

CLINICAL PRACTICE

Superior Vena Cava Syndrome with Malignant Causes

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This Journal feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the authors' clinical recommendations.

A 58-year-old man presents with a 2-week history of progressive dyspnea on exertion, neck swelling, decreased appetite, and fatigue. There is no history of syncope or dysphagia. He smoked cigarettes until 5 years ago. The physical examination reveals a heart rate of 105 beats per minute, a respiratory rate of 20 breaths per minute, and superficial vascular distention over the neck, chest, and upper abdomen. Stridor is not present. How should his case be evaluated and managed?

THE CLINICAL PROBLEM

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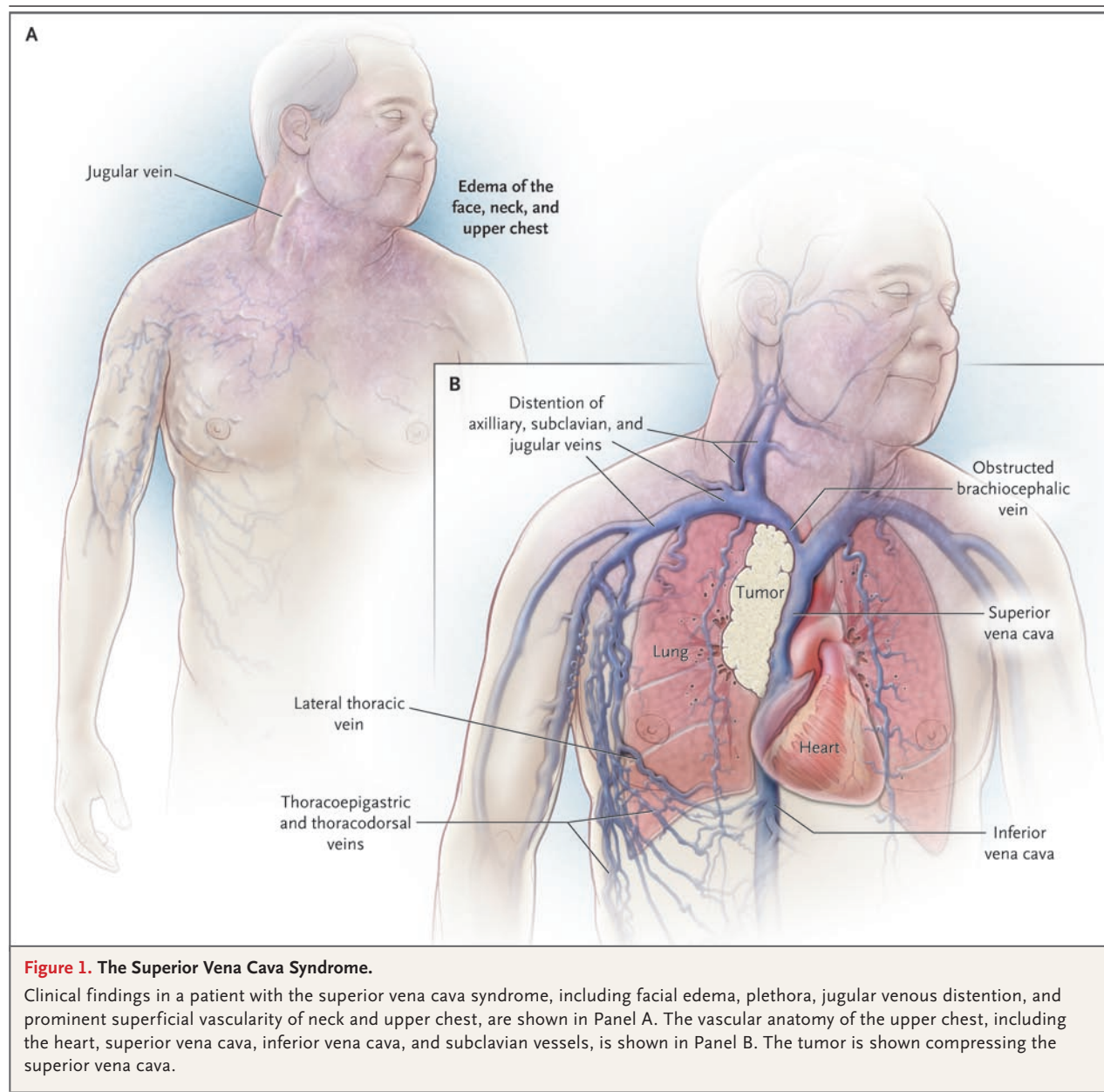
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The superior vena cava syndrome, which occurs in approximately 15,000 persons in the United States each year, encompasses a constellation of symptoms and signs resulting from obstruction of the superior vena cava. The increased venous pressure in the upper body results in edema of the head, neck, and arms, often with cyanosis, plethora, and distended subcutaneous vessels (Fig. 1A). Edema may cause functional compromise of the larynx or pharynx, manifested as cough, hoarseness, dyspnea, stridor, and dysphagia. Cerebral edema may lead to headache, confusion, and coma. The decreased venous return may result in hemodynamic compromise; this complication may be a consequence of obstruction of the superior vena cava (intrinsic or due to extrinsic compression), compression of the heart by a large mass in the chest, or both. Symptoms develop over a period of 2 weeks in approximately a third of patients, and over longer periods in other cases.¹⁻⁵

ANATOMY AND PHYSIOLOGY

The superior vena cava carries blood from the head, arms, and upper torso to the heart; it carries approximately one third of the venous return to the heart. Compression of the superior vena cava may result from the presence of a mass in the middle or anterior mediastinum (generally to the right of midline), consisting of enlarged right paratracheal lymph nodes, lymphoma, thymoma, an inflammatory process, or an aortic aneurysm, for example. Thrombosis of the superior vena cava without extrinsic compression can also occur (Fig. 1B).

When the superior vena cava is obstructed, blood flows through a collateral vascular network to the lower body and the inferior vena cava or the azygos vein. It generally takes several weeks for the venous collaterals to dilate sufficiently to accommodate the blood flow of the superior vena cava.^{6,7} In humans with obstruction of the superior vena cava, the cervical venous pressure is usually increased to 20 to 40 mm Hg (normal range, 2 to 8 mm Hg).⁸⁻¹⁰ The severity of the symptoms depends on the degree of narrowing of the superior vena cava and the speed of the onset of the narrowing.



Edema in the upper body as a result of obstruction of the superior vena cava is visually striking but often of little consequence. However, cerebral edema, although rare, can be serious or fatal. The upper respiratory tract may become narrowed by nasal and laryngeal edema. Serious effects of obstruction of the superior vena cava are rare; among 1986 patients with obstruction of the superior vena cava, only one death was documented.¹¹ In case reports of neurologic or laryngeal compromise, it is unclear whether other contributing factors such as brain metastases or tracheal compression were present.^{10,11}

ETIOLOGIC FACTORS

Infectious causes (especially syphilitic aortic aneurysm and tuberculosis) accounted for the majority of cases of obstruction of the superior vena cava until about 50 years ago. These causes became rare, and malignant conditions accounted for more than 90% of cases approximately 25 years ago.^{1,12,13} Currently, obstruction of the superior vena cava caused by thrombosis or nonmalignant conditions accounts for approximately 35% of cases, reflecting the increased use of intravascular devices such as catheters and pacemakers.¹⁴ The most common malignant causes are non–small-cell lung cancer

(approximately 50% of patients), small-cell lung cancer (approximately 25% of patients), lymphoma, and metastatic lesions (each approximately 10% of patients); the clinical features that may suggest these diagnoses are summarized in Table 1.^{1,4,5,13,15-17}

Recognition of a nonmalignant cause of the superior vena cava syndrome is typically straightforward, particularly when the syndrome is associated with the use of an implanted intravascular device. An aortic aneurysm is easily recognized on computed tomography (CT). The diagnosis of fibrosing mediastinitis, although a rare cause, requires a biopsy.

STRATEGIES AND EVIDENCE

CLINICAL EVALUATION

Clinical diagnosis of obstruction of the superior vena cava is made on the basis of signs and symptoms (Table 2).^{1,4,5,13,15,18} The history taking should attend to the duration of symptoms, previous diagnoses of malignant conditions, or previous intravascular procedures. In most cases, symptoms are progressive over several weeks, and in some cases they may improve as collateral circulation develops. The severity of the symptoms is important in determining the urgency of intervention.

Imaging

The most useful imaging study is CT of the chest after the administration of contrast material (which

is needed to evaluate the superior vena cava). Complications, including excessive bleeding from the venipuncture sites and reactions to contrast medium, are uncommon.^{11,14,19} Venography is generally warranted only when an intervention (placement of a stent or surgery) is planned.²⁰ Magnetic resonance imaging may be useful for patients who cannot tolerate the contrast medium. Positron-emission tomography (PET) is sometimes useful, because it may influence the design of the radiotherapy field (Fig. 2).²¹

The clinical history combined with CT imaging will generally differentiate between vena caval thrombosis and extrinsic compression. A tissue diagnosis is necessary to confirm the presence of malignant conditions. Clinical assessment is warranted to determine whether a peripheral biopsy site (e.g., a palpable supraclavicular lymph node) might be accessible before proceeding to an invasive procedure such as mediastinoscopy for tissue diagnosis. Cytologic examination of the sputum may result in diagnosis in patients who have endobronchial cancer. Pleural effusion is common (affecting about two thirds of patients with the superior vena cava syndrome); thoracentesis and cytologic analysis should be strongly considered because they are simple to perform and expedient, although they yield a diagnosis in only about 50% of such patients.¹⁵ Bronchoscopy has a diagnostic yield of 50 to 70% and transthoracic needle-aspiration biopsy has a yield of approximately 75%, whereas mediastinoscopy or mediastinotomy has

Table 1. Malignant Causes of the Superior Vena Cava Syndrome.*

Tumor Type	Proportion % (range)	Suggestive Clinical Features
Non-small-cell lung cancer	50 (43–59)	History of smoking; often age >50 yr
Small-cell lung cancer	22 (7–39)	History of smoking; often age >50 yr
Lymphoma	12 (1–25)	Adenopathy outside the chest; often age <65 yr
Metastatic cancer†	9 (1–15)	History of malignant condition (usually, breast cancer)
Germ-cell cancer	3 (0–6)	Usually, male sex and age <40 yr; elevated levels of β human chorionic gonadotropin or alpha-fetoprotein are common
Thymoma	2 (0–4)	Characteristic radiographic appearance on the basis of the location of the thymus; frequently associated with the parathymic syndromes (e.g., myasthenia gravis and pure red-cell aplasia)
Mesothelioma	1 (0–1)	History of asbestos exposure
Other cancers	1 (0–2)	

* Data are from Armstrong et al.,¹ Yellin et al.,⁴ Schraufnagel et al.,⁵ Chen et al.,¹³ Rice et al.,¹⁵ Nicholson et al.,¹⁶ and Detterbeck and Parsons.¹⁷

† Approximately two thirds of the patients who have metastatic cancers have breast cancer.

a diagnostic yield of more than 90%.^{9,22} Particularly in the case of lymphoma, adequate tissue is needed to characterize the nodal architecture and cell type, and also for immunohistochemistry in order to confirm the subtype.

Although some studies suggest a higher rate of complications from mediastinal procedures among patients who have the superior vena cava syndrome than among those who do not, other studies report low rates of complications even in the presence of the superior vena cava syndrome.^{9,11,14,22,23} A review involving 319 patients with the superior vena cava syndrome found major hemorrhage (not specifically defined) in 3% of patients undergoing mediastinoscopy or mediastinotomy. Bronchoscopy (both fiberoptic and rigid) was associated with low risk (risk of bleeding, 0.5%; and risk of respiratory distress, 0.5%).^{11,22}

MANAGEMENT

Management of the superior vena cava syndrome associated with malignant conditions involves both treatment of the cancer and relief of the symptoms of obstruction. Most data regarding management of the superior vena cava syndrome are from case series; randomized trials are scarce. The median life expectancy among patients with obstruction of the superior vena cava is approximately 6 months; but estimates vary widely according to the underlying malignant conditions.^{4,5,24-26} Survival among patients presenting with obstruction of the superior vena cava associated with malignant conditions does not appear to differ significantly from survival among patients with the same tumor type and disease stage without obstruction of the superior vena cava. In some patients, treatment of the superior vena cava syndrome and their malignant conditions results in the cure of both.^{3,11,27-29}

Management is guided by the severity of the symptoms and the underlying malignant conditions as well as by the anticipated response to treatment. For example, in patients with lymphoma, small-cell lung cancer, or germ-cell tumors, the clinical response to systemic chemotherapy alone typically is rapid. In the majority of patients with non-small-cell lung cancer, relief of symptoms of obstruction of the superior vena cava results from treatment of the cancer (chemotherapy for patients with stage IV disease, and chemotherapy with radiotherapy for those with stage III disease), but the degree and rapidity of response

Table 2. Symptoms and Signs Associated with the Superior Vena Cava Syndrome.*

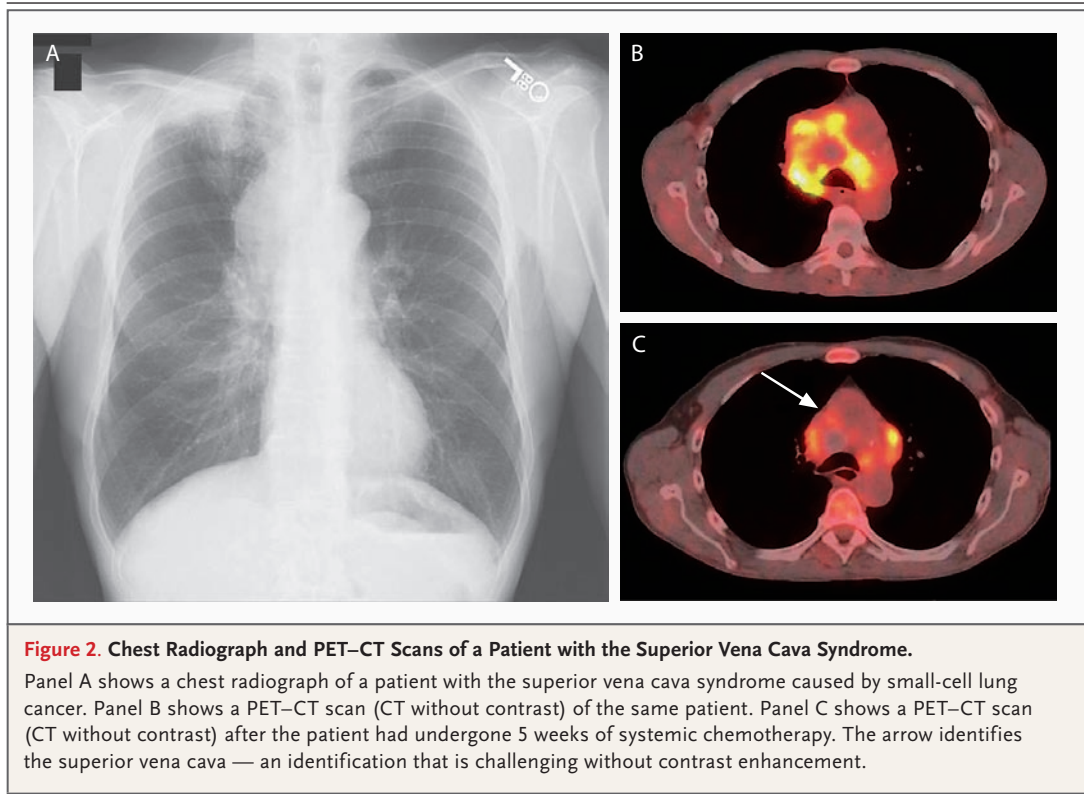
Sign or Symptom	Frequency	Range
		percent
Facial edema	82	60–100
Arm edema	46	14–75
Distended neck veins	63	27–86
Distended chest veins	53	38–67
Facial plethora	20	13–23
Visual symptoms	2	0–3
Dyspnea	54	23–74
Cough	54	38–70
Hoarseness	17	15–20
Stridor	4	0–5
Syncope	10	8–13
Headaches	9	6–11
Dizziness	6	2–10
Confusion	4	0–5
Obtundation	2	0–3

* Data are from Armstrong et al.,¹ Yellin et al.,⁴ Schraufnagel et al.,⁵ Chen et al.,¹³ Rice et al.,¹⁵ and Urruticoechea et al.¹⁸

are somewhat less than in patients with lymphoma, small-cell lung cancer, or germ-cell tumors.

Supportive Care and Medical Management

An obvious therapeutic maneuver is to elevate the patient's head to decrease the hydrostatic pressure and thereby the edema. There are no data documenting the effectiveness of this maneuver, but it is simple and without risk. Glucocorticoid therapy (dexamethasone, 4 mg every 6 hours) is commonly prescribed, although its effects have not been formally well studied, and there are only case reports to suggest the benefit. Glucocorticoids reduce the tumor burden in lymphoma and thymoma and are therefore more likely to reduce the obstruction in patients with lymphoma or thymoma than in those with other types of tumor.^{3,30} Loop diuretics are also commonly used, but it is unclear whether venous pressure distal to the obstruction is affected by small changes in right atrial pressure. In an observational study involving 107 patients with the superior vena cava syndrome due to various causes, the rate of clinical improvement (84% overall) was similar among patients receiving glucocorticoids, diuretics, or neither therapy.⁵



In patients with obstruction of the superior vena cava resulting from intravascular thrombus associated with an indwelling catheter, removal of the catheter should be considered. Removal of the catheter is performed in conjunction with anticoagulation therapy (see Areas of Uncertainty).

Radiotherapy

Radiotherapy is often used to treat symptomatic patients with malignant obstruction of the superior vena cava; its use requires a tissue diagnosis. The majority of the tumor types causing the superior vena cava syndrome are sensitive to radiotherapy. A systematic review found complete relief of the symptoms of obstruction of the superior vena cava in 78% of patients with small-cell lung cancer and 63% of those with non-small-cell lung cancer at 2 weeks. Improvement is often apparent within 72 hours.^{1,3-5,11,16,31-35}

However, objective measures of the change in vena caval obstruction have not paralleled measures of symptomatic improvement based on patients' reports. In a case series of patients receiving radiotherapy (in most patients as the sole therapy), complete relief of vena caval obstruction as measured on serial venograms was noted in 31% of the

patients and partial relief in 23% of the patients. In autopsy studies, complete patency was found in only 14% of the patients and partial patency was found in 10% of the patients, despite reported relief of symptoms in 85% of the patients.¹¹ These findings suggest that the development of collateral circulation may contribute to improvement of symptoms and underscore the uncertain value of urgent initiation of radiotherapy before chemotherapy is initiated in those patients with chemotherapy-sensitive tumors.

If radiation is given as the initial treatment, the fields should encompass gross disease and the adjacent nodal regions, taking into account the volume of pulmonary and cardiac tissue to minimize complications. CT-based simulation (for designing radiotherapy fields) and irradiation in daily fractions of 1.8 to 2.0 Gy are recommended for the majority of lymphomas. The total dose of radiation should be based on a multidisciplinary plan that incorporates systemic chemotherapy, either from the beginning of treatment or after a brief initial course of radiotherapy. A similar initial course of radiotherapy is often used to treat small-cell and non-small-cell lung cancer, with higher daily fractions of 2.0 to 3.0 Gy. The size and

configuration of the field may be altered after the administration of several fractions, as symptoms begin to subside and the staging and plans for subsequent management are organized. When the radiotherapy is palliative, the course of treatment is typically over a period of 1 to 3 weeks, with daily fractionation.

Systemic Chemotherapy

Complete relief of symptoms of vena caval obstruction is achieved with chemotherapy in approximately 80% of patients with non-Hodgkin's lymphoma or small-cell lung cancer and in 40% of those with non-small-cell lung cancer.^{5,27,30,32} A review of 2 randomized studies and 44 observational studies concluded that among patients with lung cancer, there was no clinically significant difference in the rate of relief from the superior vena cava syndrome whether chemotherapy, radiotherapy, or chemotherapy with radiotherapy was used.³⁰ In the two randomized trials, there were no significant differences in the rates of relief of symptoms, relapse, or survival with initial chemotherapy alone, as compared with either sequential chemotherapy with radiotherapy among patients with small-cell lung cancer or immediate (concurrent) chemotherapy and radiotherapy among those with non-small-cell lung cancer.^{32,33} In observational studies, manifestations of the superior vena cava syndrome caused by other chemotherapy-sensitive malignant conditions such as germ-cell tumors have also been reported to improve rapidly with systemic therapy alone.

Placement of an Intravascular Stent

Percutaneous placement of an intravascular stent to bypass the obstruction of the superior vena cava is another possible intervention. Because the stent can be placed before a tissue diagnosis is available, it is a useful procedure for patients with severe symptoms such as respiratory distress that require urgent intervention. Stent placement should also be strongly considered for patients with mesothelioma, which tends not to respond well to chemotherapy or radiation, and may also be particularly useful when obstruction of the superior vena cava is caused by a thrombus associated with an indwelling catheter.^{36,37}

Angioplasty for the narrowing of the superior vena cava is generally performed only in preparation for stent placement because of a lack of du-

erable benefit from angioplasty alone.^{38,39} Placement of an intravascular stent results in more prompt relief of symptoms than does radiation or chemotherapy (although the usually rapid response to radiation or chemotherapy in patients with tumors sensitive to these therapies means that stent placement is not typically warranted). After stent placement, cyanosis is usually relieved within hours, and edema resolves within 48 to 72 hours in most series (response rate, 75 to 100%). However, in one prospective series, symptoms resolved completely in only 17% of cases. This outcome may have been due to the fact that not all the associated symptoms actually resulted from caval obstruction.²⁶

Complications of stent placement have been reported in 3 to 7% of patients with the superior vena cava syndrome, including infection, pulmonary embolus, stent migration, hematoma at the insertion site, bleeding, and, very rarely, perforation. Late complications include bleeding (1 to 14% of patients) and death (1 to 2% of patients) due to anticoagulation, a treatment often recommended after stent placement (see Areas of Uncertainty).^{16,18,24,25,38-40}

Surgery

Surgical bypass grafting is infrequently used to treat the superior vena cava syndrome. The surgery, which involves a subcutaneous jugular-femoral graft, for example,⁴¹ can be performed with relatively few complications. The more common approach is sternotomy or thoracotomy with extensive resection and reconstruction of the superior vena cava; case series indicate an operative mortality of approximately 5% and patency rates of 80 to 90%.^{28,42-46} Thymomas are relatively resistant to chemotherapy and radiation, as compared with lymphomas, and surgery is therefore often appropriate when the superior vena cava syndrome is caused by thymoma. A curative approach generally involves preoperative chemotherapy, surgical resection and reconstruction, and postoperative radiotherapy.¹⁵

DURABILITY OF RESPONSE

The durability of various treatment strategies appears to be relatively similar and may primarily reflect the underlying malignant conditions. A systematic review found that symptomatic recurrence of the superior vena cava syndrome occurred in

nearly 20% of patients with either small-cell or non-small-cell lung cancer after chemotherapy, radiotherapy, or both.³² The rate of relapse after stent placement was 11%, although 78% of these relapses were successfully managed by repeat intravascular interventions. Relapse rates ranging from 9 to 20% after stent placement have been reported by others.^{10,16,18,24,38} Rates of occlusion of the superior vena cava of 10% have been reported after surgical reconstruction.⁴²

AREAS OF UNCERTAINTY

Standardized criteria to grade the severity of symptoms in the superior vena cava syndrome are lacking. The benefit of either short-term or long-term anticoagulation therapy for this syndrome is unclear, although thrombolytic agents have been used effectively in patients with vena caval thrombosis. Most experts recommend anticoagulation after thrombolysis (to prevent disease progression and recurrence) and aspirin after stent placement in the absence of thrombosis, but data to inform these recommendations are limited.^{16,24,39}

Whether the presence of brain metastasis should affect management of the superior vena cava syndrome is unclear. Patients with brain metastasis may undergo stent placement because of the potential of the superior vena cava syndrome to exacerbate cerebral edema, but at least temporary anticoagulation is needed and associated cerebral hemorrhage has been reported. The care of patients with both the superior vena cava syndrome and significant airway obstruction is also unclear. Some authors suggest resection of the tumor mass (complete or subtotal resection) in such patients to provide immediate relief of both clinical problems.⁴⁵⁻⁴⁷ The optimal management of recurrent obstruction of the superior vena cava is also controversial. Placement of a stent is often considered because of the limited benefit or the risk of excessive toxic effects from repeat chemotherapy or radiation, but data to guide decision making are limited.

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GUIDELINES FROM PROFESSIONAL SOCIETIES

There are no formal professional guidelines addressing the management of obstruction of the superior vena cava. A general recommendation supporting consideration of radiotherapy, stent placement for symptomatic obstruction of the superior vena cava due to lung cancer, or both has been made by both the American College of Chest Physicians⁴⁸ and the National Comprehensive Cancer Network.⁴⁹

CONCLUSIONS AND RECOMMENDATIONS

The superior vena cava syndrome is often clinically striking but rarely requires emergency intervention. The majority of cases are due to malignant conditions; a tissue biopsy is warranted to guide diagnosis and therapy and is generally safe when performed by experienced practitioners. Treatment planning should be multidisciplinary. In patients with life-threatening symptoms or signs of obstruction of the superior vena cava, the placement of an intravascular stent can provide rapid relief. In other patients, such as the patient described in the vignette, information on the tumor type and stage of the cancer should be used to guide the therapy (i.e., chemotherapy or radiotherapy or both or, in occasional cases, surgery alone or in combination with other therapies); these types of therapy can relieve the symptoms of obstruction of the superior vena cava in the vast majority of patients. The presence of the superior vena cava syndrome does not reduce the likelihood of cure of the underlying malignant condition and should not compromise the choice of appropriate therapy.

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