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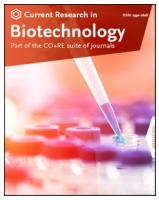

Unraveling the role of perineural invasion in cancer-associated pain: Insights and treatment strategies

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ABSTRACT

Perineural invasion (PNI) occurs when cancer cells infiltrate the space around nerves, commonly seen in head and neck, pancreatic, prostate, and colorectal cancers. PNI is clinically significant as it promotes metastasis, recurrence, and reduced survival. Mechanistically, it involves tumor-neural microenvironment interactions mediated by neurotrophic factors, inflammatory signals, and immune responses. PNI also causes severe neuropathic pain due to nerve compression, plasticity, and inflammation, resulting in sensory abnormalities from neuronal hyperexcitability, demyelination, and upregulated ion channels. This pain significantly impacts quality of life and complicates cancer management. Cells like macrophages and Schwann cells amplify pain via paracrine signaling and pro-inflammatory mediators. Standard pain management, including NSAIDs and opioids, often fails due to toxicity. Emerging therapies target PNI-specific mechanisms to limit tumor-nerve interactions and relieve pain. Research focuses on improving PNI models, dissecting tumor neuroimmune networks, and translating targeted therapies for effective pain relief.

Introduction

Perineural invasion (PNI) refers to the microscopic infiltration of cancer cells into the perineural space of small, unnamed nerves, distinguishing it from perineural spread (PNS), which involves larger, radiologically visible nerves (Liebig et al., 2009). Despite its clinical relevance, the definition of PNI remains debated, with various interpretations highlighting different aspects of nerve involvement.

PNI plays a critical role in cancer progression by leveraging nerve structures for metastasis, driven by neurotrophic factors, cytokines, and cellular interactions that remodel the perineural microenvironment. The mechanisms underlying PNI involve a complex interplay between cancer cells, the neural microenvironment, and ensuing molecular signaling pathways activation. Tumor-derived neurotrophic factors and cytokines stimulate neurite outgrowth and promote nerve infiltration, fostering a neurotropic niche conducive to cancer cell survival and proliferation (Cervantes-Villagrana et al., 2020). Interactions between cancer-associated fibroblasts, immune cells, and Schwann cells contribute to the remodeling of perineural microenvironments, thus facilitating tumor progression and dissemination along nerve fibers (Mao et al., 2021). Additionally, PNI exacerbates neuropathic pain through neural infiltration and inflammation, significantly impairing patient quality of life. Nerve infiltration by cancer cells disrupts normal neural signaling pathways, culminating in the development of neuropathic pain characterized by sensory abnormalities and hyperalgesia (Wang et al., 2020).

This dual impact on cancer progression and pain has motivated advances in diagnostic imaging and therapeutic strategies targeting neurotrophic and neuroimmune pathways. The review emphasizes the importance of understanding the multifaceted importance of PNI in cancer biology and its implications in pain manifestation and treatment strategies.

PNI microenvironment and cancer pain

PNI involves direct nerve compression from tumor contact and indirect effects influenced by the TME. These effects include nerve plasticity and inflammation, contributing to PNI-associated pain (Demir

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et al., 2015). Nociceptive receptors located on primary afferent neurons become stimulated due to peripheral nerve injury or by algogenic substances derived from the tumor microenvironment, which amplifies the afferent input to the spinal cord and promotes the propagation of pain signals. Findings from neuroanatomical and electrophysiological investigations suggest that pain associated with PNI arises through neuropathic mechanisms involving nerve damage and increased nociceptor sensitivity (Zhang et al., 2021a). This section explores changes in neuropathic alterations, heightened neuronal excitability, and the expression of mediators involved in pain pathways to elucidate PNI-related pain characteristics.

Neural injury and nociceptor sensitization in perineural invasion

Nerve damage and plasticity

The involvement of sensory nerve in tumor development and pain signaling has received increasing attention. In PNI, substantial degeneration of both myelinated and unmyelinated fibers is observed, accompanied by myelin sheath fragmentation and Remak bundle enlargement, particularly in models such as sciatic nerve-injected oral squamous carcinoma (Wang et al., 2021). Tumor infiltration into neural structures results in axonal degradation, demyelination, and overall nerve deterioration. These structural alterations correspond to nerve hypertrophy, increased nerve density, and endoneurial inflammation—key features of cancer-associated nerve plasticity (Demir et al., 2015; Jurcak and Zheng, 2019). In pancreatic cancer (PC), this neuropathological remodeling underlies the intense abdominal pain experienced by patients, with studies demonstrating increased neurite density and hypertrophy in dorsal root ganglia (DRG) and enteric plexuses exposed to PC-derived factors (Monje et al., 2020).

Nociceptor sensitization and hyperexcitability

The transition from structural nerve damage to functional nociceptor sensitization is marked by spontaneous neuronal discharges and decreased mechanical activation thresholds in A and C fibers (Zhang et al., 2020a). Co-culturing head and neck cancer (HNC) cells with human DRGs results in nociceptor hyperactivity, showing substantial spontaneous depolarizations and heightened reactivity to electrical stimuli (Uhelski et al., 2022). Mouse DRG neurons co-cultured with melanoma cells exhibited greater calcium flux responses than those with non-oncogenic keratinocytes, indicating tumor cell sensitization of nociceptors (Uhelski et al., 2022).

Transient receptor potential (TRP) channel, particularly TRPV1 (vanilloid type 1) and TRPA1 (ankyrin type 1) play central roles in translating external stimuli into nociceptive signals. These channels are markedly upregulated in DRGs innervating pancreatic tumors, and their activation correlates with increased neurite extension and heightened pain perception (Xu et al., 2024; Stopczynski et al., 2014). TRPV1 co-overexpression with toll-like receptor 4 (TLR4), and TRPV4 with extracellular signal-regulated kinase (ERK1/2), highlights a dual-phase neuroimmune response involving acute nociceptive activation and chronic neuropathic pain (Takeda et al., 2013).

Neuropeptide signaling

TRP channel activation also promote the release of neuropeptides like substance P (SP), calcitonin gene-related peptide (CGRP), and galanin (GAL), which propagate nociceptive signals to the central nervous system and exert paracrine effects locally (Takeda et al., 2013). SP, specifically, is implicated in PC pain by enhancing neurite extension and facilitating tumor cell invasion operating through the SP/neurokinin-1 receptor (NK-1R) signaling system. Elevated CGRP levels are associated with PNI, functioning via the CGRP/receptor activity modifying protein 1 (RAMP1) cascade which contributes to both tumorigenesis and cancer-induced pain (Wattiez et al., 2020). GAL, acting through galanin receptor 2 (GALR2) expressed on cancer cells, regulates cyclooxygenase-2 (COX-2) transcription and promotes the synthesis of prostaglandin E2 (PGE2), further inking neurochemical signaling with PNI-related pain (Zhang et al., 2020b; Zhang et al., 2021b). These neurochemical pathways form a complex network linking nociceptor activity to PNI-associated pain.

Key molecular and cellular mechanisms modulating PNI-associated pain

PNI s a multifaceted and evolving phenomenon, driven by molecules signals and cellular dynamics intricately linked to cancer initiation, local expansion, and metastasis spread (Li et al., 2021; Liu et al., 2022). The heightened expression of PNI-related factors observed in painful tumors highlights the critical involvement of neuron-tumor interactions in mediating PNI-related nociception (Wang et al., 2021). Elucidating the molecular signaling cascades active in both experimental and clinical models of cancer offers the potential to enhance our understanding of tumor progression and facilitate the development of novel pain-targeted therapies. A wide array of signaling pathways, including receptors and cellular mediators associated with PNI, play integral roles in amplifying nociceptive signals through increased secretion of pain-inducing substances Fig. 1. Exploring the neuronal and molecular alterations occurring within the TME that contribute to the transition from localized to chronic pain may lead to improved strategies for early cancer detection and ultimately enhance the quality of life for individuals with advanced-stage malignancies.

Molecular modulators of nociceptor sensitization

Neurotrophic factors such as nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) are central to both tumor-induced nociceptor sensitization and PNI. NGF activates receptor tyrosine kinase A (TrkA) and NGF receptors (NGFR), inducing SP and CGRP release and modulating inflammatory cytokine levels. Its upregulation is further driven by Sonic hedgehog (Shh) signaling from pancreatic tumor cells (Han et al., 2020; Fehrenbacher et al., 2016). Interruption of the hepatocyte growth factor (HGF)/hepatocyte growth factor receptor (c-Met) axis results in reduced NGF levels, thereby impeding both neural injury and the vascularization at the tumor-nerve interface (Qin et al., 2022). Similarly, brain-derived neurotrophic factor- Tyrosine kinase B (BDNF-TrkB) signaling facilitates PNI and nociceptive behavior in HNC models (Bathina and Das, 2015). Members of the GDNF family, including GDNF, neurturin (NRTN), and Artemin, enhance TRPV1 receptor sensitivity, intensifying pain perception (De Bono et al., 2014). NRTN not only contributes to PC proliferation and invasiveness but also increases transmission efficacy via elevated GDNF family receptor alpha-2 (GFRα-2) expression in PC tissue, a change associated with heightened abdominal pain severity in these patients due to the enriched NRTN environment.

Chemokines signaling constitutes another axis of pain modulation. Neuron-derived chemokines act as chemoattractant, drawing tumor cells toward peripheral nerves. Upregulation of chemokine receptors such as CXCR1, CXCR2, and CCR2 in sensory neurons sustains pain in bone cancer. Additionally, chemokine-receptor interactions like CXCL10-CXCR3 and CCL21-CCR7 facilitate the recruitment of sensory fibers to neoplastic cells. Blocking these pathways in PDAC mouse model has been shown to alleviate abdominal hypersensitivity. Clinical evidence indicates that elevated CXCR3 and CCR7 levels in PDAC patients are positively associated with more frequent and intense cancer-related pain. Chemokine-induced neural remodeling, not immune infiltration or local inflammation regulation, benefits pain reduction. Other chemokines affecting cancer-related pain need exploration (Melgarejo da Rosa et al., 2021).

Immune cell modulation of pain signaling

Cancer progression into neural tissue activates local immune cells, intensifying inflammation and contributing to PNI-associated nociception (Demir et al., 2015). Tumor-associated macrophages (TAMs), particularly, amplify pain through the TGF-β1/Smad3 signaling

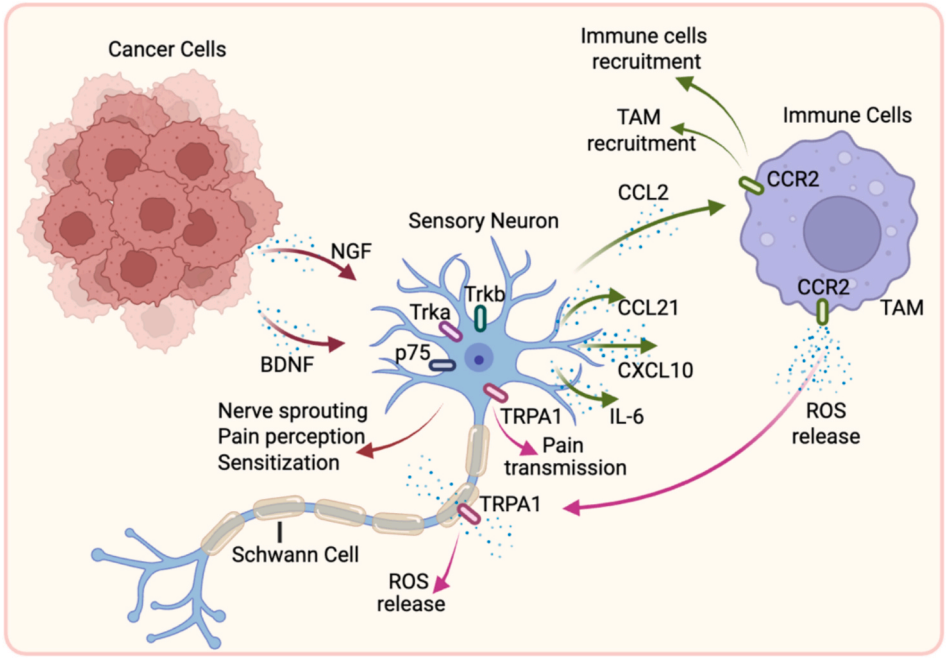

Fig. 1. Perineural invasion and signaling pathways associated to pain. Cancer cells secrete nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF), which interact with their respective receptors—TrkA, TrkB, and p75—on peripheral nerves, promoting axonal sprouting, neuronal sensitization, and sustained pain perception. Sensory neurons release chemokines such as CCL21 and CXCL10, facilitating bidirectional cancer–nerve crosstalk and enhancing nerve infiltration into the tumor microenvironment. Interleukin-6 (IL-6) further amplifies inflammatory signaling, exacerbating pain sensitivity. Neuronal CCL2 binds to CCR2 receptors on tumor-associated macrophages (TAMs), promoting immune cell recruitment and reactive oxygen species (ROS) production. Additionally, The TRPA1 channel, expressed on both sensory neurons and Schwann cells, contributes to this proinflammatory milieu by promoting ROS release from Schwann cells and mediating nociceptive signaling in neurons, thereby sustaining chronic pain.

pathway enhance nociceptive transmission via TRPV1 activation on sensory neurons (Chen et al., 2020; Yu et al., 2020). These macrophages also induce glial activation, reinforcing pain signaling loops.

Furthermore, tumor-induced sensory neuron activation influences immune function. Melanoma-secreted SLPI induces CGRP release from nociceptors, suppressing CD8 + T-cell cytotoxicity and promoting tumor growth (Donnelly et al., 2021). STING pathway conversely, offers dual anti-tumor and analgesic effects, representing a promising immunotherapeutic avenue (Donnelly et al., 2021).

Glial involvement and Schwann cell contributions

Schwann cells (SCs) play a dualistic role in PNI-associated pain. In early carcinogenesis, SCs migrate toward lesions, releasing inflammatory mediators and contributing to demyelination and nociceptor activation (Deborde et al., 2022; Su et al., 2020). Tumor-derived oxidative stress activates TRPA1 on SCs, triggering macrophage-colony stimulating factor (M−CSF) and sustaining neuroinflammation (de Logu et al., 2021). Additionally, SC-released CCL2 attracts CCR2-expressing inflammatory monocytes, which difference into cathepsin B-releasing macrophages that, disrupt nerve integrity (Bakst et al., 2017). Paradoxically, SCs can also suppress early pain signals CXCL12 from PC targets SC CXCR4/CXCR7 receptors, inducing analgesic responses and delaying symptom onset. IL-6 released from SCs similarly suppresses nociception while promoting tumor invasion via STAT3 signaling (Cai et al., 2024; Su et al., 2020). These observations suggest that SC activity may modulate both the perception and timing of cancer-associated pain.

Additional components of the tumor microenvironment

Beyond immune and glial elements, cancer-associated fibroblasts (CAFs) and neovascular elements contribute to the neurobiological landscape of PNI. CAFs secrete axon guidance cues, including SLIT proteins, facilitating perineural and vascular remodeling. Shared mediators, such as SP, CGRP, and axonal guidance molecules, further link neuroangiogenesis to cancer pain (Gysler and Drapkin, 2021; Li et al., 2013). Comprehensive characterization of these components may yield novel insights into the dual challenges of tumor progression and pain management.

Management of pain associated with perineural invasion

Clinical evidence from multiple tumor types underscores the significant association between PNI and cancer-related pain. In PDAC, one of the most aggressive malignancies with a PNI incidence ranging from 80 % to 100 %, PNI not only facilitates tumor dissemination but also serves as a major contributor to the intense abdominal and back pain frequently reported by patients (Shi et al., 2023; Yuan et al., 2025). This neural infiltration is a hallmark of PDAC and correlates with poor prognosis and high recurrence rates. Similarly, in cutaneous squamous cell carcinoma (cSCC), although PNI occurs in a smaller subset of patients (~3%), it is strongly linked to neuropathic symptoms such as pain, paresthesia, and facial weakness, often preceding diagnosis by months or years (Frunza et al., 2014; Karia et al., 2017). In prostate cancer, PNI is increasingly recognized as a mechanism of extraprostatic extension, with nerve-associated invasion being linked to adverse pathological features and elevated risks of recurrence; however, its direct role in pain generation remains less clearly defined (Kraus et al., 2019). In gastric carcinoma, where PNI prevalence ranges from 31.7 % to 65.0 %, the clinical relevance of PNI to pain has been less thoroughly investigated, though its presence is indicative of more invasive disease (Chen et al., 2022). Collectively, these findings emphasize the clinical importance of tumor-nerve interactions not only in cancer progression but also in the pathogenesis of cancer pain.

Opioids remain the preferred option for cancer pain, acting on mu receptors in the central and peripheral nervous systems, triggering descending pathways to reduce signal transmission (Scarborough and Smith, 2018). Despite opioids' general effectiveness, some patients fail to achieve optimal relief due to side effects like drug tolerance, constipation, and fatigue (Cata et al., 2022). This underscores the need for

safer, more efficient analgesics targeting the mechanisms behind cancer pain.

Given the relationship between PNI-associated pain and tumor progression, treatments aimed at managing PNI-related pain may not only reduce discomfort but also hinder cancer spread and enhance patients' quality of life.

Pharmacological treatment

Several analgesics with anticancer properties have been evaluated using repeatable murine models where cancer cells are injected near the sciatic nerve to assess their impact on tumor inhibition and cancer pain relief (Brito et al., 2017; Brito et al., 2021).

The combination of the non-opioid dipyrone and magnesium chloride has shown promise in overcoming drug tolerance, making it a viable option for cancer pain management and tumor inhibition (Brito et al., 2017).

Gabapentin, a neuromodulator commonly used for refractory cancer pain, has been found to regulate hyperalgesia and inhibit tumor progression by modulating CCL2 secretion and calcium influx in vivo and in vitro (Brito et al., 2021).

Anesthetics, which block voltage-gated sodium channels, can temporarily inhibit the transmission of aberrant neuronal signals from damaged nociceptors, offering relief from cancer-related neuropathic pain (Khan et al., 2019; Tsai et al., 2023). Lidocaine, applied via patches or intravenous infusion, has been shown to alleviate pain in patients resistant to opioids (Peixoto and Hawley, 2015). The combined application of ropivacaine-loaded liposomes (Rop-DPRL) with nutrient deprivation strategies has demonstrated efficacy in inhibiting tumor progression and mitigating persistent cancer pain, primarily through the downregulation of vascular endothelial growth factor A (VEGF-A). However, the analgesic benefits of single Rop-DPRL injections tend to be transient (Zhang et al., 2020a). In parallel, several other pharmacological agents—such as selective COX-2 inhibitors, cannabidiol, and midazolam—are under investigation for their dual capacity to alleviate pain associated with perineural invasion (PNI) and exert anticancer effects (Hussain et al., 2020; Oshima et al., 2022).

Small molecules targeting PNI may offer another avenue for pain relief. Among the most studied and promising approaches is the inhibition of the NGF-TRKA signaling pathway. NGF-targeting antibodies, such as muMab911, have shown significant reductions in bone cancer-related pain in preclinical models (Xu et al., 2016). Tanezumab, a humanized antibody derived from muMab911, has been assessed in phase II clinical trials addressing multiple forms of cancer-associated pain, including that arising from bone metastases. The trials successfully met the primary endpoint, demonstrating a significant reduction in the mean daily pain score at the targeted metastatic bone site over an eight-week treatment period (Fallon et al., 2021). Similar NGF-neutralizing antibodies are in development, offering additional avenues for pain relief.

MNAC13, another antibody targeting the TRKA receptor, prevents NGF binding to TRKA and has demonstrated synergistic effects with opioids in mouse models of neuropathic pain and inflammation (Ugolini et al., 2007). Furthermore, recombinant TRKAd5 protein, which sequesters NGF, has been shown to reduce pain signaling in models of pancreatitis and interstitial cystitis (Watson et al., 2006). However, larger proteins such as TRKA-IgG fusion proteins, while effective in preclinical models, may face challenges in clinical use due to their size and the risk of immune responses.

TRKA inhibitors, originally developed as anticancer agents, hold promises for managing PNI and cancer-associated pain. ARRY-470, a pan-TRK inhibitor, has demonstrated notable effectiveness in alleviating bone cancer-associated pain and reversing nerve remodeling in murine sarcoma models (Giraud et al., 2021). Similarly, PHA-848125—a compound that concurrently targets cyclin-dependent kinases (CDKs) and the TRKA receptor—has shown substantial antitumor activity in xenograft models of pancreatic cancer and is currently under investigation in ongoing clinical trials (Albanese et al., 2010). These TRKA-targeting agents suggest that therapies designed to block NGF-TRKA signaling could not only slow tumor growth but also inhibit PNI and alleviate pain associated with pancreatic cancer.

In addition to NGF-TRKA-targeted therapies, the development of TRPV1 antagonists has also shown potential in managing cancer-related pain (Rahman et al., 2024; Szallasi, 2024). Antagonists of the TRPV1 receptor, such as resignifications (RTX), a capsaicin derivative, have been reported to trigger programmed cell death in pancreatic cancer cells and hold potential for managing disease-related pain (Szallasi, 2023). Similarly, preclinical studies have demonstrated that TRPV1 antagonists can reduce pain in bone cancer models, suggesting that targeting TRPV1 may provide an effective approach to managing PNI-associated pain in pancreatic cancer (Rahman et al., 2024).

Another promising target in the treatment of PNI-related pain is the CX3CL1-CX3CR1 signaling axis. Recent studies have demonstrated that blocking this pathway using CX3CR1 antagonists or neutralizing antibodies can reduce cancer-related pain in preclinical models (Marchesi et al., 2010). Given its role in PNI and the metastatic progression of pancreatic cancer, CX3CL1-CX3CR1 inhibition may represent a novel therapeutic strategy for both pain relief and the suppression of cancer spread.

Therapeutic targets and corresponding pharmacological agents are summarized in Table 1.

Non-pharmacological treatment

Tumor-induced nerve infiltration often complicates pain control using conventional pharmacological methods. For patients experiencing refractory pain that does not respond to strong opioids, minimally invasive surgical interventions present a viable alternative (Scarborough and Smith, 2018). Celiac plexus neurolysis (CPN), for instance, has shown effectiveness in alleviating moderate to severe abdominal pain caused by pancreatic cancer, helping to reduce opioid use. CPN performed using endoscopic ultrasound, computed tomography (CT), or navigated magnetic resonance imaging (MRI) is recognized as a safe and effective approach for managing abdominal pain (Xue et al., 2020). Combining CPN with ultrasound-guided tumor ablation has further demonstrated improvements in both pain relief and survival in patients with inoperable pancreatic cancer (Facciorusso et al., 2017). Early nerve ablation might delay pain onset and improve survival by addressing neuroplastic changes in the early stages of the disease (Choi et al., 2016).

Radioactive iodine-125 (125I) seed implantation has emerged as an effective option for reducing tumor growth and managing abdominal and back pain in patients with unresectable pancreatic cancer (Jia et al., 2020). Non-invasive celiac plexus radiosurgery is another approach currently being investigated in international trials as a preliminary palliative treatment for advanced pancreatic cancer pain (Miszczyk et al., 2021). However, the safety and efficacy of radiosurgery needs further investigation to establish its clinical role. Although interventions aimed at the peripheral nervous system provide a compelling therapeutic approach for malignancies with high neural involvement, pharmacological treatments continue to serve as the mainstay for cancer-related pain management. In this context, interventional strategies are typically employed as supportive modalities. Continued research is essential to elucidate the potential synergistic interactions between these therapeutic avenues.

Therapeutic targets and corresponding non pharmacologic intervention are summarized in Table 2.

Challenges and future perspectives

Despite promising advances in understanding the molecular mechanisms underlying PNI and the identification of potential therapeutic targets, significant translational barriers persist. One major limitation is the lack of diagnostic methods with both high sensitivity and specificity

Table 1
Summary of therapeutic targets and corresponding agents for PNI-associated cancer pain management.

Therapeutic Target / Mechanism	Agent(s)	Mechanism of Action	Anticancer Effect	Pain Relief	References
Pro-inflammatory signaling & Neuromodulation	Dipyrone + Magnesium Chloride	Enhances analgesia, reduces tolerance	Yes	Yes	Brito et al., 2017
	Gabapentin	Modulates CCL2 secretion and calcium influx	Yes	Yes	Brito et al., 2021
Voltage-gated sodium channel blockade	Lidocaine (patch/IV)	Blocks aberrant nociceptive signaling	No	Yes (especially opioid-resistant pain)	Peixoto and Hawley, 2015
	Ropivacaine-loaded liposomes (Rop-DPRL)	Sustained sodium channel blockade, VEGF-A downregulation	Yes	Yes (transient with single dose)	Zhang et al., 2020a
COX-2 inhibition & other anti-inflammatories	Selective COX-2 inhibitors, Cannabidiol, Midazolam	Anti-inflammatory, anxiolytic, neuroprotective effects	Potential	Yes	Hussain et al., 2020; Oshima et al., 2022
NGF-TRKA signaling inhibition	muMab911, Tanezumab	NGF-neutralizing antibodies	No	Yes (especially bone cancer)	Xu et al., 2016; Fallon et al., 2021
	MNAC13	Blocks NGF-TRKA binding, synergizes with opioids	No	Yes	Ugolini et al., 2007
	Recombinant TRKAd5, TRKA-IgG fusion proteins	NGF sequestration	No	Yes (preclinical models)	Watson et al., 2006
	ARRY-470 (pan-TRK inhibitor)	Blocks TRK receptors, reverses nerve remodeling	Yes	Yes	Giraud et al., 2021
	PHA-848125	Dual CDK and TRKA inhibition	Yes (esp. pancreatic cancer)	Yes	Albanese et al., 2010
TRPV1 receptor antagonism	Resiniferatoxin (RTX), other TRPV1 antagonists	TRPV1 blockade, induces cancer cell apoptosis	Yes	Yes (bone and pancreatic models)	Szallasi, 2023; Rahman et al., 2024
CX3CL1-CX3CR1 pathway inhibition	CX3CR1 antagonists / antibodies	Inhibits cancer-induced neuroinflammation and nerve invasion	Yes	Yes	Marchesi et al., 2010

Table 2
Summary of non-pharmacological interventions for PNI-associated pancreatic cancer pain.

Intervention	Technique/Modality	Mechanism of Action	Anticancer Effect	Pain Relief	References
Celiac Plexus Neurolysis (CPN)	Endoscopic ultrasound, CT, MRI-guided injection	Destroys celiac plexus nerves, interrupting pain signal transmission	Indirect	Yes (abdominal pain, opioid reduction)	Scarborough and Smith, 2018; Xue et al., 2020
CPN + Tumor Ablation	Combined with ultrasound-guided ablation	Synergistic effect: nerve destruction + tumor load reduction	Yes	Enhanced pain relief and survival	Facciorusso et al., 2017
Radioactive Iodine-125 Seed Implantation	Local intratumoral radiotherapy	Continuous low-dose radiation suppresses tumor growth and associated pain	Yes	Yes (abdominal/back pain)	Jia et al., 2020
Celiac Plexus Radiosurgery	Non-invasive, stereotactic radiosurgery	Targets and damages pain-conducting neural pathways via focused radiation	Under investigation	Preliminary evidence for effectiveness	Miszczyk et al., 2021
Early Nerve Ablation	Surgical or radiological neurolytic procedures	Delays onset of neuroplastic pain changes by interrupting early nerve invasion	Potential (via reduced PNI)	Yes (preemptive or early-stage cases)	Choi et al., 2016

PNI, perineural invasion; CT, computed tomography; MRI, magnetic resonance imaging.

for early PNI detection, particularly in PC, where PNI is closely associated with tumor recurrence and poor prognosis (Medvedev et al., 2022; Xue et al., 2020).

On the therapeutic front, safety and immunogenicity concerns surrounding biologic agents—such as monoclonal antibodies, siRNA delivery systems, and gene-editing tools—pose challenges, particularly when targeting neuronal components where off-target effects may impair nerve integrity and function (Asmani et al., 2024; Kurki et al., 2021; Sauna et al., 2023).

. Additionally, most available preclinical models inadequately replicate the anatomical and biological complexity of human tumor-nerve interactions, especially regarding autonomic nerve involvement and tumor-associated neuroplasticity (Song et al., 2023).

Compounding this issue is the heterogeneity of the TME and the variability in PNI presentation and pain phenotypes across patients.

Since nociceptors and tumor cells share some common molecular targets, modulating pain signals and nociceptors in tumors could also contribute to cancer treatment (Song et al., 2023; Zhang et al., 2022). For instance, NGF triggers the release of neurogenic calcitonin gene-related peptide (CGRP), which promotes autophagy in cancer cells, enabling their survival during nutrient scarcity. As a result, drugs that inhibit neurogenic CGRP, such as anti-migraine treatments, could potentially offer antitumor benefits (Zhang et al., 2022). Therefore, the development of drugs targeting neurons and strategies to block nerve signals is crucial for reducing the tumor-induced nerve stimulation, thereby improving both pain relief and cancer treatment outcomes (Hunt et al., 2020). These approaches show promise in enhancing patients' quality of life and prolonging survival, key elements of palliative care. Addressing PNI-related pain could contribute to better cancer management by both controlling refractory pain and inhibiting PNI progression.

To overcome these translational hurdles, future research should focus on the development of physiologically relevant animal models, the optimization of advanced imaging technologies for in vivo PNI detection, and the incorporation of non-invasive monitoring method. Therapeutic strategies targeting neurotrophic factors, extracellular matrix remodeling enzymes, and immunosuppressive components of the TME may provide novel avenues for intervention. Precision medicine approaches, leveraging genomic and transcriptomic profiling, could also facilitate the identification of PNI-specific molecular signatures and inform personalized treatment regimens. Ultimately, a multidisciplinary framework that bridges oncology, neuroscience, imaging, and immunotherapy will be essential to translate basic research into meaningful clinical advances for managing PNI and its associated cancer pain.

Contributors

All authors contributed equally.

CRediT authorship contribution statement

Martina Catalano: Conceptualization, Data curation, Writing – review & editing. **Lorenzo Landini:** Conceptualization, Writing – review & editing. **Filippo Nozzoli:** Writing – review & editing. **Romina Nassini:** Supervision. **Giandomenico Roviello:** Visualization. **Francesco De Logu:** Supervision, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

No data was used for the research described in the article.

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