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Review Article

A Systematic Review of Interventions for Pain in Patients with Incurable Pancreatic Cancer

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Abstract

Objective: Incurable pancreatic cancer poses challenging analgesic requirements, which subsequently affect the quality of life of patients. The aim of this review was to assess the available methods of managing pain in incurable pancreatic cancer, how these are utilized, and their effectiveness in patients. **Data Sources:** A comprehensive literature search was conducted of online databases, including Medline and Embase, using MeSH terms. The study was registered with PROSPERO number CRD420251164775. **Study Selection:** Inclusion and exclusion criteria included patients >18 years and a sample size >40. This resulted in 9 papers being included in the study. Secondary outcomes included functional status, quality of life, anxiety, and depression. **Results:** The studies focused on various regional nerve blocks and oral analgesia. These used a numerical analogue scale as a self-reported outcome measure of pain. Results found that oral combination analgesia provided better analgesic effects than monotherapy. This was similarly found to have improved quality of life and psychological well-being. Eight studies found nerve blocks to be a more effective method of treating pain than oral analgesia alone. **Conclusion:** By using combination analgesics, studies found that reduced doses of opioids were required, thus reducing side effects. Celiac plexus blocks were found to be associated with lower opioid requirements and subsequently less side effects, particularly in the initial months following treatment. This demonstrates an important option in pain management for patients with complex pain in advanced pancreatic cancer.

Keywords: Analgesia, cancer, celiac-plexus block, palliative, pancreatic

Introduction

Pancreatic cancer continues to provide a large global burden of mortality, and despite medical advances, incidence continues to increase.[1] Patients with pancreatic cancer tend to present late with progressive and often incurable disease[2] with symptoms at presentation including pain, weight loss, and anorexia.[3] There are limited treatment options available for pancreatic cancer, such as surgery or systemic anticancer therapy (SACT), depending on disease staging. A large proportion of patients will not be suitable for curative therapy, and an approach to treatment including supportive and palliative care measures will be utilized.[4]

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Pain in pancreatic cancer is highly prevalent and increasingly complex in both aetiology and management. Evidence suggests that the majority of patients present with pain at diagnosis[5] and that up to 80% experience pain as the cancer progresses.[6] This can be experienced as visceral pain, caused by direct tumour damage, and/or neuropathic pain from disease extending into the celiac plexus and beyond. This can also be compounded by pain caused by cancer treatment, including surgery and SACT.[7]

The basis of managing cancer-related pain follows the World Health Organization analgesics ladder, where initial midtier opioids are used with neuropathic analgesics where appropriate, and increasing adjuvants are used if required.[8] The use of opioids and neuropathic agents is the gold standard of treatment.[9]

Celiac plexus blocks can be used in pancreatic cancer patients, particularly when high-dose oral agents are no longer providing sufficient analgesic effect or side effects become intolerable.[10,11] This was originally performed intraoperatively or percutaneously. However, since the publication of the 2011 Cochrane review, this procedure has been increasingly performed under endoscopic ultrasound guidance-celiac plexus neurolysis (EUS-CPN), which offers a less invasive approach and a lower risk profile.[12]

It is well established that the presence of pain in patients living with cancer is associated with reduced quality of life, performance status, and increased levels of distress.[13,14] This is true for patients with pancreatic cancer, not only due to the prevalence of pain, but the overall high symptom burden seen with advanced disease.

It is no uncommon for depression and anxiety to be experienced by patients with cancer diagnoses; these mental illnesses have in fact been found to precede cancer diagnosis in over one third of patients.[15] These are likely to develop both as a result of the psychological distress the diagnosis causes, but also due to direct physiological stress exerted by the malignancy itself.[16] Pain, and the associated effects it has on patients, remains challenging to manage in patients with advanced pancreatic cancer. The primary aim of this review is to assess the management options for pain in patients with incurable pancreatic cancer. Secondary outcomes that will be explored include quality of life, functional status, and psychological well-being.

Materials and Methods

A comprehensive literature search was carried out between September 1, 2024, and September 29, 2024, on online databases including MEDLINE, Embase, and Web of Science. The study was registered with PROSPERO number CRD420251164775. Key words and MeSH terms such as "pancreatic cancer," "metastatic" and "palliative" were used to identify studies, which generated 1649 results [Appendix 1]. Once duplicates and non-English studies were removed, 63 papers were for title-abstract screening. Population Intervention Comparison Outcome (PICO) criteria were used to establish inclusion and exclusion criteria, such as sample size greater than 40, non-curative interventions, and pain as a primary outcome [Table 1]. "Incurable" pancreatic cancer was defined as cancer that was not receiving curative treatment/interventions. This was collated into a PRISMA diagram [Figure 1], and 25 papers were for full text screening, resulting in 9 papers included in the study [Figure 2]. A risk of bias assessment was undertaken using the Cochrane risk of bias 2.0 tool.[17] Each study was assessed by two independent reviewers. Should disagreement occur, the chief investigator (ESJ) would review this to come to final decision. Meta-analysis was deemed inappropriate due to substantial clinical and methodological heterogeneity. Therefore, a structured narrative synthesis was undertaken to compare trends and outcomes across studies.

Results

Nine papers were included in the review; sample sizes ranged from 50 to 403 patients, all with advanced pancreatic cancer. The studies consist of four observational studies (2 prospective and 2 retrospective), four randomized controlled trials, and one meta-analysis.

The most common intervention identified was the utilization of nerve blocks, assessed in 8 of the 9 studies included in this review; the final study focused on oral analgesia.

All studies had pain as their primary outcomes. The majority (eight) of the studies utilized a numerical visual analogue scale as a self-reported outcome measure. One study used the 7-point Likert scale.[18]

Six studies explored quality of life as a secondary outcome, and one study also looked at functional status, anxiety, and depression as secondary outcomes. Table 2 shows further details on the included studies.

Table 1: Inclusion and exclusion criteria

Criteria	Inclusion criteria	Exclusion criteria
Population	Aged >18 years >40 sample size	Aged <18 years <40 sample size
	Human study	Animal study
	Noncurative cancer	Curative cancer
	Pancreatic cancer only	Multiple types/ locations of cancer
Intervention	Analgesia	Curative chemotherapy
	Localized nerve blocks	Surgical resection
	Supportive chemotherapy	
	Palliative care	
Primary outcomes	Pain	Mortality
Secondary outcomes	Quality of life	
	Functional status	
	Mental health	
Study design and details	Comparative and review articles	Studies not available in English

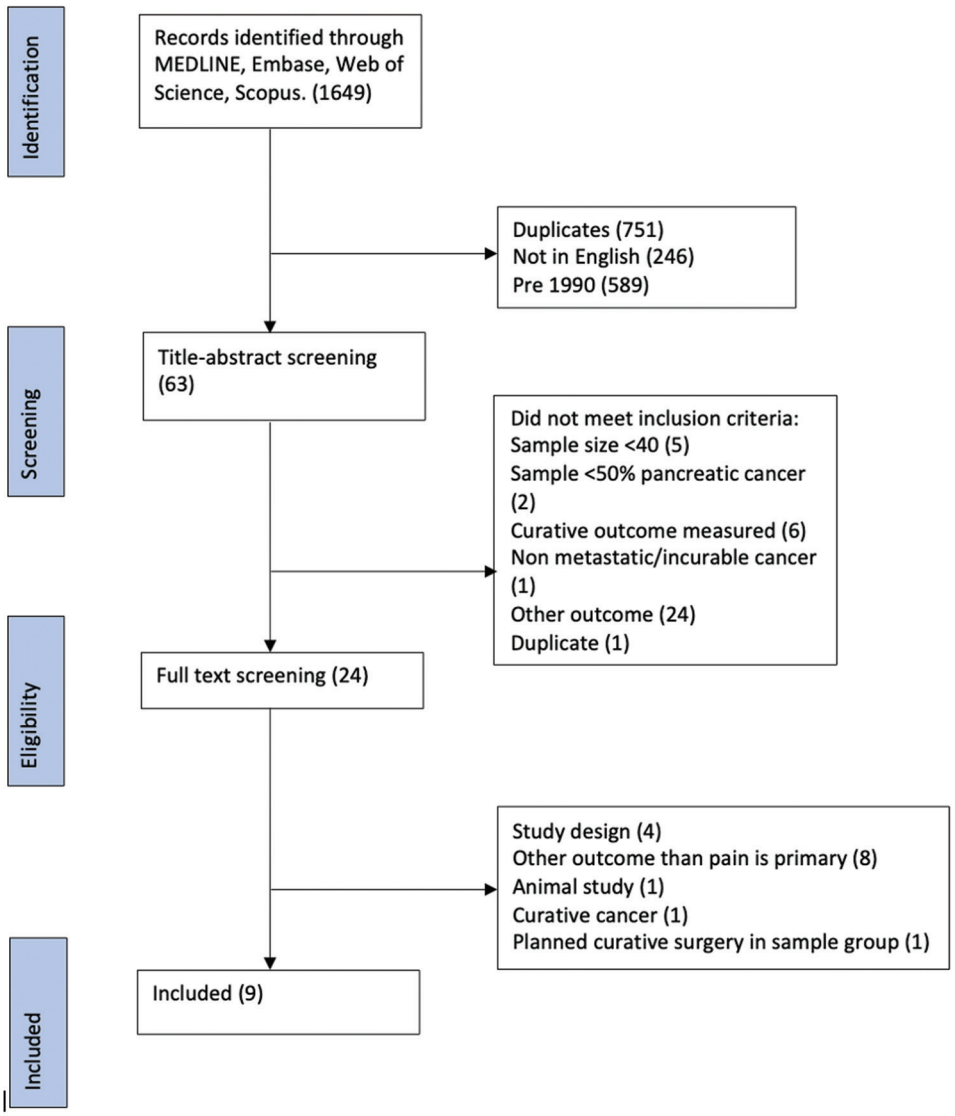

Figure 1: PRISMA diagram

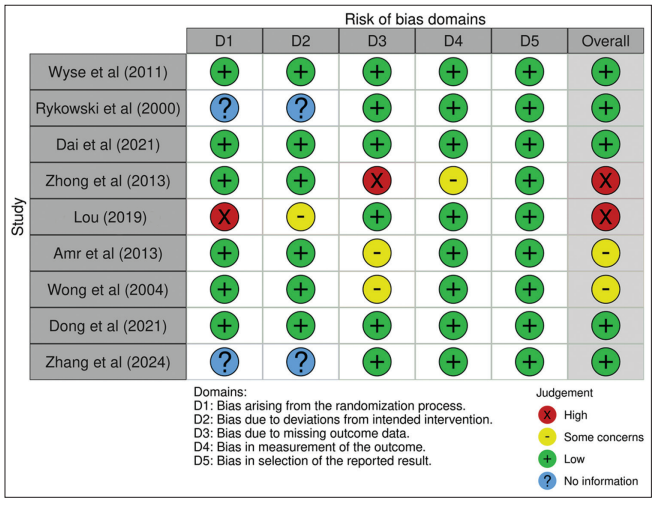

Figure 2: Risk of bias chart

Analgesia

Dai *et al*. found that pain scores were similar between the morphine monotherapy and pregabalin and morphine combination groups. However, lower doses of morphine were required in the combination therapy group.[9] which required a mean of 39.5 mg morphine daily compared to 61.5 mg in those taking opioid monotherapy. Episodes of breakthrough pain were similar in terms of frequency and severity across the two groups; however, these episodes were shorter in the combination therapy group. The incidence of side effects, including dizziness and fatigue, was higher in the combination group compared to the monotherapy group.

This study also assessed the impact on quality of life, functional status, and psychological well-being. Its findings demonstrated that the combination group experienced less interference with activities of daily living and sleep and an overall improvement in quality of life. Prevalence of depression

Table 2: Study characteristics

Study	Study type	Population (*n*, %F)	Intervention	Comparison	Outcomes
Wyse *et al.* (2011)[18]	RCT	580	Endoscopic ultrasound-guided celiac plexus neurolysis	Oral analgesia	Pain Quality of life
Rykowski *et al.* (2000)[22]	Prospective	50	Celiac plexus neurolysis in the head of the pancreas	Celiac plexus neurolysis in the body/tail of the pancreas	Pain (VAS)
Dai *et al.* (2021)[9]	Retrospective cohort	240 (42)	Pregabalin (150mg/d) and morphine combination	Morphine monotherapy	Pain (VAS) Quality of life Functional status Anxiety/depression
Zhong *et al.* (2014)[20]	RCT	403	Celiac plexus blockage	Oral analgesia	Pain (VAS)
Lou (2019)[19]	RCT	58 (34)	Endoscopic ultrasound-guided celiac plexus neurolysis	No comparison	Pain (VAS)
Amr *et al.* (2013)[21]	RCT	60 (35)	Celiac plexus block+oral analgesia	Oral analgesia	Pain (VAS) Quality of life
Wong *et al.* (2004)[25]	RCT	100 (47)	Neurolytic celiac plexus block	Oral analgesia	Pain (VAS) Quality of life
Dong *et al.* (2021)[24]	RCT	96 (44)	Neurolytic splanchnic nerve block (neurolysis)	Splanchnic nerve block with saline	Pain (VAS) Quality of life
Zhang *et al.* (2024)[23]	Retrospective cohort	81 (33)	Endoscopic ultrasound-guided celiac plexus neurolysis	Celiac plexus irradiation with iodine-125	Pain (VAS) Quality of lif

and anxiety was screened for using the hospital anxiety and depression scale (HADS) and found that the combination therapy group experienced greater improvement in HADS score, demonstrating lower levels of anxiety and depression.

Nerve blocks

All eight studies that focused on the utilization of nerve blocks found them to be effective in significantly reducing pain in patients with pancreatic cancer. Two studies quantified the response rate to treatment (i.e., proportion of patients achieving reduction in pain score from pre-treatment baseline) as 74%[22] and 79.3%.[19]

Most studies found that this analgesic effect was maintained throughout the duration of their follow-up periods, which varied from 4 to 24 weeks. Only one study by Zhong *et al*. noted a significant improvement in pain scores at 4 weeks; however, by 8 weeks, while pain scores remained improved from baseline, they were not significantly different from the control group taking oral analgesia alone.[20]

Amr *et al*. found that patients who were optimized on oral analgesia before undergoing EUS-CPN had more substantial and sustained improvements in pain compared to those who underwent EUS-CPN prior to initiation of oral analgesia.[21]

One study explored the difference in efficacy of pain management based on the location of pancreatic cancer. This study found that patients who had tumours located within the head of the pancreas had a much higher likelihood of experiencing a reduction in pain when compared with those with tumours in the body or tail of the pancreas.[22]

Zhang *et al*. compared the utilization of EUS-CPN to celiac plexus irradiation with iodine.[23] They found that while both interventions effectively reduced pain scores, EUS-CPN appeared to be most effective in the first 2 weeks postprocedure, but by 4 weeks, the group treated with irradiation had lower pain scores.

Four studies explored the impact EUS-CPN had on opioid requirements; two of these found that patients were able to reduce their opioid use after the intervention,[20,24] one study found opioid use was similar at 1 month compared to the control group, but by 3 months, opioid use had significantly reduced.[18] The final study did not find a significant difference in opioid use.[25]

No serious or persisting side effects were noted from any of the studies included in this review. One study reported that 24% of the participants experienced mild, short-lived side effects.[19]

As a secondary outcome, five of the studies also assessed the impact on quality of life following EUS-CPN. Quality of life was assessed using a variety of self-reported surveys, including European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30; Functional Assessment of Cancer Therapy, Pancreatic Cancer, and SF-36. Four of the studies found no difference in quality of life following EUS-CPN. The final study found that quality of life was improved after EUS-CPN, particularly if the patient had been taking optimized analgesia before the procedure.

Risk of bias

A risk of bias assessment was carried out on the studies using the Cochrane Risk of Bias tool 2.016. The majority of studies were high quality with a low risk of bias or some concerns. Due to the nature of the interventions used, many of which were surgical or injections, there were challenges with minimising

bias and allowing double blinding and random allocation, which resulted in a higher than usual number of studies that were high risk.

Discussion

This review aimed to explore the interventions currently available to manage pain and other symptoms in patients with advanced pancreatic cancer. The findings of this review will now be discussed in relation to the existing literature. In addition, we will aim to identify areas of focus for further research into palliative care interventions for this patient group. The strength of this study is the inclusion of more recent studies since the Cochrane 2011 paper and the additional analysis of secondary outcomes, including quality of life and psychological.

Analgesia

The one study included in this review focusing on oral analgesia[9] found that while pain scores were similar in pregabalin and morphine combination therapy versus morphine monotherapy, the combination group required lower doses of opioids. The combination group did however note some issues with pregabalin side effects, which could be a limiting factor to medication titration. It is challenging to establish whether the side-effects in this group were due to the combinational nature of the analgesia or pregabalin independently. However, given a lower dose of morphine was required compared to the monotherapy group who had fewer side-effects, this can likely be attributed to the introduction of pregabalin.

Previous literature reviews exploring the use of gabapentinoids (including gabapentin and pregabalin) for neuropathic pain in cancer generally have found varying results. One systematic review and meta-analysis suggests that the combination of a gabapentinoid and an opioid did not significantly improve pain relief.[26] Other reviews have found that this combination can increase effectiveness,[21] as well as allow opioids to be reduced.[27] A Cochrane review concluded that there is currently limited good-quality evidence for the effectiveness of pregabalin in managing cancer-related neuropathic pain.[28]

Celiac plexus blocks

The 2011 Cochrane review provided high-quality evidence that celiac-plexus block provided superior short-term pain relief compared with oral analgesia monotherapy; however, its primary focus was on pain levels and opioid intake. This review builds on this foundation by incorporating recent evidence, including studies evaluating EUS-guided techniques, in addition to assessing a broader range of outcomes relevant to holistic palliative care.[12] It suggested that further randomized controlled trial were required to evaluate the efficacy of the, at that stage, new approach of EUS-CPN. This study found that there were the most analgesic benefits from CPN in the first 2 months following the block. Following this, differences were far smaller; however, increased benefit was still found. In addition, they also found evidence of improved quality of life in the CPN group largely related to improved physical functioning, reduced opioid-side effects, and improved mental health. This evidence is however limited due to inconsistent reporting across trials. These findings highlighted that analgesic efficacy alone may be insufficiency to improve overall quality of life, reinforcing the importance of a holistic palliative care approach. Evidence suggests the CPN provides effective short-term pain relief; however, data on long-term analgesic benefit remain inconsistent.

Five of the eight studies included in this review were published after this Cochrane review, and their findings have built upon the evidence presented. Crucially, what these most recent studies have clearly demonstrated is that EUS-CPN is effective in reducing pain in patients with advanced pancreatic cancer. These results appear to be maintained at least for a few months post-procedure. Few studies had a follow-up period longer than this to allow for further conclusions to be drawn; however, this is possibly challenging to achieve due to the short prognosis associated with advanced pancreatic cancer.

Several studies included in this review noted that patients were able to reduce the doses of opioid analgesia following treatment with nerve blocks. This is in keeping with evidence presented in the Cochrane review recently discussed.[29] This is a positive finding as the reduction in opioid doses should reduce incidence and severity of opioid related side effects, some of which overlap with already problematic symptoms associated with pancreatic cancer, such as nausea, reduced appetite, and fatigue.

This review did not find sufficient evidence to suggest that there is an improvement in quality of life associated with the use of nerve blocks, despite demonstration that this intervention is able to improve levels of pain. This suggests that there are other coexisting symptoms which continue to impact quality of life even when pain is adequately controlled. One recent cohort study identified fatigue, pain, and depression as the most common moderate-severe symptoms experienced by patients recently diagnosed with pancreatic cancer, alongside high levels of psychological distress and low score for well-being overall.[29] Further research focusing on symptoms experienced in patients with advanced pancreatic cancer noted fatigue, reduced appetite, and pain to be the most problematic symptoms experience.[30]

Current palliative care guidelines recommend a stepwise approach to cancer pain management. Interventional technique may be appropriate when pain is refractory to oral analgesia. The findings of this review support the consideration of the use of nerve blocks as an adjunct, as opposed to a replacement, for comprehensive palliative care management.[31]

Limitations

There are several limitations of this review on account of both the nature of the interventions being investigated and the lack of high-quality evidence available. Several studies, including Yasser's, do not have a true control group, which limits the quality of its results. Studies that involve patient-reported

outcomes are limited by issues of possible recall bias and the diverse nature in which individuals experience pain. This study excluded papers not available in English, which prevents a full understanding of all pancreatic cancer patients. In addition, one of the studies by Wyse used a quality of life index which does not a have a domain to measure the impact on pain, which may be why they found no correlation between improvement in pain and quality of life. The exclusion of smaller studies may have resulted in the omission of relevant data, particularly in areas of emerging techniques.

In addition, there was a large focus on the utilization on EUS-CPN for pain, and only one study which examined the use of oral analgesics as the primary intervention. Therefore, it is not possible to draw wider conclusions as these given data were only available from one study. The predominance of nerve block studies reflects the focus of available current literature rather than the intended emphasis of this review.

Future research

As previously mentioned, only one study included in the review focused on the use of oral neuropathic analgesia in the management of pain in advanced pancreatic cancer. The existing literature has been unable to come to a clear consensus on the benefit of its use in this context. Therefore, further research is needed to establish the effectiveness of neuropathic analgesia in managing pain associated with pancreatic cancer.

Additionally, we recognise that while pain is an important symptom to address in this patient group, there are also other, highly prevalent and disabling symptoms associated with advanced pancreatic cancer which are likely to impact upon quality of life even when pain is adequately controlled. Therefore, while ongoing research into the management of pain in pancreatic cancer is important, the inclusion of other prevalent symptoms such as fatigue, appetite, and psychological symptoms as measured outcomes in future studies would be appropriate.

Conclusion

This review outlines the treatments available for pain in patients with advanced pancreatic cancer. We included one study that found no clear evidence that the addition of neuropathic agents improves pain scores, but may allow for reduced opioid doses and associated side effects. Celiac plexus blocks have increasing evidence to support their use as effective and well-tolerated interventions in the management of pain associated with pancreatic cancer.

As secondary outcomes, we found that the combination of morphine and pregabalin may be associated with improved functional status, improved quality of life, and reduced rates of anxiety and depression. There was little evidence from this review to suggest that the utilization of nerve blocks improves quality of life, despite improvements in pain scores.

Further research is needed into utilization of oral analgesia, including neuropathic agents, for pain, as well as focusing on other prevalent and distressing symptoms associated with advanced pancreatic cancer, which are likely to affect quality of life even when pain control is optimized.

Author contributions

ESJ and BL designed the study. ESJ, CT, CK and LH analysed the data. All authors revised the paper and approved the final manuscript.

Data availability statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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Conflicts of interest

There are no conflicts of interest.

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Appendix 1: Literature search

Search	Search term	Number of results
1	Pancreatic	198,705
2	Pancreas	61,280
3	Cancer	2,141,528
4	Malignancy	38,936
5	Metastatic	183,714
6	Palliative	61,408
7	3 OR 4 OR 5	2,271,338
8	1 OR 2	256,267
9	7 AND 8	68,501
10	5 OR 6	243,811
11	9 AND 10	6527
12	Pain	440,264
13	Analgesia	52,235
14	Opioid	82,878
15	Neuropathic	25,296
16	Nerve block	10,662
17	Celiac plexus	980
18	12 OR 13 OR 14 OR 15 OR 16 OR 17	568,463
19	11 AND 18	1646