Original Article

Vajira Med J
Journal of Urban Medicine

Survival and Related Prognostic Factors for Patients with Superior Vena Cava Syndrome in Palliative Settings

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ABSTRACT

OBJECTIVE: The safety of upfront systemic treatment without radiation is questionable in patients with superior vena cava (SVC) syndrome. Whether steroids or loop diuretics can improve patients' outcomes is unclear. This study aimed to evaluate the prognostic factors affecting overall survival (OS).

METHODS: Data of patients with SVC syndrome caused by neoplasm and treated with palliative intent were retrospectively collected. Cox proportional hazard regression was used to analyze the associations between variables and time until death.

RESULTS: A total of 104 patients were identified. The median follow-up time was 81 days. The mean age was 56.4 years (standard deviation (SD) 16.5 years). Among the patients, 22.1% received systemic therapy as an upfront treatment. Steroids and loop diuretics were administered in 50% and 34.6% of patients, respectively, and 7.7% were intubated. Multivariable analysis revealed intubation as an only significant independent factor for OS (hazard ratio 3.47; 95% confidence interval 1.2–10.05). Intubated and nonintubated patients had 1-year OS rates of 12.5% and 17.6%, respectively, and their median OS values were 6 and 86 days, respectively (p-value 0.02). For patients treated with radiotherapy and systemic treatment, 1-year OS rates were 17.1% and 17.4% (median survival of 86 and 71 days) (p-value 0.8). Symptomatic improvement was reported in 8 and 27 patients after receiving systemic therapy and radiation with mean duration of 9.4 (SD 5.4), and 8.2 (SD 4.7) days.

CONCLUSION: Intubation is a poor prognostic factor. No difference in OS was observed between the patients who received systemic treatment and radiotherapy as upfront therapy. Neither steroids nor loop diuretics showed any benefit in terms of survival.

KEYWORDS: intubation, radiotherapy, superior vena cava syndrome, systemic treatment

INTRODUCTION

Superior vena cava (SVC) syndrome is a group of signs and symptoms following blood flow obstruction in the SVC, leading to elevated venous pressure in the upper body. Approximately 15,000 cases per year are reported in the United States, and its incidence ranges from 1 in 650 to 1 in 3,100 patients[1]. The most common etiology is malignancy. Infection, particularly syphilitic aortic aneurysm

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Received: 25 October 2024
Revised: 7 January 2025
Accepted: 21 January 2025
Vajira Med J 2025;69(2):e271664
http://dx.doi.org/10.62691/vmj.2025.271664

and tuberculosis, can also cause the syndrome; however, because of the improvements in antibiotics, infection is rarely the origin of this disease nowadays. The use of intravascular devices, such as catheters and pacemakers, is another cause and could result in thrombus obstructing SVC. Other etiologies include aortic aneurysm and fibrosing mediastinitis. For SVC syndrome secondary to cancer, most of the cases resulted from non-small cell lung cancer (NSCLC) (50%), followed by small cell lung cancer (SCLC) (22%), lymphoma (12%), and metastatic diseases (9%), which mostly arise from breast cancer[2]. Meanwhile, 1.7% of NSCLC cases were reported to have SVC syndrome at diagnosis[3]. Lung cancer is the second most and most common type of cancer in Thailand and worldwide, accounting for 12.4% and 11.4%, respectively. Most patients with NSCLC are initially diagnosed at an advanced stage. In 2017, the proportion of patients with stage IV and I cancer at diagnosis was 44.1% and 29%, respectively, according to the United States Cancer Statistics database[4].

As compared to skeletal metastases, visceral metastases are significantly associated with worse overall survival (OS) due to the deterioration of the organ function. Similarly, brain metastases lead to neurological deficit and increase mortality risk in cancer patients. In addition intraluminal tumors were reported to be a poor prognostic factor, compared to extrinsic compression[5]. The management of SVC syndrome involves cancer treatment and supportive care. For patients with locally advanced cancer located in the chest and presenting with SVC syndrome, curative treatment is indicated. Patients with advanced stage disease are typically treated with upfront systemic treatment. However, in palliative settings, the necessity of upfront radiation prior to systemic therapy for patients with SVC syndrome remains controversial. In addition, the benefit of steroids and loop diuretics for these patients is yet to be proven. This study aimed to explore the prognostic factors affecting OS and evaluate the survival of patients with SVC syndrome.

METHODS

Information of patients with SVC syndrome in palliative settings who were treated between January 2012 and August 2022 was reviewed. The inclusion criteria were patients with radiological findings of SVC obstruction and histologically or cytologically confirmed neoplasm and who underwent either systemic therapy (including chemotherapy, targeted therapy, and immunotherapy) or radiotherapy as upfront treatment. Palliative treatment was defined as interventions other than curative therapy[6-8]. A chart review was performed to collect the patients' information. Death certificates were obtained when survival details were not sufficiently reported. Patients were excluded if they had SCLC and hematologic malignancy as a cause of SVC syndrome and their data were incomplete. This study was approved by the institutional review board (COA 111/2565).

After the diagnosis of SVC syndrome, a radiation oncologist and a medical oncologist were consulted to determine the suitable management for the patients. Unless neoplasm was pathologically confirmed as the cause of the disease, the tissue diagnosis proceeded. For patients with life-threatening conditions requiring immediate cancer treatment, either systemic treatment or radiation was administered before a definite diagnosis of the neoplasm in accordance with the attending physicians' discretion.

For radiotherapy, the technique and dose depended on machine availability at the time of treatment, patient's performance status, and preference of the radiation oncologist. Two radiation techniques, 2D and 3D conformal radiation (3DCRT), were adopted. The treatment fields for the 2D technique were typically the anterior–posterior/posterior–anterior fields.

The treatment planning of 3DCRT was based on target volume delineation. For the systemic treatment, the regimen was based on the histopathology and molecular markers of the tumor, patient's performance status, previous systemic treatments, and attending physician's choice.

The primary objective was to assess the OS, which was calculated from the initiation of cancer treatment for SVC syndrome, either systemic therapy or radiation, to death from any cause. Significance level of 0.05 and power of 0.8 were determined for sample size estimation. Given the survival rate difference of 0.148[9], the calculated sample size was 90. Overall response was defined by RECIST 1.1 using images from chest X-ray and computed tomography (CT) scan of the chest approximately 3 months after the last treatment. Symptomatic response was evaluated based on SVC syndrome grade[10]. Recurrence was defined as the time from the last treatment to the recurrence of signs and symptoms[2] and radiological findings of SVC syndrome. Age cutoff of 65 years was adopted because it is commonly used in oncology studies and frequently applied to define the elderly. Patients without any events were censored at their date of the last follow-up. Survival curves were drawn using the Kaplan–Meier method. Differences between survival curves were analyzed by the log-rank test and Cox regression (univariable and multivariable analyses). Other outcomes were analyzed using the Cox proportional hazards model. The effect of prognostic factors on survival was examined using the Cox regression model. Statistical significance was set at p-value ≤ 0.05. Predictive Analytics SoftWare Statistics (SPSS) 28.0 (SPSS Inc., Chicago, IL., USA) was used for the analysis.

RESULTS

A total of 156 patients were assessed for eligibility. The number of excluded patients was 52 (13 for diagnosis of lymphoma, 17 for diagnosis of SCLC, 11 for incomplete data, 9 for receiving curative treatment, and 2 for no cancer treatment given). Therefore, 104 patients matched the eligibility criteria, including 80 with lung cancer, 4 with breast cancer, 3 with cervical cancer, 2 with osteosarcoma, 3 with soft tissue sarcoma, 4 with thymic cancer, 3 with thymoma, 1 with hepatocellular carcinoma, 1 with gastric cancer, 1 with rectal cancer, 1 with nasopharyngeal cancer, and 1 with nonseminoma. The mean age of the patients was 56.4 years (standard deviation (SD) 16.5). Among them, 25% were female, 75% had an Eastern Cooperative Oncology Group score of at least 2, and nearly 60% had a history of smoking. Before or at the diagnosis of SVC syndrome, 24, 68, and 20 patients had visceral, brain, and bone metastases, respectively. SVC syndrome grade 2[8] was specified in almost 80% of the patients. Prior to the diagnosis of SVC syndrome, nonmetastatic diseases were treated with surgery, systemic treatment, and radiotherapy in 8.7%, 11.5%, and 6.7% of the patients, respectively. Previous treatment for metastatic diseases was performed as systemic treatment in 28 patients and radiation in 5 patients. Only one patient underwent an operation for a metastatic lesion. SVC thrombus and thrombus distal to SVC were found in 20 and 26 patients, respectively, and tumor thrombus was depicted in 15 patients. All of the patients had NSCLC as the cause of SVC syndrome. In total, 50%, 34.6%, and 15.4% of the patients were administered with steroids, loop diuretics, and anticoagulants, respectively, and 7.7% were intubated. Twenty-three patients were treated with upfront systemic therapy (22.1%). Only one patient received targeted therapy for lung cancer, while the rest were administered with chemotherapy. Radiation was used as an initial treatment for the syndrome in 81 patients. Table 1 shows the treatment characteristics of the eligible patients.

Table 1 Characteristics of the Patients at Baseline

Characteristics	(n = 104)
Age ≥ 65 years	29 (27.9)
Male	78 (75)
Smoking history	60 (57.7)
ECOG score	
0	6 (5.8)
1	20 (19.2)
2	45 (43.3)
3	25 (24)
4	8 (7.7)
Non-lung cancer	24 (23.1)
Visceral metastases	68 (65.4)
Brain metastases	3 (2.9)
Bone metastases	20 (19.2)
SVC syndrome grade	
0	7 (6.7)
1	8 (7.7)
2	82 (78.8)
3	4 (3.8)
4	3 (2.9)
SVC thrombus	20 (19.2)
Thrombus distal to SVC	26 (25)
Tumor thrombus	15 (14.4)
Previous surgery for non-metastatic disease	9 (8.7)
Previous systemic therapy for non-metastatic disease	12 (11.5)
Previous radiotherapy for non-metastatic disease	7 (6.7)
Previous surgery for metastatic disease	1 (1)
Previous systemic treatment for metastatic disease	28 (26.9)
Previous radiotherapy for metastatic disease	5 (4.8)
Intubation	8 (7.7)
Cancer treatment	
Systemic therapy	23 (22.1)
Radiotherapy	81 (77.9)
8 Gy single fraction	2 (1.9)
17 Gy in 2 fractions weekly	6 (5.8)
20 Gy in 5 fractions daily	10 (9.6)
30 Gy in 10 fractions daily	63 (60.6)
Steroids	52 (50)
Loop diuretics	36 (34.6)
Anticoagulants	16 (15.4)

Abbreviations: ECOG, eastern cooperative oncology group; Gy, Gray; n, number; SVC, superior vena cava
Note: Gray (Gy) is a unit of radiation dose, expressed as absorbed energy per unit mass of tissue.

The median follow-up time was 81 days. Symptomatic improvement was reported in 35 patients (8 for systemic therapy and 27 for radiation). The mean duration from initiation of the treatment to symptomatic improvement was 8.4 (SD 4.8), 9.4 (SD 5.4), and 8.2 (SD 4.7) days for the overall cohort, systemic treatment group, and radiation group, respectively. Eight patients reported their symptoms to be resolved (two for systemic therapy and six for radiation). The mean duration from the initiation of the treatment to the resolution of symptoms was 18.1 (SD 6.9), 21 (SD 0), and 17.2 (SD 7.9) days, respectively. Thirty-four patients underwent imaging 3 months after their last treatment. Among them, nine had

chest X-rays and 25 had CT scans of the chest. In addition, 6 and 28 received systemic treatment and radiotherapy, respectively. RECIST 1.1 revealed that for the radiotherapy group, 48.1%, 44.4%, and 7.4% had partial response (PR), stable disease, and progressive disease (PD), respectively. In the systemic therapy group, three, one, and two patients exhibited PR, stable disease, and PD, respectively. Three patients reported the recurrence of SVC syndrome with a disease-free interval from the last treatment ranging from 6 days to 169 days. Two patients with lung cancer received upfront radiation, and one patient with thymoma received chemotherapy. Cause of death was recorded in 28 patients, and chemotherapy-related death was the cause of death in one patient (infection). No grade 5 radiation toxicity was recorded. Sepsis due to urinary tract infection was the cause of death for one patient. One patient died due to chronic obstructive pulmonary disease, and the rest had tumor-related deaths.

Univariable analysis revealed intubation to be significantly associated with increased mortality (hazard ratio (HR) 2.29; 95% confidence interval (CI) 1.1–4.77). In multivariable analysis, the independent factor was intubation (HR 3.47; 95%CI 1.2–10.05). No treatment during SVC syndrome was significantly associated with survival (HR 1.28; 95%CI 0.72–2.28 for systemic therapy, HR 0.60; 95%CI 0.4–1.19 for steroids, HR 0.8; 95%CI 0.46–1.37 for loop diuretics, and HR 0.73; 95%CI 0.3–1.77 for anticoagulants) (Table 2).

Table 2 Univariable and multivariable analyses

Characteristics	Univariable analysis	P-value	Multivariable analysis	P-value
	HR (95% CI)		HR (95% CI)	
Age ≥ 65 years	1.14 (0.73-1.78)	0.56	0.96 (0.57-1.63)	0.96
Male	1.48 (0.92-2.38)	0.1	1.28 (0.67-2.43)	0.46
Smoking history	1.18 (0.78-1.77)	0.43	1.32 (0.72-2.42)	0.37
ECOG score > 1	1.48 (0.93-2.36)	0.1	1.54 (0.89-2.66)	0.12
Non-lung cancer	0.72 (0.44-1.16)	0.18	0.74 (0.34-1.65)	0.47
CNS metastases	1.74 (0.54-5.55)	0.35	2.65 (0.53-13.26)	0.24
Visceral metastases	1 (0.66-1.54)	0.97	0.93 (0.57-1.52)	0.77
Bone metastases	1.23 (0.73-2.06)	0.44	1.16 (0.62-2.17)	0.64
SVC syndrome grade > 2	1.25 (0.58-2.71)	0.57	1.22 (0.37-3.98)	0.75
SVC thrombus	0.68 (0.39-1.16)	0.16	2.2 (0.93-5.21)	0.07
Thrombus distal to SVC	1.05 (0.65-1.7)	0.83	0.52 (0.23-1.18)	0.12
Tumor thrombus	0.6 (0.33-1.11)	0.1	0.48 (0.21-1.14)	0.1
Previous surgery for non-metastatic disease	0.72 (0.35-1.48)	0.37	1.05 (0.4-2.81)	0.93
Previous systemic therapy for non-metastatic disease	0.72 (0.38-1.36)	0.31	0.42 (0.09-1.93)	0.26
Previous radiotherapy for non-metastatic disease	0.73 (0.34-1.59)	0.43	3.11 (0.58-16.62)	0.19
Previous surgery for metastatic disease	0.58 (0.08-4.15)	0.58	0.41 (0.04-4.14)	0.45
Previous systemic treatment for metastatic disease	1.49 (0.94-2.38)	0.09	1.4 (0.8-2.46)	0.24
Previous radiotherapy for metastatic disease	1.09 (0.44-2.69)	0.86	0.82 (0.25-2.72)	0.74
Intubation	2.29 (1.1-4.77)	0.03	3.47 (1.2-10.05)	0.02
Cancer treatment				
Systemic therapy	1.02 (0.64-1.69)	0.88	1.28 (0.72-2.28)	0.4
Radiotherapy	1		1	
Steroids	1.02 (0.69-1.54)	0.89	0.69 (0.4-1.19)	0.18
Loop diuretics	0.88 (0.58-1.36)	0.58	0.8 (0.46-1.37)	0.41
Anticoagulants	0.89 (0.5-1.58)	0.69	0.73 (0.3-1.77)	0.49

Abbreviations: CI, confidence interval; CNS, central nervous system; ECOG, eastern cooperative oncology group; HR, hazard ratio; SVC, superior vena cava

The 1-year OS for the whole cohort was 17.3%, and the median survival was 80 days (Figure 1). The intubated and nonintubated patients had 1-year OS rates of 12.5% and 17.6%, respectively, and their median survival values were 6 and 86 days, respectively (p-value 0.02) (Figure 2). The 1-year OS rates of patients who were treated with radiotherapy and systemic treatment were 17.1% and 17.4%, with median survival of 86 and 71 days, respectively (p-value 0.8).

DISCUSSION

No significant difference in OS was found between systemic treatment and radiation as an initial therapy for patients suffering from SVC syndrome. Neither steroid nor loop diuretic administration could enhance their survival. For these patients, intubation was the only independent factor. These findings provide additional evidence supporting the use of systemic treatment, especially chemotherapy, as a primary therapy for patients with SVC syndrome. Additionally, overall response, together with symptomatic improvement and resolution between upfront treatments were not significantly different.

The indication for endotracheal tube insertion due to SVC syndrome or their comorbidities is that the patient must be in a critical condition, which could lead to mortality or fatal morbidity. As a consequence, intubation was associated with a poor prognosis. Therefore, strategies to prevent intubation, such as avoiding treatment delay, should be adopted to improve the survival of these patients.

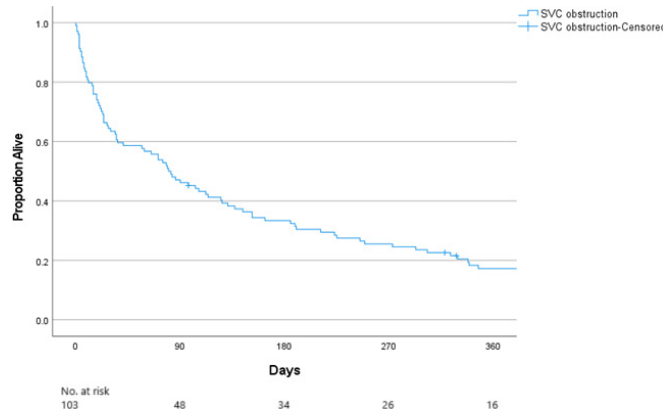

Figure 1 Overall survival among patients with SVC syndrome

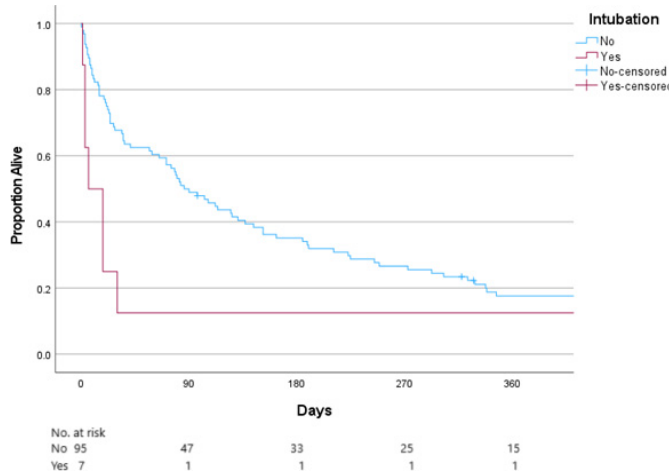

Figure 2 Overall survival among patients treated with and without intubation

Few randomized controlled trials compared upfront chemotherapy versus radiotherapy. First, in 1938, Spiro and colleagues[11] compared chemotherapy with and without radiotherapy in SVC syndrome due to SCLC and demonstrated no difference in terms of OS. Second, in 1969, Levitt et al.[12] randomized 28 patients with SVC syndrome to either nitrogen mustard and subsequent radiation or radiation alone. Most patients in this study had lung cancer; only two had lymphoma and one had malignant thymoma. No advantage of nitrogen mustard prior to radiotherapy was observed[12]. Third, in 1999, Pereira et al.[9] compared neoadjuvant chemotherapy with subsequent radiotherapy to radiotherapy alone in patients with NSCLC and SVC syndrome. Owing to the large number of treatment-related deaths in the chemotherapy arm, the study was terminated before the accrual target was reached. No significant survival benefit was observed in the patients receiving neoadjuvant chemotherapy[9]. Consistent with the present study and the improved safety profile of chemotherapy regimens in the current practice, no survival difference was observed between systemic therapy and radiotherapy. Hence, both could be used interchangeably as an upfront treatment for these patients.

Although the effectiveness of steroids has been widely explored, the limitation in recording the performance status became an apparent methodological issue. In this study, steroid administration showed no benefit in improving the survival of patients with SVC syndrome. Loop diuretics have been used as a supportive treatment for SVC syndrome for decades. Nevertheless, limited evidence supports their benefit. A mechanism of this drug that alleviates the symptoms is believed to be the reduction of venous return to the right atrium by decreasing preload, which relieves the increased venous pressure distal to the obstruction. However, this supportive treatment did not increase patient survival in this study. Therefore, the administration of these medications for symptomatic improvement is not required if cancer treatment can be performed immediately after the diagnosis of SVC syndrome.

A Japanese study found that patients with extrinsic compression (198.6 days) had better survival than those with intraluminal tumors (44.9 days)[5]. This finding was inconsistent with the current results, in which no difference was demonstrated among the patients with and without SVC thrombus (HR 2.2; 95%CI 0.93–5.21) and with thrombus distal to SVC (HR 0.52; 95%CI 0.23–1.18). The reason might be that only 14.4% of the patients in the present study had a tumor thrombus. In addition, most of the patients were at an advanced stage, and mortality from the increased risk of hematogenous spreading due to the thrombus was impossible. Therefore, SVC thrombus and thrombus distal to SVC were not determined as independent factors.

Even though a retrospective study is valuable in certain contexts, a range of drawbacks must be considered when interpreting the results and drawing conclusions and could possibly affect the reliability and validity of the findings. Selection bias, which potentially prevents the included patients to represent the general population, complicates the results and limits their generalizability. In addition, missing data, including medication dosage, variability in data collection, and uncontrolled confounding variables could substantially influence the outcomes. Apart from the study design, the heterogeneity of the primary tumor could affect the results' generalizability.

CONCLUSION

In terms of upfront treatment in palliative settings, no difference in OS was found between patients suffering from SVC syndrome who received systemic treatment and radiotherapy. Loop diuretics and steroids showed no benefit in enhancing patient survival. Intubation was identified as a poor prognostic factor.

CONFLICT OF INTEREST

None

ACKNOWLEDGEMENT

The authors extend their gratitude to the Academic Administration, Faculty of Medicine Vajira Hospital, Navamindradhiraj University, for generously supporting the funding of the language review.

DATA AVAILABILITY STATEMENT

The data underlying this article were provided by a third party by permission. Data will be shared on request to the corresponding author with permission of a third party.

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