Molecular Cancer

REVIEW

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Cancer neuroscience in head and neck: interactions, modulation, and therapeutic strategies

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Abstract

Head and neck cancer (HNC) is an aggressive malignancy with significant effects on the innervation. Not only is it at the top of the cancer spectrum with a dismal prognosis, but it also imposes considerable stress on patients and society owing to frequent neurological symptoms. With progress in cancer neuroscience, the interactions between HNC and the nervous system, as well as the underlying mechanisms, have become increasingly clear. Compelling evidence suggests communication of information between cancer and nerve cells and devastation of the neurological system with tumor growth. However, the thorough grasp of HNC in cancer neuroscience has been severely constrained by the intricacy of HNC and fragmented research. This review comprehensively organizes and summarizes the latest research on the crosstalk between HNC and the nervous system. It aims to clarify various aspects of the neurological system in HNC, including the physiology, progression, and treatment of cancer. Furthermore, the opportunities and challenges of cancer neuroscience in HNC are discussed, which offers fresh perspectives on the neurological aspects of HNC diagnosis and management.

Keywords Head and neck cancer, Nervous system, Neuro-Cancer crosstalk, Cancer treatment, Neuro-targeted therapy

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Introduction

As the primary regulatory network for muscular, sensory, and cognitive processes, the nervous system maintains homeostasis by regulating various electrical, neurotransmitter, and cytokine signals. It is crucial in carcinogenesis, cancer cell invasion, and metastasis [1–3]. With the advent of "cancer neuroscience," an increasing number of studies have begun to conduct in-depth explorations of complex interactions between various cancers and the nervous system [4–6]. From nerve invasion of cancer cells to neurological symptoms induced by the tumor itself or its treatment, these phenomena not only unveil the intricate crosstalk between cancer and the nervous system but are also intimately associated with poor patient prognosis and a significant exacerbation of diagnostic and therapeutic burdens [7–9]. Neurotargeted cancer therapies have demonstrated promising efficacy in preclinical models and early phase clinical trials [10, 11]. This provides a new potential direction for overcoming the current limitations of cancer therapies.

Head and neck cancer (HNC), originating in multiple organs including the oral cavity, pharynx, salivary glands, and thyroid gland, is a malignant tumor with high recurrence and mortality rates that consistently rank among the highest in the cancer spectrum [12]. Owing to the richer nerve aggregation and anatomical proximity to the brain in the head and neck region, patients with HNC frequently exhibit heightened levels of physical discomfort and psychological distress [13]. Compared with other malignancies, HNC has a more noticeable innervation effect [14]. For example, there are more severe symptoms of pain or numbness as well as a higher prevalence of distant central nervous system (CNS) symptoms, including mood or cognitive impairment [13, 15]. Moreover, HNC patients with neurological invasion have a worse prognosis [16–18]. Although no reliable assessment criteria have yet been established, the evaluation of structural and functional changes in the nervous system has emerged as a vital reference for clinicians to determine disease severity, guide treatment strategies, and predict outcomes in patients with HNC [19–21].

HNC development is a multifactorial pathological process involving local chronic stimulation, immune regulatory imbalance, and neurological interaction disorders [22, 23]. The rise of three-dimensional (3D) cell culture and tissue sequencing technologies has brought increasing attention to the significance of the neural components of a tumor's surrounding environment [24, 25]. Previous studies have revealed that HNC cells not only secrete neuron-related factors but also exhibit high expression levels of neuron-related receptors [26–28]. This provides a necessary molecular basis for the crosstalk between cancer cells and the nervous system. Furthermore, in vitro studies by Tjioe et al. demonstrated that neurotargeted interventions can modulate chemoresistance in HNC cells [29]. These studies suggest the vital role of cancer neuroscience in guiding future pathogenesis exploration, clinical diagnosis, and treatment of HNC. However, because of the diversity and complexity of HNC types, existing research on neuro-cancer crosstalk remains fragmented and limited, leaving investigators with little clear direction for systematic exploration. Consequently, this article focuses on the structural and functional connections between the head and neck and the associated nervous system and comprehensively reviews and summarizes the mechanisms of interactions between HNC and the nervous system, as well as their clinical implications. The commonalities and characteristics of neuro-cancer crosstalk in HNC are also discussed. To provide potential directions and new ideas for future neuro-cancer crosstalk research in HNC, we also discuss the clinical translational perspectives of cancer neuroscience in the management of HNC (Fig. 1).

Method

We searched the PubMed database for relevant articles and conducted a literature search using the following keywords: "head and neck cancer," "nervous system," "cancer neuroscience," "neuro-cancer crosstalk," "perineural invasion," "neurons," "Schwann cell," "neurotransmitters," "neurotrophic factors," "neuropeptide," "immuno-oncology," "neuroimmunity," "immune cells," "tumor microenvironment," "cytokine," "head and neck cancer treatment," "nerve damage," "neurotoxicity," "neurology," "neuromodulation," and "artificial intelligence." All keywords were used in all possible permutations and the abstracts of the search results were evaluated.

No date limit was set for this review. Older articles were identified manually by searching the reference lists of articles that satisfied the inclusion criteria. Secondary sources from the reference lists of the selected primary papers were searched, evaluated for appropriateness, and included when appropriate.

Communication between the nervous system and the head and neck

CNS regulation of the head and neck

Brain Lobes

The brain is the core of the CNS, and is responsible for sensing and handling various signals in the body. The frontal lobe, the main area that regulates the motion of an organism, not only controls the basic movements of the head, neck, and facial muscles but also participates in physiological behaviors, including coughing, biting, and articulation. By integrating the head and neck pain, touch, and temperature signals, the parietal lobe regulates the body's recognition and response to the external environment through peripheral afferent neural

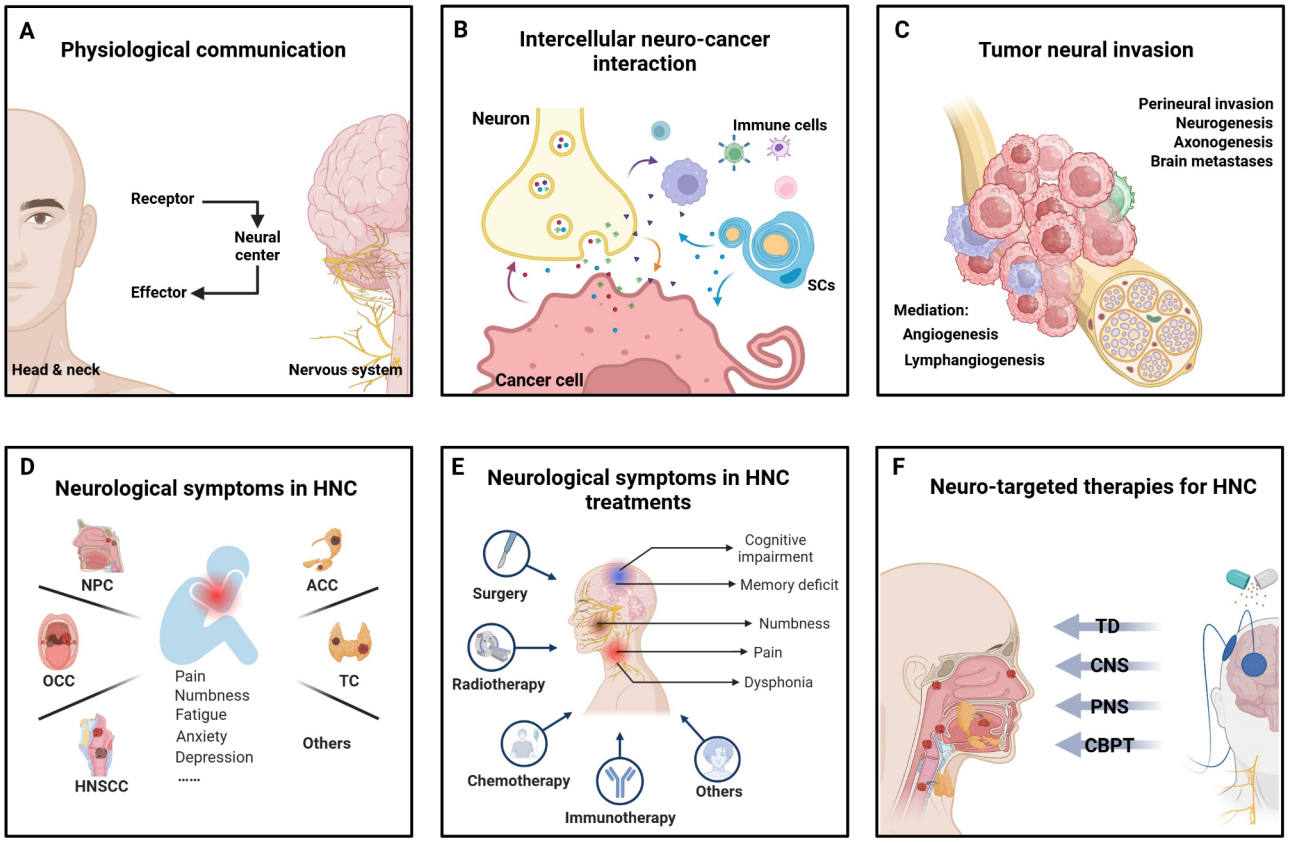

Fig. 1 Roadmap of cancer neuroscience in head and neck. (**A**) The head and neck region, serving as critical sensory receptors for receiving external information and as effectors executing neural commands, engages in close physiological communication with the nervous system. (**B**) In the tumor microenvironment, cancer cells interact with neurons through various effector molecules, while Schwann cells and immune cells also participate in this process. (**C**) Within tumor tissues, cancer cells may manifest diverse neural invasion phenotypes, such as perineural invasion, neurogenesis, axonogenesis, and brain metastasis. Additionally, cancer cells can facilitate neural invasion by enhancing angiogenesis and lymphangiogenesis. (**D**) In HNC, various types of tumors may induce a spectrum of neurological symptoms. (**E**) Current therapeutic approaches for HNC may lead to varying degrees and types of neurological damage. (**F**) Future intervention in HNC from a neuroscience perspective. Abbreviations: ACC, adenoid cystic carcinoma; CBPT, cognitive behavioral psychological therapy; CNS, central nervous system; HNC, head and neck cancer; HNSCC, head and neck squamous cell carcinoma; NPC, nasopharyngeal carcinoma; OCC, oral cavity cancer; PNS, peripheral nervous system; SCs, Schwann cells; TC, thyroid cancer; TD, targeted drug. (Figure created with BioRender)

signaling. The aforementioned brain regions are also integrated with the occipital lobe for visual information processing, temporal lobe for auditory and language management, and the limbic system for the regulation of human emotions and memories to sustain cognitive abilities, social interactions, and emotional expression. Patients experience relevant symptoms owing to changes in brain function during the disease. According to a study by Yang et al., mood abnormalities in HNC patients were closely linked to alterations in glucose metabolism in specific brain areas [30].

Brainstem, Cerebellum, and Spinal Cord

The brainstem is the central component of the body that sustains fundamental life functions, such as breathing and heartbeat, and serves as a vital connection between the brain and spinal cord. The brainstem contains multiple key neuronal nuclei that control intricate head and facial motions, including facial expressions, chewing, and swallowing. It also regulates the release of hormones and neurotransmitters affecting arousal and attentiveness. With motor coordination as its primary role, the cerebellum integrates visual, vestibular, and proprioceptive information, adjusting the head and neck position and movement to preserve the body's stability and balance. Furthermore, the cerebellum has been shown to be important in non-motor processes, such as emotion and cognition [31]. Neurons in the spinal cord act as vital carriers of motor and sensory information, and are regulated by the nervous system to enable the head and neck to respond flexibly and accurately to changes in the external environment. Clinicians are concerned about dose control and CNS safety when treating patients with HNC, particularly those receiving radiation therapy [32].

Peripheral nervous system (PNS) regulation of the head and neck

The PNS, a continuation of the structure and function of the CNS, acts as an important bridge for nerve signals to reach the periphery. As the primary "distribution center" for peripheral nerves reaching every portion of the body, the head and neck area has a highly dense nerve distribution. The cranial and spinal nerves are a part of the PNS, and their collaboration ensures the intricate and delicate physiological processes of the head and neck.

Cranial nerves (CNs) comprise 12 pairs that emanate directly from the brain and brainstem through structures such as the nasal cavity, orbits, and inner ear. They are the main participants in the regulation of sensation and movement of the head and neck [33]. The olfactory nerve (CN I), optic nerve (CN II), and vestibular nerve (CN VIII) are the sensory nerves responsible for receiving olfactory, visual, and auditory information, respectively. The oculomotor (CN III), trochlear (CN IV), extensor (CN VI), accessory (CN XI), and hypoglossal (CN XII) nerves control eyeball, shoulder, neck, and tongue motions, respectively. The trigeminal (CN V), facial (CN VII), glossopharyngeal (CN IX), and vagus (CN X) nerves receive sensory and taste information from the face and throat, and regulate the actions of the pharyngeal and facial muscles. Furthermore, some CNs, including those in the autonomic nervous system, participate in the functional control of glandular organs [34]. Multiple branches that precisely regulate local tissues are produced by CNs as they enter the head and neck, offering a possible route for HNC cells to spread and metastasize along the nerves [35]. Previous studies have demonstrated that the trigeminal and facial nerves are the most vulnerable CNs [36, 37]. Once the disease reaches them, clinical symptoms such as numbness and facial pain emerge in patients.

The spinal nerve is a mixed nerve that penetrates into the spinal canal. Through its muscular branches and cortex, particularly the C1–C4 segments of the cervical nerve, it regulates muscle movement and skin sensations in the head and neck [38]. Additionally, the cervical nerves may be connected to the sympathetic chain, which regulates the autonomic functions of vasoconstriction of the head and neck blood vessels and secretion by glands such as the thyroid gland. Therefore, the cervical nerve is a critical structure that must be meticulously protected during therapeutic interventions.

Bidirectional roles of the head and neck in the nervous system

The head and neck are critical parts of the body for breathing, eating, speaking, and perceiving and are also the parts closest to the brain. They have extremely tight and intricate anatomical structures with dense nerve dispersions [39]. The head and neck contain multiple vital sensory organs, including the eyes, ears, nose, and tongue, and a wealth of nerve endings that are key sources of information for perceiving the external environment. The head and neck region transmits visual, auditory, vestibular, olfactory, gustatory, and local tactile information to the CNS via the PNS, thereby facilitating multisensory integration. Concurrently, high-density muscles with fine regulatory capacity and glands with important physiological functions provide critical support for the execution of neural instructions received by the head and neck region. For example, when the nasal mucosa is exposed to external stimuli, the transient receptor potential vanilloid 1-positive ($TRPV1^+$) sensory neurons in the trigeminal ganglion transmit electrical signals to the ventral respiratory group of the medulla oblongata. The CNS then generates a sneeze command, which is executed by the effectors in the head and neck region [40]. Therefore, the head and neck region, acting as both sensory receptors and motor effectors within the reflex arc, plays an essential role in mediating interactions between the nervous system and the external environment, which serves as a critical structural basis for maintaining homeostasis and regulating adaptive behaviors.

Crosstalk between the nervous system and HNC

The nervous system maintains close physiological interactions with the head and neck (Fig. 2). It is also involved in the growth and development of abnormally proliferating tissues (e.g., tumors), with the most notable involvement in signaling between neurons and cancer cells. Neural cells can secrete relevant effectors that act directly or indirectly on cancer cells to promote malignant phenotypes such as proliferation, differentiation, and invasion, which in turn drive tumor progression [41, 42]. On the other hand, cancer cells can also produce specific factors that remodel the structure and function of the nervous system, further enhancing the interaction between the nerve and the tumor [43, 44]. In the tumor microenvironment (TME), immune cells, as key participants, also co-construct a complex and dynamic interaction network via multiple effector products secreted from each other during crosstalk with cancer and neural cells [45]. This multicellular synergy revealed the intricate communication mechanisms of cancer neuroscience in the TME.

Direct interactions between the nervous system and Cancer cells in HNC

Interaction between neurons and Cancer cells

Interaction via neurotransmitters Neurotransmitters are essential mediators of information exchange between neurons or with reciprocal cells and participate in tumor

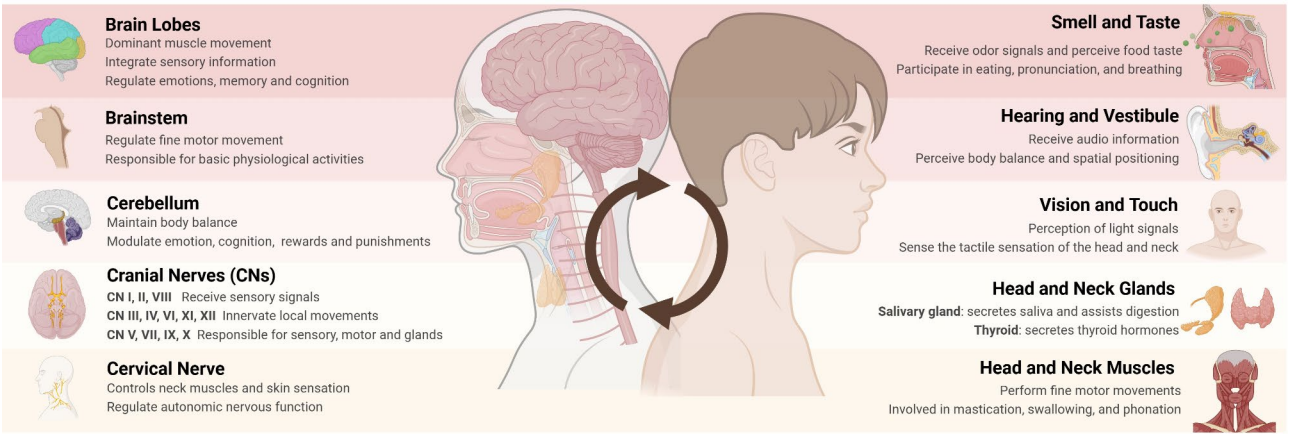

Fig. 2 Communication between the nervous system and the head and neck. (Figure created with BioRender)

initiation and progression through diverse pathways or modalities.

Catecholamines

Tobacco and chronic alcohol consumption are the main risk factors for HNC. In the reaction to tobacco and alcohol withdrawal, the sympathetic nervous system is activated by psychological stress and is usually accompanied by an increase in the release of catecholamines (i.e., norepinephrine (NE) and epinephrine) [46]. The increased NE during chronic stress binds to β-adrenergic receptors (β-AR) on oral keratinocytes causing intracellular oxidative stress, which leads to DNA strand breaks, triggering a malignant transformation of the cells [47]. NE can also suppress apoptosis by inhibiting caspase 3/7, thus worsening abnormal cell proliferation [47]. NE also influences the growth of oral squamous cell carcinoma (OSCC) cells by stimulating interleukin (IL)-6 release [48]. In addition, in human nasopharyngeal carcinoma (NPC) cells, the binding of NE to β2-adrenergic receptors (β2-AR) can affect the synthesis of matrix metalloproteinases (MMP)-2/9, which may subsequently participate in the degradation of extracellular matrix components to enhance tumor invasion [49, 50]. Researchers have simultaneously detected an increase in vascular endothelial growth factor (VEGF) accompanied by the upregulation of MMP2/9, which may collectively facilitate tumor angiogenesis and provide additional invasive pathways for cancer cells [49]. This finding was validated in an animal model of oral cancer [51]. Furthermore, activation of β2-AR by NE can enhance the expression of ATP-binding cassette subfamily G member 2 via the Akt signaling pathway in the treatment of HNC, promoting the efflux of chemotherapeutic drugs from the cells, thereby reducing the intracellular drug concentration [29]. Although these studies did not identify the exact source of NE (whether it originated from the release of noradrenergic neurons inside the tumor or was produced by the body's sympathetic-adrenomedullary axis in the bloodstream before entering the TME), it had a noticeable impact on tumors. The above research also confirmed that the application of β-AR blocker propranolol can inhibit the malignant biological process and drug resistance of cancer cells to a certain extent.

Gamma-Amino Butyric Acid (GABA)

GABA is a vital inhibitory neurotransmitter in adult mammals. Exogenous administration of GABA activates the p38 MAPK signaling pathway while inhibiting the JNK MAPK signaling pathway in OSCC, thereby affecting the cell cycle to promote cancer cell proliferation and inhibit apoptosis [52]. In head and neck squamous cell carcinoma (HNSCC), GABA induces B-cell lymphoma 2-like 1 and cyclin D2 to respectively regulate primary and cisplatin-induced apoptosis and cell cycle arrest [53]. Glutamic acid decarboxylase 1 (GAD1), which is predominantly expressed in GABAergic neurons and promotes GABA synthesis, is frequently upregulated in HNC cells. It can regulate β-catenin translocation and MMP7 activation, thereby enhancing cell invasion and migration [54].

5-hydroxytryptamine (5-HT)

Additionally, 5-HT, an important neurotransmitter that modulates tumor bioprocesses and depressive states, has been identified as one of the three potential pathways for the development of cancer-associated depression [55]. In blood samples of patients with oropharynx cancer, genetic variations in 5-HT-related regulatory genes (TPH1 and HTR1D) are closely associated with cancer development and tumor invasion [56]. Similar genetic variants have been reported in patients with depression [57]. In HNC, a cancer type with a high incidence of depression, the relevance of cancer-mediated 5-HT-related regulatory gene variants in the development of depression needs to be further systematically explored. However, another clinical study reported that the high prevalence of depression in HNC patients does not

significantly correlated with changes in the 5-HT transporter gene [58]. This requires consideration of the small and limited sample size included in this study, which cannot exclude the influence of confounding factors, such as geographic population genetic background or multifactorial-mediated environmental complexity, on the results. 5-HT has been shown to modulate the immune-inflammatory environment in both tumor and depression progression [59]. Whether the neuro-cancer crosstalk of 5-HT in HNC is worth exploring from an immunological perspective also deserves consideration.

Acetylcholine (ACh)

ACh shows more pronounced activation of the CD133-Akt pathway than other neurotransmitters in thyroid cancer (TC) [60]. This results in increased immune evasion and self-renewal of CD133 + TC cells, which play a dominant role in disease development. Although there are currently no specific studies on ACh in other HNCs, the impact of its receptors (AChRs) on cancer cell growth stimulated by the main pathogenic factor of HNC (nicotine) cannot be overlooked [61]. Nicotine promotes the recurrence and metastasis of HNC by activating nicotinic AChRs and regulating CES1 expression via the MEK/ERK signaling pathway [62]. The gene methylation status of another receptor, the muscarinic AChRs, is also strongly associated with the pathological features and risk of recurrence of HNC [63].

Interaction via neuropeptides Neuropeptides, a unique class of endogenous active substances in the nervous system, have been found to exhibit altered expression and receptor profiles in relevant afferent neurons using retrograde fluorescent tracing techniques in OSCC rat models [64].

Calcitonin Gene-Related Peptide (CGRP)

CGRP binds to its receptor CLR and promotes OSCC cell proliferation and migration [65]. In a low-glucose environment, the upregulation of nerve growth factor induced by cancer cells can also promote the secretion of CGRP from nociceptive nerves, which in turn disrupts the interaction between mTOR and Raptor via Rap 1 activation, thereby inducing the protective autophagy of OSCC cells in nutrient-deprived environments [66]. This was one of the key breakthroughs in the efficacy of nutritional starvation therapy for tumors. The formation of cancer tissues can increase the anterograde transport of CGRP in tumor-infiltrating neuronal axons and establish a positive feedback loop between neuropeptide release and cancer cell growth [67]. In addition, excess adenosine in the OSCC microenvironment may stimulate trigeminal supraganglionic adenosine receptor A2a to trigger CGRP release [68].

Galanin (GAL)

GAL, which is also derived from neural sources, activates the G protein-coupled receptor galanin receptor 2 (GALR2) in salivary adenoid cystic carcinoma (SACC) cells [69]. This activation induces epithelial-mesenchymal transition (EMT) in cancer cells, thereby promoting neural invasion of the tumor. The binding of GAL secreted by cancer cells to its own receptor GALR 2 can also promote the growth of neural protrusions by inducing NFATC2-mediated transcription, which further enhances the secretion of cyclooxygenase-2 and prostaglandin E2 in cancer cells [70]. The positive feedback mechanism of GLA formation in HNC reveals complex interactions involving neuro-cancer crosstalk. Moreover, GALR1, which antagonizes GALR2, inhibits the proliferation of HNSCC cells [71].

Substance P (SP)

In addition, when TRPV1-expressing nociceptors are stimulated, the SP released from them binds to the corresponding SP receptor NK1R on HNC cells, thus affecting electrical activity in tumor tissues, as well as the proliferation and migration of cancer cells [72].

Interaction via neurotrophic factors Neurotrophic factors play critical roles in the development and maintenance of the nervous system. Along with tumorigenesis, neurotrophic factors secreted by cancer cells or induced by other cells not only regulate neurogenesis within the tumor but also participate in the structural and functional remodeling of the TME [73, 74].

Nerve Growth Factor (NGF)

NGF, a key factor in neuronal growth, development, and damage repair, is abnormally highly expressed in HNC and is often closely associated with tumor neural invasion [75, 76]. NGF promotes the migration and spread of cancer cells through the PI3K/Akt signaling pathway, following its binding to tyrosine kinase receptor A (TrkA) [77]. Although researchers have not performed EMT-related phenotypic detection of cancer cells stimulated by NGF, EMT, an important mechanism of tumor invasion, can be influenced by the activation of the PI3K/Akt signaling pathway in multiple ways [78]. Moreover, OSCC cells expressing the endothelin receptor secrete NGF and opioid substances, which can promote the transmission of afferent nociceptor information by binding to high-affinity TrkA receptors and low-affinity p75 receptors on neuronal membranes, thereby triggering pain in patients [27]. While the effective blockade of NGF reduces nociceptive receptors on sensory neurons to decrease neuronal sensitivity, it also decreases the release of tumor necrosis factor-α (TNF-α) and IL-6, leading to the relief of tumor-induced pain [79].

Brain-Derived Neurotrophic Factor (BDNF)

BDNF, which is significantly elevated in OSCC, can be secreted by neurons and tumor cells, both of which

attach to tropomyosin receptor kinase B (TrkB) in neurons to elicit cancerous pain [80, 81]. Furthermore, the combination of BDNF and TrkB promotes the migration and invasion of SACC cells via EMT [82]. NGF and BDNF share highly similar mechanisms of neuro-cancer crosstalk in HNC, but there is a lack of definitive studies exploring whether they act synergistically or antagonistically.

Glial Cell-Derived Neurotrophic Factor (GDNF)

Additionally, in HNSCC, GDNF can upregulate programmed cell death ligand-1 (PD-L1) expression by binding to the promoter region of the PD-L1 gene via the JAK2/STAT1 signaling pathway [83]. GDNF can further enhance the invasive capacity of OSCC cells by activating the PI3K/Akt and MAPK/ERK signaling pathways, as well as regulating the expression of MMP-9/13 and remodeling the cytoskeleton of cancer cells [84]. However, the specific correlation between them requires further mechanistic investigation to clarify their interactions.

Interaction via extracellular vesicles (EVs) In recent years, EVs, especially exosomes, have been repeatedly shown to play vital communication roles in tumor-related biological pathways, including neuro-cancer crosstalk [85, 86]. In 2020, a seminal study revealed that EVs released by HNC cells could modulate the growth of axons within tumor-associated nerves [87]. Specifically, the loss of TP53, the most frequently mutated gene in HNC, induces cancer cells to secrete EVs deficient in microRNA-34a [87]. This deficiency promotes the transdifferentiation of sensory neurons into adrenergic neurons, thereby facilitating tumor progression. Additionally, small EVs derived from OSCC cells can increase the expression of activating transcription factor 3 in $TRPV1^+$ neuronal cells in a dose-dependent manner [88]. This increase alters nociceptive receptor excitability and transcriptional changes, ultimately enhancing the transmission of pain signals. These EVs are enriched with specific miRNAs, such as miR-21-5p and miR-221-3p, which target potential toll-like receptor pathways, IL-6 and its receptor (gp130) signaling pathways, and induce the sensitization of sensory neurons [89]. In addition, exosomes secreted by HNSCC cells contain the axon guidance molecule EphrinB1, which promotes the growth of neural protrusions that drive innervation in HNC [90]. Different biologically efficacious miRNAs in these EVs alter the packaging of miRNAs by modulating Cyclin D1 in cancer cells, which in turn promotes the growth of nerve fibers within the tumor [91]. It has also been found that exosomes secreted by SACC cells can induce fibroblasts to secrete NGF, and through the activation of the NGF-NTRK1 signaling pathway, feedback to cancer cells, thereby enhancing their metastatic and invasive capacities [92]. Fibroblasts in the TME are highly heterogeneous, with different fibroblast sources likely responding variably to exosomes [93]. Therefore, these findings need to be validated in a wider range of cell types.

Interaction via chemokines In cancer, chemokines guide effector cells to produce effective anti-tumor and pro-tumor responses. The chemokine CCL5 secreted by neurons can rapidly induce $Ca2^+$ transmembrane translocation and cancer cell pseudopod formation by binding to its receptor CCR5 on SACC cells, promoting cancer cell neuroinvasion [94]. In SACC cells, CXCR4, which is closely related to tumor neural invasion, can bind to CXCL12 in the infiltrated neurons and stimulate cancer cells through the Twist/S100A4 axis, causing them to acquire a phenotype and function similar to that of Schwann cells (SCs), which is professionally termed "Schwann-like cell differentiation" [95]. This process also involves CXCR5-mediated miR-187 downregulation in cancer cells [96]. Furthermore, CX3CL1 has been shown to be involved in tumor neural interactions in various cancers [97]. Although no specific studies have explored the mechanism of neuro-cancer crosstalk between CX3CL1 and HNC, its potential effect on the malignant progression of OSCC and CT underscores the need for an in-depth investigation of its interaction mechanism [98, 99].

Interaction between SCs and Cancer cells

SCs are the main supportive glial cells of the PNS and perform various important functions including rapid signal transduction, neurotrophic support, and neural repair. They are also utilized by cancer cells to promote neural invasion [100]. BDNF/TrkB, a key signaling pathway in cancer-neural interactions, affects the dispersion of cancer cells while regulating the dedifferentiation of SCs into reparative phenotypes and their own migration, thus promoting nerve invasion in tumors [101, 102]. The influence of this pathway on neuroinvasion has also been confirmed in the SC-induced EMT and Schwann-like cell differentiation of cancer cells in SACC [103]. Dietary palmitic acid intake can activate SCs within the tumor to secrete a regeneration-promoting extracellular matrix that mediates cancer cell metastasis and tumor innervation in both OSCC and melanoma [104]. This requires the involvement of GAL and the transcription factor EGR2. Salvo et al. found that a significant increase in TNF-α in cancer stimulates SCs to produce neurosensitizing mediators for the enhancement of oral cancer-associated nociceptive receptor responses [105]. While TNF-α is recognized for its pivotal role in the crosstalk between nerve cells and cancer cells, it may also activate other cell types within the microenvironment. In consideration of this complexity, additional experiments are essential to elucidate the specific or dominant effector pathways of TNF-α. Clarifying these pathways is of great

significance for the clinical application of related targeted drugs for the treatment of HNC.

Interaction between the immune system and Neuro-Cancer crosstalk in HNC

As a key component of the TME, the immune system plays a regulatory role in the interactions between nerve cells and cancer cells. In recent years, research in the fields of "neuroimmunity" and "immuno-oncology" has continuously advanced from basic to clinical applications. Many studies have confirmed the importance of the immune system in neuro-cancer crosstalk [45, 106].

Interaction between immune cells and Neuro-Cancer crosstalk

T Cells

T cells, as key effector cells of the immune system, play crucial roles in immune surveillance and anti-tumor functions in the TME of HNC and are important target cells in cancer therapy [107]. Significant infiltration of T cells, especially CD8 + T cells, was detected in HNC tissues spreading around the nerves [108]. This recruitment process may be associated with neurotransmitter-driven T cell migration toward autologous tumors and the expression of T cell receptor-associated chain [109]. The increased catecholamines in the tumor bind to the β1-adrenergic receptor on CD8 + T cells, leading to T cell exhaustion, and a decrease in the secretion of IFN-γ and TNF, thereby weakening the anti-tumor immune capacity of T cells [110]. Although the results of this study were not validated in HNC, there may be a common mechanism of action in HNC tissues that also contain high levels of catecholamines. In HNSCC, CGRP, which is closely related to neuro-cancer crosstalk, is released from the sensory nerves and subsequently promotes tumor growth by inhibiting the activity of CD8 + T cells [111]. Such neuropeptide-associated reductions in anti-tumor immunity are also observed in the innervation effects of melanoma and medullary thyroid carcinoma [112]. Certainly, receptors for CGRP are similarly expressed in other immune cells, which may also indirectly regulate or assist T-cell functions through other cells. Furthermore, Brem proposed an important new direction for enhancing anti-tumor immune responses through neuroimmune modulation, based on the increased T cell immune activity elicited by vagus nerve stimulation and the inhibitory effects on pro-inflammatory cytokines, represented by IL-6 [113]. Whether the same approach can be mimicked in HNC to efficiently inhibit tumor biological processes through higher invasiveness or by acting on nerve fibers in the head and neck region requires further research to explore and validate.

Macrophages

Macrophages are one of the most abundant immune cells in the TME and play an essential role in the immune response to tumors via phagocytosis [114]. Tumor-associated macrophages are typically polarized into a pro-tumor phenotype (M2 type) and promote tumor proliferation, invasion, and immune evasion by secreting a variety of cytokines and chemokines [115]. In OSCC, GABA secreted by cancer cells can also promote M2 macrophage polarization by activating the GABBR1/ERK/Ca2 + pathway, thereby restricting the anti-tumor immunity of macrophages and further advancing malignant progression of the tumor [26]. While MEK1/2 is an upstream target of the ERK signaling pathway, the application of corresponding inhibitors can also reduce the secretion of colony-stimulating factor 1 (CSF1) by HNC cells, which in turn reduces the number of myeloid-derived suppressor cells (MDSCs) and weakens the immunosuppressive microenvironment of the tumor [116]. However, the long-term application of MEK1/2 inhibitors also leads to the development of EMT in cancer cells, reactivating CSF1 expression to activate immunosuppression. Further clarification of the appropriate dose and cycle of targeted therapy is required. In addition, B-cell-derived GABA can promote IL-10 secretion from M2 anti-inflammatory macrophages to inhibit the activation and proliferation of CD8 + T cells, thereby suppressing the anti-tumor response [117]. In adenoid cystic carcinoma (ACC), the M2 polarization of macrophages may also be responsible for the increased angiogenesis associated with tumor invasion [118]. Moreover, HNCs are often associated with neuropathic pain, which can be induced by Ig G secretion from B cells around damaged nerves followed by binding to Fcγ receptors on macrophages [119]. It has also been suggested that chemotherapy-induced neuropathic pain can induce the neuronal release of CCL2, mediated by binding to CCR2 from M1-like pro-inflammatory macrophages [120].

MDSCs

MDSCs, as a class of cells with immunosuppressive functions, can inhibit the activity of T cells, NK cells, and other immune cells through a variety of mechanisms, thereby promoting immune escape and tumor growth [121]. In HNSCC, increased dickkopf-1 (DKK1) expression in neurons induced by cancer cells can attract MDSCs to infiltrate the tumor tissue by binding to the corresponding receptor on the surface of MDSCs [122]. After activation, β2-AR on MDSCs may also affect their own immunosuppressive function via the phosphorylation of STAT3 [123]. In melanoma, it has been discovered that tumor cells can activate sensory neurons to produce chemokines that induce MDSCs, thereby inhibiting the body's immune response and further facilitating the proliferation and dissemination of cancer cells [124]. Furthermore, inhibition of CXCR1/2 chemokine receptors

on MDSCs can also inhibit NK cell activity within HNC by affecting transforming growth factor-β [125].

Other Immune Cells

In the immune response of tumors, different immune cells can jointly participate in regulating the immune dynamic balance through their unique functions. Dendritic cells (DCs) can initiate and modulate the immune response within tumors through their potent antigen-presenting effects. CGRP expression in medullary TC may be associated with aberrant DC development, characterized by activation of the cAMP-related pathway and high levels of Kruppel-like factor 2 [126]. More importantly, there are many immune cells that are able to secrete pro-inflammatory cytokines such as IL-6 and TNF-α under chronic stress stimulation, forming TME that are conducive to cancer invasion through the STAT-3 and NF-κB signaling pathways within the immune cells, thereby ultimately affecting the proliferation and metastasis of tumors [127]. The specific mechanism involving the "neuro-immune-cancer" crosstalk in HNC should also be explored urgently.

Interaction between vascular system and Neuro-Cancer crosstalk

Blood Vessels.

Blood vessels are not only a crucial route for the delivery of immune cells, but also a core mode of nutrient supply during tumor growth. Consequently, blood vessels and nerves are constantly generated and often accompany each other within the tumor, thereby meeting the needs of tumor growth. VEGF, a highly specific provascular growth marker, is significantly upregulated in HNCs, including HNSCC and SACC, especially in tissues with nerve invasion [128, 129]. A previous study identified VEGF as a possible guidance factor for neural progenitor cells involved in neurogenesis and angiogenesis [130]. As an upstream regulator of VEGF, high expression of intercellular adhesion molecule 5 is common in HNSCC tumor tissues with neuroinvasion, which can affect tumor angiogenesis and neuroinvasion through the P13K/Akt signaling pathway [131]. Additionally, GALR2 activated by neuronal GAL can enhance angiogenesis in tumor tissues by activating ERK7 and p38 MAPK, while directly promoting cancer cell proliferation [132]. The increase in eosinophils in HNSCC not only promotes the neuroinvasion of tumor cells by releasing CCL2 but also contributes to angiogenesis within the tumor tissue [133]. Netrin-1, which tends to increase in HNCSS, is also a potent factor for stimulating angiogenesis, in addition to neuronal axon guidance. It may participate in tumor growth, invasion, and apoptosis through the NFκB signaling pathway [134].

Lymphatic Vessels

In addition to nerve and blood vessel interpenetration, lymphatic vessels are crucial in tumor metastasis and the immune microenvironment. The body's lymphatic system is heavily innervated by adrenergic neurons, and β2-AR signaling regulates tissue lymphocyte infiltration [135]. Previous study has also found that β2-AR is markedly up-regulated in HNC, blocking it can inhibit tumor growth and invasion [136]. Moreover, the trend of sensory nerve differentiation into adrenergic neurons in HNC seems to offer a significant physiological foundation for tumor neuroimmunity [87]. Certainly, nociceptors can also directly participate in the neural innervation of lymph nodes and may modulate local immune responses [137]. Furthermore, the chemokine CX3CL1, which has a potential role in the direct interactions between cancer cells and neurons, may also promote the malignant invasion of OSCC by stimulating lymphangiogenesis and transendothelial migration of tumor cells in the lymphatic circulation [138]. The axon guidance molecule semaphorin 3 F, although conservatively expressed in most HNCs, has also been shown to exhibit growth-inhibitory activity in OSCC cells and interfere with tumor invasion [139]. Notably, re-expression of semaphorin 3 F in HNSCC cells may also reduce lymphangiogenesis and exert anticancer effects [140].

Summary of mechanistic insights

In conclusion, the neuro-cancer crosstalk in HNC is a complex pathophysiological process involving multiple cells and factors. At present, an increasing number of studies have begun to focus on cancer neuroscience in HNC. Synapses are key connecting structures for transferring information between neurons. The presence of neural-tumor synaptic structures in the cancerous tissues of HNSCC patients was clearly demonstrated in a study by Restaino [72]. It is an essential channel for communication between neurons and cancer cells. In addition, tumor and nerve cells can release reciprocal signals in an autocrine or paracrine manner and transmit information by binding to corresponding receptors on effector cells [141]. This is also critical for cancer cells to achieve perineural diffusion and metastasis, independent of vascular and lymphatic channels. In the interaction summary diagram (Fig. 3) of this review, we summarize the classical routes, including the synaptic and nonsynaptic forms, along with their results and typical modes of action. However, it is important to note that the sources, pathways, and targets of most effectors are not singular [70]. Nerves, cancer, and immune cells alike may secrete specific substances or have corresponding effector receptors. This suggests that it is crucial to clarify whether there are primary or secondary effects of the effector molecule sources or action sites as well as positive/negative feedback regulation, which are key issues that must

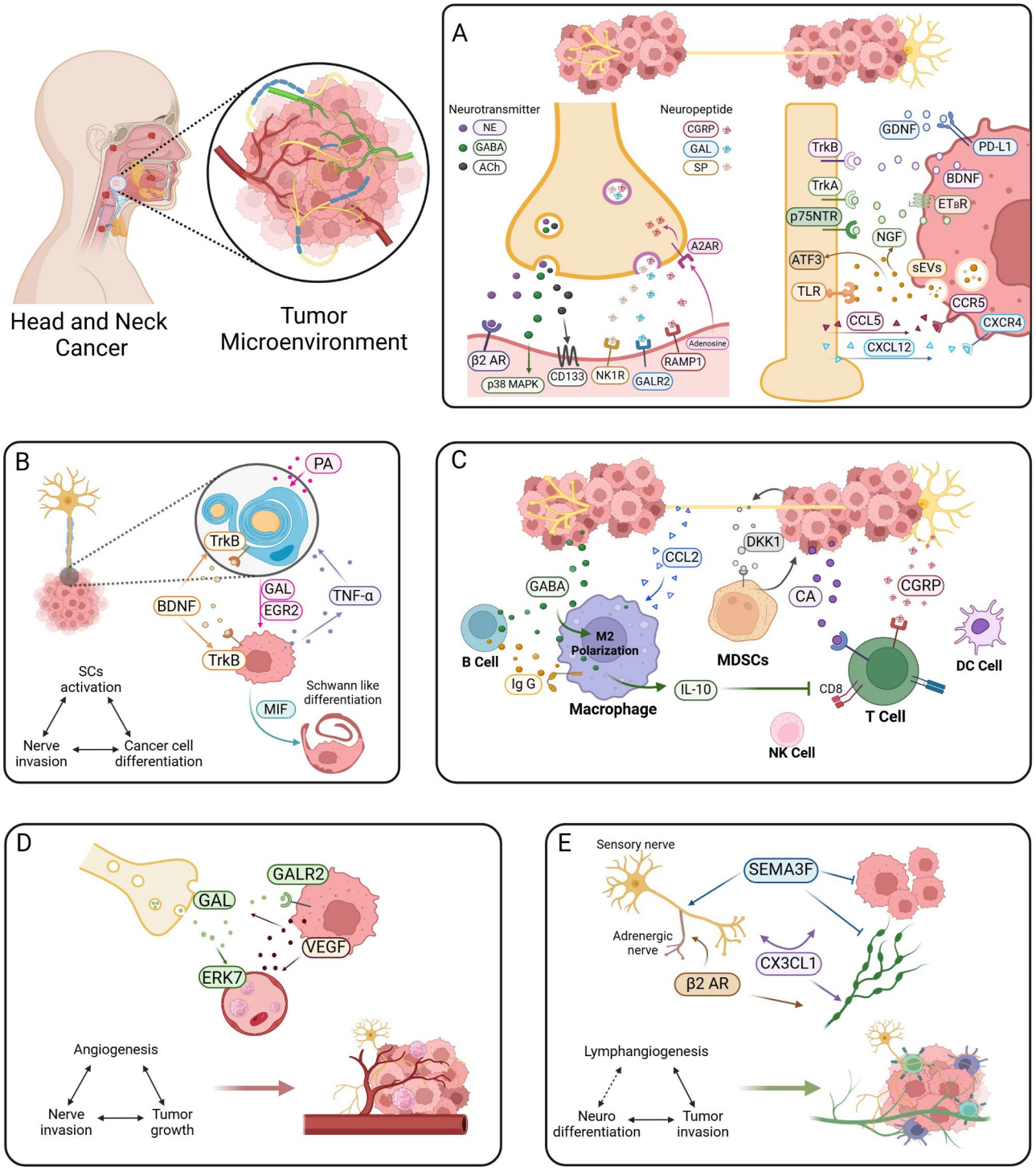

Fig. 3 The mode of action of neuro-cancer crosstalk in HNC. (**A**) Direct interactions between nerve and cancer cells. (**B**) Interactions between Schwann and cancer cells. (**C**) Interactions between immune cells and neuro-cancer crosstalk. (**D**) Interactions between blood vessels and neuro-cancer crosstalk. (**E**) Interactions between lymphatic vessels in neuro-cancer crosstalk. (Figure created with BioRender)

be addressed when translating basic research into clinical applications.

Furthermore, previous studies have identified several effectors involved in various forms of neuro-cancer crosstalk in HNC (Table 1 [142–164]). However, most studies have only focused on clinical correlation analysis between target molecular phenotypes and neuroinvasion or simple mechanism validation in a single cell. They did

Table 1 Nerve-related effectors in HNC (supplementary indicators not mentioned in the text)

Effect Factors	Disease	Source	Expression Level	Verification Method	Pathways or Biological processes	Potential impact on tumor neural interactions	Reference
BCAR3	HNSCC	Cancer cell	Increase	Cellular intervention experiment	Cell adhesion, actin binding, cadherin binding, and angiogenesis	Associated with tumor PNI	Zhang Z, et al. 2021 [142]
CD44	OSCC	Unknown	Overexpression	Clinical sample validation	Unknown	Associated with tumor PNI	Lee JR, et al. 2018 [143]
CELSR3	OSCC	Cancer cell	Increase	Clinical sample validation	Axonogenesis, neuron migration, and cell-cell adhesion	Predict tumor PNI	Zheng K, et al. 2022 [144]
CFL1	HNSCC	Neuron	Increase	Cellular intervention experiment	Unknown	Associated with tumor PNI	Liu R, et al. 2024 [145]
Circular RNA RNF111	SACC	Cancer cell	Increase	Cell and animal model validation	miR-361-5p/HMGB2 axis	Associated with tumor PNI	Su R, et al. 2023 [146]
C-Kit	ACC	Cancer cell	Increase	Clinical sample validation	Activated after stem cell factor stimulation	Associated with tumor PNI	Phuchareon J, et al. 2014 [147]
DKK1	HNSCC	Cancer cell	Increase	Cellular intervention experiment	PI3K/Akt signaling pathway	Induction of neurogenesis in tumors and promotion of PNI	Wang J, et al. 2020 [148]
EMMPRIN	SACC	Cancer cell	Positive	Cell and animal model validation	Mediate the expression of MMP-2 and MMP-9	Associated with tumor PNI	Yang X, et al. 2012 [149]
L1CAM	OSCC	Cancer cell	Positive	Clinical sample validation	PI3K/AKT/ERK signaling pathways and EMT	Associated with tumor PNI	Kim JH, et al. 2023 [150]
Laminin-5	OSCC	Cancer cell	Positive	Clinical sample validation	Unknown	Associated with tumor PNI	Tarsitano A, et al. 2016 [151]
IGFBP2	SACC	Cancer cell	Increase	Cell and animal model validation	NF-κB/ZEB1 signaling pathway	Associated with tumor PNI	Yao X, et al. 2018 [152]
IL-6	HNSCC	Cancer cells and neurons co-culture media	Increase	Cell co-culture modeling and electrophysiological recordings	IL-6 receptor	Associated with cancer pain after tumor PNI	Uhelski ML, et al. 2022 [153]
IMP3	OSCC	Cancer cell	Positive	Clinical sample validation	Unknown	Associated with tumor PNI	Tarsitano A, et al. 2016 [151]
ITGB1	OSCC	Cancer cell	Increase	Cellular intervention experiment	The adhesion to neuronal cells, resistance to radiation, and invasion and migration of radioresistant OSCC	Associated with tumor PNI and radioresistance	Park SJ, et al. 2023 [154]
ITGB6	OSCC	Cancer cell	Increase	Cellular intervention experiment	Unknown	Associated with tumor PNI	Geyer M, et al. 2024 [155]
MAG	OSCC	Cancer cell	Increase	Clinical sample validation	Unknown	Associated with tumor PNI	Mk H, et al. 2016 [156]
MIF	SACC	Cancer cell	Increase	Cellular intervention experiment	EMT and Schwann-like cell differentiation	Associated with tumor PNI	Zhang M, et al. 2013 [157]
Nanog	MEC	Cancer cell	Positive	Clinical sample validation	Unknown	Associated with tumor PNI	Destro Rodrigues MF, et al. 2017 [158]
NgR3	NPC	Cancer cell	Increase	Cellular intervention experiment	The downregulation of E-cadherin and enhanced cytoskeletal rearrangement and cell polarity	Associated with tumor lymph node metastasis which is correlated with nerve involvement	He JY, et al. 2018 [159]

Table 1 (continued)

Effect Factors	Disease	Source	Expression Level	Verification Method	Pathways or Biological processes	Potential impact on tumor neural interactions	Reference
Notch-4	ACC	Cancer cell	Unknown	Cellular intervention experiment	Unknown	Regulate the PNI activity of cancer cells	Chen W, et al. 2013 [160]
NRP2	HNC	Cancer cell	Increase	Cellular intervention experiment	RSK1/Sox2/Zeb1 axis	Its role as an axon guidance protein in neural development can influence the aggressive behavior of cancer cells	Ahn MH, et al. 2024 [161]
Oct4	MEC	Cancer cell	Positive	Clinical sample validation	Unknown	Associated with tumor PNI	Destro Rodrigues MF, et al. 2017 [158]
PAR2	HNSCC	Neuron	Unknown	Cell and animal model validation	Unknown	Associated with cancer pain	Lam DK, et al. 2010 [162]
Podoplanin	OSCC	Cancer cell	Positive	Clinical sample validation	Unknown	An independent pre-operative variable significantly related to tumor PNI	Gabusi A, et al. 2024 [163]
POFUT1	HNSCC	Cancer cell	Increase	Cellular intervention experiment	Unknown	Affecting PNI of tumor cells	Barlak N, et al. 2023 [164]
SLC7A11	OSCC	Unknown	Overexpression	Clinical sample validation	Unknown	Associated with tumor PNI	Lee JR, et al. 2018 [143]

The abbreviations in Table 1: ACC, adenoid cystic carcinoma; BCAR3, breast cancer anti-estrogen resistance protein 3; CELSR3, cadherin EGF LAG seven-pass G-type receptor 3; CFL1, cofilin-1; DKK1, dickkopf-1; EMMPRIN, extracellular matrix metalloproteinase inducer; EMT, epithelial-mesenchymal transition; HMGB2, high mobility group box 2; HNC, head and neck cancer; HNSCC, head and neck squamous cell carcinoma; L1CAM, L1 cell adhesion molecule; IGFBP2, insulin-like growth factor binding protein 2; IL-6, interleukin 6; IMP3, insulin-like growth factor-II mRNA binding protein-3; ITGB, integrin beta; MAG, myelin associated glycoprotein; MEC, mucoepidermoid carcinoma; MIF, macrophage migration inhibitory factor; MMP, matrix metallopeptidase; NF-κB, nuclear factor kappa B; NgR3, nogo receptor 3; Notch-4, notch receptor 4; NPC, nasopharyngeal carcinoma; NRP2, neuropilin-2; OCC, oral cavity cancer; Oct4, organic cation/carnitine transporter4; OSCC, oral squamous cell carcinoma; PAR2, protease-activated receptor 2; PI3K, phosphatidylinositol 3-kinase; PNI, perineural invasion; POFUT1, protein o-fucosyltransferase 1; SACC, salivary adenoid cystic carcinoma; SLC7A11, solute carrier family 7 member 11; ZEB1, zinc finger E-box binding homeobox 1

not conduct a deeply excavated one-to-one correspondence of the interaction routes between tumor cells and neurons or neural-related cells, yet provided us with a substantial number of research directions. We also found that most nerve-related factors in HNC tended to be protumorigenic effects (Table 2). Although excitatory and inhibitory neurotransmitters have opposite effects under physiological conditions, previous studies have primarily focused on their roles in promoting tumor growth, invasion, and therapeutic resistance. Whether this is associated with multiple factors such as intervention dosage and duration requires further validation through comparative analysis and time/concentration gradient experiments. In addition, the mechanisms underlying most of these effects are common across different types of HNCs and include the Akt signaling pathway, ERK signaling pathway, and EMT (Fig. 4). These mechanisms may become important targets or reference indices for future neurovision-related interventions in the management of HNC.

Clinical findings of HNC in the nervous system

Nerve invasion within HNC tissue

The effects of cancer cells on the nervous system begin with nerve invasion within the tumor tissue. In tumors, invasion of the nerve sheath by cancer cells or infiltration along at least 33% of the nerve circumference is termed perineural invasion (PNI) [165]. As early as the 1980s, researchers found the perineural spread of cancer cells in the tumors of patients with HNC, which was the earliest definition of PNI [166]. They also discovered a clear association between increased tumor recurrence and decreased patient survival [167]. In subsequent studies, researchers have continued to improve the detection efficiency of PNI through various methodologies, and the results have consistently shown that PNI is a key pathological feature strongly associated with the prognosis of patients with HNC [168, 169]. The prevalence rate has been reported to reach 82% in oral cavity cancer [170]. In addition, in ACC, TC, and sinonasal squamous cell carcinoma, the presence of PNI predicts an increased risk of tumor recurrence or death, regardless of the detection rate [171–173].

To more accurately identify PNI in HNC, Lee et al. used the Domain-KEY algorithm to successfully simulate a PNI diagnosis [174]. Weusthof et al. additionally applied single-cell sequencing to create a predictive model for the PNI in patients with HNSCC [175]. Both studies aimed to assist with routine pathology testing and enhance the identification of neuro-invasions using a more standardized and objective method. The directionality of PNI in the prognostic evaluation of patients with HNC further suggests the significance of its accurate assessment as a reference value for guiding therapeutic regimens. The US

Table 2 Key molecules and specific mechanisms involved in neuro-cancer crosstalk in HNC.

Molecules		Characteristics	Sources	Target Receptors	Intervention Methods	Signaling Pathways	Mechanisms
Neurotransmitters	NE	Excitatory neurotransmitter	Neurons or sympathetic-adrenal medullary axis	β-AR	Receptor antagonist	1 ROS 2 Caspase 3/7 3 MMP 4 VEGF 5 Akt-ABCG2 6 IL-6	1 DNA damage leading to cellular malignancy 2 Inhibition of apoptosis, promoting abnormal proliferation 3 Degradation of extracellular matrix, facilitating cancer cell migration 4 Promotion of intratumoral angiogenesis 5 Facilitation of chemotherapeutic drug efflux, leading to drug resistance
	GABA	Inhibitory neurotransmitter	Neurons	GABAR	Receptor antagonist or downstream gene knockdown	1 p38 MAPK (+) /JNK MAPK (-) 2 BCL2L1 and CCND2	Promotion of cell proliferation and interference with cell cycle progression
			Cancer cells	GABABR	Knockdown of GAD1	GABBR1/ERK/Ca^{2+}	Promotion of M2 macrophage polarization, limiting anti-tumor immunity
			B cells	Unknown	B cell deficiency or B cell-specific inactivation of GAD67	IL-10	Inhibition of $CD8^+$ T cell activation and proliferation
	ACh	Excitatory/ Inhibitory neurotransmitter	Unknown	AChRs	Receptor antagonist	1 CD133-Akt 2 MEK/ERK-CES1	1 Self-renewal and immune evasion capabilities 2 Cancer cell proliferation and migration

Table 2 (continued)

Molecules		Characteristics	Sources	Target Receptors	Intervention Methods	Signaling Pathways	Mechanisms
Neuropeptides	CGRP	Unknown	Sensory neuron	CLR	Receptor antagonist	Rap1-mTOR/Raptor	Induction of protective autophagy and promotion of cancer cell proliferation
	GLA	Unknown	Neurons and cancer cells	GALR2	Receptor blockade	NFATC2-COX2/PGE2	1 Modulation of neurite outgrowth, facilitating perineural invasion 2 Promotion of cancer cell EMT
Neurotrophic factors	NGF	Unknown	Cancer cells	TrkA/p75 receptor	NGF neutralizing antibody	1 PI3K/Akt 2 TNF-α and IL-6	1 Promotion of cancer cell migration and dissemination 2 Increased neural sensitivity
	BDNF	Unknown	Neurons and cancer cells	TrkB	Receptor antagonist	Unknown	1 Promotion of cancer-related pain 2 Modulation of cancer cell EMT
	GDNF	Unknown	Unknown	Unknown	JAK2 inhibitor	1 JAK2-STAT1-PD-L1 2 PI3K/Akt and MAPK/ERK-MMP	1 Upregulation of immune checkpoint expression 2 Modulation of cancer cell cytoskeleton and remodeling
Exosomes	Exosome	Lacking miR-34a	Cancer cells	Unknown	Sensory nerve ablation and AR blockade	TP53 mutations	Promotion of sensory neuron remodeling towards adrenergic phenotype

Table 2 (continued)

Molecules		Characteristics	Sources	Target Receptors	Intervention Methods	Signaling Pathways	Mechanisms
Chemokines	CCL2	Unknown	Neurons	CCR2	Receptor antagonist	Unknown	Induction of chemotherapy-related neuropathic pain
	CCL5	Unknown	Neurons	CCR5	Blocking of CCL5 or CCR5	Unknown	Rapid induction of Ca^{2+} transmembrane transport and formation of cancer cell pseudopodia
	CXCL12	Unknown	Neurons	CXCR3	Twist knockdown	Twist/S100A4 axis	Promotion the Schwann cell-like differentiation of cancer cell

The abbreviations in Table 2: ABCG2, ATP-binding cassette sub-family G member 2; ACh, acetylcholine; AChRs, acetylcholine receptors; β-AR, β-adrenergic receptor; BDNF, brain-derived neurotrophic factor; BCL2L1, BCL2-like 1; CCL, C-C motif chemokine ligand; CCND2, cyclin D2; CCR, C-C motif chemokine receptor; CES1, carboxylesterase 1; CGRP, calcitonin gene-related peptide; CLR, calcitonin receptor-like receptor; COX2, cytochrome c oxidase subunit II; CXCL12, C-X-C motif chemokine ligand 12; CXCR4, C-X-C motif chemokine receptor 4; EMT, epithelial-mesenchymal transition; ERK, extracellular signal-regulated kinase; GABA, gamma-aminobutyric acid; GABABR, gamma-aminobutyric acid type B receptor; GABAR, gamma-aminobutyric acid receptor; GAD, glutamic acid decarboxylase; GLA, galanin; GLAR2, galanin receptor 2; GDNF, glial cell-derived neurotrophic factor; HNC, head and neck cancer; IL, interleukin; JAK2, janus kinase 2; MAPK, mitogen-activated protein kinase; MEK, mitogen-activated protein kinase kinase; MMP, matrix metalloproteinase; mTOR, mechanistic target of rapamycin kinase; NE, norepinephrine; NFATC2, nuclear factor of activated T-cells, cytoplasmic, 2; NGF, nerve growth factor; PGE2, prostaglandin E2; Rap1, ras-related protein 1; Raptor, regulatory-associated protein of mTOR; ROS, reactive oxygen species; STAT1, signal transducer and activator of transcription 1; TrkA, tropomyosin receptor kinase A; TrkB, tropomyosin receptor kinase B; VEGF, vascular endothelial growth factor

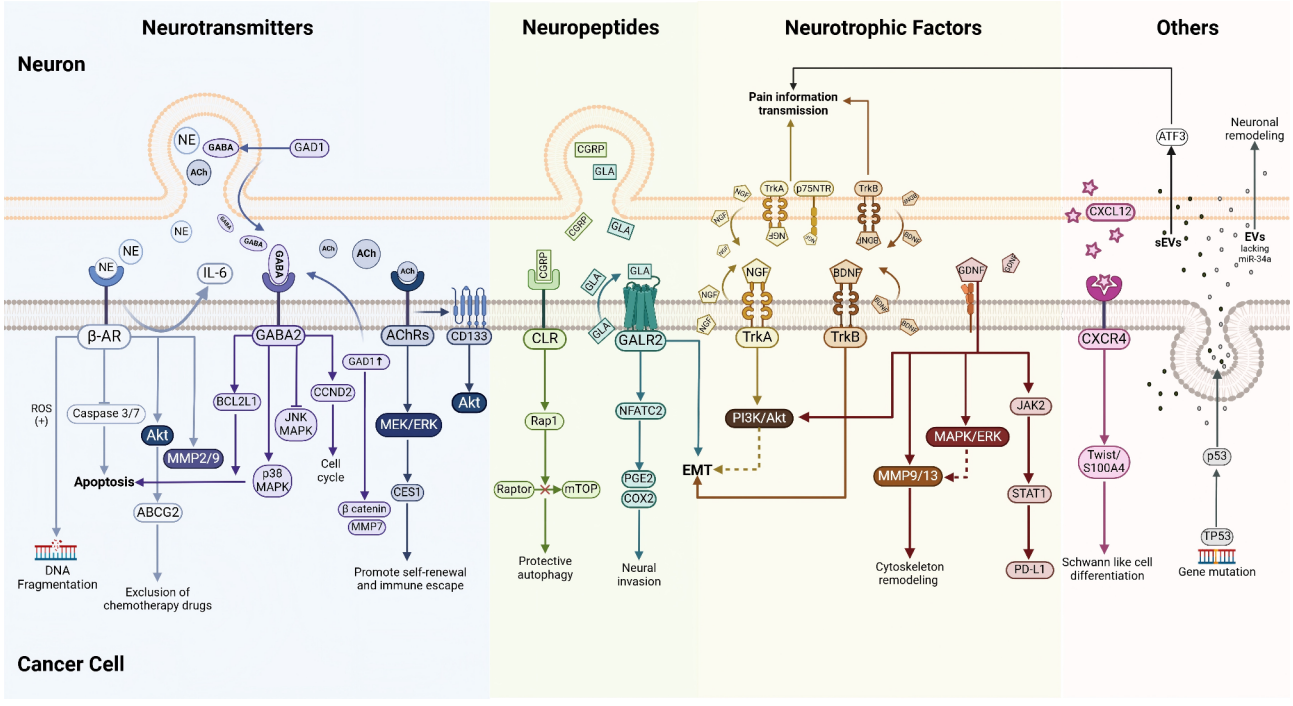

Fig. 4 The key mechanisms of neuro-cancer crosstalk in HNC. In neuro-cancer crosstalk in HNC, cancer cells and neurons can interact with each other through various effector molecules, including neurotransmitters, neuropeptides, neurotrophic factors, extracellular vesicles and chemokines. Among these mechanisms, the roles of MMP, Akt signaling pathway, MEK/ERK signaling pathway and EMT in neuro-cancer crosstalk have been validated many times. (Figure created with BioRender)

2022 guidelines for the diagnosis and treatment of HNC identify PNI as the primary adverse pathological feature of oropharyngeal cancer and recommend its use in guiding the decision-making process for postoperative adjuvant therapy [176]. However, this has not been applied to the full spectrum of HNCs in clinical practice. Therefore, it is necessary to consider the complexity of the anatomical structure of the head and neck region and the diversity of the tumor histopathology. More thorough and extensive clinical data collection, together with the development of new technologies, is essential for incorporating PNI assessments into clinical decision-making.

Additionally, cancer cells within a tumor have various effects on the growth and development of nerve cells, thus creating a self-serving TME [4]. Cancer cells not only specialize in undifferentiated protrusions on tumor-infiltrating neurons into axons through various regulatory mechanisms, a process known as axonogenesis, but can also recruit neural progenitor cells to the primary tumor site to form new neurons, a process referred to as neurogenesis, thereby promoting malignant proliferation and dissemination of cancer cells within the tumor [90, 177]. This series of clinical neural structural changes was mostly observed through pathological detection. A more common criterion for judgment is an increase or decrease in neural density within tumor tissues. An increase often indicates poor prognosis [178–180].

Neurological symptoms caused by HNC

In HNC, the PNS and CNS experience comparable clinical symptoms, regardless of whether cancer cells produce pathological damage in nerve cells or tumor tissues induce mechanical damage to the nervous system. Table 3 [8, 18, 181–201] summarizes the neurological symptoms associated with HNC.

5.2.1 Symptoms of the PNS

Owing to the high density of nerve distribution and tight anatomy, patients with HNC often experience neurological symptoms such as pain, hoarseness, tinnitus, visual disturbances, and numbness. According to the collected data, pain was the most frequent symptom, with 19–100% of patients experiencing pain of varying degrees. It may be difficult to relieve this pain effectively during therapy [202]. An early meta-analysis showed that patients with HNC have much higher pain rates than those with other types of cancer [203]. Pain is also an independent predictor of patient survival [183]. In addition to the compression of nearby nerves by tumors, various patterns and degrees of cancer cell invasion of the nerves also contribute to pain in patients with HNC. Salvo et al. further demonstrated in a mouse model of PNI that the destruction of nerve axons by oral cancer cells via high-threshold mechanoreceptors is essential for sensitizing sensory neurons and eliciting pain [204]. Moreover, while mediating tumor invasion, paracrine signals released by neurons and tumor cells can bidirectionally modulate peripheral sensory nerves, exacerbating the patient's pain response [205]. Pain is a frequent clinical manifestation of all HNC types, and facial nerve numbness is a common symptom, especially in parotid gland-related malignancies [206]. Reduced or even loss of vision may result from the invasion of the optic nerve by the tumor [190]. Myasthenia gravis, a disorder of the peripheral nerve-muscle junction, has also been observed in patients with HNC [207]. However, its association with tumor-induced nerve injury remains unclear.

Symptoms of the CNS

Fatigue is more prevalent and persistent than pain in most cancer patients [208]. However, owing to the lack of distinctive and sensitive clinical manifestations, fatigue is often overlooked. Although most oncological fatigue is closely linked to treatment, it can also result from CNS inflammation or metabolic competition in the body caused by the tumor itself [209, 210]. However, some individuals with symptoms of fatigue may be more concerned about decreased sleep quality [193]. An earlier study also demonstrated that HNC patients are more likely to experience emotional distress than patients with other cancers, which indicates a strong connection to patient survival rates [211]. These symptoms are not only related to benign or malignant tumors or to the stimulation of cancer pain, but may also be associated with a non-inflammatory biological pathway induced by the tumor or even to the patient's own hyperlipidemia and systemic inflammation [212–214]. Emotional symptoms in the early stages of the disease can also influence the incidence of anxiety and depression in later stages as management progresses [196]. Additionally, patients with HNC may have cognitive impairments that affect their adherence to treatment. This may be because some brain regions or nerves that regulate emotions, sleep, or cognition are damaged to various degrees in HNC [215]. However, their direct interactions require further exploration.

Neurological symptoms caused by HNC treatment

Treatment of HNC is primarily based on surgery and/or radiochemotherapy. With the development of medical technology, emerging immunotherapies and targeted therapies have shown great potential for HNC treatment. However, following various treatments for the head and neck, which are involved in multiple physiological functions, patients become more susceptible to side effects, such as pain, that considerably affect their quality of life [216, 217]. Neuropsychological disorders are also more frequent in HNC survivors.

Table 3 Neurological symptoms associated with HNC.

Nervous system region	Symptom	Disease	Numbers	Prevalence	Research method	Reference
Peripheral nervous system	Neuropathic pain	HNC	25	100%	Clinical questionnaires	Ye Y, et al. 2023 [181]
	Neuropathic pain	HNSCC	60	54%	Prospective clinical study	Salwey L, et al. 2020 [182]
	Severe pain	HNSCC	2340	19%	Prospective clinical questionnaire	Reyes-Gibby CC, et al. 2014 [183]
	Pain	HNC	27	78%	Clinical questionnaires	Buchakjian MR, et al. 2017 [184]
	Pain	OSCC	113	37%	Clinical research	Sato J, et al. 2010 [185]
	Pain	OSCC	138	39%	Clinical research	Haya-Fernández MC, et al. 2004 [186]
	Pain/tenderness	PT	200	54%	Retrospective clinical study	Inaka Y, et al. 2021 [187]
	Facial nerve palsy	PT	200	18%	Retrospective clinical study	Inaka Y, et al. 2021 [187]
	Facial nerve palsy	HNSCC	19	42%	Retrospective clinical study	Zhang M, et al. 2023 [188]
	Orbital apex syndrome	HNC	4	-	Cases report	Prado-Ribeiro AC, et al. 2017 [189]
	Visual loss	HNSCC	1	-	Case report	Fang KH, et al. 2007 [190]
	Headaches, double vision, facial numbness	NACC	1	-	Case report	Liang YF, et al. 2014 [191]
	Facial paralysis, conductive type hearing loss, and ophthalmoplegia	LLC	1	-	Case report	Katar O, et al. 2021 [192]
Central nervous system	Poor sleep quality	HNC	560	44%	Cross-sectional study	Santoso AMM, et al. 2021 [193]
	Decreased sleep quality	HNC	412	43%	Prospective cohort study	Santoso AMM, et al. 2021 [194]
	Anxiety	HNC	219	32%	Clinical research	Henry M, et al. 2019 [195]
	Anxiety	HNC	75	30%	Clinical scale assessment	Neilson KA, et al. 2010 [196]
	Anxiety/depression	HNC	84	61.9%	Clinical scale assessment	Krebbers I, et al. 2021 [197]
	Depression	HNC	55,069	11.52%	Retrospective clinical study	Huang RW, et al. 2022 [198]
	Depression	HNC	817	48.7%	Clinical questionnaires	Hammermüller C, et al. 2021 [18]
	Depression	HNC	113	11.5%	Clinical scale assessment	Lee Y, et al. 2020 [199]
	Depression	HNC	219	19.4%	Clinical scale assessment	Henry M, et al. 2019 [195]
	Depression	HNC	75	15%	Clinical scale assessment	Neilson KA, et al. 2010 [196]
	Depression	HNC	133	34.3%	Clinical scale assessment	Sehlen S, et al. 2003 [200]
	Cognitive impairment	HNC	83	55%	Clinical scale assessment	Williams AM, et al. 2017 [8]
	Neurocognitive impairment	HNC	55	38%	Neuropsychological test	Bond SM, et al. 2016 [201]

The abbreviations in Table 3: HNC, head and neck cancer; HNSCC, head and neck squamous cell carcinoma; LLC, lower lip carcinoma; NACC, nasopharyngeal adenoid cystic carcinoma; OSCC, oral squamous cell carcinoma; PT, parotid tumor

Surgery

Surgery is the most common treatment for HNC. However, it is also the most direct way to cause nerve damage to the head and neck, especially if the tumor is adjacent to or invades a nerve. In patients with HNC accompanied by cervical lymph node metastasis, the incidence of spinal accessory nerve injury caused by different ranges of cervical lymph node dissection is 27.9–33.0%, while it can be as high as 94.8% in radical neck dissection; the incidence of facial nerve injury is 12.7–13.1% [218]. In TC, the incidence of transient recurrent laryngeal nerve damage caused by surgery is 5–8%, and the prevalence of permanent damage is 0.3-3% [219]. Hoarseness, facial paralysis, and pain caused by surgical nerve damage can exacerbate emotional disorders in patients with HNC [220, 221]. This direct neural damage caused by surgery can be classified from mild to severe as "neurapraxia," "axonotmesis," and "neurotmesis." [222] Patients with the former type of injury usually recover completely in the short term; however, those with more severe nerve damage may require surgical repair and may not fully recover. Surgeons also need to pay attention to the potential threat of heat-generating instruments to nerves during operations near nerve areas. Therefore, intraoperative nerve monitoring during HNC surgery is critical for reducing the rate of nerve damage [223]. This places a high demand on the surgeon's operating ability and underscores the urgent need for continuous exploration and optimization of techniques to repair or prevent nerve injuries.

Radiotherapy

Radiotherapy is an important treatment for HNC because of its high sensitivity to malignant tissues in the

head and neck [224]. Radiotherapy at a certain dose can effectively improve patient prognosis, especially when cancer cells invade the nerves [225]. However, this localized radiation intervention can result in injury to brachial plexus nerves, CNs, and nerve endings in the skin and mucous membranes of these regions. This injury can lead to pain; numbness; muscle weakness; and vision, olfaction, swallowing, and articulation disorders. Radiotherapy for nasopharyngeal carcinoma can lead to high-frequency hearing loss, with an injury rate as high as 42.2% [226]. This damage can not only be caused by radiation-induced cellular DNA damage, nerve axonal damage, demyelination, and neurovascular edema, but can also be exacerbated by radiation therapy-induced chronic inflammation and neural or peripheral tissue fibrosis [227]. In addition, radiation can affect local neurotrophic signaling pathways that regulate the secretory function and regeneration of salivary glands [228]. Neuroagonists can significantly reduce radiation-induced damage [229]. According to previous statistics, the incidence rate of radiation-induced nerve damage is approximately 2–14%, while the occurrence rate of radiation-induced cranial neuropathy is 2–9% [226].

Furthermore, radiation exposure affects the CNS, particularly the temporal lobe, resulting in memory deficit and cognitive impairment [230]. The incidence of radiotherapy-associated depression is high in patients with HNC [231]. In pediatric patients, radiation therapy to the head and neck can lead to growth hormone secretion disorders related to the hypothalamic-pituitary axis in up to 56.9% of children, thereby severely affecting their growth [232]. The prognosis of radiation-induced brain injury varies significantly depending on the stage of onset. Patients with acute phase injuries have the potential to recover over time, whereas delayed-onset brain injuries often result in irreversible damage [233]. Therefore, in HNC radiotherapy, the maximum radiation dose to critical CNS regions should be prioritized [234]. Patients' tolerance to radiation significantly limits the clinical use of radiotherapy. Although new radiotherapy techniques, such as intensity-modulated radiation therapy and stereotactic radiosurgery, have optimized radiation dose distribution and reduced damage to healthy tissues as much as possible, neurocognitive disorders still have a gravely poor prognosis [235].

Chemotherapy

Most patients with HNC are already in an advanced stage at initial diagnosis, and chemotherapy is an important component of the comprehensive treatment strategy for HNC. According to previous studies, both the type and dosage of chemotherapy can harm the PNS and CNS in patients with HNC to varying degrees [236–238]. The incidence rate of chemotherapy-related PNS injuries can reach up to 30–80% [239, 240]. One reason is that most chemotherapeutic medications are neurotoxic and inhibit cancer cell survival. Cisplatin, a first-generation, platinum-based chemotherapeutic drug, is currently the core option for HNC chemotherapy. However, cisplatin can cause neurotoxicity and ototoxicity resulting in hearing deficits and tinnitus [241]. Cisplatin neurotoxicity is closely associated with oxidative stress-induced DNA damage in neural cells and ferritinophagy-triggered cell death [242]. Moreover, early platinum-based chemotherapeutic drugs can cause SC dysfunction and demyelination during HNC treatment. This phenomenon can be effectively inhibited by the third-generation platinum drug oxaliplatin, thereby preventing the development of chemotherapy-induced peripheral neuropathy in patients [243]. Methotrexate, a substitute for patients with HNC who are not suitable for cisplatin treatment, may also lead to the dysfunction of intracranial microglia and affect cognition-related neurological disorders [244]. Furthermore, chemotherapy can cause CNS symptoms such as headaches, epilepsy, and hypersomnia. The incidence of chemotherapy-induced cognitive impairment in some cancers can reach 69–78% [245]. During chemotherapy, acute episodes of neurotoxicity such as pain and sensory abnormalities may be alleviated by certain neurotransmitter drugs [246]. Nonetheless, chemotherapy-induced neuropathy may persist during or after treatment and progress to long-term or permanent damage. Moreover, some delayed neuropathies may have been overlooked, thereby missing an optimal treatment window. Hence, it is crucial to select appropriate chemotherapy regimens, dose adjustments, and preventive measures for HNC patients to minimize the neurological damage caused by chemotherapy.

Immunotherapy

The discovery of immune checkpoint inhibitors (ICIs) in the complex interactive network of the TME has become a major breakthrough in cancer therapy. ICIs have also made significant strides in the treatment of HNC in recent years, particularly in patients with metastatic and/or recurrent HNSCC [247]. In previous studies, it was also discovered that PD-L1 produced by cancer cells can inhibit the excitability of nociceptive neurons and act as an endogenous pain inhibitor [248]. This may represent an important pathway for tumor-related pain suppression and the evasion of neural surveillance. Moreover, while immunotherapy aims to block cancer cell immune evasion and enhance anti-tumor immunity, overactivation of the immune response may inevitably lead to erroneous attacks on the normal nervous system, thereby causing immune-related adverse events [249]. These include hypophysitis, encephalitis, aseptic meningitis in the CNS, and Guillain-Barré syndrome, CNs injury, and

neuromuscular disorders in the PNS [250]. On the bright side, current statistical data indicate that the incidence of neurotoxicity associated with immunotherapy is only 1–5%, and most neural injuries are salvageable [250]. The use of corticosteroids is an important countermeasure against neurotoxicity.

Other treatments

Neurological damage that occurs during cancer treatment or at a later stage makes it difficult to determine the triggering factors because of the persistence and delayed onset of symptoms. For example, pain rates in survivors of HNC can be as high as 62.3% [251]. This pain is not solely caused by transient stimuli during treatment but can persist and accompany patients until death. Opioid painkillers used by patients also present a risk of nerve damage [252]. Additionally, cancer therapy-related fatigue, which is extremely common, may also persist due to its nature or because the patients tend to associate it with therapeutic behaviors rather than the actual treatment itself [253]. The head and neck contain several sensory organs. If HNC treatment causes degradation or defects in sensory function, it can seriously influence cognitive abilities and general quality of life [254]. This is one of the main causes for the high prevalence of depression among patients with HNC. Treatment-related depression can lead to a vicious cycle of treatment discontinuation and a subsequent decline in the overall outcomes of HNC patients [255]. This cycle is further affected by underlying biological responses to depression. In addition, the neuropsychological symptoms of patients with HNC deteriorate over time following treatment, which may be closely related to peripheral inflammation during therapy [256]. Cognitive behavioral therapy and educational interventions may improve the prognosis and quality of life of these patients to a certain extent [257].

Comparative analysis of nerve damage in HNC treatments

Treatment regimens for HNC are usually formulated based on a comprehensive multidisciplinary and multifactorial assessment with the aim of balancing tumor control with potential side effects. Although various therapeutic modalities have shown significant efficacy in tumor control, the associated neural injury, a vital adverse reaction affecting patient prognosis, exhibits significant differences in the incidence probability and reversibility of damage among the different treatment methods. This is often considered as a priority in treatment decisions (Table 4). The incidence of nerve injury caused by surgery is often related to the scope of the surgery and the type of tumor, which shows relative selectivity. In contrast, radiotherapy, which is also a regional treatment, inevitably damages normal tissues. Comparatively, chemotherapeutic drugs not only have significant neurotoxicity, but are also systemic treatments, indicating a higher risk of nerve damage. Therefore, owing to the high prevalence of chemotherapy-related neurotoxicity, cancer research centers in different countries have developed relevant assessment scales to facilitate a more systematic and objective evaluation of patients' neurological damage. Immunotherapy, a novel therapeutic modality, is recognized for its efficacy, and its low incidence of neurotoxicity has demonstrated an essential advantage in its clinical application. However, with the widespread use of immunotherapy, the neurological complications mediated by immunotherapy have also shown a high correlation with mortality [258]. Further large-scale clinical studies are required to clarify the potential neurotoxicity risks associated with emerging anti-tumor therapies.

Additionally, we found that most of the neurological damage associated with HNC treatment was reversible during the acute phase. However, when the damage transforms into a persistent chronic state or manifests as delayed neurotoxicity, recovery is often more difficult, especially when the damage involves the CNS, which often presents an irreversible state. Therefore, immunotherapy appears to have significant advantages. Management strategies for neurotoxicity also need to be individualized based on the severity of the damage. Strictly categorizing neurotoxicity according to its severity and dynamically adjusting the patient's comprehensive treatment plan are of great clinical significance for optimizing treatment outcomes and reducing the neurotoxic burden on patients [259].

Opportunities and challenges of Cancer neuroscience in HNC

Cancer neuroscience, as an emerging frontier interdisciplinary field, marks a breakthrough in traditional cancer diagnosis and treatment frameworks, delving deeper into the comprehensive regulatory mechanisms of the tumor neuroimmune microenvironment. Recent research has also continuously confirmed and highlighted the significance of "neuro-cancer crosstalk" in HNC. However, our current understanding of this emerging field remains limited, and there are still substantial challenges in deciphering the complex crosstalk mechanisms and achieving applicable clinical translation.

Depth and expansion of basic research areas

Excavation and Hindrance of Molecular Interaction Networks

At the level of molecular interaction network analysis, tissue sample multi-omics sequencing has become the core technical approach for exploring the interactions between nerves and tumors. Conventional genomics, transcriptomics, and proteomics are widely used for molecular characterization due to their cost-effectiveness

Table 4 Comparative analysis of nerve damage in the HNC treatments

Treatment method	Neurological damage characteristics			Injury mechanism	Assessment method	Clinical manifestations	Incidence rate	Limitations of treatment	Current intervention measures
	Main damage type	Temporal feature	Reversibility						
Surgery	Mechanical injury	Acute	Partially or completely reversible Individual cases are irreversible	①Neurapraxia ②Axonotmesis ③Neurotmesis	①Preoperative imaging evaluation ②Intraoperative nerve monitoring ③Postoperative symptom assessment	Mainly related to the affected nerve, with symptoms such as hoarseness, facial palsy, pain, etc.	Cervical lymph node dissection: ①Spinal accessory nerve: 27.9–94.8% ②Facial nerve: 12.7–13.1% TC surgery (recurrent laryngeal nerve): ①Transient: 5–8% ②Permanent: 0.3-3%	①Existing tumor nerve invasion ②Intraoperative unavoidable maneuvers	②Neurorrhaphy or nerve grafting ②Neurotrophic drugs ③Neurorehabilitation training ④Perioperative nerve monitoring
Radiotherapy	Radiation injury	Acute Delayed	Partially reversible Essentially irreversib	①DNA damage in neural cells ②Axonal damage ③Demyelination ④Neurovascular edema ⑤Chronic neuroinflammation ⑥Neurofibrosis or perineural fibrosis	①Clinical symptoms and signs ②Imaging evaluation ③Neuroelectrophysiological examination ④Neurobiomarker detection	**PNS**: pain, numbness, visual impairment, olfactory dysfunction, dysphagia, dysarthria, xerostomia, etc. **CNS**: epilepsy, memory deficit, cognitive impairment, depression, endocrine dysfunction, etc.	①Radiation-associated neurological injury: 2–14% ②Radiation-induced cranial neuropathy 2–9% ③NPC radiotherapy causing high-frequency hearing loss: 42.2% ④Children's radiation-induced endocrine dysfunction: 56.9%	①Damage to normal tissues ②Limitation of radiation dose ③Variability in tumor type response ④Cancer cell radioresistance ⑤Long-term treatment risks ⑥Patient's physical condition requirements	①Improving radiation delivery techniques ②Analgesics and corticosteroids ③Nerve decompression surgery ④Hyperbaric oxygen therapy ⑤Repetitive transcranial magnetic stimulation ⑥CBPT

Table 4 (continued)

Chemotherapy	Toxic damage	Acute Chronic Delayed	Partially reversible Partially irreversible Essentially irreversib	①DNA damage in neural cells ②Ferritinophagy-induced cell death ③SC dysfunction ④Demyelination ⑤Microglial cell dysregulation	①Chemotherapy-related neurotoxicity assessment scales ②Medical history and clinical manifestations ③Imaging evaluation ④Neuroelectrophysiological examination ⑤Neurobiomarker detection	**PNS**: pain, numbness, sensory regression or abnormality, hearing loss and tinnitus, etc. **CNS**: cognitive impairment, headache, epilepsy, hypersomnia, etc.	①CIPN: 30–80% ②CICI: 69–78%	①Drug dose dependence and accumulation ②Systemic administration ③Non-specific toxicity ④Cancer cell drug resistance ⑤Persistence of drug toxicity ⑥Patient's physical condition requirements	①Alternative chemotherapy regimens or drug dose control ②Neurotransmitter and hormone-related drugs ③Neuroprotective drugs ④Sensory-motor training ⑤Compression or cryotherapy ⑥CBPT
Immunotherapy	Immune-mediated injury	Acute Subacute Chronic	Reversible Partially reversible Partially irreversible	①Immune cell over-infiltration ②Immune-mediated inflammatory response	①Clinical symptoms and signs ②Regular swallowing and breathing tests ③Imaging evaluation ④CK and neurobiomarker detection ⑤Multidisciplinary discussion	**PNS**: GBS, cranial nerve injury, neuromuscular diseases, etc. **CNS**: hypophysitis, encephalitis, aseptic meningitis, etc.	①Overall incidence rate: 1–5% ②GBS: 0.2–0.4%	①Immune-related adverse events ②High interindividual variability in treatment efficacy ③Complexity of combined therapy ④Limitations of biomarkers ⑤Limitations of applicable cancer types	①Corticosteroids ②Immunoglobulin or plasma exchange ③Discontinuation or substitution of the drug ④Symptomatic and Supportive Treatment

The abbreviations in Table 4: CBPT, cognitive-behavioral-psychological therapy; CICI, chemotherapy-induced cognitive impairment; CIPN, chemotherapy-induced peripheral neuropathy; CK, creatine kinase; CNS, central nervous system; GBS, Guillain-Barré syndrome; HNC, head and neck cancer; NPC, nasopharyngeal carcinoma; PNS, peripheral nervous system; SC, Schwann cell; TC, thyroid cancer

[260–262]. Single-cell sequencing technology, which deciphers cellular subpopulation heterogeneity and identifies novel cell types, significantly enhances research resolution [263]. Spatial transcriptomics, on the other hand, overcomes the limitations of traditional omics, enabling precise localization of the spatial topological relationships between nerve fibers and tumor cells as well as their microregional signal interactions [168]. However, these technologies still face challenges such as high costs, complexity of multidimensional data integration, and requirements for high-quality sample preparation.

Status and Limitations of Basic Functional Verification

In the construction of functional validation models, the current main approaches involve the use of in vitro co-culture systems of nerve cells and cancer cells, orthotopic xenograft animal models of the sciatic nerv, and conditional gene knockout mouse models to investigate the mechanisms of neural invasion [264]. However, such experiments inherently carry the bias of artificial intervention due to the predetermined selection of cell types, which makes it difficult to accurately simulate the synergistic effects of multicellular populations in vivo. Although 3D organoid models partially compensate for these deficiencies by integrating the heterogeneity of the TME, they still face significant technical bottlenecks, such as limited gene editing efficiency and long-term culture stability [265, 266]. Furthermore, although animal models can reflect the in vivo state of diseases to some extent, species differences lead to inconsistencies in physiological and immune responses and cannot fully replicate the complex pathological processes of human diseases. Construction of humanized mouse models may mitigate these limitations [267, 268].

Breakthroughs and Innovations in Interdisciplinary Technological Integration

To overcome the limitations of existing technologies, HNC research is accelerating the deep integration of classical neuroscience techniques with oncological research. Optogenetics and chemogenetics enable the precise regulation of specific neuronal activity, revealing the spatiotemporal specificity of neural circuits in tumor progression [269, 270]. Two-photon calcium imaging combined with patch-clamp technology allows the real-time monitoring of electrical signal transmission between neurons and cancer cells [271]. Furthermore, virus-mediated retrograde monosynaptic tracing provides a novel strategy for deciphering projection patterns

of tumor-related neural circuits [272]. Notably, these techniques have already become well-established in the realm of neuroscience, their application and integration through interdisciplinary collaboration are of paramount importance for the development of cancer neuroscience.

Prediction and assessment of Disease-Related risks

Biomarker Mining for Tumor Nerve Invasion

Nerve invasion, a key characteristic of HNC, plays a significant role in early diagnosis, prognostic stratification, and therapeutic target identification through the systematic exploration of its biomarkers. Based on prior bioinformatics analyses and experimental validation, researchers have identified a series of critical differential factors associated with nerve invasion. Among these, nerve-related factors such as catecholamines, GAD1, NGF, BDNF, and EphrinB1 have demonstrated evaluation value as predictive biomarkers. In addition, SC scoring groups distinguished by differential cytokine expression can serve as tools for assessing the neural richness around tumors [273]. Similarly, peptide probes for SC MHC-II molecules have been developed to verify the occurrence of PNI in ACC patients [274]. Furthermore, the preoperative plasma levels of CGRP and the methylation status of neuropeptide genes have significant reference values for evaluating lymph node metastasis and prognostic risk in patients [65, 275]. The potential of BDNF to predict the cognitive impairment associated with HNC was confirmed in a prospective study conducted in 2023 [276]. However, most studies have focused on the correlation between static single targets and clinical parameters while neglecting the fluctuation and specificity of neuro-related molecules in the TME interaction network and over time. This also leads to an insufficient generalization ability of the predictive indicators in complex pathophysiological states. Therefore, we should not only include more large-sample validations of regional and various types of HNCs to reduce the impact of sample heterogeneity, but also establish standardized sample processing and analysis procedures to reduce the resulting bias caused by technical differences.

Development of Artificial Intelligence (AI) Models for Disease Risk Prediction

With the rapid development of AI technology and big data analysis, as well as their multidisciplinary integration in the medical field, deep learning-based disease prediction models have shown significant advantages in core links such as clinical indicator prediction, disease stratified diagnosis, and prognosis evaluation [277]. In the assessment of tumor neural invasion, traditional diagnostic approaches primarily depend on radiological interpretation and histopathological examination. There are two limitations: first, it is subject to diagnostic heterogeneity due to differences in physician experience; second, it is susceptible to objective technical factors, such as staining batch effects and imaging resolution, which affect diagnostic consistency and accuracy. Notably, deep learning models constructed based on multicenter prospective cohort studies may achieve highly sensitive identification of neural invasion microlesions by integrating deep features from cross-modal medical imaging data (including computed tomography, magnetic resonance imaging, and digital pathology slides) [278, 279]. This technical approach not only breaks through the visual limitations of traditional manual interpretation, but the standardized feature extraction algorithm can also effectively eliminate systematic errors caused by staining batch differences, providing a quantifiable objective basis for clinical decision-making.

Importance of Standardized Protocols in Research

Although diverse mechanistic exploration and detection assessment methods have greatly advanced the development of cancer neuroscience in HNC, the potential risks of model heterogeneity and information source differences still exist. This can lead to a low adaptability rate of biological indicators or AI models during external validation or clinical translation. Therefore, it is crucial to establish standardized protocols for basic and clinical research. On one hand, we must ensure the reproducibility of the research results through standardized sample collection and processing procedures. Simultaneously, multi-cell line and multi-index comparative validation of the target cancer types should be ensured to overcome the challenges related to heterogeneity. On the other hand, to improve the efficiency and accuracy of clinical research, it is necessary to establish standardized clinical diagnostic and treatment guidelines and criteria for evaluating neural damage caused by cancer treatment. However, the formulation of such standardized protocols is often limited by differences in multicenter ethical reviews and lack of long-term follow-up data. The federated learning approach in machine learning may promote the development of universal guidelines or consensus, while protecting data privacy and security [280].

Optimization and innovation of disease interventions

The management of HNC remains a critical focus in clinical research. Despite advancements, current therapeutic strategies continue to pose significant risks of neurologic injury. How to effectively treat and prevent such nerve damage has become an urgent issue that needs to be addressed. Exploring interventions from a neuroscience perspective, which could even potentially synchronize the control of cancer progression, may provide an innovative therapeutic way in HNC (Fig. 5).

Treatment by Nerve Related Factors

Several studies have confirmed the regulatory role of the nervous system in HNC progression and resistance

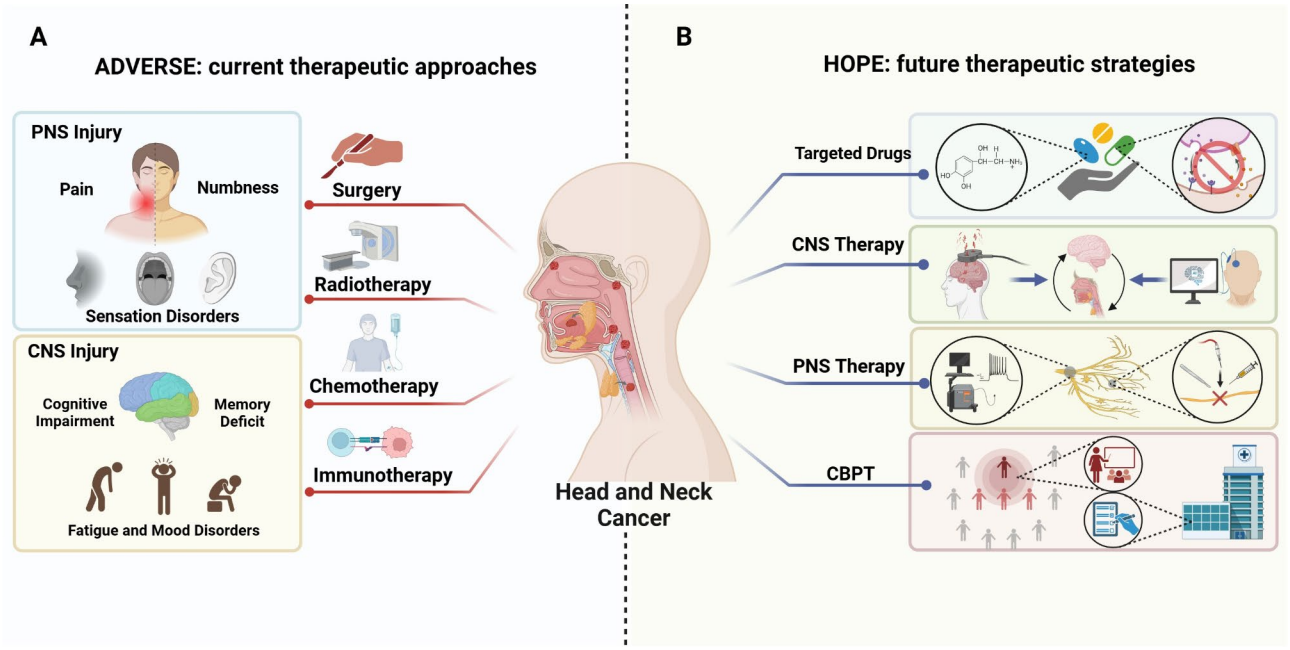

Fig. 5 Neurological perspectives in the treatment of HNC: current status and outlook. (**A**) Current treatment approaches present a risk of neurological impairment. (**B**) Emerging directions for neurocentric interventions in HNC. (Figure created with BioRender)

to treatment. The development of targeted intervention strategies based on neurological perspectives has a significant translational value. Clarifying the critical targets and developing small-molecule inhibitors or specific antibodies to block neuro-cancer crosstalk in tumors are also important avenues for future therapies. Notably, the roles of adrenergic neurons and related neurotransmitters or receptors in HNC have been addressed multiple times. The commonly used β-adrenergic receptor antagonist in clinical practice has also shown promise in inhibiting HNC tumor progression or improving anti-tumor efficacy with adjuvant immunotherapy, in addition to its cardiovascular indications [87, 281, 282]. According to a study by Saussez et al., numerous neurotransmitters and neuropeptides have been shown to bind to T-cell receptors and initiate T-cell-mediated immunological responses [109]. On this basis, the study proposed "neuroimmunotherapy" for HNC, which uses intravenous or intratumoral infusion of T-cells after they have been activated in vitro by neurotransmitters. However, a number of challenges remain to be resolved. For instance, significant biological heterogeneity exists among neuronal populations under physiological and pathological conditions, as well as the expression of nerve-related factors or receptors exhibits mutual exclusivity across different cancer types and disease effects [53, 283]. More critically, most of these factors lack tumor tissue specificity. Hence, there is an urgent need to resolve the molecular signature profiles of tumor-associated nerves and develop precise drug delivery dosages and methods to maximize the benefits of nerve-specific regulation in HNC.

Treatment through CNS

HNC is often accompanied by CNS symptoms such as mood disorders and cognitive impairments, which can be closely related to abnormal changes in neuronal activity in the brain mediated by the TME [215]. Zhang et al. also demonstrated the feasibility of regulating peripheral cancer progression through central neurons [284]. Based on existing evidence, the use of non-invasive neuromodulation techniques, such as transcranial magnetic stimulation, to interfere with central pro-cancer neural signaling or to modulate specific neural circuit activity through brain electrical stimulation, may dynamically inhibit tumor progression [285–288]. This approach has significant advantages in terms of treatment synergism and patient acceptance, particularly for cancer patients with CNS symptoms. Furthermore, breakthroughs in brain-computer interface technology have opened new avenues for alleviating neurological symptoms and addressing speech disorders in patients with HNC [289]. However, this remains a preliminary concept, and translating this diagnostic and therapeutic approach from basic research to clinical applications requires extensive exploration to identify precise regulatory targets and optimize neuromodulation parameters.

Intervention through PNS

For HNC, which is a solid tumor, radical surgery remains the primary clinical strategy under the premise

of meeting the tumor staging criteria and patient physiological tolerance thresholds. Compared to nonsurgical therapies, surgical intervention has higher controllability in nerve protection through direct structural identification and preservation. However, high standardization of unified surgical techniques is difficult to achieve owing to differences in the medical experience of surgeons. Therefore, the introduction of auxiliary equipment or techniques, including dynamic nerve monitoring and 3D reconstruction visualization guidance, can effectively reduce the risk of iatrogenic nerve damage [223, 290]. In addition, blocking or inhibiting potential "pro-cancer" nerves may also contribute to disease control. Thiel et al. have demonstrated that denervation in pancreatic cancer effectively augments the therapeutic efficacy of immunotherapy [263]. This enhancement is partly attributed to the blockade of catecholaminergic neurons, which are known to play a pivotal role in neuro-cancer crosstalk in HNC. However, the nerves involved in HNC often also participate in other important physiological functions. Thus, it is necessary to precisely identify nerve fibers using molecular markers to achieve an optimal balance between therapeutic benefits and the risk of functional impairment.

Education of "Cognitive-Behavioral-Psychological"

HNC, as a typical psychosomatic comorbidity, often leads to multidimensional health damage, such as dysphagia, speech impairment, and facial disfigurement, owing to its pathological characteristics and aggressive treatment methods. This, in turn, induces complex psychological adaptation disorders, such as fear of treatment and social withdrawal. In clinical practice, implementation of systematic psychological intervention programs can effectively improve patients' emotional regulation ability and treatment compliance [291–293]. However, this is difficult to achieve in current medical processes. First, clinical medical staff face high workloads, which makes it difficult to ensure the time cost of individualized psychological counseling. Second, patients experience a sense of stigma towards psychological interventions and are sensitive to economic burdens, which may result in resistance to proactive medical treatment. To address these issues, we can popularize knowledge about tumors and related mental health through public social platforms, and encourage family members to actively participate in the patient's diagnosis and treatment process. Medical institutions can integrate psychological assessments into standard diagnostic and treatment pathways and promote the development of "cognitive-behavioral-psychological" education modules based on mobile health, thereby enhancing patient compliance while reducing manual time costs.

Conclusion

This review comprehensively summarizes and categorizes the potential forms and mechanisms of the interactions between HNC and the nervous system. Our findings systematically reveal the multifaceted roles of the nervous system in the physiology, occurrence, and treatment of HNC. However, in the process of organizing the literature, we found that many effectors in "neuro-cancer crosstalk" have multiple sources or targets as well as heterogeneous functional effects, which greatly limit the precision and controllability of neurotargeting in HNC. Therefore, identifying specific effector targets or loops of action that interact with the nervous system is a key task that should be addressed in future studies.

The development of cancer neuroscience has been a major breakthrough in human cancer resistance [294]. Although many studies support the importance of "neuro-cancer crosstalk" in HNC, higher-quality research and safer clinical application strategies are required to achieve efficient diagnosis and treatment of tumors from a neurological perspective [295]. This not only requires multidisciplinary collaboration, including ENT, neurology, and oncology, but also the development of emerging technologies and accumulation of large sample data.

In conclusion, advances in cancer neuroscience have provided new perspectives and potential therapeutic strategies for the diagnosis and treatment of HNC. We hope that more in-depth and comprehensive studies, as well as more accurate auxiliary diagnostic and therapeutic tools, will be developed in the future to enhance the blueprint of cancer neuroscience for HNC.

Abbreviations

3D	three-dimensional
5-HT	5-hydroxytryptamine
ACC	adenoid cystic carcinoma
ACh	acetylcholine
AI	Artificial Intelligence
β-AR	β-adrenergic receptor
BDNF	brain-derived neurotrophic factor
CGRP	calcitonin gene-related peptide
CNS	central nervous system
CN	cranial nerves
CSF1	colony-stimulating factor 1
DCs	dendritic cells
DKK1	dickkopf-1
EMT	epithelial-mesenchymal transition
EVs	extracellular vesicles
GABA	gamma-amino butyric acid
GAL	galanin
GALR	galanin receptor
GDNF	glial cell-derived neurotrophic factor
HNC	head and neck cancer
HNSCC	head and neck squamous cell carcinoma
IL	interleukin
MDSCs	myeloid-derived suppressor cells
MMP	matrix metalloproteinases
NE	norepinephrine
NGF	nerve growth factor
OSCC	oral squamous cell carcinoma
PD-L1	programmed cell death ligand-1

PNI	perineural invasion
PNS	peripheral nervous system
SACC	salivary adenoid cystic carcinoma
SCs	Schwann cells
TC	thyroid cancer
TME	tumor microenvironment
TrkA	tyrosine kinase receptor A
TrkB	tropomyosin receptor kinase B
TRPV1	transient receptor potential vanilloid 1
VEGF	vascular endothelial growth factor

Acknowledgements
Not applicable.

Author contributions
XC Song, C Ren, and YK Mou conceptualize the manuscript topic and provide administrative support; HR Wang, XY Song, and H Shen originally drafted the manuscript and summerized the related papers; WC Liu, Y Wang, and MJ Zhang designed and summarized the tables; HR Wang, XY Song, and T Yang designed the figures; XC Song, C Ren, and H Shen reviewed and revised the manuscript. All authors have read and agreed to the submitted version of the manuscript.

Funding
This work was funded by the Key Research and Development Program of Shandong Province (Competitive Innovation Platform Project: no. 2022CXPT023 and no. 2024CXPT091), the Taishan Scholar Project (NO. tsqn202312392 and NO.ts20190991).

Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Received: 18 January 2025 / Accepted: 10 March 2025
Published online: 31 March 2025

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