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SYSTEMATIC REVIEW

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Neuroendocrine carcinoma of esophagus: systematic review and meta-analysis of case series

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Abstract

Background Neuroendocrine carcinoma of the esophagus is a highly aggressive and rare type of cancer, making diagnosis and treatment challenging for clinicians. The current guidelines provide conflicting recommendations, and no standardized treatment protocol is available. We aim to deliver a systematic review of esophageal neuroendocrine carcinoma, including patient characteristics, treatment options, and prognostic factors.

Methods PubMed, Web of Science, Scopus, and Embase were searched up to May 2025 to retrieve the relevant studies containing at least 5 cases that reported treatment details, survival outcomes, or patient characteristics. Meta-analysis was conducted using a random-effects model for prognostic factors reported in at least three studies. We calculated survival information using the Kaplan–Meier method and estimated the median 1, 3, and 5-year survival rates in studies with available individual data that did not directly report the survival outcomes.

Results Overall, 24 articles with 1618 cases were included. The median overall survival of patients was 22.5 months, with median 1-, 3-, and 5-year survival rates of 76%, 47%, and 34%, respectively. Distant metastasis (HR, 2.68; 95% CI: 2.10 to 3.41; $P < .01$) and lymph node involvement (HR, 1.44; 95% CI: 1.04 to 1.99; $P = .02$) were significantly associated with poor prognosis. Surgery in selected cases improved the survival outcomes with an HR of 0.36 (95% CI, 0.28 to 0.46; $P = < .01$).

Conclusion The current study demonstrates that distant metastasis and lymph node involvement are significant predictors of poor prognosis in esophageal neuroendocrine carcinoma. Survival outcomes were comparable between patients with resectable tumors undergoing surgery and those receiving definitive chemoradiotherapy, both of which outperformed chemotherapy alone or no treatment. While adjuvant therapy may improve survival in node-positive cases post-surgery, this evidence remains limited by small sample sizes in existing studies. Further large-scale, prospective studies are needed to validate optimal treatment strategies, particularly the role of multimodal therapy in advanced disease.

Keywords Cancer, Systematic Review, Gastrointestinal tract, Neuroendocrine Tumors

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Background

Esophageal neuroendocrine carcinoma (ENEC) is a rare and highly aggressive malignancy, first described as small cell carcinoma of the esophagus by Dr. McKeon in 1952 [1]. Recent World Health Organization (WHO) classification systems categorize neuroendocrine neoplasms into well-differentiated neuroendocrine tumors (NET) and poorly differentiated (high-grade) neuroendocrine carcinoma (NEC) [2–4]. NECs typically have TP53 or RB1 mutations and are poorly differentiated neuroendocrine neoplasms characterized by a Ki-67 proliferation index greater than 20% and a mitotic index over 20 per mm^2. NECs can be categorized into small-cell type (SCNEC), large-cell type (LCNEC), and mixed neuroendocrine neoplasm when combined with adenocarcinoma or squamous cell carcinoma (SCC) [5, 6]. ENEC is extremely rare, accounting for 0.05% to 7.6% of all esophageal cancers [3, 6–8]. Their rarity, combined with an aggressive clinical course, makes diagnosis and management challenging [6]. NECs were associated with a worse prognosis than esophageal adenocarcinomas and SCCs [9, 10]. Previous studies reported that the 5-year survival rate for localized or regional ENEC was approximately 25% and was correlated with tumor location, invasion depth, and differentiation [10–12]. However, the 5-year survival rate in metastatic cases was less than 5% [12, 13].

The epidemiology and clinicopathological features of ENEC remain poorly defined due to the limited and heterogeneous available data. The majority of tumors were identified in the distal or middle segments of the esophagus and mainly affected male patients aged 66 to 72 years. [6, 8, 11, 12, 14–19]. The most common manifestations were dysphagia and weight loss, while the diagnosis was frequently made at an advanced stage when significant luminal obstruction and local invasion occurred [19]. Definitive diagnosis of ENEC is often challenging when relying solely on endoscopic evaluation. Histopathological differentiation from poorly differentiated SCC and basaloid SCC is challenging, particularly when only small biopsy samples are available [8, 9, 20]. Immunohistochemistry (IHC) and neuroendocrine markers such as synaptophysin (Syn), chromogranin A (CgA), and CD56 can help with accurate diagnosis. However, their sensitivities and specificities were not optimal, and more accurate diagnostic markers are still needed [9, 19]. Currently, there is no standardized treatment protocol for ENEC, and guidelines are conflicting, especially regarding the role of surgery. While some recommend resection only in selected cases, others support surgery except in advanced disease. Chemoradiotherapy, either alone or as adjuvant therapy, has demonstrated survival benefits in several studies. [9, 11, 12, 21, 22].

Given the rarity and complexity of ENEC tumors, high-quality evidence to guide management is limited. To address this gap, our systematic review and meta-analysis comprehensively synthesize the current literature on ENEC, focusing primarily on the impact of surgical resection with or without adjuvant therapy on long-term survival. Additionally, we aimed to investigate patient characteristics and prognostic factors in ENEC.

Method

This systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The study protocol was prospectively registered in PROSPERO (CRD42023456447). A comprehensive literature search was performed across PubMed, Web of Science, Scopus, and Embase to identify relevant studies published up to May 2025. The search strategy employed the keywords *"neuroendocrine carcinoma"* AND *"esophagus"*. The complete search queries for each database are presented in Supplemental Table 1. The primary objective of this systematic review and meta-analysis was to evaluate the impact of surgical treatment (surgery alone and surgery combined with adjuvant therapy) on long-term survival, compared to no treatment or non-surgical management. Secondary objectives included investigating prognostic factors associated with survival outcomes and describing the clinicopathological characteristics of ENEC cases reported in the literature.

Eligibility criteria

The following inclusion criteria were applied to select eligible studies: (1) the study includes at least five definitive cases with ENEC, and (2) the survival outcomes (e.g., overall survival, progression-free survival) or provided comprehensive patient characteristics and treatment details. We excluded case reports, reviews, book chapters, expert opinions, conference abstracts, and non-English language publications.

Data extraction

Two reviewers (S.M.P and F.O.) independently screened the titles and abstracts of retrieved studies. Studies meeting the inclusion criteria underwent full-text review. We extracted the following data from each eligible study: patient demographics and tumor characteristics, survival outcomes including median survival and 1-, 3-, and 5-year survival rates, and hazard ratios with 95% confidence intervals for prognostic factors. Prognostic factors extracted included lymph node involvement, distant metastasis, tumor location, gender, and treatment modalities. Treatment-related data collected explicitly for surgical interventions (including type and extent of

surgery), neoadjuvant and adjuvant therapies, chemotherapy regimens, chemoradiotherapy protocols, and use of somatostatin analogs where reported. Clinicopathological and treatment data from all relevant studies were consolidated for comprehensive analysis. Data derived from the SEER database were analyzed separately to avoid duplication. When overlapping variables were reported in multiple sources, cumulative values provided a more complete overview. Percentages for specific characteristics were calculated based on the number of patients with available data for each variable rather than the total study population, ensuring an accurate representation of clinicopathological and treatment features. Survival data were calculated using survival analysis and the Kaplan–Meier method when individual patient data were available, while the study did not report overall survival. We contacted the corresponding authors to request the necessary information for studies that did not directly report the survival statistics. If no response was received, we extracted data from Kaplan–Meier curves using WebPlotDigitizer, enabling estimation of median survival and 1-, 3-, and 5-year survival rates.

Quality assessment

Quality assessment was performed using the Newcastle–Ottawa Scale (NOS) checklist to evaluate the overall quality of included studies based on key elements such as patient selection, comparability, and outcomes [23]. Two reviewers (S.M.P. and F.O.) performed the assessing process separately, and disagreements were resolved by another reviewer (N.M.). The quality of each study was classified as very good (score of 9–10), good (score of 7–8), satisfactory (score of 5–6), or unsatisfactory (score of 0–5).

Statistical analysis

Meta-analysis was performed for any prognostic factor reported by more than two studies. The inverse variance method with a Random effect model was used to synthesize the cumulative result for each variable. Heterogeneity Was examined through both quantity methods, using the DerSimonian-Laird and Cochrane heterogeneity tests. Heterogeneity was classified based on the I^2 values as follows: low ($I^2 < 25\%$), moderate ($25\% < I^2 < 50\%$), and high ($I^2 > 50\%$). The sensitivity analysis using the leave-one-out method was performed to evaluate the robustness of the results. Statistical analysis was conducted in R (version 4.3.3) using the"meta"package and SPSS (IBM version 27.0). Statistical significance was assessed based on 2-tailed tests, with a threshold of *P* value less than 0.05 to report statistical significance.

Results

Literature search and screening results

A total of 3805 records were found in a primary search through PubMed ($n = 491$), Web of Science ($n = 496$), Scopus ($n = 1204$), and Embase ($n = 1614$). After removing 1944 duplicate articles, 1861 studies were evaluated based on the title and abstract. After excluding 1774 articles, the full texts of 87 articles were investigated. Overall, 24 [7–9, 14, 15, 24–42] articles were included in the current review. Figure 1 shows the PRISMA flow diagram of the inclusion process.

The included articles were published between 2008 and 2025, and their study design was retrospective. The studies were primarily conducted in China ($n = 9$), Japan ($n = 10$), and the USA ($n = 2$). The sample size of articles ranged from 7 to 604 cases. The quality assessment of included studies is shown in Supplemental Table 2. The majority of the articles demonstrated very good quality ($n = 14$), with the remaining articles categorized as good ($n = 6$) and satisfactory ($n = 4$) in terms of quality. Table 1 indicates detailed information on the baseline characteristics of included articles, reported survivals and summary of treatment approaches used or suggested by each article.

Demographic and pathological features

A total of 1618 cases with ENEC were included in the current review, 604 cases from the SEER database and 1014 patients were found from other published case series. Supplemental Table 3 demonstrates the detailed characteristics of all selected patients. The mean age of patients was 63.93 years, and the average size of the tumor was 4.16 cm for patients with reported values. The tumor location was the lower segment of the esophagus in half (50.7%) of the cases, followed by the middle segment in 39.9% of patients. The histopathology of tumors was a small cell in most patients (80.2%), and only 19.8% of cases had a large cell type of cellularity pattern. Regarding the homology of cancer, ENEC cases mainly had a pure-type tumor (68.2%) rather than the mixed-type (31.8%). Syn, CgA, CD56, Neuron-specific enolase, P53, and Cytokeratin 5/6 were the most reported diagnostic immunohistochemical markers, respectively. Synaptophysin and CD56 were positive in more than 80% of patients with ENEC. The patients mainly were found to have stage I-III of cancer (72.4%). Lymph node involvement was observed in 61.2% of patients, while only 20.8% of cases had distant metastases. Lymphovascular invasion (LVI) and Perineural invasion (PNI) were reported for a limited number of cases. LVI and PNI were invaded only in 35.8% and 21.7% of patients with reported status. The liver (49.0%) was the most common site of

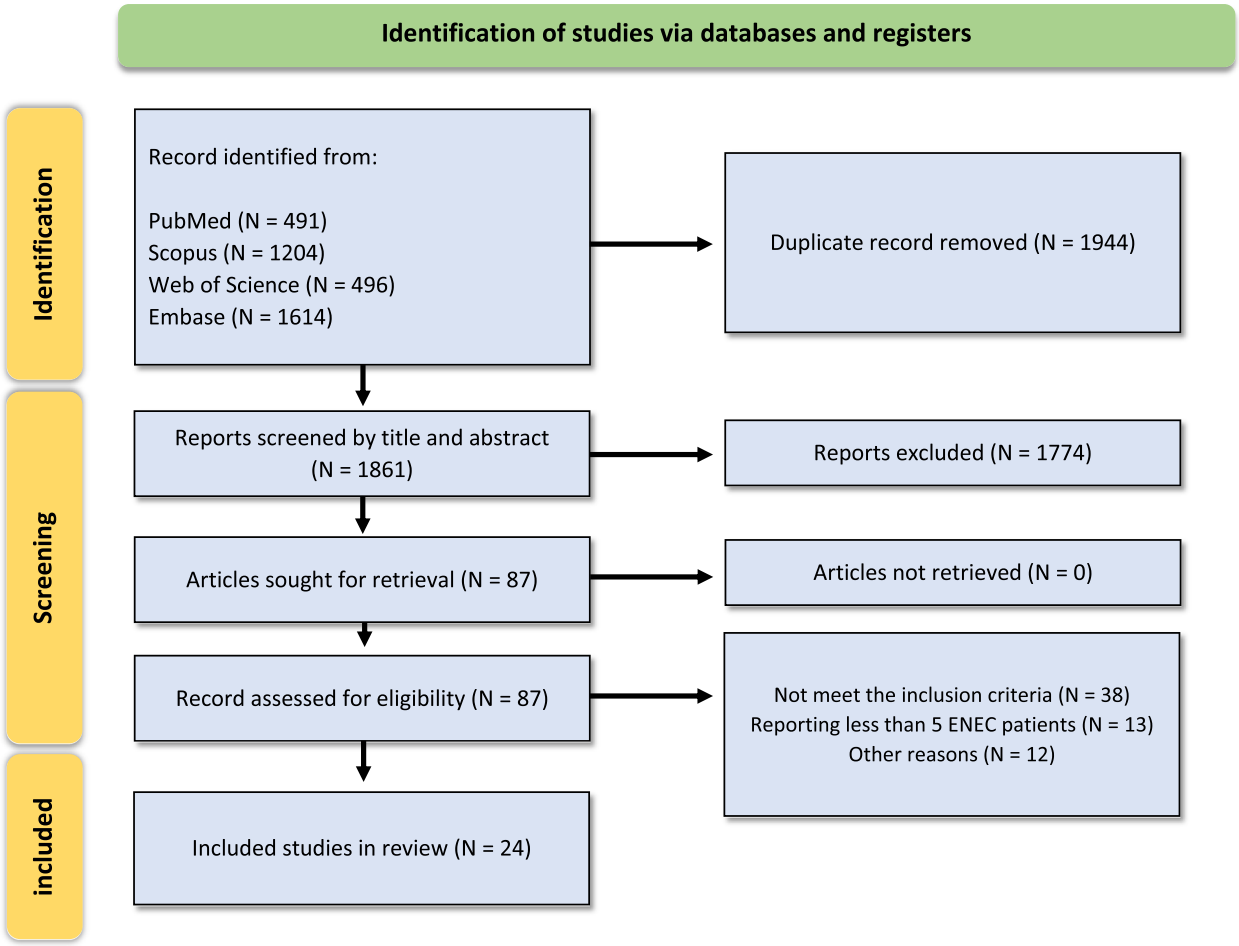

Fig. 1 The PRISMA flow diagram of selected studies

metastasis, followed by distant Lymph nodes (37.0%), bone (15.0%), lung (15.0%), and brain (9%). Dysphagia was the primary clinical symptom in patients with ENEC cancer, and other common symptoms are shown in Supplemental Table 3.

Survival outcomes

Supplemental Table 4 indicates summary of survival outcomes. The median overall survival of ENEC was 22.5 months, ranging from 8.3 to 46 months in 19 studies that reported median OS. Of these, 12 articles reported 1-year survival (median 76.0%, range 50%–93%), 11 studies reported 3-year survival (median 47.0%, range 14%–79.0%), and 10 studies reported 5-year survival (median 34%, range 8%–52.0%). The patients with mixed-type tumors (37.25 months) had better median survival than pure-type tumors (19.25 months), based on the eight [8, 9, 24, 26–28, 30, 42] studies that reported this outcome (Fig. 2A). Lymph node involvement worsened the survival of ENEC cases in five [7, 8, 26, 29, 40] studies that reported the difference in survival (19 vs 33 months) (Fig. 2B). The median survival of patients with middle-segment tumors (24.8 months) was slightly higher than cases with ENEC tumors in the lower segment (20.1 months) or upper segment (21.36 months). In three [26, 35, 40] studies, the survival of patients who received adjuvant therapy was compared with those who did not. The results showed that patients who underwent adjuvant therapy had a higher median survival time of 39 months, compared to 16.3 months for those who did not receive adjuvant therapy (Fig. 2C).

Meta-analyses of prognostic factors

Seven studies [7, 26, 29, 33, 35, 39, 41] that reported the HR of lymph node involvement were included. The overall HR of lymph node involvement was 1.44 (95% CI: 1.04 to 1.99; $P = 0.02$), and the between-study heterogeneity was Moderate ($I^2 = 39.6\%$; $P = 0.12$) (Fig. 3A). The sensitivity analysis revealed that the pooled HRs ranged from 1.27 (95% CI: 0.95 to 1.71) (omitting Liu's [35] study) to

Table 1 Clinicopathological Characteristics, survival outcomes, and management strategies of esophageal neuroendocrine carcinoma

Study information			Sample demographics			Survival outcomes				Staging system	Treatment strategies
Author	**Location**	**Year**	**Sample size, no**	**Male, no**	**Age**	**Median OS**	**1-year**	**3-year**	**5-year**		
Maru [24]	USA	2008	40	35	63 (34–82)	14	-	-	-	AJCC6	Stage I: Surgery only; Stages II/III/IVA: CRT (± surgery) or surgery alone; Stage IVB: Systemic therapy (platinum-based CT); Radiation dose: 45 Gy/25 F or 50.4 Gy/28 F to primary + involved nodes
Huang [8]	China	2013	42	33	62 (47–79)	28.5	93%	61%	25%	AJCC7	NR
Akazawa [9]	Japan	2014	10	9	61.8 ± 11.2	35.5	90.00%	78.80%	39.40%	JCEC	EMR for Tumor with T1 depth and N0-M0, Esophagectomy in more advanced tumor; Combined therapy with CT with CP and 5-FU or CT with irinotecan and CP
Deng [25]	China	2016	49	35	58.4 ± 8.2	22.4	74.90%	35.30%	-	AJCC7	Initial treatment: Surgery only (no neoadjuvant therapy) for resectable stage I/II ENECs. Adjuvant therapy: CT, RT, or CRT in 26 patients with lymph involvements or lymphovascular invasion
Egashira [15]	Japan	2017	14	11	70.35 ± 9.3	10	50%	14%	-	AJCC7	ED: CT only in 7 cases, platinum-based CT (irinotecan/VP-16/5-FU); CRT for symptom control in 1 case LD: Surgery alone in stage I and II, CT alone with CP/irinotecan or 5-FU/irinotecan
Hong [7]	China	2017	67	47	58.5 (44–75)	-	-	-	-	AJCC8	All patients had surgical resection and lymphadenectomy without any neoadjuvant treatments
Deng [26]	China	2018	72	55	59.7 ± 8.3	21.5	75%	33.40%	28.40%	AJCC7	Resectability criteria: Clinical T1-3, N0, or resectable N1 (confirmed by CT scan); Primary treatment: Surgery (for all resectable cases); Adjuvant therapy: Recommended for node-positive patients
Van der Veen [27]	Netherlands	2018	21	16	62.9 ± 9.5	37	71%	50%	35%	UICC	LD: neoadjuvant CRT using RT (41.4 Gy) + CB/paclitaxel or RT (50–50.4 Gy) + CP/VP-16; Transthoracic or transhiatal esophagectomy were the most surgical approaches used; Adjuvant therapy (CP/VP-16 or oxaliplatin/capecitabine) used in node-positive/high-risk cases
Author	**Location**	**Year**	**Sample size, no**	**Male, no**	**Age***	**Median OS**	**1-year**	**3-year**	**5-year**		
Ye [28]	China	2019	53	35	59.92 ± 7.96	42.36/84[a]	-	-	-	AJCC8	Primary therapy: Surgery (first choice for operable patients, including palliative surgery for inoperable cases); Adjuvant therapy: CT was standard post-resection treatment
Honma [29]	Japan	2019	22	12	62 (51–81)	37.5	85.70%	53%	45.40%	UICC7	Extensive LD: dCRT only using Platinum + VP-16 with RT (60 Gy/30 F) or CP + 5-FU with RT (60 Gy/30 F); CE-RT treated cases showed better prognosis but more hematologic toxicity

Table 1 (continued)

Study information			Sample demographics			Survival outcomes				Staging system	Treatment strategies
Author	Location	Year	Sample size, no	Male, no	Age	Median OS	1-year	3-year	5-year		
Fujimasa [30]	Japan	2019	10	8	69	8.3	-	-	-	AJCC8	NR
Katada [31]	Japan	2020	7	6	70 (46–74)	32	-	-	-	UICC7	Clinical stage I/II resectable tumors: dCRT using: 50.4 Gy in 28 F combined with CT using CP and VP-16 or CB and VP-16
Morita [32]	Japan	2020	22	18	67 ± 8.8	22.5	-	-	-	UICC8	Surgery: (subtotal esophagectomy or total gastrectomy) for all cases, regardless of stage (I-IVA); Adjuvant Therapy: for Node-positive or advanced stages (IIB-IVA) with CP +VP-16; Metastatic recurrence: CP +VP-16
Sohda [34]	Japan	2021	142	112	67.7 ± 8.8	18.48	69.20%	33.20%	33.20%	JCEC11	Stage I-II Disease: Equivalent outcomes for surgery vs. non-surgical options such as CRT (55 Gy ± CP/VP-16) or CT alone approaches; Stage III-IV Disease: dCRT using CP +VP-16 (CDDP +VP-16) with RT (55 Gy)
Sohda [33]	Japan	2021	81	63	67.14 ± 1.26	16.8	-	-	-		NR
Chen [43]	USA	2021	9	7	67.77 ± 11.67	13	60%	-	-	AJCC8	NR
Liu [35]	China	2021	67	57	63.69 ± 7.15	32	76.10%	46.80%	30.70%	AJCC8	Patients underwent radical esophagectomy with regional lymphadenectomy using: Left thoracic or right thoracic esophagectomy + 2-field lymph node dissection or Thoracoscopic + 3-field lymph node dissection (more extensive); combined with adjuvant therapy (CT/CRT)
Cheng [37]	China	2022	39	33	67.26 ± 7.01	46	85.30%	51.80%	46.10%	AJCC8	NR
Hou [38]	China	2023	28	19	66 (46–87)	-	88.50%	-	-	AJCC8	NR
Zhou [39]	China	2023	89	57	65 (42–78)	41.7	-	-	-		NR
Okumura [40]	Japan	2023	36	26	62.5 ± 6	-	-	-	51.70%	UICC7	All patients underwent radical esophagectomy (subtotal/lower esophagectomy with 2- or 3-field lymphadenectomy; Adjuvant therapy: CRT in most of stage II-IV patients received platinum-based adjuvant using CP/VP-16 or CP/irinotecan
Zhang [41]	China	2023	82	64	64 (46–77)	13	-	-	-	AJCC7	Tumor stage I/II: Surgery ± adjuvant therapy (CRT); stage III: CRT or Surgery with CRT; stage IV: CRT or CT alone; CT regimens: VP-16 +CP/CB
Yang [14]	SEER database	2025	604	439	-	-		15.7%[b]	8.45%		Localized/Regional (I-III): first option was dCRT, and surgery was the alternative, both had significantly better survival compared to other options; Metastatic (IV): Palliative CT or CRT

Table 1 (continued)

Study information			Sample demographics			Survival outcomes				Staging system	Treatment strategies
Author	**Location**	**Year**	**Sample size, no**	**Male, no**	**Age**	**Median OS**	**1-year**	**3-year**	**5-year**		
Yamashita [42]	Japan	2025	12	5	69 (45–84)	23				JCEC11	NR

NR Not reported, *CRT* Chemoradiation therapy, *CT* Chemotherapy, *RT* Radiotherapy, *dCRT* Definitive chemoradiation therapy, *F* Fractions, *Gy* Gray, *EMR* Endoscopic mucosal resection, *LD* Limited disease, *ED* Extensive disease, *CP* Cisplatin, *VP-16* Etoposide, *CB* Carboplatin, *AJCC* American Joint Committee on Cancer, *UICC* International Union Against Cancer, *JCEC* Japanese classification of esophageal cancer

[a] Median survival of pure and mixed tumor, respectively

[b] only 2-year survival was reported

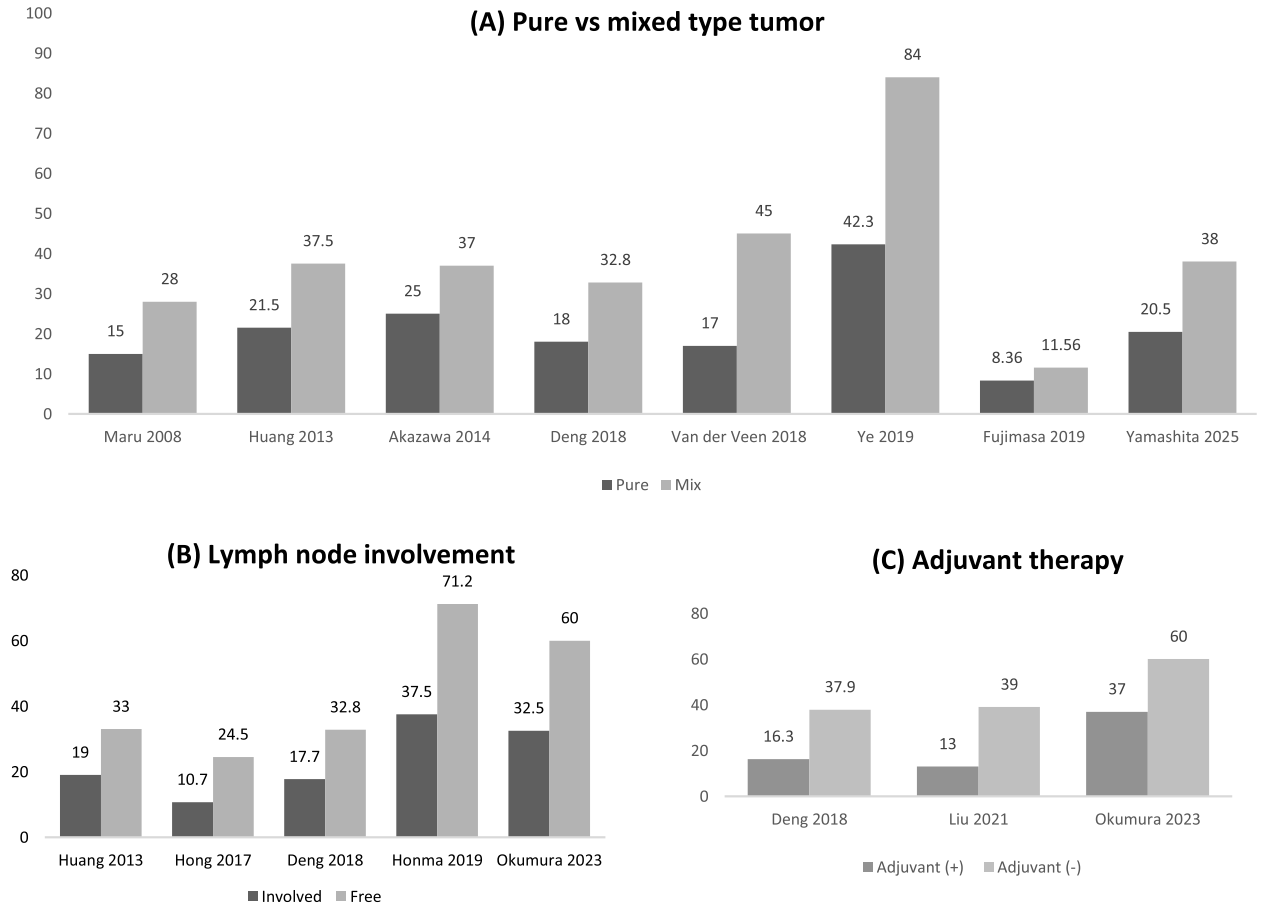

Fig. 2 Summary of median survival of ENEC cancer patients based on the (**A**) Histological homology (**B**) Lymph node involvement (**C**) Receiving adjuvant therapy

1.60 (95% CI: 1.06 to 2.40) (omitting Zhou's [39] study). The association remained statistically significant in most scenarios except when any of Liu's [35], Sohda's [33], or Zhang's [41] studies were removed. The heterogeneity (I^2) ranged from 21.8% to 49.4% across the analyses, suggesting low to moderate heterogeneity (Supplemental Fig. 1). Cumulative results based on the six [7, 14, 29, 33, 38, 39] studies that reported the HR of distant metastasis revealed that distant metastasis was significantly associated with poor prognosis in ENEC cases (HR, 2.68; 95% CI: 2.10 to 3.41; $P< 0.01$) (Fig. 3B), with moderate and non-significant between-study heterogeneity ($I^2= 33.4\%$; $P= 0.18$). The leave-one-out analysis indicated significant pooled HR by omitting any included articles (Supplemental Fig. 2). Hong's [7] study had the most impact on observed heterogeneity ($I^2= 8.7\%$ by removing Hong's study). The pooled results ranged from 2.61 (95% CI: 2.04 to 3.33) by removing Honma's [29] study to 3.82 (95% CI: 1.58 to 9.27) by removing Yang's [14] study (SEER database). Four [14, 26, 29, 35] articles were included in the meta-analysis of tumor location (Supplemental Fig. 3). The polled result showed no significant difference in the survival of patients with lower-segment tumors compared with upper-segment tumors (HR, 0.82; 95% CI, 0.62 to 1.07; $P= 0.14$), and selected studies were homogeneous ($I^2= 0\%$, $P= 0.77$). The sensitivity analysis demonstrated that removing any included articles did not significantly change the synthesized results (Supplemental Fig. 4). Removing Yang's [14] study (SEER database) achieved the highest pooled HR (1.00; 95% CI: 0.42 to 2.40). Eight [7, 14, 26, 29, 35, 38, 39, 41] articles reported the HRs for males compared to females (Supplemental Fig. 5). The subsequent meta-analysis indicated a non-significant difference in survival between male and female patients diagnosed with ENEC (HR, 0.94; 95% CI, 0.80 to 1.10; $P= 0.43$). The included studies were homogeneous with $I^2= 0.0\%$ ($P= 0.64$). The leave-one-out analysis revealed no significant changes by omitting any study (Supplemental Fig. 6). The pooled HR was lowest (HR, 0.92; 95% CI, 0.78 to 1.08) when Zhang's [41] study was removed and highest (HR, 1.02; 95% CI, 0.75 to 1.37) when Yang's [14] study (SEER database) was excluded.

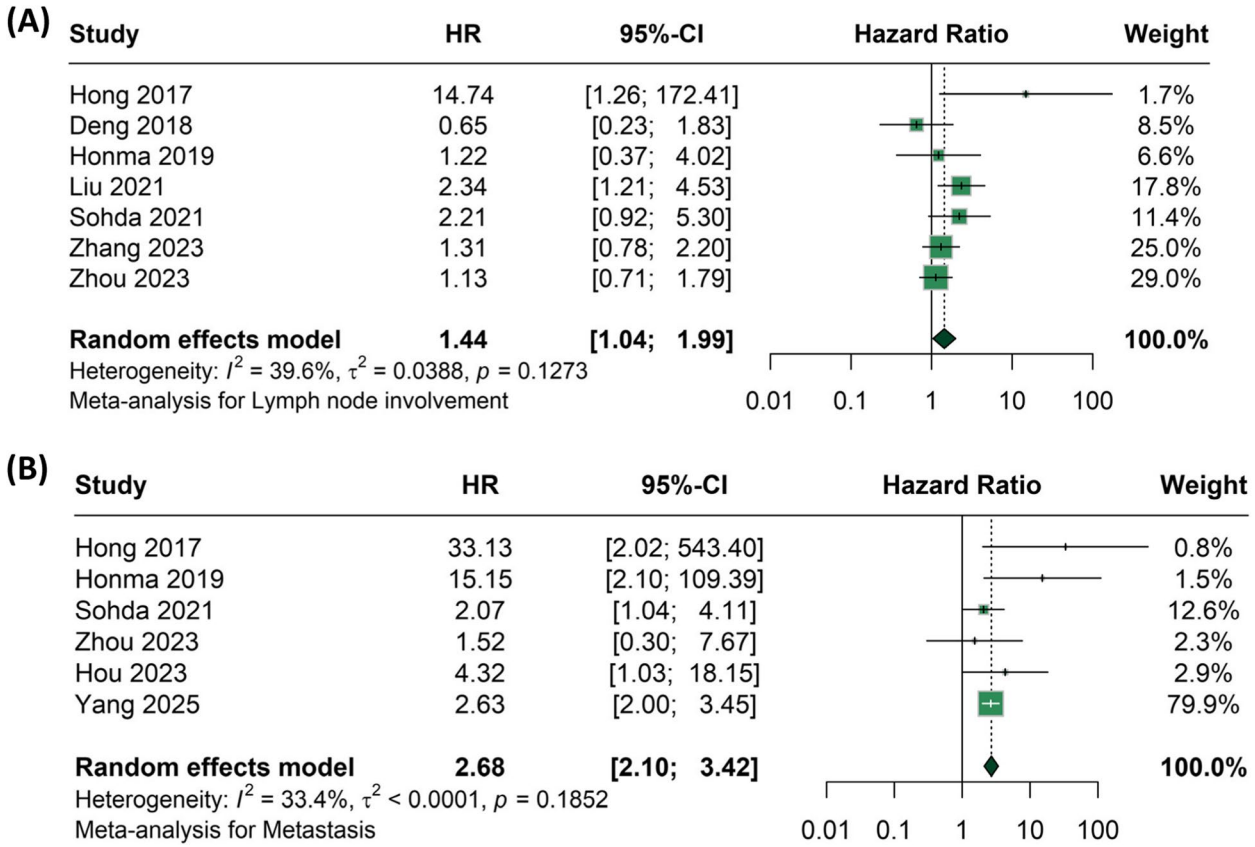

Fig. 3 Forest plots representing meta-analysis results of (**A**) Lymph node involvement and (**B**) Distant metastasis

Four [14, 26, 35, 38] articles reported the HR of surgery compared to no treatment in the ENEC cases mortality. The pooled HR was 0.36 (95% CI, 0.28 to 0.46; $P = < 0.01$), representing the beneficial role of surgery in selected cases (Fig. 4). The heterogeneity between included studies was low ($I^2 = 0.0\%$, $P = 0.83$), and sensitivity analysis

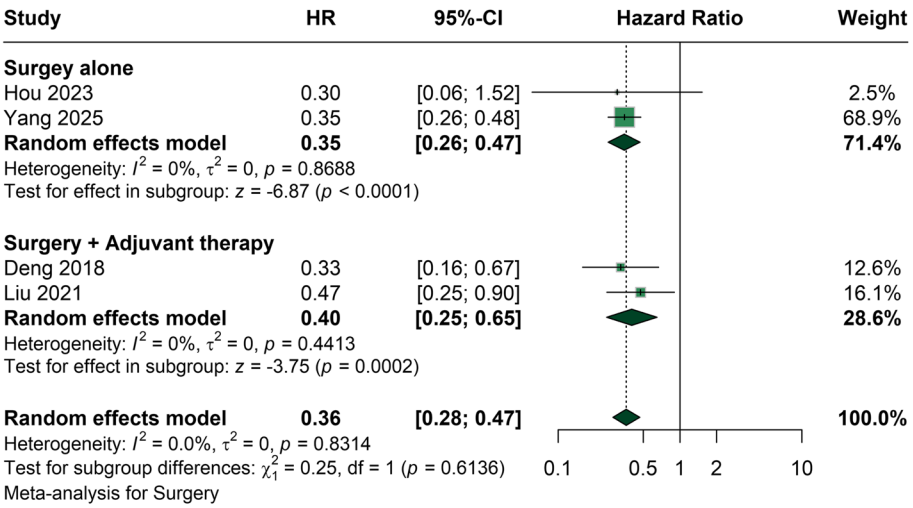

Fig. 4 Forest plots representing meta-analysis results of surgical intervention and subgroup analysis of surgery alone and combined with adjuvant therapy

indicated that the significance of pooled results remained similar by omitting any study (Supplemental Fig. 7). The findings of subgroup analyses of studies with surgery alone (HR, 0.35; 95% CI, 0.26 to 0.47; $P < 0.01$) or surgery with adjuvant therapy (HR, 0.40; 95% CI, 0.25 to 0.64; $P < 0.01$) were also statistically significant.

Discussion

In this systematic review and meta-analysis, we evaluated the clinicopathological features, prognostic factors, and treatment outcomes of ENEC based on the available literature. Our main objective was to investigate the impact of surgical resection, with or without adjuvant therapy, on long-term survival compared to non-surgical management. Based on the four articles, our meta-analysis confirmed that surgical resection, combined with adjuvant therapy, is a significant protective factor for survival in ENEC patients. Additionally, we analyzed prognostic variables and summarized the clinicopathological characteristics of ENEC cases from diverse populations.

Clinicopathological and prognostic heterogeneity

The incidence of ENEC, consistent with patterns observed in most gastrointestinal cancers, was higher in males (74.3%) [8, 44]. This finding aligns with the global esophageal cancer incidence, especially esophageal SCC, where nearly 70% of cases were reported in men [45]. The findings of the current meta-analysis showed no significant difference in the OS between male and female cases. The anatomical distribution of primary tumors differed between the two patient groups. The lower segment of the esophagus was the most common site in the SEER database (based on the white population). In contrast, cumulative results from other articles that mainly investigated the Chinese and Japanese populations identified the middle segment as the predominant location of the tumors [8, 12]. Several theories have been suggested to explain the distribution of tumor location. The predominance of ENEC in the lower esophagus may be related to neuroendocrine or amine precursor uptake and decarboxylase (APUD) cells in this section of the mucosa [25, 35]. Several hypotheses have been proposed to explain the variation in tumor location. The predominance of ENEC in the lower esophagus may be related to neuroendocrine or amine precursor uptake and decarboxylase cells in this part. Conversely, the high incidence of ENEC in the middle esophageal segment has been linked to the possible presence of synchronous esophageal SCC and the potential involvement of Merkel cells, which are primarily found in the middle esophagus [25, 28]. The findings from the current meta-analysis indicated no significant differences in OS among patients based on the involvement of different esophagus segments. The prevalence of pure-type NEC was higher than that of mixed-type NEC in the published case series. The prognostic role of a tumor's purity remains ambiguous. Several studies revealed no significant difference in the survival and relapse rates between pure and mixed types [8, 25, 26, 35, 40]. However, the cumulative results presented in our study showed that patients with the pure-type tumor probably had worse survival than those with mixed-type. The finding may be attributed to the NEC component's worse response to chemotherapy (CT) than the squamous carcinoma response, which was reported as a mixed component in many cases [25, 28].

The clinicopathological staging system varied across the studies. The primary method utilized in the included articles was the American Joint Commission on Cancer (AJCC) TNM staging system. The combined incidence of stage IV ENEC from all studies was 27.6%. In 2025, Yang et al. [14] identified 31.4% of ENEC cases were stage IV disease in the SEER database. Yoshinori Kikuchi's study [46] reported a 36% incidence of stage IV cases based on the cumulative results of Japanese case reports. The incidence of stage IV disease was comparable among patients diagnosed with ENEC and those with esophageal SCC [7, 28, 35, 46]. Reports based on the SEER data revealed a significant disparity in metastatic tumor incidence among ENEC patients compared to other literature. According to the SEER database, 63.9% of ENEC cases had distant metastasis, while other reports indicated a pooled distant metastasis rate of 20.1%. Although the available data on sites of metastasis were limited, our accumulative results showed that the liver was the most common site, followed by distant lymph nodes, bone, and lung. The distant metastasis pattern of ENEC was almost similar to that of other esophageal cancers, especially esophageal adenocarcinoma. This phenomenon may be because NEC and adenocarcinoma were mainly located in the distant esophagus, and venous drainage of the distal part is supplied by the left gastric vein, which drains directly into the liver [47, 48]. The role of the overall TNM stage as a prognostic factor is still controversial. Some articles found ENEC patients with stage III or IV tumors had significantly worse survival [25, 28, 34, 41, 49]. In contrast, several studies did not reveal the overall stage as a significant prognostic factor, while they found lymph node involvement and distant metastasis status to predict long-term survival [7, 8, 29, 35, 36, 50]. Our meta-analysis confirmed the poor prognosis of distant metastasis or lymph involvement in ENEC cases.

Role of immunohistochemical and neuroendocrine markers in the diagnosis and prognosis

According to WHO recommendations, three neuroendocrine markers, Syn, CgA, and CD56, are widely used

in studies of ENEC tumors. Syn, a peptide of small synaptic vesicles, was positive in most cases with ENEC because this vesicle is found in almost all neuroendocrine cells. This finding aligns with previous research indicating the presence of Syn in high-grade NENs [33, 51, 52]. Another marker is CD56 (also known as neural cell adhesion molecule), which was demonstrated as a sensitive marker in NET, particularly in small-cell type ENEC [53]. Since most ENEC cases were small-cell type, the CD56 staining was positive in most patients with reported CD56 staining status [53]. We recommend continuing to use IHC analysis for Syn and CD56 to provide a more accurate histological diagnosis of ENEC. CgA is a protein found in neurosecretory vesicles. In our study, CgA staining was positive only in half of patients. This observation may be related to the poorly differentiated nature of ENEC tumors, which limits the number of vesicles within the tumor structure [52]. In 2023, Yao Zhang et al. [41] reported that patients positive for CgA exhibited improved survival, potentially due to higher CgA expression in well-differentiated tumors. However, most studies demonstrated no significant relation between these immunohistochemical markers and prognosis [15, 28, 35]. Novel markers such as neuron-specific enolase (NSE), typically expressed in poorly differentiated neuroendocrine tumors, have been investigated. Honma et al. and Sohda et al. [29, 33] reported that an elevated NSE level was a significant prognostic factor for worse survival outcomes. Nevertheless, prospective studies are needed to confirm the possible role of NSE in determining the prognosis of ENEC.

Available treatment options

Due to the rarity of ENEC, no randomized controlled trials have evaluated optimal treatment strategies. However, recent larger studies have provided better insight into therapeutic approaches. The surgical intervention rate was 18.9% among ENEC cases in the SEER database. In contrast, cumulative reports from case series showed a significantly higher rate (73.6%). Historically, ENEC cancers were considered to behave like small-cell lung cancer, which was usually treated non-surgically. Therefore, experts limited the role of surgery for ENEC patients in the past [11]. Another reason Yang et al. [14] suggested was the comparable outcomes of definitive CRT and surgery in the SEER database patients. These may have contributed to the low rate of surgery in the SEER database. Surgical resection combined with adjuvant therapy (CT or CRT) has improved survival in well-selected ENEC patients, particularly those with localized or regional disease (stage I/II) [11, 22, 25, 28, 32, 35, 36, 46, 54]. Several studies showed that surgery with lymphadenectomy, followed by cisplatin-etoposide-based adjuvant therapy, significantly prolonged survival in node-negative cases, while lymph node metastasis remained a poor prognostic factor [25, 26, 32]. In a study by Ye et al., surgery was performed in all operable cases regardless of the stage of the disease. The median survival of patients ranged between 42 and 84 months, which was relatively higher compared to other studies [28]. Liu et al. defined resectable cases based on the absence of distant metastasis and revealed the same findings about the benefit of esophagectomy combined with adjuvant therapy [35]. The SEER database analysis [14] confirmed surgery as an independent protective factor in selected cases, while limited surgical rate (< 20%) and undefined resectability criteria may biased their findings. Despite the abovementioned studies supporting the role of surgery in the management of stage I or II ENEC patients, some studies proposed definitive CRT as a leading treatment, even in resectable cases [14, 46]. Two relatively large studies revealed that stage I-III cases who underwent CRT had a better prognosis than those who received other treatments [14, 46]. Honma et al. reported a 5-year survival rate of 45.4% in locally advanced ENEC patients treated with definitive CRT using cisplatin plus etoposide and radiotherapy, with this regimen outperforming cisplatin plus 5-fluorouracil in progression-free survival outcomes [29]. Similarly, a nationwide study by Sohda et al. found no significant survival differences among surgery, chemotherapy, and CRT for early-stage disease. However, they demonstrated superior 5-year survival for stage III/IV patients treated with CRT compared to surgery. Moreover, neoadjuvant chemotherapy (NAC) was associated with worse survival in stage II/III ENEC, except when cisplatin plus etoposide was used [34]. Some data suggest that delaying surgery for NAC may worsen outcomes due to the tumor's aggressive nature. Van der Veen et al. reported shorter median survival across cases who underwent NAT compared to those who did not, despite most cases treated with CRT [27]. In contrast, Kikuchi et al. reported better survival in patients who received NAT compared to cases with surgery alone treatment [46]. Therefore, the role of NAT in managing ENEC patients is still unclear.

Limitations

While this systematic review and meta-analysis provide valuable insights into ENEC, several limitations must be acknowledged. All included studies were retrospective, which may have risks of selection bias, incomplete data, and unmeasured confounding variables. The rarity of ENEC resulted in a small pooled sample size (1,618 cases), with heterogeneity in patient demographics, treatment strategies, and staging systems across studies. Such variability may affect the generalizability of our findings. Most studies'lack of individual patient data restricted

our ability to perform more granular subgroup analyses or adjust for confounding factors like comorbidities, performance status, or detailed treatment regimens. Some studies extracted Survival outcomes from Kaplan–Meier curves, which may introduce estimation errors. The meta-analysis was limited by the few studies reporting hazard ratios for certain prognostic factors (e.g., only four studies for the role of surgery). Finally, no RCTs or prospective cohort studies preclude definitive conclusions about optimal treatment strategies.

Conclusions

To the best of our knowledge, this systematic review and meta-analysis is the first to investigate ENEC specifically. Our findings demonstrate that ENEC predominantly affected males in their seventh decade of life, with tumors frequently located in the middle esophagus. Dysphagia was the most common presenting symptom, and the liver was the primary metastatic site. The median overall survival was 22.5 months, with a 5-year survival rate of 34%. Distant metastasis and lymph node involvement were significantly associated with a worse prognosis, while adjuvant therapy showed potential survival benefits in node-positive cases after surgery. Survival outcomes were similar between resectable tumors treated with surgery or definitive chemoradiotherapy, both outperforming chemotherapies alone or no treatment. However, these conclusions are restricted by the limited sample sizes and heterogeneity observed in studying this rare malignancy. Future large-scale, prospective studies are needed to validate optimal treatment strategies, particularly the role of multimodal therapy in advanced ENEC, and to establish standardized management guidelines.

Abbreviations

NEC	Neuroendocrine carcinoma
ENEC	Esophageal neuroendocrine carcinoma
WHO	World Health Organization
SCC	Squamous cell carcinoma
HR	Hazard ratio
CI	Confidence interval
AJCC	American Joint Commission on Cancer
TNM	Tumor, Node, Metastasis
LN	Lymph node
LVI	Lymphovascular invasion
PNI	Perineural invasion
APUD	Amine precursor uptake and decarboxylase
NANETS	North American Neuroendocrine Tumor Society
ENETS	European Neuroendocrine Tumor Society
IHC	Immunohistochemistry
Syn	Synaptophysin
CgA	Chromogranin A
NSE	Neuron-specific enolase
CK	Cytokeratin
SEER	Surveillance, Epidemiology, and End Results
OS	Overall survival
CRT	Chemoradiotherapy
NAT	Neoadjuvant therapy
NAC	Neoadjuvant chemotherapy
CE	Cisplatin plus Etoposide
RCT	Randomized controlled trial

Supplementary Information

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Supplementary Material 1.

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Authors' contributions
S.M.P., A.J., and N.M. conceptualized the project. S.M.P., F.O.S., D.S., and S.M. completed the methodology. S.M.P., F.O.S., D.S., and S.M. contributed to the data extraction. S.M.P. performed the data analysis. S.M.P., A.J., F.O.S., D.S., and S.M. contributed to the writing of the manuscripts. All authors read and approved the final manuscript.

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