



Mini Review

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Current Evidence on the Surgical Treatment of Pancreatic Cancer Related Pain-A Mini-Review

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Abstract

Pancreatic cancer-related pain significantly impairs quality of life in patients with inoperable pancreatic cancer, a condition associated with poor prognosis. Despite the standard use of opioids and non-steroidal anti-inflammatory drugs for pain management, many patients experience refractory pain that remains unsolved despite escalating of the doses of medication. In those cases, interventional pain control techniques may play an important therapeutic role. This mini review explores surgical options within that field, focusing on thoracoscopic splanchnicectomy and neurolytic techniques. The review highlights the challenges in interpreting outcomes due to methodological variability in pain scoring and quality of life measurements. Pure statistical significance in numeric pain relief or raw quality of life scoring does not always equate to meaningful clinical benefit, emphasizing the need for careful patient selection and comprehensive approach to evaluation of outcomes. While interventional techniques can alleviate pancreatic cancer-related pain (PCRP) and improve quality of life, they do not prolong survival, particularly in patients with advanced pancreatic cancer. These findings underscore the importance of a multidisciplinary approach in managing PCRP and tailoring treatment strategies to individual patient needs.

Key words: Pancreatic Cancer; Pain; Quality of Life; Splanchnicectomy; Neurolysis

Abbreviations: PC: Pancreatic Cancer; QOL: Quality of Life; PCRP: Pancreatic Cancer-Related Pain; TS: Thoracoscopic Splanchnicectomy; AJCC: American Joint Committee on Cancer; EUS-CPN: Endoscopic Ultrasound Guided Celiac Plexus Neurolysis

Introduction

Annually eight per 100 000 people are newly diagnosed with pancreatic cancer (PC), which is expected to become a second leading cause of cancer-related death in the western countries [1, 2]. Despite many efforts to improve the prognosis by earlier detection and novel therapies, the prognosis remains poor and one-year survival is estimated to be less than 20% [3]. As symptoms occur late, only approximately 20% of patients qualify for surgical resection [4]. Most common symptoms of PC are nausea, abdominal and back pain, weight loss and lack of appetite. All these symptoms contribute to decreased quality of life (QOL) in pancreatic cancer, but severe abdominal and back pancreatic cancer-related pain (PCRP) is the most debilitating clinical manifestations of PC and its intensity directly correlates with the disease progression [5-8]. PCRP is also the main determinant of decrease in quality of life measured among PC patients [8].

Moreover, pain intensity significantly influences the quality of life (QoL) in pancreatic cancer patients, as evidenced by various studies. High pain levels correlate with increased symptom burden, emotional distress, and functional impairment, ultimately leading to a diminished QoL. Pain intensity is linked to emotional factors such as pain catastrophizing, which negatively affects QoL [9].

QOL is a multidimensional concept, importance of which has been underlined in many clinical trials involving PC. Due to character of symptoms, low survival rate, numerous side effects of treatment, and the PCRP itself, PC patients are group with significantly decreased QOL. PCRP, besides being bad sensation, also contributes to lack of appetite, higher anxiety and depression symptoms and worse survival [10-12]. Opioids and non-steroidal anti-inflammatory drugs remain a standard for pain management;

however, many interventional methods were proposed to alleviate refractory pain and improve QOL [6, 7, 12-15]. The purpose of this mini review is to present a brief overview and rationale for consideration of surgical management of PCRP.

PCRP has a complex etiology, however understanding its pathophysiology is crucial for conscious using of surgical technique. The main mechanisms contributing to PCRP sensation are: i) pancreatic neuropathy (with perineural infiltration of cancer cells), ii) autonomic plexus invasion, iii) local progression (malignant obstruction of pancreato-biliary tree), iv) distant metastases, v) high interleukin-6 levels and overexpression of indoleamine 2,3-dioxygenase (with subsequent disturbance in tryptophan and serotonin metabolism) [16]. Surgical strategies involve destruction of PCRP signalling by interference in autonomic nervous system. Therefore, it can be effective for pancreatic neuropathic and autonomic plexus invasion components. Although investigated [17, 18], routine application of cytoreductive surgery does not seem to be beneficial for PC patients. Local progression is usually resolved by use of endoscopic interventions, which are not a subject of this review, however pancreato-biliary tree obstruction leading to intrapancreatic enzyme activation and elevated intraductal pressure should be considered as a clinical priority. Surgical strategies, defined as invasive interventions, can be specifically categorized into thoracoscopic splanchnicectomy (TS) and neurolysis of the celiac plexus or celiac ganglia.

Neurolytic Techniques

Celiac plexus neurolysis (CPN) is a pivotal intervention for managing pain in patients with pancreatic cancer, particularly those with inoperable tumors. This procedure involves the injection of a neurolytic agent, typically ethanol or phenol, into the celiac plexus to disrupt pain transmission. The technique can be performed using various imaging modalities, including CT [19] and endoscopic ultrasound (EUS) [20], ensuring precision and safety during the procedure.

Neurolysis of celiac plexus or celiac ganglia is well-established, widely discussed technique of PCRP alleviation. The technique of neurolysis has been extensively studied, focusing on aspects such as procedure visualization [21,22], choice of neurolytic agent [23], target structures (celiac plexus or celiac ganglia) [24], and variations in approach, including bilateral versus unilateral [25] and central versus peripheral techniques [6]. In a meta-analysis by Asif et al. [6] endoscopic ultrasound guided celiac plexus neurolysis (EUS-CPN) has been reported to provide pain relief in as much as 70% of patients with central neurolysis technique. In reviews by Arcidiacono et al. [26] (six randomized-controlled trials), Nagels et al. [27] (five randomized-controlled trials), Zhong et al. [28] (eight randomized-controlled trials), the pain scores after celiac plexus neurolysis were significantly lower at four weeks [29]. Pain scores at eight weeks did not show a significant reduction in the meta-analyses conducted by Nagels

et al. [27] and Zhong et al. [28], although a trend toward lower scores was observed in the analysis by Arcidiacono et al. [26]. Therefore, the expected pain relief effect is relatively transient; however, the procedure can be repeated. Nevertheless, data on the efficacy of repeated procedures remain limited. Complications associated with neurolytic techniques are rare and generally mild. In the meta-analysis by Asif et al. [6], complications were reported in 0.2% of procedures, while Alvarez-Sanchez et al. [30] reported a higher incidence of 21%. Despite the variability in reported complication rates, the benefits of EUS-CPN appear to outweigh the associated risks.

Thoracoscopic Splanchnicectomy

Thoracoscopic splanchnicectomy is a minimally invasive surgical procedure used to treat intractable abdominal pain, primarily in patients with chronic pancreatitis or pancreatic cancer [31]. It involves the division of the greater and lesser splanchnic nerves using a thoracoscopic approach, which allows for direct visualization and precise targeting of the nerves [32]. This technique is performed under general anesthesia, with the patient in a hemilateral position or prone position, with isolated bronchus intubation or with positive CO₂ intrathoracic pressure [31, 32].

As mentioned above, thoracoscopic splanchnicectomy can be performed using either a bilateral or unilateral approach. However, an analysis of multiple studies by Masuda et al. [33] found no clear advantage of the bilateral approach. Instead, a unilateral approach was recommended, with the side of intervention determined based on the specific location of the patient's pain, i.e., predominantly left-sided. Complications associated with TS are rare and, in addition to common surgical risks associated with thoracoscopy- such as pneumothorax, transient intercostal neuralgia, and bleeding-they may include transient hypotension, diarrhoea, and pneumonia. TS has not been widely instituted as a standard method of PCRP treatment, however, several reports on its effect on QOL, pain relief and survival can still be found in the recent literature [11, 34-36]. The limited use of TS can be attributed to its invasive nature and the growing availability of less invasive alternatives, such as neurolysis, stereotactic body radiotherapy, and high-intensity ultrasound. Furthermore, there is insufficient evidence to favor TS over these less invasive techniques. A prospective study comparing TS and neurolysis found no significant superiority of either approach [32]. Although high-level evidence-based recommendations are lacking, TS is regarded as a more radical alternative to neurolytic techniques and may be considered a second-line treatment option for PCRP.

Discussion

The overall effect of TS and neurolysis on survival was investigated in meta-analysis by Ye et al. [11]. Analysis of four randomized-controlled trials and two prospective studies revealed any relevant effect of neurolysis of TS on overall survival.

Subgroup analysis based on tumor stage in this study revealed that overall survival was reduced in patients with American Joint Committee on Cancer (AJCC) stage III, but not in those with stage IV disease. While improving overall survival is not the primary goal of interventional techniques in PCRP treatment, these findings underscore the need for caution and careful patient selection. Both surgical techniques of TS and neurolysis were proven effective in alleviating pain [6, 33], however there are several considerations regarding the data interpretation. The substantial heterogeneity in pain scoring methodology, QOL measurements, and various endpoints in the reported results makes interpreting data on the efficacy of pain-alleviating techniques challenging. Furthermore, relying solely on statistical differences in pain and QOL scores is not an optimal approach for clinical decision-making. Pure statistical significance in changes to pain and QOL measures may represent a mathematical outcome rather than a true clinical benefit.

Since pain and QOL are inherently subjective experiences, their representation through scales and subsequent statistical analyses should be interpreted with caution, considering the significant potential for bias. A common clinical measure of procedural success is a reduction of three points in the Visual Analog Scale pain score. However, this level of improvement may not be sufficient for all patients, many of whom may still require pharmacological support. Researchers should also use clinically significant and various psychometric tools to monitor the patient's response to the therapy as closely as possible [7]. Another crucial consideration in selecting candidates for interventional pain treatment is the potential for complications. Although rare, these complications could significantly impair QOL and overall survival, particularly in patients with a poor prognosis.

Conclusion

Interventional treatment of pancreatic cancer-related pain PCRP is an effective option for alleviating refractory pain that significantly impairs the quality of life in patients with inoperable PC. Clinical decision-making for the interventional treatment of PCRP involves several important considerations. Interventional techniques do not address all mechanisms of PCRP, and patients may continue to depend on pharmacological support. EUS-CPN is regarded as the most effective and minimally invasive option, while TS may be considered for patients ineligible for EUS-CPN or as a second-line treatment. Notably, surgical interventions do not improve overall survival and should be used with caution in patients with AJCC stage III pancreatic cancer. Data on pain relief outcomes should not rely solely on statistical analyses but must be interpreted alongside demonstrated clinical benefits. Although complications are rare, their potential impact on QOL should not be underestimated. Despite the availability of interventional and pharmacological treatments, the prognosis for this patient group remains poor, emphasizing the need for careful patient selection and comprehensive care. The authors declare no conflicts of

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