

Minimally invasive techniques versus opioids in patients with unresectable pancreatic cancer: a systematic review and meta-analysis of randomised controlled trials

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Background: Pancreatic cancer (PC) has a low chance of resection, and a consistent burden of disease, with pain greatly impacting the quality of life (QoL). We aim to find the most efficient method to treat pain in patients with unresectable PC.

Methods: Our study was registered on PROSPERO (CRD42023477094). On the 29th of October 2023, a systematic search was performed, including only randomised controlled trials (RCTs) reporting on patients with unresectable PC-associated pain, QoL, survival, analgesics use, and adverse events (AEs). Different random-effects meta-analyses were performed on the Visual Analog Scale (VAS) and AEs. Survival curves of treatments were estimated based on individual patients’ data from the reported Kaplan-Meier curves.

Results: Twenty-one RCTs were eligible. At 4 weeks from a moderate to severe baseline pain level, the VAS score decreased to 2.27 [95% confidence interval (CI): 1.63–2.91] with percutaneous celiac plexus neurolysis (P-CPN), and 2.80 (95% CI: 2.17–3.42) with opioids, while in individual studies to 1.30 (95% CI: 0.68–1.92) with endoscopic ultrasound-guided celiac plexus neurolysis (EUS-CPN), and 1.45 (95% CI: 1.37–1.53) with high-intensity focused ultrasound (HIFU). At 8 and 12 weeks, there was an increase in pain scores for all treatment groups. AEs associated with interventional techniques were transient, the most common being diarrhoea, haemodynamic changes, and procedure-related pain. The median survival time in days was 126.22 (95% CI: 87.21–165.31) for opioids and 86.71 (95% CI: 62.45–136.88) for P-CPN.

Conclusions: Interventional techniques reduce pain and opioid use with few adverse effects; they should be considered more often and earlier in the management of patients with unresectable PC.

Keywords: Adenocarcinoma; pain; Visual Analog Scale (VAS); celiac plexus neurolysis (CPN); high-intensity focused ultrasound (HIFU)

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Introduction

Background

Pancreatic cancer (PC) is currently the sixth leading cause of cancer-related death worldwide. With a 5-year survival rate of only 12.8% and a worldwide incidence of more than 510,000 cases in 2022, PC is expected to become the second-leading cause of cancer-related mortality by 2030 (1,2). Even with highly performing diagnostic modalities, the cancer is unresectable at the initial diagnosis in 80–90% of cases (3). A survey analysis from the Pancreatic Cancer Action Network showed that 93% of PC patients had tumour-related pain during the disease course, while for the majority, the pain ranged between moderate to severe (4). The burden of the disease's physical manifestations significantly deteriorates quality of life (QoL), affecting mental, physical and social

well-being. As the course progresses, the focus turns to symptomatic management, with pain control being at the centre of palliative care in PC (5).

Rationale and knowledge gap

The pathophysiology of pain in PC is complex, being the sum of visceral, somatic, and neuropathic factors (6). Even though the three-step treatment ladder established by the World Health Organisation (WHO) has been the criterion formally preferred, opioids are often misused and associated with adverse events (AEs) further decreasing QoL (7). The necessity for an additional step on the treatment ladder has thus arisen, with the celiac plexus (CP) receiving increasing attention in the pain management of PC patients, and various procedures being shown to ablate it and reduce the disease burden. New minimally invasive techniques have been proposed, such as high-intensity focused ultrasound (HIFU), microwave ablation, cryoablation, irreversible electroporation, and stereotactic body radiation therapy. Previous meta-analyses have shown that celiac plexus neurolysis (CPN) is safe and effective with the advantage of fewer AEs compared to standard analgesia (8,9). However, the studies included followed the patients for a maximum of 8 weeks and focused only on one type of intervention. In summary, while some methods have shown promising results in pain control, there is still a gap in the knowledge regarding the best-performing method (10).

Objective

We aimed to compare all literature evidence from randomised controlled trials (RCTs) to find the most effective intervention to treat pain, with minimal risk of AEs, in patients with unresectable PC. This manuscript is written in accordance with the PRISMA reporting checklist (available at <https://tgh.amegroups.com/article/view/10.21037/tgh-24-141/rc>).

Highlight box

Key findings

- Endoscopic ultrasound-guided celiac plexus neurolysis (CPN) can contribute to better pain control with fewer adverse events, as well as slightly longer survival compared to opioids. High-intensity focused ultrasound seems a promising tool.

What is known and what is new?

- Pancreatic cancer (PC) has increasing incidence and is associated in most cases with debilitating pain, making its management a challenge. CPN is an effective technique for PC pain.
- This is the first meta-analysis on the topic to examine endoscopic and percutaneous guided CPN separately, following their effects up to 12 weeks after the procedure. Moreover, the novelty consists of the dynamic comparison of follow-ups after multiple types of minimally invasive techniques used for pain treatment.

What is the implication, and what should change now?

- Minimally invasive procedures should be considered more often and earlier in the pain treatment of patients with unresectable PC, and more randomised controlled trials should be conducted in this field.

Methods

This systematic review and meta-analysis is reported based on the recommendation of the PRISMA 2020 guideline (11) (Table S1), while the Cochrane Handbook methodology was followed (12). Initially, a network analysis was planned; however, due to the low number of available articles, only a meta-analysis using a 2-level model with direct and a 3-level model with indirect comparison could be performed. Additionally, we could estimate survival curves based on individual patients' data extracted from reported Kaplan-Meier curves. Besides, the study protocol was fully adhered to and is registered on PROSPERO (CRD42023477094).

Eligibility criteria

Only RCTs were included, irrespective of publication date or language. Studies were eligible for inclusion if they reported exclusively on (P) adult patients (human subjects with a minimum age of 18 years) with a proven diagnosis of unresectable PC and who received cancer-related pain-reducing interventions independent of other tumour characteristics. The main intervention groups accepted (I) were CPN, ablative techniques, and drug administration, compared to (C) pharmacological treatment (opioids, non-opioids, oncological therapies) or placebo. Our outcomes of interest (O) were pain, QoL, survival, AEs, and analgesic drug use.

Information sources

Our systematic search was conducted on October 29, 2023, in five major databases: MEDLINE (via PubMed), Embase, CENTRAL (The Cochrane Central Register of Controlled Trials), Scopus, and Web of Science. No filters or restrictions were used. The Scopus database was searched using the "Article title, abstract, keywords" option. The search key included terms and synonyms for "pancreatic cancer", "pain", and "randomised controlled trials". The entire search key can be found in the Table S1.

Selection process

Two independent review authors (IIR and OCI) performed the selection. All references were imported into Endnote 20 (Clarivate, 2013) to remove duplicates. Title-abstract selection was performed in *Rayyan*, followed by full-text selection. A third senior independent reviewer (A.R.)

resolved any disagreements. Cohen's kappa coefficient (κ) was calculated to assess inter-rater reliability during the selection. The reference lists of all the included articles were checked to identify additional eligible papers on November 29, 2023, on *citationchaser*, and title-abstract selection was performed in *Rayyan*. Five full-text articles could not be retrieved, despite efforts to contact the authors.

Data collection process

Data were collected independently from the eligible articles by three authors (I.I.R., I.C.M., and O.C.I.) in a standardised form, and a third independent reviewer (A.R.) resolved any disagreements. The following data were extracted from the eligible articles: title, first author, DOI code, year of publication, period of data collection, country, single/multicentre study, study design, inclusion and exclusion criteria, the total number of patients, patient demographics, the number of patients in the intervention and control groups, interventions, outcomes, and outcome dynamics over time. The sample size, mean and corresponding standard deviation (SD), and median with the corresponding quartiles were extracted for continuous outcomes. For dichotomous outcomes, the total number of patients and those with the event of interest in each group separately were extracted or calculated from the studies where it was available. The hazard ratio (HR) with its 95% CI was extracted for time-to-event data. However, several articles did not report the desired HR as an outcome measure and used a different outcome measure for time-to-event data. Where a Kaplan-Meier curve was given, an attempt was made to gather or estimate the individual patient's data based on these plots at the first step of the analysis. The WebPlotDigitizer tool was used to extract the values from the plot. Where possible, the extracted and calculated data (e.g. median time-to-event times, given year survival probabilities, HR based on Kaplan-Meier estimates and Cox-proportional hazard model) were compared with the published data. This difference was found to be neglectable. Where studies provided incomplete data, the corresponding authors were contacted with requests for additional information necessary for analysis.

Study risk of bias (RoB) assessment

Two authors independently performed the RoB assessment with the ROB-2 Tool (I.I.R. and O.C.I.), and an independent third investigator (A.R.) resolved the disagreements.

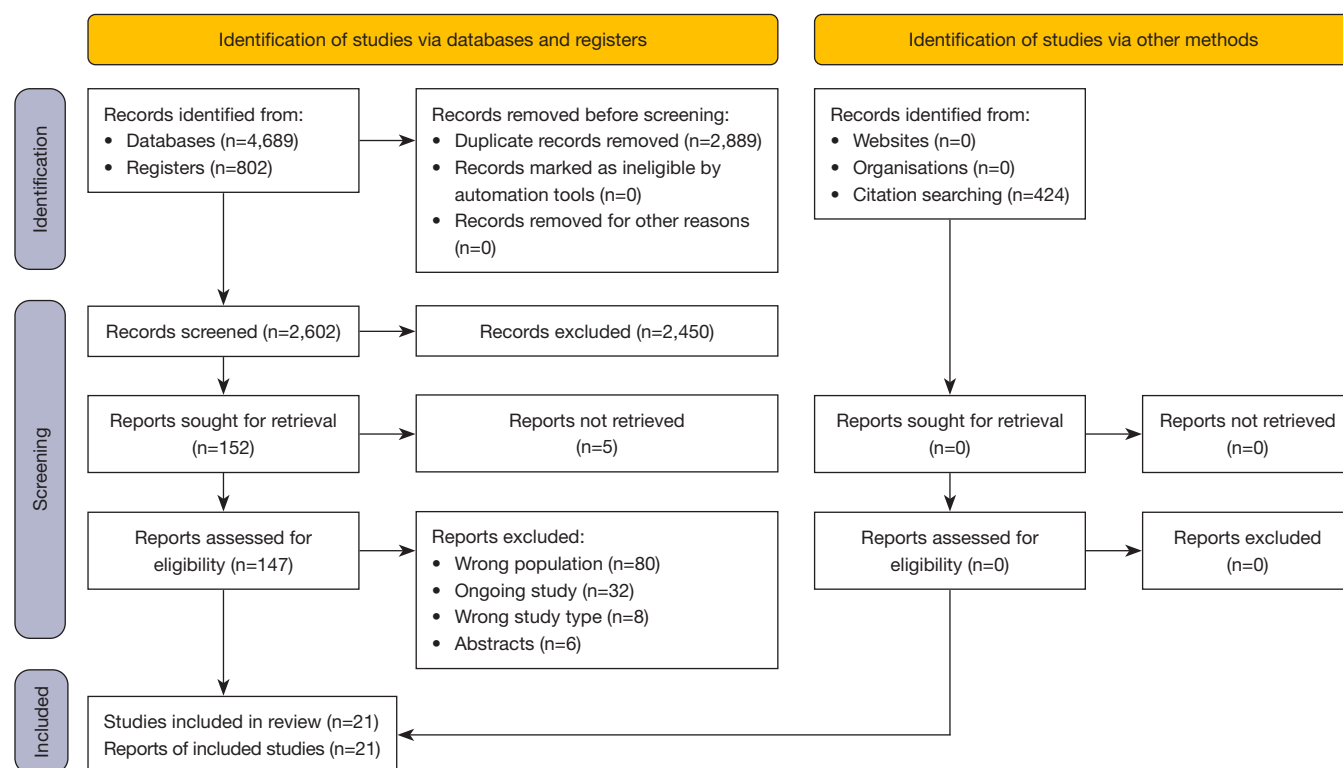


Figure 1 The flowchart of the included studies selection according to PRISMA guidelines.

Statistical analysis

As considerable heterogeneity was assumed among studies' populations, the random effects models were used in a frequentist framework.

To assess pain, an analysis of Visual Analog Scale (VAS) scores was performed. As more interventions may be available in the same study and create a dependent effect, a "3-level" (multilevel) model was used to include one, two and multi-arm studies together for pooling the VAS means and proportions for the presence or absence of given AEs. The analyses were performed separately for different time points. Details of the models used can be found in [Appendix 1](#).

The survival probabilities at specific time points were estimated and pooled with a 3-level model to indirectly compare the survival in all groups. An estimation for distribution-free pooled survival curves was also performed using the curve estimate method.

Results were considered statistically significant if the pooled CI did not contain the null value. The findings were summarised in tables, on forest plots, and on estimated survival curves. If appropriate, between-study heterogeneity was described by the between-study variance (τ^2) and I^2

statistics based on the 3-level model. Prediction intervals were not reported, as the study number was small. Potential outlier publications were explored using different influence measures and plots.

All statistical analyses were calculated by *R software* using the *meta* (v7.0.0) package for basic meta-analysis calculations and plots and *dmetar* (v0.1.0) package for additional influential analysis calculations. Package *metafor* (v4.4.0) was used for the multilevel models. *Survival* (v3.5.8) and *survminer* (v0.4.9) packages were used for individual patient data-based calculations. *MetaSurvival* (v0.1.0) package was used to estimate survival curves, which were plotted using the *ggplot2* (v3.5.0) package. Publication bias was not assessed because less than 10 studies were included in the meta-analysis.

Results

Search and selection

The systematic literature search yielded 5,491 results. No additional study was found with *citationchaser*. A summary of the selection process is available in [Figure 1](#). In total, 21

RCTs were included.

Basic characteristics of included studies

The included studies reported on 1,644 patients from nine countries. Out of these, 1,085 patients were randomised to different minimally invasive treatment options for the management of cancer-related pain. A summary of the baseline characteristics of the included studies is detailed in *Table 1*. The most used procedure was percutaneous CPN (P-CPN) (ten studies) (13–22), while pharmacological management consisting of opioids was the main control (nine studies) (15,17,20,22–27). Other methods for performing CPN were intraoperatively (I-CPN) and with endoscopic-ultrasound guidance (EUS-CPN). A small part of the included studies analysed different techniques, such as HIFU (27–29), radiofrequency ablation (30), interventional chemotherapy (31) and external-beam radiotherapy (32). Only seven studies were double-blinded (13,15,17,20,25,26,33). Except for one, the rest were randomised 1:1 (23). All studies reported several of our outcomes of interest, at multiple time points from study initiation, most frequently at 4 and 12 weeks. The patient demographics were similar across studies regarding age and gender distribution.

Pain relief

All included studies reported pain scores measured at different time points, most frequently at 4, 8, and 12 weeks from randomisation (range, 1–32 weeks). The most common way to assess pain was on the 11-point VAS or equivalents, with only two studies choosing different scales (*Table S2*) (26,30). The baseline pain values ranged from moderate (4.5–7.4) to severe (7.5–10) in all studies (34). Six studies with almost 440 patients were available for analysis 4 weeks after the intervention (*Figure S1*) (13,15,20,22,24,27). VAS values decreased with 3.5 to almost 6 points in all study groups after receiving the intervention compared to the initial assessment. *Figure 2* showcases a summary of the dynamic of pooled means for pain scores with each intervention, at each follow-up.

P-CPN

By the end of the 4 weeks, the pooled mean scores for pain were 2.27 (95% CI: 1.63–2.91) with P-CPN, and 2.80 (95% CI: 2.17–3.42) with opioids. At eight weeks, these scores started to increase slowly and at the 12-week follow-

up, pain scores higher than 3 on the VAS scale were noted (*Figures S2,S3*). Results of the direct comparison between P-CPN and opioids using the 2-level model are available in *Figure S4*.

EUS-CPN

Individual studies showed at 4 weeks from randomisation, pain scores of 1.30 (95% CI: 0.68–1.92) with EUS-CPN and at 8 weeks values of 2.50 (95% CI: 0.97–4.03). At 12 weeks from baseline, while P-CPN and opioids showed a similar potency, the pain scores after EUS-CPN were slightly lower, 1.47 (95% CI: –0.44 to 3.38) as shown in individual studies (*Figures S2,S3*).

I-CPN

One study analysing I-CPN showed, at 8 weeks, pain scores similar to those achieved 4 weeks after EUS-CPN (25).

HIFU

At 4 weeks from randomisation, pain values from individual studies were 1.45 (95% CI: 1.37–1.53) with HIFU.

QoL

QoL was assessed in 754 patients from 11 studies with 18 reporting scales (*Table 2*) (13,15,19–24,26,30,33). All provided results concerning different types of CPN techniques. In most cases, a rise in the scale value meant an increase in the QoL. A significant difference between study arms was observed in only 4 of the 11 studies included (15,19,23,30), with an additional one (24) reporting a significant improvement for the intervention group compared to its baseline, although only for “communication with the medical staff”. In the other cases, the QoL assessment showed the same tendency for both compared treatments, with an initial increase followed by an eventual decrease.

P-CPN

Compared to opioid treatment, P-CPN was shown to statistically increase the values on the physical domain of the Short Form Health Survey (SFHS) QoL scale, at 4, 8 and 12 weeks from baseline (15). When two different approaches of P-CPN were analysed, the transaortic P-CPN demonstrated a significant superiority concerning the QoL evaluation compared to the bilateral splanchnicectomy (19).

EUS-CPN

EUS-CPN significantly improved the general QoL of

Table 1 Baseline characteristics of included studies

Study	Country	Population					Intervention		Control		Follow-up (weeks)
		Number of randomised patients (female), n (%)	Age in the intervention; control groups (mean ± SD or range) (years)	Number of tumours per location (head + neck/body + tail) in intervention; control groups	Number of tumours per stage (II/III/IV) in intervention; control groups	Baseline cancer treatment (% patients) [health status]	Procedure, guidance, approach	Procedure details	Procedure, guidance, approach	Procedure details	
Abdel-Ghaffar <i>et al.</i> , 2022 (13) ^{†,‡}	Egypt	23 (N/A)	56±6.3; 59.1±6.5	N/A	N/A	CXT (100%) [N/A]	P-CPN, ultrasound-guided, anterior	20 mL, 70% ethanol	P-CPN, ultrasound-guided, anterior	40 mL, 70% ethanol	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12
Abdelbaser <i>et al.</i> , 2022 (14)	Egypt	70 (27.1%)	55.4±9.1; 55.7±11.9	N/A	N/A	N/A [N/A]	I-CPN	20 mL, 90% ethanol	P-CPN, CT-guided, posterolateral	20 mL, 90% ethanol	1, 2, 4, 8, 12, 24
Dong <i>et al.</i> , 2021 (15) ^{†,‡,§}	China	96 (43.7%)	61.2±11.5; 60.2±10.8	20/28; 21/27	0/18/30; 0/15/33	Palliative care, no prior CXT or RXT (100%) [N/A]	P-CPN, fluoroscopy-guided, posterolateral	12–18 mL, 100% ethanol	Opioids	N/A	4, 8, 12, 16, 20, 24, 28, 32
Ischia <i>et al.</i> , 1992 (16)	Italy	61 (N/A)	39–73	N/A	N/A	N/A [N/A]	P-CPN, fluoroscopy-guided, transaortic	30 mL, 100% ethanol	P-CPN, fluoroscopy-guided, posterolateral	15 mL, 100% ethanol	Until death
							Percutaneous, fluoroscopy-guided, bilateral splanchnicectomy	7 mL, 100% ethanol			
Polati <i>et al.</i> , 1998 (17) [‡]	Italy	24 (29.1%)	57±11.5; 60±10.1	N/A	N/A	N/A [N/A]	Percutaneous, fluoroscopy-guided, bilateral splanchnicectomy	7 mL, 100% ethanol	Opioids	+ NSAIDs	Until death
Saeed <i>et al.</i> , 2019 (18)	Pakistan	100 (47%)	51.1±11.4; 52.1±12.4	N/A	N/A	N/A [N/A]	P-CPN, fluoroscopy-guided, posterolateral	15 mL, 50% ethanol	P-CPN, fluoroscopy-guided, posterolateral	15 mL, 100% ethanol	Unclear
Süleyman <i>et al.</i> , 2004 (19) [§]	Turkey	39 (33.3%)	57±7; 61±8	N/A	N/A	N/A [N/A]	P-CPN, fluoroscopy-guided, transaortic	30 mL, 96% ethanol	Percutaneous, fluoroscopy-guided, bilateral splanchnicectomy	4.5 mL, 96% ethanol	2, 4, 6, 8, 10, 12, 14, 16, 18
Wong <i>et al.</i> , 2004 (20) ^{†,‡,§}	USA	100 (47%)	62.6±11.3; 63.4±11.5	N/A	0/17/33; 0/17/33	Prior CXT (20%), prior RXT (13%) [N/A]	P-CPN, fluoroscopy-guided, posterolateral	10 mL, 100% ethanol	Opioids	N/A	1, 4, 8, 12, 16, 20, 24
Yoon <i>et al.</i> , 2020 (21) [§]	Korea	60 (41.6%)	58.4±9.6; 61.2±7.4	15/19; 17/13	0/4/26; 0/6/24	CXT-refractory (91.6%) [N/A]	EUS-CPN	15 mL, 99.5% ethanol	P-CPN, fluoroscopy-guided, transdiscal	10 mL, 99.5% ethanol	1, 2, 4, 8, 12
Zhang <i>et al.</i> , 2008 (22) [†]	China	56 (37.5%)	38–75	N/A	N/A	N/A [N/A]	P-CPN, CT-guided, posterolateral	20 mL, 100% ethanol	Opioids	Morphine	1, 2, 4, 8, 12
Gao <i>et al.</i> , 2014 (23) [†]	China	100 (N/A)	65.6±10.2; 66.6±9.9	N/A	N/A	N/A [N/A]	EUS-CPN	10 mL, 100% ethanol	Opioids	Morphine, oxycodone NSAIDs	12
Kanno <i>et al.</i> , 2020 (24) ^{†,§}	Japan	46 (50%)	69±10; 69±9	8/16; 5/17	1/13/10; 0/4/18	CXT (63%) [N/A]	EUS-CPN	15–30 mL, 99% ethanol	Opioids	Oxycodone and fentanyl	1, 2, 4, 8, 12
Lillemoe <i>et al.</i> , 1993 (25) ^{†,‡,§}	USA	137 (41.6%)	64±N/A; 69.3±N/A	48/17; 54/18	0/39/26; 0/46/26	N/A [N/A]	I-CPN	20 mL, 50% ethanol	Opioids	N/A	8, 16
Wyse <i>et al.</i> , 2011 (26) [‡]	Canada	98 (52%)	66.6±9.3; 66.5±10	N/A	N/A	N/A [N/A]	EUS-CPN	20 mL, 100% ethanol	Opioids	Morphine	4, 12
Li <i>et al.</i> , 2017 (27)	China	162 (43.2%)	62.9±8.5; 61.8±8.9	14/63; 13/65	0/43/38; 0/40/41	No prior CXT or RXT [N/A]	HIFU	0.8 MHz, 250–350 W for 1,500–3,500 s, 30–50 min once every day, 21 days	Opioids	Oral morphine hydrochloride, 1–1.5 pill (20–30 mg) for every 12 hours	2, 3
Li <i>et al.</i> , 2016 (28) ^{†,§}	China	120 (50%)	50.1±19.8; 55.2±18.1	31/30; 32/27	0/0/61; 0/0/59	CXT-refractory (100%) [ECOG <3]	HIFU + CXT	HIFU + S-1 oral	CXT	S-1 oral, twice a day on days 1–14, then rest for a week; cycles repeated every 21 days	Up to 76
Lv <i>et al.</i> , 2016 (29) ^{†,§}	China	45 (37.7%)	N/A	N/A	N/A	N/A [Karnofsky score >70]	HIFU + CXT	0.97 MHz, 350 W for 1,560 s, overall average energy 725,000 J + GEMZAR iv.	CXT	GEMZAR iv. Once a week	Up to 48

Table 1 (continued)

Table 1 (continued)

Study	Country	Population					Intervention		Control		Follow-up (weeks)
		Number of randomised patients (female), n (%)	Age in the intervention; control groups (mean ± SD or range) (years)	Number of tumours per location (head + neck/body + tail) in intervention; control groups	Number of tumours per stage (II/III/IV) in intervention; control groups	Baseline cancer treatment (% patients) [health status]	Procedure, guidance, approach	Procedure details	Procedure, guidance, approach	Procedure details	
Bang <i>et al.</i> , 2019 (30)	USA	26 (50%)	62.8±13.7; 65.7±12.1	8/4; 8/6	2/3/7; 6/3/5	CXT (34.6%) [N/A]	EUS-RFA	10 W, radiofrequency	EUS-CPN	20 mL, 98% ethanol	4
Han <i>et al.</i> , 2006 (31) ^{†,§}	China	140 (21.4%)	N/A	N/A	N/A	No prior CXT or RXT [Karnofsky score >60]	Interventional CXT	FAM regimen, 6-day cycle at 1-month intervals, implanted percutaneous left subclavian artery port-catheter drug delivery system	CXT	FAM regimen, 6-day cycle at 1-month intervals, via peripheral vein	Unclear
Shinchi <i>et al.</i> , 2002 (32)	Japan	31 (51.6%)	62.9±2.8; 64.6±4	7/9; 10/5	N/A	N/A [Karnofsky score >60]	EBRT + CXT	1.8–2 Gy/day, 5 days/week + 5-FU continuous venous infusion	No therapy	Best supportive care for symptoms	Until death
Levy <i>et al.</i> , 2019 (33) [‡]	USA	110 (39.1%)	67.1±11.3; 66±10.2	24/34; 26/20	2/27/31; 1/20/27	No prior CXT or RXT [N/A]	EUS-CPN	20 mL, 99% ethanol	EUS-CGN	3 mL/ganglia, 99% ethanol	4, 8, 12, 24, 36, 48

[†], study included in the pain meta-analysis; [‡] double-blind study; [§], study included in the survival meta-analysis. ECOG performance status scale: 0 = fully active, able to carry on all pre-disease performance without restriction; 1 = restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature; 2 = ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours, 3 = capable of only limited self-care; confined to bed or chair more than 50% of waking hours, 4 = completely disabled; cannot carry on any self-care; totally confined to bed or chair, 5 = dead. Karnofsky performance score: 100 = normal, no complaints; 90 = able to carry on normal activity; 80 = normal activity with effort; 70 = cares for self; 60 = requires occasional assistance; 50 = requires considerable assistance and frequent medical care; 40 = disabled; 30 = severely disabled; 20 = hospital admission necessary; 10 = moribund; 0 = dead. 5-FU, 5-Fluorouracil; CGN, celiac ganglia neurolysis; CT, computed tomography; CXT, chemotherapy; EBRT, external beam radiation therapy; ECOG, Eastern Cooperative Oncology Group; EUS-CGN, endoscopic ultrasound celiac ganglia neurolysis; EUS-CPN, endoscopic ultrasound-guided celiac plexus neurolysis; EUS-RFA, endoscopic ultrasound-guided radiofrequency ablation; FAM regimen, 5-fluorouracil, adriamycin, and mitomycin; GEMZAR, gemcitabine; HIFU, high intensity focused ultrasound; I-125, Iodine-125; I-CPN, intraoperative celiac plexus neurolysis; iv., intravenous infusion; N/A, not available; NSAIDs, non-steroid anti-inflammatory drugs; P-CPN, percutaneous celiac plexus neurolysis; RXT, radiotherapy; SD, standard deviation; USA, United States of America.

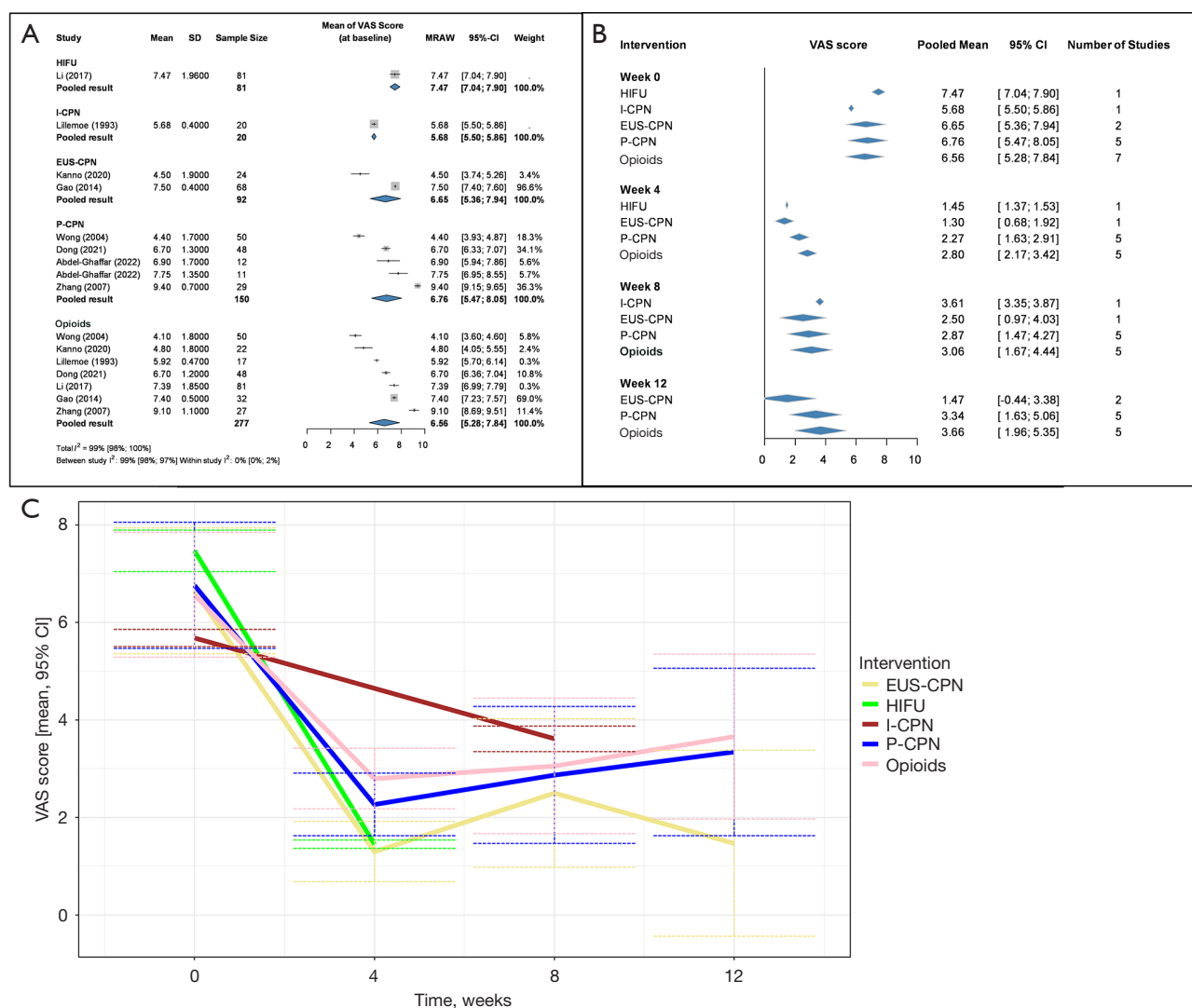


Figure 2 The dynamic of the pain scores. (A) Pooled means for baseline pain scores, (B) summary of pooled means of pain scores at each follow-up time, (C) time dynamic of the pooled means for pain scores with each intervention. CI, confidence interval; EUS-CPN, endoscopic ultrasound-guided celiac plexus neurolysis; HIFU, high-intensity focused ultrasound; I-CPN, intraoperative celiac plexus neurolysis; MRAW, raw mean; P-CPN, percutaneous celiac plexus neurolysis; SD, standard deviation; VAS, Visual Analogue Scale.

patients compared to opioids at 12 weeks from baseline in one of the included studies (23). However, EUS-RFA provided a significantly better result than EUS-CPN for the functional and symptomatic domains of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire core questionnaire 30 (EORTC C30) scale at 4 weeks from procedures (30).

Survival analysis

The survival analysis included nine RCTs, in which a total

of 680 patients were observed (15,19-21,24,25,28,29,31). Based on the estimated survival curve from individual patients' data (detailed statistical description in [Appendix 1](#)), the median survival time in days was 126.22 (95% CI: 87.21–165.31) for opioids. Given the relatively small number of deaths in most of the articles and the short follow-up time, 95% CI could not be calculated for all interventions, and the median number of days survived was 250.61 with chemotherapy. *Figure 3* shows a summary of the survival curves after each intervention (for individual calculations, see [Figure S5](#)).

Table 2 Quality of life assessment

Study	Intervention	Control	Quality of life scale	Range of scale	All reported time intervals from baseline (weeks)	Statistical difference between groups	Values at 4 weeks, intervention vs. control (mean ± SD)	Values at 12 weeks, intervention vs. control (mean ± SD)
Abdel-Ghaffar <i>et al.</i> , 2022 (13)	P-CPN (20 mL)	P-CPN (40 mL)	FACT-G: physical domain	0–28	4, 8, 12	No	14.2±2.8 vs. 13.3±2.2	15.5±2.3 vs. 14.6±2.2
			FACT-G: social domain	0–28			19.7±1.1 vs. 17.6±2.5	15.7±1.2 vs. 15.6±1.6
			FACT-G: functional domain	0–28			19±2.3 vs. 18.9±2.3	10.±2.2 vs. 9.5±2.7
Bang <i>et al.</i> , 2019 (30)	EUS-RFA	EUS-CPN	EORTC C30: functional domain; symptom domain [†]	0–100	4	Yes	39.6 [§] vs. 32.7 [§]	N/A
Dong <i>et al.</i> , 2021 (15)	P-CPN	Opioids	SFHS: physical domain	0–100	4, 8, 12	Yes	36±12.8 vs. 29.7±14.8	31.4±7.8 vs. 28±11
					16, 20, 24, 28, 32	No		
			SFHS: mental domain	0–100	4, 8, 12, 16, 20, 24, 28, 32	No	32.6±13.3 vs. 30.9±14.5	29.7±7.9 vs. 28.7±10.5
Gao <i>et al.</i> , 2014 (23)	EUS-CPN	Opioids	QLQ: general	0–100	12	Yes	N/A	65.6±0.4 vs. 51.3±0.5
			QLQ: physical domain	0–100			N/A	89.7±1.1 vs. 78.1±1.3
			QLQ: emotional domain	0–100			N/A	82.2±1.2 vs. 64.2±1.3
			QLQ: cognitive domain	0–100		No	N/A	88.6±2.3 vs. 85.7±2.5
			QLQ: social domain	0–100			N/A	66.1±1.6 vs. 65.1±1.7
Kanno <i>et al.</i> , 2020 (24)	EUS-CPN	Opioids	VAS	0–10	1, 2, 4, 8, 12	No	6.1±2.5 vs. 5.7±2	6.6±1.8 vs. 6±1.6
			4-points descending scale [†] : appetite domain		4	No	2.3±0.8 vs. 2±0.9	N/A
			4-points descending scale [†] : sleep domain				2.1±0.8 vs. 1.7±0.8	N/A
			4-points descending scale [†] : communication with medical staff domain			No*	1±0.2 vs. 1.3±0.6	N/A
Levy <i>et al.</i> , 2019 (33)	EUS-CPN	EUS-CGN	FACT-Hep	0–180	4, 8, 12	No	116.6±21.4 vs. 117.8±21.1	115.8±23.4 vs. 119.3±21.6
			MSAS [†]	0–4			1.7±0.4 vs. 1.7±0.4	1.7±0.5 vs. 1.6±0.4
			BPI	0–10			2.5±2 vs. 2.6±2.7	2.6±2.2 vs. 2.1±1.7
			Karnofsky score	0–100			75±10.4 vs. 67.5±18.1	70.5±8.8 vs. 65.8±13.6
Süleyman <i>et al.</i> , 2004 (19)	P-CPN (transaortic)	P-CPN (bilateral splanchnicectomy)	PSS [†]	0–10	4	Yes	5.3 ^a vs. 4.3 ^a	6 ^a vs. 5.2 ^a
					2, 6, 8, 10, 12, 14, 16, 18	No		
			PS [†]	0–4	6	Yes	2.1 ^a vs. 1.6 ^a	3.5 ^a vs. 2.9 ^a
					2, 4, 8, 10, 12, 14, 16, 18	No		
Wong <i>et al.</i> , 2004 (20)	P-CPN	Opioids	FACT-PA	N/A	1, 4, 8, 12, 16, 20, 24	No	58.5±14.6 vs. 63.6±16.2	58.5±18.8 vs. 60.9±17.5
Wyse <i>et al.</i> , 2011 (26)	EUS-CPN	Opioids	DDQ-15	N/A	4, 12	No	14% (7–19%) vs. 6% (0–11%) [‡]	19% (10–27%) vs. 18% (12–26%) [‡]
Yoon <i>et al.</i> , 2020 (21)	EUS-CPN	P-CPN	NFHSI	0–72	1, 2, 4, 8, 12	No	28.8 [§] vs. 27 [§]	30.7 [§] vs. 28.5 [§]
			GPES	1–7			0.9 (–0.5 to 2.2) [¶]	1.2 (–0.5 to 2.8) [¶]
Zhang <i>et al.</i> , 2008 (22)	P-CPN	Opioids	Appetite domain	0–10	1, 2, 4, 8, 12	No	2.5±1.4 vs. 2.8±1.9	3.5±2.1 vs. 3.2±2.4
			Sleep domain	0–10			2.5±1.8 vs. 3±2.2	2.7±2.2 vs. 2.9±2.4
			Communication domain	0–10			3.6±2.5 vs. 2.5±1.9	2.8±1.9 vs. 3.2±2.1

[†], higher scores mean worse quality of life; [‡], results reported as relative (%) change from baseline with 95% CI; [§], adjusted mean; [¶], mean difference between groups with 95% CI; ^a, median; *, significant difference from baseline for the intervention group. Data are presented as mean ± standard deviation unless otherwise stated. BPI, Brief Pain Inventory; CI, confidence interval; DDQ-15, Digestive Disease Questionnaire-15; EORTC C30, the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire core questionnaire 30; EUS-CGN, endoscopic ultrasound-guided celiac ganglia neurolysis; EUS-CPN, endoscopic ultrasound-guided celiac plexus neurolysis; EUS-RFA, endoscopic ultrasound-guided radiofrequency ablation; FACT-G, Functional Assessment of Cancer Therapy scale-Gastric; FACT-Hep, Functional Assessment of Cancer Therapy scale-Hepatobiliary; FACT-PA, Functional Assessment of Cancer Therapy scale-Pancreas; GPES, Global Perceived Effect of Satisfaction; MSAS, Memorial Symptom Assessment Scale; N/A, not available; NFHSI, National Comprehensive Cancer Network Functional Assessment of Cancer Therapy Hepatobiliary-Pancreatic Symptom Index; P-CPN, percutaneous celiac plexus neurolysis; PS, performance status; PSS, Patient Satisfaction Scale; QLQ, Quality of Life Questionnaire; SD, standard deviation; SFHS, Short Form Health Survey; VAS, Visual Analog Scale.

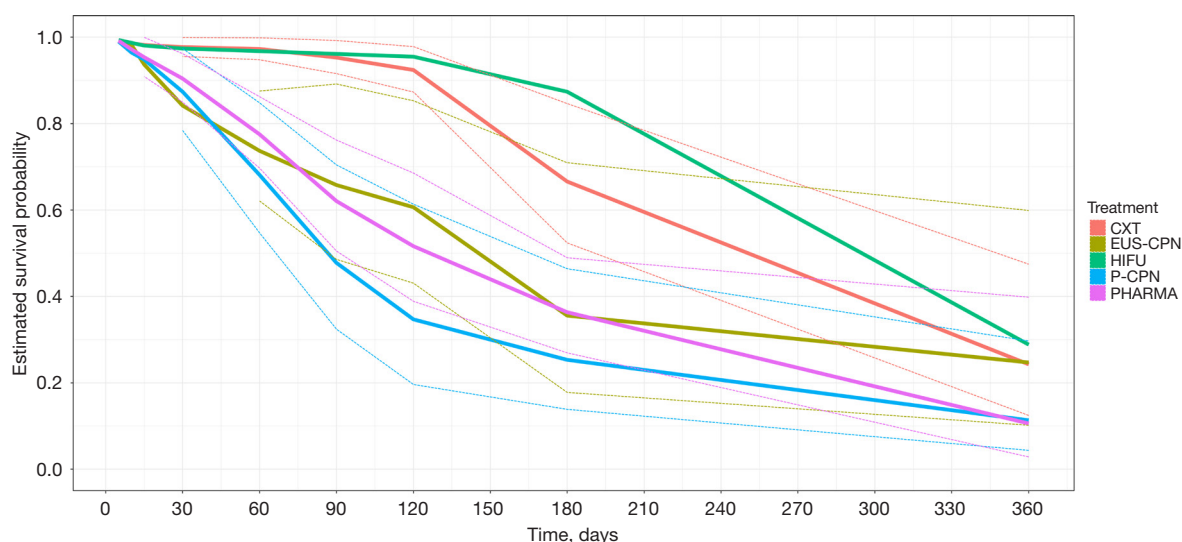


Figure 3 The summary of median survival time curves with each intervention analysed. CXT, chemotherapy; EUS-CPN, endoscopic ultrasound-guided celiac plexus neurolysis; HIFU, high-intensity focused ultrasound; P-CPN, percutaneous celiac plexus neurolysis.

P-CPN

The median survival time in days was 86.71 (95% CI: 62.45–136.88) for P-CPN. This value was the lowest among the rest.

EUS-CPN

The median number of days survived after EUS-CPN was 145.38.

HIFU

The median number of days survived was 294.97 after receiving HIFU.

Analgesic drugs use

Fourteen studies involving a total of 1,010 patients reported results concerning analgesic drug use in patients randomised to CPN interventions, CP ablation, HIFU, or opioid treatment (*Table 3*) (13-15,17,19-24,26,27,30,33). All patients received at least one opioid (in most cases, oral morphine), and in two studies, the consumption of non-steroid anti-inflammatory drugs (NSAIDs) was also reported (17,23). A statistically significant difference between the study groups was observed in seven articles (15,17,19,21-23,27), with a decreased need for opioids after CPN (six articles) (15,17,19,21-23) and HIFU (one article) (27). However, following the same dynamic as the pain relief, analgesic drugs were less consumed at

4 weeks from study initiation, but the consumption showed an increase at 12 weeks.

P-CPN

Three of the included studies (15,17,22) showed a statistically significant decrease in the use of analgesic drugs, at multiple time points after baseline, for patients who received P-CPN. When directly compared to EUS-CPN, one study highlighted a statistically significant difference in analgesics consumption, at 8 weeks from randomisation, favouring P-CPN (21).

EUS-CPN

Only one study reported a significant change in the analgesic drugs use after EUS-CPN. The results were measured at 12 weeks from baseline and analysed the consumption of morphine, oxycodone and NSAIDs separately (23).

I-CPN

Our study included only one article that compared the effects on analgesic drugs use after I-CPN and P-CPN. There was no statistically significant difference at any of the time points given concerning tramadol intake (14).

HIFU

At 2 and 3 weeks from baseline, one study showed that morphine use significantly decrease after HIFU (27).

Table 3 Analgesic drug use assessment

Study	Intervention	Control	Analgesic drug as mentioned in the study	All reported time intervals from baseline (weeks)	Statistical difference between groups at reported intervals	Values at 4 weeks, intervention vs. control (mg/day)	Values at 12 weeks, intervention vs. control (mg/day)
Bang <i>et al.</i> , 2019 (30)	EUS-RFA	EUS-CPN	Opioids (MED)	4	No	112.7 [†] vs. 105.4 [†]	N/A
Gao <i>et al.</i> , 2014 (23)	EUS-CPN	Opioids + NSAIDs	Morphine	12	Yes, favours EUS-CPN	N/A	88.9±0.4 vs. 12.3±0.5 [¶]
			Oxycodone	12	Yes, favours EUS-CPN	N/A	78.2±1.2 vs. 9.8±0.3 [¶]
			NSAIDs	12	Yes, favours EUS-CPN	N/A	66.1±0.3 vs. 11.5±0.6 [¶]
Kanno <i>et al.</i> , 2020 (24)	EUS-CPN	Opioids	Opioids (MED)	1, 2, 4, 8, 12	No	62±2.5 vs. 35±2	33±1.8 vs. 53±1.6
Levy <i>et al.</i> , 2019 (33)	EUS-CPN	EUS-CGN	Opioids (MED)	12	No	N/A	93 (64–150) vs. 105 (45–150)
Yoon <i>et al.</i> , 2020 (21)	EUS-CPN	P-CPN	Opioids (MED)	8	Yes, favours P-CPN	289.5±77.9 vs. 174.6±68.8	
				1, 2, 4, 12	No	198.1±71.5 vs. 161.9±63.4	249.7±91.4 vs. 188.2±81.4
Abdelbaser <i>et al.</i> , 2022 (14)	I-CPN	P-CPN	Tramadol	1, 2, 4, 8, 16, 24	No	50 (50–50) vs. 50 (50–100)	100 (50–100) vs. 75 (50–100)
Abdel-Ghaffar <i>et al.</i> , 2022 (13)	P-CPN (20 mL)	P-CPN (40 mL)	Opioids (MED)	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12	No	42±25.82 vs. 36±20.68	117±23.45 vs. 95±28.12
Dong <i>et al.</i> , 2021 (15)	P-CPN	Opioids	Opioids (MED)	4, 8, 12, 16, 20	Yes, favours P-CPN	71±63.5 vs. 162.3±50.5	97.4±47.2 vs. 180.5±59.4
				24, 28, 32	No		
Polati <i>et al.</i> , 1998 (17)	P-CPN	Opioids + NSAIDs	Opioids (MED)	First ½ survival time	Yes, favours P-CPN	30±17 vs. 58±25	
				Day before death	No	59±44 vs. 92±51	
			Diclofenac	First ½ survival time	Yes, favours P-CPN	98±63 vs. 171±45	
				Day before death	Yes, favours P-CPN	119±54 vs. 179±45	
Süleyman <i>et al.</i> , 2004 (19)	P-CPN (transaortic)	P-CPN, bilateral splanchnicectomy	Codeine	2, 4, 6, 8, 10	Yes, favours P-CPN (bilateral splanchnicectomy)	115 [‡] vs. 84 [‡]	–
				1, 12, 14, 16, 18	No	–	140 [‡] vs. 84 [‡]
Wong <i>et al.</i> , 2004 (20)	P-CPN	Opioids	Opioids (MED)	1, 4, 8, 12, 16, 20, 24	No	128 (48–238) vs. 155 (31–628)	249 (62–643) vs. 231 (30–555)
Wyse <i>et al.</i> , 2011 (26)	EUS-CPN	Opioids	Morphine	4, 12	No	53 (28–89) [§] vs. 54 (20–96) [§]	50 (28–79) [§] vs. 100 (49–180) [§]
Zhang <i>et al.</i> , 2008 (22)	P-CPN	Opioids	Morphine	1, 2, 4, 8, 12	Yes, favours P-CPN	54±50 vs. 133±53	105±65 vs. 169±71
Li <i>et al.</i> , 2017 (27)	HIFU	Opioids	Morphine	2, 3	Yes, favours HIFU	10.68±1.19 vs. 25.05±3.37	N/A

Data are presented as mean ± standard deviation or median (IQR) unless otherwise stated. [†], adjusted; [‡], median without IQR reported; [§], change from baseline expressed as mean with confidence intervals; [¶], result reported as % reduction from baseline. EUS-CGN, endoscopic ultrasound-guided celiac ganglia neurolysis; EUS-CPN, endoscopic ultrasound-guided celiac plexus neurolysis; EUS-RFA, endoscopic ultrasound-guided radiofrequency ablation; HIFU, high intensity focused ultrasound; I-CPN, intraoperative celiac plexus neurolysis; IQR, interquartile range; MED, oral morphine equivalent dose; mg, milligram; N/A, not available; NSAIDs, non-steroid anti-inflammatory drugs; P-CPN, percutaneous celiac plexus neurolysis.

AEs

The AEs found most were gastrointestinal (*Table 4*, *Figures S6-S10*). Results from individual studies show opioids had a high risk for nausea and vomiting. Haematological AEs, such as anaemia, leukopenia, and thrombocytopenia, were found only after treatments that included the use of chemotherapy (31,32). No important neurological damage was reported for any of the minimally-invasive procedures (*Figure S10*).

P-CPN

Pooled proportions for diarrhoea were 0.23 (95% CI: 0.14–0.35) with P-CPN (*Figure S6*). Pooled proportions for nausea and vomiting with P-CPN were 0.18 (95% CI: 0.05–0.47) (*Figure S7*). For cardiovascular AEs, the pooled proportions were 0.26 (95% CI: 0.14–0.45) for P-CPN (*Figure S8*). Among these, the most frequently cited were hypotension and orthostatic hypotension. Acute pain related to the procedure was rarely mentioned, with the pooled proportions of 0.12 (95% CI: 0.07–0.21) (*Figure S9*).

EUS-CPN

With EUS-CPN, pooled proportions for diarrhoea were 0.11 (95% CI: 0.05–0.22) and for cardiovascular AEs were 0.13 (95% CI: 0.04–0.39). For acute pain emerged after procedure, the pooled proportions were 0.23 (95% CI: 0.12–0.39), almost double than the ones of P-CPN.

I-CPN

Compared to a sham intervention, I-CPN showed similar surgery-related risks for cholangitis and biliary leaks (25). The incidence of diarrhoea, nausea and vomiting, and cardiovascular events was lower than with the other types of CPN.

HIFU

The AEs cited in the HIFU groups were in strong connection with the chemotherapy that was simultaneously administered. However, the incidence of the haematological AEs was lower than in the groups randomised to receive only chemotherapy.

RoB assessment

The results of the RoB assessment are presented in *Figures S11-S15*. The results for pain and QoL were similar, as they are patient-reported outcomes. The domains

with the highest risk were the measurement of outcomes and the selection of reported outcomes. Most of the studies did not blind the patients who were the assessors of their symptoms. Moreover, as there is no standard protocol for pain and QoL evaluation, multiple outcome surveys and different effect measures were used. The variety of statistical calculations also raised the RoB in the case of analgesic drug use. Other general factors contributing to the RoB for all outcomes were the lack of a registered protocol, scarce information on the randomisation process, and missing patient data. However, the studies presented no risk concerning deviations from the intended interventions.

Heterogeneity

There was a high I^2 value among the studies included in the meta-analysis of pain scores [total $I^2=89\%$ (64%–98%)]. The reason behind this may be the wide variety of interventions, with different approaches, types of imaging guidance, and alcohol dilutions used for the CPN.

Discussion

Key findings

Our analysis showed that based on individual studies' results EUS-CPN provided slightly better pain scores at 4-, 8-, and 12-week measurements, with fewer associated AEs, significantly improved QoL, and median survival time moderately enhanced compared to opioids. Even if they provided good pain relief, P-CPN and opioids were associated with slightly higher pain increases in time. In the short term, promising results were also achieved with HIFU, which significantly decreased the pain scores compared to opioid treatment at 21 days after randomization (27).

Strengths and limitations

One of the main strengths of our analysis is the large number of diverse procedures included. This is the first systematic review and meta-analysis to compare various intervention types. Moreover, conducting analyses at multiple time points is an important factor in our study, as it allowed us to observe the dynamic of patients' symptoms in both the short and long term. We included only RCTs, so as to provide the highest quality of evidence, and we followed a strict methodology for performing our research.

We acknowledge the limitations of our research, such

Table 4 Adverse events assessment

Adverse event	Opioids ± NSAIDs	P-CPN [95% CI]	EUS-CPN [95% CI]	I-CPN	EUS-RFA	HIFU + CXT	I-CXT	CXT
Gastroenterological								
Diarrhoea [†]	16.7% (2/12); 1 RCT ^b	23% [14–35%]; 7 RCTs ^{†,b}	11% [5–22%]; 4 RCTs ^{†,b}	2.8% (1/36); 1 RCT ^a	0% (0/12); 1 RCT ^a	13.1% (8/61); 1 RCT ^b	N/A	15.3% (9/59); 1 RCT ^b
Nausea and vomiting [†]	87.2% (34/39); 2 RCTs ^d	18% [5–47%]; 3 RCTs ^{†,b}	7.9% (3/38); 2 RCTs ^a	8.3% (3/36); 1 RCT ^a	33.3% (4/12); 1 RCT ^c	21.3% (13/61); 1 RCT ^b	48.6% (34/70); 1 RCT ^c	30.2% (39/129); 2 RCTs ^c
Constipation	82.1% (32/39); 2 RCTs ^d	24.4% (10/41); 2 RCTs ^b	N/A	N/A	N/A	N/A	N/A	N/A
Cholangitis	11.1% (8/72); 1 RCT ^b	N/A	N/A	9.2% (6/65); 1 RCT ^a	N/A	N/A	N/A	N/A
Biliary leak	2.8% (2/72); 1 RCT ^a	N/A	N/A	3.1% (2/65); 1 RCT ^a	N/A	N/A	N/A	N/A
Cardiovascular								
Altogether [†]	6% (5/84); 2 RCTs ^a	26% [14–45%]; 7 RCTs ^{†,c}	13% [4–39%]; 2 RCTs ^{†,b}	4% (4/101); 2 RCTs ^a	N/A	N/A	N/A	N/A
Orthostatic hypotension	16.7% (2/12); 1 RCT ^b	47.1% (57/121); 3 RCTs ^c	N/A	N/A	N/A	N/A	N/A	N/A
Hypotension	N/A	14% (13/93); 3 RCTs ^b	8.9% (8/90); 2 RCTs ^a	2.8% (1/36); 1 RCT ^a	N/A	N/A	N/A	N/A
Other cardiovascular events	4.2% (3/72); 1 RCT ^a	10.5% (2/19); 1 RCT ^b	N/A	4.6% (3/65); 1 RCT ^a	N/A	N/A	N/A	N/A
Haematological								
Anaemia	N/A	N/A	N/A	N/A	N/A	24.6% (15/61); 1 RCT ^b	N/A	22% (13/59); 1 RCT ^b
Neutropenia	N/A	N/A	N/A	N/A	N/A	18% (11/61); 1 RCT ^b	N/A	20.3% (12/59); 1 RCT ^b
Thrombocytopenia	N/A	N/A	N/A	N/A	N/A	16.4% (10/61); 1 RCT ^b	N/A	13.6% (8/59); 1 RCT ^b
Leukopenia	N/A	N/A	N/A	N/A	N/A	N/A	5.7% (4/70); 1 RCT ^a	80% (56/70); 1 RCT ^d
Myelosuppression	N/A	N/A	N/A	N/A	N/A	N/A	0% (0/70); 1 RCT ^a	4.3% (3/70); 1 RCT ^a
Other								
Pneumonia and pleurisy	2.8% (2/72); 1 RCT ^a	4.9% (3/61); 1 RCT ^a	N/A	3.1% (2/65); 1 RCT ^a	N/A	N/A	N/A	N/A
Acute pain [†]	N/A	12% [7–21%]; 5 RCTs ^{†,b}	23% [12–39%]; 3 RCTs ^{†,b}	2.8% (1/36); 1 RCTs ^a	8.3% (1/12); 1 RCT ^a	N/A	N/A	N/A
Fever	N/A	N/A	7.1% (1/14); 1 RCTs ^a	N/A	0% (0/12); 1 RCT ^a	N/A	N/A	N/A
Neurologic damage [†]	N/A	7% [2–20%]; 2 RCTs ^{†,a}	0% (0/60); 1 RCTs ^a	N/A	N/A	6.6% (4/61); 1 RCT ^a	N/A	8.5% (5/59); 1 RCT ^a
Lethargy and drunkenness	N/A	37.7% (29/77); 2 RCTs ^c	12.5% (3/24); 1 RCT ^b	N/A	N/A	N/A	N/A	N/A
Wound infection	8.3% (6/72); 1 RCT ^a	N/A	N/A	12.3% (8/65); 1 RCT ^b	N/A	N/A	N/A	N/A
Bleeding NSAIDs-related	8.3% (1/12); 1 RCT ^a	0% (0/12); 1 RCT ^a	N/A	N/A	N/A	N/A	N/A	N/A

[†], included in the meta-analysis; ^a, between 0–10%; ^b, between 10–25%; ^c, between 25–50%; ^d, more than 75%. CI, confidence interval; CXT, chemotherapy; EUS-CGN, endoscopic ultrasound-guided celiac ganglia neurolysis; EUS-CPN, endoscopic ultrasound-guided celiac plexus neurolysis; EUS-RFA, endoscopic ultrasound-guided radiofrequency ablation; HIFU, high intensity focused ultrasound; I-CPN, intraoperative celiac plexus neurolysis; I-CXT, interventional chemotherapy; N/A, not available; NSAIDs, non-steroid anti-inflammatory drugs; P-CPN, percutaneous celiac plexus neurolysis; RCT, randomised controlled trial.

as not being able to compare the interventions directly due to the low number of available RCTs. Other limitations included the variety of effect measures, types of statistical analyses, and patient-reported scales used in every study, which, together with the lack of clear criterion standard for pain and QoL assessment, meant that we could not evaluate the results from every available trial altogether. Finally, the control groups distributed to pharmacological treatment were followed only for opioid intake in most cases, while palliative oncological care, other types of painkillers, and illicit drugs were disregarded.

Comparison with similar studies

Our results are consistent with a previous meta-analysis of six RCTs on CPN in unresectable PC (8). When comparing the dynamics of pain after each intervention, a similar trend can be observed in all cases. There was an initial decrease in the VAS score, followed by several escalations of pain values at each reported time point. The same pattern applied to analgesic drugs intake. Another meta-analysis of ten RCTs showed improved results at the 12-week follow-up compared to the earlier time points reported, but the authors chose to analyse P-CPN and EUS-CPN altogether (35). In our case, irrespective of the low number of studies, the most promising interventional technique was shown to be EUS-CPN, with better pain scores at 12 weeks from baseline, improved QoL, and fewer AEs. Its superior safety results from the real-time precise anatomical visualisation that helps avoid retrocrural neurological structures. This can be further improved using colour Doppler to identify interposing vessels (36). However, its best efficacy was reported at 4 weeks, with one study showing that EUS-CPN had similar pain scores as oxycodone and fentanyl at longer follow-ups (24).

Explanations of findings

Our analysis did not find a clinically relevant difference between the pain control provided by P-CPN and opioids at any of the measured time intervals. Regarding techniques, three of the included studies presented a posterior approach [two with fluoroscopy guidance (15,20), one by the means of CT (22)], while in another study, a US-guided anterior approach was chosen (13). Although the most frequent is the posterior, the anterior CPN can lead to a lower risk for spinal cord and kidney injuries (36). Other possibilities have been described. The transaortic approach (16,19) provides a more reliable spread of the neurolytic

agent, with the cost of a higher risk for retroperitoneal haemorrhage, while the transdiscal (21) can be used if the patient's anatomy obstructs the para-aortic approach but has a higher risk for disc trauma (36). We did not have sufficient data to investigate the most efficient approach for P-CPN. Some authors consider that the analgesic results are independent of the technique, but others argue that specific methods should be used based on the characteristics of the tumour. For example, Ischia *et al.* found no difference in pain control with either bilateral splanchnicectomy, retrocrural neurolysis, or transaortic neurolysis, but they preferred the last as it had the lowest incidence of post-intervention orthostatic hypotension with limited spread of the alcohol in the psoas compartment (16). Süleyman *et al.* showed that the bilateral splanchnicectomy had better results for tumours localised in the body and tail of the pancreas compared to transaortic P-CPN and suggested an explanation could be the inappropriate distribution of alcohol during CPN due to the extension of the tumour (19).

It is crucial to notice that the number of patients available for analysis rapidly decreased between follow-ups. As patients in palliative care have more pain and shorter life expectancy, the full effect of the performed interventions could not be assessed in all the randomised patients. Only one study presented the observed values compared to the carry-forward ones, with small discrepancies (20). EUS-CPN was associated with slightly better survival rates between all CPN modalities, outperforming P-CPN. It should be mentioned that in the studies that analysed CPN, the population comprised palliative terminally ill patients. This was not the case for the patients from the HIFU studies, with Eastern Cooperative Oncology Group (ECOG) scores of 0–2 (27–29). These baseline differences translate into the significant diversity of our survival analysis results. However, when compared to chemotherapy alone, HIFU seemed to prolong survival. The mechanism behind it has not been explained, but possible theories include its effect on the small vessels around the tumour by blocking vasa vasorum, and on the activation of the immune system (27,29,37). The synergistic effect of HIFU and chemotherapy contributed to the best outcome, with improved QoL and prolonged survival, as it changed cell membrane permeability and enabled easier penetration of the drug in the tumour cells (29).

It is essential to note that the AEs of interventional methods usually lasted for up to a maximum of 1 week from the procedure, as they occurred from the transient loss of the sympathetic tone (38). For example, in the case of

CPN and HIFU, diarrhoea was reported to last only 3 days (15-17,22,33). Haemodynamic disturbances were commonly described in the first days after P-CPN and EUS-CPN (14-17,21,22,33), with only one study reporting the requirement of inotropic support (19). Procedure-related transient pain was present in 12% of patients with P-CPN compared to 23% with EUS-CPN, although the latter included one study on EUS-CGN with 44% of the patients in pain after the intervention. Opioids can be associated with long-term AEs throughout the treatment period (39). As the follow-up time increases, the opioid use rate and the total doses consumed are expected to grow (40). Considering the impact of prolonged AEs, minimally invasive techniques seem to have more advantages over opioids. Two studies showed a significantly improved QoL at 12 weeks from P-CPN and EUS-CPN, respectively (15,23). However, we did not find any similar differences at longer follow-ups.

Implications and actions needed

Implementing scientific findings in practice is crucial (41,42). We suggest that minimally-invasive procedures should be considered more often and sooner in the management of patients with painful unresectable PC. Our analysis showed that EUS-CPN can control pain for up to 12 weeks. However, the maximal effect of CPN is achieved when given early in the disease course (43). While EUS-CPN can be performed at the time of the diagnosis and staging, results from RCTs emphasise the need to consider it early in the pain management of unresectable PC (26). Additionally, in a case series of abdominal cancers, early bedside CPN proved to be a satisfying first-line therapy and a good alternative to opioids (44).

Neurolytic procedures have been used for more than a century, gradually evolving and becoming more readily available (43,45). Nowadays, they are believed to be the second most used modality for treating PC pain after opioid intake (36). However, the specific uptake rates of these procedures among PC patients are not well-documented in the available literature. Their world-wide distribution is also proven by the studies included in our analysis, with RCTs conducted in many different countries, from Europe, Asia and the United States of America. The utilization of CPN may be influenced by factors such as patient selection criteria, availability of specialized medical professionals trained in the technique, and the clinical judgment of healthcare providers regarding its appropriateness for individual patients. Moreover, the healthcare policies of

each country play a crucial role in the access people have to these techniques (36).

Still, some barriers prevent the implementation of early interventional pain management in patients with PC. These procedures depend greatly, on one hand, on the local expertise and skills, as well as on the available treatment modalities. The lack of awareness among practitioners and the low number of trained specialists detain access to early cancer pain management through interventional procedures. Even though CPN has already been proven safe (36), there are still misconceptions about the risks related to the invasiveness of these techniques. On the other hand, precise timing is also crucial, as malignant infiltration of the plexus may prevent achieving optimal results (45). Often, the focus on systemic therapies such as chemotherapy and radiotherapy overshadows early pain management. This results in a delay for interventional treatments until the pain becomes severe and refractory when the success rate of these procedures is significantly decreased. There can also be cases when other associated pathologies must be initially treated, such as coagulopathies, thrombocytopenia and intraabdominal infections, which are contraindications for CPN (36). Hence, even though already established as a potent intervention with a moderate level of recommendation (2A+), CPN is sometimes missing from the routine clinical protocol of PC pain. The reasons that still need to be addressed are the inadequately trained physicians, the scarce healthcare system resources and the lack of multidisciplinary team discussion (46).

PC is considered to be the most expensive type of cancer in terms of overall costs, combining direct costs for the healthcare system and indirect costs from work absence of the diseased (47). Opioids currently represent the standard cancer pain treatment. However, there is a marked inter-individual variability in the response to them, with many patients reporting insufficient pain control or diverse side effects (39). In our analysis, the most common AEs connected to opioid intake were nausea, vomiting, and constipation. Treating these side effects increases the financial cost of the medical treatment. With a total of almost 7,000 US\$ during best supportive care, PC has the highest financial burden of both inpatient and outpatient expenses compared to other types of cancers (48). Our results showed that EUS-CPN and I-CPN had the lowest rate of AEs, but the EUS-guided approach had the advantage of being less invasive. Moreover, the studies included in our analysis showed a significant decrease in the number of analgesic drugs used after procedures such

as P-CPN and EUS-CPN, with better outcomes after the ladder. This translates to reduced long-term medication costs and a lower burden of opioid-induced side effects. From a financial perspective, EUS-CPN appears superior again, with a total price lower than CT-guided P-CPN (1,100 versus 1,400 US\$) (49). Therefore, even if initial procedure costs seem higher, performing EUS-CPN could reduce the overall costs of unresectable PC pain management. Regarding cost-effectiveness, interventional procedures seem to be superior, with durable decreased medication use and improved patient outcomes. However, cost-analysis data in this clinical setting remains limited.

There are more options for pain treatment not yet included in RCTs, such as microwave ablation, cryoablation, irreversible electroporation, or stereotactic body radiation therapy. As technical failures can occur, whether these interventions should be repeated or combined is still unknown (16). One prospective study on 156 patients showed that multiple repetitions of EUS-CPN provided superior pain control compared to the initial treatment (50). The analgesic effect of CPN was seen to diminish in time, with pain scores increasing again after 3 months from intervention. However, since these procedures are usually offered to late-stage patients and only almost a third of them have the chance for repeated CPN, there is no high level of evidence yet to support this practice (45). Hence, more and stricter RCTs must be conducted in this field, with rigorous methodologies comparing interventional procedures to one another, and multiple repetitions to a one-time intervention.

To find the most effective management, patient-reported outcomes (such as pain and QoL assessments) need standardisation. While one meta-analysis tried to identify the minimal clinically significant differences in chronic pain, it was focused on non-cancer pain (51). Future studies are needed to conclude what clinically relevant change is from the baseline, as there is no clear definition in use.

Conclusions

Minimally invasive techniques are potent tools for providing pain reduction with fewer associated adverse effects and reduced opioid use for unresectable PC patients. Future RCTs are needed to define the characteristics of the most appropriate method for patient-tailored management.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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