MedPeer Publishers
Empowering Evidence-Based Medicine Through Peer-Reviewed Excellence

Open Access Original Research Article

MedPeer Publisher
Abbreviated Key Title: MedPeer
ISSN : 3066-2737
homepage: https://www.medpeerpublishers.com

Primary esophageal small-cell neuroendocrine carcinoma managed with induction chemotherapy followed by definitive chemoradiotherapy in an elderly patient: A case report

DOI: 10.70780/medpeer.000QGUM

AUTHOR AND AFFILIATION

Salma Ichou[1, 2,3], Imane Hassnaoui[1, 2,3], Amine Lachgar[1, 2,3], Karima Nouni[1, 2,3], Hanan ElKacemi[1, 2,3], Tayeb Kebdani[1, 2,3], Khalid Hassouni[1, 2,3]

[1.] Department of Radiation Therapy, National Institute of Oncology, Rabat, Morocco
[2.] Faculty of Medicine and Pharmacy of Rabat, Morocco
[3.] University Mohammed V, Rabat, Morocco

Corresponding author: Dr Salma Ichou

ABSTRACT

Background: Primary small-cell neuroendocrine carcinoma of the esophagus is a rare and aggressive malignancy, accounting for less than 3% of esophageal cancers. Its biological behavior resembles that of small-cell lung cancer, with rapid growth, early lymphatic spread, and a poor prognosis. No standardized treatment exists, and management in elderly patients is particularly challenging given the balance between disease control and treatment-related toxicity.

Case Presentation: An 85-year-old man with a history of hypertension and chronic tobacco exposure presented with progressive dysphagia, vomiting, and a 9-kg weight loss over one month. Endoscopy revealed a circumferential ulcerated and budding lesion of the thoracic esophagus. Histopathology and immunohistochemistry confirmed primary small-cell neuroendocrine carcinoma (synaptophysin- and CD56-positive, Ki-67 approaching 100%). Staging with computed tomography and ^{18}F-FDG PET/CT showed locally advanced, nonmetastatic disease (cT3N1M0, clinical stage III). Given the patient's preserved performance status despite advanced age, he received three cycles of induction carboplatin–etoposide chemotherapy followed by definitive concurrent chemoradiotherapy (50.4 Gy in 28 fractions with concurrent platinum–etoposide). Treatment was overall well tolerated, although the patient required a two-week hospitalization for management of dysphagia to liquids and odynophagia. At one year of follow-up, disease control remained favorable.

Conclusion: This case illustrates that individualized, multimodal treatment combining induction chemotherapy and definitive chemoradiotherapy can be safely delivered and achieve favorable outcomes in a very elderly patient with locally advanced esophageal small-cell neuroendocrine carcinoma, provided that performance status and patient preferences are carefully considered.

KEYWORDS

Case report; Chemoradiotherapy; Elderly; Esophageal neoplasms; Induction chemotherapy; Neuroendocrine carcinoma; Small-cell carcinoma

MAIN ARTICLE

INTRODUCTION:

Primary small-cell neuroendocrine carcinoma of the esophagus is a rare histological subtype, accounting for less than 3% of all esophageal malignancies in most published series [1–3]. It occurs predominantly in men and most commonly involves the middle or distal thoracic esophagus [2–4]. Despite its extrapulmonary location, its biological behavior resembles that of small-cell lung cancer, with rapid tumor growth, early lymphatic involvement, frequent hematogenous dissemination, and a generally unfavorable prognosis [1,2,4].

The clinical presentation is usually nonspecific and does not differ substantially from that of conventional esophageal carcinoma. Progressive dysphagia, weight loss, retrosternal discomfort, vomiting, and reduced oral intake are the most frequently reported manifestations [1–4]. The diagnosis is based on the combination of characteristic small-cell morphology and immunohistochemical evidence of epithelial and neuroendocrine differentiation. Synaptophysin, CD56, and chromogranin A are commonly expressed, while the Ki-67 proliferation index is generally very high, reflecting the marked proliferative activity of these tumors [3].

Because of the rarity of this malignancy, no universally accepted therapeutic standard has been established. Available treatment strategies are mainly derived from retrospective studies and are frequently extrapolated from the management of small-cell lung cancer. Platinum-based chemotherapy combined with etoposide represents the most commonly used systemic regimen, while surgery or radiotherapy may be incorporated for locoregional control in patients with limited-stage disease [5,6].

Several retrospective studies have suggested that definitive chemoradiotherapy may provide meaningful locoregional control and prolonged survival in selected patients with locally advanced nonmetastatic disease [7–10]. However, therapeutic decisions should remain individualized according to tumor stage, resectability, performance status, comorbidities, nutritional condition, and patient preference.

We report the case of an 85-year-old man with a locally advanced primary small-cell neuroendocrine carcinoma of the thoracic esophagus treated with induction carboplatin–etoposide chemotherapy followed by definitive concurrent chemoradiotherapy. This report was prepared in accordance with the CARE recommendations for clinical case reports.

CASE PRESENTATION:

An 85-year-old man with a history of controlled hypertension and chronic tobacco exposure of approximately 25 pack-years presented with progressive solid-food dysphagia, vomiting, deterioration of general condition, and an unintentional weight loss of 9 kg over one month. Upper gastrointestinal endoscopy demonstrated a circumferential ulcerated and budding lesion involving the thoracic esophagus between 29 and 38 cm from the dental arch. (Figure 1).

Thoracoabdominopelvic computed tomography revealed a circumferential esophageal mass extending from D4 to D9, measuring approximately 104.5 mm in craniocaudal length and 22.4 mm in maximal thickness, associated with paraesophageal lymphadenopathy. ^{18}F-FDG PET/CT showed no evidence of distant metastatic disease and brain imaging was negative.

An initial endoscopic biopsy yielded only a scant and crushed malignant proliferation, which was insufficient for definitive histological and immunohistochemical characterization. A repeat endoscopy with additional deeper sampling was therefore performed. Histopathological examination of repeated esophageal biopsies showed a poorly differentiated malignant proliferation composed of small cells with scant cytoplasm and hyperchromatic nuclei. Immunohistochemistry demonstrated positivity for synaptophysin and CD56, focal epithelial cytokeratin expression, and weak focal chromogranin A staining. P40 and thyroid transcription factor-1 were negative, while the Ki-67 proliferation index approached 100%. These findings supported the diagnosis of primary small-cell neuroendocrine carcinoma of the esophagus. The disease was classified as cT3N1M0, stage III according to the eighth edition of the TNM classification.

Considering the locally advanced nonmetastatic presentation and the patient's preserved performance status, systemic treatment was initiated with three cycles of carboplatin plus etoposide. The patient was subsequently referred for definitive concurrent chemoradiotherapy. Treatment was delivered using volumetric modulated arc therapy

(VMAT). The gross tumor volume of the primary esophageal lesion (GTV-T) and the gross nodal volume (GTV-N) were both delineated on the post-induction chemotherapy volumes, based on the residual tumor and nodal extent observed after the three cycles of carboplatin–etoposide. Radiotherapy delivered a prescribed dose of 50.4 Gy in 28 daily fractions of 1.8 Gy to the primary tumor and involved regional lymphatic areas, with concurrent platinum–etoposide chemotherapy. (Figure 2)

Given the significant pretreatment weight loss and dysphagia, prophylactic feeding gastrostomy was discussed with the patient to support nutritional status during treatment; however, the patient declined this intervention, and this decision was respected in accordance with his autonomy and preferences.

At one year follow-up, the patient remained under regular oncological surveillance with good disease control. Treatment was overall well tolerated, although the patient required a two-week hospitalization during chemoradiotherapy for management of dysphagia to liquids and odynophagia.

DISCUSSION:

Primary small-cell neuroendocrine carcinoma of the esophagus represents an exceptionally uncommon and aggressive malignancy. Its natural history is characterized by rapid progression, early lymph-node involvement, and a high risk of distant metastasis, even when the disease initially appears confined to the esophagus and regional lymph nodes [1,2,4]. These biological characteristics explain the poor outcomes historically reported with local treatment alone and support the early incorporation of systemic chemotherapy [1,5].

The diagnosis may be particularly challenging when it relies on small endoscopic biopsies. Small-cell carcinomas are frequently associated with extensive necrosis and crush artifact, which may compromise morphological interpretation and limit the amount of tissue available for immunohistochemical analysis [3]. In our patient, the initial biopsy showed only an exiguous and crushed malignant proliferation, making repeat endoscopy and additional sampling necessary before a definitive diagnosis could be established.

Histologically, these tumors are composed of relatively uniform small cells with scant cytoplasm, a high nuclear-to-cytoplasmic ratio, hyperchromatic nuclei, inconspicuous

nucleoli, and frequent mitotic activity. Immunohistochemical confirmation relies on the expression of epithelial markers, such as pancytokeratin, together with neuroendocrine markers including synaptophysin, CD56, and chromogranin A [3]. In the present case, diffuse synaptophysin expression, CD56 positivity, weak focal chromogranin A staining, focal pancytokeratin expression, and a Ki-67 proliferation index approaching 100% supported the diagnosis of a poorly differentiated small-cell neuroendocrine carcinoma.

The main differential diagnosis was secondary esophageal involvement by a pulmonary small-cell carcinoma. The absence of a suspicious pulmonary primary lesion on thoracic imaging, together with the presence of a dominant circumferential esophageal tumor documented histologically on repeated esophageal biopsies, favored a primary esophageal origin. Although TTF-1 was negative in our patient, this finding cannot independently establish the primary site, because TTF-1 expression is neither uniformly present in pulmonary small-cell carcinoma nor completely absent in extrapulmonary small-cell carcinoma [11]. In addition, negativity for p40, a marker of squamous differentiation, argued against a poorly differentiated squamous cell carcinoma and further supported the diagnosis of small-cell neuroendocrine carcinoma.

No standardized therapeutic algorithm has been established for primary esophageal small-cell carcinoma. Nevertheless, chemotherapy is considered a central component of treatment because of the high probability of occult micrometastatic disease at diagnosis. Etoposide combined with either cisplatin or carboplatin is the most frequently used regimen, largely based on its established activity in small-cell lung cancer and on retrospective experience in esophageal small-cell carcinoma [5].

For limited-stage disease, chemotherapy is generally combined with a local treatment. Surgery may be considered in carefully selected patients with early-stage and technically resectable tumors. However, its role in locally advanced or node-positive disease remains controversial because esophagectomy is associated with substantial morbidity and does not address the high risk of systemic relapse [6,9]. Retrospective studies have not consistently demonstrated the superiority of a surgical strategy over chemoradiotherapy for limited-stage disease [6,9].

Definitive chemoradiotherapy constitutes an important organ-preserving alternative for patients with locally advanced disease, medically inoperable tumors, or an unfavorable

surgical risk. Honma et al. reported encouraging outcomes in patients with locally advanced esophageal neuroendocrine carcinoma treated with definitive chemoradiotherapy, including a high clinical response rate and prolonged survival in a proportion of patients [7]. Other retrospective studies have similarly supported the contribution of radiotherapy to locoregional control and survival, particularly when combined with systemic chemotherapy [8–10].

In the present case, the tumor extended over approximately 10 cm of the thoracic esophagus and was associated with regional paraesophageal lymphadenopathy. The advanced local stage, the patient's age, and the expected morbidity of esophagectomy favored a nonsurgical strategy. Nevertheless, chronological age was not considered an absolute contraindication to curative-intent therapy because the patient had a preserved performance status, controlled hypertension, and no major organ dysfunction.

The patient initially received three cycles of carboplatin plus etoposide. In this context, the term induction chemotherapy is more appropriate than neoadjuvant chemotherapy because surgery was not planned. Carboplatin was selected instead of cisplatin during induction to reduce the risks of nephrotoxicity, severe nausea, electrolyte disturbances, and excessive treatment-related morbidity in this very elderly patient.

Following systemic chemotherapy, definitive concurrent chemoradiotherapy was initiated. A total dose of 50.4 Gy in 28 fractions of 1.8 Gy was prescribed to the primary tumor and involved regional lymphatic areas. Published radiotherapy schedules for esophageal small-cell carcinoma remain heterogeneous, with doses generally ranging from approximately 45 to 60 Gy according to treatment intent, tumor extension, institutional practice, and concurrent systemic therapy [7–10]. Notably, the same treatment strategy used in the present case — induction platinum-etoposide chemotherapy followed by definitive chemoradiotherapy to 50.4 Gy in 28 fractions — has been reported in a small Japanese series of resectable esophageal small-cell neuroendocrine carcinoma, in which all seven patients completed treatment with a 100% complete response rate and a median survival of 32 months [12].

The use of a sequential induction phase followed by concurrent chemoradiotherapy offered several potential advantages in this patient. It allowed early treatment of possible occult systemic disease, provided an opportunity to assess chemotherapy tolerance, and potentially reduced tumor volume before definitive irradiation. However, no prospective randomized study has established the optimal sequencing of chemotherapy and radiotherapy in this rare

disease, and this approach should therefore be presented as an individualized multidisciplinary decision rather than a validated standard of care [5,6,9].

Particular attention was given to nutritional management because the patient presented with dysphagia, vomiting, and a 9-kg weight loss before treatment. Nutritional deterioration may compromise tolerance to chemotherapy and thoracic radiotherapy and may increase the risk of treatment interruption. A prophylactic feeding gastrostomy was therefore discussed to maintain adequate nutritional intake during definitive treatment; however, the patient declined this intervention. This decision was respected in accordance with the patient's autonomy and preferences, underscoring the importance of shared decision-making in the management of elderly patients, even when a medically reasonable intervention is proposed.

The principal strength of this report is the description of an uncommon malignancy treated with a multimodal, curative-intent strategy in a patient aged 85 years. It illustrates that treatment decisions in older patients should not be based on chronological age alone but should integrate functional status, comorbidity burden, nutritional reserve, organ function, anticipated toxicity, and the patient’s preferences.

Several limitations must nevertheless be acknowledged. First, the diagnosis was established on limited endoscopic biopsy material without confirmation from a surgical specimen. Second, the treatment strategy was extrapolated from retrospective evidence and from small-cell lung cancer management because prospective trials specific to esophageal small-cell carcinoma are lacking. Finally, the definitive oncological outcome cannot be established until objective post-treatment assessment and sufficient follow-up have been documented.

CONCLUSION:

Primary small-cell neuroendocrine carcinoma of the esophagus is a rare and highly aggressive malignancy requiring accurate pathological characterization and multidisciplinary management. The diagnosis should be based on the integration of endoscopic findings, imaging, small-cell morphology, and immunohistochemical evidence of neuroendocrine differentiation.

For locally advanced nonmetastatic disease, platinum–etoposide chemotherapy combined with definitive radiotherapy represents a rational organ-preserving strategy, particularly when

esophagectomy is not appropriate. This case suggests that induction chemotherapy followed by concurrent chemoradiotherapy may be feasible in a carefully selected very elderly patient with preserved functional status. Nevertheless, objective response assessment and adequate follow-up are required before concluding that treatment was successful.

FIGURES :

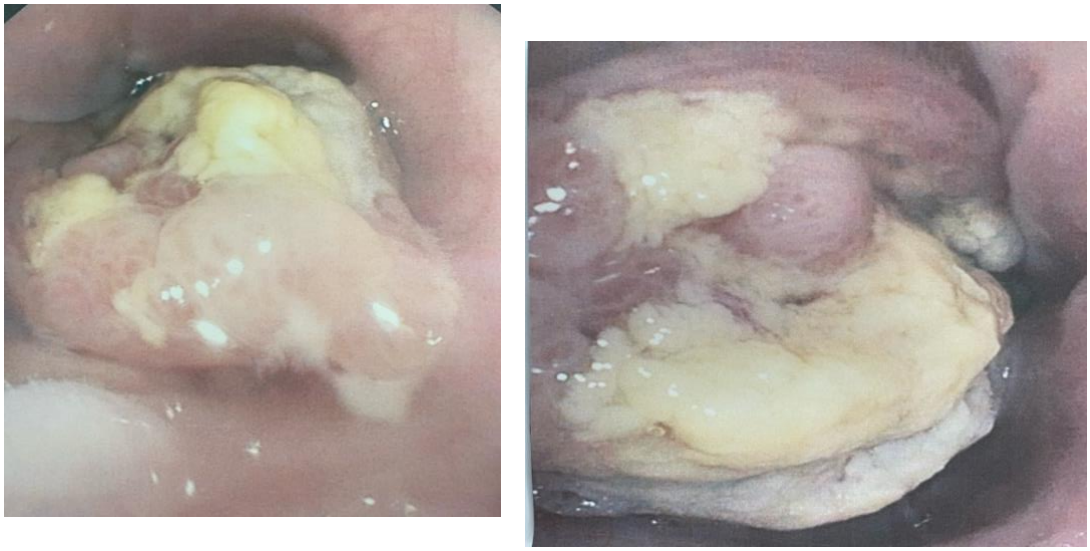

Figure 1. Upper gastrointestinal endoscopy showing a circumferential, ulcerated, and budding lesion of the thoracic esophagus, extending from 29 to 38 cm from the dental arch. (A, B) Endoscopic views at different levels of the tumor.

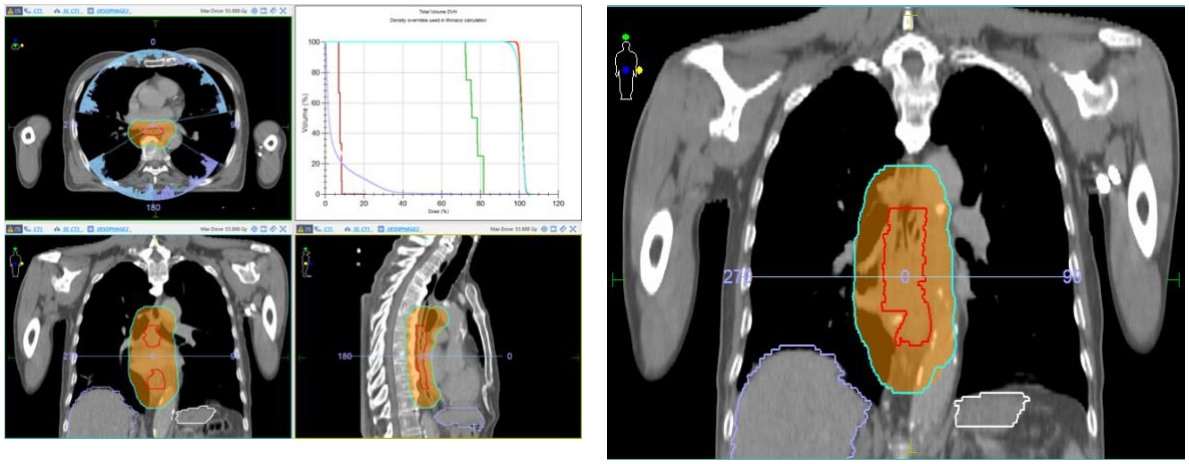

Figure 2. Radiotherapy treatment planning using volumetric modulated arc therapy (VMAT).

ACKNOWLEDGEMENTS

The authors have no acknowledgements to declare and report no conflicts of interest.

REFERENCES

1. Medgyesy CD, Wolff RA, Putnam JB Jr, 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):262-267.
https://doi.org/10.1002/(SICI)1097-0142(20000115)88:2<262::AID-CNCR3>3.0.CO;2-K

2. Ku GY, Minsky BD, Rusch VW, Bains M, Kelsen DP, Ilson DH. Small-cell carcinoma of the esophagus and gastroesophageal junction: review of the Memorial Sloan-Kettering experience. Ann Oncol. 2008;19(3):533-537. doi:10.1093/annonc/mdm476.
https://doi.org/10.1093/annonc/mdm476

3. Yun JP, Zhang MF, Hou JH, et al. Primary small cell carcinoma of the esophagus: clinicopathological and immunohistochemical features of 21 cases. BMC Cancer. 2007;7:38. doi:10.1186/1471-2407-7-38.
https://doi.org/10.1186/1471-2407-7-38

4. Xiao Q, Xiao H, Ouyang S, Tang J, Zhang B, Wang H. Primary small cell carcinoma of the esophagus: comparison between a Chinese cohort and Surveillance, Epidemiology, and End Results data. Cancer Med. 2019;8(3):1074-1085. doi:10.1002/cam4.2001.
https://doi.org/10.1002/cam4.2001

5. Gao R, Zhang Y, Wen XP, Fu J, Zhang GJ. Chemotherapy with cisplatin or carboplatin in combination with etoposide for small-cell esophageal cancer: a systemic analysis of case series. Dis Esophagus. 2014;27(8):764-769. doi:10.1111/dote.12149.
https://doi.org/10.1111/dote.12149

6. Xu L, Li Y, Liu X, et al. Treatment strategies and prognostic factors of limited-stage primary small cell carcinoma of the esophagus. J Thorac Oncol. 2017;12(12):1834-1844. doi:10.1016/j.jtho.2017.09.1966.
https://doi.org/10.1016/j.jtho.2017.09.1966

7. Honma Y, Nagashima K, Hirano H, et al. Clinical outcomes of locally advanced esophageal neuroendocrine carcinoma treated with chemoradiotherapy. Cancer Med. 2020;9(2):595-604. doi:10.1002/cam4.2708.
https://doi.org/10.1002/cam4.2708

8. Chen B, Yang H, Ma H, et al. Radiotherapy for small cell carcinoma of the esophagus: outcomes and prognostic factors from a retrospective study. Radiat Oncol. 2019;14:210. doi:10.1186/s13014-019-1415-9.
https://doi.org/10.1186/s13014-019-1415-9

9. Zhao K, Huang Z, Si Y, Sun L, Yu J, Meng X. Use of chemoradiotherapy as a treatment option for patients with limited-stage primary small cell carcinoma of the esophagus. Cancer Manag Res. 2021;13:613-623. doi:10.2147/CMAR.S278914.
https://doi.org/10.2147/CMAR.S278914

10. Yang H, Li Y, Ge H. The role of radiotherapy in small cell carcinoma of the esophagus: a retrospective study. Radiat Oncol. 2025;20:79. doi:10.1186/s13014-025-02662-3.
https://doi.org/10.1186/s13014-025-02662-3

11. Cheuk W, Kwan MY, Suster S, Chan JKC. Immunostaining for thyroid transcription factor 1 and cytokeratin 20 aids the distinction of small cell carcinoma from Merkel cell carcinoma, but not pulmonary from extrapulmonary small cell carcinomas. Arch Pathol Lab Med. 2001;125(2):228-231. doi:10.5858/2001-125-0228-IFTTFA.
https://doi.org/10.5858/2001-125-0228-IFTTFA

12. Katada C, Komori S, Yoshida T, et al. A retrospective study of definitive chemoradiotherapy in patients with resectable small cell neuroendocrine carcinoma of the esophagus. Esophagus. 2020;17(2):135-140. doi:10.1007/s10388-019-00686-9.
https://doi.org/10.1007/s10388-019-00686-9