Superior vena cava obstruction (SVCO) in patients with advanced non small cell lung cancer (NSCLC)

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Abstract

Introduction

To report on prognostic and treatment factors influencing the response of SVCO and related survival outcomes in advanced non small cell lung cancer.

Material and Methods

From November 2008 through December 2011, 18 consecutively diagnosed NSCLC patients with SVCO were included in this study. The patient, tumor and treatment related factors were analyzed. Median overall survival (OS), Kaplan -Meier survival plots, T-test, Cox Proportional Hazards models were generated by multiple covariates (MVA) and analyzed on SPSS software (version 19.0; SPSS, Inc., Chicago, IL).

Results

Thirteen patients (72%) had presented with SVCO before the pathological diagnosis of underlying lung malignancy, while 5 (28%) progressed to SVCO after initiating treatment with chemotherapy. Twelve (68%) patients achieved subjective relief from the obstruction at the completion of palliative radiation therapy. Treating oncologists preferred 4 Gy per fraction in 11 (62%), while the median biologically equivalent dose delivered was 28 Gy. Six (33%) patients received chemotherapy during the course of treatment. Median OS of the entire cohort was 3±1.85mths and 1-year survival rate of 7%. Univariate analysis confirmed that SVCO patients with good performance score (p=0.02), and partial response to chemotherapy (p= 0.001) have superior OS. However, Cox regression modeling for MVA demonstrated only good performance SVCO patients (p = 0.05) have a better OS.

Conclusion

RT effectively relieves SVCO but overall poor survival associated in our clinical scenario needs to be improved with multimodality approach. Adjuvant chemotherapy is to be considered after initial radiation therapy in good performance patients.

Key words

superior vena cava obstruction (SVCO), radiation therapy, chemotherapy, non small cell lung cancer (NSCLC), BED (biologically equivalent dose)

Introduction

Lung cancer is the leading cause of cancer death in both men and women[(1)] Non-small cell lung cancer (NSCLC) represents majority (four-fifth) of lung cancer cases, and most of these cases were locally advanced (Stage III) or metastatic (stage IV) at the time of presentation[(2)] Superior vena cava obstruction (SVCO) is an uncommon manifestation of carcinoma of the bronchus (both small cell and non-small cell) and is considered a medical emergency[(3)] More than 80% of cases of SVCO syndrome are caused by malignant lung tumors and this syndrome results from the impairment of blood flow through the superior vena cava (SVC) to the right atrium[(4)] The diagnosis of SVC syndrome is often made on clinical presentation and presence of an

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associated factor like underlying malignancy. Common symptoms include swelling of the face, neck, and both arms, and occasional life-threatening presentation, often with neurologic and respiratory sequel such as cerebral and laryngeal oedema proceeding to severe respiratory compromise[4, 5] CT is diagnostic and provides accurate information about the location of the obstruction and about other critical surrounding structures[6,7] Recommended treatments for cancer-related SVC syndrome include steroids, chemotherapy and radiation to shrink the tumor that is causing the obstruction[5,8] Overall, patients with advanced NSCLC typically have a poor prognosis, with a median survival of 6 months.[8, 9]

The primary objective of this study was to report on prognostic and treatment factors influencing the response of SVCO and related survival outcomes.

Materials and Methods

Patient population

We retrospectively reviewed the records of 138 consecutively diagnosed patients with stage III & IV NSCLC from November 2008 through December 2011. Staging/restaging was done as per the 7th edition of American Joint Committee on Cancer (AJCC) staging system[9] Eighteen patients with SVCO were selected and analyzed after the institutional review board approval. The included patients were evaluated initially by a multidisciplinary team of radiation, medical and surgical oncologists. Pretreatment staging investigations for managing primary lung malignancies included detailed clinical evaluation, chest X ray, chest computed tomography (CT) scans, bone scans or (18F) 2-fluoro-2-deoxy-D glucose positron emission tomography scans, and central nervous system imaging with either contrast-enhanced CT or magnetic resonance imaging wherever indicated. Pathological diagnosis was established either by fine needle aspiration cytology (FNAC) or a bronchoscopic biopsy. All patients have a syndrome of superior vena cava obstruction secondary to lung malignancy.

Treatment

As per our institute's policy, patients with SVCO are initiated on symptomatic treatment immediately after clinical assessment at the time of admission and planned for histopathological evaluation within 24-48 hrs. Patients with SVCO are started on corticosteroids, diuretics with strict nursing orders of lower limb intravenous cannulation and elevation of head end. Airway saturation is maintained through external O2 supply through face mask or nasal prongs. The routine protocol of treatment for stage III NSCLC at our institute is induction chemotherapy (4-6 cycles, 3 weekly) followed by chest radiation therapy. Stage IV patients are managed with systemic chemotherapy, guided by performance status and extent of distant disease. Otherwise only palliative radiation therapy is offered to the involved site.

SVCO patients are prescribed chest radiation therapy upon histopathological confirmation of underlying NSCLC. Chest radiation therapy (RT) in the latter half of 2008 was delivered through two-dimensional planning while three-dimensional conformal radiation therapy with CT-based planning was used effective 2010 onwards. However, the planning discretion and radiation dose fractionation was varied among the treating radiation oncologists' over the period of study. While those with 3 Gy or 4 Gy per fraction, total intended prescription was either 30-39Gy or 20Gy, respectively. Only once-daily fractionation schedule was used for all the patients in this study. Treatment planning was done with the ONCENTRA planning system (Nucleotron Medical Systems,). In order to enable the comparison of the physical dose values with different fractionation schemes, we calculated the biologically equivalent dose (BED) using the linear quadratic formula: BED = $(nd)\ (1 + d/(\alpha/\beta))$, n is the number of fractions, d is the fraction size, α/β ratio is 10 Gy. [10]

Study end points and Statistical analysis

A decrease in the clinical symptoms of SVCO at the conclusion of RT was termed as good response. An increase in symptoms or no relief was defined as progressive or persistent,

respectively. Overall Survival (OS) was the primary endpoint of this study which was measured from the start date of any treatment to patients' death from any cause or the last follow-up. OS analysis and actuarial probabilities were calculated with the Kaplan-Meier test. Patients at our center are generally followed up at 3-4 months interval for the first 2 years, and then every 6 months thereafter. Although we request for patients physical presence on every follow up, we routinely utilize telephonic services to do the same if otherwise. The OS was compared to the grouped variables using the log-rank test. Cox's proportional hazards model was used for multivariate analysis (MVA) to estimate the simultaneous impact of covariate factors on OS. All p values were two-sided with $p \leq 0.05$ considered significant. This study was statistically analyzed on SPSS software (version 19.0; SPSS, Inc., Chicago, IL). The retrospective nature of this study did not allow for detailed assessment of treatment related toxicity, however no related mortality was observed.

Results

Clinical and pathological characteristics

The clinical and pathological characteristics are summarized in (Table 1). From 2008-2011, 18 patients with SVCO were eligible for analysis. Patient age ranged from 45-85 years (median 60 years). Sixty- one percent of the patients had KPS ≥ 70% while 72% had superior vena cava obstruction (SVCO) diagnosed at presentation. Clinical features of facial edema and venous engorgement was seen in all the patients. Diagnostic/staging thoracic CT scan was done in 83% of the patients. Bronchoscopy guided tissue sampling was done in 39% of the patients while image guided FNAC contributed to the remaining 61% of the pathological diagnosis. Squamous cell histology was established in 17%, while 83% were classified as poorly differentiated carcinomas termed under the category of NSCLC NOS. Seventy-two percent had stage III NSCLC; III A-22% and III B-50%, and 28% had stage IV NSCLC disease at presentation.

Treatment and outcome characteristics

Treatment and outcome characteristics are summarized in (Table 2). In the initial management of SVCO, all the patients received

Patient Characteristic	Entire Cohort, N=18 (100%)
Media age (range), y	60 (45-85)
Sex	
Men	17 (95)
Women	1 (5)
Karnofsky Performance Status	
≥ 70	11(61)
< 70	7 (39)
SVCO development	
At presentation	13 (72)
Post treatment	5 (28)
Clinical symptoms of SVCO	
Facial edema	18 (100)
Conjunctival injection	14 (78)
Venous engorgement	18 (100)
Arm swelling	12 (67)
Shortness of breath	12 (67)
Stridor	0
NSCLC Histology	
Non squamous	3 (17)
Squamous	15 (83)
AJCC Stage	
IIIA	4 (22)
IIIB	9 (50)
IV	5 (28)
CT Chest	
Yes	15 (83)
No	3 (17)
Bronchoscopy	
Yes	7 (39)
No	11 (61)

Table 1. Clinico-pathological characteristics

Acronyms: SVCO, Superior Vena Cava Obstruction; NSCLC, non small cell carcinoma; CT, Computed Tomography

Treatment Characteristic	Entire Cohort, N=18 (100%)
Medical management SVC	
Steroids	18 (100)
Diuretics	5 (27)
Anticoagulants	0
Mediastinal radiation therapy	18 (100)
Radiotherapy dose; BED, Gy	
≤28	12 (67)
>28	6 (33)
Radiotherapy dose per fraction, Gy	
3	7 (39)
4	11 (61)
Radiotherapy compliance	
Completed course	13 (72)
Defaulted	5 (28)
SVCO response	
Good	12 (68)
Progressive	3 (17)
Persistent	3 (17)
SVCO recurrence	0
Chemotherapy	
Received	6 (33)
Not received	12 (67)
Chemotherapy compliance	
Completed course	2 (33)
Incomplete/defaulted	4 (67)
Chemotherapy response	
Partial	2 (33)
Progressive	4 (67)
Stable/No response	4 (5)
Status at Last Follow up	
Died of disease	16 (89)
Lost to follow up	2 (11)

Table 2. Treatment & outcome characteristics

Acronyms: BED - Biologically equivalent Dose; Gy, Gray-unit of radiotherapy dose; RT- radiation therapy

intravenous steroids (100%), while 27% were prescribed additionally with diuretics. All the patients received radiation therapy (100%). Median radiation therapy dose (BED) was 28 Gy, 33% patients received RT dose > 28Gy. Sixty-one percent of the patients was prescribed 4 Gy per fraction schedule for RT plan of 20 Gy in 5 fractions while remaining 39% received 3 Gy per fraction for a planned schedule of 30 Gy in 10 fractions. Thirteen (72%) patients completed radiation therapy. At completion of RT, 12 (68%) patients had good relief from the obstruction. Six patients (33%) received induction chemotherapy; 2 patients completed the prescribed chemotherapy schedule while 4 patients defaulted due to disease progression. Two patients did show partial response to chemotherapy.

At the completion of study, 16 (89%) patients had died due to disease and 2 (11%) were lost to follow up. None of the patients had recurrent SVCO. The median overall survival for the entire cohort was 3 ±0.42 months (95% CI: 2.18, 3.8) and the 1-year overall survival was 7%. The overall survival analysis is tabulated in Table 3. In the univariate analysis (UVA), good performance patients, initial good SVCO response and partial responders to chemotherapy had superior OS. Age, sex of the patient, histology, stage of the disease, dose of RT and size of radiation dose in patients with SVCO had no effect on overall survival. In the subsequent Cox regression modeling for MVA, good performance (p=0.05) and initial good SVCO response (p=0.03) remained significant as being strong predictors for OS. (Figure 1a. & 1b.)

Discussion

SVCS results from impaired blood flow through the SVC to the right atrium. The common signs and symptoms seen in our study were facial edema and venous distension, and concur with other studies related to SVCO[5] The severity of the syndrome depends on the rapidity of the onset of obstruction and its location.[10] The symptoms are mild when the obstruction is slow and progressive as the collateral pathways develop over this period[11] Steroids were used in all of the patients in our study. Experts have used steroids, diuretics and anticoagulants as the initial medical management in SVCO patients, although the benefit of either short-term or long-term anticoagulation therapy for this syndrome is unclear.[10, 12] Although SVCO is a medical emergency, tissue diagnosis is often necessary to direct treatment decisions for the underlying malignant pathology[3, 10] After confirmation of histopathological diagnosis of underlying NSCLC in our study, all the patients

Dichotomized variables	Univariate Analysis		
	Group	Median Overall Survival, OS months±SE(95%CI)	**Log Rank** *p*
Age			*NS*
Sex			*NS*
KPS (Karnofsky Performance Scale)	≥ 70 < 70	3±1.9 (0,0.68) 2±0.29 (1.4,2.5)	*0.02*
Histology	Non squamous Squamous		*NS*
Chemotherapy	Received Not received		*NS*
Response to Chemotherapy	Partial Progressive	3±1.14 (0,6.8) Not assessable,< 1	0.001
Radiotherapy dose Fractionation	3 Gy 4 Gy		*NS*
BED Biologically Equivalent Dose	>28 Gy ≤28 Gy		*NS*
SVCO Response	Good Progressive/Persistent	3±1.94(0,6.8) Not assessable	.001
Multivariate Analysis Variable	**Associated group**	**Stage III** OS **Hazard Ratio**(95%CI)	*p*
KPS	< 70 (versus ≥ 70)	1.27 (0.91,3.16)	0.05
SVCO Response	Progressive/Persistent (versus Good)	3.6 (1.07,12.2)	0.03

Table 3. Overall survival analysis

Acronyms: NS, not significant; CI, confidence interval; SE, standard error

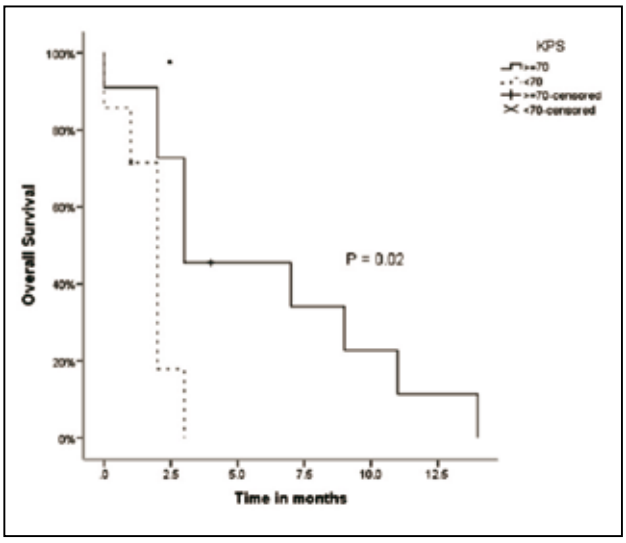

Fig. 1(a): Relation of KPS to overall survival in SVCO patients

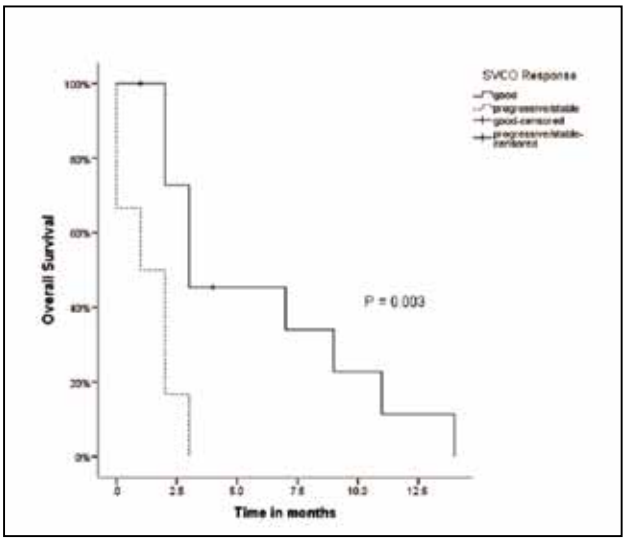

Fig. 1(b): Response of SVCO to initial treatment and its impact on overall survival

underwent mediastinal radiation therapy. Recommended treatments for cancer-related SVC syndrome include radiation therapy and chemotherapy directed to relieve the obstruction through debulking of tumour.[10, 13, 14, 15] Newer interventions like percutaneous angioplasty and the use of intravenous stents are becoming increasingly common and are effective in rapidly relieving SVCO.[3] It seems that financial considerations in our region have inhibited the use of stent as a successful modality in SVCO patients. A bypass of the SVC may be indicated in some cases.[3] Overall good response is seen after mediastinal radiation in relieving the symptoms of SVCO and response is almost universal despite a wide range of radiation fractionation and total dose used [13, 16] SVCO relief was seen in 68% of our cohort after mediastinal radiation therapy. In our study, we have preferred hypofractionation schedules largely due to logistic reasons in view of high volume of patients and durability of palliation achieved. RT fraction size > 3 Gy/ day have shown better results than conventional fractionation[9, 17]. Although lately studies have obviated the need of large fraction size schedules[13,16]. Studies however do report the preference for mediastinal radiation therapy as the initial modality in SVCO, although the response rates are quite similar for both radiation and chemotherapy[10, 16]. Systemic therapy in the form of chemotherapy is certainly essential in containing the underlying malignancy and is a good prognosticator for overall survival[2]. There is a strong feeling amongst our oncologists that the poor prognosis associated with advanced NSCLC and good immediate relief from SVCO after palliative RT inhibits the patients to pursue further course of adjuvant therapies, essentially chemotherapy and further primary thoracic radiation therapy. One of the studies demonstrated the median survival in favorable good response SVCO in SCLC patients was 9.5 months, and the 2-year survival was 10%[16]. The persistent or recurrent SVCO group had a median survival of 3 months[16]. Our overall median survival was 3 months, with good performance patients and good response SVCO patients faring with better OS than their counterparts. However, the OS is quite dismal in our study and is attributed to the advanced stage, lack of maintenance of adjuvant treatment owing to logistics, finance or lack of multidisciplinary approach. Overall, this study despite having relatively small population and bears inherent flaws of retrospective design does reflect the beneficial role of radiation therapy in achieving good palliation in SVCO patients with advanced NSCLC and highlights the positive role of aggressive adjuvant multimodality approach, essentially optimal use of chemotherapy in such patients.

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