Influence of Superior Vena Cava Syndrome on the Prognosis of Small Cell Lung Cancer

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Abstract

Objective: To evaluate the influence of superior vena cava syndrome on the prognosis of cases with small cell lung cancer (SCLC), and on the complications due to the diagnostic procedures.

Design: A prospective, randomized and comparative study.

Setting: A chest diseases hospital

Patients: 29 SCLC patients with superior vena cava syndrome (SVCS) (Group I) and 29 SCLC patients without SVCS (Group II) were evaluated according to their survival times.

Results: One case with SVCS and two cases without SVCS were excluded from the study as they could not be followed. There were no serious complications related to the invasive diagnostic procedures [fever after bronchoscopy: 1 (3.6%) patient in group I and 1 (3.7%) patient in group II and hemoptysis due to bronchoscopy: 3 (10.7%) patients in group I and 2 (7.4%) patients in group II]. There were no significant differences between the groups regarding complications. The cases with and without SVCS showed no significant difference regarding the prognostic factors for SCLC such as age (in group I mean age: 52.03±10.6 years, in group II mean age: 54.2±8.8 years), sex (group I male/female ratio: 27/1, group II male/female ratio: 25/2), stage of disease (group I limited/extensive disease ratio: 18/10, group II limited/extensive disease ratio: 14/13), performance of the patient (group I ECOG 0-2: 78.6%, group II ECOG 0-2: 85.2%), and serum lactate dehydrogenase (LDH) level (group I LDH mean: 466.9±195.9U/L, group II LDH mean: 435.2±255.1U/L) ($p>0.05$). Therapeutic response was 72% (partial and complete response rates: 60%, 12%, respectively) in group I and 64% (partial and complete response rates: 52%, 12%, respectively) in group II ($p>0.05$). The mean survival times of cases with and without superior vena cava syndrome were 41.8±27.8, 34.1±26.5 weeks, respectively ($p=0.43$, log-rank test). There were no significant differences between the groups regarding prognostic factors, and survival times ($p>0.05$).

Conclusion: Superior vena cava syndrome is not an unfavourable prognostic factor for small cell lung cancer. Invasive diagnostic procedures are not contraindicated in small cell lung cancer with superior vena cava syndrome.

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Key Words: *Small cell lung cancer, prognostic factors, superior vena cava syndrome*

Abbreviations: *Abbreviations: SVCS: Superior vena cava syndrome, SVC: Superior vena cava, SCLC: Small cell lung cancer, LDH: Serum lactate dehydrogenase, CT: Computed tomography, VATS: Video-assisted thoracic surgery, CTx: Chemotherapy, RTx: Radiotherapy*

Introduction

Superior vena cava syndrome (SVCS) is a clinical presentation in which the venous return of the head, neck and upper extremities is seriously reduced by the obstruction of the superior vena cava (SVC). Many mediastinal conditions may cause obstruction of the SVC either by compression or invasion, and some by thrombus formation (1,2). Malignancy constitutes the most frequently encountered cause of SVCS. The most common malignant disease in the etiology of SVCS is bronchogenic carcinoma with a rate of 46-90% (3,4).

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SCLC accounts for 20-25% of all lung cancers (5). The effects of different factors on the prognosis of SCLC have been investigated. The most important prognostic factors determined in many researches are the stage of the disease and the performance of the patient. In addition, age below 70 years, female sex, white race and normal level of serum lactate dehydrogenase (LDH) are accepted as good prognostic findings (2,4,5). In this report, the influence of SVCS on the prognosis of the cases with SCLC, and the diagnostic methods used in these cases with SVCS were investigated.

Materials and Methods

Between January 1995 and December 1997, the prognostic effect of SVCS on biopsy-proven cases of SCLC treated in our center was investigated prospectively.

Generalized swelling of the face, head, and neck, venous dilatation, and swelling of the upper part of the trunk or upper limbs with a mediastinal or paramediastinal lesion on chest roentgenogram or computed tomographic scan were accepted as a SVCS (1,4).

The patients included in the study were randomly allocated into two groups:

Group I: Cases of SCLC with SVCS (n=29)

Group II: Cases of SCLC without SVCS (n=29)

All the patients were followed until death. The death date of patients included in the study were obtained either from their hospital records or from their relatives by telephone. One case with SVCS and two cases without SVCS were excluded from the study as they could not be followed.

Staging: Cases were staged as extensive or limited disease. For the staging thoracic computed tomographic (CT) scan, abdominal CT scan, cranial CT scan, and radionuclide bone scanning were performed. Patients with disease confined to one hemithorax, including ipsilateral supraclavicular adenopathy, were considered to have limited disease, and all the others were considered to have extensive disease (5)

Performance: The Eastern Cooperative Oncology Group (ECOG) performance scale was used (4).

Therapy: For extensive disease: at least 6 courses of chemotherapy, and for limited disease: 3 courses of chemotherapy followed by thoracic radiotherapy, and then 3 more courses of chemotherapy were given.

Chemotherapy Regimens: One of two chemotherapy regimens, Cisplatin (60mg/m²/day) + Etoposide (120mg/m² days $\rightarrow$ 13) or Cisplatin (60mg/m²/day) + Epirubicin (90mg/m²/day) was given every 21-28 days.

Radiotherapy: Dosage of thoracic radiotherapy was 3000cGy/10fr (300cGy/day). Cranial radiotherapy was applied to the patients with cranial metastases.

Therapeutic Response: The therapeutic response was evaluated and categorized into four groups according to the chest x-ray changes at least 3-4 weeks after the second cycle of therapy (5,7).

Complete Response: Complete disappearance of all known tumor signs for at least one month.

Partial Response: A decrease of 50% or greater in all measurable tumor parameters for at least one month.

Stable disease: A decrease of less than 50% in tumor size.

Progressive Disease: An increase in the size of tumor, or occurrence of new lesions elsewhere.

Unevaluable: One patient who died in the first three weeks of the treatment, could not have been evaluated with respect to therapeutic response

Data Analysis: Statistical analyses were performed by using " SPSS for Windows". Categorical data were analysed by the χ^2 or Fisher's exact test. In order to compare continuous data, the Student t test was used. Survival curves were drawn by using calculations obtained through the Kaplan – Meier method and compared by log-rank test. A "p" value of less than 0.05 was considered significant.

Results

58 patients were included in the study (29 cases with SVCS and 29 cases without SVCS). One case with SVCS and two cases without SVCS were excluded from the study as they could not be followed. Of the 55 patients categorised as the cases with SVCS in group I (n=28) and cases without SVCS in group II (n=27), 52 were male (94.5%), 3 female (5.5%), the mean age was 53.3±9.6 years (range: 25-70 years).

The most common symptoms in cases with SVCS were swelling of the face and neck, dyspnea, cough, chest and back pain (Table 1). The most common physical signs were swelling of the upper extremities or trunk, venous dilatation of the upper part of the trunk and congestion in the head and neck veins (Table 2).

Table 1. Symptoms of the patients with SVCS

Symptoms	n	(%)
Swelling of the upper extremities or trunk	17	(60.7)
Dyspnea	17	(60.7)
Cough	16	(57.1)
Pain	15	(53.6)
Stridor	4	(14.2)
Dysphagia	1	(3.5)
Orthopnea	1	(3.5)

Table 2. Physical signs of the patients with SVCS

Signs	n	(%)
Swelling of the upper extremities or trunk	23	(82.1)
Venous dilatation of the upper part of the trunk	15	(53.6)
Venous congestion of the head and neck	15	(53.6)
Facial plethora	6	(21.4)

The pathologic diagnosis was proven in all cases. The most common diagnostic procedure used in both groups was bronchoscopy (Table 3). There were no serious complications related to the invasive diagnostic procedures in both groups. Fever after bronchoscopy: 1 (3.6%) patient in group I and 1 (3.7%) patient in group II and hemoptysis due to bronchoscopy: 3 (10.7%) patients in group I and 2 (7.4%) patients in group II. There were no significant differences between the groups regarding complications (p>0.05).

Table 3. Diagnostic Procedures

	Group I (n=28) n (%)	Group II (n=27) n (%)
Bronchoscopy	15 (53.6)	22 (81.5)
Peripheral lymph node biopsy	8 (28.6)	3 (11.1)
Transthoracic needle aspiration biopsy	2 (7.1)	–
Pleural biopsy	1 (3.6)	–
Thoracotomy	1 (3.6)	–
Mediastinoscopy	1 (3.6)	–
Soft-tissue aspiration biopsy	–	1 (3.7)
VATS*	–	1 (3.7)
TOTAL	28	27

* Video-assisted thoracic surgery

Of the 21 patients with detected distant metastasis; 10 had brain, 6 had bone, 4 had liver and 1 had adrenal metastasis. Cranial metastases were determined in 21.4% (n=6) of the patients with SVCS, and in 14.8% (n=4) of the patients without SVCS; there was no significant difference between the two groups regarding cranial metastases (p=0.4). Of the cases with SVCS, 18 had limited disease, 10 had extensive disease while 14 of the cases without SVCS had limited disease, 13 had extensive disease according to stage.

The therapeutic response of the cases were categorised into four groups. Five cases who could not have been followed for at least 3 weeks were considered to be unevaluable regarding therapeutic response. When group I (n=25) and II (n=25) were compared with respect to therapeutic response, there was no significant difference between them (p=0.9) (Table 4).

Table 4. Overall therapeutic response to chemotherapy, and chemotherapy plus radiotherapy*

	Group I n	(%)	Group II n	(%)
Complete Response	3	(10.7)	3	(11.1)
Partial Response	15	(53.6)	13	(48.2)
Stable Disease	4	(14.3)	5	(18.5)
Progressive Disease	3	(10.7)	4	(14.8)
Unevaluable	3	(10.7)	2	(7.4)
TOTAL	28	(100)	27	(100)

*P= 0.9 no significant difference according to therapeutic response (complete + partial) between the groups

When the cases in group I and II were compared regarding the prognostic factors for SCLC, such as age, sex, stage of the disease, performance of the patient and serum LDH level, no statistically significant difference was found. There was also no difference between the two groups regarding the treatment protocol (Table 5).

Table 5. The prognostic factors in the two groups*

Factor	Group I (n=28)	Group II (n=27)
Age (years) (mean SD)	52.03±10.6	54.2±8.8
Sex n(%)		
Female	1 (3.6)	2 (7.4)
Male	(96.4)	25 (92.6)
Stage n (%)		
Limited	18 (64.3)	14 (51.9)
Extensive	10 (35.7)	13 (48.1)
Performance Status [n (%)]		
0	2 (7.1)	3 (11.1)
1	13 (46.4)	14 (41.9)
2	7 (25.0)	6 (22.2)
3	5 (17.9)	4 (14.8)
4	1 (3.6)	0
Serum LDH (U/L) (mean±SD)	466.9±195.9	453.2±255.1
Treatment		
CTx**	15 (53.6)	18 (66.7)
CTx + RTx***	13 (46.4)	9 (33.3)

* There was no statistically significant difference regarding the prognostic factors between the two groups (p>0.05).
** Chemotherapy
*** Radiotherapy

Among the cases with SVCS, 13 had chemotherapy and radiotherapy while 15 had only chemotherapy alone. In group I, Cisplatin + Etoposide protocol was applied to 22 (78.6%) patients and Cisplatin + Epirubicin protocol was applied to 6 (21.4%) patients. In group II Cisplatin + Etoposide protocol was applied to 23 (85.2%) patients and Cisplatin + Epirubicin protocol was applied to 4 (14.8%) patients.

All of the SCLC cases had a mean survival of 39.1±27.0 (4-124) weeks. The survival of the cases with SVCS was between 4-100 weeks with a mean of 41.3±27.8 weeks, and the survival of the cases without SVCS was between 4 and 124 weeks with a mean of 34.1±26.5 weeks. There was no significant difference between the two groups regarding survival (p=0.43, log-rank test) (Figure 1).

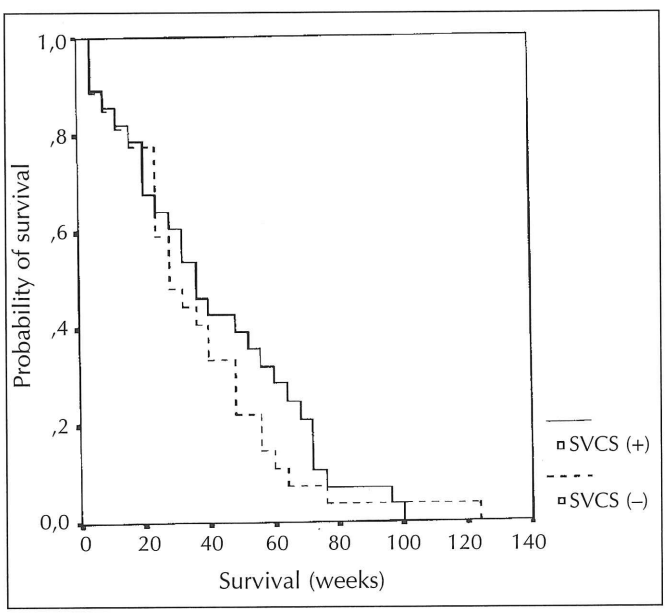

Fig. 1. Survival in cases of SCLC with and without SVCS

Discussion

SVCS is a clinical presentation which can be caused by many benign or malignant mediastinal diseases. Formerly, SVCS was regarded as an oncologic emergency condition as this situation causes neurologic and respiratory system complications. In addition, radiotherapy was recommended in all patients without establishing the diagnosis of the etiology as the invasive diagnostic procedures had been thought to be hazardous (6,8). But, in 10-21% of the cases with SVCS benign diseases such as tuberculosis, intrathoracic goiter, syphilitic aortic aneurysm, iatrogenic thrombosis, mediastinal fibrosis, Behçet's syndrome may also cause SVCS, and in these cases applying radiotherapy would be inappropriate (1,3,6,9,10). Therefore, the investigation of the etiology in SVCS is important. Today SVCS is not considered as an emergency condition. It has been stated that many invasive procedures can be safely used in SVCS cases, so planning the therapy according to the detected etiology will be a more appropriate approach (1,3,6,9). In our series, the etiology has been detected in all 29 cases with SVCS before the initiation of the therapy. In these cases, bronchoscopy, transthoracic needle aspiration biopsy, lenf node biopsy, mediastinoscopy and thoracotomy were used as diagnostic procedures. There were no serious complications and mortality due to the invasive diagnostic procedures in our cases, and there were no significant differences between the groups regarding complications.

The etiology is an important factor in determining the therapeutic approach for the patient with SVCS. It's not only important to eliminate the benign causes, but also to detect the histologic type of the tumor for determining the therapeutic choices. The first-choice treatment for patients with SCLC is systemic chemotherapy (1,7,11,12). In our cases, chemotherapy was the first choice to be applied, and for limited cases radiotherapy was added to the treatment protocol after 3 courses of chemotherapy. With chemotherapy, there was a 68% overall response (complete and partial). Meanwhile, there was a 72% therapeutic response in cases with SVCS, and 64% response in those without, showing no significant difference in between.

It is reported that the incidence of initial brain metastases are increasing in the patients with SVCS. Decreased blood flow through the superior vena cava system with blood stasis and hypothetical microthrombosis phenomena could explain the high rate of initial brain metastases (1). In our study, in patients with SVCS the rate of cranial metastases was not found to be significantly higher. The occurrence of SVCS in SCLC may be a risk factor for brain metastases. Computed tomography of the head should be performed routinely in patients with SVCS. The effect of prophylactic cranial irradiation on the overall survival and disease-free survival is controversial (13,14). In our study prophylactic cranial irradiation was not applied.

SCLC is with the shortest survival among lung cancers (15). In different series mean survival time is reported as 35-53 weeks (1,16,17). Limited disease, good performance, younger age (<70), white race, female sex, and normal serum LDH level are accepted as good prognostic factors (4,5,17). SVCS has also been studied as a prognostic factor, but in many studies, it has been reported to have no effect on prognosis (1,5,6,17). In

our study, with respect to the above-mentioned prognostic factors, there was no significant difference between the cases with SVCS and those without. When survivals in two groups were compared, there was also no significant difference found. Therefore, in our series SVCS was not found to be an unfavorable prognostic factor on the therapeutic response and survival time in SCLC.

From the results of this study, we deduced that SVCS was not a contraindication for invasive diagnostic procedures, and on the other hand it was not an unfavorable prognostic factor in SCLC.

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