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REVIEW ARTICLE

EXTRAPULMONARY SMALL CELL CARCINOMA: CURRENT STATUS AND STRATEGY

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ABSTRACT

Extrapulmonary small cell carcinoma is very rare. Its prognosis is poor and there is no established treatment modality. It has been considered as a distinct clinicopathological entity. It is distinct from small cell carcinoma of the lung, though it shares similar clinicopathologic features to the latter. It has a similar staging and treatment modality. The aim is to review existing studies and provide new results on diagnosis and current management strategy for patients with Extrapulmonary small cell carcinoma. The study involves the review of the literature using the electronic database MEDLINE and hand searching of journals. The outcome measures are addressed and analyzed. Studies have shown wide variations of treatment modalities adopted and the outcome observed. Almost all studies are of inadequate power to establish standard treatment modality. Multi-centre studies are required to institutionalize standard treatment modality.

Key words: *ESC (Extrapulmonary small cell carcinoma), PCI (prophylactic cranial irradiation), SCC (small cell carcinoma).*

INTRODUCTION

Extrapulmonary small cell carcinoma (ESC) may occur in many sites. It is rare. Its prognosis is poor and there is no established treatment. It has been considered as a distinct clinicopathological entity from small cell carcinoma (SCC) of the lung. It has a similar staging and treatment modality. The aim of the current study is to report the clinical features, management and natural courses of the cases with ESC. Few data are available on ESC in literature.

DISCUSSION

Undifferentiated small cell carcinoma (SCC) is an aggressive lung tumour accounting for 15% of all lung cancers. [1] Extrapulmonary small cell carcinomas (ESCs) are uncommon malignant neoplasms with a reported incidence of 0.1 to 0.4% of all cancers.[2] ESC was first described in 1930 in mediastinal glands.[4] Approximately 2.5% of all SCC's arise in extrapulmonary sites[2] including large bowel,[5] kidney,[6] bladder,[7] breast, [8,9] esophagus [10,11] stomach,[12] urethra,[13] uterine neck,[14] appendix,[15] liver,[16] common bile duct,[17] gall bladder,[18] mediastinum,[19] and even in unusual sites including submandibular gland,[20] bone[21] and pancreas.[22] Age and sex distribution for ESC are similar to that seen in adenocarcinoma of the colon.[3]

The morphologic, immunohistochemical and ultrastructure are similar to those described in pulmonary small cell carcinoma (PSCC).The differential diagnosis includes PSCC, small blue

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cell tumors, metastatic melanoma, lymphoma and poorly differentiated non-small cell carcinomas.[23] Monoclonal antibody 123C3 might be useful for immunohistochemical differentiation of small cell carcinomas from non-neuroendocrine carcinomas on paraffin sections. [24] In contrast to the loss of one of the short arms in small cell carcinoma, retention of both short arms of chromosome 3 is observed in four patients with ESC. [25]

Small cell lung carcinoma is thought to originate from neuroendocrine cells which are found in the epithelium of many mucosal surfaces including the gastrointestinal tract (Demellawy DE et al.). In spite of the evidence of neuroendocrine involvement, origin of ESC is still unclear as it may develop from undifferentiated airway epithelium along with the amine precursor uptake and decarboxylation (APUD) system hypothesis which proposes a common ancestral cell derived from the neural crest.[26] Histopathological diagnosis can be made by its classic appearance of small round to oval shaped cells with a finely granular and hyperchromatic nucleus, inconspicuous nucleoli and scanty cytoplasm on light microscopy. [27] The percentages of SCC samples with positive immunoreactivity were synaptophysin (Syn) 95.2%, neuronal cell adhesion molecules (CD56) 76.2%, thyroid transcriptional factor-1 (TTF-1) 71.4%, neuron specific enolase (NSE) 61.9%, chromogranin A (CgA) 61.9%, cytokeratin (CK) 57.1%, epithelial membrane antigen (EMA) 61.9%, and S100 protein (S100) 19.0%, respectively. [10] SCC can show a strong and diffuse immunoreactivity for CD56 and 80% positivity for TTF-1 tumour markers.[24,28] Histological diagnosis is based in all cases of ESC according to WHO criteria[29] for small cell carcinoma. Similar staging approach is applied to that used in SCLC as proposed by the Veterans' Administration Lung Group; limited disease (LD) is a tumour mass can be encompassed within a tolerable radiation therapy port with or without regional lymph node involvement, and extensive disease (ED) includes rest of the cases. [30]

The role of chemotherapy[31] in SCLC is well established (Agra et al, 2005). Evidence suggests that extrapulmonary small cell carcinoma [32] is also a chemosensitive disease (Levenson et al., 1981).The standard cisplatin, etoposide (PE) regimen for patients with ED-SCLC is etoposide 80mg/m2,cisplatin 20 mg /m2 and all are given intravenously on days 1 to 3 for every three weeks for 3 to 6 cycles. Topotecan (0.75mg/m2) combined with standard PE regimen for patients with ED-SCLC was failed to provide any benefit in terms of response and survival in patients of this group. [33] The clinical benefit of second-line therapy for relapsed small cell lung carcinoma is also limited. [34] However, a long survival time is observed by using combination chemotherapy with tegafur/ gimeracil/oteracil potassium + cisplatin and irinotecan hydrochloride + cisplatin after gastrectomy. [12]

Among 24 ESC cases studied in their single institution and the median overall survival (OS) of 9.2 months is observed when 16 patients with LD were treated with varieties of treatment modalities and patients with ED received partly platinum based chemotherapy for which the response rate was 57% with LD- SCC of cervix showed a favourable clinical course. [35]

Similarly, 25 of 34 ESC patients treated with surgery, followed by chemotherapy or radiotherapy showed tumour recurrence and/or systemic metastasis and they also demonstrated stage (LD vs ED) was a significant factor for overall survival. [39]

Most institutional series report a poor outcome with surgery alone. A total of 65 small cell oesophageal cancer (SCOC) cases who had undergone surgery in combination with chemotherapy and/or radiation

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therapy, a 1, 3 and 5 –year survival rates of patients in stage one and two are 76%, 30% and 18%; in contrast to 30%, 0% and 0% in patients with stage three and four. [36] The largest retrospective analysis has been carried out by Brenner B et al, [37] who evaluated data on 544 cases of gastrointestinal(GI) small cell carcinoma represented 0.1% to 1% of all GI malignancies. They suggested chemotherapy can achieve significant palliation, surgery may have a potential impact on long term survival of patients with locoregional disease. Four LD-SCOC patients treated at the MD Anderson Cancer Center with chemotherapy followed by radiotherapy and/ or oesophagectomy. One patient remains alive and disease-free, 57 months after diagnosis. [38]

The median overall survival of 17 months is reported when 18 LD-ESC patients treated with three dimensional conformal radiotherapy or intensity modulation radiation therapy and chemotherapy. No patient received prophylactic cranial irradiation (PCI). Median dose given was 62 Gy (range 23-85 Gy) with combined chemotherapy of platinum and etoposide in 88% of patients. 2(11%) patients had locoregional failure; and 14 of 18 (78%) had a distant failure. [40] The study of 101 patients with ESC in a Canadian province found that the patients with LD had a median overall survival of 34 months compared with 2 months in patients with ED-ESC. Patients with gynaecologic small cell cancer had a median survival of 54.4 months. [41]

The recent study on prophylactic cranial irradiation (PCI) seems to reduce the incidence of symptomatic brain metastases and can prolong disease-free and overall survival. They used PCI of 20 to 39 Gy in 8 to 12 fractions in all patients with small-cell lung cancer who have a response to chemotherapy. ESC is most likely to benefit in the similar way that small-cell lung cancer does. However, the role of PCI is unanswered question for extrapulmonary neuroendocrine tumors or other neuroendocrine tumors of the lung. [42]

Some authors studied 90 ESC- patients treated in their institution between 1995 and 2005; female gender, limited stage disease and combined modality treatment have been found as favourable prognostic factors in multivariate analysis. [43]

CONCLUSION

Studies have shown wide variations on treatment modality adopted and the outcome observed. Almost all studies were of inadequate power to establish standard treatment modality. The role of radiotherapy and surgical intervention remain limited, with surgery often only being used for the treatment of localized disease. It does seem that platinum based combination chemotherapy and radiotherapy might be effective to provide local control. The role of PCI can be considered in individual basis. For cases with metastases, palliative chemotherapy with radiotherapy can be applied. The response to various treatment modalities and the median survival time observed are discouraging.

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