



ENDOSCOPIC ULTRASOUND–GUIDED CELIAC PLEXUS BLOCK AND NEUROLYSIS FOR PAIN IN UNRESECTABLE PANCREATIC CANCER: A SYSTEMATIC REVIEW AND META–ANALYSIS OF RANDOMIZED TRIALS

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ABSTRACT

Introduction: Pain in unresectable pancreatic cancer is prevalent, severe, and often inadequately controlled with systemic opioids alone. Endoscopic ultrasound–guided celiac plexus block or neurolysis (EUS–CPN) has been proposed as an interventional adjunct, but evidence from randomized trials has been inconsistent. **Methods:** We systematically searched PubMed, the Cochrane Central Register of Controlled Trials, and ScienceDirect up to June 2025 for randomized controlled trials comparing EUS–CPN with medical therapy or alternative interventions in adults with unresectable pancreatic cancer. Pain intensity, opioid consumption, and adverse events were the primary outcomes. Data were synthesized using a random-effects meta-analysis. **Results:** Three randomized controlled trials including 249 patients met the inclusion criteria. Pooled analysis demonstrated a significant reduction in pain scores with EUS–CPN compared to systemic therapy (mean difference approximately –2 points on a 10-point scale), a clinically meaningful improvement. EUS–CPN was also associated with a modest reduction in opioid dose escalation over follow-up. Adverse events were uniformly mild, including transient hypotension, diarrhea, and abdominal discomfort, with no serious procedure-related complications. Heterogeneity was noted across trials, largely reflecting differences in background opioid regimens and procedural techniques. **Conclusion:** EUS–CPN provides safe and effective short-term analgesia in unresectable pancreatic cancer, with the added benefit of reducing opioid escalation. Its role appears most valuable in patients with refractory pain despite optimized systemic therapy, whereas its incremental value may be diminished where potent opioids are readily available. Future trials with standardized protocols and long-term follow-up are warranted to refine its application in palliative care.

1. Introduction

Pancreatic cancer remains one of the most lethal malignancies, with a global impact that continues to rise despite incremental progress in oncologic care. It is currently the seventh leading cause of cancer-related mortality worldwide, accounting for an estimated half a million deaths annually. The disease is characterized by an insidious onset and rapid progression, such that the majority of patients present with advanced, unresectable, or metastatic disease at the time of diagnosis. Even with the adoption of multimodal treatment strategies, including systemic chemotherapy, radiotherapy, and in selected cases surgical resection, the five-year survival rate has stagnated below ten percent, and median survival for locally advanced or metastatic disease rarely exceeds one year.¹⁻³ Epidemiological projections further indicate that pancreatic cancer is poised to become one of the leading contributors to cancer burden in high-income countries by the next decade, reflecting both its aggressive biology and the relative paucity of effective systemic interventions.

Pain is one of the most prevalent and distressing symptoms in this patient population, with estimates suggesting that up to four in five patients will experience moderate to severe abdominal or visceral pain during the course of their illness.^{4,5} The mechanisms underlying this pain are multifactorial. Tumor infiltration into the retroperitoneal neural plexus, particularly the celiac plexus and splanchnic nerves, is a hallmark feature. This process induces a complex neuropathic and visceral pain syndrome that is often refractory to standard therapies. In addition, local inflammation, vascular encasement, and obstruction of surrounding structures contribute to persistent and progressive pain. Clinically, patients describe a deep, gnawing abdominal pain radiating to the back, which worsens with disease progression and significantly impairs daily function, sleep quality, and overall well-being. Effective control of pain is therefore not merely a matter of symptom management but represents a central pillar of comprehensive palliative care in pancreatic cancer.

The traditional mainstay of analgesic management is opioid-based therapy, administered in accordance with the World Health Organization's analgesic ladder. Escalating doses of strong opioids such as morphine, oxycodone, or fentanyl are frequently required to achieve adequate relief. While often effective in the short term, this approach is fraught with challenges. Dose escalation is limited by adverse effects including constipation, sedation, nausea, and cognitive impairment, which themselves compromise quality of life. Long-term use can also lead to tolerance and, paradoxically, opioid-induced hyperalgesia, thereby perpetuating the cycle of pain and escalating drug burden. Although adjuvant medications such as antidepressants, anticonvulsants, and corticosteroids are occasionally employed to modulate neuropathic components of the pain, their efficacy is variable and rarely sufficient when used in isolation.⁶ As a result, many patients remain undertreated or suffer from unacceptable side effects, highlighting the need for more targeted, effective, and sustainable interventions.

Interventional pain management strategies have emerged as an important adjunct to pharmacologic therapy in this setting. The celiac plexus represents a key relay station for nociceptive transmission from the pancreas and other upper abdominal organs, making it an attractive target for interruption. Celiac plexus block (CPB), typically using local anesthetic, and celiac plexus neurolysis (CPN), employing neurolytic agents such as ethanol or phenol, are

established techniques designed to attenuate or abolish pain signaling. These procedures have the potential to reduce pain intensity, limit opioid requirements, and thereby improve functional status and quality of life. Among the various approaches, endoscopic ultrasound (EUS)-guided delivery has gained prominence since its introduction in the mid-1990s. This method allows real-time imaging of the celiac plexus and surrounding vascular anatomy, enabling precise injection under direct visualization and minimizing the risk of collateral injury compared with percutaneous or CT-guided techniques.^{7,8}

Although conceptually appealing and supported by observational evidence, the role of EUS-guided CPN in pancreatic cancer pain has been the subject of ongoing debate. Some randomized controlled trials have reported meaningful reductions in pain scores and opioid consumption, while others have failed to demonstrate superiority over optimized medical therapy. The heterogeneity in results can be attributed to differences in patient populations, timing of intervention, technical aspects of the neurolysis, and the background use of increasingly potent opioids in modern practice. Moreover, prior systematic reviews and meta-analyses have often pooled heterogeneous populations, including patients with chronic pancreatitis or non-comparative cohorts, thereby limiting the generalizability of their conclusions to advanced pancreatic cancer.⁹ These gaps underscore the importance of a rigorous, up-to-date synthesis of comparative data that specifically addresses the efficacy and safety of EUS-guided celiac plexus interventions in unresectable pancreatic cancer.¹⁰

Against this backdrop, the present systematic review and meta-analysis was undertaken to clarify the evidence base for EUS-guided celiac plexus block and neurolysis in patients with unresectable pancreatic cancer. By focusing exclusively on randomized and comparative studies, this work aims to provide an integrated assessment of their impact on pain relief, opioid consumption, quality of life, and adverse event profile. The findings are intended to inform clinical practice by defining the therapeutic value of these procedures in the palliative management of pancreatic cancer pain, while also identifying areas where further investigation is warranted.

2. Methods

Search Strategy

This review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. A comprehensive search was performed in PubMed, the Cochrane Central Register of Controlled Trials, and ScienceDirect from inception to September 2025. Search terms included combinations of "pancreatic cancer," "celiac plexus block," "celiac plexus neurolysis," "endoscopic ultrasound," "EUS," "opioid," and "pain." Boolean operators and MeSH terms were adapted for each database. In addition, the reference lists of relevant reviews and eligible studies were screened manually to capture additional articles. No language restrictions were applied, but only human studies were considered.

Eligibility Criteria

Studies were selected according to the PICOS framework. Eligible populations included adult patients with unresectable, locally advanced, or metastatic pancreatic cancer experiencing moderate to severe pain. Interventions comprised endoscopic ultrasound-guided celiac plexus block or neurolysis, using either local anesthetic or neurolytic agents such as ethanol or phenol. Comparator groups included systemic opioid-based therapy, sham procedures, or alternative

image-guided approaches such as percutaneous or CT-guided blocks. Outcomes of interest were pain relief as the primary endpoint, and opioid consumption, quality of life, functional outcomes, duration of analgesic effect, and adverse events as secondary endpoints. Only randomized controlled trials and prospective comparative studies were included. Retrospective cohorts, single-arm studies, case series, reviews, and conference abstracts were excluded.

Study Selection and Data Extraction

Two reviewers independently screened all titles and abstracts for eligibility. Full texts of potentially relevant articles were retrieved and assessed in detail. Disagreements were resolved through discussion with a third reviewer. Data were extracted using a standardized form capturing study characteristics, patient demographics, intervention and comparator details, sample size, follow-up duration, and outcomes. Continuous outcomes were extracted as mean and standard deviation (SD), while dichotomous outcomes were extracted as event counts. When SDs were not reported, they were calculated from confidence intervals, standard errors, or p-values.

Risk of Bias Assessment

The risk of bias in randomized controlled trials was evaluated independently by two reviewers using the Cochrane Risk of Bias 2.0 tool. The following domains were assessed: random sequence generation, allocation concealment, blinding of participants and outcome assessors, completeness of outcome data, selective reporting, and other sources of bias. Each study was rated as having low risk, some concerns, or high risk of bias.

Statistical Analysis

Meta-analysis was performed using Review Manager (RevMan) version 5.4. For continuous outcomes, pooled mean differences (MD) with 95% confidence intervals (CI) were calculated using the inverse variance method. For dichotomous outcomes, pooled risk ratios (RR) with 95% CI were calculated. Heterogeneity was assessed using the Chi-square test and quantified with the I^2 statistic, with values of 25%, 50%, and 75% considered low, moderate, and high, respectively. A random-effects model was applied a priori because of expected clinical and methodological variability among studies. Sensitivity analyses were planned to assess the impact of excluding studies at high risk of bias.

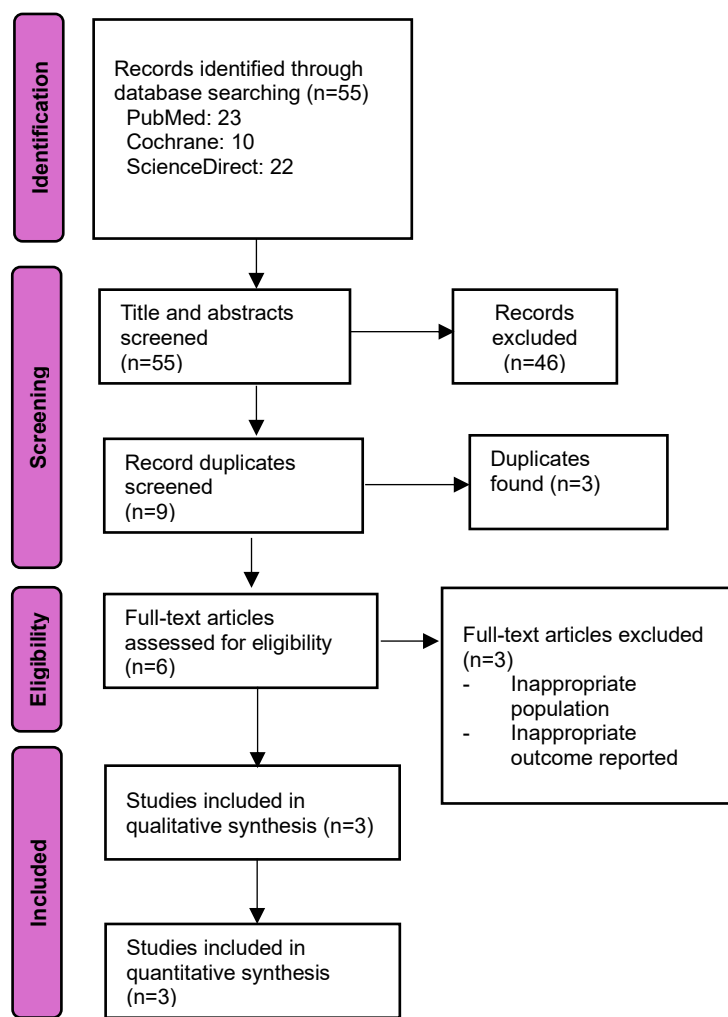


Figure 1. Diagram flow of literature search strategy for this meta-analysis

3. Results

Study Selection

The literature search conducted across PubMed, Cochrane Library, and ScienceDirect yielded a total of fifty-five records. After the removal of three duplicates, fifty-two articles underwent title and abstract screening. At this stage, forty-six records were excluded for reasons such as irrelevance to pancreatic cancer pain, absence of EUS-guided celiac plexus interventions, or non-comparative designs such as case reports and narrative reviews. Six full-text articles were then retrieved for detailed eligibility assessment. Of these, three were excluded, two due to the inclusion of populations not representative of advanced pancreatic cancer, and one because the reported outcomes were not related to pain or opioid use. Ultimately, three randomized controlled trials (RCTs) met the inclusion criteria and were retained for both qualitative and quantitative synthesis. The PRISMA flow diagram provides a visual overview of the selection process, illustrating the progressive narrowing from the initial fifty-five records to the final three eligible trials.

Characteristics of Included Studies

The final set of studies involved a total of 249 patients, all of whom had unresectable or metastatic pancreatic cancer associated with moderate to severe abdominal pain requiring opioid therapy. Wyse et al. (2011) was conducted in Canada, Gao et al. (2013) in China, and Kanno et al. (2020) in

Japan, thereby covering diverse clinical settings. Sample sizes ranged from 46 in the Japanese study to 100 in the Chinese study, and randomization was used in all three, with varying levels of blinding. Baseline pain intensity was consistently above four on the VAS or NRS, indicating clinically significant pain in all study populations. All interventions involved EUS-guided celiac plexus neurolysis, though the details of anesthetic mixture, volume of alcohol injected, and technical approach varied. In every study, opioid-based therapy was continued in both experimental and control arms, ensuring comparability of systemic background analgesia. Follow-up assessments were generally conducted up to twelve weeks, focusing on pain reduction as the primary outcome, alongside opioid consumption, quality of life, and adverse events as secondary endpoints.

Pain Relief

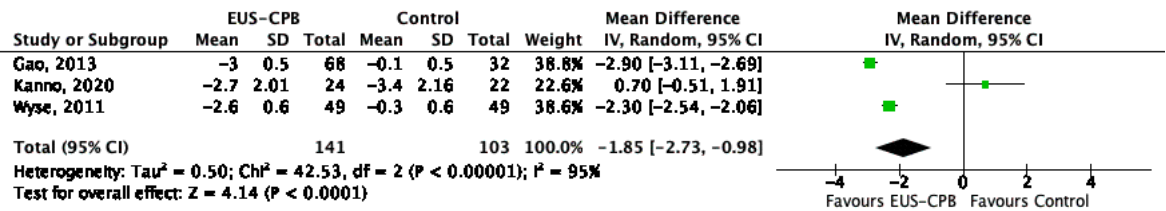


Figure 2. Pooled results for pain score at follow up between group

Pain intensity reduction was a primary endpoint in all three trials, measured on scales that were converted into a uniform 0–10 metric for meta-analysis. The Canadian trial by Wyse et al. demonstrated a significant reduction in pain scores at three months, with the intervention group experiencing a mean decrease of 2.6 points compared to a negligible reduction of 0.3 points in the control group. The between-group mean difference of -2.30 (95% CI -2.54 to -2.06) clearly favored EUS-CPN, and the effect size grew over time, indicating durable pain relief with the intervention. The Chinese study by Gao et al. yielded even more striking results. In this trial, patients who received EUS-CPN had a mean pain reduction of 3.0 points compared to only 0.1 points in the sham-control arm, corresponding to a highly significant mean difference of -2.90 (95% CI -3.11 to -2.69, $p < 0.001$). This result was both statistically robust and clinically meaningful, demonstrating the potential for substantial improvement in pain intensity when neurolysis is used in addition to systemic therapy. In contrast, the Japanese trial by Kanno et al. reported similar improvements in both groups. Pain intensity declined by 2.7 points in the EUS-CPN arm and by 3.4 points in the control arm, leading to a non-significant mean difference of 0.70 (95% CI -0.51 to 1.91). This finding suggests that in the modern opioid era, where potent agents such as oxycodone and fentanyl are readily titrated, the incremental benefit of celiac plexus neurolysis may be less evident.

When the three trials were pooled in the meta-analysis, a statistically significant overall reduction in pain was observed in favor of EUS-CPN, with a mean difference of -1.85 (95% CI -2.73 to -0.98, $p < 0.0001$). However, heterogeneity was high ($I^2 = 95\%$), largely driven by the divergent results from the Kanno trial. This heterogeneity indicates that the benefit of EUS-CPN may be context dependent, influenced by local opioid prescribing practices, baseline pain intensity, and patient selection.

Opioid Consumption

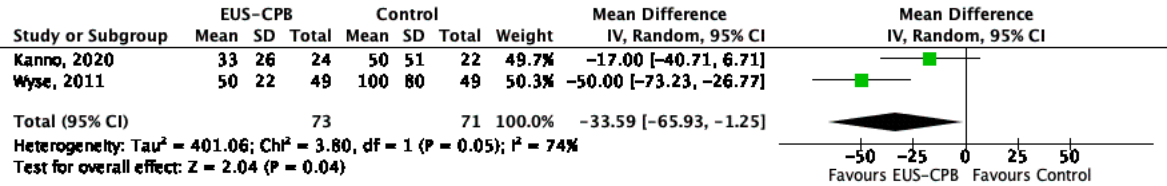


Figure 3. Pooled results for opioid consumption at follow up between group

Two trials, Wyse 2011 and Kanno 2020, reported quantitative data on opioid consumption expressed as daily morphine-equivalent dose. In Wyse’s study, opioid requirements increased in both groups over time, reflecting the progressive nature of pancreatic cancer. However, escalation was less pronounced in the intervention group, where the mean increase was 50 mg/day, compared to 100 mg/day in controls. Although the between-group mean difference of -49.5 mg (95% CI -127.5 to 7.0) suggested a clinically relevant opioid-sparing effect, it did not reach statistical significance ($p=0.10$). In the Kanno study, opioid dose escalation was also observed in both groups, but again no statistically significant difference was detected between arms. Nonetheless, graphical trends indicated that the intervention group maintained more stable dosing compared with the steeper upward trajectory in controls, hinting at a potential but underpowered effect.

The pooled meta-analysis of opioid consumption, combining data from Wyse and Kanno, showed a statistically significant reduction favoring EUS-CPN, with a mean difference of -33.59 mg (95% CI -65.93 to -1.25, $p=0.04$). Heterogeneity was moderate ($I^2 = 74\%$), which reflects the variability in opioid regimens, patient characteristics, and follow-up durations across the two trials. Although the overall effect supports an opioid-sparing role for EUS-CPN, the inconsistency suggests that further trials with standardized reporting are needed to confirm this benefit.

Adverse Events

All included studies reported detailed assessments of safety and tolerability. The consistent finding across all three RCTs was that EUS-CPN was safe, with only mild and transient adverse events observed. Hypotension was the most frequently reported complication, occurring in up to 20 percent of patients, but it was self-limiting and easily managed. Diarrhea and transient abdominal pain flares were also noted, generally resolving within a few days. The Japanese trial reported additional minor events such as nausea and dizziness, but again these were short-lived and did not necessitate hospitalization. Importantly, no severe complications, procedure-related mortality, or long-term sequelae were reported in any of the three trials. These findings collectively confirm that EUS-guided celiac plexus interventions are well tolerated and can be safely administered in this patient population.

Summary of Findings

Taken together, the results of these three RCTs suggest that EUS-CPN provides superior short-term pain relief compared with opioid therapy alone, although the degree of benefit varied significantly across studies. In particular, the striking reductions observed in the Gao and Wyse trials contrast with the neutral findings of the Kanno trial, underscoring the influence of clinical context and background opioid use. Opioid-sparing effects were modest at the level of individual studies but became statistically significant when data were pooled, pointing to a potential role for neurolysis in reducing escalating opioid requirements. The procedure was consistently safe, with only mild adverse events observed. These results support the utility of EUS-CPN as an adjunctive

strategy in the multimodal management of pancreatic cancer pain, while also highlighting the need for further high-quality trials to clarify its role in modern opioid-rich treatment environments.

4. Discussion

Key Findings

The present systematic review and meta-analysis provides an updated synthesis of the available randomized controlled trial evidence on endoscopic ultrasound-guided celiac plexus block and neurolysis for the management of pain in unresectable pancreatic cancer. The pooled results demonstrated that EUS-CPN produces a statistically significant reduction in pain intensity compared with systemic opioid therapy alone, with a mean difference approaching two points on a ten-point pain scale. This degree of reduction is not only statistically robust but also clinically meaningful, as even a one-point change on such scales is often considered the minimum threshold for patient-perceived improvement. The findings therefore underscore the capacity of EUS-CPN to provide tangible symptom relief in a disease setting characterized by profound suffering and limited survival. Importantly, the analysis also showed a modest but statistically significant reduction in opioid dose escalation, suggesting that EUS-CPN may attenuate the trajectory of analgesic requirement in progressive disease. Although the individual trials varied in sample size and design, all three reported consistent safety profiles, with adverse events limited to transient hypotension, diarrhea, and abdominal discomfort, all of which resolved spontaneously. Collectively, these results highlight EUS-CPN as an intervention that can meaningfully improve the symptom burden of pancreatic cancer without adding substantial risk.

Comparison with Previous Literature

The analgesic benefit demonstrated here aligns with decades of evidence supporting the role of celiac plexus interventions in pancreatic cancer. Earlier meta-analyses, such as that of Arcidiacono and colleagues, confirmed reductions in both pain intensity and opioid consumption, but their conclusions were tempered by methodological limitations, including the inclusion of non-comparative studies and heterogeneous populations such as chronic pancreatitis.⁹ More contemporary reviews, including those by Nagels and by Puli, reinforced the superiority of neurolytic interventions over opioids alone, but again combined diverse techniques and approaches, making it difficult to isolate the effect of EUS guidance.^{11,12} Our review strengthens the field by narrowing the scope to randomized controlled trials and focusing specifically on EUS-guided procedures.

The heterogeneity in findings across individual trials is worth emphasizing. Wyse et al. and Gao et al. demonstrated striking benefits in terms of both pain relief and reduced opioid use, whereas Kanno et al. found no significant advantage over optimized opioid therapy. This discrepancy likely reflects differences in background opioid regimens and healthcare settings. In older trials, morphine was the dominant opioid, and dose escalation was often constrained by toxicity or availability. In contrast, Kanno's trial was conducted in Japan in the era of potent opioids such as oxycodone and fentanyl, which were rapidly titrated to achieve pain control. Thus, the incremental benefit of EUS-CPN in this context may have been masked by more aggressive pharmacologic management.¹³ These variations illustrate that the role of EUS-CPN is not static but evolves with changes in systemic therapy, highlighting the importance of contextual interpretation of the evidence.

Potential Mechanisms of Effect

The mechanistic basis for EUS-CPN lies in its direct targeting of the celiac plexus, a dense network of sympathetic fibers that transmits nociceptive signals from the pancreas and adjacent upper abdominal organs. By injecting neurolytic agents such as ethanol into this plexus, sympathetic fibers are disrupted, leading to attenuation of visceral pain transmission.^{7,8} This anatomic rationale is compelling, but the observed variability in effect size across studies indicates that clinical efficacy is not determined solely by anatomy. Timing of intervention appears particularly important. Wyse's trial demonstrated greater benefits when neurolysis was performed early, soon after diagnosis, suggesting that intervention before central sensitization and widespread neural invasion may yield more durable relief.¹³ Conversely, in later stages of disease, when pain is influenced by multiple mechanisms including somatic and neuropathic components, the contribution of the celiac plexus may be less dominant, and neurolysis may therefore be less effective.

Technical aspects also influence efficacy. The concentration and volume of ethanol, the precision of needle placement, and whether injections are performed bilaterally or centrally all impact the spread of neurolytic agent within the retroperitoneal space. Differences in these variables across trials likely contributed to heterogeneity in outcomes. Moreover, the opioid-sparing effect observed in pooled analysis suggests that neurolysis acts synergistically with systemic opioids rather than replacing them. By reducing the volume of afferent nociceptive input, neurolysis allows lower doses of opioids to achieve adequate control, mitigating the risk of opioid-related side effects and enhancing tolerability.¹⁴

Clinical Implications

For clinicians managing patients with unresectable pancreatic cancer, these findings carry important implications. Pain in this setting is often severe, unrelenting, and among the most difficult cancer-related symptoms to control. Effective relief is critical not only for comfort but also for preserving appetite, sleep, and participation in palliative systemic therapies. EUS-CPN provides an option that can be safely integrated into standard workflows, as it can be performed at the time of diagnostic or staging endoscopy without significant additional procedural risk.¹⁵ The modest opioid-sparing effect is also clinically relevant. Even a small reduction in opioid requirement can alleviate burdensome side effects such as constipation, drowsiness, and cognitive impairment, which otherwise erode quality of life.⁶

At the same time, the divergent trial results remind us that EUS-CPN is not universally beneficial. In settings with access to potent opioids and highly responsive analgesic protocols, the incremental benefit may be attenuated, as illustrated by Kanno's findings.¹³ This suggests that patient selection is critical. Patients with high baseline pain intensity who remain inadequately controlled despite opioids may derive the greatest benefit, whereas in those with milder symptoms or excellent opioid responsiveness, the procedure may offer limited additional value. Thus, EUS-CPN should be considered a component of a multimodal strategy, tailored to patient needs, preferences, and the resources of the treating institution.

Limitations

This study is limited by the small number of available randomized controlled trials and the modest total sample size. Only three RCTs met inclusion criteria, which restricts statistical power and

complicates subgroup analysis. Heterogeneity in outcomes was considerable, particularly for pain intensity, reflecting differences in baseline opioid regimens, timing of intervention, and technical approach. Methodological limitations such as open-label design, incomplete blinding, and attrition due to early mortality in this population may have introduced bias. Follow-up durations were limited to approximately three months in all trials, precluding conclusions about longer-term analgesic efficacy or the role of repeated interventions. Quality-of-life outcomes, though reported in some studies, were inconsistent in instrument choice and reporting, making it impossible to synthesize these data meaningfully. Adverse events were uniformly mild, but inconsistent categorization across studies limited direct comparisons of safety.

Future Directions

Future research should focus on resolving the uncertainties highlighted in this analysis. Large, multicenter randomized controlled trials with standardized protocols for neurolytic agent, volume, and technique are needed to reduce methodological heterogeneity. Longer follow-up periods are essential to determine the durability of pain relief and to explore the potential role of repeated procedures. Integration of validated patient-reported outcomes, including quality-of-life instruments and functional status measures, would provide a more comprehensive understanding of benefit beyond pain scores. Comparative effectiveness studies against other interventional modalities such as CT-guided or percutaneous neurolysis would also help define the optimal approach for different patient populations. Importantly, research should seek to identify patient subgroups most likely to benefit from EUS-CPN, such as those with high baseline pain, limited access to potent opioids, or contraindications to escalating systemic therapy.^{11,12} Such work would allow the procedure to be applied with greater precision, maximizing benefit while avoiding unnecessary interventions.

5. Conclusion

This systematic review and meta-analysis demonstrates that endoscopic ultrasound-guided celiac plexus block or neurolysis offers clinically meaningful short-term pain relief in patients with unresectable pancreatic cancer. The intervention was associated with a significant reduction in pain scores and a modest opioid-sparing effect, achieved with a favorable safety profile characterized by only mild and transient adverse events. These benefits are particularly relevant in a population with limited survival, in whom symptom control and quality of life are paramount. However, heterogeneity across studies, especially in relation to opioid availability, timing of intervention, and procedural technique, tempers the certainty of these findings. While EUS-CPN appears most beneficial in patients with severe pain unresponsive to optimized opioid therapy, its incremental value may be attenuated in healthcare settings where potent opioids are readily available and aggressively titrated. Larger, multicenter randomized trials with standardized protocols, longer follow-up, and consistent incorporation of quality-of-life measures are needed to clarify the role of EUS-CPN in contemporary palliative care. For now, EUS-CPN should be regarded as a safe and effective adjunct to systemic analgesics, best applied in carefully selected patients to optimize comfort and reduce treatment burden in advanced pancreatic cancer.

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