Recent progress and therapeutic strategies in the treatment of cervical neuroendocrine neoplasms (Review)

YANPENG TIAN[1], YU ZHANG[2], LILING WANG[2], ZHONGKANG LI[3], XIAOTONG XU[3], SHOUZE LIU[3], SHENYU YANG[4], XIANGYANG REN[4], MENGHAN XU[5], XINGZI CHANG[6], XIANGHUA HUANG[3], QIAN ZHAO[2] and RUIXIA GUO[2]

[1]Department of Pathophysiology, Medical School, Hunan University of Chinese Medicine, Changsha, Hunan 410208, P.R. China; [2]Department of Gynecology, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, Henan 450052, P.R. China; [3]Department of Gynecology, The Second Hospital of Hebei Medical University, Shijiazhuang, Hebei 050000, P.R. China; [4]Medical 3D Printing Center, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, Henan 450052, P.R. China; [5]Laboratory of Marine Pharmaceutical Compound Screening, College of Pharmacy, Jiangsu Ocean University, Lianyungang, Jiangsu 222005, P.R. China; [6]Center for Reproductive Medicine, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, Henan 450052, P.R. China

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Abstract. Neuroendocrine neoplasms (NENs) are a rare type of tumor originating from peptidergic neurons and neuroendocrine cells, which exhibit neuroendocrine differentiation and neuroendocrine marker expression. NENs can occur in any part of the body, with the cervix being the most common organ for their presentation within the female reproductive system. Small-cell neuroendocrine carcinoma (NEC) is the most common subtype of cervical NENs, followed by large-cell NEC. Similar to cervical squamous cell carcinoma (SCC), cervical NENs are closely related to human papillomavirus (HPV) infection, with HPV16 and HPV18 representing the most important subtypes. Cervical NENs are prone to early local spread and distant metastasis, with high malignancy and mortality rates. Currently, there are no clinical guidelines for their diagnosis and treatment, and therapy plans focus on multimodal treatment, combining the experience of cervical adenocarcinoma and SCC with small-cell lung cancer. Platinum chemotherapy, radical surgery and/or radiotherapy are performed according to staging, and some progress has been made in the use of immunotherapy and targeted therapy. The present review discusses the pathogenesis, treatment, prognosis and future development direction of treatments for NENs.

Correspondence to: Dr Yanpeng Tian, Department of Pathophysiology, Medical School, Hunan University of Chinese Medicine, 300 Xueshi Road, Changsha, Hunan 410208, P.R. China
E-mail: tianyanp2020@163.com

Dr Ruixia Guo, Department of Gynecology, The First Affiliated Hospital of Zhengzhou University, 1 Jianshe East Road, Erqi, Zhengzhou, Henan 450052, P.R. China
E-mail: grxcdxzzu@163.com

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Contents

1. Introduction

Neuroendocrine neoplasms (NENs) are a heterogeneous group of tumors with neuroendocrine differentiation that can arise in virtually any organ, including the gastrointestinal tract, lungs, head and neck, thymus, thyroid, breasts, skin and genitourinary system. NENs often secrete peptide hormones or biogenic amines, such as serotonin and gastrin, leading to endocrine imbalances (1,2). In the uterine cervix, NENs account for 0.9-1.5% of all cervical malignancies (1). Small-cell neuroendocrine carcinoma (SCNEC) is the most common subtype, followed by large-cell NEC (LCNEC), and their etiology is typically linked to human papillomavirus (HPV) infection, particularly HPV16 and HPV18 (3,4). The 2014 World Health Organization (WHO) classification divided NECs of the cervix (NECCs) into low-grade (carcinoid and atypical carcinoid) and high-grade (small cell carcinoma and LCNEC) groups (5,6). With the growing recognition of notable differences in etiology, pathogenesis, clinical behavior, pathological features, molecular alterations, treatment responses and prognoses, the 2020 WHO classification further distinguished well-differentiated neuroendocrine tumors (NETs) from poorly differentiated NECs (7).

Clinically, patients with NECC often present with abnormal vaginal bleeding or post-coital bleeding, sometimes accompanied by abdominal pain or dysuria, whereas overt carcinoid syndrome is rare (8-12). Gynecological examination may reveal visible lesions, and liquid-based cytology of cervical samples can aid screening (8,13). Compared with cervical squamous cell carcinoma (SCC) or adenocarcinoma (ADC), NECC is markedly more prone to lymphovascular space invasion, lymph node involvement, and both local and distant recurrence (14). However, in clinical practice, the diagnosis of NECC presents notable challenges, as these lesions often share morphological features with poorly differentiated ADC and SCC, rendering routine histopathological evaluation insufficient for accurate classification. Therefore, immunohistochemistry has become essential for differential diagnosis. Neuroendocrine differentiation is typically confirmed by detecting the expression of markers such as chromogranin A (CgA), synaptophysin (SYN), CD56 and neuron-specific enolase (NSE); among these, SYN and CD56 offer the highest sensitivity, whereas CgA is the most specific. More recently, insulinoma-associated protein 1 (INSM1) has emerged as a highly sensitive and specific adjunctive diagnostic marker. Given that nearly all cervical high-grade NECCs are associated with high-risk HPV infection, immunohistochemical staining for p16 also serves as a useful surrogate marker supporting diagnosis (15).

Due to its rarity and the absence of prospective clinical trials, no disease-specific treatment guidelines currently exist; despite advances in genomic profiling, NECC remains an orphan disease in terms of therapeutic development because of its rarity. Clinical decisions are mainly derived from two sources: Surgical options follows the principles of cervical cancer treatment (for example, radical hysterectomy), whereas chemotherapy and chemoradiation regimens are borrowed from small-cell lung cancer (SCLC) (16). This hybrid approach often leads to inconsistent outcomes and high recurrence rates. Moreover, the lack of standardized diagnostic criteria contributes to misclassification. The uncertainty at both diagnostic and therapeutic levels represents an urgent clinical problem to be addressed; moreover, since >60% of patients with stage I-II NECC already exhibit early lymphovascular invasion or lymph node metastasis, this poses additional challenges for prognosis (17).

Current treatment strategies include radical hysterectomy followed by adjuvant chemotherapy or concurrent chemoradiation for early-stage disease; definitive concurrent chemoradiation with or without neoadjuvant chemotherapy for locally advanced disease; and palliative chemotherapy for metastatic disease (1). Platinum combined with etoposide is the most commonly used regimen for advanced stages (18). For recurrent or progressive disease, chemotherapy agents such as topotecan and paclitaxel, as well as the anti-angiogenic targeted agent bevacizumab, are often employed (19,20). Notably, the rapid development of targeted therapies and immunotherapies has provided novel options for treatment. For example, immune checkpoint inhibitors (ICIs), such as the anti-programmed cell death protein 1 (PD-1) monoclonal antibody pembrolizumab, have shown activity against small-cell NECC (SCNECC) and may also benefit HPV-associated metastatic or recurrent non-SCNECC (21,22). Combining ICIs with radiotherapy and chemotherapy holds promise for improving clinical outcomes. Nevertheless, current evidence remains limited to case reports, and the lack of robust clinical trials and evidence-based guidelines poses notable challenges for gynecological oncologists. Furthermore, recent studies have identified potentially actionable molecular alterations in NECC, including delta-like 3 (DLL3) expression and activation of the PI3K/AKT/mTOR (PAM) pathway (23,24). Therefore, translating these molecular insights into targeted interventions has academic importance and clinical value. The present systematic review summarizes the pathogenesis, pathological features, treatment modalities and overall prognosis of NECC, explores future therapeutic prospects, and offers practical recommendations to aid clinicians in diagnosing and managing this aggressive disease. A deeper understanding of NECC biology is expected to reveal novel therapeutic targets for personalized treatment, ultimately leading to innovative and effective therapies.

2. Classification and pathological characteristics

Albores-Saavedra *et al* (25) first described NENs in 1979. In 1997, a seminar organized by the American Society of Pathologists Cancer Committee and the National Cancer Institute recommended a unified term for these tumors, similar to the classification found in the lungs, including small-cell carcinoma, LCNEC, carcinoid tumors and atypical carcinoid tumors (8). In recent years, the classification of NEN has been updated. According to the degree of differentiation, NENs can be divided into NETs and NECs. Essentially, tumors composed of cells that retain the molecular and morphological characteristics of neuroendocrine cells and are well-differentiated are considered NETs. According to the 2020 WHO classification of female genital tumors, cervical NETs are graded based on mitotic count and Ki-67 proliferation index into G1 and G2; however, G3 NETs are not recognized in the uterine cervix (26-28). By contrast, tumors composed of cells with severe dysplasia, abnormal molecular or genetic features, retained expression of neuroendocrine markers and poor differentiation are classified as NECs, which are high-grade neoplasms. NECs are further divided into SCNEC and LCNEC. In addition, a few mixed neuroendocrine-non-NENs exist, in which the non-neuroendocrine component may include ADC or SCC (28). Cervical NETs are rare and rely on histopathology for diagnosis; they exhibit structural and cellular characteristics similar to non-tumor neuroendocrine cells, including nest-like and trabecular growth patterns, punctate chromatin and prominent blood vessels (Table I) (29-33). Table II lists the changes in WHO classification from 2014 to 2020, which have clinical importance. First, the clear distinction between NET (G1/G2) and NEC (G3) avoids the previous confusion between indolent and aggressive NENs, thereby preventing overtreatment of NETs with systemic chemotherapy or undertreatment of NEC with limited surgery alone. Second, the introduction of specific diagnostic criteria and grading thresholds (based on mitotic counts and Ki-67) enables more reproducible histopathological diagnosis and risk stratification. Third, the combination of molecular features (for example, p53/Rb status) aids in differential diagnosis and provides potential options for targeted therapy. Finally, a unified classification framework facilitates cross-center comparisons, multicenter

Table I. Pathological characteristics of cervical neuroendocrine neoplasms.

Type	Cell morphology	Cytoplasm	Chromatin	Nucleus	Mitosis/Ki-67 proliferation index	Necrosis
CC	Uniform cells, arranged in a nest, organoid or trabecular pattern	Abundant	Characteristic granular chromatin	Prominent nucleoli with a nested, island, organoid, spindled or trabecular pattern	Ki-67 ≤3%; ≤2/10 HPF	Rare
CAC	Epithelioid/spindled cell, arranged in a nest, trabecular or palisade shape	Scant or abundant	Characteristic granular chromatin	Greater degree of nuclear atypia than CC	Ki-67 >3%; 2-10/10 HPF	Rare
SCNECC	Ovoid, poorly cohesive tumor cells with diffuse growth, arranged in a trabecular, nested or rosette-like manner	Scant	Condensed	Nuclear molding	Ki-67 >20%; >20/10 HPF	Numerous necrotic and apoptotic bodies
LCNECC	Large and polygonal tumor cells arranged in a nest, organoid, trabecular, rosette-like or palisade patterns, with well-defined borders	Moderate	Coarse, dispersed	Vesicular or hyperchromatic nuclei, single or multiple prominent nucleolus	Ki-67 >20%; >20/10 HPF	Extensive necrosis

CAC, cervical atypical carcinoid; CC, cervical carcinoid; HPF, high power fields; LCNECC, large-cell NECC; NECC, neuroendocrine carcinoma of the cervix; SCNECC, small-cell NECC.

clinical trials and standardized management of NENs of the female reproductive tract (7,28,34-36).

In the presence of these typical morphological features, immunohistochemical diagnosis is not necessary (1); however, poorly differentiated NECC is easily confused with poorly differentiated ADC, adenosquamous cell carcinoma (ADSCC) or undifferentiated carcinoma, resulting in misdiagnosis or delayed diagnosis. Immunohistochemical markers serve an important role in differential diagnosis and targeted therapy. The four most commonly used neuroendocrine markers include Syn, CD56, NSE and CgA, with Syn and CD56 being the most sensitive (33). However, CD56 is also positive in other types of cervical cancer and therefore has the lowest specificity (37). In addition, single CgA-positive neuroendocrine cells have been detected in a few cases of NET-related intraepithelial or infiltrating ADC (38). Therefore, accurate diagnostic classification requires the combined use of multiple molecular markers. The expression of other neuroendocrine markers, such as serotonin, somatostatin, gastrin and glucagon, have been detected in SCNEC (39). Thyroid transcription factor 1 (TTF-1), a typical marker of SCLC, is rare in cervical SCNEC. McCluggage *et al* (38) tested 13 cases of SCNEC and 8 cases of LCNEC, of which 15 cases were TTF-1 positive (11 SCNEC cases and 4 LCNEC cases). Furthermore, p16 is a cyclin-dependent kinase inhibitor associated with high-risk HPV, and NECC typically exhibits strong expression of p16 (4). In recent years, new immunohistochemical markers have been applied for the diagnosis of NECC. Kuji *et al* (40) studied the expression of INSM1 in high-grade NECC, and revealed that the sensitivity and specificity of INSM1 expression were 94 and 98%, respectively. The notable expression of transcription factors, such as causal-type homeobox transcription factor 2 and somatostatin receptor (SSTR) subtypes SSTR2-SSTR5, also provides potential novel biomarkers for the differential diagnosis and targeted treatment of this rare disease (41). For the present review, a retrospective analysis of >60 cases of data reported in the literature in recent years was conducted; the results revealed that both pure and mixed samples exhibit expression of at least two neuroendocrine markers (Table III) (30,42-46). The positivity rates of the aforementioned indicators were 74.6% (CgA), 87.5% (SYN), 77.6% (CD56) and 54.2% (NSE), respectively. Almost all tumors exhibited a high Ki67 proliferation index of 45-98% (median, 87.5%). In some cases, mixed cervical neoplasms with a NECC component (intraepithelial or invasive) were found, strongly suggesting a cervical origin. Overall, further research is needed to validate the prognostic and predictive value of immunohistochemical expression in patients with NECC. Table IV lists the major mutated pathways and potential targeted drugs for NECC (47-49).

Table II. Comprehensive comparison of WHO 2014 and 2020 classifications of cervical NENs.

Criterion	WHO 2014 (4th edition) (6)	WHO 2020 (5th edition) (26-28)
Classification framework	NENs scattered across organ chapters; non-uniform nomenclature	Under the WHO/International Agency for Research on Cancer NEN framework, the distinction between well-differentiated NETs and poorly differentiated NECs is emphasized
NET vs. NEC distinction	Low-grade and high-grade NENs were recognized, but terminology and grading were less harmonized; carcinoid/atypical carcinoid and SCNEC/LCNEC were listed as separate entities rather than being integrated into a unified NET/NEC framework	Clear binary classification: • Well-differentiated NET (G1/G2) • Poorly differentiated NEC (SCNEC and LCNEC types) • No evidence of NET progression to NEC
Diagnostic criteria for NET	Not defined	Must meet all: i) Morphology: Organoid/trabecular/glandular pattern; ii) IHC: Positivity of more than one neuroendocrine marker (Syn, CgA, CD56); iii) absence of high-grade nuclear atypia and geographical necrosis
Grading of NET	No explicit grading	G1: Mitoses <2/mm^2 or Ki-67 ≤3% G2: Mitoses 2-20/mm^2 or Ki-67 3-20% Thresholds derived from cross-system consensus; caution needed in the gynecological tract
Diagnostic criteria for NEC	Morphology-based, no quantitative standards	NEC: High grade (G3) • High mitotic count (usually >20/mm^2) • Common geographic necrosis • SCNEC vs. LCNEC types • Ki-67 usually >20% (ancillary)
Molecular features	No molecular information included	• G3 NEC: Cervical NECs are commonly associated with high-risk HPV infection, particularly HPV16 and HPV18, and often show diffuse p16 expression; alterations involving TP53/RB pathways have been reported, but molecular testing is not yet required for routine classification • G1/G2 NET: May involve MEN1, DAXX, ATRX mutations (mainly evidence from pancreatic NETs)
Prognostic stratification	No unified prognostic model; all treated as 'small cell carcinoma'	• G1/G2 NET: Very rare in the gynecological tract; overall better prognosis than NEC • G3 NEC (SCNEC/LCNEC): G3 NECs are aggressive and usually require multimodal treatment, commonly including platinum/etoposide-based chemotherapy with surgery and/or radiotherapy depending on the circumstances

CgA, chromogranin A; HPV, human papillomavirus; IHC, immunohistochemistry; LCNEC, large-cell NEC; NEC, neuroendocrine carcinoma; NEN, neuroendocrine neoplasm; NET, neuroendocrine tumor; SCNEC, small-cell NEC; Syn, synaptophysin; WHO, World Health Organization.

3. Pathogenesis

NENs are rare diseases that develop in neuroendocrine cells, most commonly involving the gastrointestinal, pancreatic and pulmonary systems (50). Cervical NENs are most likely to undergo neuroendocrine metaplasia and proliferation from normal cervical endometrial neuroendocrine cells or cervical epithelial neuroendocrine multipotent reserve cells (51). However, the specific pathogenesis remains unclear. High-risk HPV is involved in the occurrence of tumors, as well as a series of molecular biological events, such as gene mutations and epigenetic regulation (30).

With the continuous advancement of sequencing technology and publication of a large number of publicly available pan-cancer studies, mutations driving the occurrence and development of NECC are constantly being discovered and

Table III. Expression of neuroendocrine markers in NECC.

First author, year	Type	Phase	SYN	CD56	NSE	CgA	CK8/18	CK5/6	p16	Ki-67	EMA	Vim	LCA	TTF-1	CDX2	CK7	P40	p53	SSTR2A	SSTR5	ER	PR	(Refs.)
Inzani, 2020	LCNEC	IB1-IVB	6 (6)	4 (6)		6 (6)			5 (6)	6 (6)				2 (6)	6 (6)		0 (6)	6 (6)	4 (6)	4 (6)			(41)
Habeeb, 2019	LCNEC	IIA2	1 (1)	1 (1)		1 (1)	1 (1)	0 (1)	1 (1)	1 (1)													(42)
Inzani, 2020	SCNEC	IA2-IVA	10 (10)	10 (10)		9 (10)			10 (10)	10 (10)				3 (10)	2 (10)		0 (10)	10 (10)	5 (10)	7 (10)			(41)
Lu, 2022	SCNEC	IB-IV	13 (14)	11 (13)	2 (4)	11 (14)	3 (3)	2 (5)	5 (5)	8 (8)	1 (3)	1 (4)											(5)
Pang, 2021	SCNEC	I-IV	17 (20)	13 (20)	11 (20)	13 (20)				12 (20)				5 (20)									(43)
Sah, 2022	LG-NET	IA1-IIIC1	2 (3)	2 (3)		2 (3)	2 (3)		1 (3)	3 (3)				1 (3)	0 (3)						0 (0)		(44)
Ortiz, 2022	NEC	IVB	1 (1)	1 (1)				0 (1)	1 (1)					0 (1)		1 (1)					1 (1)		(45)
Lamiman, 2024	LCNEC	IB2-IVB	2 (2)			1 (2)		0 (1)	2 (2)								1 (2)						(46)
	SCNEC	IVB	1 (3)	2 (3)		1 (3)			1 (3)								0 (3)						
	MiNEN	IB1-IIB	1 (2)			1 (2)		0 (2)	2 (2)								0 (2)						
	LCNEC + SCNEC	IIB	1 (1)			1 (1)		0 (1)	0 (1)														
Ling, 2018	CAC	-	1 (1)	1 (1)		1 (1)			1 (1)	1 (1)													(30)

Numbers are presented as positive cases (total tested cases). Blank cells indicate that the marker was not tested in the corresponding study. CAC, cervical atypical carcinoid; CDX2, causal-type homeobox transcription factor 2; CgA, chromogranin A; CK, cytokeratin; EMA, epithelial membrane antigen; ER, estrogen receptor; LCNEC, large-cell NEC; LG-NET, low-grade neuroendocrine tumor; MiNEN, mixed neuroendocrine-non-neuroendocrine neoplasm; NEC, neuroendocrine carcinoma; NECC, NEC of the cervix; NSE, neuron-specific enolase; PR, progesterone receptor; SCNEC, small-cell NEC; SSTR, somatostatin receptor; SYN, synaptophysin; TTF-1, thyroid transcription factor 1; Vim, vimentin.

Table IV. Signaling pathways in NECs.

A, SCNECC

Mutated pathway	Potential therapeutic targeted drugs	(Refs.)
PI3K/AKT/mTOR (PIK3CA, PTEN, AKT3, NF1, ERBB4, RICTOR, TSC1/2, ATR)	mTOR inhibitor: Everolimus; AKT inhibitor: Uprosertib; PI3K inhibitor: BEZ235	(55,95-98)
MAPK (RAS, MEK)	MEK inhibitor: Trametinib; BRAF inhibitor: Dabrafenib; KRAS inhibitor: AMG510	(47,48)
RTK (ERBB2, FLT3, ROS1)	RTK inhibitor: Sunitinib	(49,60)
p53 (TP53, ATM, MDM4)	ATM inhibitor: AZD0156	(102,149)
Myc (L-Myc, N-Myc)	Myc inhibitor: MRT-2359	(155)
JAK/STAT, GNAS, SOX2, CTNNB1, SMAD4	None	(52,60,89,156)

B, HGNECC

Mutated pathway	Potential therapeutic targeted drugs	(Refs.)
RB1	CDK4/6 inhibitor: Abemaciclib	(154)

NECC, NEC of the cervix; SCNECC, small-cell NECC.

proven. Comparative genomic data have shown that SCNECC is genetically closer to common subtypes of cervical cancer than other small-cell neuroendocrine cancers of the lungs and bladder (52). A high-level NECC (n=97) genome map containing 79 SCNECCs revealed that the most frequently altered genes were PIK3CA (19.6%), Myc (15.5%), TP53 (15.5%) and PTEN (11.3%) (53). Additionally, somatic mutations such as ERBB2, c-Myc, Notch1, BCL6, NCOA3, RB1, BRCA1/2 and ARID1B are involved (53), and research into the underlying molecular mechanisms and clinical trials are currently being carried out. The application of the PAM pathway inhibitors everolimus/uprosertib (54,55), the RTK/RAS pathway inhibitors sunitinib/trametinib and the VEGF pathway inhibitor bevacizumab suggest great promise for gene-targeted therapy in NETs (56-60).

Research has suggested that integration of HPV into the host genome is the most important event in the evolution of cervical cancer. In a large-scale international study on invasive cervical cancer, it was revealed that the distribution of HPV types in NET is similar to that in ADC and ADSCC, and the detection rate of HPV18 is higher than that of HPV16, indicating that HPV18 has a higher affinity for glands and neuroendocrine cells (61). SCNECC is the most common subtype of NEC, whereas the incidence of large-cell NECC (LCNECC) is relatively low. This may be because of the recognition of focal areas based on squamous or glandular differentiation. The neuroendocrine characteristics of LCNECC are easily overlooked, making differential diagnosis between poorly differentiated SCC and ADC more difficult (62). In a previous study, Grayson *et al* (63) reported that the positivity rates of HPV16 and HPV18 were 77.8 and 22.2% in LCNECC, respectively. After integrating the viral genome into infected host cells, the encoding proteins E6 and E7 isolate the cell ubiquitin proteasome system, promoting rapid degradation of the tumor suppressor proteins p53 and Rb1, respectively (64). In addition, the E6 protein leads to cell immortalization by activating the telomerase catalytic subunit (65). In addition to binding to Rb, E7 promotes cell proliferation and reduces apoptosis by upregulating the expression of phosphorylated-cdc2 and activating cyclin-dependent kinase 2 (66). Furthermore, BRCA1 interacts with the HPV oncoprotein and antagonizes the inhibition of c-Myc transactivation by BRCA1 through the zinc finger domains of E6 and E7, which may be involved in NENs (67). Targeted drugs for HPV oncogene E6/E7 are constantly being developed (68).

In addition to its direct oncogenic effects, persistent high-risk HPV infection may profoundly shape the immune microenvironment of NECC. The viral oncoproteins E6 and E7 are continuously expressed in HPV-associated cervical cancer and can theoretically serve as tumor-specific antigens; however, HPV-driven tumors often develop multiple mechanisms to evade immune surveillance. HPV E6 and E7 have been reported to interfere with antigen processing and presentation by downregulating components of the major histocompatibility complex class I pathway, impairing transporter associated with antigen processing activity, and suppressing interferon-related antiviral signaling. These changes may reduce the recognition of tumor cells by cytotoxic $CD8^+$ T lymphocytes and contribute to immune escape during cervical carcinogenesis (69-72).

HPV-associated tumorigenesis may also alter T-cell function and promote an immunosuppressive microenvironment. Persistent viral antigen stimulation can induce T-cell exhaustion, which is characterized by increased expression of inhibitory receptors, such as PD-1, T cell immunoglobulin and mucin-domain containing-3 (TIM-3) and lymphocyte activation gene-3 (LAG-3), and reduced effector cytokine production (73). Furthermore, tumor cells and tumor-associated

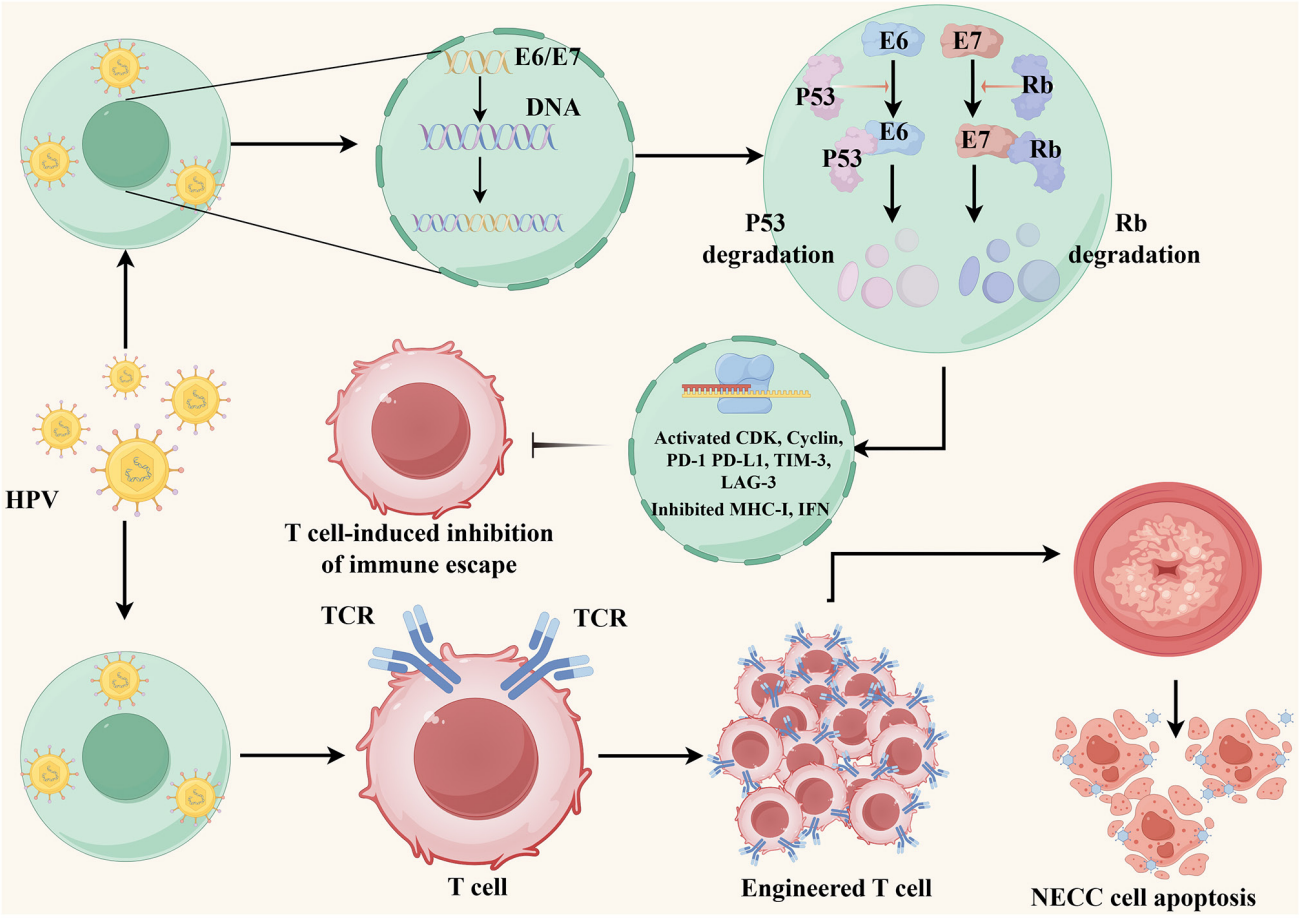

Figure 1. Mechanism of HPV infection, genetic alterations, tumor immune microenvironment and therapeutic resistance in NECC. Persistent infection with HPV drives the formation of an immunosuppressive tumor microenvironment. A critical step in this process is the integration of the HPV genome into the host DNA, leading to the constitutive upregulation of the viral oncoproteins E6 and E7. These oncoproteins not only drive malignant transformation by targeting host tumor suppressors (P53 and Rb) but also contribute to immune evasion. Chronic antigenic stimulation by HPV E6/E7 leads to T-cell exhaustion, characterized by the upregulation of inhibitory receptors such as PD-1, TIM-3 and LAG-3, alongside impaired secretion of effector cytokines. Concurrently, both tumor cells and tumor-associated immune cells upregulate the expression of PD-L1, which engages the PD-1/PD-L1 axis to further suppress antitumor T-cell activity. Engineering T cells, which could express TCRs and recognize cancer cells, may be a promising immune therapy. Created with Figdraw (www.figdraw.com). CDK, cyclin-dependent kinase; HPV, human papillomavirus; IFN, interferon; LAG-3, lymphocyte activation gene-3; MHC-I, major histocompatibility complex I; NECC, neuroendocrine carcinoma of the cervix; PD-1, programmed cell death protein 1; PD-L1, programmed death ligand 1; TCR, T-cell receptor; TIM-3, T cell immunoglobulin and mucin-domain containing-3.

immune cells may upregulate programmed death ligand 1 (PD-L1), thereby suppressing antitumor T-cell activity through the PD-1/PD-L1 axis (74). In NECC, PD-L1 expression has been reported to possess considerable heterogeneity across studies, and its expression has been observed in tumor cells and/or tumor-infiltrating immune cells (75-77). This heterogeneity may partly explain the inconsistent responses to ICIs in NECC and highlights the need for a more comprehensive immune profiling strategy rather than reliance on PD-L1 alone (78).

The immune microenvironment of NECC may also be influenced by neuroendocrine lineage programs and HPV-related molecular alterations. High-grade NECs frequently exhibit abnormalities in TP53, RB1, PAM and Notch signaling, which may interact with inflammatory and immune regulatory pathways (79-81). For example, activation of the PAM pathway has been linked to PD-L1 regulation and immune resistance in several types of cancer, suggesting that HPV-related oncogenic signaling may indirectly contribute to immune suppression (82). Future studies should therefore characterize NECC using multiplex immunohistochemistry, spatial transcriptomics, single-cell sequencing, and integrated analyses of HPV integration, antigen presentation machinery, T-cell infiltration, immune checkpoint expression and myeloid cell composition. Such approaches may help identify patients who are more likely to benefit from immune checkpoint blockade, or combinations of immunotherapy with chemotherapy, radiotherapy, poly(ADP-ribose) polymerase inhibitors (PARPi), anti-angiogenic agents or targeted therapy. Fig. 1 shows the mechanism of HPV infection, genetic alterations, tumor immune microenvironment and therapeutic resistance in NECC.

The angiogenic microenvironment in solid tumors generates hypoxic regions, which can regulate the differentiation of certain tumors and pluripotent stem cells (83,84). Kubota *et al* (85) established a cancer tissue-originated spheroid cell line to study the effect of hypoxia on the neuroendocrine differentiation of SCNECC. The results showed that under hypoxic conditions, the dedifferentiation of SCNECC was regulated by hypoxia inducible factor-1α (HIF-1α) and

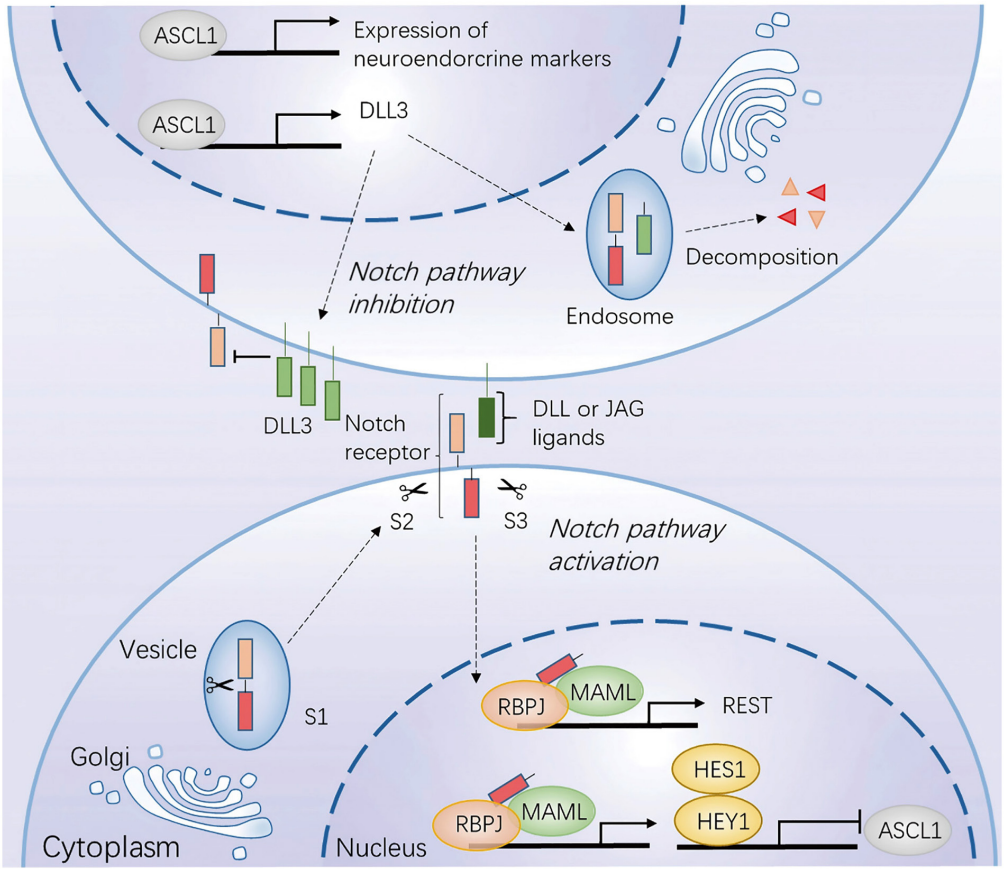

Figure 2. Notch pathway signaling (based on studies in small-cell lung cancer and other neuroendocrine neoplasms). The Notch receptor is synthesized into a single peptide precursor in the Golgi apparatus and is then cleaved three times to activate the Notch receptor, thereby transmitting signals from the cell surface to the nucleus. The first cleavage (S1) is mediated by furin-like convertase in the Golgi, forming a heterodimer consisting of the Notch extracellular domain, Notch transmembrane fragment and NICD, which can migrate to the cell membrane. After the Notch complex binds to the ligand (DLL3 or JAG) to complete S2 and S3 cleavages, NICD is released into the cytoplasm and translocated into the nucleus where it binds to the RBPJ/MAML complex, recruiting the protein family (MAML1-3) and inducing the expression of multiple target genes, including HES and HEY family genes. HES1 and HEY1 are transcriptional repressors of ASCL1 that have critical functions in neuroendocrine cell development. ASCL1 can enhance the expression of DLL3, an inhibitory ligand of the Notch receptor. DLL3 is transcribed and synthesized in the nucleus, expressed in large amounts in the Golgi apparatus and in small amounts on the cell surface. DLL3 binds to Notch in the Golgi and retains it in the endosomal compartments. In addition, DLL3 inhibits Notch on the surface of small-cell lung cancer cells through cis-interactions. ASCL1, achaete-scute homolog 1; DLL3, delta-like protein 3; JAG, Jagged; MAML, mastermind-like family of proteins; NICD, Notch intracellular domain; RBPJ, recombination signal binding protein for immunoglobulin κJ region.

Notch signaling (85), and the Notch pathway has been shown to be activated under hypoxic conditions in the aforementioned cancer tissue-originated spheroid cell line (85,86). By contrast, knockdown of HIF-1α and the Notch inhibitor DAPT have been shown to attenuate the hypoxia-induced expression inhibition of the neuroendocrine markers CgA, SYN and CD99 (membrane protein marker of SCNECC), thus indicating that hypoxia might be one of the factors regulating the differentiation status of NECC. In summary, these results suggest that hypoxia may be an important factor in regulating neuroendocrine differentiation in SCNECC; however, gene mutations and activation of some signaling pathways may also serve important roles in this process.

The Notch pathway is a highly conserved cellular signaling pathway associated with malignant transformation, cell proliferation, cell cycle arrest and apoptosis, epithelial-mesenchymal transition and inhibition of neuroendocrine differentiation (87). DLL3 is an atypical inhibitory ligand of Notch receptors involved in NEC/NET development, which is located in the cytoplasm and can also be expressed on the tumor cell membrane (88). A large NECC cohort study on potential targeted biomarkers showed that high expression of DLL3 was observed in 81% of tumors (89). DLL3 regulates Notch signaling by blocking the localization of Notch receptors on cell surfaces and redirecting them to endosomes for degradation, thereby promoting tumor development (90). The combination of DLL3 inhibition and immunotherapy is considered a therapeutic option for LCNECC (91). DLL3-negative NECCs tend to carry PIK3CA and PTEN mutations, which are involved in the regulation of the PAM signaling pathway (89). A previous study revealed that a Notch1 mutation was present in SCNEC without PIK3CA mutation, and that mutant Notch1 can activate c-Myc and PAM signals through transcriptional inhibition of PTEN, and promote growth factor receptor signal transduction to PI3K/AKT (56). Fig. 2 shows the molecular mechanisms of Notch signaling pathway in NETs.

Abnormal activation of the PAM pathway is common in numerous types of cancer, leading to malignant growth and treatment resistance. Thus, it is a promising therapeutic target for cancer treatment in clinical studies (92,93). The crosstalk between this pathway and HPV oncogenes depends on the cellular metabolism and oxygenation state (94). Under normoxic

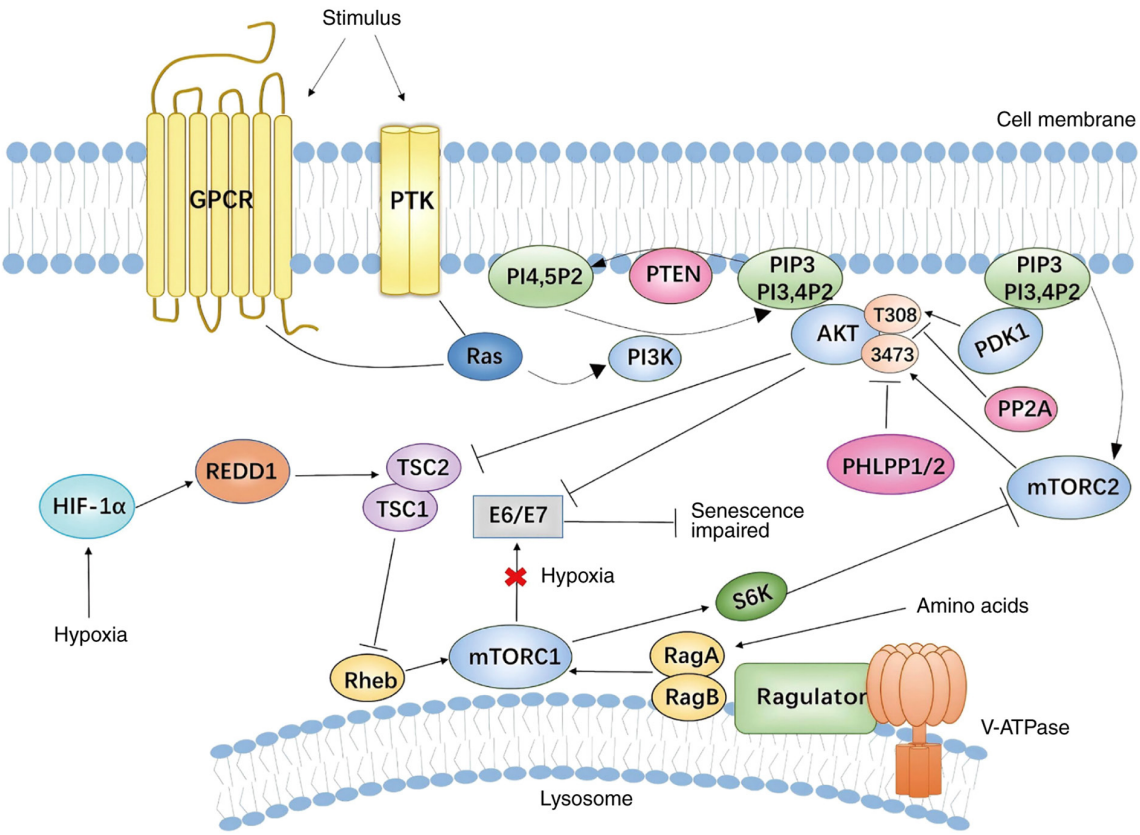

Figure 3. Crosstalk between carcinogenic HPV and the PI3K/mTOR/AKT signal cascade. After receiving extracellular stimulation, GPCR or RTK activate PI3K under the mediation of Ras GTPases, and active PI3K produces PIP3 and PI(3,4)P2, thus recruiting AKT to the cell membrane. Phosphoinositol-dependent PDK1 and mTORC2 activate AKT via phosphorylation. Activated AKT is negatively regulated by direct dephosphorylation through PP2A and PHLPP1/2, and by dephosphorylation of phosphoinositides through PTEN. AKT can inhibit TSC2, which is combined with TSC1 as a GTPase-activating protein of Rheb to activate mTORC1. mTORC1 can also coordinate negative feedback regulation and suppress mTORC2 by activating S6K. Rheb and RagA:RagB heterodimers are necessary for mTORC1 activation. Amino acid-dependent RagA:RagB interacts with the lysosomal-associated protein complex Ragulator, which binds to the lysosomal V-ATPase. Under normoxia, active mTORC1 signaling promotes cellular senescence upon E6/E7 repression. Under hypoxia, however, mTORC1 signaling is impaired, allowing HPV-positive cancer cells to evade senescence. In parallel, hypoxia induces activation of the PI3K/mTORC2/AKT cascade, which mediates downregulation of the viral oncogenes E6/E7. Under hypoxia, HIF-1α mediates the expression of REDD1 to activate TSC2, thus inhibiting mTORC1 signaling. GPCR, G protein-coupled receptor; HIF-1α, hypoxia inducible factor 1α; HPV, human papillomavirus; mTORC, mTOR complex; TSC, tuberous sclerosis complex.

conditions, active mTOR complex 1 (mTORC1) signaling inhibits E6/E7 expression to achieve cellular senescence. However, when mTORC1 signaling is damaged by hypoxia, under the regulation of the upstream regulator mTORC2 and active PI3K, AKT mediates E6/E7 downregulation, causing HPV-positive cancer cells to escape senescence (95). Extensive research over the past few years has provided a better understanding of the mechanism of this complex network (94,95). Fig. 3 shows the crosstalk between carcinogenic HPV and the PI3K/mTOR/AKT signaling cascade. Studies have revealed that PAM pathway inhibitors regulate tumor cells by regulating immune cells and affecting the tumor microenvironment (96,97). Targeting the PAM pathway can reduce PD-L1 expression in tumor cells to enhance the antitumor effect of immune checkpoint blockage (98). A previous study reported that the KRAS mutation rate was 12% in NECC in human patients worldwide (3). A case report showed that one patient with a KRAS mutation (c.35G>Ap.G12D) received treatment with the MAPK kinase (MEK) inhibitor trametinib and achieved complete imaging remission after 3 cycles (99), thus indicating that patients with KRAS mutations may benefit from MEK inhibitors. G12D mutations can simultaneously activate the PI3K/AKT and MAPK pathways; however, G12V KRAS mutations activate MEK signaling and result in KRAS losing its ability to bind to PAM. Tumor cells with G12V KRAS mutations may be more sensitive to MEK inhibitors (Fig. 3) (59).

4. Treatment

NECs arising from different organs often share aggressive biological behavior, high Ki-67 index, early metastatic potential and dependence on immunohistochemical confirmation. Our previous reports on gallbladder NEC and endometrial NEC further support the diagnostic and therapeutic challenges of rare extrapulmonary NECs, providing a useful reference for understanding NECC (100,101).

Because NECC is rare, treatment strategies have historically been extrapolated from SCLC, especially the use of platinum-etoposide-based chemotherapy and, more recently, ICI combinations. This extrapolation is biologically reasonable to some extent. SCNECC and SCLC share several aggressive neuroendocrine features, including poorly differentiated morphology, high proliferative activity, a high Ki-67 index, expression of neuroendocrine markers such as SYN,

CgA, CD56 and INSM1, early lymphovascular invasion and a propensity for distant metastasis (33,102-106). These shared features partly explain why platinum-etoposide regimens, which are active in SCLC, have been adopted as the chemotherapy backbone for high-grade NECC (107).

However, these similarities should not obscure important disease-specific differences. Unlike SCLC, which is strongly associated with tobacco exposure and is characterized by near-universal inactivation of TP53 and RB1 (108), NECC is predominantly driven by high-risk HPV infection, particularly HPV16 and HPV18 (81). HPV E6 and E7 oncoproteins mediate functional inactivation of p53 and Rb and create a distinct viral oncogenic background that is absent in SCLC (109). In addition, genomic studies have suggested that NECC is molecularly closer to HPV-associated cervical carcinoma than to pulmonary SCLC, with recurrent alterations involving PIK3CA, Myc, PTEN, KRAS, ERBB2, and components of the PAM and Notch pathways (79,81). By contrast, SCLC typically shows a smoking-related mutational signature, very high genomic instability and frequent concurrent TP53/RB1 loss; therefore, SCLC should be considered a useful but imperfect therapeutic model for NECC (108).

These biological distinctions have direct clinical implications. Although platinum-etoposide remains a rational first-line regimen for high-grade NECC, its benefit and optimal combination partners should be validated in NECC-specific cohorts (110). Similarly, the success of adding PD-1/PD-L1 inhibitors to platinum-etoposide in extensive-stage SCLC cannot be directly translated to NECC, because NECC shows heterogeneous PD-L1 expression, generally preserved mismatch repair (MMR) status, variable immune-cell infiltration and an HPV-driven tumor microenvironment (111-113). Future studies should therefore stratify patients according to NECC-specific biomarkers, including HPV status, PD-L1/tumor-infiltrating lymphocytes (TILs), microsatellite instability (MSI)/MMR status, PARP1 expression, DLL3 expression and actionable genomic alterations. Dedicated multicenter trials or rare-tumor basket studies are needed to determine which SCLC-derived regimens are truly applicable to NECC and which strategies should be developed specifically for this disease.

Given the invasiveness of NECC, current treatment plans focus on multimodal therapy, combining the experience of cervical ADC and SCC with SCLC, and performing platinum chemotherapy, radical surgery and/or radiotherapy according to staging (114). Owing to the higher incidence of early lymph node metastasis and distant metastasis in NECC, the prognosis of NECC is worse than that of other types of cervical cancer, such as SCC (16). Late stage, lymph node metastasis, deep interstitial infiltration, lack of chemotherapy and large tumor volume are all associated with a poor prognosis (29). A study of 172 patients with NET revealed that patients receiving radiotherapy had a better 5-year overall survival (OS) rate and 5-year progression-free survival (PFS) rate than those of patients not receiving radiotherapy, but the difference was not statistically significant (29). In addition, Ruiz *et al* (115) demonstrated that the 5-year OS of patients with stage I NECC treated primarily with radiotherapy and chemotherapy was similar to that of patients treated with surgical intervention. Hou *et al* (116) also reported that there was no significant difference in 5-year OS between patients with high-grade NECC undergoing radical surgery and those undergoing initial radiotherapy without surgery. Surgery combined with adjuvant radiotherapy and chemotherapy may be the best treatment for patients with early NET. Research has shown that the combination of external radiation therapy and close-range radiation therapy improves the median survival of locally advanced NECC (117). Research on the treatment of distant metastatic NECC is limited, and radical pelvic radiotherapy combined with chemotherapy may improve the survival rate of patients with stage IVB NECC (118). NECC does not have a standardized chemotherapy regimen; therefore, it is usually treated in a similar manner to pulmonary NEC, which includes systemic platinum chemotherapy or platinum combined with etoposide chemotherapy. Effective treatment options for recurrent high-grade NECC main unknown. Chemotherapy with topotecan, paclitaxel and bevacizumab has been shown to improve NECC prognosis (119). Furthermore, combination therapy with nivolumab and iprivumab may be a potential novel treatment option for recurrent SCNECC (120).

Numerous genomic analyses have revealed a high degree of similarity between NECC and non-neuroendocrine cervical cancer (56,121,122). Identifying common genetic and immune microenvironmental features in non-endocrine cervical cancer may help in selecting targeted treatment options for rare and difficult-to-treat NECC. Immunotherapy for cervical cancer is considered to have future potential, especially after the approval of pembrolizumab (anti-PD1) combined with chemotherapy as a first-line treatment for metastatic and recurrent PD-L1-positive cervical cancer (52). In addition, immunotherapy and targeted therapy for NEC also progressed, including PD-1/PD-L1 inhibitors and PARPi. Previous case reports on metastatic NECC have described notable therapeutic effects using the anti-PD1 drug nivolumab as monotherapy or in combination with radiotherapy (123). As an anti-PD-1 antibody, pembrolizumab has been approved by the United States Food and Drug Administration for the treatment of recurrent cervical cancer with PD-L1 expression [combined positive score (CPS) ≥1] (124). In a comprehensive analysis of two prospective studies, pembrolizumab has been shown to be safe for use in metastatic high-grade NENs, but its efficacy as a single drug is limited (125). Furthermore, a double-blind, placebo-controlled phase III trial (n=403) targeting previously untreated patients with extensive SCLC confirmed that adding the ICI atezolizumab (anti-PD-L1) to carboplatin and etoposide chemotherapy markedly improved OS and PFS compared with chemotherapy alone (126).

However, treatment methods for advanced NECC remain unclear. In a study of 20 patients with NECC, 70% (n=14) had high expression of PD-L1 (112), and similar results were found in other cohorts of NECC (127). Another case report described a patient with late-stage NECC with liver metastasis who achieved sustained complete remission using neoadjuvant platinum therapy and a multimodal approach of atezolizumab, surgical resection and atezolizumab maintenance (128). Furthermore, patients with stage IVB SCNECC and bone and liver metastases have achieved notable outcomes with a combination of pembrolizumab and chemoradiation (129). Another PD-1 inhibitor, nivolumab, combined with radiotherapy has shown therapeutic efficacy in patients with LCNECC (130). In

addition, one patient with metastatic SCNECC has achieved complete remission following treatment with nivolumab and radiotherapy (131). Unfortunately, a phase II trial using pembrolizumab monotherapy for recurrent SCNECC was discontinued owing to unsatisfactory efficacy (132,133). Based on these experimental results, it may be hypothesized that targeting PD-1/PD-L1 alone, especially with ICI monotherapy, may not ensure sufficient control of NECC after first-line treatment failure. Nonetheless, the potential utility of ICIs in combination with radiotherapy and chemotherapy deserves further study; for example, the data from the KEYNOTE-604 study emphasized that adding pembrolizumab to etoposide + cisplatin as first-line treatment improved PFS (HR=0.75; P=0.0023) and OS (HR=0.8; P=0.0164) in patients with extensive SCLC (134). The PD-L1 blockers atezolizumab and durvalumab have also been shown to be effective in extensive-stage SCLC as first-line treatments (HR value for OS rate for atezolizumab, 0.70; P=0.007, and HR value for OS rate for durvalumab, 0.73; P=0.0047) (126,135). These findings suggest that adding ICIs to the current chemotherapy regimens may enhance therapeutic efficacy in SCNECC.

The response to ICIs in NECC remains heterogeneous, and PD-L1 expression alone is unlikely to be sufficient for patient selection. Reported PD-L1 positivity rates in NECC vary widely, ranging from ~10 to 70% across different studies (77,89,112,127,136,137). This discrepancy may be explained by several factors, including small cohort sizes, differences in antibody clones and scoring systems, variable cut-off values for PD-L1 positivity, evaluation of tumor cells vs. tumor-infiltrating immune cells, and differences in sample source, such as primary tumors, metastatic lesions, biopsies or resection specimens. In addition, intratumoral heterogeneity and prior chemotherapy or radiotherapy may alter PD-L1 expression and immune-cell infiltration. Therefore, PD-L1 should be interpreted together with the broader immune contexture rather than as an isolated biomarker. In particular, tumors with low T-cell infiltration, low antigen presentation activity or scarce inflammatory cytokine signaling may represent an 'immune-cold' phenotype, which could partly explain the limited activity of ICI monotherapy observed in recurrent SCNECC (132).

The DNA MMR system can correct errors that occur during DNA replication, and its defects can lead to the accumulation of coding and non-coding microsatellite mutations. This phenotype is called MSI, and immunohistochemical detection of MMR proteins (MLH1, MSH2, MSH6 and PMS2) can accurately predict MSI tumors. In cancer cells, a MMR deficient (dMMR) state has been shown to result in upregulation of PD-1/PD-L1 (138,139). Notably, PD-1 inhibitors have been approved in clinical trials for the treatment of advanced/recurrent MSI-high (MSI-H) solid tumors owing to the efficacy of ICIs in the treatment of advanced solid tumors (140,141). Therefore, MMR status is another important factor in the selection of anti-PD-L1 drugs (142). Pagès *et al* (143) reported that, in colorectal cancer, the infiltration rate of $CD8^+$ cytotoxic T lymphocytes (CTLs) and T helper 1 (Th1) cells could inhibit tumor growth and metastasis. These results provide a new insight about immune therapy for NECC. Tumors with high Th1/CTL infiltration exhibit a dMMR state, leading to MSI (142,144). An increased mutational load in MSI tumors can lead to the production of new antigens, thereby increasing the immunogenicity of tumor cells. Fig. 4 shows the relationship between MSI status and immune response. In a large cohort study, NTRK protein expression was observed in 21% of cases, but none exhibited an NTRK gene fusion (89). In addition, Chen *et al* (136) evaluated the expression of PD-L1, proteins associated with MMR and NTRK fusion using immunohistochemical techniques, and revealed that all SCNECCs in the cohort were stable in MMR and exhibited NTRK fusion deficiency. In another study, 5% (1/22) of patients with SCNECC and 50% of patients with mixed NEC showed positive PD-L1 expression in tumor samples, and a stable MMR status was detected in 28 cases of SCNECC (137). However, the clinical value of the immune microenvironment in NECC has not yet been fully studied. Notably, 68.5% of patients with SCNECC exhibit PD-L1 CPS positivity, and PD-L1 CPS is markedly positively associated with tumor-associated immune cell levels, possibly involving the regulation of the tumor inflammatory microenvironment, which provides potential biomarkers for SCNECC immunotherapy (77). Notably, in a patient cohort, Carroll *et al* (137) reported that all patients with high-grade NECC presented with microsatellite stability status, the expression of PD-L1 was negative in the vast majority of specimens and PARP1 expression was detected in most of the tested tumors. PARP1 has been shown to serve an important role in DNA repair and methylation, as well as in transcription processes. A previous study showed that PARP1 is highly expressed at the mRNA and protein levels in SCLC, and SCLC is sensitive to PARPi, thereby enhancing the efficacy of chemotherapy (145). Therefore, the inclusion of PARPi may be considered in clinical trials of high-grade NECC (137). A recent case study analyzed the expression of PD-L1 and PARP1 in NECC and revealed that the positive expression rates of both markers were high, and that their expression statuses were consistent with each other in the MSI subgroup (P=0.004), indicating that MSI patients with PD-L1 and PARP1 co-expression may benefit from a combination of immune checkpoint therapy and PARPi targeted therapy (112). Sen *et al* (146) reported that PARP inhibition can enhance antitumor immunity induced by PD-L1 inhibitors in SCLC, and the corresponding mouse models also confirmed this result. In these models, the combination of PD-L1 and PARPi showed significantly higher efficacy than a single drug. This indicates that PARP inhibition may induce the expression of PD-L1, and PD-1/PD-L1 inhibitors in combination with PARPi may be a promising therapeutic option. The University of Kentucky has developed three small-molecule mixed inhibitors of PARP and PD-L1 that have more pronounced apoptotic and cytotoxic effects than single drugs (147). Further studies have found that PARPi cause upregulation of PD-L1 through GSK3β inactivation, but the specific mechanism remains to be explored (148).

Mutations in the TP53 gene can lead to loss or upregulation of protein expression, which is closely related to tumor prognosis. The high mutation rate of TP53 in NECC indicates that the TP53-related pathway has important research value for targeted therapy. Abnormal expression of p53 is closely related to the expression of PD-L1, and this should be taken into account in clinical studies concerning anti-PD-1/PD-L1 immune checkpoint blockade therapy. Research has indicated

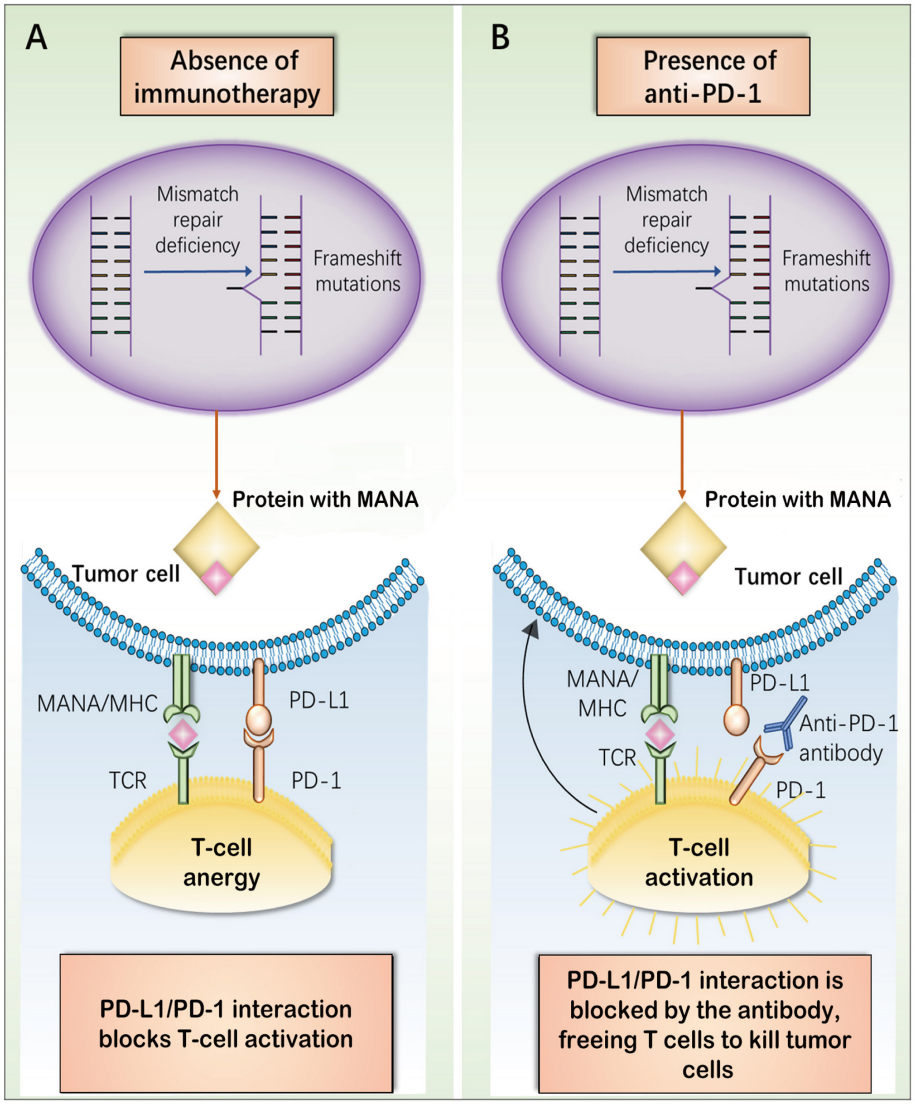

Figure 4. Relationship between MSI status and immune response. (A) In the absence of immunotherapy, dMMR leads to MSI, causing frameshift mutations and generation of MANAs. These MANAs are presented by MHC-I on tumor cells, engaging the TCR. However, concurrent upregulation of PD-L1 (often from tumor-infiltrating macrophages or lymphocytes) binds PD-1 on T cells, inducing inhibitory signaling and T-cell anergy/exhaustion, thereby permitting immune evasion. (B) Administration of anti-PD-1 antibody blocks the PD-1/PD-L1 interaction, reversing T-cell suppression and restoring TCR signaling, leading to T-cell activation, cytokine release and tumor cell lysis. This mechanistic basis underlies the clinical efficacy of PD-1 inhibitors in MSI-H/dMMR tumors. dMMR, MMR deficiency; MANA, mutation-associated neoantigen; MHC, major histocompatibility complex; MMR, mismatch repair; MSI, microsatellite instability; PD-1, programmed cell death protein 1; PD-L1, programmed death ligand 1; TCR, T-cell receptor.

that p53 reactivation can promote innate and adaptive immunity through various molecular pathways and increase the immunogenicity of tumor cells, providing a theoretical basis for targeted p53 drug combination immunotherapy (149). Furthermore, anti-angiogenic drugs have been widely used in the clinical treatment of cancer by single drug or combined drug regimens to inhibit tumor neovascularization, reshape the tumor microenvironment, modulate tumor-induced immunosuppression, and thereby enhance the efficacy of radiotherapy, chemotherapy, immunotherapy and targeted therapy (150-152). The efficacy of anti-angiogenic drugs in cervical NENs requires further investigation.

From a translational perspective, these biomarkers should be integrated into a clinically meaningful decision framework. PD-L1 positivity, especially when accompanied by abundant TILs, may support the use of ICIs, preferably in combination with chemotherapy, radiotherapy or anti-angiogenic therapy, rather than as monotherapy. MSI-H/dMMR status, although uncommon in SCNECC according to available studies, should still be assessed because it represents a tumor-agnostic indication for PD-1 blockade (136-138,153). PARP1 expression or other DNA damage repair-related alterations may identify patients who could benefit from PARPi, particularly in combination with platinum chemotherapy or immune checkpoint blockade (112,137,146). By contrast, NTRK fusion appears to be rare or absent in reported SCNECC cohorts (136); nevertheless, NTRK testing remains clinically relevant because patients with confirmed NTRK fusions may benefit from TRK inhibitors. Thus, a practical biomarker-driven strategy for NECC should include combined assessment of PD-L1/TILs, MSI/MMR status, DNA damage repair markers such as PARP1, and actionable gene fusions such as NTRK, thereby linking molecular features to rational treatment selection.

5. Future development and prospects

The current understanding of the pathogenesis of NECC is limited and low-quality evidence hinders the development of clinical management. Radical surgery and combined or non-combined radiotherapy with cisplatin and etoposide are the main treatment methods for early stage disease, whereas chemotherapy with cisplatin and etoposide or topotecan, paclitaxel and bevacizumab is suitable for women with locally advanced or recurrent NECC. In the future, multi-omics integration may serve a central role in refining the biological classification and individualized treatment of NECC. With the increasing number of genomes in The Cancer Genome Atlas database, genetic testing provides broad prospects for personalized treatment of cervical NENs with targeted drugs. Further research is needed to investigate the molecular, biological and therapeutic associations between cervical NETs and extracervical NETs arising from other organs (for example, lungs, gastrointestinal tract and pancreas). In-depth exploration of the underlying molecular abnormalities and signal transduction, including genetic and epigenetic factors, is key to improving therapeutic efficacy.

Current histopathological classification mainly relies on morphology, neuroendocrine marker expression, mitotic activity and Ki-67 index; however, these parameters are insufficient to fully capture the molecular heterogeneity of NECC. Genomic studies have demonstrated that high-grade NECC harbors recurrent alterations in several cancer-related genes and pathways, including PIK3CA, TP53, Myc, PTEN, RB1, KRAS, ARID1A, and components of the PAM and Notch signaling pathways (57,60,79,102,109,154,155). Eskander *et al* (53) reported a unique genomic landscape of high-grade NECC and highlighted frequent alterations in PIK3CA, Myc, TP53 and PTEN, suggesting that genomic profiling may help identify therapeutically actionable subgroups. Similarly, Wang *et al* (156) performed whole-exome sequencing of cervical and endometrial SCNECs and identified shared mutational features, supporting the value of comparative genomic analysis in defining NEC across gynecological sites.

Beyond DNA-level alterations, transcriptomic, epigenomic, proteomic and immune microenvironmental profiling may further improve the precision of NECC stratification. For example, expression of neuroendocrine lineage regulators such as ASCL1, NEUROD1, DLL3 and Notch pathway-related molecules may help distinguish biologically distinct NECC subsets (75,85,88,157). In addition, immune biomarkers, including PD-L1 expression, TILs, MSI/MMR status, tumor mutational burden and DNA damage repair-related markers such as PARP1, may contribute to predicting sensitivity to ICIs or DNA damage response-targeted therapy. Previous studies have reported heterogeneous PD-L1 expression, largely preserved MMR status and frequent PARP1 expression in NECC, indicating that single biomarkers may be insufficient for treatment selection (113,158). Therefore, a multi-dimensional model integrating histology, HPV status, somatic mutations, transcriptional programs, epigenetic changes, immune contexture and druggable surface antigens may provide a more reliable framework for precision diagnosis and risk stratification.

For clinical translation, future studies should incorporate next-generation sequencing, RNA sequencing, methylation profiling, multiplex immunohistochemistry, spatial transcriptomics and single-cell sequencing into prospective NECC cohorts. Such approaches may help clarify tumor origin, distinguish well-differentiated NETs from poorly differentiated NECs, identify mechanisms of treatment resistance and guide rational combination strategies. Given the rarity of NECC, international multi-center collaboration and shared molecular databases are essential for validating molecular subtypes and establishing biomarker-driven clinical trials.

Notably, antibody-drug conjugates (ADCs) represent another promising direction for the treatment of recurrent or metastatic NECC. ADCs combine the target specificity of monoclonal antibodies with the cytotoxic potency of chemotherapy payloads, allowing selective delivery of highly active agents to tumor cells expressing specific surface antigens (159). This strategy may be particularly attractive for NECC because conventional chemotherapy has limited durability, while several potentially targetable antigens, including DLL3, HER2, TROP-2, tissue factor and SSTRs have been explored in neuroendocrine or cervical malignancies (41,89,104,160-162).

DLL3 is one of the most biologically relevant targets in high-grade NEC. Other ADC targets may also be relevant to NECC. The future development of ADCs in NECC should be biomarker-driven rather than empiric. Routine assessment of DLL3, HER2, TROP-2 and tissue factor by immunohistochemistry or molecular assays may help identify patients suitable for ADC-based therapy. Moreover, ADCs may be combined with ICIs, PARPi, anti-angiogenic agents or radiotherapy to enhance antitumor activity, especially in tumors with DNA damage repair deficiency, high antigen expression or immune-active microenvironments. However, because direct clinical evidence in NECC remains limited, prospective basket trials, rare tumor registries and translational studies using patient-derived organoids or xenograft models are urgently needed. Overall, ADCs provide a rational and potentially effective precision treatment strategy for NECC, but their success will depend on accurate target selection, toxicity management and collaborative clinical trial design.

Various clinical trials are currently underway to expand the existing options for monotherapy and combination therapies. In a phase II clinical trial (NCT05910177) on neoadjuvant therapy for cervical NEN, the application of camrelizumab in combination with etoposide and cisplatin was investigated (163). In addition, the safety and tolerability of AK104 as a new chemotherapy drug for advanced/recurrent high-grade NECC are currently being studied (phase II-NCT05063916) (164). Camrelizumab (an anti-PD-1 antibody) has antitumor activity in NEN, and its efficacy combined with cisplatin/paclitaxel/bevacizumab in the treatment of recurrent or advanced NECC is currently being evaluated (phase II-NCT04635956) (165). In an ongoing phase II clinical trial, the role of XmAb20717 in advanced rare cancers, such as NEC, was evaluated to explore its prognostic biomarkers (NCT05337735) (166). Upregulation of SSTR2A has been detected in NECC (167), which is an important target for nuclear medicine molecular imaging diagnosis and peptide receptor-mediated radionuclide therapy (168). The efficacy of ^{177}Lu-DOTA-TATE in treating patients with SSTR-positive NET (phase II-NCT01876771) (169), and the combination of ^{177}Lu and nivolumab for the treatment of grade 3 well-differentiated NETs or poorly differentiated NEC is currently being

Table V. Current clinical trials.

Clinical Trials.gov identifier	Number of patients	Inclusion criteria	Treatment	Outcomes	(Refs.)
NCT05910177	30	Cervical neuroendocrine cancer or mixed cancer with neuroendocrine components accounting for 60%/FIGO stage I-II	Camrelizumab 200 mg D1 q3w plus cisplatin 75 mg/m^2 D1 q3w with etoposide 100 mg/m^2 D1-3 q3w	Currently ongoing/phase II	(163)
NCT05063916	18	Previously treated recurrent or metastatic high-grade neuroendocrine cervical cancer	AK104 (cadonilimab)	Currently ongoing/phase II/ single arm	(164)
NCT04635956	20	Recurrent or advanced cervical NEC	Platinum/etoposide/bevacizumab/camrelizumab for six treatments and bevacizumab/camrelizumab for 12 months	Currently ongoing/phase II/ single arm	(165)
NCT05337735	140	Extra-pulmonary high-grade NEC; previously treated with a platinum-based chemotherapy regimen, not anti-PD-1/anti-PD-L1; locally advanced or metastatic solid tumors	XmAb20717 D1 and D15 of each cycle	Currently ongoing/phase II	(166)
NCT01876771	500	Somatostatin receptor-positive neuroendocrine tumors	Induction therapy with 150 mCi (5.55 GBq) ^{177}Lu-DOTA-TATE q10w-q14w (four treatments); maintenance therapy with 75 mCi (2.78 GBq) ^{177}Lu-DOTA-TATE q22w-q40w (eight treatments)	Currently ongoing/phase II	(167)
NCT04525638	30	Grade 3 neuroendocrine tumors	Nivolumab (240 mg) plus 7.4 GBq ^{177}Lu-DOTA-TATE	Currently ongoing/phase II/ single arm	(170)
NCT05747729	60	Extra-pulmonary NEC or mixed cancer with neuroendocrine components accounting for 30%	Surufatinib administered at a starting dose of 250 mg, with dose adjustment based on dose-limiting toxicity during the dose-finding phase, followed by the addition of serplulimab (300 mg on day 1, every 3 weeks) plus platinum/etoposide	Currently ongoing/phase II/ single arm	(174)
NCT05262556	10	Advanced and metastatic extra-pulmonary NEC	NP-101 (TQ formula) given as five tablets (600 mg/tablet) q3w for four induction cycles, followed by a 12-week maintenance period. During induction, NP-101 combined with nivolumab (3 mg/kg) and ipilimumab (1 mg/kg) on day 1 of each q3w cycle for four cycles. Nivolumab then continued alone at 240 mg every 2 weeks for six maintenance cycles	Currently ongoing/phase I	(175)
NCT05076786	28	Advanced extra-pulmonary NEC	Chidamide (20 mg twice weekly on D0, D4, D7, D11) plus etoposide and cisplatin/carboplatin for 4-6 cycles (21-day cycle). Two platinum-based regimens permitted: i) Etoposide (100 mg/m^2 on D1-3) plus cisplatin (75 mg/m^2 on D1); ii) etoposide (100 mg/m^2 on D1-3) plus carboplatin (AUC 5 on D1) or cisplatin (25 mg/m^2 on D1-3)	Currently ongoing/phase II/ single arm	(179)

AUC, area under the curve; D, day; NEC, neuroendocrine carcinoma; PD-1, programmed cell death protein 1; PD-L1, programmed death ligand 1; q3w, every 3 weeks.

studied (phase II-NCT04525638) (170). MSI-H/dMMR tumors express a large number of new antigens due to high mutation, forming a microenvironment of immune-cell infiltration and upregulated expression of immune checkpoint proteins in tumor cells (153). The application of pembrolizumab and nivolumab in MSI-H/dMMR tumors has shown the potential of ICIs and marks the progress of precision medicine (171). Surufatinib is a potent small molecule tyrosine kinase inhibitor that selectively targets VEGF receptors 1, 2 and 3, fibroblast growth factor receptor 1 and colony stimulating factor 1 receptor, and NENs are highly vascularized tumors (172). Surufatinib may therefore have potential in treating NENs. In a dose escalation/expansion study, the 4-month and 11-month PFS rates in an extrapancreatic NET cohort treated with surufatinib were 93.8% (95% CI: 63.2, 99.1) and 51.1% (95% CI: 12.8, 80.3), respectively, supporting the antitumor efficacy of surufatinib for extrapancreatic NETs (173). Serplulimab is a novel anti-PD-1 antibody; serplulimab and surufatinib combined with standard chemotherapy (platinum/etoposide) are being studied to determine whether they can improve the efficacy in patients with NEN (phase II: NCT05747729) (174).

Furthermore, new drugs are being tested in advanced or metastatic extra-pulmonary NECs. NP-101 has antioxidant and anti-angiogenic effects; combined with immunotherapy drugs, such as nivolumab and ipilimumab, it may enhance efficacy in advanced neuroendocrine cancer (NCT05262556) (175). Histone deacetylase (HDAC) serves an important role in tumor development by modifying the structure of chromosomes and regulating gene expression, and the anticancer effect of HDAC inhibitors is notable (176). Among them, chidamide is being studied as a single treatment drug or in combination with cyclo-oxygenase (COX)-1/COX-2 inhibitors and ICIs for a variety of solid malignant tumors, which can slow tumor progression by altering the tumor immune microenvironment (177,178). In addition, the efficacy and safety of chidamide combined with etoposide and cisplatin/carboplatin in the treatment of advanced extrapulmonary NEC are being studied (NCT05076786) (179). The results of these clinical trials are awaited, and by evaluating various combinations of treatments for better tumor control, it is hoped that in the near future, effective management models can be developed to improve patient with NECs prognosis and quality of life (Table V).

The metastatic potential, morphological characteristics and manifestations of endocrine paraneoplastic syndrome, such as carcinoid syndrome and syndrome of inappropriate antidiuretic hormone secretion, in cervical NENs provide evidence for early diagnosis (180). Our latest understanding of the histological, pathological and genetic factors of these tumors may help to provide better diagnostic markers and treatment options, thereby improving prognosis. Various clinical trials are being extensively conducted with the aim of expanding the selection of single and combination therapies for NENs. Although ICIs may be beneficial, there is a lack of effective strategies to predict response, manage immune-related adverse events or select suitable patients for these therapies. Improvements in molecular analysis and further mechanistic research are required to determine which patients will benefit from immunotherapy, targeted monotherapy or combination therapy, and to customize personalized treatment plans according to different situations, which will markedly improve the treatment effectiveness of patients. Further research is needed to evaluate the potential of MSI status in guiding immunotherapy across tumor types. This represents a notable advancement in precision medicine. Targeted therapies, such as somatostatin analogs, PAM inhibitors and anti-angiogenic drugs, have been used in extra-cervical NEN therapy (181,182). However, to the best of our knowledge, there are currently no data available on their application in cervical NENs, which urgently requires strong cooperation between gynecological oncologists and relevant researchers to ensure progress in the treatment of these invasive diseases.

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Availability of data and materials

Not applicable.

Authors' contributions

YT, XH and RG conceptualized the study. YT, YZ and XX wrote the first manuscript. ZL, LW, SL, SY and XR participated in writing the manuscript, and generated the figures and tables. MX, XC and QZ edited, reviewed and supervised the manuscript. YT, QZ and RG provided the funding. Data authentication is not applicable. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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