REVIEW PAPER

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Lung cancer invading the superior vena cava – surgical treatment. A short and up-to-date review

Eleftherios Nikolaidis[1], Nikolaos Bolanos[1], Dimitrios Anagnostopoulos[1], Vasileios Leivaditis[2], Konstantinos Grapatsas[3], Efstratios Koletsis[4], Athanasios Papatriantafyllou[2], Ioannis Panagiotopoulos[4], Francesk Mulita[5], Nikolaos Baltayiannis[1], Manfred Dahm[2], Antonios Chatzimichalis[1]

[1]Department of Thoracic Surgery, "Metaxa" Cancer Hospital, Piraeus, Greece
[2]Department of Cardiothoracic and Vascular Surgery, Westpfal-Klinikum, Kaiserslautern, Germany
[3]Department of Thoracic Surgery and Thoracic Endoscopy, University Medicine Essen – Ruhrlandklinik, Essen, Germany
[4]Department of Cardiothoracic Surgery, University Hospital of Patras, Patras, Greece
[5]Department of Surgery, General University Hospital of Patras, Patras, Greece

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Abstract

Lung cancer is one of the leading causes of cancer-related deaths worldwide. Superior vena cava syndrome (SVCS) is a rare but potentially life-threatening complication of lung cancer, occurring in approximately 5–10% of cases. There are difficulties in the process of surgical treatment of SVC infiltrated by lung tumors but the contribution of technological evolution and innovation is promising. At the same time, the amelioration of survival rates of patients subjected to surgical treatment is equally promising. The reported outcomes of surgical treatment for SVC invasion due to lung tumors vary depending on the extent of the tumor and the patient's overall health status. However, studies clearly suggest that surgical treatment can improve survival and quality of life in selected patients. The literature review showed that the surgical approach to lung cancer invading the SVC constitutes the most indispensable treatment which helps to achieve the long-term survival of patients.

Key words: lung cancer, surgical treatment, superior vena cava invasion, vena cava reconstruction.

Introduction

Lung cancer is the most common type of cancer among the male population and its prevalence competes with breast cancer in women. At the same time, it is the first cause of death among malignant diseases. According to Surveillance, Epidemiology, and End Results (SEER), lung cancer is the primary cause of cancer-related deaths globally, with a 5-year survival rate of only 18–21% when all cases are taken into account and only 6% for advanced disease [1, 2]. In recent years, great progress has been made in surgical techniques in lung cancer surgery. Significant progress in correct patient selection as well as complete preoperative preparation has also been demonstrated [3].

Infiltration of superior vena cava (SVC) due to lung cancer is a rare but serious complication. It has been proven that SVC is particularly sensitive to tumor invasion by neoplasms originating predominantly from pulmonary (particularly right-sided), thymus gland, thyroid and stem cell tumors [4]. The SVC obstruction brought on by an aneurysmal dilation that prevented normal blood venous return was first noted by William Hunter in a postmortem examination in 1757, establishing the so-called superior vena cava syndrome (SVCS) [5]. Nowadays, it is well-established knowledge that SVCS occurs more frequently in cases of malignancies of the right lung (75%) and 50% of the cases involve small cell lung cancer (SCLC) [4]. SVC is as mentioned before vulnerable to tumor invasion due to its localization and anatomy and cancer invasion constitutes the major factor leading to SVC resection or reconstruction. Infiltration and obstruction of the SVC can cause SVCS, which can lead to a range of symptoms such as facial swelling, upper extremity edema, and dyspnea [5, 6]. Overall survival depends on the primary volume and the effectiveness of the treatment rather than on the removal of the mechanical cause [4].

This study aims to present the available therapeutic options and investigate the value of surgical treatment of this clinical entity. In the case of T4 disease or upper thoracic syndrome, the extended resection for SVC invasion of non-small cell lung cancer (NSCLC) is still considered to be a controversial method which is however reported to provide a survival benefit [7].

Address for correspondence: Dr. Francesk Mulita, Department of Surgery, General University Hospital of Patras, Patras, Greece, e-mail: oknarfmulita@hotmail.com

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Diagnosis of vena cava invasion

The diagnosis of lung cancer invading the SVC is usually made through a combination of clinical evaluation, imaging studies, and biopsy. The most common presenting symptoms are dyspnea, facial swelling, and upper extremity edema. Cervicobrachial edema and cyanosis are also among the symptoms of the characteristic clinical presentation, which varies depending on how quickly the SVC becomes blocked and obstructed [8]. When the symptoms worsen, they may also cause cerebral edema, cerebellar herniation, and even death. Computed tomography (CT) scans and magnetic resonance imaging (MRI) are the most common diagnostic tools available. Positron emission tomography (PET) can also be useful to confirm diagnosis and assess the extension of the infiltration. On imaging, SVC invasion is characterized by a large mediastinal mass, usually located in the anterior mediastinum, which may be associated with dilatation of the SVC. Biopsy of the mass confirms the diagnosis of lung cancer [8].

Treatment options

Chemotherapy

Chemotherapy is a commonly used treatment option for patients with lung cancer that has infiltrated the SVC [9]. It can help to reduce the size of the tumor, alleviate symptoms, and improve quality of life. However, chemotherapy is generally considered to be less effective in achieving long-term survival than surgery [9, 10].

Immunotherapy

Immunotherapy has nowadays a crucial role among the therapeutic strategies in the treatment of pulmonary malignancies. With the emergence of new therapeutic options including immune checkpoint inhibitors (ICIs) and several molecular targeted medications, the management of advanced lung cancer has considerably improved. For the past ten years, ICIs, in particular inhibitors of the PD-1 axis, have changed how NSCLC is managed [11]. When administered as first-line therapy for patients whose tumors express PD-L1 on at least 50% of cells, ICIs improve overall survival compared to chemotherapy [12]. Moreover, ICIs plus chemotherapy have been shown to increase patient survival in both squamous and non-squamous types of NSCLC [13, 14]. However, complete remissions remain rare [14]. After progression under immunotherapy, several retrospective research and case reports show an unexpectedly positive response to chemotherapy. In those trials, the idea that immunotherapy and chemotherapy had a synergistic impact was debated [14, 15].

Radiation therapy

Radiation therapy involves the use of high-energy X-rays to destroy cancer cells. It can be used as a primary treatment for inoperable tumors or as an adjunct to surgery [16]. Radiation therapy can help to shrink the tumor and alleviate symptoms, but it may also cause side effects such as fatigue, skin irritation, and nausea. Stereotactic body radiotherapy (SBRT) has been gradually tried for SVCS, but is limited to small lesions with a diameter of less than 5 cm [16, 17].

Endovascular stenting

Endovascular stenting is a minimally invasive treatment option that involves the insertion of a stent into the SVC to maintain patency. It is generally reserved for patients who are not suitable for surgery or who have a poor prognosis. It can however significantly relieve symptoms, although it provides no improvement of the prognosis [18]. Due to its quick and efficient symptom relief compared to conventional therapy by radiotherapy and chemotherapy, SVC stenting has grown in popularity in the management of SVCS since its initial description by Charnsangavej *et al.* in 1986 [19].

Once conventional therapy fails, stenting of the SVC is typically offered as a salvage therapy. Due to its encouraging outcomes, an increasing number of hospitals have started to explore primary stenting as a first-line therapy before conventional therapy in recent years [20, 21]. Nevertheless, the outcomes of primary stenting before conventional therapy and salvage stenting following the failure of conventional therapy have not yet been directly compared in trials. There were no statistically significant differences between primary stenting and salvage stenting in terms of the quantity of stents used, success rates, procedure times, rates of symptom relief, complication rates, and re-procedure rates [21].

Stenting provides overall symptomatic relief in 95% of patients with an 11% symptom recurrence rate and is the most efficient and quick treatment for SVCS symptoms, according to a systematic review by Rowell and Gleeson [21]. However, only 60–77% of patients were able to have symptomatic alleviation after receiving radiotherapy or chemotherapy, and 17–19% of patients experienced symptom recurrence [21]. Overall, for NSCLC patients with SVCS, endovascular stent insertion is efficient and secure, and it may be suggested as the primary option for palliative therapy of SVC obstruction [8, 21, 22].

Palliative care

Palliative care is an important component of the treatment of patients with SVC infiltration due to lung cancer. It focuses on improving quality of life and alleviating symptoms such as pain, dyspnea, and anxiety. Palliative care may include medication management, counseling, and physical therapy. Conservative supportive measures include head elevation, diuretic therapy, supplemental oxygen therapy, and steroids. Thrombolysis is required emergently in patients with airway compromise or symptoms secondary to cerebral edema [18].

Surgical treatment of lung cancer invading the superior vena cava

As mentioned before, the malignant invasion to the SVC may cause serious symptoms which can signifi-

cantly reduce the quality of life of the patient or even become life threatening [23, 24]. The surgical treatment consisting of extended resection of mediastinal or pulmonary tumors invading SVC is well documented and is considered technically feasible with low morbidity rates. The patients are selected on the basis of a range of factors such as the expanse of SVC invasion, the extent of resection and the presence of mediastinal lymph node metastases. It should be however stressed that surgical treatment of lung cancer invading the SVC is a complex and challenging procedure that requires a highly skilled surgical team. The aim of the surgery is to remove the tumor and reconstruct the SVC to restore blood flow to the right atrium. The procedure can involve the use of a cardiopulmonary bypass and may require the use of synthetic grafts or autologous tissue to reconstruct the SVC [23, 24].

While surgical treatment of lung cancer invading the SVC is a major operation that carries certain risks, it can offer significant benefits for patients in terms of improved quality of life and increased survival rates. It is however important to select the appropriate patients and to carefully weigh other available options before reaching the final decision. During the investigation process of diagnosis of lung cancer, the exact staging is one of the most important factors influencing the outcome of the disease. The exact staging is important to determine the prognosis and the choice of the most appropriate therapeutic approach. Surgical treatment remains the cornerstone in the treatment of lung cancer and is the only way of improving long-term survival [4].

The clinical experience indicates that there are various techniques of SVC resection and also a variety of prosthetic materials (polyethylene terephthalate fiber, saphenous vein spiral grafts, glutaraldehyde-preserved porcine pericardium) [25]. When polytetrafluoroethylene (PTFE) prostheses are used, patients having complete prosthetic replacement frequently need a different surgical technique, intra-operative SVC cross-clamping, and anticoagulation [26]. Leo *et al.* investigated the possibility that PTFE replacement would affect the perioperative result [26]. They came to the conclusion that full prosthetic replacement can be safely carried out when other reconstruction techniques cannot provide a sufficient tumor-free resection margin or cannot ensure adequate blood flow and does not increase overall postoperative morbidity in patients undergoing SVC resection [26]. Radiotherapy or chemotherapy can be combined with surgical treatment in some cases. In the case of the existence of circumferential stenosis of SVC the endovascular treatment is slow while radiotherapy is of doubtful effectiveness [27].

The surgical techniques include whole SVC replacement, tangential resection and venous plasty and the palliative bypass, depending on the extent of the infiltration and the aim of the operation. In cases where a complete SVC replacement should be carried out, the following surgical steps are usually performed: 1) anterolateral or posterolateral thoracotomy to access the lung and the mediastinum, 2) careful dissection of the lower pulmonary ligament, 3) dissection of the azygos vein, 4) dissection of the superior vena cava preserving the phrenic nerve and the vagus nerve, 5) the pericardium is opened to access the intrapericardial part of the superior vena cava, 6) dissection of the intrapericardial part of the superior vena cava, 7) dissection of the right pulmonary artery inside the pericardium, 8) section of the azygos vein to improve access to the superior vena cava using ligatures or an autosuture device, 9) cross-clamping of the right atrial appendage after systemic administration of heparin, 10) the right atrial appendage is opened to create an opening for the placement of a prosthetic graft, 11) anastomosis of a ringed PTFE prosthesis to the right atrial appendage, 12) intrapericardial transection of the intrapericardial superior vena cava using an autosuture device, 13) clamping of the distal superior vena cava or both innominate arteries, 14) resection of the extrapericardial superior vena cava, 15) proximal anastomosis of the PTFE prosthesis to the superior vena cava, 16) removal of both the proximal and distal clamps to restore blood flow to the superior vena cava prosthesis and administration of protamine to restore coagulation, 17) further completion of the planned lobectomy or pneumonectomy to remove the tumor, combined with systematic lymph node dissection.

A potential complication of SVC surgery is anastomotic stenosis at proximal and distal suture lines, while stenosis may also be caused by proximal kinking due to excessive dissection or excessive length of the graft. Another serious complication could be graft thrombosis and infection, which could lead to sepsis, and in most such cases the graft should be removed [28]. The short- and long-term effects of various methods of SVC resection and reconstruction for T4 NSCLCs were thoroughly examined by Dell'Amore *et al.* [29]. In their multicenter retrospective research, 80 patients underwent SVC surgery along with anatomical lung resection. Sixty-four patients were part of the partial resection and direct suture or patch reconstruction group, while 16 patients were part of the total resection and prosthesis reconstruction group. Oncological, surgical, and survival results, as well as general characteristics, did not differ between the two groups. Their findings demonstrated that SVC resection, independent of the degree of circumferential involvement and the style of reconstruction, had favorable oncological and survival outcomes [29].

It is estimated that operative mortality lies between 5 and 10% while the survival rate after radical resection of mediastinal tumors invading the SVC is quite satisfactory compared to other forms of cancer [6]. More specifically, Dartevelle reported that the 5-year survival rate ranges up to 60% in other forms of malignancies but in the case of lung cancer ranges at 30% [6]. Spaggiari *et al.* mention that the estimation of 5-year survival rate for patients undergoing SVC resection and reconstruction for lung cancer is 30–50% for anterior mediastinal malignancies [30]. The survival rate after the extended surgical resection is therefore considered satisfactory [4]. However, as Lanuti

et al. report, the selection of suitable patients for surgical treatment including extended resections remains challenging, although it is well understood that it is directly connected to preoperative diagnostic imaging and accurate determination of tumor stage [4].

Thomas *et al.* performed a study regarding extended operations on patients with lung cancer invading the SVC and recruited 845 patients who were subjected to surgical treatment for right lung cancer [31]. The operative results showed that the 5-year survival for patients with SVC involvement was 24%, the 2-year survival corresponded to 32% and the 1-year survival to 46.7%. The authors concluded that extended resection is justified as it provides control of the primary tumor in cases where operative risk is considered acceptable [31]. The study of Misthos *et al.* regarding surgical management of lung cancer invading the SVC focused on the role of surgical treatment with extended resection [32]. The participants were patients suffering from NSCLC located in the right upper lobe accompanied with SVC invasion and they received surgical treatment through thoracotomy. The results showed a 5-year survival rate of 11% for patients with SVC involvement [32]. Nakahara *et al.* in their study recruited 6 patients with lung cancer subjected to reconstruction of SVC with ringed polytetrafluoroethylene grafts [33]. Patients in their study survived 34, 18, 17, 12, 4 and 5 months after surgery. This study shows how limited the survival rate for these patients can be, which demonstrates how essential the proper selection of patients as candidates for extended resections can be [13].

Spaggiari *et al.* investigated the oncologic value of surgical treatment of lung cancer invading the SVC through the evaluation of clinical data of patients subjected to surgery [30]. They investigated the clinical outcomes of 70 cases and concluded that SVC resection is potentially effective as a treatment strategy for those patients who had been defined as inoperable 10 years ago. Moreover, infiltration of SVC could succeed compensatory long-term health outcomes after neoadjuvant chemotherapy [30]. Kozu *et al.* also focused on survival rates after SVC resection for lung cancer. More specifically, the case study refers to a 65-year-old patient with lung cancer and SVC syndrome who was subjected to right pneumonectomy [27]. The SVC was reconstructed and R0 resection was achieved. The patient remained for 39 months free of disease after the second surgery. The authors report that in this case surgical treatment was chosen as the PET results were encouraging for such therapeutic treatment. The PET scan showed that recurrent disease was deemed localized to the mediastinal lymph node. The authors concluded that the surgical treatment approach, although considered aggressive, is warranted for cases of relapsed lung cancer and in cases of exclusion of existence of metastatic lesions which would have been detected through diagnostic tools such as PET tomography [27]. Moreover, Suzuki *et al.* suggest that the pattern of SVC invasion is a significant prognostic factor, and it should be taken into consideration for evaluating the outcome of clinical trials for T4 lung cancer [34]. They report a 10% 30-day mortality rate in their trial. The median follow-up time for patients who were still alive was 67 months, and the 5-year survival rate was 24%. When the prognoses of patients with SVC invasion by metastatic nodes and those with SVC invasion by direct tumor infiltration were examined, the difference in survival (5-year survival rate, 6.6% versus 36%) was statistically significant [34]. Even in the palliative setting, palliative surgery may be a good management choice for a clinically troublesome lesion, which may worsen with chemotherapy or immunotherapy [35].

Another study which included 48 patients was published by Chenesseau *et al*. [36]. Seventeen patients received neoadjuvant therapy, and 31 patients received adjuvant therapy. 85% of the patients had an R0 resection. Postoperative death was significantly higher in cases of right pneumonectomy. There were no SVC clamping-related neurologic occurrences. In 2 individuals, graft thrombosis occurred. The average survival was 24 months; the 3-, 5-, and 10-year survival rates were 45%, 40%, and 35%, respectively, while the equivalent survival rates without disease were 37%, 37%, and 30%. Only margin-free (R0) resection was found to be associated with improved survival [36]. The authors came to the conclusion that mortality in carefully chosen patients with NSCLC affecting the SVC is acceptable following total en-bloc resection and prosthetic replacement performed in an experienced facility. SVC involvement should therefore not prevent some patients from considering curative resection [36].

Several data support the safety of the procedure when it is planned carefully. For instance, Zhang *et al.* report a series of 35 patients with SVC disease who received prosthetic vascular reconstruction through median thoracotomy [37]. They stated that every single procedure in their series was successfully completed. Six occurrences of arrhythmia, 5 cases of hypoxemia, one case of myasthenia crisis, one case of heart hernia, and 2 cases of fungal infection were recorded among the postoperative complications. With a mortality rate of 5.12%, 2 patients perished from lung infection and myocardial infarction, respectively. Thirty-three further cases were successfully treated. 15 days of hospital stay were on average required after surgery. In 8 of the 10 patients with SVCS who underwent surgery, symptoms were relieved, with the exception of 2 patients who developed intraoperative intravascular thrombosis [37]. They suggested using a programmed procedure for prosthetic repair of the SVC in order to standardize the treatment and reduce surgical risk. This approach is supported by the safe surgical techniques used [37].

As previously indicated, although the indications for vessel resection are still debatable, it is generally accepted that it improves the long-term prognosis of certain patients; yet, little agreement has been established on the most effective technique for vascular reconstruction [38]. While the SVC is frequently replaced during an unprotected cross-clamp, it may also be preferred to implant a temporary venous shunt in order to maintain periprocedural safety and sim-

plify postoperative treatment. For instance, Yotsukura *et al.* propose SVC reconstruction surgery involving the insertion of a temporary extravascular shunt through a lateral thoracotomy and the use of an autologous pericardial patch [38]. Lee *et al.* created a hybrid and secure approach [39]. They advise using a stent while removing a malignant tumor from the SVC. This method makes such surgery simpler and increases the likelihood of success. A sufficient margin was left around the metastatic lymph node that was invading the SVC, and it was removed. The excisional margins were then sutured to the stent. This method prevented bleeding through the defect and fastened the stent securely [39].

Due to the wide and continuous development of minimally invasive procedures and tools, video-assisted thoracic surgery (VATS), as well as robotic thoracic surgery (RATS) can be used to partially resect and repair SVC [40]. Nevertheless, there are not many publications that mention VATS surgical methods. In their study, Xu *et al.* described the essential methods for VATS-assisted partial resection of the SVC [40]. Two significant technical issues with the procedure utilized in this study are how to ensure safe resection without bleeding margins of the sidewall and how to ensure thoracoscopic resection with negative margins while maintaining adequate blood flow in the remnant conduit [40].

Discussion

The prognosis of lung cancer invading the SVC is generally poor and the median survival rate of patients with lung cancer invading the SVC subjected to surgical operation is 11 months [41]. However, surgical resection can improve survival and quality of life in selected patients. The reported 5-year survival rates after surgery may be improved from 15% up to 40%, depending on the extent of the tumor and the patient's overall health status [41]. Thus, the surgical operation remains the most indispensable treatment approach which helps to achieve long-term survival. SVC involvement was once thought to be a technical and oncological contraindication to operative treatment [29, 32]. The boundaries of surgical resection in locally advanced NSCLCs have been significantly changing over the last decades as a result of developments in thoracic and cardiovascular surgery [29]. Fewer than 250 SVC resections for lung cancer have been documented in the literature, with 52 individuals being included in the largest one [29, 30]. Many studies examine individuals who underwent outdated oncological treatments for mediastinal and lung malignancies, which have varied treatment modalities and prognoses and require extensive mediastinal staging. Moreover, some of them involved SVC resection for N2 disease, which led to disappointing long-term survival statistics [42].

The reconstruction and resection of the SVC is required in the context of the surgical treatment approach of intrathoracic neoplasms. However, surgical treatment still remains a risky approach as the graft thrombosis may be a serious complication [43]. Moreover, complications such as stenosis and graft infection are possible [29].

Many reports in the literature show that long-term survival rates have increased thanks to advances in our understanding of tumor biology and adjuvant therapy [36, 41]. Nonetheless, despite advances in surgical and anesthesiologic care, recent studies have shown that the morbidity and mortality of these extended surgical procedures still remain much greater than that of normal lung resections [29, 36]. As a result, improving patient prognoses requires careful patient selection in a multidisciplinary team discussion, an expert anesthetist, and a surgical team. Despite the technical difficulties of surgical treatment of SVC metastatic malignancy, it has been shown that it could be performed with success in select patients. Thus, the well-designed and correct selection of patients is the most significant factor for successful surgical treatment [44, 45].

Conclusions

Lung cancer invading the SVC is a rare but potentially life-threatening complication of lung cancer. The treatment of SVC infiltration due to lung cancer depends on a range of factors, including the extent of the tumor, the patient's overall health status, and the availability of treatment options. Chemotherapy, immunotherapy and radiation therapy can be effective in alleviating symptoms and improving quality of life, but surgery remains the most effective treatment option for achieving long-term survival. Endovascular stenting and palliative care may also play a role in the management of this condition. Therefore, a multidisciplinary approach involving medical and surgical oncologists, radiation oncologists, interventional radiologists, and palliative care specialists is essential in the management of patients with SVC infiltration due to lung cancer. The procedure is technically challenging and carries a high risk of complications, but can improve survival and quality of life in selected patients. Therefore, careful patient selection and surgical expertise are essential in the management of this condition.

Disclosure

The authors report no conflict of interest.

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