Original Article

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Outcome of Primary Small Cell Carcinoma of Esophagus: A Single Institutional Experience

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Abstract

Background: Background and Objectives: Primary small cell carcinoma of esophagus (SCCE) is a very aggressive disease and accounts for 0.8–3.1% of all esophageal cancers. The study analysed clinical characteristics and survival outcome of 24 treated cases. **Subjects & Methods:** Out of total 3,440 cases of esophageal cancers diagnosed from 2013 to 2016 at Dr B Borooah Cancer Institute, clinical data were obtained from 24 histologically and immunohistochemically confirmed cases of primary SCCE. Patients received surgery, chemotherapy and/or radiotherapy, either alone or in combinations. **Results:** The median age of patients was 54 years with male preponderance. Out of 24 cases, 15 cases have pure small cell carcinoma histology and 9 cases had mixed pathology (poorly differentiated carcinoma with neuroendocrine differentiation). The median overall survival time was 14 months. The 6-, 12-, 24- and 36- month's survival rates of these patients were 91.6%, 54.1%, 33.3% and 25.0% respectively. The 3-year survival rate for patients with localised disease was 62.6% vs. 6.3% for those with metastatic disease (p=0.007). Nine patients had relapses within first 6 months from the completion of any therapy. Patients with pure small cell carcinoma histology (vs. mixed histology, p=0.008), with distant organ involvement (vs. no organ involvement, p=0.022) and those who are non-responders to treatment (vs. responders, p<0.0001) were correlated with shorter overall survival in univariate analysis. **Conclusion:** Primary SCCE presents with early metastasis and have a poor prognosis, with the existing modalities of treatment. Combined therapy based on platinum-based combination chemotherapy may improve the short term survival in these patients.

Keywords: Small cell carcinoma, neuroendocrine tumor, combination chemotherapy, survival outcome.

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Introduction

Small cell carcinoma usually arises in the lung which accounts for 16% of all lung cancers, but can also originate in a wide range of extra-pulmonary sites, most frequently in the urinary bladder, prostate, esophagus, stomach, colon and rectum, gallbladder, larynx, salivary glands, cervix, and skin. Primary small cell carcinoma of the esophagus (SCCE) is a very rare disease. It represents 0.8-3.1% of all esophageal cancers and approximately 2.5-4.1% of all small cell carcinomas.[1,2] The diseasewas first described by McKeown in 1952.[3] Reports of SCCE indicate retained primitive cells with potential differentiation into small cells.[4] Primary SCCE being an aggressive disease, early dissemination, frequent recurrences, and poor prognosis are some of the characteristics features of this disease entity.[5,6] Although chemotherapy and/or radiotherapy with or without surgery form the mainstay of therapy, still the outcome of this disease remains to be poor. Patients who present with loco-regional disease are treated with aggressive therapy, but majority of them relapses and the overall prognosis is poor, with 5-year survival less than 15%.[7] Various studies have shown that the median survival for limited and extensive disease ranges from 1.4 to 3.5 years and 8 to 12 months, respectively.[8]

Because of its rarity, an optimal management strategy has not been recognized, and various combinations of surgery, radiotherapy, and chemotherapy have been described in the literature. Little is known about the clinico-pathological and prognostic features of SCCE. Controversies exist with regard to the staging of the tumour. Some prefer American Joint Committee on Cancer (AJCC) staging for esophagus cancer while other authors have used staging similar to small cell lung cancer.[9]

SCCE being a rare disease, much work has not been done in this field. As very limited data exists in our country, particularly in the North-Eastern part of India, where the incidence of esophageal cancer is very high, we sought to analyse the clinical characteristics and survival outcome of this subset of oesophageal malignancy.

Subjects and Methods

Study design and participants:

This was a retrospective observational study to evaluate the demographic profile, clinical presentations, and treatment

compliance and survival pattern of SCCE patients in the North-East Indian population.Out of total 3,440 cases of oesophageal cancers diagnosed from 2013 to 2016 at Dr B Borooah Cancer Institute, clinical data were obtained from 24 confirmed cases of SCCE. The inclusion criteria included are: 1) biopsy or immunohistochemistry (IHC) proven small cell cancer of oesophagus, 2) Age ≥ 18 years. Exclusion criteria included: 1) presence of other synchronous or metachronous tumours,2) age < 18 years, and 3) patients with histologies other than small cell carcinoma. This study received approval from the Institutional Ethics Committee (IEC).

Data collection and follow up:

Data were collected retrospectively from hospital based cancer registries, individual medical case notes, electronic patient records and pathology reports, including age, gender, performance status, history of smoking, history of tobacco and/or alcohol intake, history of any medical risk factors, symptom burden, grade of dysphasia, size of primary tumour, histological subtype including IHC findings, stage, site and socio-economic background. A detailed retrospective chart review was performed to document staging, endoscopic findings, treatment history, follow-up, and survival outcome. Stage was determined according to the American Joint Committee on Cancer Staging System.[10] All patients received an endoscopic biopsy before treatment. Staging workup included a physical examination,chest radiography, CT scan of the abdomen andradioactive isotope bone scans.Patients received surgery, chemotherapy and/or radiotherapy, either alone or in combinations.Patients with stages II, III, and IVA disease were treated with chemo-radiation with or without subsequent oesophageal resection or with oesophageal resection only. All patients with stage IVB disease were treated with systemic therapy. The chemotherapy regimenmainly consisting of a platinum agent (cisplatin or carboplatin) and etoposide based chemotherapy regimen. Patients who received radiation to the oesophagealtumour underwent computed tomography scan treatment simulation followed by a radiation dose of 59.4Gy in 33 fractions, prescribed to cover 95% or more of a clinical target volume encompassing the primary tumour and involved lymphatic regions. Survival status was determined from the date of registration for each patient at BBCI. The overall survival (OS) was defined as the time from the date of registration to the date of death or to the date of last follow-up for patients who had not died before the censor date. Follow-up was done every 3 months. The contents of follow-up are disease progression, recurrence of disease, use of salvage treatment, and response to salvage treatment and survival days.

Statistical analysis:

Patient and demographic features were summarized using median/centiles, means and standard deviations (SD).To look for significance of difference between patient and treatment variables “independent sample t-test” was used. Survival curves were estimated with the Kaplan-Meier method. The associations of the various clinical parameters with survival were evaluated in univariate and multivariate Cox-regression models. In the multivariate model, all variables with a statistically significant univariate association were included. Hazard ratios (HR) and 95% confidence intervals (CI) were provided for univariate and multivariate Cox-regression models. A Cox proportional hazards model wasfitted to all individual prognostic variables to determine their independent effect. Analyses were performed in SPSS 19.0 software.

Results

Table 1: Demographic and treatment characteristics.

Characterises (N=24)	Frequency, n (%)
Stage:	
II	1 (4)
III	7 (30)
IV	16 (66)
Lymph Node Involvement:	
Yes	13 (55)
No	11 (45)
Distant Organ Involvement:	
Yes	11 (45)
No	13 (55)
Histology:	
Pure small cell histology	15 (63)
Mixed histology	9 (37)
Intent of Therapy:	
Radical	8 (34)
Palliative	16 (66)
Upfront Surgery:	
Yes	2 (8)
No	22 (92)
NACT:	
Yes	5 (20)
No	19 (80)
Concurrent chemo-RT:	
Yes	7 (30)
No	17 (70)
Chemotherapy cycles received:	
Mean +/- SD (range)	4 +/- 1 (1-6)
Median (Q1 – Q3)	5 (2 – 6)

Table 2: Response to therapy and survival rates.

Characteristics (N=24)	Frequency, n (%)
Treatment Responses:	
CR	3 (14)
PR	11 (46)
SD	5 (20)
PD	5 (20)
Relapsed Disease:	
Yes	14 (58)
No	9 (38)
Not known	1 (4)
Median Overall Survival (months)	14.0
Survival Rates (%):	
At 6 months	91.6%
At 12 months	54.1%
At 24 months	33.3%
At 36 months	25.0%

Demographic and disease characteristics:

Twenty-four patients of SCCE were eligible for the analysis. The median age at presentation was 54 years(range

33 to 64 years).Fourteen out of 24 patients (58%) were males & 10/24 (42%) were females. History of tobacco usage and alcohol intake was present in 45 % and 37% of patients respectively. Sixty per cent of patients had a known medical risk factor, most common being hypertension and type II diabetes mellitus. Most common presentation was dysphagia (16/24 of the patients).Most common grade of dysphagia was grade II (10/24; 40%). Most common site of involvement was the upper third of esophagus, followed by middle third, lower third and cervical region. Fifty-fourper cent of patients had nodal involvement. Majority of patients presented with advanced stage disease (n=16/24, 66% with stage IV; and n=7/24, 30% with stage III), whereas, only 4% presented with early stage disease (stage II). Distant organ involvement was seen in 45% of patients [Table 1]. Most common site of distant metastasis was liver followed by lung, distant nodal areas and bone. Most common histologic pattern was pure small cell carcinoma (15/24 patients, 63%), and mixed neuroendocrine differentiation histology was seen in 37%.

Treatment characteristics:

Eight out of 24 (34%) patients received radical intent treatment. Upfront surgery was done in 2 patients. Neo-adjuvant chemotherapy (NACT) was used in 5 patients (20%), while concurrent chemo-radiotherapy (CCRT) in 7 patients (30%).Most common chemotherapy regimen used was combination of cisplatin or carboplatin plus etoposide based chemotherapy. Median number of chemotherapy cycles used was 5 (range 2-6). Median radiotherapy dose used was 59.4 Gy in 33 fractions. The best response to treatment achieved was partial response (PR) in 45% patients [Table 2]. Complete response (CR) rate was 14% and 20% had stable disease (SD) as per RECIST criteria. Twenty per cent had disease progression (PD).

Table 3: Subgroups affecting survival in univariate analysis.

Sub-groups	Survival rate	P value
3-year Survival Rate (%): Localised disease Metastatic disease	 62.6% 6.3%	 P=0.007
Survival rate: Pure small cell histology Mixed histology	 9.5 NR	 P=0.008
Survival rate: Distant organ involvement absent Distant organ involvement present	 29.0 8.6	 P=0.022
Survival rate: Treatment responder Non-responder	 29.0 7.1	 P<0.0001

Survival analysis:

The median follow-up period for the study was 15 months(range 4.5 to 49.0 months).At the time of last analysis, 6/24 (25%) were alive, 10/24 (42%) were dead, 8/24 (33%) were lost to follow up. The median overall survival time from diagnosis was 14 months [Figure 1]. The 6-, 12-, 24- and 36- month's survival rates of these patients were 91.6%, 54.1%, 33.3% and 25% respectively [Table 2]. The median survival for metastatic staged patients was 9.5 months and it did not reach (NR) for localised stage patients The 3-year survival rate for patients with localized disease was 62.6 % vs. 6.25 % for those with metastatic disease (p=0.007) [Figure 2]. Majority (9/14 patients) had relapses within first 6 months from the completion of any therapy. Patients with pure small cell carcinoma histology (vs. mixed histology, p=0.008), with distant organ involvement (vs. no organ involvement, p=0.022) and those who are non-responders to treatment (vs. responders, p<0.0001) were correlated with shorter overall survival in univariate analysis [Table 3] [Figures 3 a-c]. Other factors such as age, gender, smoking status, grade of tumour and site of disease did not significantly affect the survival on univariate analysis.

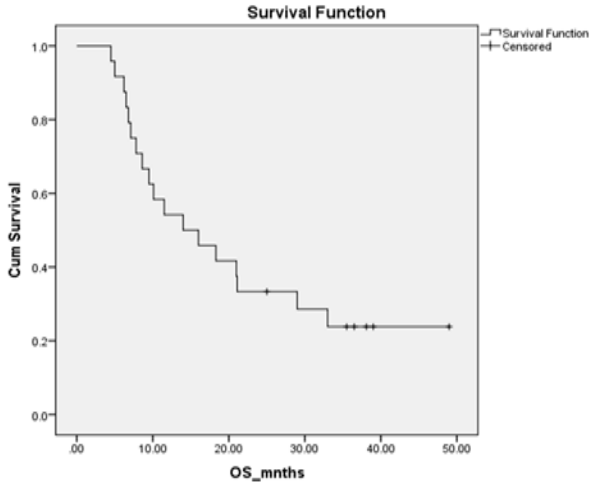

Figure 1: Showing survival curve of the whole study population.

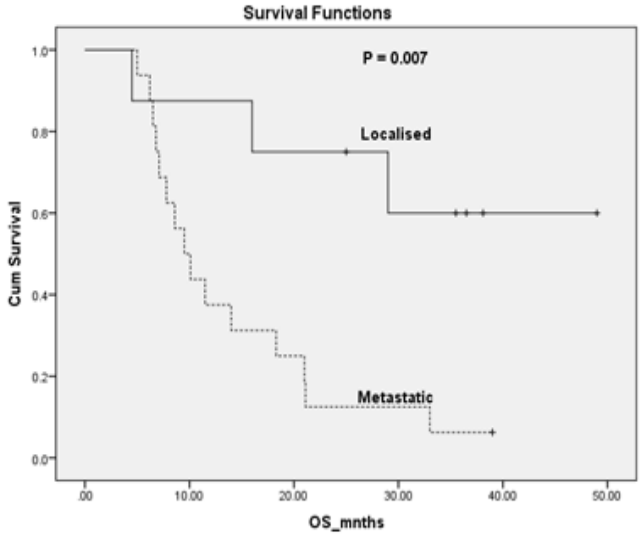

Figure 2: Showing survival advantage (3-year survival rates) for patients with localised disease versus those with metastatic disease.

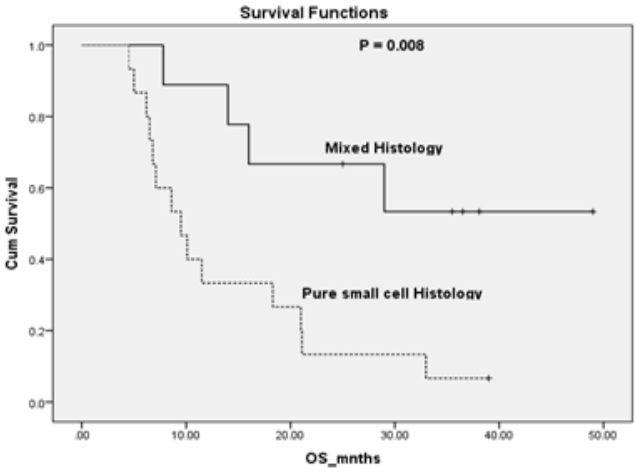

Figure 3a: Showing survival advantage for patients with mixed histology versus those with pure small cell histology.

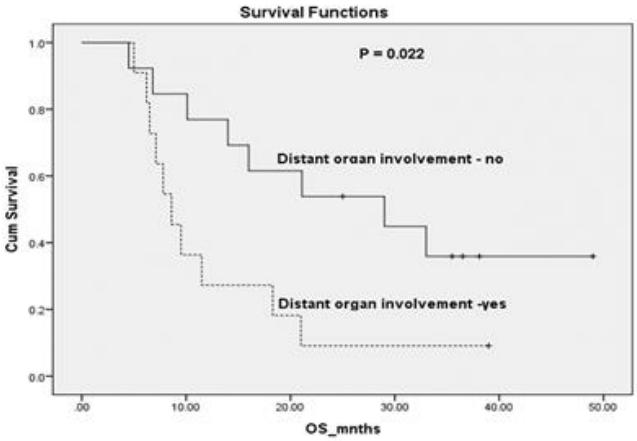

Figure 3b: Showing survival advantage for patients without distant organ involvement versus those with distant organ involvement.

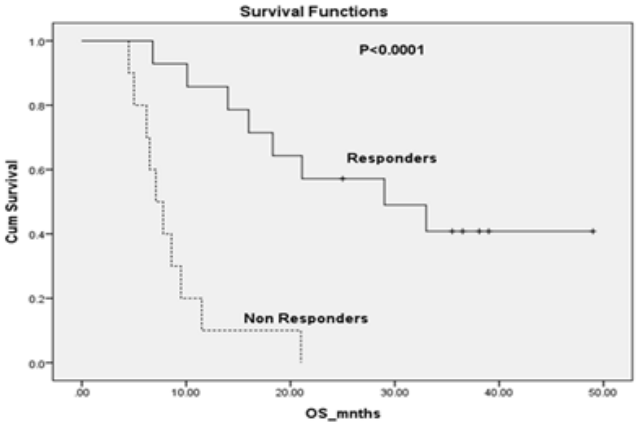

Figure 3c: Showing survival advantage for responders versus non-responders to therapy.

Discussion

Primary SCCE is a very aggressive and uncommon disease with tendency of early dissemination and poor prognosis.[5,6] In our study, out of 3,440 registered cases of oesophageal cancer, only 24 were diagnosed as primary SCCE, which constitutes only 0.6% of all cases. This is in line with a study done by Brenner et al.[11] where they have reported incidence of SCCE in the range of 0.4% to 2.8% of all oesophageal cancers. The median age of the patients in our study was 54 years old, which was lower than the median age of 63.8 years in one previous report,[5] and close to the median age of 58 years in another report.[4,12] Male to female ratio of patients was 1.4:1, which is almost similar to 1.3:1 in previous reports.[5] Although, in one study by Hudson et al.[13] reported Male to Female ratio of 1:4, the reasons attributed to this contrast finding as stated was recent increase in the proportion of female smokers and small sample size.

The clinical presentation of primary SCCE is similar to those with esophageal carcinomas. The most common symptom reported in various studies in dysphagia.[14-16] Our study results were also in line with other studies with dysphagia being the most common symptom in 66%. The most site of involvement was the upper third oesophagus followed by the middle third, both of which constitute 71% of all cases. This finding is different from another study done by Casas et al.,[5] where the most common site (95% of tumours) was situated in the mid- and lower oesophagus. History of smoking was prevalent in 50% of cases in this study, whereas in another study by Song et al.[17] there were 66% smokers. Aggressive nature of the disease was supported by the results of this study that includes the presence of systemic disease at presentation in almost two-third (66%) of the patients, high relapse rate (58%) and lower overall survival (median overall survival of 14 months). The most common site of distant metastasis was liver followed by lung, distant lymph nodes and bone. An interesting finding was that, those patients who had distant organ involvement had a significantly inferior survival than those who did not have organ involvement, indicating that the metastasis to distant organs might be a stronger predictor for survival than nodal involvement.

As far as histological origin of SCCE is considered, there are two hypotheses. First, being SCCE originates from neuroendocrine cells of the submucosal gland or stratum basal, which is thought to be the major precursor uptake and decarboxylation cells that has been histologically confirmed. The second hypothesis states that SCCE originates from multipotent stem cells of the endoderm. Majority of these cells may be differentiated into squamous cell carcinoma, and some are differentiated into adenocarcinoma or small cell carcinoma. In this study, 63% were pure small cell histology, whereas, 37% had mixed histology pattern. In the study by Song et al.[17] mixed type histology was detected in 8.6% of patients. Also the survival of patients with pure small cell type was significantly inferior than mixed type cases in our study, similar to Maru et al.[18]

Because of its rarity and in the dearth of randomised trials, the optimum treatment strategy for SCCE remains uncertain. For limited disease, many reports have combined

surgery with chemotherapy and/or radiotherapy, with different survival rates. In general, the median survival rate in these patients with localised disease is between 8 to 24 months.[5,13,15,16] In this study, the 3-year overall survival rate was 62.6% for localised disease which was significantly better than metastatic disease (6.3%). This suggests stage at presentation is one of the important prognostic parameter for long-term survival.

The National Comprehensive Cancer Network (NCCN) guidelines for small cell carcinoma of the lung are usually used as references to determine the management of SCCE. The most common treatment used in our study population was palliative chemotherapy for metastatic (stage IV) disease and NACT-CCRT modality in limited stage (stage II/III) disease. The most common chemotherapy regimen used was cisplatin (or carboplatin) and etoposide based chemotherapy as is used in small cell lung cancer. The overall response rate (CR+PR) in entire study population was 60%. This similar finding was also seen in another study by Chen et al.[19] Some of the case reports have also used cisplatin plus 5-Florouracil based chemotherapy regimen.[20] A study from Japan[21] has also used combination of cisplatin and irinotecan based chemotherapy as NACT. There was a significant survival benefit for the treatment responders group as opposed to non-responders. The median overall survival for entire cohort of our study was 14 months which was better than the cohort of patients in a study by Ohmura et al.[22] study where median survival was 6 months.

Surgery is of limited benefit in SCCE as shown by various studies.[2,23,24] In our study, only 2 patients had upfront surgery. However, surgery can be done in clinically selected patients as salvage after documented local failure following chemo-radiation, as done in one published case report.[25] Multimodality treatment using CCRT remains the main treatment option for this type of cases.

In the dearth of data for SCCE patients from India, this study has provided some insight, which to the best of our knowledge is the only study from the North-eastern part of India. Ours study being retrospective one has various limitations. Small sample size might have resulted in non-significant p-values for many sub-group analyses. High loss to follow-up rate is another limitation of this study.

Conclusion

Primary SCCE is a rare, aggressive and systemic disease, presented in advanced stage with distant organ involvement. Similar to small cell lung carcinoma, management of SCCE remains to be a challenge. Response to treatment remains an independent prognostic factor. Cure is not possible with local therapy alone, and should be treated by multi-drug chemotherapy including platinum, with or without radiation as the first line treatment.

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