Systematic review of case reports of Japanese esophageal neuroendocrine cell carcinoma in the Japanese literature

Yoshinori Kikuchi^{1,2} · Hideaki Shimada^{2,3} · Kazuhisa Yamaguchi¹ · Yoshinori Igarashi¹

Received: 25 December 2018 / Accepted: 17 January 2019 / Published online: 18 February 2019
© The Japan Society of Clinical Oncology 2019

Abstract

Esophageal neuroendocrine cell carcinoma (NEC) is extremely rare, and its treatment strategy has not been established. Systematic review and meta-analysis were carried out to assess the treatment and prognosis of patients with esophageal NEC in Japan. The Ichushi-Web database was searched from January 1964 to May 2018. In total, 141 cases of esophageal NEC were included in the analysis. The survival of the chemotherapy group with stage II/III esophageal NEC was better than that of the surgery group. Meanwhile, the survival of the adjuvant treatment group with stage II/III esophageal NEC was significantly better than that of the surgery alone group. In patients with stage IV esophageal NEC, no significant differences were observed in terms of treatment response from the three regimens: irinotecan/platinum and etoposide/platinum compared with 5-fluorouracil/platinum. Moreover, no significant differences were observed in the survival of patients who received the chemotherapy regimens. However, the 2-year survival rates of the irinotecan/platinum (26%) group and etoposide/platinum (27%) group were higher than that of the 5-fluorouracil/platinum (0%) group. In esophageal NEC, chemotherapy may be used as the first-line treatment. Irinotecan/platinum or etoposide/platinum can be the first-line regimen for chemotherapy. However, the additive effects of surgery remain unclear.

Keywords Esophageal neuroendocrine cell carcinoma · Surgery · Chemotherapy · Overall survival

Abbreviation

NEC Neuroendocrine cell carcinoma

Introduction

Esophageal neuroendocrine cell carcinoma (NEC) was first reported by McKeown [1]. In Japan, more than 90% of esophageal carcinomas are squamous cell carcinoma (SCC); thus, esophageal NEC only accounts for 0.3% of the cases [2]. The standard therapy for stage II/III esophageal SCC is neoadjuvant chemotherapy, followed by radical surgery.

Meanwhile, the standard regimen of neoadjuvant chemotherapy for esophageal SCC is 5-fluorouracil plus cisplatin (FP) [3].

Only few reviews on esophageal NEC have been reported [4–6], and they did not suggest a preferred treatment strategy. The Japanese treatment guideline for NEC [7] showed that the standard chemotherapy regimens for pancreatic and gastrointestinal NEC were irinotecan plus platinum (CP) or etoposide plus platinum (EP). However, neither the standard treatment nor the standard regimen of chemotherapy for esophageal NEC has been established.

Previously, we evaluated the treatment strategy for the several types of rare carcinomas via systematic review and meta-analysis of Japanese case reports in the Ichushi-Web database [8–11]. These articles were referred to practice. Therefore, we performed a systematic review and meta-analysis of Japanese case reports to evaluate the treatment strategy and chemotherapy regimens for esophageal NEC.

✉ Hideaki Shimada
hideaki.shimada@med.toho-u.ac.jp

¹ Division of Gastroenterology and Hepatology, Department of Internal Medicine (Omori), Toho University, Tokyo, Japan

² Department of Clinical Oncology, Toho University Graduate School of Medicine, Toho University, Tokyo, Japan

³ Department of Surgery, School of Medicine, Toho University, 6-11-1 Omori-nishi, Ota-ku, Tokyo 142-8541, Japan

Materials and methods

Materials

Between January 1964 and May 2018, we screened case reports in the Ichushi-Web database using the following key words: “esophageal small cell carcinoma” or “esophageal neuroendocrine cell carcinoma.” We identified a total of 170 cases from 140 Japanese case reports on esophageal NEC [12–151]. Among these reports, we excluded 6 patients with unverified age [12–17], 5 with indefinite staging [18–22], 1 with recurrence [96], 2 with unclear survival time [23, 24], 4 who underwent radiation alone without surgery [25–28], 1 who received the best supportive care [62], and 10 who underwent chemotherapy, excluding FP, CP, and EP in stage IV [29–36, 48] (Fig. 1). After excluding more than 29 cases, we analyzed 141 cases to assess for treatment options and chemotherapy regimens.

Statistical analysis

The Kaplan–Meier survival curves were obtained using the survival time from the start of treatment, as described in the reports. Differences in the survival time were evaluated using the log-rank test. Meanwhile, differences in the response rate were evaluated using the Mann–Whitney *U* test. Differences in the rate of second-line chemotherapy were evaluated using the Fisher’s exact probability test. All

statistical analyses were performed with StatMate V for Win&Mac Hybrid (ATMS Co., Ltd., Tokyo, Japan). *P* values < 0.05 were considered statistically significant.

Results

The median age of the 141 patients was 64 (range: 38–88) years. Of the patients, 111 were men and 30 were women. There were 21, 69, and 51 cases of stage I, II/III, and IV esophageal NEC, respectively. In total, 6, 68, and 67 cases were treated with endoscopic therapy, surgery ± adjuvant chemotherapy, and chemotherapy ± radiation, respectively (Table 1).

The median survival time (MST) of the patients with stage I and II/III esophageal NEC was 25 months. Meanwhile, the MST of patients with stage IV esophageal NEC was 13 months. No statistically significant difference was observed in the overall survival between patients with stage I and II/III esophageal NEC ($P = 0.854$). Although the difference was not statistically significant, patients with stage IV esophageal NEC showed a poorer survival than those with stage II/III esophageal NEC ($P = 0.053$). The 5-year survival rates of patients with stage I, II/III, and IV esophageal NEC were 34.1%, 35.8%, and 27.9%, respectively (Fig. 2).

The MST of the surgery alone, adjuvant, and neoadjuvant groups with stage I/II/III esophageal NEC were 9, 31, and 25 months, respectively (Fig. 3). The postoperative adjuvant group showed a significantly higher overall

Fig. 1 Study profile

Study Enrollment

Table 1 Baseline characteristics of the patients

	Number (<i>n</i> = 141)
Median age (years)	64 (38–88)
Gender	
Male	111
Female	30
Clinical stage	
I	21
Endoscopic therapy	6 (0)
Surgery alone	6 (0)
Surgery plus adjuvant therapy	7 (0)
Chemotherapy ± radiation	2 (1)
II/III	69
Surgery alone	10 (0)
Surgery plus adjuvant therapy	13 (1)
Surgery plus neoadjuvant therapy	18 (4)
Chemotherapy ± radiation	28 (12)
IV	51
Surgery alone	4 (0)
Surgery plus adjuvant therapy	6 (0)
Surgery plus neoadjuvant therapy	4 (0)
Chemotherapy ± radiation	37 (8)
Therapy	
Endoscopic therapy	6
Endoscopic submucosal dissection	5 (0)
Endoscopic submucosal dissection	1 (0)
Surgery	68
Surgery alone	20 (0)
Surgery plus adjuvant therapy	26 (1)
Surgery plus neoadjuvant therapy	22 (4)
Chemotherapy	67
5-Fluoropyrimidine plus platinum ± radiation	16 (11)
Irinotecan plus platinum ± radiation	31 (2)
Etoposide plus platinum ± radiation	20 (8)

(0): Cases of combination therapy with radiation

survival than the surgery alone group ($P = 0.002$). Similarly, the neoadjuvant group showed a significantly higher overall survival than the surgery alone group ($P = 0.018$). However, no significant difference was observed between the postoperative adjuvant and neoadjuvant groups ($P = 0.792$). Moreover, no significant difference was found between the chemotherapy ± radiation and neoadjuvant groups ($P = 0.895$) (Fig. 3).

The radiation combination rate was 57.1% (4/7) in the FP group, 4.7% (1/21) in the CP group, and 33.3% (3/9) in the EP group with stage IV esophageal NEC. The MST of the FP, CP, and EP groups were 13, 13, and 15 months, respectively (Fig. 4). No significant difference was observed in the survival rate of the CP, EP, and FP groups with stage IV esophageal NEC. However, the CP and EP groups showed a

higher 2-year survival rate than the FP group (0%, 26%, and 27%, respectively) (Fig. 4).

We summarized the efficacy of chemotherapy in patients with stage IV esophageal NEC (Fig. 5). The treatment responses of the FP group were as follows: CR, 4 cases; PR, 1 case; SD, 1 case; and unknown, 1 case. The treatment responses of the CP group were as follows: CR, 3 cases; PR, 15 cases; PD, 2 cases; and unknown, 1 case. The treatment responses of the EP group were as follows: CR, 3 cases; PR, 3 cases; and unknown, 3 cases (Fig. 5). We compared the response rates of the treatment groups. No significant difference was observed between the FP and CP groups ($P = 0.078$). Moreover, no significant difference was found between the FP and EP groups ($P = 0.855$). The CP and EP groups did not significantly differ ($P = 0.970$).

Then, we summarized the second-line chemotherapy (Fig. 6). In the first-line FP group, 2 of 6 patients were treated with chemotherapy as the second-line treatment. In the other three patients, two were treated with radiation and one did not receive any second-line treatment. In the CP group, 13 of 20 patients were treated with chemotherapy as second-line treatment. In the other 7 patients, 4 were treated with radiation and 2 underwent endoscopic treatment. In the EP group, 2 of 9 patients were treated with chemotherapy as second-line treatment. In the other 7 patients, 3 were treated with radiation and 4 did not receive any second-line treatment. Therefore, the rate of the second-line chemotherapy after FP was 50% (3/6). Meanwhile, the rates after CP and EP were 65% (13/20) and 22.2% (2/9), respectively. Thus, the first-line EP group less likely received second-line treatment than the first-line CP group ($P = 0.044$).

Discussion

We found 141 cases of esophageal NEC in the Ichushi-Web database. Based on the systematic review and meta-analysis of such database, chemotherapy may be used as the first-line treatment for individuals with stage I/II/III esophageal NEC. CP or EP therapy may be used as the first-line chemotherapy for stage IV esophageal NEC.

The 5-year survival rate of patients with stage I esophageal squamous cell carcinoma was 76.8% [3]. However, in the present study, the 5-year survival rate of patients with stage I esophageal NEC was as low as 34.1%. Therefore, patients with stage I esophageal NEC must be strictly followed up.

Neoadjuvant chemotherapy, followed by radical surgery, was a standard treatment for patients with stage II/III esophageal squamous cell carcinoma in Japan [3]. Similarly, according to our results, adjuvant chemotherapy may improve the survival of patients with stage I/II/III esophageal NEC. The best timing for adjuvant chemotherapy was not

Fig. 2 Overall survival curves according to each staging

Fig. 3 Overall survival curves of patients with stage I/II/III esophageal NEC according to each treatment

clearly presented in the current study. Moreover, the significance of surgery was not clear because there was no significant difference between the surgery plus neoadjuvant chemotherapy group and the chemotherapy ± radiation group.

Sugiura et al. have summarized several case reports between 1980 and 2002, and they have reported that the 5-year survival rate and MST were only 2% and 6 months in individuals with stage IV esophageal NEC [68]. Our present

data showed a significantly better prognosis than that in the report of Sugiura. Such discrepancy may be explained by the frequency of chemotherapy in patients with stage IV esophageal NEC. After 2003, 80% (33/41) of patients with stage IV esophageal NEC were treated with chemotherapy. The treatment response rate for CPT-11-based therapy for lung carcinoma was significantly higher in patients with extensive small cell carcinoma than those with non-small

Fig. 4 Overall survival curves of patients with stage IV esophageal NEC according to each treatment

Fig. 5 Overall response of patients with stage IV esophageal NEC according to each treatment

cell carcinoma (more than 60% versus 40%, respectively) [152–156]. Similarly, because esophageal NEC was also sensitive to CPT-11, the improvement of patients' survival might be reflected by the use of CPT-11.

Noda et al. have reported that patients who received CP showed a significantly higher survival than those who received EP for extensive small cell lung carcinoma [155].

Fig. 6 Number of second-line chemotherapy enforcements according to each treatment for individuals with stage IV esophageal NEC

After this report, CP was generally used for NEC of various types of carcinoma in Japan. However, EP therapy is often used in western countries because two reports have shown that there was no significant difference in the survival of individuals who received CP and EP for small cell lung

Fig. 7 Treatment algorithm model

carcinoma [156, 157]. Similarly, Yamaguchi et al. have also reported that the response rates of CP and EP were similar in patients with gastrointestinal NEC [158]. Thus, the first-line chemotherapy regimen for esophageal NEC should be determined in the future. One of the proposals on how to determine the first-line chemotherapy could be based on adverse events. Because Yamada et al. have reported that CPT-11 when combined with radiation therapy causes 28.3% of grade 2 or higher pneumonitis [159], CP therapy should not be used with radiation therapy. We proposed a treatment algorithm on how to select the first-line regimen in Fig. 7. EP + radiation therapy might be selected for cases where primary tumor needs radiotherapy. And CP therapy might be selected for cases where the primary tumor does not require radiotherapy.

Regarding the second-line chemotherapy regimen, topotecan or amrubicin is generally used as second-line treatment for lung NEC [160]. von Pawel et al. have reported that patients with refractory lung NEC who received amrubicin treatment had a statistically significant survival benefit than those who received topotecan [161]. However, the second-line regimen for esophageal NEC remains controversial.

The present study had a limitation. That is, the study was a meta-analysis based on case reports in the Ichushi-Web database. Therefore, the collected cases may have some selection biases. In particular, it could have included more good responders and/or long-time survivors. Thus, consecutive cases based on a large-scale multicenter study must be assessed.

In conclusion, chemotherapy should be the first-line treatment for esophageal NEC. Irinotecan/platinum or etoposide/platinum may be used as the first-line regimen. However, the additive effects of surgery remain unclear.

Compliance with ethical standards

Conflict of interest The authors have no conflicts of interest associated with this manuscript.

Ethical statement This article does not contain any studies with human participants or animals performed by any of the authors.

Ethical approval Ethical approval is not required because all data in this study uses Ichushi-Web database.

Informed consent Informed consent is not required because all data in this study uses Ichushi-Web database.

References

- McKeown F (1952) Oat cell carcinoma of the esophagus. *J Pathol Bacteriol* 64:889–891
- Chino O, Makuuchi H, Ozawa S et al (2017) Endoscopic diagnosis of the esophageal neuroendocrine cell carcinoma: its morphological and histopathological features and clinical problems. *Stomach Intest* 52:402–411. (in Japanese)
- Japan Esophageal Society (2014) Guidelines for diagnosis and treatment of carcinoma of the esophagus. Kanehara, Tokyo (Japanese)
- Tsutsumi F, Takeda FR, Uema RH et al (2017) Primary neuroendocrine neoplasm of the esophagus—report of 14 cases from a single institute and review of the literature. *Arq Gastroenterol* 54:4–10
- Deng H-Y, Ni P-Z, Wang Y-C et al (2016) Neuroendocrine carcinoma of the esophagus: clinical characteristics and prognostic evaluation of 49 cases with surgical resection. *J Thorac Dis* 8:1250–1256
- Hong L, Zhang Y, Liu Z (2018) Neuroendocrine carcinoma of esophageal and gastric cardia: clinicopathologic and immunohistochemistry study of 80 cases. *Oncotarget* 9:10754–10764
- Japan Esophageal Society (2015) Guidelines for Diagnosis and Treatment of Neuroendocrine cell carcinoma of the Pancreas and Gastrointestinal. Kanehara, Tokyo (Japanese)

8. Kikuchi Y, Matsuzaki M, Tokura N et al (2009) Gastric small-cell carcinoma: analysis of cases at Toho University and in Japan. *J Med Soc Toho* 56:421–428 (in Japanese)
9. Kikuchi Y, Matsuzaki M, Tokura N et al (2010) Disseminated carcinomatosis of the bone marrow due to gastric cancer: Analysis of cases at Toho University and in Japan. *J Med Soc Toho* 57:127–136 (in Japanese)
10. Kikuchi Y, Hirose M, Otsuka T et al (2011) Survival and effectiveness of chemotherapy in Japanese patients with gastric metastasis: a case series. *J Med Soc Toho* 58:35–49 (in Japanese)
11. Kikuchi Y, Kishimoto Y, Ito K et al (2012) Peritoneal malignant mesothelioma: analysis of cases at Toho University and in Japan. *J Med Soc Toho* 59:174–182 (in Japanese)
12. Takeuchi M, Kobayashi M, Ajioka Y et al (2009) Primary esophageal endocrine cell carcinoma of small cell type, which was 4 mm in size and pT1a-MM in invasion depth, report of a case. *Stomach Intest* 44:1759–1766 (in Japanese)
13. Oyama T, Takahashi A, Miyata Y et al (2017) A case of superficial esophageal neuroendocrine carcinoma treated by endoscopic submucosal dissection and chemo-radiotherapy. *Stomach Intest* 52:461–468 (in Japanese)
14. Yamano T, Takahashi T, Hondo M et al (2008) Advanced small cell esophageal carcinoma with liver metastasis having a long survival; a case report. *Nuclear Med Clinic* 41:18–20 (in Japanese)
15. Kishino T, Oyama T, Tomori A et al (2011) Esophageal endocrine cell carcinoma; report of a case. *Stomach Intest* 46:781–787 (in Japanese)
16. Nagao M, Okamoto T, Nishimura J et al (2014) A case of endocrine cell carcinoma with gastric adenocarcinoma successfully treated by chemotherapy. *Yamaguchi Med J* 63:61–67 (in Japanese)
17. Yokota M, Koike J, Sano M et al (2017) An elderly case of esophageal small cell carcinoma responding to chemoradiotherapy. *Progress Dig Endosc* 90:78–79 (in Japanese)
18. Takiyama W, Fujii M, Moriaki S (1988) Small cell carcinoma of the esophagus: report of a case treated with Chemotherapy. *Jpn J Surg* 18:330–335
19. Ogino M, Ogino Y, Sakai F et al (2005) A case of paraneoplastic neurological syndrome associated with small cell carcinoma of the esophagus with benign prognosis. *Peripheral Nerve* 16:130–133 (in Japanese)
20. Torii K, Kawabe J, Hayashi T et al (2004) A case of small cell carcinoma of the esophagus detected incidentally by FDG-PET. *Ann Nucl Med* 18:699–702
21. Watanabe K, Ogata S, Nagata M et al (2003) A case of primary esophageal small cell type undifferentiated carcinoma. *Stomach Intest* 38:1604–1607 (in Japanese)
22. Wada D, Nishikawa K, Iwase K et al (2009) A case report of esophageal small cell carcinoma with peritoneal dissemination which could be treated temporally by chemotherapy. *J Clin Surg* 64:1145–1150 (in Japanese)
23. Hosokawa O, Kaizaki Y, Tanigawa K et al (2000) Esophageal small cell carcinoma followed up with endoscopy for one year and six months, report of a case. *Stomach Intest* 35:573–578 (in Japanese)
24. Yamaguchi E, Ito M, Matsuzaki S et al (1995) A case of primary small cell carcinoma in the esophagus. *Nagasaki Med J* 70:1–4 (in Japanese)
25. Uno T, Itami J, Shiina T et al (1993) A primary small cell carcinoma of the esophagus—a case of an aged patient given palliative irradiation -. *Jpn J Cancer Clin* 39:1565–1568 (in Japanese)
26. Okamoto K, Kanai H, Okamoto K et al (1998) An autopsy case of subacute cerebellar degeneration with small cell carcinoma of the esophagus. *Clin Neurol* 28:793–796 (in Japanese)
27. Ohtsu A, Yoshida S, Boku N et al (1993) Small cell carcinoma of the esophagus with an esophago-mediastinal fistula successfully treated by chemoradiation therapy and Intubation: a case report. *Jpn J Clin Oncol* 23:373–377
28. Ichimonji I, Ishizuka T, Yonezu M et al (2000) Rapidly progressive clinical course in a patient with small cell carcinoma of the esophagus diagnosed with liver biopsy. *Jpn J Cancer Clin* 46:912–915 (in Japanese)
29. Uchiada N, Akazawa S, Tanaka Y et al (1991) A case report of small cell carcinoma of the esophagus treated by chemotherapy alone. *Jpn J Cancer Dig Organs* 1:105–110 (in Japanese)
30. Tanabe S, Imamura K, Tanabe Y et al (1989) A case of report of small cell carcinoma of the esophagus with bone marrow metastasis. *Progress Dig Endosc* 34:232–235 (in Japanese)
31. Saitoh S, Yoda M, Kimura T (1993) Primary small cell carcinoma (SCC) of the esophagus. *Med J Ushioda General Hosp* 8:17–27
32. Sairenji T, Fujii Y, Eriguchi M (2001) A case of esophagus small cell carcinoma responding to chemotherapy with CPT-11. *Jpn J Cancer Chemother* 28:1283–1286 (in Japanese)
33. Yamamoto M, Kamiya K, Tanaka T et al (2008) Long-surviving case of advanced esophageal small cell carcinoma with a multidisciplinary treatment approach. *Esophagus* 5:99–103
34. Takita M, Noutomi K, Suetsugu M et al (1987) A case of esophageal small cell carcinoma with miliary brain metastasis beginning with generalized convulsion. *Clin Psychiatry* 29:1341–1343 (in Japanese)
35. Shinohara Y, Takeno S, Takahashi Y et al (2014) Successful chemoradiotherapy for small-cell carcinoma of the esophagus in an octogenarian Japanese woman: report of the oldest case and review of long-term survival cases. *Ann Thorac Cardiovasc Surg* 20:237–242
36. Furukawa Y, Tanaka Y, Mafune K et al (1996) A case of primary esophageal small cell carcinoma. *J Saitama MS* 30:877–882 (in Japanese)
37. Kotake K, Yoneyama K, Miyata J et al (1985) Small cell carcinoma (Oat cell type) of the esophagus—report of a case. *J Jpn Soc Clin Surg* 46:1107–1113 (in Japanese)
38. Zeze K, Nakashima K, Iyota N et al (1986) Two cases of oat cell carcinoma of the esophagus. *J Jpn Soc Clin Surg* 47:1588–1594 (in Japanese)
39. Sugiyama A, Harada H, Kumaki T et al (1990) A case of oat cell carcinoma of the esophagus. *Endosc Forum Dig Dis* 6:32–37 (in Japanese)
40. Takagi K, Tashiro T, Mashima Y et al (1993) Endocrine cell carcinoma of the esophagus—report of a case. *J Jpn Soc Clin Surg* 54:946–950 (in Japanese)
41. Ozawa Y, Inagaki Y, Yonei Y et al (1993) Oat cell carcinoma of the esophagus: report of a case. *J Jpn Soc Cancer Ther* 28:929–935 (in Japanese)
42. Muto I, Nishimaki T, Aizawa K et al (1995) Primary small cell carcinoma of the esophagus: report of a case. *Surg Today* 25:830–833
43. Komada H, Kawaguchi Y, Nakagawa A et al (1996) A case report of small cell carcinoma of the esophagus treated with multidisciplinary treatment. *J Jpn Soc Clin Surg* 57:1120–1124 (in Japanese)
44. Kumegawa H, Tanaka T, Mori S et al (1996) A case report of small cell carcinoma of the esophagus with remarkable response to neoadjuvant chemotherapy. *Jpn J Cancer Chemother* 23:487–490 (in Japanese)
45. Sano T, Akao M (1996) A case of small cell carcinoma (oat-cell type) of the esophagus. *J Jpn Assn Thorac Surg* 44:955–958 (in Japanese)

46. Ohmura Y, Takiyama W, Mandai K et al (1997) Small cell carcinoma of the esophagus: a case report. *Jpn J Clin Oncol* 27:95–100
47. Kuwabara H, Maruyama M, Yoshida T et al (1998) Early small cell carcinoma of the esophagus associated with Wernicke-Korsakoff Syndrome—report of a case. *J Jpn Soc Clin Surg* 59:127–131 (in Japanese)
48. Suda H, Tozawa H, Funakoshi K et al (1998) Small cell carcinoma of the esophagus—report of 3 case. *Endosc Forum Dig Dis* 14:146–50 (in Japanese)
49. Hosoya Y, Shibusawa H, Waki Y et al (1998) A case report of small cell carcinoma of the esophagus. *J Jpn Soc Clin Surg* 59:1833–1837 (in Japanese)
50. Ii K, Hirono M, Kitajima K et al (1999) Case of primary small cell carcinoma of the esophagus review of endoscopic features reported in the Japanese literatures. *Gastroenterol Endosc* 41:2368–2373 (in Japanese)
51. Tajiri M, Yamamoto O, Suganaga Y et al (1999) A case of erythroderma associated with esophageal small cell carcinoma. *Nishinohon J Dermatol* 61:426–429 (in Japanese)
52. Yoshikawa T, Kato H, Nikkuni K et al (1999) A case report of esophageal small cell carcinoma responding well to chemotherapy of 5-FU and cisplatin combined with radiotherapy. *Gan To Kagaku Ryoho* 26:1181–1184 (in Japanese)
53. Nakazawa K, Shiozawa S, Kubota S et al (1999) A case of primary small cell carcinoma of the esophagus. *J Jpn Soc Clin Cytol* 38:268–271 (in Japanese)
54. Hayashi Y, Shindo H, Tachiyama Y et al (2000) Two cases of small cell carcinoma of esophagus concomitant with invasive squamous cell carcinoma and carcinoma in situ. *Jpn J Diagn Pathol* 17:372–375 (in Japanese)
55. Matsumoto H, Hanashi T, Yoshida M et al (2000) Small-cell carcinoma of the cervical esophagus, found one year after subtotal thoracic esophagectomy for early cancer—A case report. *J Jpn Soc Clin Surg* 61:356–361 (in Japanese)
56. Komoto D, Kayashima Y, Tomiyoshi H et al (2001) A case of esophageal small cell type undifferentiated carcinoma. *Medl Bull Onomichi General Hosp* 11:45–47 (in Japanese)
57. Nagahama T, Maruyama M, Tokairin Y et al (2001) A patient with small-cell carcinoma of the esophagus with synchronous liver metastasis surviving 48 months after surgery. *Jpn J Cancer Chemother* 28:1655–1658 (in Japanese)
58. Iwamura T, Shibata N, Termuhlen P et al (2001) Superficial neuroendocrine carcinoma of the esophagus. *Dig Endosc* 13:216–219 (in Japanese)
59. Komura Y, Uemura N, Okamoto S et al (2001) A case of small cell carcinoma of esophagus successfully treated by chemotherapy with CPT-11 and CDDP. *J Jpn Soc Gastroenterol* 98:25–30 (in Japanese)
60. Takeshita H, Matsuzaki M, Kamiya I et al (2002) A case of small cell carcinoma of the esophagus relating rapidly after surgery. *J Jpn Soc Clin Surg* 63:2423–2427 (in Japanese)
61. Takada M, Takenouchi N (2002) A long-term survival patient with primary small-cell cancer of the esophagus. *J Jpn Soc Clin Surg* 63:357–360 (in Japanese)
62. Yamamoto J, Ohshima K, Kikuchi M et al (2003) Primary esophageal small cell carcinoma preoperatively diagnosed as esophageal squamous cell carcinoma; endoscopic findings and Histopathological Feature. *Jpn J Cancer Clin* 49:1417–1424 (in Japanese)
63. Kikuchi Y, Fujitsuka Y, Takeuchi M et al (2003) A case of esophageal small cell carcinoma responding to chemotherapy with 5-FU and Nedaplatin combined with radiation. *Jpn J Cancer Clin* 49:1451–1455 (in Japanese)
64. Tsujie M, Shibata N, Nomura T et al (2003) A patient with stage IVb small cell carcinoma of the esophagus who survived 23 months after systemic cancer chemotherapy. *Jpn J Cancer Chemother* 30:271–275 (in Japanese)
65. Koide N, Hiragauri M, Kishimoto K et al (2003) Small cell carcinoma of the esophagus with reference to alternating multiagent chemotherapy: report of two cases. *Surg Today* 33:294–298
66. Noguchi T, Takeno S, Sato T et al (2003) Coexistent multiple adenocarcinomas arising Barrett's esophagus 23 years after total gastrectomy and esophageal small cell carcinoma. *Jpn J Thoracic Cardiovasc Surg* 51:259–262
67. Kubota M, Sueyoshi S, Fujita H et al (2003) Spontaneous regression in small cell esophageal carcinoma. *Jpn J Thoracic Cardiovasc Surg* 51:660–664
68. Sugiura K, Ozawa S, Kitagawa Y et al (2004) A resected of a small cell carcinoma of the esophagus and analysis of cases in the literature. *Jpn J Gastroenterol Surg* 37:123–129 (in Japanese)
69. Shioaki Y, Koide K, Kurioka H et al (2004) Case of superficial small cell carcinoma of the esophagus with liver metastasis. *Gastroenterol Endosc* 46:1340–1345 (in Japanese)
70. Takahashi T, Machida K, Honda N et al (2004) Extraosseous accumulation of ^{99m}Tc-MDP in lymph node metastases of small cell carcinoma of the esophagus. *Ann Nucl Med* 18:157–160. A
71. Onishi Y, Fujisawa T, Maeda M et al (2004) Primary composite tumor with bipartite differentiation of the esophagogastric junction. *Dig Endosc* 16:66–70
72. Matsuhashi N, Nagao N, Tanaka C et al (2004) Case of small cell carcinoma of the esophagus who failed to be diagnosed correctly by preoperative endoscopic biopsy. *J Jpn College Surg* 29:872–877 (in Japanese)
73. Watanabe S, Udagawa I, Ishida Y (2004) A case report of esophageal small cell carcinoma; a long-term survival by radio-chemotherapy with carboplatin and etoposide. *J Jpn Soc Gastroenterol* 101:1217–1220 (in Japanese)
74. Hattori M, Kaizaki Y, Hosokawa O et al (2004) Esophageal endocrine cell carcinoma: report of a case. *Stomach Intest* 39:89–94 (in Japanese)
75. Kawai T, Yoshizumi Y, Tsuwano S et al (2004) A case of esophageal small cell carcinoma with survival 5 years after resection. *J Saitama MS* 39:207–211 (in Japanese)
76. Matsuoka M, Boku N, Yoshino T et al (2005) Small cell carcinoma of the esophagus responding to fourth-line chemotherapy with weekly paclitaxel. *Int J Clin Oncol* 10:429–432
77. Kobayashi K, Aoki T, Nishioka K et al (2005) Superficial-type small cell-type undifferentiated carcinoma of the esophagus, Report of a case. *Stomach Intest* 40:1067–1072 (in Japanese)
78. Higashidani Y, Tamura S, Yokoyama Y et al (2005) Small cell carcinoma of the esophagus with metastasis to the brain: a case report. *Esophagus* 2:97–102
79. Komoto M, Takashima T, Nakata B et al (2005) A case of esophageal carcinosarcoma of which carcinoma component was small cell carcinoma. *Jpn J Gastroenterol Surg* 38:31–35 (in Japanese)
80. Nagahama T, Ando M, Ohbu M et al (2006) A case report of small cell carcinoma of the esophagus successfully treated by irinotecan and cisplatin. *Jpn J Cancer Chemother* 33:1869–1871 (in Japanese)
81. Akaike H, Kono K, Sugai H et al (2006) A case report of small cell carcinoma of the esophagus with difficulty in preoperative diagnosis and rapid progression. *J Jpn College Surg* 31:822–826 (in Japanese)
82. Masuda R, Yasuda Y, Tarao H et al (2006) A case of esophageal small cell carcinoma. *J Ther* 88:2050–2053 (in Japanese)
83. Furihata M, Ono Y, Fujimori T et al (2006) Esophageal small cell carcinoma effectively treated by cisplatin and irinotecan. *Esophagus* 3:61–64
84. Shimada T, Koizumi W, Tanabe S et al (2006) Small-cell carcinoma of the esophagus associated with a paraneoplastic

- neurological syndrome: a case report documenting a complete response. *Jpn J Clin Oncol* 36:109–112
85. Mori N, Fujita H, Sueyoshi S et al (2006) Small cell carcinoma in the esophagus rapidly developing multiple fistulae. *Esophagus* 3:7–12
 86. Furukita Y, Taniki T, Fukui Y et al (2006) A resected case of small cell carcinoma of the esophagus. *Med J Kochi Health Sci Center* 1:33–37 **(in Japanese)**
 87. Hashimoto T, Izumi Y, Oota M et al (2007) Superficial small cell carcinoma of esophagus treated by endoscopic mucosal resection combined with chemoradiotherapy. *Jpn J Cancer Chemother* 34:81–84 **(in Japanese)**
 88. Kanno K, Hikichi T, Saito K et al (2007) A case of esophageal small cell carcinoma associated with hypercalcemia causing severe acute pancreatitis. *Fukushima J Med Sci* 53:51–60
 89. Goto T, Watanabe H, Kawakami T et al (2007) A case of small cell carcinoma of the esophagus with remarkable response to chemotherapy with CPT-11 and CDDP. *J Jpn Soc Gastroenterol* 104:1204–1211 **(in Japanese)**
 90. Kontani T, Shimada K, Iwakura S et al (2007) A case of small cell carcinoma of the esophagus. *J Wakayama Med Soc* 58:84–86 **(in Japanese)**
 91. Nagahama T, Ando M, Ohbu M et al (2007) A case report of local recurrence of esophageal cancer after chemoradiation successfully treated by placement of tracheal stent. *Jpn J Cancer Chemother* 34:1985–1987 **(in Japanese)**
 92. Fujita E, Imanishi A, Fujii T et al (2007) A case of esophageal small cell carcinoma. *Progress Dig Endosc* 71:58–59 **(in Japanese)**
 93. Yamamoto S, Tsuda H, Sakano T et al (2007) Esophageal pleomorphic giant cell carcinoma combined with small cell carcinoma combined with small cell carcinoma. *Pathol Int* 57:523–528
 94. Hashida H, Komuro K, Iwashiro N et al (2007) A long-term recurrence-free survivor after surgery and chemotherapy for small cell carcinoma of the esophagus. *J Jpn Surg Assoc* 68:1932–1936 **(in Japanese)**
 95. Ohshino Y, Terashima H, Ougouchi N et al (2007) A case of esophageal small cell carcinoma with Long-term survival for 8.5 years after surgery. *Operation* 61:1173–1178 **(in Japanese)**
 96. Chin K, Baba S, Hosoka H et al (2008) Irinotecan plus cisplatin for therapy of small-cell carcinoma of the esophagus: Report of 12 cases from single institution experience. *Jpn J Clin Oncol* 38:426–431
 97. Masuzawa T, Fujitani K, Hirao M et al (2008) A fatal case of small cell type undifferentiated carcinoma of the esophagus with sudden diarrhea and bloody discharge by CPT-11. *Jpn J Cancer Chemother* 35:1741–1744 **(in Japanese)**
 98. Kaneda K, Nishimura T, Sendo H et al (2008) A case of small cell carcinoma of the esophagus with rapid recurrence after curative resection. *J Jpn Surg Assoc* 69:1053–1057 **(in Japanese)**
 99. Yoshii T, Motohashi O, Nishimura K et al (2008) Experiences of salvage EMR for patient with local failure of chemoradiotherapy. *Progress Dig Endosc* 73:30–35 **(in Japanese)**
 100. Yamamoto S, Chino O, Shimada H et al (2008) A case of esophageal small cell carcinoma and its difficult in preoperative diagnosis. *Progress Dig Endosc* 73:132–133 **(in Japanese)**
 101. Kurokawa D, Yasui Y, Kotake J et al (2008) A case of endocrine cell carcinoma of the esophagus. *Aijinkai Med J* 40:226–229 **(in Japanese)**
 102. Sano A, Kikuchi J, Kobayashi Y et al (2008) A resected case of endocrine cell carcinoma of the esophagus. *Jpn J Gastroenterol Surg* 41:1898–1903 **(in Japanese)**
 103. Haruta S, Ueno M, Udagawa H et al (2009) Treatment process and tumor marker of esophageal cancer: A case of small cell carcinoma of the esophagus with specific histological features. *Esophagus* 6:139–142
 104. Watanabe G, Itami A, Kondo M et al (2009) A difficult-to-diagnosis case of small cell carcinoma with polypoid features that arose in the cervical esophagus. *Jpn J Gastroenterol Surg* 42:362–367 **(in Japanese)**
 105. Hirota M, Nakamura E, Yamashita N et al (2009) A case of superficial small cell carcinoma of the esophagus. *Jpn J Cancer Chemother* 36:1537–1539 **(in Japanese)**
 106. Hatakeyama M, Saito H, Asai M et al (2009) A case of small cell carcinoma of esophagus. *J Naylor City Hosp* 17:30–34 **(in Japanese)**
 107. Mizuiri H, Hihara J, Okada M (2009) CDDP + CPT-11 therapy is useful for stage IVb esophagus small cell carcinoma. *Jpn J Cancer Chemother* 36:831–834 **(in Japanese)**
 108. Nakajima S, Hidaka H, Umekita Y et al (2009) A 4-year survivor of small cell carcinoma of the esophagus with liver metastases managed by multidisciplinary treatment. *J Clin Surg* 64:1605–1610 **(in Japanese)**
 109. Aoyama T, Saeki H, Fujisawa J et al (2009) A long-term recurrence-free survivor after chemotherapy with 5-FU plus CDDP and surgery for small cell carcinoma of the esophagus. *Jpn J Cancer Chemother* 36:637–640 **(in Japanese)**
 110. Aizawa R, Takakura K, Kubo Y et al (2009) A case of primary small cell carcinoma of the esophagus responding remarkably to carboplatin (CBDCA) + etoposide (VP-16) combination therapy and radiation therapy. *J Jpn Soc Gastroenterol* 106:1334–1342 **(in Japanese)**
 111. Kitagawa H, Akimori T, Namikawa T et al (2009) A case of small cell undifferentiated carcinoma of the esophagus successfully treated by chemoradiotherapy. *Jpn J Cancer Chemother* 36:1737–1739 **(in Japanese)**
 112. Ozawa T, Wachi E (2009) Endocrine cell carcinoma of the esophagus resected by ESD after magnifying endoscopy with narrow band imaging. *Gastroenterol Endosc* 51:2437–2446 **(in Japanese)**
 113. Atsumi K, Shinoyama Y, Nomoto S et al (2010) Chemoradiation for small cell esophageal carcinoma: report of 11 cases from multi-institution experience. *J Radiat Res* 51:15–20
 114. Kubo H, Kijima D, Tada K et al (2010) A case of synchronous endocrine cell carcinoma and squamous cell carcinoma of esophagus. *Surgery* 72:1225–1228 **(in Japanese)**
 115. Kanzaki M, Muto Y, Yoshinouchi S et al (2010) A case of esophageal small cell carcinoma with syndrome of inappropriate antidiuretic hormone secretion. *Jpn J Cancer Chemother* 37:1941–1944 **(in Japanese)**
 116. Mizuuchi Y, Anbe K, Yamagata N et al (2010) A case of stage IVb small cell carcinoma of the esophagus obtained prolonged survival after combined modality therapy. *Jpn J Cancer Chemother* 37:715–718 **(in Japanese)**
 117. Suzuki S, Goto M, Okamoto T et al (2010) A case of small cell carcinoma of the esophagus with SIADH. *Jpn J Cancer Chemother* 37:123–126 **(in Japanese)**
 118. Shibahara H, Yoshida K, Kuze S et al (2010) A case of esophageal small cell carcinoma with survival for 6 years due to resection only against repeated recurrence lymph node. *Operation* 64:1579–1582 **(in Japanese)**
 119. Suzuki K, Oh K, Yada A et al (2010) A case of undifferentiated small-cell carcinoma of the esophagus. *JJCS* 35:164–167 **(in Japanese)**
 120. Isohata N, Naritaka Y, Shimakawa T et al (2010) A case of multiple esophageal cancers with coexisting small-cell and squamous cell carcinoma. *JJCS* 35:158–163 **(in Japanese)**
 121. Matsui S, Harasawa S, Ban S (2010) A case of esophageal small cell carcinoma for which chemotherapy (etoposide + carboplatin) was effective. *Progress Dig Endosc* 76:54–55 **(in Japanese)**

122. Kanamori J, Shiomi M, Sekoguchi E et al (2011) A case of superficial small cell carcinoma of the esophagus. *Surgery* 73:299–302 **(in Japanese)**
123. Asama H, Wakatsuki T, Asano T et al (2011) A case of endocrine cell carcinoma of the esophagus with remarkable response of combination chemotherapy with CPT-11 and CDDP. *Fukushima Med J* 61:88–94 **(in Japanese)**
124. Murakami K, Akutsu Y, Miyazawa Y et al (2011) A case of small-cell esophageal cancer with chronic renal failure undergoing hemodialysis safely treated with cisplatin and etoposide. *Esophagus* 8:209–215
125. Kato K, Chiba T, Oyama K et al (2011) A case of neuroendocrine carcinoma of esophagus with a remarkable to chemo-radiotherapy. *Jpn J Cancer Chemother* 38:2643–2645 **(in Japanese)**
126. Ando T, Hosokawa A, Yamawaki H et al (2011) Esophageal small-cell carcinoma with syndrome of inappropriate secretion of antidiuretic hormone. *Intern Med* 50:1099–1103
127. Kudoh K, Doi K, Ogata K et al (2011) A case of small cell carcinoma of esophagus treated by chemotherapy with CDDP plus CPT-11 and radiotherapy. *Jpn J Cancer Chemother* 37:2403–2405 **(in Japanese)**
128. Fujimoto C, Nakaya M, Oonuki Y et al (2011) Thyroid metastasis of esophageal small cell carcinoma. *Otolaryngology-Head Neck Surg* 83:333–336 **(in Japanese)**
129. Kobayashi K, Aoki T, Nishioka K et al (2011) A case of esophageal endocrine cell carcinoma that recurred in the lymph nodes around the thoracic aorta after ESD. *Gastroenterological Endoscopy* 53:28–34 **(in Japanese)**
130. Tanizaki K, Kobayashi K, Takachi K et al (2011) A case report of long-term survival of endocrine cell carcinoma of the esophagus with chemo-radiation therapy. *Jpn J Cancer Chemother* 38:2391–2393 **(in Japanese)**
131. Tokunaga N, Itaba S, Nakamura K et al (2012) A case of lymph node metastasis from esophageal small-cell-type endocrine cell carcinoma diagnosed by endoscopic ultrasound-guided fine-needle aspiration. *J Jpn Soc Gastroenterol* 109:1360–1366 **(in Japanese)**
132. Murase T, Higurashi T, Akatsuka S et al (2012) A case of endocrine cell carcinoma of the esophagus successfully treated by chemoradiotherapy. *Jpn J Cancer Chemother* 39:111–113 **(in Japan)**
133. Matsumori T, Murakami S, Araki O et al (2012) A case report of primary small cell esophageal carcinoma responding successfully to radiochemotherapy. *Jpn J Cancer Chemother* 39:1119–1121 **(in Japanese)**
134. Kasuga A, Naruge D, Arima S et al (2012) A case of simultaneous double cancer of esophageal neuroendocrine carcinoma and squamous cell carcinoma of the lung with chest wall invasion. *Clin Oncol* 10:572–577 **(in Japanese)**
135. Isshiki H, Satou S, Yajima H et al (2012) A case of esophageal endocrine cell carcinoma with multiple liver metastases that had a complete response to multidisciplinary therapy. *J Jpn Soc Gastroenterol* 109:1902–1909 **(in Japanese)**
136. Nishimura M, Kaiho T, Yanagisawa S et al (2012) A case of recurrent hepatic resection after surgery for esophageal cancer with neuroendocrine component. *Jpn J Gastroenterol Surg* 45:359–368 **(in Japanese)**
137. Kanazawa N, Mashima H, Jin M et al (2013) A case of metachronous esophageal cancer of small cell and squamous cell carcinoma. *Gastroenterol Endosc* 55:1986–1994 **(in Japanese)**
138. Takeoka T, Hirao M, Fujitani K et al (2013) A case of neuroendocrine cell carcinoma of the esophagus with lung metastases successfully treated with CPT-11/CDDP. *Jpn J Cancer Chemother* 40:2121–2123 **(in Japanese)**
139. Takeuchi D, Koike N, Okumura M et al (2013) A case of small cell neuroendocrine carcinoma of the esophagus after radiotherapy for breast cancer. *Jpn J Gastroenterol Surg* 46:401–408 **(in Japanese)**
140. Nishiguchi Y, Tanaka T, Takayama T et al (2013) A case of large cell endocrine cell carcinoma of the esophagus. *J Jpn Surg Assoc* 74:2446–2452 **(in Japanese)**
141. Nagasaki E, Yuda M, Tanishima Y et al (2013) Complete response of esophageal small cell carcinoma amrubicin treatment. *J Infect Chemother* 19:770–775
142. Mochitsuki N, Kobayashi M, Nishioji K et al (2013) A case of esophageal endocrine cell carcinoma detected by esophagogastroduodenoscopy during a health check-up. *J Gastrointest Cancer Screen* 51:557–563 **(in Japanese)**
143. Mita Y, Hoshino I, Toyozumi T et al (2013) A case of esophageal endocrine cell carcinoma with a remarkable response to neoadjuvant chemotherapy. *J Jpn Surg Assoc* 74:380–385 **(in Japanese)**
144. Watanabe K, Hikichi T, Sato M et al (2014) A case of endocrine cell carcinoma combined with squamous cell carcinoma of the esophagus resected by endoscopic submucosal dissection. *Fukushima J Med Sci* 60:187–191
145. Maeda N, Shirakawa Y, Koujima T et al (2014) Complete response of primary esophageal endocrine cell carcinoma resected after neoadjuvant chemotherapy with docetaxel/cisplatin/5-fluorouracil. *Journal of Okayama Med Assoc* 126:39–43 **(in Japanese)**
146. Urabe K, Tahara K, Hotei H et al (2014) A case of endocrine cell carcinoma (small cell type) of the esophagus which was combined and diagnosed squamous cell carcinoma before operation. *Surgery* 76:421–424 **(in Japanese)**
147. Tomiyasu T, Maeda H, Nagano H et al (2014) A case of esophageal cancer combined with small cell carcinoma and squamous cell carcinoma. *Jpn J Clin Exp Med* 91:108–114 **(in Japanese)**
148. Akagi I, Miyashita M, Makino H et al (2014) Small cell carcinoma of the esophagus: A case report. *J Nippon Med Sch* 81:97–100
149. Yamakoshi Y, Kubo N, Ohira M et al (2014) Stage IV small cell esophageal carcinoma that responded to various chemotherapeutic regimens with relative longevity: a case report. *Jpn J Cancer Chemother* 41:2021–2023 **(in Japanese)**
150. Terashima T, Sudo T, Kakuta T et al (2014) A case of superficial endocrine cell carcinoma of esophagus with long-term recurrence-free survival after surgery. *Niigata Med J* 129:274–280 **(in Japanese)**
151. Saito R, Harata TJ, Mizuno Y et al (2015) A case of small cell carcinoma of the esophagus with skin metastasis. *J Hiroshima Med Ass* 68:270–273 **(in Japanese)**
152. Yamada K, Saito H, Kondo T et al (2015) Multicenter phase II study of nedaplatin and irinotecan for patients with squamous cell carcinoma of the lung: Thoracic Oncology Research Group 0910. *Anticancer Res* 35:6705–6712
153. Han J-Y, Lee DH, Lee SY et al (2005) Phase II study of weekly irinotecan plus capecitabine for chemotherapy-naïve patients with advanced non-small cell lung carcinoma. *Cancer* 104:2759–2765
154. Ohe Y, Ohashi Y, Kubota K et al (2007) Randomized phase III study of cisplatin plus irinotecan versus carboplatin plus paclitaxel, cisplatin plus gemcitabine, and cisplatin plus vinorelbine for advanced non-small-cell lung cancer: Four-Arm Cooperative Study in Japan. *Ann Oncol* 18:317–323
155. Noda K, Nishiwaki Y, Kawahara M, Japan Clinical Oncology Group et al (2002) Irinotecan plus cisplatin compared with etoposide plus cisplatin for extensive small-cell lung cancer. *N Engl J Med* 346:85–91
156. Lara PN Jr, Natale R, Crowley J et al (2009) Phase III trial of irinotecan/cisplatin compared with etoposide/cisplatin in extensive-stage small-cell lung cancer: clinical and pharmacogenomic results from SWOG S0124. *J Clin Oncol* 27:2530–2535

157. Mitry E, Baudin E, Ducreux M et al (1999) Treatment of poorly differentiated neuroendocrine tumors with etoposide and cisplatin. *Br J Cancer* 81:1351–1355
158. Yamaguchi T, Machida N, Morizane C et al (2014) Multicenter retrospective analysis of systemic chemotherapy for advanced neuroendocrine carcinoma of the digestive system. *Cancer Sci* 105:1176–1181
159. Yamada M, Kudoh S, Hirata K et al (1998) Risk factors of pneumonitis following chemoradiotherapy for lung cancer. 34:71–75
160. Japan Esophageal Society (2016) Guidelines for diagnosis and treatment of carcinoma of the lung. Kanehara, Tokyo (**in Japanese**)
161. von Pawel J, Jotte R, Spigel DR et al (2014) Randomized phase III trial of amrubicin versus topotecan as second-line treatment for patients with small-cell lung cancer. *J Clin Oncol* 32:4012–4019

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.