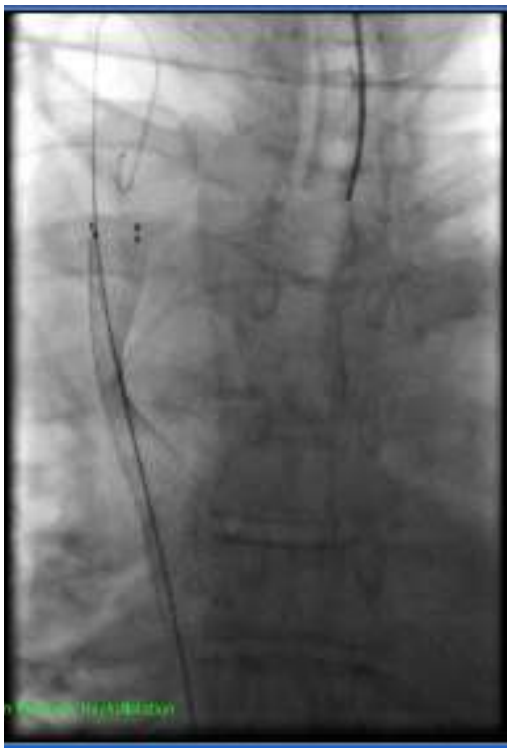


Figure 4a

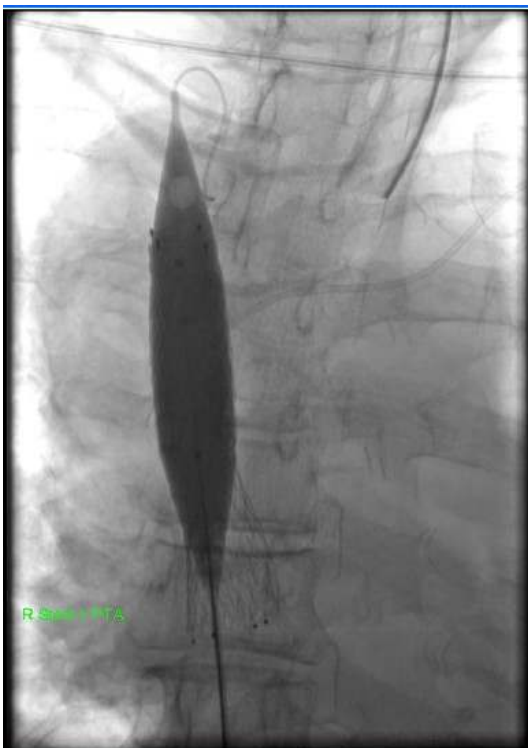


Figure 4b

Figures 4a-b. (J. G. 22.01.2009) Images showing (a) stent deployed through the tumor and (b) balloon dilatation of the stent

Phlebography in 2 planes was performed after the intervention to check the unrestricted free venous drainage through the expanded stent and to exclude venous rupture. In a few cases, a second or a third stent was required to obtain a free flow.

Local thrombolysis, aspiration thrombectomy and/or rotation thrombectomy were rarely needed to pass through the thrombus prior to stenting. After releasing the stent, we resorted to local thrombolysis in a few cases if flow within the stent was severely obstructed.

After removing the sheath and performing manual tamponade at the puncture site, a compression bandage was applied and the patient was requested to remain in bed for 8 hours after the procedure. Between 1997 and 1999, we used anticoagulant therapy in the form of full heparinization over the first three days. However in the later years, this routine heparinization was abandoned. In cases where good free venous drainage was seen, no other anticoagulant therapy was given.

3.5 Implanted Stents

Various endovascular stents were used to relieve the stenosis. They come in a variety of sizes and lengths. Stents may be classified in two categories: self-expanding stents and balloon expandable stents. Once released, self-expanding stents (Gianturco-Z stent, Wall stent, Memotherm stent) continuously push radially outward against the stenosis until they reach their maximum size. Also they are more resistant against external pressure e.g. in-growth of the surrounding tumor compared to balloon expandable stents. In our study, we only used self-expanding stents.

Gianturco-Z stent (Cook, Blomington, USA), self-expanding stent is made from 0.10 inch stainless steel wire which expands in a zigzag pattern to form a cylinder. It comes in various sizes from 15 to 35 mm in diameter and 5 cm length. Usually tandem stents connected by stainless steel wire are used to prevent slippage of the stent. The stents are compressed and introduced through a 8F to 12F teflon introducer catheter, depending on the diameter of the stent (Nguyen et al., 2009). Accurate placement can be difficult and they are not fully MR-compatible.

Wall stent (Boston Scientific, Ratingen, Germany) is flexible, long and easy to insert. It has a smaller diameter (up to 1.6 cm and less radial strength), and is best suited for smaller vessels such as brachiocephalic vein stenosis or long curvatures. Its mesh-like structure prevents infiltration of the tumour through the stent (Nguyen et al., 2009). When released, this stent shortens depending mainly on the length and diameter of the stent used, which sometimes could be significant.

Memotherm aorta-stent (Bard GmbH, Karlsruhe, Germany) or Memotherm stent is a self-expanding stent made of "shape memory" Nitinol, which gives it exceptional flexibility as well as radial strength. Its unique diamond design minimizes shortening of the stent after deployment, unlike other self-expandable stents which may shorten by as much as 60% once deployed (Nguyen et al., 2009). It was available in diameters up to 22 mm and in lengths up to 100 mm, however the production of Memotherm stent stopped since 2006 and since then we resorted to the use of the Sinus-XL stent.

Sinus-XL stent (Optimed- Medizinische Instrumente GmbH, Ettlingen, Germany) has nearly the same characteristics as the Memotherm aorta-stent. Although its flexibility is inferior, it is the other stent beside the Gianturco stent which are officially approved for intravenous use.
Our criteria in choosing the stent were a stent diameter 5-10 % over the non-constricted vein diameter and a length that exceeds the obstruction length 10 mm from both ends.

3.6 Follow-up

No routine follow-up imaging protocols were used. Most patients were usually followed-up clinically in the hospital or by their referring clinicians. Repeat venography or CT was carried out only if symptoms recurred.

In our retrospective study, we extracted the following data from early ward reports following stent implantation:

- Subjective improvement
- Regression of the SVC Obstruction signs (during the hospital stay)
- State of radiological patency of the stent (as documented), commonly with CT.

Late clinical signs and symptoms as well as further tumor treatments and the date of death were obtained from the day clinic or inpatient hospital records. Any missing data from our hospital regarding post-procedure outcomes was collected through fax- or post-correspondence and sometimes from telephone questionnaire with the treating doctors and tumor centers.

Time interval between stent implantation and patient's mortality was calculated. State of stent patency at time of death was recorded from: available clinical reports, late questionnaire of the practitioners, cancer treatment centers and rarely from living relatives of the patients. Regarding stent patency, we accepted the reporting of a re-occurrence of SVC Syndrome as a proof of stent re-closure, and in cases where no such reports were found we choose to enroll these cases as clinically open till death.

3.7 Success and Complications

We stated both clinical and/or radiological patency during the first hospital stay directly upon patient discharge and from hospital reports. We defined complications occurring during the interventional procedure or during that hospital stay or within the 30 days

after the procedure as early complications. Late complications were defined as complications occurring following hospital discharge.

3.8 Statistical Analysis of the Data

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0 (Leslie et al., 1991; Kirkpatrick and Feeney, 2013). Qualitative data were described using number and percent. Quantitative data were described using mean and standard deviation, median, minimum and maximum values.

Comparison between different groups with categorical variables was tested using Chi-square test. When more than 20% of the cells had expected count less than 5, correction for chi-square was done using Fisher's Exact test or Monte Carlo correction.

The distributions of quantitative variables were tested for normality using Kolmogorov-Smirnov test, also Histogram and QQ plot were used for visual evaluation. If the normal data distribution (curve of significance p=0.05) was accepted, parametric tests were applied. If the data were not normally distributed, non-parametric tests were used. For not normally distributed data, Kruskal-Wallis test was used to compare between different groups. Test results are quoted as two-tailed probabilities. Significance of the obtained results was judged at the 5% level.

4 Results

All 95 patients presented with radiologically proven SVC obstruction secondary to an underlying malignant disease. All patients had obvious clinical signs of SVC obstruction, and stent insertion was attempted in all 95 patients. 86 patients had primary intrapulmonary malignancy, of which 36.8% were SCLC and 53.7% were NSCLC and the remaining 9 cases (9.5%) had extra-pulmonary primary malignancy with intrathoracic lymph node metastasis (Figure 5).

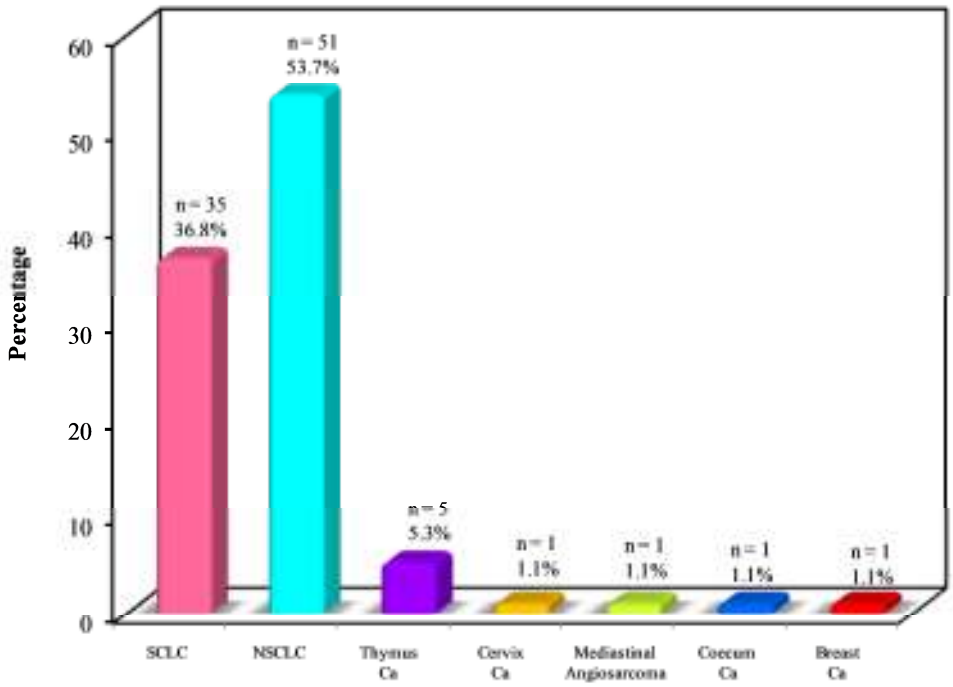


Figure 5. Underlying tumor type in patient population

4.1 Staging of Malignancies in the Studied Cases

Each underlying malignant condition was staged at the time of stent implantation. Staging of primary pulmonary cancer was done according to the TNM Classification of 2009 (Sobin et al., 2009) as follows: 10.5% were stage IIIA (n=9), 34.9% stage IIIB (n=30) and 54.6% stage IV (n=47) (Figure 6).

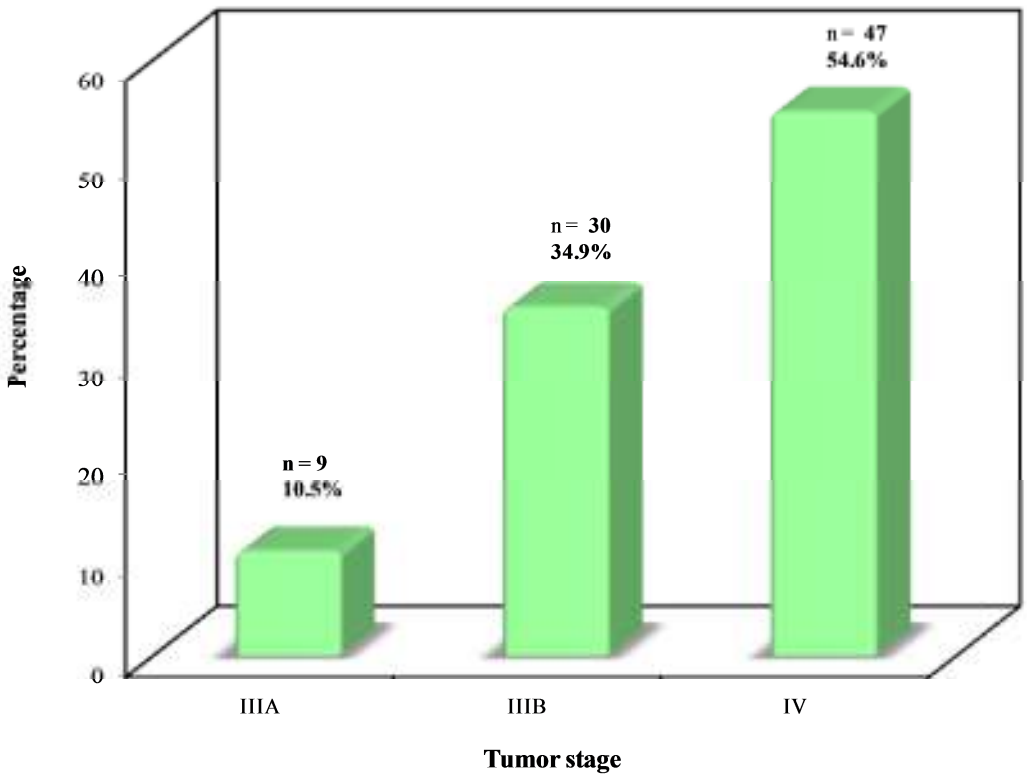


Figure 6. Cancer staging of the included primary pulmonary malignancies (n=86)

Staging for extrapulmonary malignancy (n=9) had the following results:

- All thymus cancers (n=5) were Category II according Levine and Rosai
- The exact stage of the Mediastinal Angiosarcoma (n=1) could not be extracted from the records
- The cancer of the cervix (n=1) was stage1c/IVB according to the TNM/ FIGO classification system
- The breast cancer (n=1) was stage IV according to the breast cancer stage grouping based on the last American Joint Committee on Cancer TNM system of 2012
- The caecum cancer (n=1) was stage IIB according to the seventh edition of the American Joint Committee on colon cancer

Over half of the patients were treated with either chemotherapy or radiotherapy and only 11 patients underwent surgery (Table 2). 46% of all patients had a newly diagnosed tumor, that is to say they presented with SVCO of unknown cause at the time of hospital admission.

Table 2. Distribution of studied cases according to earlier treatment (n = 95)

Earlier treatment	n	%
No treatment	44	46.3
Chemotherapy	23	24.2
OP	2	2.1
Radiotherapy	5	5.3
Chemotherapy& Radiotherapy	10	10.5
Chemotherapy & OP	5	5.3
Radiotherapy & OP	1	1.1
Chemotherapy, Radiotherapy & OP	5	5.3

Regarding patients with primary pulmonary cancer, we observed that there was a higher prevalence of SVCO among those who had received previous cancer treatment both in patients with NSCLC as well as in those with SCLC..

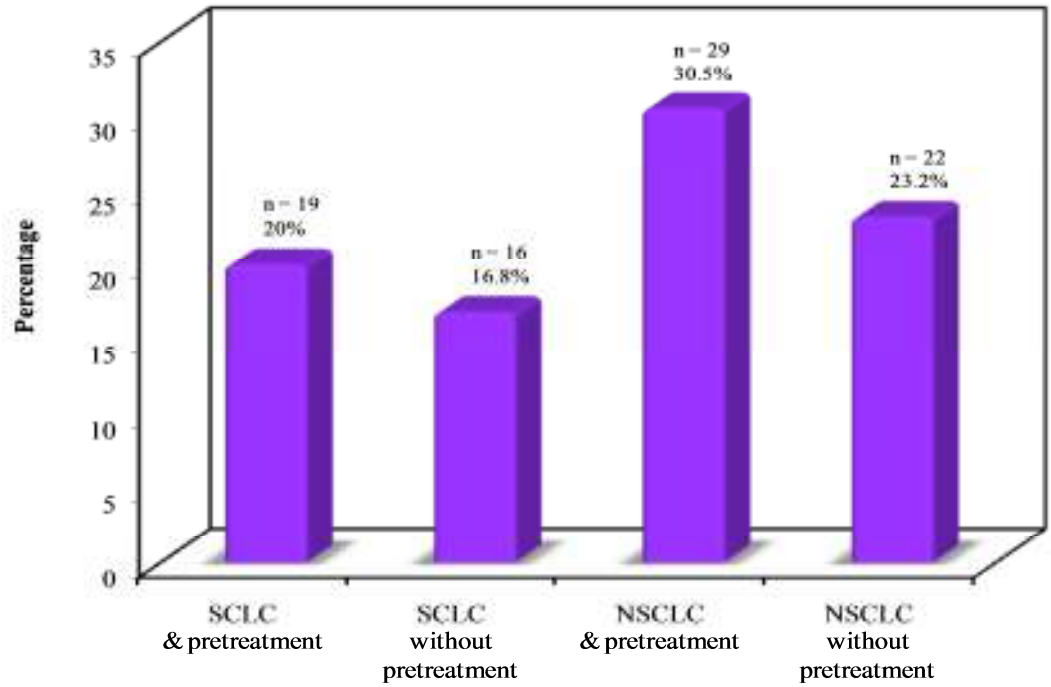


Figure 7. Distribution of intrapulmonary malignancies according to tumor type and pretreatment (n=86)

4.2 Results of Stent Implantation

93 of the total 95 intended approaches ended with actual stent implantation, achieving a technical success rate of 97.9%. The stenting procedure was abandoned in two patients due to early cardiovascular complications occurring on-table (mentioned in the complications section).

We implanted 1 stent per patient in 70 cases, 2 stents per patient in 19 cases and 3 stents per patient in 4 cases to overcome the obstruction, making a total of 120 stents successfully implanted in 93 cases.

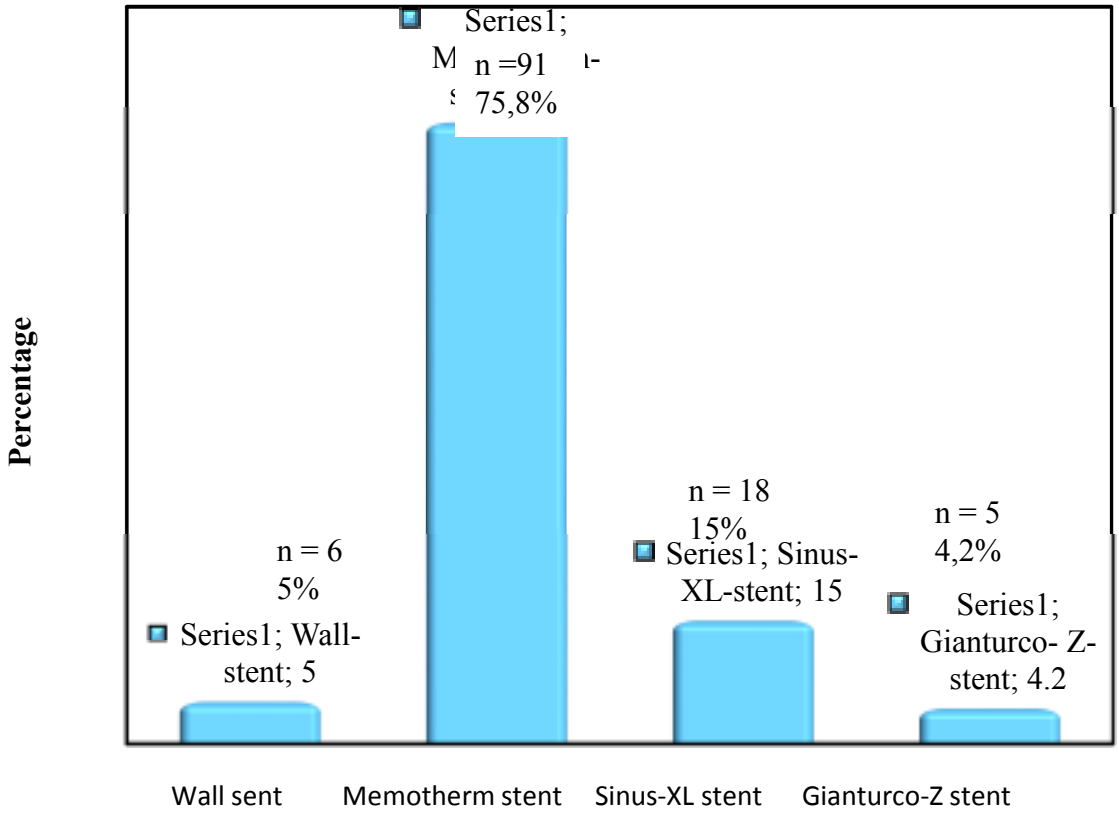


Figure 8. Procentual distribution of the different implanted stents

The various stents used were 6 Wall stent, 91 Memotherm stent, 18 Sinus-XL and stent und 5 Gianturco- Z stent. The length and diameter of the implanted intravascular stents are described in Table 3.

Table 3. Length and diameter of the used stents (n = 120).

	Range	Mean ± SD	Median
Length (mm)	22.0 – 100.0	58.29 ± 15.10	60.0
Diameter (mm)	8.0 - 40.0	19.08 ± 5.42	20.0

For three out of the 93 cases, we repeated the intervention at different time intervals due to re-obstruction (F. B. 29/07/1998 & 26/01/1999, I. M. 04/09/2009 & 13/11/2009, C. S. 12/06/2009 & 12/10/2009).

In another separate case we performed a second implantation for a patient suffering from re-obstruction after stenting, in whom the first procedure was done in another hospital a month before (W.T. 03.02.2003).

We implanted stents mostly in the SVC only, rarely at the brachiocephalic junction, and in one patient only in the right brachiocephalic vein (U.M. 07.01.2000) (Figure 9).

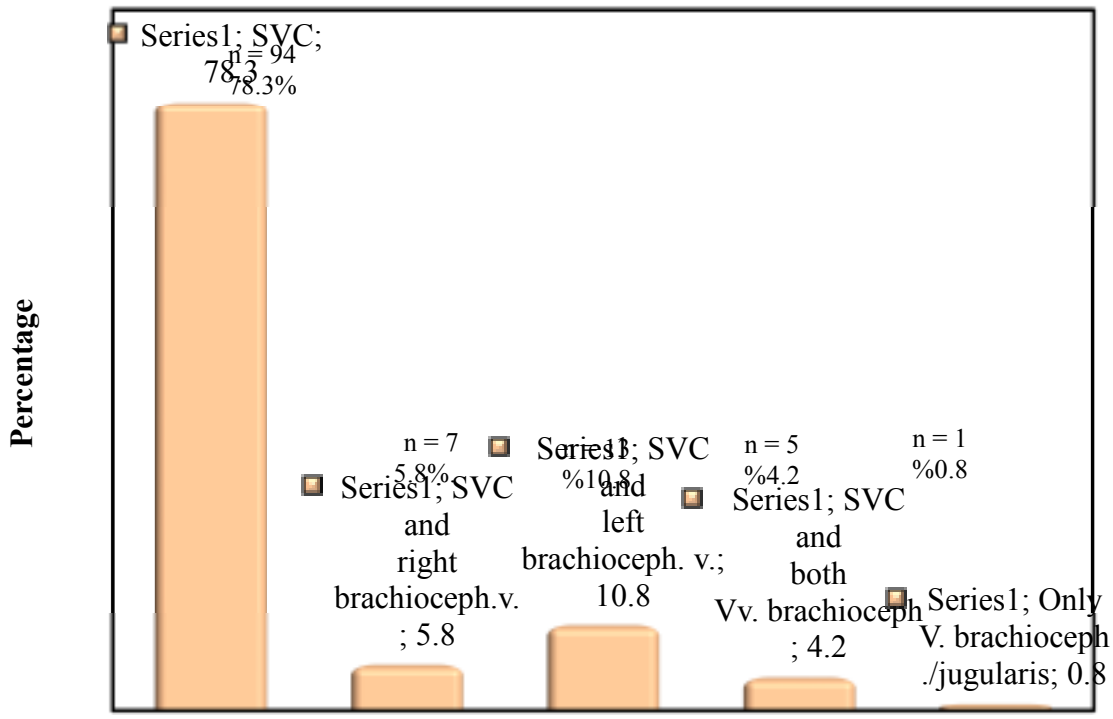


Figure 9. Distribution of implanted stents according to their location (n=120)

4.3 Variations of the Procedure

In 6 out of 95 cases, we applied local thrombolysis during the stenting procedure using a low dose of rt-PA (Actilyse, Fa. Boering Ingelheim, Germany) because of presence of thrombus (Figure 10).

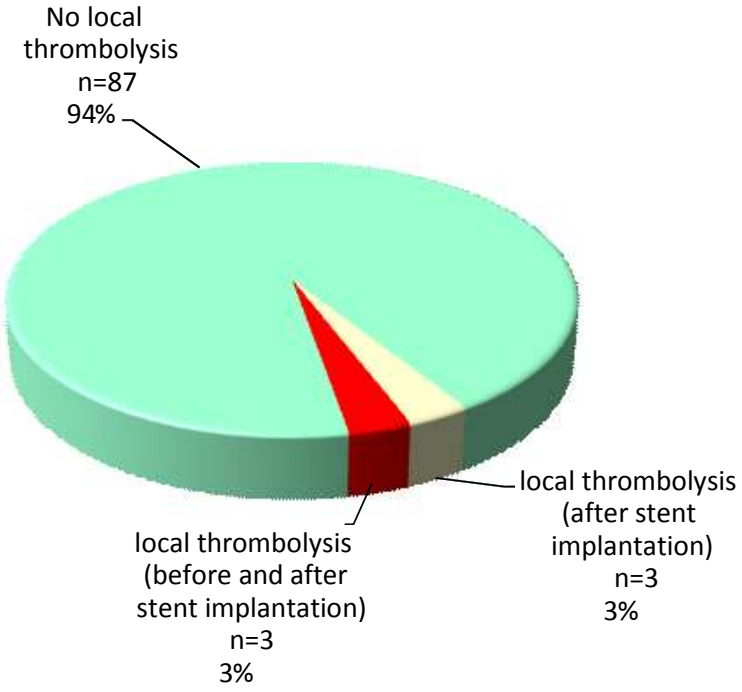


Figure 10. Distribution of studied cases according to local thrombolysis (n= 93)

In cases of extreme obstruction, pre-stenting dilatation was indicated in 19 cases out of 93 patients to allow us to pass the obstruction.

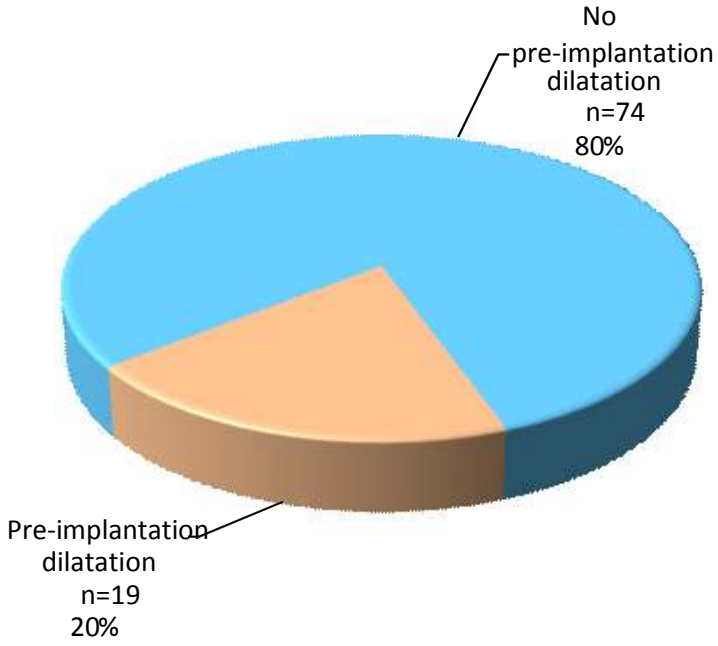


Figure 11. Application of pre-implantation dilatation (n = 93)

We performed angioplasty of the implanted stent in 55 out of 95 cases to overcome a remaining obstruction (Figure12). In our study, a documented post-procedure heparinization was performed in 27.4 % of the cases (Table 4). We found no significant relationship between post-procedure heparinization and stent patency at the late course of the disease before death (Table 5).

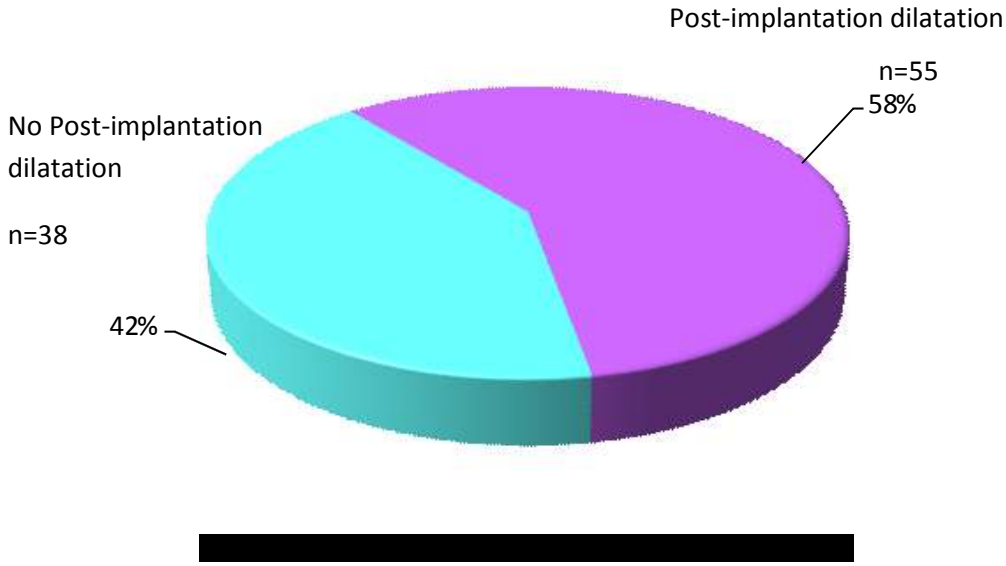


Figure 12. Post-stenting dilatation (n = 93)

Table 4. Distribution of cases according to post-intervention heparin intake (n = 93)

History of heparinization	n	%
no heparin intake	67	72.6
heparin intake	26	27.4

4.4 Success Rate

Stent patency and effectiveness was described using the following terms:

- "clinically open" with absence/no re-occurrence of obstruction symptoms i.e. asymptomatic cases and
- "radiologically closed", if proven by imaging procedure. Two patients had radiologically closed stents, but with good collateralization and both patients were asymptomatic i.e. clinically open (Table 5).
- We abandoned using the term "radiologically open" as not every patient had a post-procedural radiological examination to prove stent patency.

Heparinization for 3 days had no significant influence on stent patency rate (Table 5).

Table 5. Relation between stent patency and post-procedure heparinization (n=93)

Stent patency	Total		Post-procedure heparinization				P
			Not proven heparin intake (n = 67)		Heparin intake (n = 26)		
	n	%	n	%	n	%	
Clinically open	65	67.4	48	69.6	17	65.4	χ^2p = 0.555
Radiologically closed but clinically open	2	2.1	2	2.9	0	0.0	^{FE}p =1.000
Clinically closed	18	18.9	13	18.8	5	19.2	χ^2p = 0.985
Clinically unknown	8	8.4	4	5.8	4	15.4	^{FE}p =0.213

χ^2 p: p value calculated by Chi square test
FEp: p value calculated by Fisher Exact test

We described stent patency as clinically open at the time of death based on the available data from the last hospital stay based on the assumption that the clinical condition of SVCO is always mentioned in the death report if it existed (Table 6).

Table 6. Distribution of studied cases according to stent patency in the last available patient report before death (n = 93)

Stent patency	n	%
Clinically no signs and symptoms of SVC obstruction	65	69,9
Radiologically proven SVC obstruction without Clinical signs and symptoms of obstruction	2	2.2
Clinical signs and symptoms of SVC obstruction	18	19,3
No definite clinical report of SVC obstruction	8	8.6

4.5 Survival

We calculated the time from histological diagnosis of cancer until stent insertion and the post-stenting survival time in days (Table 7). As all patients were deceased, the survival time was expressed as the length of the follow-up period from stenting until death. We had a follow-up period ranging from 0 to 33.5 months with a mean of 8.4 ± SD of 9 months.

Table 7. Analysis of studied cases according to time from histological diagnosis of cancer until stenting and survival after stenting (n = 93)

	Range	Mean ± SD	Median
Time from diagnosis until stenting in days	(-19) – 3004	246 ± 499	46
Post-stenting survival in days	0 – 1006	252 ± 269	152

As the studied cases were distributed over a 12 years period, we also checked if there was any significant change of the patient's survival in different time periods of stenting (Table 8).

Table 8. Analysis of procedure in the different time periods (n = 95, including the two patients with intention to treat).

	Time periods			p
	05/1997 -12/1999 (2.5 years, 33pts.)	**01/2000 - 12/2004 (1st 5 years, 34pts.)**	**01/2005 - 11/2009 (2nd 5 years, 28pts.)**	
Survival after stenting in days				
Range	0.0-1006.0	3.0- 691.0	2.0-931.0	
Mean ± SD	322.33±301.66	203.24 ± 203.86	205.54±234.10	0.161
Median	241.0	119.50	128.50	

p value calculated by Kruskal Wallis test

There was a longer survival period in the first group, however, this was not statistically significant (p = 0.161). No statistical analysis was performed for stent patency at time of death in relation to the three time periods of the procedure as the numbers suggest no significant difference (Table 9).

Table 9. Analysis of stent patency at time of death for different time periods in which stenting was performed (n = 93)

	Time periods	Clinically open	Clinically closed	unknown
Stent patency	05/1997 -12/1999 (2,5 years)	23	6	4
	01/2000 - 12/2004 (1st 5 years)	24	5	3
	01/2005 - 11/2009 (2nd 5 years)	20	7	1

4.6 Complications

Early complications were observed in 12 out of 95 cases. In two cases, stent implantation was abandoned, where one patient developed cardiac arrhythmia and the other suffered from a heart arrest. Thus 2 of the 95 procedures ended without actual intravascular prosthesis insertion**.**

In the ten remaining cases, different early complications were observed. These manifested as follows: re-closure was observed in seven patients, partial stent dislocation in the right atrium in two cases (Figures 13 and 14) and intermittent arrhythmia in one patient.

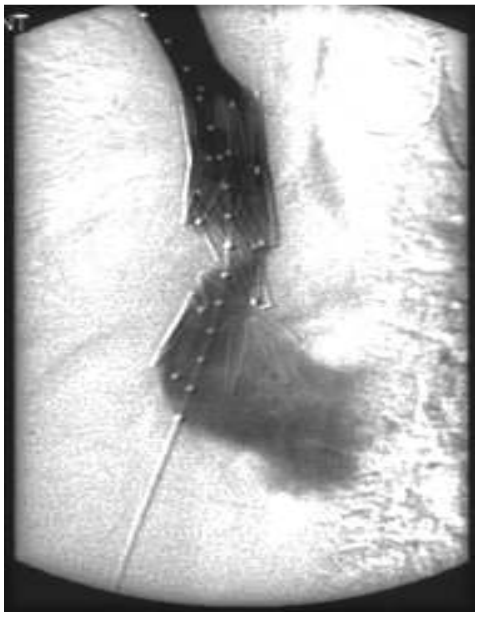


Figure 13a

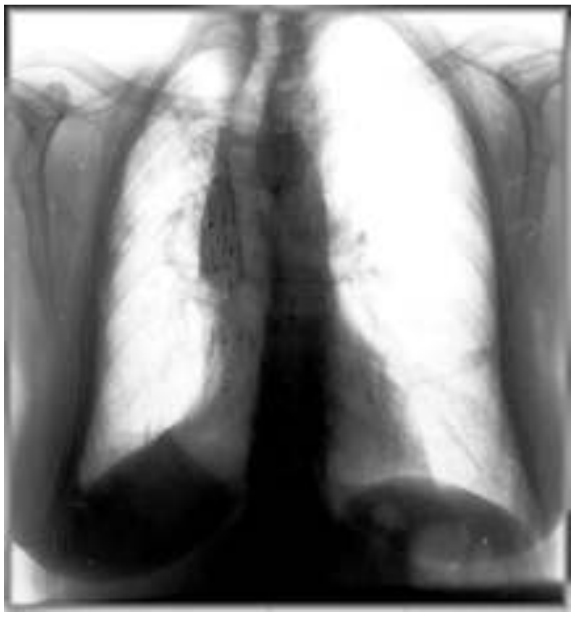


Figure 13b

Figure 13. Dislocation of the stent in a 66 year-old female patient (U.B. 02/12/1997), having right central SCLC (T4N2M0) and suffering from SVCS (see text)

Examples:

In one patient, primary imaging showed a high-degree stenosis between the azygos vein and the right atrium, where two Gianturco-Z stents were inserted with good overlap, centrally reaching the boundary of the right atrium on 02/12/1997 (Figure 13a). The chest x-ray done in February 1999 showed an asymptomatic partial stent displacement into the upper part of the right atrium (Figure 13b). The patient died 33 months afterwards from her cancerous condition.

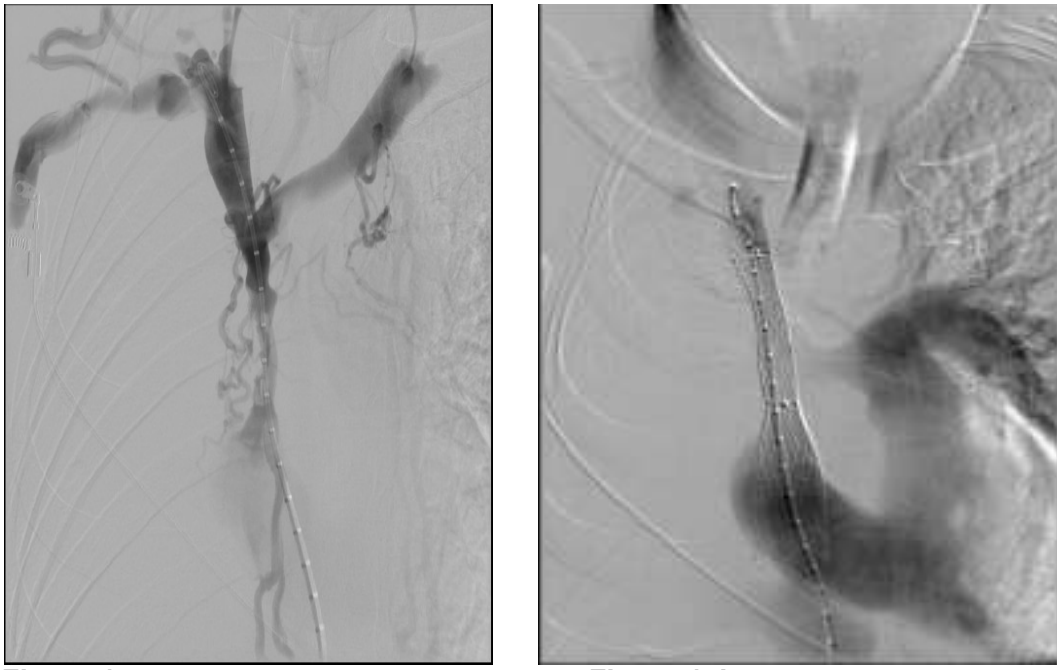


Figure 14a **Figure 14b**

Figure 14: Dislocation of the stent in a 53 year-old male patient (W.R. 20/05/2009), suffering from a right central NSCLC (T4N2M0) with a resulting SVCO (see text)

Transfemoral stent implantation (Sinus XL 24-60) was performed at the level of the stenosis where the level of stenosis is shown in Figure 14a. Due to a technical mistake during the extraction of the stent-carrying catheter, the stent was partially dislocated into the right atrium. Thereafter fixation of the stent through implantation of a second stent (Sinus XL 24-80) with a good overlap and post stenting dilation using a 12/60 mm balloon catheter was performed (Figure 14b). This patient died six months afterwards.

The distribution of complications based on the type of stent used is shown in Table 10. No difference in the rate of early complications relating to stent type was observed.

Table 10. Relation between stent type and early complications (n=120)

Stent type	Total Number of stents	early complications			
		No (n = 110)		Yes (n = 10)	
		n	%	n	%
Wall-stent	6	5	83,3	1	16,7
Memotherm-stent	91	84	92,3	7	7,7
Sinus-XL-stent	18	17	94,1	1	5,9
Gianturco- Z-stent	5	4	75	1	25.0

Late complications manifested as late re-closure in eight out of the 93 patients.
In three patients, we succeeded in re-gaining venous flow through implantation of another stent after occlusion of the primary one (Figures16 and 17). One of those patients had the primary stent implanted in another center.

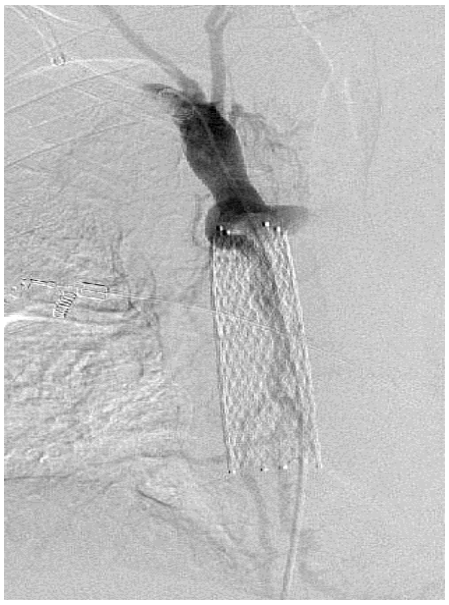


Figure 15a

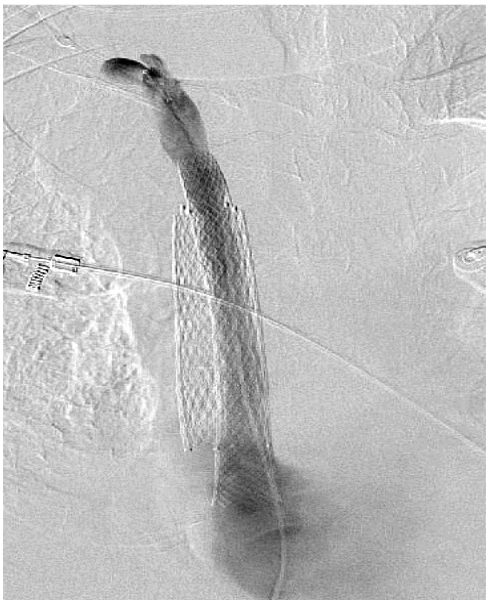


Figure 15b

Figure 15. A 67 year-old female patient (I.M. 04/09/2009) with a primary stent implantation and (b) a secondary stent insertion (I.M. 13/11/2009)

One patient (I.M. 04/09/2009) had a primary stent implantation using Sinus XL stent (20-80) for SVCO secondary to a right central SCLC (T4N2M1) in September 2009. In November 2009, SVCO re-occurred and radiologic imaging proved stent occlusion

(Figure 15a). On the 13th of November 2009, re-intervention and implantation of three stents was performed (Figure 15b). The patient died six weeks after the second intervention without any signs of SVCO.

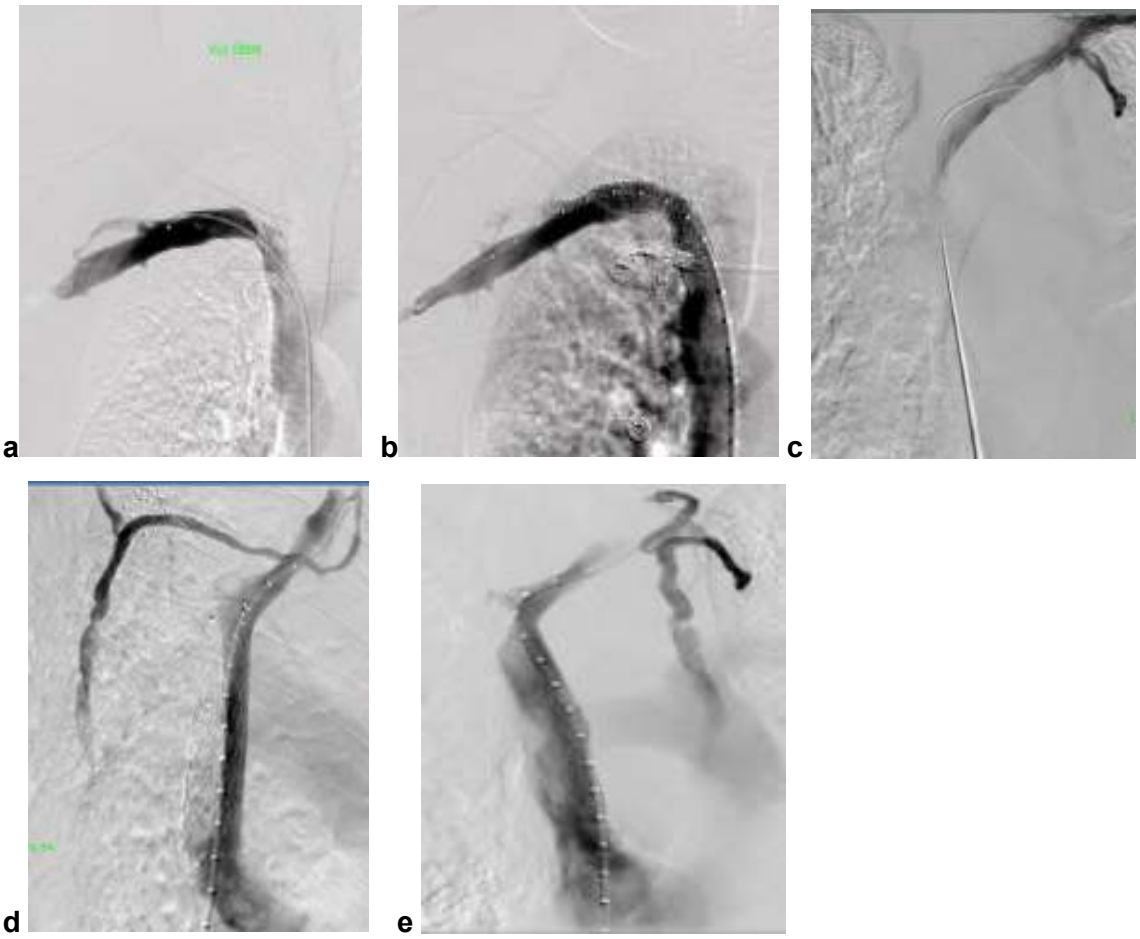


Figure 16. **A 53 year-old female patient (C.S. 12/09/2009) with SVCO (first presenting symptom) secondary to an underlying left central NSCLC (T4N3M1) (see text)**

In another patient, implantation of a Sinus XL stent was performed on the 12th of September 2009 (Figure 16a,b). In October 2009, SVCS re-occurred. Implantation of two more stents (Sinus XL 24-80 and 16-60) was done (Figure 16c-e). Afterwards the patient showed regression of symptoms only for a short time interval with re-occurrence of SVCS two days later and radiological imaging showed a new occluding thrombus. This patient died 10 days after the second interventional procedure.

The distribution of late complications according to the type of the applied stents is shown in Table11. Again there was no difference in the rate of late complications relating to stent type. However there is an obvious discrepancy between the large

number of implanted Memotherm stents and the small number of implanted stents of other types. Thus the bias in the numbers and types of stents used does not allow us to reliably detect differences between these stents.

Table 11. Relation between stent type and late complications (n=120)

Stent type	Total Number of Stents	late complications			
		No (n = 112)		Yes (n = 8)	
		n	%	n	%
Wall-stent	6	6	100	0	0.0
Memotherm- stent	91	85	93,4	6	6,6
Sinus-XL-stent	18	16	88,9	2	11,1
Gianturco- Z-stent	5	5	100	0	0.0

5 Discussion

5.1 The patient group

Our study group of 95 patients (age range 43-86 years) coincides with the literature concerning the average age of patients presenting with SVC obstruction. Male to female ratio in our study was 4:1, which is comparable to the reported literature where the ratios range from 3:1 (Nagata et al., 2007) and up to 11:1 (Lanciego et al., 2009).

We only enrolled malignant SVC obstruction, where only palliative treatment was considered. Intrapulmonary malignancy was the leading cause of SVCO, consistent with the results from other studies (Rice et al., 2006; Cheng et al., 2009; Gompelmann et al., 2011; Warner and Uberoi, 2013). The majority of patients (53.7%) had NSCLC and 36.8 % had SCLC, similar to other studies (Rice et al., 2006; Thony et al., 1999), while in studies with smaller cohorts more patients had SCLC (Cheng, 2009 Warner et al., 2013; Lanciego et al., 2009). The theory that SVCO is more common in patients with SCLC (Gompelmann et al., 2011) was not demonstrated in our study.

Besides lung cancer, other cancer conditions (n=9) included five cases of thymus cancer, one case of mediastinal angiosarcoma, as well as mediastinal lymph node metastasis in the following cancer types cervical cancer, caecal cancer and breast cancer. Unlike other studies (Rice et al., 2006; Chan et al., 2013), we did not have any cases of lymphoma.

In 46.3% (n=44) of patients, the first hospital stay coincided with the first presentation of malignant SVCO. In the remaining 53.7% (n=56), SVCO occurred later in the course of the already known malignant condition under therapy. Moreover 5 of the 44 newly diagnosed malignancies presented to our center with a full blown SVCO as the first presenting sign of the underlying cancerous condition. In these cases, stents were therefore implanted prior to the definitive diagnosis of the underlying malignancy and that is why stenting came before the pathology report, explaining the negative figures in time interval from diagnosis till stenting (Table 7). Talens et al. described for a comparable cohort (n=120) that in one third of the cases, SVCO was the first presenting symptom of the underlying intra-thoracic tumor (Talens et al, 2013).

5.2 Different Treatment Modalities for Superior vena cava Syndrome

Palliative treatment is the mainstay in the management of malignant SVCO. Chemo- and radiotherapy (Ines et al., 2011) are effective in relieving SVCO in a proportion of patients, usually requiring a longer duration especially in patients with NSCLC.

Operative treatment usually has a limited role and is not preferred in malignant SVCO. This is because of the poor prognosis and the high rate of complications in these patients (Kühn et al., 2013). Only in thymoma the surgical resection, even in extensive disease, is of great importance (Kim et al., 1013; Dong et al., 2014).

Other possible symptomatic treatment strategies include medication (sedatives, analgesics), positioning, oxygen therapy and anticoagulation therapy (Smayra et al., 2001).

5.3 Stent Implantation

5.3.1 History of Superior Vena Cava Stenting and its Indication

SVC stenting has been proven to be the method of choice in treating malignant SVCO (Uberoi, 2006). It usually provides symptomatic relief in a high proportion of patients and has a more rapid effect (Rowell and Gleeson, 2002) together with fewer complications (Sahin et al., 2014).The success rate is remarkably higher than with angioplasty alone (Aldoss et al., 2012), whereas angioplasty is generally performed in preparation for stent placement (De Raet et al., 2012).

The pioneers of managing SVCO with expandable metallic stents were Charnsangavej C together with Gianturco C using the stent of the latter (Charnsangavej et al., 1986). Stenting procedures were first conducted in dogs and then applied on humans in 1986, since then stenting is being applied with great success using different types of stents.

5.3.2 Different Types of Stents used

The first stents applied were Gianturco stents, then followed by Palmaz and Wall stents (Kee et al., 1998). In our study, we preferred self-expandable Nitinol stents because of their flexibility, kink resistance, high radial force and their large inner diameter with a length reaching till 120mm (Stoeckel et al., 2004). The most commonly used stent was the Memotherm stent (75.8%). From 2007, we applied exceedingly more Sinus-XL stents (15%) and other stents such as Wall-stents (5%), while Gianturco-Z stents (4.2%) were rarely used. In other centers, SMART (stent from Cordis) were much

rarely used as described by other authors (Hennequin et al.,1995; Oukkerk et al.,1996 ; Masuda et al., 2013; Kühn et al., 2013).

To prevent stent migration, a stent with an appropriate diameter, a diameter 5-10 % greater than that of the non-stenosed vessel, should be used. It is also important to avoid using stents with narrow diameter, which could lead to early thrombosis or stent migration following the expected tumor shrinkage with therapy (Srinathan, 2005).

The first covered stent to be inserted in a case of SVCO was in 1996 and it was a Gianturco stent with a covering membrane (Lau et al., 2003). The Role of covered stents remains uncertain (Ines et al., 2008). It was stated that covered stents have higher cumulative patency than uncovered stents. However the clinical success rate of both is similar (Gwon et al., 2013). It was also suggested that the presence of an intra-caval tumor will prevent correct endothelialisation of the stent and that tumor might grow beyond the interspace of the stent struts. In these cases, covered stents could be effective (Chin et al., 1996; Hennequin et al., 1995). Others believed that tumor growth through the stent or significant thickening of the intimal layer was not observed during follow up. Thus it was thought that there is no need to use covered stents for this indication (Thony et al., 1999), especially regarding the short life expectancy of patients with malignant stenosis. On the other hand, in case of benign stenosis such stents might be more advantageous due to the longer patency rate. We have no personal experience in applying covered stents at SVCO.

5.3.3 Indication and Contraindication

Some institutions have detailed indication criteria for stent insertion including SVCS over one month, no intravascular tumor invasion, caval pressure higher than 22 mm Hg at the peripheral end of the stenosis, patient considered to tolerate partial cardiac volume overload, alternative anticancer therapy no longer effective or available, presence of developing upper airway obstruction or central nervous system-related symptoms due to SVCS (Kishi et al., 1993). By many centers, SVCO was considered as serious condition that requires immediate intervention (Shama et al., 1986).

Others defined contraindications for the procedure with extensive thrombosis of the SVC, tumor-ingrowth and deranged clotting (Gompelmannet al., 2011; Thony et al., 1999; Oudkerk et al., 1993; Lee-Elliott et al., 2004). However there are no absolute contraindications for the stenting procedure (Uberoi, 2006).

In our study, the procedure was indicated when the patient´s condition was extremely affected by the symptoms and when chemo- and radiotherapy were ineffective, and also in cases with expected delayed impact of such therapies.
Where there is no absolute contraindication, relative contraindications included a debilitated general condition and multiple co-morbidities with an extremely shortened life expectancy.

5.4 The Procedure

We achieved venous access via the right femoral vein, this is the preferred route of access as described in other studies as well (Masuda et al., 2013). The Direct way from the right femoral vein to the SVC facilitates the access, where the wide vessel diameter reduces the complication as bleeding and thrombus formation. The brachiocephalic access was preferred by some authors especially when introducing stents in both brachiocephalic veins simultaneously (Hennequin et al., 1995).

5.4.1 Angioplasty and Stenting

The literature recommends pre-stenting dilatation using a low pressure balloon angioplasty catheter to allow assessment of the location, rigidity and length of the stenosis. This is particularly desirable prior to stenting of benign SVC obstruction (Ines et al., 2008; Okay and Bryk, 1969). In the majority of cases, we were able to bypass the obstruction without the need for pre-stenting dilatation. Only in 19 out of 95 cases (20%), we chose to perform balloon dilation prior to stent deployment.

In the majority of our cases, post-stenting balloon dilation was required to achieve full expansion of the stent and overcome any remaining-stenosis. We resorted to balloon dilatation in 55 out of 95 cases (58%) after stent application. Some studies advocate that it is important to obtain the widest SVC channel as quickly as possible at the end of the stenting procedure by using balloon angioplasty and not to wait for a spontaneous widening of the stent (Thony et al., 1999).

It is mentioned that post-stenting angioplasty causes the thrombus to be compressed against the stent, thus reducing the risk of embolic complications (Ines et al., 2008). According to the recommendations of the French Society of Cardiovascular Imaging, angioplasty must be performed using a low pressure balloon with diameter slightly inferior (2 mm) to the stent diameter, without seeking immediate complete stent expansion, which would occur spontaneously over the next few hours or days and that

in order to avoid local hemorrhagic complications such as venous wall dissection, rupture or pericardial tamponade (Ines et al., 2008).

In one patient (S.S. 21/04/2005), we observed during stent implantation procedure a thrombus located within the stent and extending distally. Mechanical thrombectomy was attempted followed by short time thrombolysis using 20.000 IU Urokinase with no effect. We then decided to abandon systemic thrombolysis because of the risk of tumor bleeding. This patient died 15 days after the stenting procedure where he was under symptomatic therapy.

5.4.2 Anticoagulants and Stenting

During stent insertion, intravenous heparin was routinely used in our hospital via a peripheral root as well as other institutions (Ines et al., 2008). Anticoagulant therapy following successful stent implantation varies considerably in literature, ranging from no treatment to the combined use of anticoagulants and platelet aggregation inhibitors (Ines et al., 2008) over variable periods of time.

Short-term anticoagulant therapy is often recommended after stent insertion (De Raet et al., 2012), but there are still debates whether long-term anticoagulation is required or not (Nguyen et al., 2009; De Raet et al., 2012). It is believed that following stent insertion, intimal hyperplasia in the form of fibroblastic proliferation could be reduced by the use of platelet aggregation inhibitors (Ines et al., 2008).

Although post-procedural heparinization was documented in 27.4 % of cases, we could not demonstrate any statistical relationship between heparinization and clinical success. This supports the lack of evidence in the literature that supports the necessity of giving heparin after stenting (Thony et al., 1999). Others suggest giving LMWH because of the associated lower bleeding risk (Sofue et al., 2013; Iaccarino et al., 2014). Thus one can advocate that by achieving a good venous flow post-stenting, heparin regimen would not be required. Various complications following anticoagulant therapy are reported in the literature especially bleeding (Nguyen et al., 2009; Iaccarino et al., 2014). However this was not encountered in our study and we did not use any platelet aggregation inhibitors.

Current guidelines recommend the use of LMWH alone in the prevention and post procedural (6 months) care of cancer patients. Furthermore, long-acting LMWH is available that can be easily administered subcutaneously once a day (Iaccarino et al., 2014).

5.5 Outcome

5.5.1 Success Rate

The technical and clinical success rates of SVC stenting are reported to be high (Uberoi, 2006, Cho et al., 2014, Masuda et al., 2013), where technical success is defined as successful stent insertion without any remaining high stenosis and clinical success is defined as the relief of symptoms (Gompelmann et al., 2011).

In our study, clinical relief of symptoms was achieved shortly after stent implantation. Relief of symptoms was reported while still on the angiographic table (Kee et al., 1998; Luo et al., 2013) or within 0-72 hours of stent implantation (Ines et al., 2008; Karaca 2009). Endothelial intima usually covers the stents and incorporates then into the physiological vascular system within a few weeks following stent placement (Nguyen et al., 2009).

In our study, we achieved a clinical success rate of 86.3 %. In two patients success was achieved after the second intervention. This is consistent with other published reports where success rates in terms of the effectiveness of the stent in relieving malignant SVC obstruction following failure of primary cancer therapy ranges between 81-100 % and the effectiveness in relieving symptoms prior to primary cancer therapy ranges between 87-100 % (Nguyen et al., 2009) where the latter usually precedes an established pathological diagnosis (Cho et al., 2014; Cordial et al., 2014).

5.5.2 Factors Influencing the Success Rate

We observed that technical and clinical success rates are strongly influenced by efficient widening of the obstruction during the procedure to avoid any residual obstruction. In many cases with re-obstruction, inefficient stent dilation was reported early at the time of the first intervention.

Compared with balloon expandable stents, Wall-stents are preferred by many interventionists (Nguyen et al., 2009; Ines et al., 2008) because their flexibility and expandability are very effective in stenting tumor stenosis of the SVC (Thony et al., 1999). However the relative small diameter of the expanded stent (maximum diameter of 16 mm) is a considerable drawback (Thony et al., 1999) limiting its effectiveness (Hennequin et al., 1995) that's why its use was limited in the early years in our study.

Z-Stents were found to be rigid requiring a larger venous introducer than the one used for other stents. Moreover, migration or fracture has been observed more with the

Gianturco-Z stent (Thony et al., 1999). In our study, we also experienced a partial migration of a Z-stent into the right atrium (Figure 13).

We preferred Nitinol-stents due to their greater radial force yet with equal flexibility as the Wall-stents. We mainly used Nitinol-stents with an inner diameter of 20-22 mm.

It has been reported that stent effectiveness is unrelated to the stent type (Nguyen et al., 2009), however some stated that recurrence of stenosis would appear more after secondary retraction if the stent was misplaced because it was pushed down by „milking" due to stenosis. This is regarded as a great disadvantage of Wall-stent endoprothesis (Hennequin et al., 1995), especially with using short stents. We could not find a correlation between the stent type and success rate. However we used a small number of Wall stents (6 patients) and Gianturco -Z stents (5 patients) versus a larger number of Memotherm stents (91 patients) and Sinus –XL stents (18 patients).

To achieve clinical success, we concluded that it is sufficient to establish a venous drainage through the SVC with a connection to at least one side of the body through a patent right subclavian vein or brachiocephalic trunk. This also correlated with similar reports in the literature (Hennequin et al., 1995) where the patency of one brachiocephalic vein was generally sufficient to avoid recurrence of SVCS. Otherwise in a study, technical failure was described in SVCO and primarily with bilateral innominate vein occlusion (Sobrinho and Aguiar, 2014). We did not experience such a technical failure.

Centers that applied kissing stents, reported that "kissing" Wall stents in the SVC did not have sufficient radial strength to maintain an adequate lumen and that it was necessary to deploy Palmaz stents inside the Wall stents (Kee et al. 1998; Uberoi, 2006; Nagata et al., 2007). Also it was reported that bilateral stenting (kissing stents) resulted in higher complication rate and lower survival (Uberoi, 2006). The French society of Cardiovascular Imaging recommends that obstructive lesions at the SVC confluence should be treated with unilateral stenting due to the presence of cervico-thoracic venous collaterals between both systems (Ines et al., 2008).

In cases with obstruction of venous drainage at both sides, we attempted re-canalization of the veins of at least one side. We only implanted kissing stents in one patient (R.H. 19/04/1999).

5.6 Survival

The cut-off period of data analysis was 31/10/2013. We had a follow-up period ranging from 0 to 33.5 months with a mean of 8.4 ± SD of 9 months. Other studies reported follow-up periods ranging from 2 to 7 months (Nguyen et al., 2009), with a mean of 7.1 months (Ines et al., 2008), 7 months (Kee et al. 1998), 4.4 months (Hennequin et al., 1995), and 5.8 months (Cho et al., 2014). The longest follow up period recorded in literature was 29.1 months (Cho et al., 2014) versus ours of 33.5 months.
Compared to other studies, we had by far the longest period of follow-up data after actual stent implantation and at the time of statistical analysis none of the patients were alive. This long follow-up period in a target group of cancer patients, mainly with terminal and inoperable conditions (Hennequin et al., 1995) demonstrated a long survival time in some of these patients. A similar observation was demonstrated in other studies (Hennequin et al., 1995).

We did not have a systematic follow-up program as post-interventional radiological visualization of the stent is only recommended in cases with recurrent symptomatic SVCS. As described in other studies, stenting in cancer patients usually has a poor prognosis as stents are inserted in these patients primarily for palliation of the presented SVCO in an advanced state of cancer. However this fact should not by any means underestimate the efficiency and role of the procedure.

We found no significant correlation between the rate of complication and the stent type. The comparison between three equally large patient groups at three different time intervals showed no significant difference in the survival or the stent-patency rates (Table 8). It is worth mentioning that in the first period of 2.5 years, the number of patients was almost equal to that in the following 2 periods of 5 years each. We concluded that this was probably due to the progress in chemotherapy subsequently leading to fewer patients being referred for stenting. On the other hand, the success rate of the interventional procedure in different patient groups remained the same.

Therefore survival rates are mainly dependent on the underlying cancerous condition and to a lesser extent on the type of stent. The reported overall survival rates are known to be poor, in the rates for 6 and 12 months survival were 29 % and 16 % respectively (Thony et al., 1999).

5.7 Complications

The most common complication we encountered was re-obstruction observed in 19 % of the cases (n=18). In the majority of cases, we diagnosed re-obstruction clinically without imaging confirmation depending on the symptoms and signs documented at the time of death.

The possibility still remains that a part of our patients had a slowly progressive re-obstruction with good collateral circulation, so the patients remained without symptoms and were declared as “clinically open”.

In other centers, reported recurrence rates were similar e.g. 10.7% (Gompelmann et al., 2011), 11% (Karaca et al., 2009), 19% (Ines et al., 2008), 18% (Nguyen et al., 2009).

Re-obstruction was attributed to thrombosis or tumor invasion (Nguyen et al., 2009; Ines et al., 2008; Karaca et al., 2009; Hennequin et al., 1995), where it is believed that it is more due to thrombosis than tumor growth (Oudkerk et al., 1996). Hence relapse is usually treated by thrombus-aspiration, thrombolysis and further stent insertion (Karaca et al., 2009). It is also reported that recurrence can be due to incomplete expansion of the original stent (Thony et al., 1999). When re-obstruction occurs slowly, thus allowing good collaterals to develop, it remains asymptomatic and does not require re-intervention.

Complications are generally rare especially when compared with other therapeutic modalities. We reported early and late complications in 12.6 % and 8.4% respectively. In literature, complications include occlusion, infection, SVC rupture, hemorrhage, hemoptysis, epistaxis, pericardial tamponade, cardiac failure, recurrent laryngeal palsy, stent migration, pulmonary emboli and groin hematoma. However complications during and post-procedure are generally low, occurring in 0-19% of patients (Uberoi, 2006). Others reported complications in 3-7% of patients (De Raet et al., 2012).

We experienced early complications in 12 cases out of 95 cases:

1. In 2 cases of the 95 was the procedure abandoned due to occurring serious cardiovascular problems, one patient having maintained arrhythmia and the second patient suffered heart arrest where the patient was rapidly resuscitated. Both cases ended without actual intravascular prosthesis application.
2. One patient had a trivial arrhythmia.

3. In 2 cases the stent was dislocated into the right atrium.
4. In 7 cases we reported an early re-closure;
    - In one of those we did local thrombolysis without success.
    - 6 of those patients got a symptomatic therapy without re-intervention.

Late complications were seen in 8 out of the 93 cases, all of them experienced late occurrence of the re-obstruction. In three cases, we performed a new stent implantation of the obstruction. Whereas in one of those patients the second stent was again complicated with early re-obstruction (Figure 16).

We did not experience any hemodynamic changes as described in the literature (Nguyen et al., 2009; Warner and Uberoi, 2013; Iaccarino et al., 2014), nor did we observe any mediastinal or pericardial bleeding due to vessel wall perforation as reported by others (Ines et al., 2008). We experienced no complications on the venous access site and we found no significant correlation between the rate of complication occurrence and the stent type. This correlates with the results of the literature (Bosma et al., 2014) of Rowell and Gleeson 2001and others (Fagedet et al., 2013) which stated the recommendation of stenting to treat symptomatic SVCO as follows:

- In newly diagnosed cases of NSCLC and those under treatment.
- In SCLC under treatment.

In non-cytologically and non-histologically confirmed malignant tumor.

6 Summary

There are many causes leading to a SVCS: some are of benign origin but the majority is associated with malignant condition. Malignant SVCS is usually caused by extrinsic compression and less common by invasion of the superior vena cava.

Stent implantation as a treatment of superior vena cava syndrome is a safe and effective procedure especially in cases of acute occurring symptoms. It is a palliative procedure appropriate in advanced cancer conditions. Advantages of endovascular treatment include a low complication rate, prompt regression of symptoms following stenting compared to chemotherapy and/or radiotherapy, and a low rate of recurrence.
Stenting is done in newly diagnosed malignancy with acute severe SVCS or in cases where obstruction is the presenting symptom of a condition most probably of malignant nature, prior to further diagnostic procedures including histology. The main aim of stent implantation here is relieving the patients' symptoms. The exact histological diagnosis of the tumor condition can be done after beginning the therapy when improvement of SVCO has been achieved.
When re-obstruction slowly occurs allowing good collaterals to develop, it remains asymptomatic not requiring re-intervention; re-stenting is indicated with re-occurrence of symptomatic SVCO.

The study aimed to assess the applicability and effectiveness of SVC stenting in the management of superior vena cava syndrome in cancer patients. The study included 95 cases with superior vena cava obstruction due to histologically confirmed malignant tumors as the underlying cause of obstruction.
120 SVC stents were implanted in the time interval between 05/1996 and 11/2009. The technical and clinical success rates of SVC stenting were high. In our study, we achieved a clinical success rate of 86.3 %. We used different stent types and found no significant correlation between the rate of complication and the stent type.
Complications of this procedure are generally rare especially when compared with other therapeutic modalities. The most common complication we encountered was re-obstruction observed in 19 %.

We tried to define the role of SVC stenting as follows:

-In newly diagnosed NSCLC and in cases which respond poorly to chemotherapy, stenting could be done for symptomatic SVCO.

-Newly diagnosed SCLC with SVCO is an indication for chemotherapy and/or stenting.

-In cases under treatment, stenting is considered when the aimed symptom regression could not be achieved.

-Stenting is the first line of therapy in SVCO occurring during Chemo- or Radiotherapy.

-Stenting is indicated in acute SVCO due to suspected malignant intra thoracic tumor even prior to the histological diagnosis.

References

Abdelkafi S, Dubail D, Bosschaerts T, et al. Superior vena cava syndrome associated with Nocardia farcinica infection. Thorax 1997; 52:492-493.

Ahmann FR. A reassessment of the clinical implications of the superior vena caval syndrome. J Clin Oncol 1984; 2:961-969.

Aldoss O, Arain N, Menk J, Kochilas L, Gruenstein D. Endovascular stent provides more effective early relief of SVC obstruction compared to balloon angioplasty. Catheter Cardiovasc Interv 2014; 83(7):E272-6.

Bakken AM, Protack CD, Saad WE, Lee DE, Waldman DL, Davies MG. Long-term outcomes of primary angioplasty and primary stenting of central venous stenosis in hemodialysis patients. J Vasc Surg 2007; 45:776-783.

Bechtold RE, Wolfman NT, Karstaedt N, Choplin RH. Superior vena caval obstruction: detection using CT. Radiology 1985; 157:485-487.

Bolad I, Karanam S, Mathew D, John R, Piemonte T, Martin D. Percutaneous treatment of superior vena cava obstruction following transvenous device implantation. Catheter Cardiovasc Interv 2005; 65:54-59.

Bosma JW, Veenstra J, Vasmel WL. Patients with superior vena cava syndrome: pitfalls in recognition. Ned Tijdschr Geneeskd. 2014; 158(1):A6858.

Chamorro H, Rao G, Wholey MH. Superior vena cava syndrome: a complication of transvenous pacemaker implantation. Radiology 1978; 126:377-378.

Chan R C-L, Chan YC, Cheng SW-K. Mid- and long- term follow-up experience in patients with malignant superior vena cava obstruction. Interactive Cardiovascular and Thoracic Surgery 2013; 16:455-458.

Charnsangavej C, Carrasco CH, Wallace S, Wright KC, Ogawa K, Richli W, Gianturco C. Stenosis of the vena cava: preliminary assessment of treatment with expandable metallic stents. Radiology 1986; 161(2):295-298.

Chen JC, Bongard F, Klein SR. A contemporary perspective on superior vena cava syndrome. Am J Surg 1990; 160:207-211.

Cheng S. Superior vena cava syndrome: a contemporary review of a historic disease. Cardiol Rev 2009; 17:16-23.

Chin DH, Petersen BD, Timmermans H, Rösch J. Stent-Graft in Management of Superior Vena Cava Syndrome. Cardiovasc Intervent Radiol.1996; 19(4):302-304.

Cho Y, Gwon DI, Ko GY, Ko HK, MD, Kim JH, Shin JH, Yoon HK, Sung KB. Covered Stent Placement for the Treatment of Malignant Superior Vena Cava Syndrome: Is Unilateral Covered Stenting Safe and Effective? Korean J Radiol. 2014; 15(1):87-94.

Cordial R, Moussavian MR, Corvalan J, Görtz H, Teßarek J. Percutaneous Endovascular Y Stenting of a Malignant Superior Vena Cava and Innominate Vein Obstruction. Vasc Endovasc Surg. 2014; 48(1):77-79.

Dempke W, Behrmann C, Schöber C, Büchele T, Grothey A, Schmoll HJ. Diagnostic and therapeutic management of the superior vena cava syndrome. Med Klin (Munich). 1999; 94(12):681-684.

de Paiva TF Jr, Ribeiro HB, Campanholo CB, Goncalves CR, Terigoe DY, de Souza BD. Behcet's disease associated with superior vena cava syndrome without thrombosis. Clin Rheumatol 2007; 26:804-806.

De Raet JM, Vos JA, Morshuis WJ, Van Boven W-J P. Surgical management of superior vena cava syndrome after failed endovascular stenting. Interactive Cardiovascular and Thoracic Surgery 2012; 15:915-917.

Dinkel HP, Mettke B, Schmid F, Baumgarten 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(4):788-97.

Dong YQ, Liang JS, Zhang XM, Zhu SB, Xu JH, Ji T, Yin GL. Surgical treatment of invasive thymoma extending into the superior vena cava and right atrium. World Journal of Surgical Oncology 2014; 12:6.

Eren S, Karaman A, Okur A. The superior vena cava syndrome caused by malignant disease. Imaging with multi-detector row CT. Eur J Radiol 2006; 59:93-103.

Fagedet D, Thony F, Timsit JF, Rodiere M, Monnin-Bares V, Ferretti GR, Vesin A, Moro Sibilot D. Endovascular Treatment of Malignant Superior Vena Cava Syndrome: Results and Predictive Factors of Clinical Efficacy. Cardiovasc. Intervent. Radiol 2013; 36(1):140-149.

Ganeshan A, Hon LQ, Warakaulle DR, Morgan R, Uberoi R. Superior vena caval stenting for SVC obstruction: current status. Eur J Radiol 2009; 71:343-349.

Gompelmann D, Eberhardt R, Herth FJF. Advanced malignant Lung disease: what specialists can offer. Respiration 2011; 82:111-123.

Gonzalez-Fajardo JA, Garcia-Yuste M, Florez S, Ramos G, Alvarez T, Coca JM. Hemodynamic and cerebral repercussions arising from surgical interruption of the superior vena cava. Experimental model. J Thorac Cardiovasc Surg 1994;107:1044-1049.

Goudevenos JA, Reid PG, Adams PC, Holden MP, Williams DO. Pacemaker-induced superior vena cava syndrome: report of four cases and review of the literature. Pacing Clin Electrophysiol 1989; 12:1890-1895.

Gwon DI, Ko GY, Kim JH, Shin JH, Sung KB. Malignant superior vena caa syndrome: A comparative cohort study of treatment with covered stents versus uncovered stents. Radiology 2013; 266(3):979-987.

Gwon DIL, Paik SH. Successful Treatment of Superior Vena Cava Syndrome Uusing a stent graft. Korean J Radiol 2012; 13(2):227-231.

Hennequin LM, Fade O, Fays JG, Bic JF, Jaafar S, Bertal A, Anthoine D, Bernadac PA. Superior Vena Cava Placement: Results with the Wallstent Endoprothesis. Radiology 1995; 196:353-361.

Iaccarino V, Venetucci P, Brunetti A, Ramundo V, Di Minno G. Anticoagulant Therapy in Oncologic Patients Undergoing Venous Stenting for Superior Vena Cava Syndrome

and Other Interventional Procedures. Cardiovasc Intervent Radiol 2014; 37(5):1401-1402.

Ines D Da, Chabrot P, Cassgnes L, et al. Endovascular treatment of SCV syndrome from neoplastic origin: a review of 34 cases. J Radiol 2008; 89: 881-889.

Karaca O, Akçakyun M, Esen Ö, Esen AM. Endovascular stenting for treatment of superior vena cava syndrome. Türk Kardiyol Dern Arş -Arch Turk Soc Cardiol 2009; 37(6):414-416.

Kee ST, Kinoshita L, Razavi MK, Nyman UR, Semba CP, Dake MD. Superior Vena Cava Syndrome: Treatment with Catheterdirected Thrombolysis and Endovascular Stent Placement. Radiology 1998; 206:187-193.

Khanna S, Sniderman K, Simons M, Besley M, Uldall R. Superior vena cava stenosis associated with hemodialysis catheters. Am J Kidney Dis 1993; 21:278-281.

Kim HJ, Cho SY, Cho WH, Lee do H, Lim do H, Seo PW, Park MH, Lee W, Lee JH, Kim DH. An Unusual Case of Superior Vena Cava Syndrome Caused by the Intravascular Invasion of an Invasive Thymoma. Tuberc Respir Dis (Seoul) 2013; 75(5): 210-213.

Kim HJ, Kim HS, Chung SH. CT diagnosis of superior vena cava syndrome: importance of collateral vessels. AJR Am J Roentgenol 1993; 161:539-542.

Kim JY, Lim CM, Koh Y, Choe KH, Kim WS, Kim WD. A case of superior vena cava syndrome caused by Klebsiella pneumoniae. Eur Respir J 1997; 10:2902-2903.

Kirkpatrick LA, Feeney BC. A simple guide to IBM SPSS statistics for version 20.0. Student ed. Belmont, Calif.: Wadsworth, Cengage Learning 2013; x, 115 p. p. 104

Kishi K, Sonomura T, Mitsuzane K, Nishida N, Yang RJ, Sato M, Yamada R, Shirai S, Kobayashi H. Self-expandable Metallic Stent Therapy for Superior Vena Cava Syndrome: Clinical Observations. Radoiology 1993; 189:531-535.

Kitamura J, Murakami Y, Shimada T, et al. Morphological observation by intravascular ultrasound in superior vena cava syndrome after pacemaker implantation. Cathet Cardiovasc Diagn 1996; 37:83-85.

Kretschmer S, Schneider W. The superior vena cava syndrome as an oncological emergency. Dtsch Med Wochenschr 1992; 17:1650-1655.

Kühn J-P, Mensel B, Ewert R, Bollmann T. Interventional Treatment of the Acute and Subacute Vena Cave Superior Syndrome. Pneumologie. 2013; 67(10):573-579.

Lanciego C, Pangua C, Chaón J I,Velasco J, Boy, R C, Viana A, Cerezo J, Gracia L G. Endovascular management as the first step in the overall management of malignant superior vena cava obstruction. Am J Roentgenol 2009; 193:549-558.

Lau KY, Tan LTH, Wong WWC, Lee ASL. Brachiocephalic- superior vena cava metallic stenting in malignant superior vena cava obstruction. Ann Acad Med Singapore 2003; 32:461-465.

Lee-Elliott CE, Abubacker MZ, Lopez AJ. Fast-track management of malignant superior vena cava syndrome. Cardiovasc Intervent Radiol 2004; 27:470-473.

Leslie E, Geoffrey J, James M. Statistical analysis. In: Interpretation and uses of medical statistics (4th ed). Oxford Scientific Publications(pub) 1991; pp.411-416.

Lin J, Zhou KR, Chen ZW, Wang JH, Yan ZP, Wang YX. Vena cava 3D contrast-enhanced MR venography: a pictorial review. Cardiovasc Intervent Radiol 2005; 28:795-805.

Luo J, Chen B, Jiang S, Zhou SW. Interventional therapy for lung cancer patients with superior vena cava syndrome. Zhonghua Zhong Liu Za Zhi 2013; 35(8):627-631.

Mackie GC, Thomas A, Greenspan B, Singh A. Focal hepatic activity during ventilation perfusion scintigraphy due to systemic-portal shunt due to superior vena cava obstruction from histoplasmosis-induced fibrosing mediastinitis. Clin Nucl Med 2007; 32:707-710.

Masuda E, Sista AK, Pua BB, Madoff DC. Palliative Procedures in Lung Cancer. Semin Intervent Radiol. 2013; 30(2):199-205.

Mehta SV, Koo DJ. Radiation-induced SVC syndrome. BMJ Case Rep 2014; pii: bcr2013203446. doi: 10.1136/bcr-2013-203446.

Mineo TC, Ambrogi V, Nofroni I, Pistolese C. Mediastinoscopy in superior vena cava obstruction: analysis of 80 consecutive patients. Ann Thorac Surg 1999; 68:223-226.

Nagata T, Makutani S, Uchida H, Kichikawa K, Maeda M, Yoshioka T, Anai H, Sakaguchi H, Yoshimura H. Follow-up results of 71 patients undergoing metallic stent placement for the treatment of a malignant obstruction of the superior vena cava. Cardiovasc Int Radiol 2007; 30:959–967.

Nguyen NP, Borok TL, Welsh J, Vinh-Hung V. Safety and effectiveness of vascular endoprosthesis for malignant superior vena cava syndrome. Thorax 2009; 64:174-178.

Nieto AF, Doty DB. Superior vena cava obstruction: clinical syndrome, etiology, and treatment. Curr Probl Cancer 1986; 10:441-484.

Okay NH, Bryk D. Collateral pathways in occlusion of the superior vena cava and its tributaries. Radiology 1969; 92:1493-1498.

Oudkerk M., Heystraten F. M. J, Stottert G. Stenting in Malignant Vena Caval Obstruction. Cancer 1993; 71:142-146.

Oudkerk M, Kuijpers TJA, Schmitz PIM, Loosveld O, de Wit R. Self-Expanding Metal Stents for Palliative Treatment of Superior Vena Caval Syndrome. Cardiovasc Intervent Radiol. 1996'; 19:146-151.

Parish JM, Marschke RF Jr, Dinesh DE, Lee RE. Etiologic considerations in superior vena cava syndrome. Mayo Clin Proc 1981; 56:407-413.

Park YJ, Ryu YJ, Hwang MJ, Shin SH, Cho JS, Park MH, Yoon JH, Lim HS, Lee JS. Superior Vena Cava Syndrome Arising from Central Venous Port Catheter in a Breast Cancer Patient. Journal of Breast Disease 2013; 1(1): 39-41.

Plekker D, Ellis T, Irusen E M, Bolliger CT, Diacon A.H. Clinical and radiological grading of superior vena cava obstruction. Respiration 2008; 76:69-75.

Power CK, Buggy D, Keogh J. Acute superior vena caval syndrome with airway obstruction following elective mediastinoscopy. Anaesthesia 1997; 52:989-992.

Rice TW, Rodriguez RM, Light RW. The superior vena cava syndrome: clinical characteristics and evolving etiology. Medicine (Baltimore) 2006; 85:37-42.

Rosenbloom SE. Superior vena cava obstruction in primary cancer of the lung. Ann Intern Med 1949; 31:470-478.

Rowell NP, Gleeson FV. Steroids, radiotherapy, chemotherapy and stents for superior vena caval obstruction in carcinoma of the bronchus: a systematic review. Clin Oncol (R Coll Radiol) 2002; 14:338-351.

Sahin MS, Aktu Rk SL, Bulut M, Kırma C. Percutaneous treatment of superior vena cava syndrome caused by chronic thrombosis. Turk Kardyol Dern Ars 2014; 42(1):76-79.

Savarese DM, Zavarin M, Smyczynski MS, Rohrer MJ, Hutzler MJ. Superior vena cava syndrome secondary to an angiotropic large cell lymphoma. Cancer 2000; 89:2515-2520.

Schechter MM. The superior vena cava syndrome. Am J Med Sci 1954; 227:46-56.

Smayra T, Otal P, Chabbert V, Chemla P, Romero M, Joffre F, Rousseau H. Long-Term Results of Endovascular Stent Placement in the superior caval venous system. Cardiovasc Intervent Radiol. 2001; 24(6):388-394.

Sobin LH, Gospodarowicz MK, Wittekind C, editors. TNM classification of malignant tumours. 7th ed. Oxford: Wiley-Blackwell 2009; p. 181-193.

Sobrinho G, Aquiar P. Stent Placement for the Treatment of Malignant Superior Vena Cava Syndrome - A Single-Center Series of 56 Patients. Arch Bronconeumol 2014; 50(4):135-140.

Sofue K, Takeuchi Y, Arai Y, Sugimura K. Reply to Letter re: Anticoagulant Therapy in Oncologic Patients Undergoing Venous Stenting for Superior Vena Cava Syndrome and Other Interventional Procedures. Cardiovasc Intervent Radiol 2014; 1337(5):1405-1406.

Srinathan S, McCafferty I, Wilson I. Radiological Management of superior Vena Caval Stent Migration and Infection. Cardiovasc. Intervent. Radiol 2005; 28:127-130.

Stanford W, Doty DB. The role of venography and surgery in the management of patients with superior vena cava obstruction. Ann Thorac Surg 1986; 41:158-163.

Stanford W, Jolles H, Ell S, Chiu LC. Superior vena cava obstruction: a venographic classification. AJR Am J Roentgenol 1987; 148:259-262.

Stoeckel D, Pelton A, Duerig T. Self-Expanding Nitinol Stents ‐ Material and Design Considerations Eur Radiol 2004; 14(2):292-301.

Talens A, Ferrer S, González-Cruz A, Blanco E, García-Ferrer L, Iranzo V, Camps C. Effectiveness of endovascular prostheses as initial treatment for superior vena cava syndrome of malignant cause. Med Clin (Barc) 2013; 140(2):59-65.

Thornton MJ, Ryan R, Varghese JC, Farrell MA, Lucey B, Lee MJ. A three-dimensional gadolinium-enhanced MR venography technique for imaging central veins. Am J Roentgenol 1999; 173:999-1003.

Trigaux JP, Van Beers B. Thoracic collateral venous channels: normal and pathologic CT findings. J Comput Assist Tomogr 1990; 14:769-773.

Uberoi R. Quality assurance guidelines for superior vena cava stenting in malignant disease. Cardiovasc Intervent Radiol 2006; 29:319-322.

Warner P, Uberoi R. Superior vena cava stenting in the 21st century. Postgrad Med J 2013; 89(1050):224-230.

Wilson LD, Detterbeck FC, Yahalom J. Clinical practice. Superior vena cava syndrome with malignant causes. N Engl J Med 2007; 356:1862-1869.

Witt C, Schmidt B, Borges AC, Doerffel W, Baumann G, Romaniuk P. Superior vena cava syndrome. From the bronchus to the vessel. Diagn Ther Endosc 1997; 4:83-93.

Yu JB, Wilson LD, Detterbeck FC. Superior vena cava syndrome--a proposed classification system and algorithm for management. J Thorac Oncol 2008; 3:811-814.

Propositions of Thesis

1. Superior vena cava obstruction occurs secondary to occlusion or stenosis of the SVC mainly due to extensive or metastasizing lung cancer where we resort to symptomatic and palliative therapy.
2. Treatment options include medical therapy (sedatives and analgesics), nursing (positioning and oxygen therapy), chemo- and radiotherapy. Surgery with a palliative goal can be associated with various hazards and has a high complication rate.
3. The interventional procedure by applying a stent is much superior to the balloon dilatation. Diagnostic imaging (MSCT, phlebography of the SVC) is performed at first to determine the stent type, length and diameter.

Between May 1997 and December 2009, we applied 120 self-expandable stents (6 Wallstent, 91 Memotherm-stent 18 Sinus-XL-stent and 5 Gianturco- Z-stent) in 93 out of 95 patients (86 with lung cancer and 9 patients with mediastinal lymph node metastasis of an extra- pulmonary primary tumor) in the superior vena cava and its afferent veins. Stenting was abandoned in two patients when life-threatening conditions occurred.

4. Stenting has a low complication rate. We encountered early complications in 12 of 95 cases (the intended procedure was abandoned in two cases, asymptomatic stent dislocation occurred in two cases and early lumen re-closure in nine patients). Late complications occurred in the form of late lumen re-closure more than 30 days following stent implantation. We did not encounter other complications such as vessel injury, mediastinal bleeding or procedure-related death.
5. Stent-patency ratio depends on the correct dilatation of the stenosis possibly without any remaining stenosis. There was no relation between the types of implanted stents and patency rates. Clinical patency was documented in 67 patients (71%), 18 patients (19%) had re-occurring SVCO and documentation of stent patency at time of death was not available in eight patients. In three of the 67 patients, stent patency was achieved following a second intervention with a new stent implantation.
6. Post-procedural anticoagulation therapy for three days had no effect on stent patency as the closure rate in the 67 non-heparinized patients was 18.8% versus 19.4% in the 26 heparinized patients.
7. A patent venous drainage of one side of the body (right subclavian vein or left brachiocephalic trunk) was sufficient to overcome symptomatic SVCO.

We only used diagnostic imaging after the procedure when a patient experienced symptomatic SVCO.

8. The survival rate after stent implantation, ranging from 251 to 269 days with a median of 152 days, depends on the underlying cancerous condition in our study group and the available treatment options.

9. Indication for stenting should be decided upon in an interdisciplinary setting based on the patient´s symptoms, his/her clinical condition, life expectancy and other available treatment modalities.

10. Our recommendations for treatment of symptomatic SVCO are as follows:

- In newly diagnosed cases of NSCLC and those under treatment, stenting is the first line of choice.
- In newly diagnosed SCLC, chemotherapy is usually the main line of treatment.
- In SCLC already under treatment SVCO is treated with stenting.
- In emergency situations the treatment of choice is stenting.

Curriculum Vitae

Personal Data:

Surname:	Antakia
First name:	Noha
Address:	Weimarische Straße 2, 99438 Bad Berka
Date of Birth:	13.04.1976
Place of Birth:	Alexandria, Egypt
Marital status:	married, two children

School education:

1979-1994	Deutsche Schule der Borromärinnen Alexandrien

College education / vocational education and training:

1994-2000	Medical studies, Faculty of Medicine, Alexandria University
1997-1999	Medical Visitations (Bonn and Alexandria)
2001	Final clinical year (Alexandria)
2004 -	Master study at Department of Clinical Chemistry at the Medical Research Institute, Alexandria University.
08/07-05/11	Radiological Residency in the Center of Diagnostic and Interventional Radiology, Zentralklinik Bad Berka
06/11-08/12	Parental leave
09/12-04/13	Radiological Residency in the Clinic of Radiology and Nuclear medicine, Sophien- und Hufeland Klinikum Weimar.
07/13-10/13	Parental leave
Since 11/13	Radiological Residency in the Center of Diagnostic and Interventional Radiology, Zentralklinik Bad Berka

Acknowledgement

I want to express my gratitude to my supervisor Dr. med. habil. Hans-Jürgen Strauß, who continuously encouraged and supported me. Without his guidance and patient help this dissertation would not have been possible.

I am also immensely grateful to Prof. Dr. med. Rolf Peter Spielmann for his constant help and comments.

A special thanks to the S&S Office of Statistical analysis for their valuable help in the design and performance of the statistical analysis.

Also I would like to acknowledge Dr. med A. Petrovitch the head of Interventional Radiology department for what he taught me.

Declaration

Hereby I declare that I wrote the submitted dissertation independently and thereby served me only the specified sources and literature.
Earlier dissertation attempts have not been made.

Erklärung

Hiermit versichere ich, die vorgelegte Dissertation eigenständig verfasst und mich dabei nur der bezeichneten Quellen und Literatur bedient zu haben.
Frühere Dissertationsversuche sind nicht erfolgt.