Small Cell Carcinoma of the Esophagus: Clinicopathological Features and Outcome of 22 Cases

Sare Hosseini, Roham Salek, Hamid Nasrolahi, Mohammad Mohammadianpanah, and Mona Judi

1Cancer Research Centre, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, IR Iran
2Shiraz University of Medical Sciences, Shiraz, IR Iran
3Colorectal Research Center, Shiraz University of Medical Sciences, Shiraz, IR Iran
4Cancer Research Centre, Mashhad University of Medical Sciences, Mashhad, IR Iran

*Corresponding Author: Roham Salek, Cancer Research Centre, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, IR Iran. Tel/Fax: +98-5138414499, E-mail: salekr@mmm.ac.ir

Received 2014 May 27; Revised 2015 March 26; Accepted 2015 April 28.

Background: Small cell esophageal carcinoma (SCEC) is a highly aggressive and rare neoplasm.

Objectives: This study aimed to report the characteristics, prognostic factors, and treatment outcomes of 22 patients with SCEC.

Patients and Methods: This brief report was carried out by reviewing the medical records of 22 patients with newly histologically proven SCEC that were treated between 2000 and 2010 at 2 tertiary academic hospitals. All the potential prognostic variables, including the patients' characteristics, tumor features, and treatment modalities were analyzed to establish their influence on the patients' survival rates.

Results: This study was conducted on 7 males and 15 females with a median age of 61 years. Dysphagia and weight loss were the most prevalent symptoms. According to the results, 14 patients (64%) had limited diseases and 8 cases (36%) had extensive diseases. In those with extensive diseases, liver, lung, and lymph nodes (LNs) were the most metastatic sites. Besides, most tumors were located in lower (50%) and middle (32%) part of the esophagus. Most patients (91%) were treated with sequential (55%) or concurrent (36%) chemoradiation (CRT). Surgical resection was also performed for 7 patients. Chemotherapy regimen consisted of cisplatin and etoposide in 14 patients (64%). The median follow up time was 12 months. The 1, 3, and 5-year overall survival rates were 27%, 14%, and 4%, respectively. Yet, no prognostic factors were found because of the small sample size of the study.

Conclusions: Primary SCEC is a rare and highly aggressive tumor. However, prognosis is poor and long-term survival is exceptional. CRT could be an appropriate alternative to operation.

Keywords: Small Cell Carcinoma, Esophagus, Prognosis, Surgical Procedures, Chemotherapy

1. Background

Iran, especially its northern provinces, with an esophagus cancer incidence rate of more than 100 per 100000 populations is among the countries which make the "esophageal cancer belt" region (1). Worldwide, the most common histological subtypes of esophageal carcinoma are squamous cell carcinoma and adenocarcinoma (2, 3). In 1952, McKeown found 2 cases with oat cell carcinoma in 9000 autopsies (4). This disease is so rare that no standard treatment has been accepted for these aggressive tumors so far. Data on its clinical course and outcome are also limited to some retrospective small reports (5-7). Even, controversies exist with regard to the staging of the tumor. Sometimes staging is performed based on American Joint Committee on Cancer (AJCC) for esophagus cancer and sometimes it is done similar to small cell lung cancer (8). Small cell carcinoma (SCC) can affect all organs but the most common anatomical sites are lung, gastrointestinal tract, genitourinary system, gynecologic organs, and head and neck region (9). Reports of SCC arising in the esophagus indicate retained primitive cells with potential differentiation into small cells (10). Histologically, SCC is characterized by small cells with scant cytoplasm, round nuclei, and granule formation. Immunohistochemistry (IHC) would aid the diagnosis if there was immunoreactivity for neuroendocrine markers (11, 12).

2. Objectives

Considering the rarity of this histology in esophagus and lack of any report from Iran, this study assessed clinicopathological features, and oncologic outcomes of SCEC cases in northeast of Iran.
3. Patients and Methods

The study data were collected from the cancer records of two referral specialized oncologic hospitals, Omid and Imam Reza, affiliated to Mashhad University of Medical Sciences (Mashhad, Iran) from January 2000 to December 2012. The clinical, pathological, and imaging records were reviewed in this study. All patients who had histologically proven diagnosis of SCEC by endoscopic biopsy or surgery (except those without follow up) entered the study. The patients' characteristics, including sex, age, history of smoking, presenting symptoms, and performance status, tumor location, tumor size, clinical stage, and endoscopic upper gastrointestinal imaging findings were recorded. The treatment modalities and patients' outcomes were collected, as well. The preliminary evaluation included comprehensive history, physical examination, complete blood count (CBC), liver function tests (LFT), renal function tests (RFT), chest x ray, abdominal and pelvic CT-scans or sonography, and in case of bone pain, radionuclide bone scan.

According to the results of these evaluations, the patients whose diseases were confined to the primary site and/or regional nodes were classified as having limited disease, while the others were considered to have extensive disease (6).

3.1. Statistics

All potential clinical and pathological variables were analyzed using the SPSS for Windows version 18 (SPSS, Chicago, IL). Five-year overall survival rate was defined as the percentage of patients who were alive at 5 years. Nonparametric variables of patients' characteristics, tumor characteristics, and treatment modalities were compared by using Chi-square test; Student t-test and analysis of variance (ANOVA) were used for continuous variables such as patients' age and radiation dose. The overall survival durations were measured from the date of diagnosis till the death from any reason or the last follow-up. Kaplan-Meier was used to estimate survival of diagnosis till the death from any reason or the last follow-up. Kaplan-Meier was used to estimate survival. The log-rank test was used to compare treatment modalities and patients' outcomes were collected, as well. The preliminary evaluation included comprehensive history, physical examination, complete blood count (CBC), liver function tests (LFT), renal function tests (RFT), chest x ray, abdominal and pelvic CT-scans or sonography, and in case of bone pain, radionuclide bone scan.

According to the results of these evaluations, the patients whose diseases were confined to the primary site and/or regional nodes were classified as having limited disease, while the others were considered to have extensive disease (6).

3.2. Ethical Consideration

All obtained data were kept confidential and used after taking the formal consent.

4. Results

4.1. Patients' Characteristics

Out of 4163 patients with esophageal malignancies through a period of 12 years, 24 patients (0.5%) were identified to have primary SCEC. Two of them who lost the follow up were excluded from the study. The patients' median age at the time of diagnosis was 61 years (range 43 - 88 years). There were 15 (68.2%) female and 7 (31.8%) male with a male to female ratio of 0.46. Dysphagia (21 cases, 95%) and weight loss (18 cases, 80%) were the most prevalent presenting symptoms with a mean duration of 6 months before diagnosis. According to Karnofsky score system, 12 patients (55%) showed performance status of 80 - 100. In addition, 5 patients (23%) obtained the score of 70 and 5 patients (23%) gained 60. Moreover, only 3 patients (14%) were smoker and none of them had the history of alcohol consumption.

4.2. Tumor Characteristics

The tumor characteristics have been summarized in Table 1. The tumors tended to involve the lower and middle third of the esophagus and to have larger size. Approximately two-thirds (13) of the patients had limited diseases, while the other 8 cases had extensive diseases. Among those with extensive diseases, liver, lung, and lymph node (LN) were the most metastatic sites. Furthermore, ulcerative tumors were the most prevalent endoscopic feature of the tumor and were reported in 10 patients. However, 7 cases had polypoid lesions and 5 had no specified lesions. In upper gastrointestinal (GI) series, 12 patients had only mucosal irregularity, while stenosis and filling defect were reported in 8 and 2 patients, respectively.

4.3. Pathological Features

In our study, the histological diagnosis of the patients was primarily based on hematoxylin and eosi-stained examination. All the patients' tumors had small round cells with hyperchromatic nuclei and scant cytoplasm with characteristic pattern of crush artifact in 5 patients. Immunohistochemical (IHC) examination to confirm SCEC was required only for 6 patients (27%). The IHC results of the patients are shown in Table 2.

4.4. Treatment

In this study, 21 patients received various treatment modalities and the remaining one did not have enough chance to receive any treatment. One patient received radiotherapy as a sole treatment modality. Twenty patients received chemotherapy either alone (6 cases, 27%) or in combination with radiotherapy (14 cases, 64%). CRT was given concurrently in 9 patients (41%) and sequentially in 5 ones (23%). Some patients received both concurrent CRT and chemotherapy. In addition, 7 patients (32%) underwent surgery, 1 received neoadjuvant CRT, and 2 received neoadjuvant chemotherapy. Concurrent CRT was also performed in 5 patients after the operation.

The combination regimen of cisplatin and etoposide was given to a group of 14 patients (63%). The other 6 patients (27%), on the other hand, received a combined regimen of cisplatin and fluorouracil (5-FU). The mean radiotherapy dose was 46 Gy (range 19 - 60 Gy).
4.5. Outcome

The median survival of the 22 patients was 11 months (95% CI, 5.25 - 16.75) (Figure 1). In addition, 1, 3, and 5-year overall survival rates were 27%, 14%, and 4%, respectively. In fact, one of our patients who did not receive any treatment survived for 1 month and 2 patients with long-term survival had received concurrent CRT without surgery. (3-6, 12). In other studies, as in ours, brain metastasis was not common. In this study, 2 patients developed second primary malignancy. One of them presented with headache, nausea, vomiting, and occipital mass in MRI 6 years after the diagnosis of SCEC. Biopsy showed metastatic adenocarcinoma with unknown origin. She received brain radiotherapy and died 2 months after the diagnosis. The primary esophageal pathology was reviewed and primary small cell tumor was reconfirmed. The other patient was a 61-year-old woman who presented with axillary lymphadenopathy due to invasive ductal carcinoma of breast. She underwent mastectomy, adjuvant chemotherapy, and radiotherapy and was well at the last follow up.

She underwent mastectomy, adjuvant chemotherapy, and radiotherapy and was well at the last follow up.

4.6. Prognostic Factors

The results of the present study revealed no association between the overall survival rate and age (≤ 61 years versus > 61 years, median survival 13 months versus 7 months, P = 0.824), sex (female versus male, median survival 13 months versus 7 months, P = 0.385), performance status (≥ 70 versus < 70, median survival 14 months versus 4, P = 0.074), tumor stage (limited versus extensive, median survival 13 months versus 8 months, P = 0.198), size (< 4 cm versus ≥ 4 cm, median survival 14 months versus 7 months, P = 0.251), radiation dose (≥ 40 Gy versus < 40 Gy, median survival 14 months versus 8 months, P = 0.759), location (upper versus middle versus lower, median survival 2 months versus 14 months versus 11 months, P = 0.924), and treatment modality (surgical versus nonsurgical, median survival 13 months versus 5 months, P = 0.243).

Table 1. Tumor Characteristics

| Variables                     | No. (%) |
|-------------------------------|---------|
| Age (Median 61 years)         |         |
| < 61                          | 10 (45) |
| ≤ 61                          | 12 (55) |
| Gender                        |         |
| Male                          | 7 (32)  |
| Female                        | 15 (68) |
| Location                      |         |
| Upper                         | 2 (9)   |
| Middle                        | 7 (32)  |
| Lower                         | 11 (50) |
| Unspecified                   | 2 (9)   |
| Size, cm (Mean)               |         |
| < 4                           | 9 (41)  |
| ≥ 4                           | 13 (59) |
| Stage                         |         |
| Limited                       | 14 (64) |
| Extensive                     | 8 (36)  |
| Metastatic Site a (n = 12)    |         |
| Liver                         | 5 (31)  |
| Lung                          | 4 (25)  |
| Distant lymph node            | 4 (25)  |
| Bone                          | 2 (13)  |
| Brain                         | 1 (6)   |
| Number of Metastatic site b a (n = 12) |       |
| 1                             | 9 (75)  |
| 2                             | 2 (17)  |
| 3                             | 1 (8)   |

a At the end of follow up.

Table 2. Immunohistochemical Results of 6 Patients a

| Patient | CK | LCA | NSE | Chromogranin | Synaptophysin |
|---------|----|-----|-----|--------------|---------------|
| 1       | +  | -   | NP  | +            | +             |
| 2       | -  | -   | +   | +            | NP            |
| 3       | +  | NP  | +   | +            | +             |
| 4       | +  | NP  | +   | +            | NP            |
| 5       | +  | -   | NP  | +            | +             |
| 6       | +  | NP  | NP  | NP           | NP            |

a Abbreviations: CK: Cytokeratin; LCA: Leucocyte antigen; NSE: Neuron specific enolase; NP: not performed.

Figure 1. Kaplan-Meier Survival Curve
5. Discussion

In this study, we reviewed and analyzed the clinico-pathological features and oncologic outcome of 22 cases with SCEC. Women in the sixth and seventh decades of life were more affected. According to our study results, SCEC tends to present at a locally advanced stage, with a high frequency of distant failure and has a poor outcome. In the literature, primary SCEC is an uncommon disease constituting less than 1% of esophageal malignancies (14). The prognosis is generally poor and most patients have metastasis at the time of diagnosis (15). Almost similarly, we found that at least 0.5% of our esophageal cancer patients had SCEC. Similar to the other histological subtypes of esophageal cancer, SCEC has been reported predominantly in males with a male to female ratio of 1:5.3 (3, 14, 15). However, almost in concordance with the more common occurrence of squamous cell carcinoma among the women in our local area (16), our study showed that women were more vulnerable to this subtype of esophageal cancer with a 2:1 female predominance ratio. Gender dominance is another matter of debate in this disease (13, 14). In addition, the patients' median age at the time of diagnosis was 61 years, which is almost concordant with other studies reporting the disease occurrence between the sixth and eighth decade of life (14, 15). Although it is not well defined yet, history of smoking and alcohol consumption seem to be related to SCEC (3, 14). In this study, most of the patients were nonsmokers and none of them consumed alcoholic beverages. Only 2 patients were smokers in our study. In general, most SCEC's are located in middle and lower parts of esophagus; however, this factor has no prognostic value (6, 17). We found no studies indicating a higher ratio of tumor in the upper part of the esophagus.

Due to the small number of cases and lack of randomized clinical trials, there is no consensus regarding the optimal treatment of SCEC. Several reports have used a variety of combination therapies, including surgery, chemotherapy, and radiotherapy (18-20). Casas et al. in a review of literature found that the type of treatment was one of the most important prognostic factors (19). Some researchers have suggested surgery to be an important part of the treatment; nevertheless, these conclusions have been drawn from small retrospective series (3, 21, 22). Most researchers believe that SCEC should be treated in the same way as small cell lung cancers (4, 22, 23). In a study which was conducted by Lu on 15 patients with superficial SCEC who underwent operation, the mean survival was 23 months and only 1 patient was alive at the time of report. The longer survival rates reported by Lu might be due to the fact that all patients had superficial diseases (23). Compared to esophageal superficial squamous cell carcinoma with the same stage, prognosis of SCEC was dismal (24). In superficial esophageal squamous cell carcinoma, 5-year survival rate can be more than 80%, while it was 6.7% in Lu et al. study. They administered adjuvant treatment for only 7 cases. Nonetheless, it may be a better idea not to deprive any patient from adjuvant treatments. On the other hand, it is noteworthy that the patient with prolonged survival (108 months) had not been treated by chemotherapy or radiotherapy after the operation (23). In our study, 7 patients underwent surgery with no improvement in the outcome compared to those who did not undergo resection.

Based on the probable similarities with small cell lung carcinoma, most reports have used platinum based chemotherapy. Unfortunately, the outcome is not satisfying yet. Nakajima et al. (7) reported 18 patients with SCEC and found no significant difference between the extensive and limited disease patients regarding survival. Survival in the patients with limited and extensive diseases was 17.3 and 13.9 months, respectively (P = 0.57). In that study, most of the patients had lower or middle part esophageal lesions. In addition, 10 patients were treated by both chemotherapy (cisplatin based) and radiotherapy and only 2 patients were alive after 54.2 and 76.2 months followup, respectively. Among the other patients who were treated by chemotherapy alone, 1 patient had 58.8 months survival, but developed liver metastasis. In that study, the main cause of death was metastasis and only 2 cases developed local recurrence (6). In our patients, all disease mortality was due to metastasis. Moreover, the longest survivals in our patients were related to two patients who received concurrent CRT.

Although it is generally believed that SCEC is a catastrophe for the patients, the results are controversial. Various studies have shown diverse ranges of survival in a small group of patients (5). In Chiu et al. study, 20% of the patients were alive for more than 40 months even after the local recurrence (5). Similar results have also been obtained in other studies (13). Ku et al. reported 25 patients from Memorial center, out of them 3 patients were alive for more than 3 years. Interestingly, one of the patients had local recurrence and was alive for 5.5 years (25). Kuo et al. also reported a 65-year-old man with 221 months survival. He was undergone operation followed by 2 cycles of etoposide and cisplatin chemotherapy (3).

Although SCEC's are usually treated in the same way as small cell lung carcinoma, brain metastasis is not so prevalent in esophageal cases (3, 7). In other studies, as in ours, brain metastasis was not common.

Regarding the strength of the study and to the best of our knowledge, this is the first report of SCEC from Iran. However, it must be noted that the small number of patients in this study imposed a limitation in statistical analysis as well as finding any association between the clinicopathological features and oncologic outcomes. IHC confirmation in less than one-third of cases was another limitation of the study. In conclusion, SCEC is a tumor with poor prognosis, which mostly affects females. CRT could be an appropriate alternative to surgical resection.
Acknowledgments

The authors are grateful to Ms. Keivanshekouh at the Research Improvement Center of Shiraz University of Medical Sciences for English editing of the manuscript.

Authors’ Contributions

Sare Hosseini and Roham Salek made substantial contributions to the conception, design, data collection, writing and revising the manuscript, as well as approval of the final revision. Hamid Nasrolahi, Mohammad Mohammadianpanah, and Mona Jundi made substantial contributions to data collection, writing and revising the manuscript, as well as approval of the final revision.

References

1. Terada T. Small cell neuroendocrine carcinoma of the esophagus: report of 6 cases with immunohistochemical and molecular genetic analysis of KIT and PDGFRα. Int J Clin Exp Pathol. 2013;6(3):485-91.
2. Khademi H, Kamangar F. Esophageal cancer incidence trends in northeastern Iran: comparing rates over 36 years. Arch Iran Med. 2012;15(4):194-5.
3. Kuo CH, Hsieh CC, Chan ML, Li AF, Huang MH, Hsu WH, et al. Small cell carcinoma of the esophagus: a report of 16 cases from a single institution and literature review. Ann Thorac Surg. 2011;91(2):373-8.
4. McKeown F. oat-cell carcinoma of the oesophagus. J Pathol Bacteriol. 1952;64(4):889-95.
5. Chin K, Baba S, Hosaka H, Ishiyama A, Mizunuma N, Shinozaki E, et al. Trinitotecan plus cisplatin for therapy of small-cell carcinoma of the esophagus: report of 12 cases from single institution experience. Jpn J Clin Oncol. 2008;38(6):426-31.
6. Hou X, Wei JC, Wu JX, Wang X, Fu JH, Lin P, et al. Multidisciplinary modalities achieve encouraging long-term survival in resectable limited-disease small cell carcinoma. PLoS One. 2013;8(7):e69259.
7. Nakajima Y, Zendra S, Minashi K, Yano T, Tahara M, Doi T, et al. Non-surgical approach to small cell carcinoma of the esophagus: does this rare disease have the same tumor behavior as SCLC? Int J Clin Oncol. 2012;17(6):806-5.
8. Wang SY, Mao WM, Du XL, Xu YP, Zhang SZ. The 2002 AJCC TNM classification is a better predictor of primary small cell esophageal carcinoma outcome than the VALS2 staging system. Chin J Cancer. 2013;32(6):542-52.
9. Dakhlil CS, Wick JA, Kumar AK, Satyan MT, Neupeane P. Extrapulmonary small cell carcinoma: The University of Kansas experience and review of literature. Med Oncol. 2014;31(10):387.
10. Medgyesy CD, Wolff RA, Putnam JJ, Ajani JA. Small cell carcinoma of the esophagus: the University of Texas M. D. Anderson Cancer Center experience and literature review. Cancer. 2000;88(2):262-7.
11. Yun JP, Zhang MF, Hou JH, Tian QH, Fu J, Liang XM, et al. Primary small cell carcinoma of the esophagus: clinicopathological and immunohistochemical features of 21 cases. BMC Cancer. 2007;7:38.
12. Osugi H, Takemura M, Morimura K, Kaneko M, Higashino M, Takada N, et al. Clinicopathologic and immunohistochemical features of surgically resected small cell carcinoma of the esophagus. Oncol Rep. 2002;9(6):1245-9.
13. Hudson E, Powell J, Mukherjee S, Crosby TD, Brewster AE, Maughan TS, et al. Small cell oesophageal carcinoma: an institutional experience and review of the literature. Br J Cancer. 2007;96(5):708-11.
14. Vos R, Rozema T, Miller RC, Hendlitz A, Van Laethem JL, Khanfir K, et al. Small cell carcinoma of the esophagus: a multicentre Rare Cancer Network study. Dis Esophagus. 2012;25(4):556-64.
15. Chen WW, Wang F, Chen S, Wang L, Ren C, Luo HY, et al. Detailed analysis of prognostic factors in primary esophageal small cell carcinoma. Ann Thorac Surg. 2014;97(3):937-81.
16. Salek R, Bezenjani SE, Saedi HS, Ashikli MH, Hosainzade SM, Mohtashami S, et al. A geographic area with better outcome of esophageal carcinoma: is there an effect of ethnicity and etiology factors? Oncology. 2009;77(3-4):372-7.
17. Chen SB, Yang JS, Yang WP, Weng HR, Li H, Liu DT, et al. Treatment and prognosis of limited disease primary small cell carcinoma of esophagus. Dis Esophagus. 2011;24(2):184-9.
18. Lu XJ, Luo JD, Ling Y, Kong YF, Feng LL, Zhou J, et al. Management of small cell carcinoma of esophagus in China. J Gastrointest Surg. 2013;17(7):1381-7.
19. Casas F, Ferrer F, Farrus B, Casals J, Biete A. Primary small cell carcinoma of the esophagus: a review of the literature with emphasis on therapy and prognosis. Cancer. 1997;80(4):1366-72.
20. Kudoh K, Doi K, Ogata K, Hirano Y, Ohchi T. [A case of small cell carcinoma of esophagus treated by chemotherapy with CDDP plus CPT-11 and radiotherapy]. Gan To Gakkai Rocho. 2010;17(12):2403-5.
21. Tanaka T, Matono S, Nagano T, Nishimura K, Murata K, Yamana H, et al. Surgical management for small cell carcinoma of the esophagus. Dis Esophagus. 2007;20(5):502-5.
22. Zhang BH, Yang WJ, Zhao L, He J, Wang YG, Zhang HT. [Surgical treatment and prognostic analysis of 109 patients with primary esophageal small cell carcinoma]. Zhonghua Zheng Li Za Zhi. 2012;34(9):958-702.
23. Lu J, Xue LX, Lu N, Zou SM, Liu XY, Wen P. Superificial primary small cell carcinoma of the esophagus: clinicopathological and immunohistochemical analysis of 15 cases. Dis Esophagus. 2010;23(2):453-9.
24. Zhu Y, Qiu B, Liu H, Li Q, Xiao W, Hu Y, et al. Primary small cell carcinoma of the esophagus: review of 64 cases from a single institution. Dis Esophagus. 2014;27(2):532-8.
25. Ku GY, Minsky BD, Rutsch JW, Rains M, Kelsen DP, Elson DH. Small-cell carcinoma of the esophagus and gastroesophageal junction: review of the Memorial Sloan-Kettering experience. Ann Oncol. 2008;19(3):533-7.