Progress in the treatment of esophageal neuroendocrine carcinoma (Review)

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Abstract. Esophageal neuroendocrine carcinoma (ENEC) is a rare and highly aggressive gastrointestinal malignancy with a markedly worse prognosis compared with other pathological types of esophageal cancer. The present study aimed to provide a systematic review of the pathological features, diagnostic strategies and advances in stratified treatment of ENEC, with a focus on current therapeutic approaches. The management of ENEC requires a multimodal approach. Among these modalities, surgery remains the cornerstone for achieving long-term survival. For patients with initially unresectable disease, neoadjuvant therapy can convert cases to a resectable status. Additionally, combined chemoradiotherapy has been demonstrated to markedly improve survival rates. Beyond conventional treatments, the potential of targeted therapy in combination with chemotherapy has been suggested, and the synergy between immune checkpoint inhibitors and either radiotherapy or targeted drugs has achieved long-term remission in certain cases.

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1. Introduction

Neuroendocrine neoplasms (NENs) are tumors with neuroendocrine differentiation and expression of neuroendocrine markers, which can occur in various organs; however, they most commonly in the gastrointestinal tract, accounting for 55-70% of all NEN cases (1). Esophageal neuroendocrine carcinoma (ENEC) is a rare subtype within digestive tract NENs, comprising only 0.4-1% of gastroenteropancreatic NENs. ENEC is highly aggressive, prone to widespread metastasis and has a markedly worse prognosis compared with other common types of esophageal cancer, such as squamous cell carcinoma and adenocarcinoma (2).

Epidemiological studies have indicated that ENEC is more common in middle-aged and elderly men, and that it shows geographical clustering with higher incidence rates in certain regions, such as East Asia (including in China and Japan) (2,3). The risk factors for ENEC partially overlap with those of esophageal squamous cell carcinoma (ESCC), such as smoking, alcohol consumption, and a diet characterized by the frequent consumption of foods and beverages at very high temperatures (>65˚C has been classified as probably carcinogenic to humans by the International Agency for Research on Cancer) (4), which may induce DNA damage and epigenetic changes in the esophageal mucosa (5,6). Certain patients with ENEC also present with Barrett's esophagus, which suggests that chronic inflammation might drive neuroendocrine differentiation through abnormal proliferative signaling pathways (7).

ENEC exhibits high biological heterogeneity. Early studies have suggested that it originates from amine precursor uptake and decarboxylation cells in the esophageal mucosa, derived from the neuroectoderm (8,9). However, more recent research has proposed that it likely originates from pluripotent basal epithelial stem cells in the esophagus, which can differentiate into squamous or glandular epithelium under normal conditions but may aberrantly differentiate into NEC under epigenetic or microenvironmental pressure, forming mixed tumors (10).

The present review particularly focuses on ENEC due to its distinct clinicopathological features and highly aggressive biological behavior. This focused approach is predicated on the distinct clinicopathological and molecular features of ENEC,

which are justified by the fundamental differences between ENEC and other gastrointestinal NECs, particularly gastric NEC (GNEC). First, ENEC and GNEC possess unique molecular profiles; ENECs are characterized by a high frequency of co-mutations in tumor protein 53 and retinoblastoma gene 1, resembling small cell lung cancer, whereas GNECs exhibit considerable heterogeneity with alterations in genes such as low-density lipoprotein receptor-related protein 1B and dysregulation of pathways such as Wnt/β-catenin (11). Second, they arise from different epidemiological origins; ENEC shares strong associations with risk factors for ESCC (for example, smoking and alcohol) (12), whereas GNEC is often associated with chronic atrophic gastritis analogous to gastric adenocarcinoma (13). Notably, ENEC is associated with a markedly worse prognosis compared with GNEC, as confirmed by large-scale database analyses (3). Current evidence for the management of ENEC is often extrapolated from small cell lung cancer or aggregated with other NECs, underscoring the need for this particular synthesis of ENEC-specific data to provide clinicians with a nuanced overview of contemporary management and potential future directions.

While the seminal review by Ma *et al* (1) provided a key foundation to understand ENEC, the subsequent 8 years (2017-2025) have witnessed a paradigm shift in its management, which forms the core contribution of current research. The present review synthesizes these recent advances, which include the successful application of immune checkpoint inhibitors (for example, nivolumab and camrelizumab) (14-16), the emergence of combination immunotherapy strategies targeting cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and programmed cell death protein-1 (PD-1) (17,18), and novel regimens combining anti-angiogenic tyrosine kinase inhibitors (TKIs) with immunotherapy (for example, anlotinib plus camrelizumab) (19-21). The present review also provides a key evaluation of refined chemotherapeutic approaches, such as the validation of folinic acid + fluorouracil + irinotecan (FOLFIRI) in second-line settings (22,23) and the exploration of modified folinic acid + fluorouracil + irinotecan + oxaliplatin (mFOLFIRINOX, which typically involves dose adjustments of the constituent drugs to improve tolerability) (22), moving beyond the traditional platinum-etoposide (EP) backbone. Furthermore, to translate evidence into practice, the present review offers structured guidance for clinicians, incorporating insights from recent trials (24-26) and summaries of ongoing clinical studies (for example, NCT04325425 and NCT04169672) (21,26). This comprehensive and up-to-date review aimed to equip clinicians with the knowledge to navigate the rapidly evolving therapeutic landscape of this aggressive malignancy in the future.

2. Pathological features and diagnosis

Pathological classification. According to the 2019 World Health Organization classification of digestive system NENs (27), NENs are classified into well-differentiated neuroendocrine tumors (NETs), poorly differentiated NECs and mixed neuroendocrine-non-NENs (MiNENs). NETs are graded G1 to G3 based on mitotic count and Ki-67 index (27). NECs are divided into small cell NEC (SCNEC) and large cell NEC (LCNEC), with SCNEC accounting for ~90% of all ENEC cases. Grossly, NECs often present as invasive submucosal masses or ulcerative lesions with esophageal lumen narrowing (28). Histologically, SCNEC exhibits oat cell-like nests with necrosis, whereas LCNEC features vesicular nuclei, prominent nucleoli and rosette structures. MiNENs contain ≥30% neuroendocrine components and may also exhibit adenocarcinoma or squamous differentiation (29). In China, MiNENs are usually squamous-dominant, whereas in Western countries, they often coexist with adenocarcinoma (30) (Table I).

Diagnosis. Pathological confirmation of NENs necessitates a multimodal diagnostic approach. Immunohistochemically, synaptophysin (Syn) exhibits high sensitivity (>95%) and is expressed in virtually all NENs. Chromogranin A (CgA) is more specific but less expressed in poorly differentiated NECs, requiring additional markers such as CD56 and neuron-specific enolase (31). Insulinoma-associated protein 1, a sensitive and specific nuclear marker for neuroendocrine differentiation, is increasingly used in diagnostic panels, particularly when conventional markers are equivocal (31-33). However, the interpretation of immunohistochemical markers in NECs poses notable challenges. Key interpretative pitfalls include: i) Heterogeneous or weak expression levels of Syn and CgA in poorly differentiated tumors, which may lead to false-negative diagnoses; ii) non-specific staining of CD56 observed in a range of non-neuroendocrine malignancies, such as small cell lung carcinoma, lymphoma, melanoma and certain types of sarcoma; and iii) highly variable expression patterns in MiNENs, underscoring the necessity of extensive tumor sampling and the application of a comprehensive antibody panel to prevent misclassification (32).

Imaging features of ENEC markedly overlap with ESCC and esophageal adenocarcinoma (EAC), making radiological distinction challenging. Specifically, ENEC typically presents on X-ray barium swallow as irregular mucosal destruction, strictures or filling defects, similar to the appearances seen in ESCC and EAC. On CT and enhanced CT, ENEC commonly manifests as focal or circumferential wall thickening with heterogeneous enhancement, patterns that are also frequently observed in advanced ESCC and EAC. For ENEC, enhanced CT is crucial for assessing primary tumor location, local invasion and distant metastasis (particularly to the liver), with reported sensitivity for detecting liver metastases reaching up to 79% (34,35). Furthermore, endoscopic ultrasound accurately assesses tumor origin, size and invasion depth, although it cannot reliably differentiate ENEC from ESCC or EAC based solely on imaging characteristics (34). PET-CT is used for staging and recurrence detection (36). Somatostatin receptor (SSTR) scintigraphy, using 111In-labeled octreotide, is more sensitive for the detection of well-differentiated NETs and their metastases (particularly in the liver and lungs). The sensitivity of SSTR scintigraphy for poorly differentiated NECs is generally lower due to reduced or absent SSTR expression (37).

The assessment of SSTR expression via functional imaging also has potential therapeutic implications. Peptide receptor radionuclide therapy (PRRT), such as ^{177}Lu-oxodotreotide, is a well-established treatment option for well-differentiated, SSTR^{+} NETs (38). However, to the best of our knowledge, its role in poorly differentiated NECs, including ENEC, remains

Table I. Classification of NENs.

Type of NEN	Morphological and molecular features
NET	
G1	Mitotic count, <2/2 mm^2 (or <2/10 HPF); Ki-67 index, ≤3%
G2	Mitotic count, 2-10/2 mm^2 (or 2-20/10 HPF); Ki-67, 3-20%
G3	Mitotic count, >10/2 mm^2 (or >20/10 HPF); Ki-67, >20%
NEC	
Small cell NEC (accounts for ~90% of esophageal NEC cases)	High mitotic count, >10/2 mm^2 (or >20/10 HPF); Ki-67, >20% (often >55%)
Large cell NEC	High mitotic count, >10/2 mm^2; Ki-67, >20% (often >55%)
MiNEN	Biphasic tumor with ≥30% each of neuroendocrine (NET/NEC) and non-neuroendocrine components

HPF, high power field; MiNEN, mixed neuroendocrine-non-NEN; NEC, neuroendocrine carcinoma; NEN, neuroendocrine neoplasm; NET, neuroendocrine tumor.

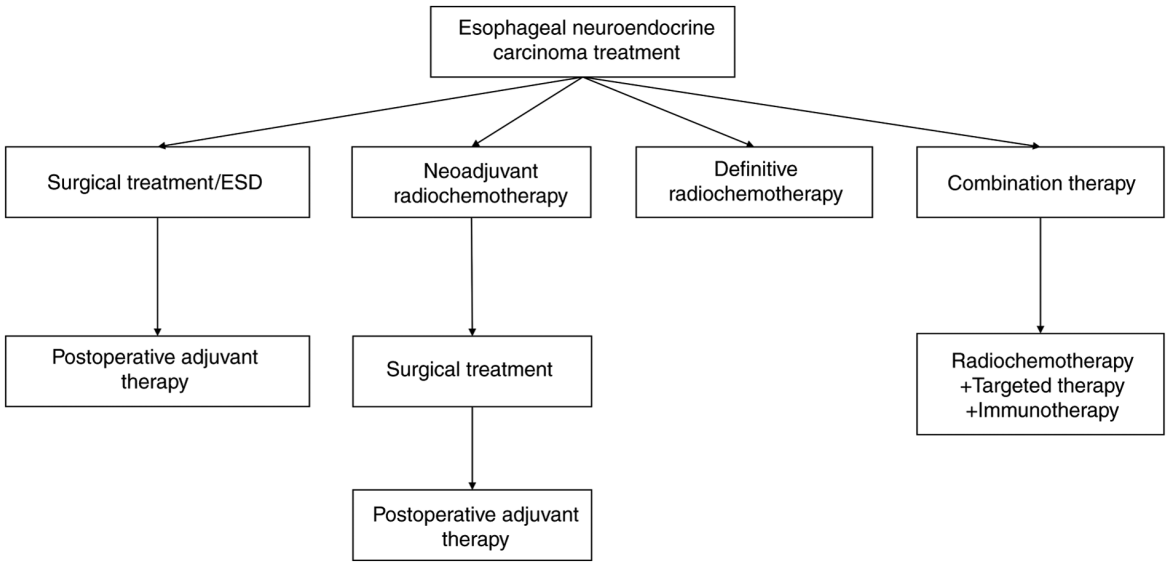

Figure 1. Main treatment modalities for esophageal neuroendocrine carcinoma. ESD, endoscopic submucosal dissection.

limited and non-standard; this is primarily due to the frequent absence or low density of SSTR expression in poorly differentiated NECs, which precludes the use of SSTR-targeted therapies (36). Therefore, patient selection for PRRT in high-grade disease hinges on demonstrating adequate SSTR expression on functional imaging, a finding that is uncommon in NEC. Although anecdotal case reports exist (38,39), robust clinical trial data supporting the efficacy of PRRT in ENEC are currently lacking.

3. Treatment strategies

The management of ENEC involves a multimodal approach, including surgery, platinum-based chemotherapy, radiotherapy, targeted therapy and immunotherapy (Fig. 1).

Endoscopic treatment. Endoscopic submucosal dissection (ESD) can be considered for highly selected cases of early ENEC confined to the mucosa (Tis or T1a according to the American Joint Committee on Cancer TNM staging system, 8th edition) (40) with a diameter of <1 cm (41). Although rare, such early cases have been successfully treated with ESD. Case reports have described patients achieving long-term disease-free survival following ESD without adjuvant therapy (42,43). For example, Fukui *et al* (42) documented a patient with pT1a ENEC (muscularis mucosae invasion) who declined adjuvant therapy post-ESD and remained recurrence-free during the 15-month follow-up. Similarly, Cheng *et al* (43) reported a 3-year disease-free survival in a case of NEC arising at the esophagogastric junction without lymphovascular invasion, treated solely by ESD.

Neoadjuvant and/or adjuvant combined surgery. Multimodal therapy combining neoadjuvant and/or adjuvant therapy with surgery is standard for locally advanced ENEC. Patients with resectable tumors and no lymph node metastasis may undergo

Table II. Comparison between first-line chemotherapy regimens.

Regimen	Key data	Toxicity profile	Evidence level
EP/EC	mOS, 12.5 months (25); ORR, 14-75% (56,57); mPFS, 5.36 months (25)	Neutropenia (90%), anemia and thrombocytopenia	Guideline-recommended (69)
IP	mOS, 10.9 months; no notable difference vs. EP (25)	Diarrhea (50%), neutropenia (60%)	Phase III trial
CAPTEM	mOS, 12.6 months; mPFS, 2.43 months (markedly lower compared with EP) (24)	Grade 3/4 adverse events, 29% (markedly lower compared with EP)	Phase II trial
FOLFOX	DCR, 91.3% (first-line); mPFS, 10 months (66)	Mild toxicity (neurotoxicity and diarrhea)	Retrospective study
FOLFIRI	DCR, 91% (metastatic GI NEC) (67)	Neutropenia and diarrhea	Small-sample study
FOLFIRINOX	ORR, 46%; mOS, 17.8 months (n=8) (62)	High toxicity (hematological and gastrointestinal)	Early exploratory
mFOLFIRINOX	ORR, 77%; mOS, 20.6 months (n=35) (22)	Markedly higher severe toxicity risk in women	Modified regimen study

ORR, objective response rate; mPFS, median progression-free survival; mOS, median overall survival; DCR, disease control rate; FOLFIRI, folinic acid + fluorouracil + irinotecan; FOLFOX, folinic acid + fluorouracil + oxaliplatin; CAPTEM, capecitabine with temozolomide; FOLFIRINOX, folinic acid + fluorouracil + irinotecan + oxaliplatin; mFOLFIRINOX, modified FOLFIRINOX; EP/EC, etoposide with carboplatin; IP, irinotecan + platinum; GI, gastrointestinal; NEC, neuroendocrine carcinoma.

surgery first, followed by adjuvant chemoradiotherapy if necessary (13). For initially unresectable cases, neoadjuvant therapy may enable surgery (1). Previous studies have suggested that neoadjuvant chemoradiotherapy followed by surgery markedly improves median overall survival (mOS) compared with surgery or chemoradiotherapy alone (44-46).

In patients with initially unresectable locally advanced ENEC, neoadjuvant therapy may facilitate surgical conversion, followed by personalized adjuvant regimens (47). A multicenter trial by Shapiro *et al* (48) demonstrated that neoadjuvant chemoradiotherapy combined with surgery markedly improved mOS in locally advanced ESCC (81.6 vs. 21.1 months) and adenocarcinoma (43.2 vs. 27.1 months), establishing this approach as the standard of care. Although ENEC was not included in this previous study, extrapolation of these principles supports guideline recommendations. The Clinical Practice Guidelines for Gastrointestinal and Pancreatic Neuroendocrine Tumors conditionally endorse neoadjuvant chemotherapy for borderline resectable ENEC (49).

A previous systematic review revealed notably increased survival outcomes with perioperative chemotherapy (neoadjuvant, 31 months; adjuvant, 25 months) versus surgery alone (9 months) in stage I-III ENEC, although no notable difference existed between the adjuvant and neoadjuvant groups (50). Notably, adding radiotherapy to neoadjuvant chemotherapy enhances surgical resectability and pathological complete response rates but does not improve survival (13). Awada *et al* (51) documented a case of poorly differentiated ENEC treated with neoadjuvant chemoradiotherapy and surgery, achieving >5 years of survival.

Radiation therapy. For patients with locally advanced, inoperable ENEC tumors, definitive chemoradiotherapy is recommended (52). Treatment plans should be based on the extent of invasion and lymph node involvement. Combined chemoradiotherapy yields a 3-year survival rate of ~31.6% (53). A Japanese retrospective study further supported chemoradiotherapy as a viable option for locally advanced ENEC (45). However, unlike in limited-stage small cell lung cancer where it is a standard of care, prophylactic brain irradiation is not routinely recommended due to the low incidence of brain metastases in ENEC (3).

4. Chemotherapy

First-line treatment. For advanced ENEC, systemic chemotherapy remains essential (46). First-line regimens are platinum-based doublets, either etoposide + platinum (EP) or irinotecan + platinum (IP). Capecitabine with temozolomide (CAPTEM), folinic acid + fluorouracil + oxaliplatin (FOLFOX), FOLFIRI and FOLFIRINOX have also demonstrated activity (Table II) (54). Previous studies have reported variable response rates [objective response rate (ORR), 14-75%] and a median progression-free survival (PFS) time of 1.8-8.9 months (25,54-56).

The EP or etoposide and carboplatin (EC) regimen is widely used in NEC, while IP demonstrates comparable efficacy but distinct toxicity profiles. Retrospective studies have indicated variable response rates (ORR, 14-75%) and a median PFS time of 1.8-8.9 months (57). The phase III JCOG1213 TOPIC-NEC trial identified no notable difference in mOS between EP and IP regimens (EP group, 12.5 months vs. IP group, 10.9 months). The ENEC subgroup (15.5% in EP vs. 9.3% in IP) demonstrated no clear advantage in overall survival compared with the IP regimen. Toxicity profiles differed; for example, neutropenia occurred in 90% of patients treated with EP, whereas diarrhea affected ~50% of patients treated with IP, necessitating regimen selection based on individual tolerance (25). For patients who are cisplatin-intolerant, the EC regimen serves as an alternative, indicating efficacy comparable to EP (58).

Table III. Second-line chemotherapy regimens comparison.

Regimen	mOS, months	mPFS, months	ORR, %	DCR, %	Evidence level
Platinum rechallenge	11.7 (71)	3.2 (71)	17/31 (56,70)	62 (71)	Retrospective study
FOLFIRI	5.9-18 (63,64,72)	4.4-5.8 (63,64,72)	-	44-80 (63,64,72)	Heterogeneous evidence
FOLFOX	-	-	-	64 (65)	Retrospective study
CAPTEM	12.1-22 (74,76)	5.86 (76)	26 (61)	-	Evidence from studies with conflicting results
Topoisomerase I inhibitors	4.3 (78)	1.8 (78)	-	15 (78)	TLC388 trial

ORR, objective response rate; mPFS, median progression-free survival; mOS, median overall survival; DCR, disease control rate; FOLFIRI, folinic acid + fluorouracil + irinotecan; FOLFOX, folinic acid + fluorouracil + oxaliplatin; CAPTEM, capecitabine with temozolomide.

Notably, patients with Ki-67 >55% exhibit lower ORR to platinum-based chemotherapy but improved survival, a paradoxical phenomenon requiring further mechanistic study and context-specific clinical strategies (59).

Despite high response rates, the short PFS of first-line platinum-based regimens has prompted exploration of alternative therapies. It is important to distinguish high-grade NENs here; while the CAPTEM regimen is an option for advanced well-differentiated G3 NET (neoplasia), it is not a standard first-line therapy for poorly differentiated NEC. The role of CAPTEM has primarily been explored in later-line settings (24,60). Trials such as NCT04325425 are ongoing to compare mFOLFIRINOX and EP regimens (61). FOLFOX and FOLFIRI are being evaluated as alternatives or second-line regimens, with varying degrees of disease control (62-64). These exhibit antitumor activity in NEC; however, to the best of our knowledge, randomized prospective phase II studies remain limited and no international consensus exists. In a previous study by Merola *et al* (65) involving 72 patients with advanced cases (44.5% NET; 55.5% NEC), FOLFOX achieved a disease control rate (DCR) of 75% and mPFS of 8 months, with first-line DCR reaching 91.3% (mPFS, 10 months) and manageable toxicity. Extended treatment cycles were recommended for well-tolerated patients. Du *et al* (66) reported a DCR of 91% for FOLFIRI in 11 metastatic gastrointestinal NEC cases. An early small-sample study (n=8) of FOLFIRINOX demonstrated an ORR of 46% and mOS of 17.8 months in first-line treatment (61). A mFOLFIRINOX regimen (n=35) achieved an ORR of 77% (mOS, 20.6 months), although severe toxicity in female patients warrants caution (22). Most of these aforementioned studies were retrospective with small sample sizes (n, 8-72), which warrants the validation of FOLFOX efficacy. The ongoing randomized phase II trial NCT04325425 comparing mFOLFIRINOX and EP regimens may provide higher-level evidence for first-line NEC treatment (26).

Second and multiple lines of treatment. Second-line treatments have demonstrated limited effectiveness (ORR, ~18%) (56). Platinum rechallenge is considered for patients with progression >6 months after first-line therapy (67). Irinotecan-based (FOLFIRI) and oxaliplatin-based (FOLFOX) regimens are used in platinum-resistant cases (62,64). Temozolomide-based regimens have exhibited modest activity, particularly in O6-methylguanine-DNA methyltransferase (MGMT)-deficient tumors. Randomized trials are ongoing to refine second-line therapy strategies. Table III compares the main second-line chemotherapy regimens.

Platinum rechallenge. Current consensus, as reflected in international guidelines such as those from the National Comprehensive Cancer Network (NCCN) and expert group recommendations, recommends regimen selection based on the duration of response to first-line chemotherapy (67,68). Patients with a time to progression of >6 months may consider EP rechallenge, whereas those with a time to progression of ≤6 months may benefit from regimens such as FOLFIRI or CAPTEM (67). Platinum-based rechallenge strategies have achieved ORRs of 17 and 31% in extrapulmonary NEC (55,69). In a nationwide multicenter study by Hadoux *et al* (70), platinum rechallenge chemotherapy demonstrated a DCR of 62% (mPFS, 3.2 months; mOS, 11.7 months). Patients with relapse-free intervals ≥3 months after first-line EP chemotherapy who received rechallenge therapy had markedly longer mOS (12 vs. 5.9 months). However, ENEC-specific subgroup analyses were lacking.

FOLFIRI program. Irinotecan-based regimens have been demonstrated to have heterogeneous efficacy. Previous studies have reported DCRs of 62-80% with FOLFIRI after platinum resistance (mPFS, 4-5.8 months; mOS, 11-18 months) (62,63). The PRODIGE 41-BEVANEC study validated FOLFIRI as a second-line option but identified no added benefit with bevacizumab (23). By contrast, Bardasi *et al* (71) demonstrated a lower DCR (44.1%; mOS, 5.9 months; mPFS, 4.4 months), highlighting discrepancies possibly due to study design or population characteristics. While FOLFIRI remains feasible after EP failure, its efficacy requires confirmation in prospective trials with controlled confounding factors. The NET-02 trial (n=102) compared liposomal irinotecan + 5-fluorouracil versus docetaxel in extrapulmonary NEC. Although no notable difference in mPFS or mOS was observed, the 6-month PFS rate doubled (29.6 vs. 13.8%), suggesting subgroup benefits. The trial failed its primary endpoint, Therefore, the potential advantage of the liposomal irinotecan combination regimen over docetaxel remains to be fully elucidated (72).

FOLFOX program. A retrospective study by Hadoux *et al* (64) demonstrated antitumor activity of FOLFOX as second- or third-line therapy in EP-refractory patients, with a DCR of

64% and <30% incidence of major hematological toxicity. These findings suggested that FOLFOX may offer survival benefits with manageable toxicity for aggressive ENEC lacking backline options.

CAPTEM program. Temozolomide efficacy remains debatable. Retrospective studies have reported an ORR of 26% and mOS of 22 months with CAPTEM in high-grade gastroenteropancreatic NEC after first-line failure (60,73). However, a prospective phase II study of temozolomide monotherapy (B160101021) demonstrated a lower ORR and mOS with an mPFS of 1.8 months, albeit with minimal toxicity (74). Notably, MGMT-deficient patients exhibited partial responses, suggesting that MGMT deficiency may serve as a potential predictive biomarker for sensitivity to temozolomide-based chemotherapy. The recent NCT04122911 trial reported improved outcomes (mPFS, 5.86 months; mOS, 12.1 months) for second-line temozolomide (75). These findings indicate modest efficacy and manageable toxicity, particularly in combination or MGMT-deficient subgroups.

The NCT03387592 trial compared CAPTEM and FOLFIRI in metastatic NEC. At 12 weeks, DCRs were 39.1% (CAPTEM) and 28.0% (FOLFIRI), with no notable difference in 12-month survival (28.4 vs. 32.4%). Both regimens demonstrated mild toxicity (<35% incidence). High microRNA expression was associated with poor prognosis, offering insights for stratification. Early termination of the trial (n=53) limited conclusions, but safety and similar antitumor activity were confirmed (76).

Topoisomerase I inhibitors. Topoisomerase I inhibitor monotherapy lacks notable efficacy in multiple studies and is not recommended in in major oncology guidelines, such as the NCCN Guidelines for Neuroendocrine and Adrenal Tumors (26,68). The NCT02457273 trial evaluated the novel camptothecin analog TLC388 in EP-refractory metastatic NEC, demonstrating a DCR of 15% (mPFS, 1.8 months; mOS, 4.3 months). The trial was halted due to unmet efficacy endpoints. However, MutS homolog 6 mutations (40% of samples) in the studied cohort of poorly differentiated NEC (including cases from various primary sites) have been associated with tumor mutational burden, thus suggesting potential for targeted therapies (77).

5. Targeted therapy

Targeted therapy inhibits tumor growth and proliferation by interfering with specific molecular targets. While molecular-targeted drugs are approved for various solid tumors, such as non-small cell lung cancer, breast cancer and renal cell carcinoma (78-80), their efficacy in NEC remains to be elucidated. Current research focuses on mammalian target of rapamycin (mTOR) inhibitors and anti-angiogenic agents. It is considered that with the continuous development of research, traditional treatment combined with targeted therapy may provide hope for patients in the future.

mTOR inhibitors. mTOR, a key kinase regulating cell proliferation, metabolism and angiogenesis, promotes tumor progression and represents a potential therapeutic target. Everolimus, an mTOR inhibitor, has demonstrated limited efficacy as monotherapy in phase II trials (mPFS, 1.2-1.3 months), but has shown enhanced antitumor activity in combination regimens (81,82). The NCT02695459 study reported that everolimus combined with cisplatin was effective as first-line therapy for advanced extrapulmonary NEC, which improved quality of life by avoiding etoposide-related side effects. Subgroup analysis identified three patients with sustained remission >1 year, suggesting there may be molecular predictors of sensitivity that remain to be identified; however, their specific identities remain to be elucidated due to a lack of correlative biomarker analysis in the trial (83). Similarly, NCT01317615 reported that everolimus combined with carboplatin and paclitaxel was effective and well-tolerated in metastatic lung LCNEC (84). In contrast to the potential benefits of mTOR inhibitors, trials such as PRODIGE 41-BEVANEC did not report notable survival benefits from the addition of bevacizumab to FOLFIRI (85).

Antitumor neovascular drugs. Bevacizumab, an anti-angiogenic agent, exhibits variable efficacy in NEN. Early retrospective studies have suggested that bevacizumab combined with temozolomide may provide benefits for patients with poorly differentiated NEC, although incomplete data have limited conclusions (23,73). The PRODIGE 41-BEVANEC trial (NCT02820857) identified no survival difference between FOLFIRI with or without bevacizumab in platinum-resistant gastrointestinal-pancreatic NEC (6-month OS, 53 vs. 60%) (23). This may reflect the high Ki-67 index (>55%) and complex angiogenesis of NEC compared with vascular-dependent NET (G1-G2), which may demonstrate improved response to bevacizumab. Retrospective studies have supported combining bevacizumab with FOLFIRI, FOLFOX, FOLFIRINOX or temozolomide for NET (23,85).

6. Immunotherapy

Checkpoint inhibitors [PD-1, programmed cell death-ligand 1 (PD-L1) and CTLA-4] offer potential but lack large-scale ENEC-specific evidence (72). Case reports have described complete remission (CR) when combining immunotherapy with radiotherapy or targeted agents, such as anlotinib or apatinib (14,15,19,20). Dual immunotherapy (for example, nivolumab + ipilimumab) demonstrates promise in high-grade NENs (17,18).

Immunotherapy combined with radiotherapy. Takagi *et al* (14) reported complete response in a patient with metastatic ENEC treated with nivolumab and radiotherapy, maintaining relapse-free survival for 42 months despite ≤1% PD-L1 expression, which suggests radiotherapy may modulate the immune microenvironment. Hanzawa *et al* (15) described sustained disease control in unresectable esophagogastric NEC with nivolumab and radiotherapy, achieving >4.5-year survival.

Immunotherapy combined with chemotherapy. Based on previous trials of extensive-stage small cell lung cancer (86-89), immunotherapy combined with platinum-based chemotherapy has been hypothesized to benefit gastrointestinal NEC. Ongoing phase II trials (NCT03901378, NCT03147404 and NCT03352934) are evaluating pembrolizumab-chemotherapy and avelumab monotherapy. However, the NET-001/002 trial reported a DCR of only 21% for avelumab in grade 2-3 NEN (90), which underscores the need for optimized regimens.

Dual immunotherapy. Dual immunotherapy (CTLA-4 + PD-1 inhibition) targets complementary immune pathways. The SWOG S1609 DART trial reported a 26% ORR and 32% 6-month PFS with ipilimumab and nivolumab in high-grade NEN, with manageable toxicity (grade 3/4 alanine aminotransferase elevation was most common) (17). The GETNE 1601 trial achieved a 36.1% 9-month survival rate with durvalumab and tremelimumab in chemotherapy-refractory gastroenteropancreatic NEN (18). While promising, dual therapy requires caution due to potential toxicity.

Immunotherapy combined with targeted therapy. Combining checkpoint inhibitors with multi-target TKIs such as surufatinib, anlotinib or apatinib demonstrate promise. Previous studies have reported DCRs of >80% and durable remission in certain cases (18,21). The combination benefits from synergistic effects on the tumor immune microenvironment (91).

Sulfatinib, a multi-target kinase inhibitor [VEGF receptor VEGFR)1-3, fibroblast growth factor receptor 1 (FGFR1) and colony stimulating factor 1 receptor], approved for non-pancreatic NET in China, combined with toripalimab (PD-1 inhibitor) achieved an 80% DCR (mPFS, 4.1 months; mOS, 13.7 months) in advanced NEC with manageable toxicity in the NCT04169672 trial (21). No further subgroup analyses were performed in this trial.

Camrelizumab (a PD-1 inhibitor) has demonstrated efficacy in esophageal cancer, including ENEC. In a specific trial including patients with esophageal cancer, ORRs ranging from 17.4 to 73.1% and a mOS of 8.3 months were reported, with efficacy appearing to be influenced by PD-L1 expression and other biomarkers , such as tumor mutational burden or microsatellite instability (16). Liu *et al* (16) reported camrelizumab combined with apatinib (VEGFR-2 inhibitor) in third-line ENEC recurrence, achieving >10-month PFS, which suggests that tumor microenvironment modulation enhances efficacy.

Anlotinib, a multi-target TKI (VEGFR, platelet-derived growth factor receptor, FGFR and c-Kit), improved survival in the ALTER 1202 trial for small cell lung cancer (92). Zhou *et al* (19) described a patient with metastatic ENEC achieving 29-month PFS and >50-month OS with camrelizumab and anlotinib after chemoradiation failure, reaching CR on PET/CT.

Tislelizumab (PD-1 inhibitor), which has been approved for the treatment of multiple malignancies such as non-small cell lung cancer and hepatocellular carcinoma (93), combined with anlotinib in second-line metastatic ENEC achieved CR (PFS, 16 months; OS, 21 months) with minimal toxicity in an elderly patient (20).

Targeted-immunotherapy combinations synergistically regulate the tumor microenvironment, offering a novel strategy to overcome traditional treatment limitations. While current evidence derives from small studies or case reports (14-16,19,20), preliminary data have suggested manageable toxicity and survival benefits. Future high-quality trials and translational research are warranted to validate efficacy and optimize personalized treatment.

Immunotherapy summary. Immunotherapy exploration in ENEC highlights multidimensional advances. Radiotherapy combinations may enhance efficacy by modulating the immune microenvironment. Dual immunotherapy (CTLA-4 + PD-1 inhibition) improves ORR and survival in high-grade NEN but requires caution regarding toxicity. Chemotherapy combinations lack randomized trial validation in gastrointestinal NEC despite success in small cell lung cancer. Targeted-immunotherapy regimens remodel the tumor microenvironment, achieving survival benefits. To the best of our knowledge, current evidence is limited to small studies or case reports with heterogeneous populations and undefined biomarkers. Future efforts should prioritize prospective trials, tumor microenvironment dynamics and epigenetic analyses to establish precision treatment models and address drug resistance.

7. Conclusion

ENEC is a rare, highly aggressive gastrointestinal tumor with diagnosis dependent on pathology and treatment requiring stratified management. Endoscopic or surgical resection is preferred in early stages, although curable cases are rare. For locally advanced disease, neoadjuvant/adjuvant therapy plus surgery or chemoradiotherapy improves survival. Platinum-based chemotherapy remains first-line in advanced stages, with individualized second-line regimens. Emerging therapies, particularly immunotherapy and targeted therapies, have achieved long-term remission in individual cases. Future large-scale clinical trials are warranted to optimize molecular subtyping, refine therapeutic strategies and improve outcomes for this high-grade malignancy. Finally, although the exclusive focus on ENEC in the present review is justified by its distinct biology, the omission of direct comparisons with other gastrointestinal NECs (such as GNEC) represents a limitation. Future studies integrating multi-origin NEC data may help refine both site-specific and common therapeutic strategies.

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Authors' contributions

JS and BH conceptualized the present review, curated the literature, devised the methodology and prepared the original draft. HZ and CJ contributed to the study conception and data acquisition, performed systematic literature retrieval, data

extraction and validation, conducted the comparative analysis and interpretation of data from the included literature, and were responsible for the design and creation of all tables and figures. HZ and CJ also participated in drafting and critically reviewing the manuscript. LZ made substantial contributions to the conception of the work, participated in drafting the manuscript and provided critical revision for important intellectual content. Data authentication is not applicable. All authors read and approved the final manuscript.

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Not applicable.

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Competing interests

The authors declare that they have no competing interests.

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