Pain in patients with pancreatic cancer: prevalence, mechanisms, management and future developments.

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Abstract/ Summary

Pain affects approximately 80% of patients with pancreatic cancer, with half requiring strong opioid analgesia, namely: morphine-based drugs on step three of the WHO analgesic ladder (as opposed to the weak opioids: codeine and tramadol). The presence of pain is associated with reduced survival. This article reviews the literature regarding pain: prevalence, mechanisms, pharmacological and endoscopic treatments, and identifies areas for research to develop individualised patient pain management pathways. The online literature review was conducted through: PubMed, Clinical Key, Uptodate and NICE Evidence. There are two principal mechanisms for pain: pancreatic duct obstruction and pancreatic neuropathy which respectively activate mechanical and chemical nociceptors. In pancreatic neuropathy several histological, molecular and immunological changes occur which correlate with pain including: transient receptor potential cation channel activation and mast cell infiltration. Current pain management is empirical rather aetiology-based and is informed by the WHO analgesic ladder for first line therapies, and then endoscopic ultrasound guided celiac plexus neurolysis (EUS-CPN) in patients with resistant pain. For EUS-CPN, there is only one clinical trial reporting a benefit, which has limited generalisability. Case series report pancreatic duct stenting (PDS) gives effective analgesia, but there are no clinical trials. Progress in understanding the mechanisms for pain and when this occurs in the natural history, together with assessing new therapies both pharmacological and endoscopic, will enable individualised care and may improve patients' quality of life and survival.

Keywords: pancreatic cancer, pain, endoscopic ultrasound-guided coeliac plexus neurolysis, pancreatic duct stenting, pharmacotherapy, analgesia.

Introduction

Pancreatic cancer has the worst prognosis of any tumour and there has been little improvement in survival in recent decades despite the availability of new treatments. Approximately 266,000 pancreatic cancer related deaths are recorded worldwide every year, making it the fourth commonest cause of cancer-related death (3), (4). Most patients have surgically inoperable disease and are referred for palliative care. This paper reviews several

aspects of pain in patients with pancreatic cancer including: its prevalence, the mechanisms of pain, the pharmacological and endoscopic treatment options and future developments in this clinical area. The literature review was conducted online from February to June 2016, using: PubMed, Clinical Key, Uptodate and NICE Evidence Search. Different search terms were used for different sections of the article, namely: 'prevalence of pain in pancreatic cancer', 'pancreatic neuropathy', 'pharmacotherapy in pancreatic cancer pain', 'endoscopic ultrasound guided coeliac plexus neurolysis', 'pancreatic duct stent' and ' chemotherapy for pain relief'. Included papers were: systematic reviews, randomised controlled trials, cohort studies, case-control studies and case reports. The bibliographies were scanned for other relevant references not detected at the initial search.

Prevalence of pain at presentation and its clinical significance

Abdominal pain in patients with pancreatic cancer is a common complication, associated with reduced performance status and decreased survival. Pain is the third commonest symptom (72%) in patients with cancer in the head of pancreas after weight loss (92%) and jaundice (82%) and second (87%) when the tumour is in the body or tail (6). At diagnosis 30-40% of patients report abdominal pain, 80% develop pain as the cancer progresses and in 44% of these it is described as severe (7). Pain scores are nearly four times higher in patients with impaired performance status scores i.e. ECOG (Eastern Co-operative Group) ≥1 or KPS (Karnofsky Performance Score) ≤80%, compared to those with normal scores ($p< 0.001$) (8). Pain at diagnosis predicted poor survival in a case series of 136 patients who underwent palliative gastric bypass [hazard ratio for death of patients with pain to patients without was 1.61 (95%CI, 1.06 -2.44) ($p= 0.025$)] (9). The median survival times during an 18 month follow up period for patients with: 'occasional', 'daily' and 'daily and strong' pain were: 9.4, 7.6 and 3.5 months respectively ($p=0.0017$) (9). Another observational study of 149 patients, who underwent pancreatic tumour resection were classed pre-operatively into three pain groups based on their pain intensity and frequency, and measured survival as the time between surgery and cancer-specific death (14). The median survivals for patients with no pain, mild pain and moderate to severe pain were 21.5, 15.0 and 10.0 months respectively ($P= 0.0015$) (14). It is unclear why patients with pain have worse survival than those without and whether better analgesia would prolong survival. Pain is probably an indicator of other predictors of survival such as advanced cancer staging or poor nutritional status and such patients have impaired performance status scores, therefore are more likely to be ineligible for chemotherapy. Importantly, the natural history of pain, including its time of onset after diagnosis, progression and clinical characteristics, are poorly documented in the literature, an understanding of which would help guide the timing of therapeutic interventions to promote better analgesia.

Pain mechanisms in pancreatic cancer

Pancreatic neuroanatomy

An appreciation of the neuroanatomy of the pancreas is important to understand the mechanisms of pain and the potential for therapeutic options. There are complex neuronal pathways which transmit pain signals generated in the pancreas itself to the cerebral cortex. The gland is innervated by both sympathetic and parasympathetic fibres of the autonomic nervous system. Mechanical or chemical noxious stimuli activate nerve endings within the gland releasing several neurotransmitters (10) including the endecapeptide Substance P (SP)

and the 37 amino-acid peptide Calcitonine Gene Related Peptide (10). Afferent neurons from the pancreas connect to the coeliac plexus and the electrical signals are then transmitted through the dorsal horns to the dorsal route ganglia at the T2- L2 spinal level. Impulses ascend through the spinothalamic, spinoreticular, spinomesencephalic, spinohypothalamic fibres to higher centres in the: thalamus, hypothalamous, brainstem and terminate in the primary somatosensory cerebral cortex (10). The stimulus for pain in pancreatic cancer is due to both neural activation and nerve damage. The longstanding exposure to noxious stimuli, plus the release of molecular products from the tumour, promote altered neuroplasticity including altered pain perception (allodynia), hyperexcitability of the nervous system, inflammatory cell infiltration and activation of mitogenic pathways in afferent neurons which are quiescent in normal pancreatic tissue. There are two principal mechanisms which probably lead to pain in pancreatic cancer namely: ductal obstruction and pancreatic neuropathy.

Pancreatic Ductal Obstruction

Pancreatic duct obstruction by the cancer typically causes epigastric or right upper quadrant pain and is provoked by release of pancreatic juices on eating. The mechanism of ductal obstructive pain has not been fully investigated, however, it is thought to be similar to that of chronic pancreatitis. Occlusion of the duct blocks the flow of digestive enzymes and leads to increased interstitial and intraductal pressures (11). These promote parenchymal oedema and decreased pancreatic blood flow and, similar to the pain of compartment syndromes, generate ischaemic pain. Obstructive flow causes dilatation of the pancreatic duct, which is detectable on CT, MR imaging of the pancreas and ERCP. The correlation between *obstructive type pain* and *radiological duct dilatation* has not been reported in the literature. Biliary stenting for jaundice may also relieve pancreatic ductal obstruction and hypothetically promote analgesia.

Several clinical case series have reported that pancreatic ductal stenting in patients with typical obstructive-type pancreatic abdominal pain and radiologically confirmed pancreatic duct dilatation led to either a complete resolution or at least improvement of the pain (12), (13) (table 1). These clinical studies did not include a comparative group where patients were treated with drug analgesia only. Duct stenting involves deep cannulation of the major pancreatic duct and insertion of a guidewire across the stricture. Dilatation is then performed, using either a catheter or a balloon followed by stent insertion. The most recent such case series performed pancreatic stenting in 20 patients with typical obstructive pain and documented decreases in: the (VAS) pain score compared to pre-treatment [from 6.7 points to 3.1 points at 4 weeks ($P < 0.001$)], in fentanyl consumption [from 85.5 µg/h, to 57.9 µg/h at 4 weeks ($P < 0.01$), to 60.5 µg/h at 8 weeks ($P<0.01$) and to 64.1 µg/h at 12 weeks ($P < 0.01$)]. Four other case series have reported total pain resolution between 41% to 87% of patients (13). Bleeding and dislodgement of the stent were documented but were not associated with mortality (13). In the above case series, none of the 70 patients who underwent pancreatic duct stenting developed clinical pancreatitis, cholangitis, ductal rupture, guidewire fracture requiring surgical removal or stent migration into the gland. These are complications described in patients stented for other pathologies (chronic pancreatitis, pancreas divisium, benign pancreatic duct strictures, autoimmune cholangiopathy). The current literature reports, namely clinical series, that pancreatic duct stenting is safe and beneficial for inducing pain relief and decreasing opioid consumption. Randomised controlled trials are required to investigate any efficacy of stenting before it may be considered as part of standard care for inducing analgesia. Such trials would be logistically difficult to conduct as patients at this time maybe

undergoing other intensive treatments such as chemotherapy and endoscopic relief of jaundice.

Pancreatic neuropathy

The second mechanism for the generation of pain involves direct damage to the pancreatic nerves themselves. Several histopathological and molecular changes have been observed in pancreatic cancer specimens which are associated with pain namely: increased nerve density and nerve hypertrophy, peri- and endo- neural cancer cell invasion, altered expression of nociceptors, parenchymal immune cell infiltration in the pancreas and release of neurotrophic growth factors which are undetectable in the normal pancreas. These changes comprise a phenomenon referred to either as: pancreatic neuropathy, neuritis or neurogenic inflammation. Pancreatic tissue architecture is distorted by cancer cell infiltration, promoting activation of local immune cells and further damage due to inflammation (10).

The first histological observation in pancreatic neuropathy, the number of nerve endings per unit area (nerve density) in the pancreas and the total nerve area (nerve hypertrophy) were examined in 149 human surgical specimens post-pancreatic cancer resection (14). Prior to surgery pain was classified based firstly on its intensity (0=none, 1= mild, 2= moderate, 3= strong) and secondly its frequency (3=daily, 2= weekly, 1= monthly) and the multiple of the two was the registered pain score. Nerve density and hypertrophy were increased 14 and 2 times respectively, compared to that in non-cancerous tissue obtained from organ donors ($p<0.01$) (14). Patients with pancreatic cancer who reported *severe pain* had a threefold greater nerve hypertrophy compared to those with mild pain ($P<0.0001$) or were *pain free* ($P<0.0001$). Immune cell infiltration, perineural invasion and neurotrophic cytokines released by the tumour and immune cells lead to mitotic phenomena that increased the number and size of pancreatic neurons (14).

The second histopathological observation in pancreatic neuropathy is the invasion of malignant cells into the perineurium, the connective tissue that surrounds and supports the neurons which is detected in 79% of pancreatic adenocarcinomas (14). In adenocarcinoma, the invasion is typically more extensive than in the other neoplasms as it can also involve the endoneurium, axons and Schwann cells. In pNETS and IPMNs cancer cell invasion is restricted to the perineurium. In the above series (14) the severity of neural invasion was classified as either: i) no invasion= 0, ii) perineural invasion=1 or iii) endoneural invasion=3 and the frequency as i) absent=0. ii) low= 1, iii) frequent= 2 and iv) excessive= 3. The multiple of those two was the mean *neural cancer cell invasion score*. Patients reporting *severe pain* had nearly the twice mean *neural cancer cell invasion score* compared to those with *no pain* ($p< 0.05$) and *mild pain* ($p<0.001$) (14) (scores were 3.8, 2 and 1.8 respectively).

Thirdly, local inflammation activates the expression of TRPV1 (transient receptor potential cation channel) in the intrapancreatic nerves endings, a cation channel that conducts sodium and calcium influx into the neurons and facilitates the generation of action potentials (15). This releases Substance P (SP) and Calcitonin Gene- Related Peptide (CGRP) (10), (15), two neurotransmitters which conduct pain signals from the parenchyma to the dorsal root ganglia. These also have cytokine-like properties including: chemotaxis, neutrophil extravasation, further macrophage activation, mast cell degranulation and release of pro-inflammatory molecules namely TNF-a, IL1,-2,-6,-8 (14). TRPV1 is overexpressed in pancreatic cancer tissue and is associated with the development of pain (14). The pain scores of 32 patients [mean age 64.1 years] prior to Whipple's surgery were measured and classified into one of three groups

(1= no pain, 2= controlled pain with non-steroidal anti- inflammatory drugs, 3= use of opioid analgesics). Post-operative real time PCR (polymerase chain reaction) and immunohistochemistry quantified and localised TVPR1 in the resected pancreas. There was a positive linear association between TVRP1 mRNA levels and the intensity of pain reported ($p< 0.0001$). This over-expression of the cation channel facilitates the influx of cations into the nociceptive neurons and may be responsible for their increased sensitivity and therefore lowers the threshold for generating action potentials promoting hyperalgesia (a weak stimulant perceived as strong one), hyperexcitability and allodynia (perception of a non-painful stimulant as painful) (16).

Fourthly, immune cell clusters around the local pancreatic nerves are observed in pancreatic cancer tissue (17). These clusters are predominantly mast cells, T-lymphocytes and macrophages whilst others, such as eosinophils, B-lymphocytes and plasma cells, are rarely present (17). A clinical study investigated the association between reported pain and the presence of specific types of immune cells, in 20 tissue specimens from patients [mean age 66 years] who underwent pancreatectomy. Prior to surgery, pain was documented in participants. Patients who reported pain had pancreatic tissue infiltrated predominantly by mast cells, as opposed to those without pain where there was infiltration by T-lymphocytes ($p <0.05$) (17). This observation, in addition to the fact that SP, CGRP and NGF bind to mast cells receptors and promote their degranulation and release of proteases, tryptases and histamine supports a link between the immune and the nerve systems in the generation of pancreatic cancer pain (17).

Finally, another important molecule in the nociceptive pathway is Nerve Growth Factor (NGF). This is a neuropeptide, normally undetectable in the healthy pancreas but secreted by fibroblasts, immune, pancreatic and Schwann cells in response to neural injury to promote repair and regeneration (15). NGF is a pro-inflammatory cytokine, promoting chemotaxis and further release of SP and CGRP. This peptide binds to the TrkA receptor (Tropomyocin kinase receptor), which promotes cancer cell proliferation in the perineural spaces (25). NGF and TrkA mRNA levels were increased 2.7-fold and 5.6-fold, respectively ($P <0.05$ and $P <0.05$) in pancreatic cancer tissue and were associated with high pain scores ($P <0.01$) (14). Moreover, NGF caused hyperalgesia when exogenously administered in mice (14).

In summary, there are several histopathological and molecular changes contributing to the generation of neuropathic pain in patients with pancreatic cancer, although the relative contributions of each to symptoms are unknown. Clarifying this uncertainty is important, as it may lead to the development of new pharmacological agents to target these systems such as TVRP1 blockers or NGF, SP, CGRP antagonists.

Analgesic drugs for pancreatic cancer pain

The requirement for analgesia should always be assessed in patients with pancreatic cancer by clinicians at diagnosis and at all subsequent follow up visits. There are both pharmacological and endoscopic options for relieving pain but drugs are invariably prescribed initially. The main therapeutic aim is to prevent pain, rather than control pain when it is already established. The choice of appropriate pharmacotherapy is informed by the WHO analgesic ladder (18), starting with prescribing mild painkillers, such as paracetamol and non-steroidal anti-inflammatory

drugs. Clinicians may progress to prescribing weak opioids, such as codeine, dihydrocodeine or tramadol (18). If these drugs are ineffective, stronger morphine-based analgesics are indicated. If the patient is unable to tolerate oral medications, strong opioid analgesics can be administered transdermaly. Alfentanyl is used in patients with renal impairment, as it does not accumulate systemically like other opioid analgesics. Formulations containing combinations of oxycodone and the opioid antagonist naloxone minimise opioid-related side effects, particularly constipation. Other adverse effects include: nausea, sedation, cough suppression, dry mouth, and pruritus all of which impair patients' quality of life (19). When strong opioids have failed methadone and ketamine, two NMDA (N-methyl-D –aspartate) receptor antagonists are options (19). NMDA acts in the dorsal route ganglia and transmits pain signals to the central nervous system. Patients with pancreatic cancer have severe gastrointestinal symptoms due to the cancer itself which are similar to the side effects of the opioid analgesics themselves and complicate their use. For this reason there are alternative routes of administration of analgesics including rectal, transdermal and subcutaneous ones (18).

Tricyclic antidepressants (TCAs) and gabapentinoids also have a role in controlling neuropathic pain. The neuroplasticity of the central nervous system has been studied in malignant and non-malignant peripheral neuropathies and other painful disorders, such as non-erosive oesophageal reflux disease (NERD) and irritable bowel syndrome (IBS). This may be altered when peripheral pain persists, leading to hyperexcitability of neurons and lowering of pain thresholds to stimuli that would not normally generate nociceptive signals in healthy individuals (19). Tricyclic antidepressants (TCAs) and gabapentinoids both have peripheral and central pharmacological actions and have been investigated for their analgesic effects in patients with several types of cancer. The TCAs, amitriptyline and nortriptyline, antagonise centrally-acting neurotransmitters at receptors, namely norepinephrine and NMDA, and can be used as adjuvant treatments in the WHO ladder of drugs. However, TCAs have anticholinergic side effects namely: dry mouth, constipation, urinary retention, blurred vision and orthostatic hypertension which can limit their use (19). Gabapentinoids, i.e. gabapentin and pregabalin, block calcium channels in nociceptors and decrease the release of substance P, norepinephrine and glutamate. They are effective treatments for allodynia, although their therapeutic action requires several weeks to become established (19). Side effects of gabapentinoids include: dizziness, peripheral oedema, dry mouth and somnolence (19). Table 2 summarises the most commonly used analgesics in treating pain in pancreatic cancer.

Treatment of pancreatic cancer pain often requires use of combinations of analgesics and a regular review of their efficacy, tolerance and side effects. As the pain mechanisms are not yet fully understood and several mechanisms can promote pain, use of pharmacotherapy is currently empirical instead of mechanism-based. TCAs, gabapentinoids, and NMDA receptor antagonists (ketamine and methadone) inhibit pathways known to contribute to pain in pancreatic cancer although, those that opioids influence are uncertain. More research is required to understand the relevant pathways, where opioid receptors are expressed and the interactions between these neurotransmitters. An appreciation of the pain mechanisms will ultimately lead to improved analgesia and enable clinicians to prescribe medications on a more personalised basis.

Endoscopic Ultrasound Guided Celiac Plexus Neurolysis (EUS-CPN)

Relevant anatomy and technique

When analgesics do not give adequate pain relief, endoscopic techniques can be employed. Celiac plexus neurolysis (CPN) is the irreversible chemical ablation of this structure which consequently interrupts the nociceptive impulses originating in the pancreas. CPN can promote pain relief in patients with either pancreatic cancer or chronic pancreatitis (20) (21). An appreciation of the relevant neuroanatomy is important when considering application of this technique. Preganglionic sympathetic interconnecting fibres of the greater and lesser splachnic nerves, originating from the upper abdominal viscera, namely: pancreas, liver, spleen, kidneys, adrenals and alimentary track between stomach and transverse colon and connect to form the upper abdominal ganglia, i.e. the celiac, superior mesenteric and aorticorenal ganglia (23). The celiac ganglia are located in the retroperitoneal space, laterally and inferiorly to the root of the celiac artery at the T12-L2 level (22). Inferior to the celiac artery is the superior mesenteric ganglion, above the superior border of the superior mesenteric artery. The complex of the celiac, the superior and aorticorenal mesenteric ganglia form the celiac plexus. The number of ganglia in the plexus varies between two to five (23). The efferent nerve fibres that exit the celiac ganglia, constitute the greater and lesser splachnic nerves which then synapse at the dorsal route ganglia and enter the spinal cord. Nerve fibres from other intra-abdominal organs connect to the celiac plexus namely: the oesophagus, stomach, liver, biliary ducts, adrenal glands, small and large intestines and abdominal blood vessels.

Different techniques to approach and destroy the celiac ganglia have evolved historically namely: surgical, fluoroscopic-guided, computerised tomography (CT)- guided, ultrasound-guided and more recently endoscopic ultrasound guided (EUS) methods. The latter is now the preferred technique as it allows direct visualisation of the celiac ganglia in 70-80% of patients (23). At EUS, an ultrasound probe, incorporated into the tip of the gastroscope, is placed against the lesser curvature of the stomach enabling the sonographer to visualise the abdominal aorta and the root of the celiac artery (21). This allows, injection of local anaesthetic followed by neurolytic, dehydrated alcohol into both sides of the celiac trunk (bilateral injection technique) (21). Alternatively a single injection can be administered at the base of the celiac trunk (central injection technique). The potential benefit of bilateral injection is the wider spread of the neurolytic agent and therefore greater pain relief. However, this is technically more difficult as it requires double puncture and deeper needle insertion (24). Recently, a new practice has emerged where if the celiac ganglia are directly visualised the needle is advanced further and injection is given directly into the ganglia instead of around, a technique called Ganglia Plexus Neurolysis (21). Another variation of the EUS-guided technique described by a Japanese group is injection at the level of the superior mesenteric artery root. This later technique achieves better distribution of the injectate and is called Endoscopic Ultrasound Guided Broad Plexus Neurolysis (EUS-guided BPN) (25).

Efficacy of EUS-CPN

The efficacy of EUS-CPN in inducing analgesia, over conventional drug therapy has been reported in one clinical trial (28) and three meta-analysis of case series (29), (22), (30). Early administration of EUS-CPN at diagnosis versus conventional drug therapy was investigated in a randomised controlled trial of 98 patients with histologically proven, locally advanced

pancreatic adenocarcinoma, with pain assessed at 1 and 3 months post-procedure. The primary outcomes were differences between trial arms in the mean percentage and mean absolute changes in the 7-point Likert pain score. The secondary outcomes were: the differences in the mean percentage and mean absolute change in morphine equivalent units (MEQ) consumption, mean percentage change in DDQ-15 score (Digestive Disease Quality of life instrument) and survival (28). The baseline demographic and clinical characteristics at diagnosis were comparable between the two groups and the mean daily morphine consumptions in morphine equivalent units were 36.8 and 41.9 for the pharmacotherapy and the intervention group, respectively. The differences between the mean percentage changes in Likert-pain score between the two groups at 1 month was -28.9 % (95%CI, -67 to 2.8) (p=0.09) and at 3 months -60.7 % (95% CI, -86.6 to -25.5) (P=0.01) in favour of the EUS-CPN group (28). The mean morphine consumption increased in both groups by the first month [mean absolute change in morphine consumption +54 MEQ (CI 95% +20 to +96) in pharmacotherapy group vs +53 MEQ (CI 95%, +28 to +89) in the EUS-CPN group (P=0.99)]. This plateaued for the EUS-CPN patients at 3 months [+50 MEQ (CI 95%, +28 to +79)], but continued to increase in the pharmacotherapy group [+100 MEQ (CI 95%, +49 to +180) (P=0.10)] (28). Quality of life scores improved in both arms but there was no statistically significant difference between them and the mean survival was similar in both groups (data not provided) (28). To date, this is the only clinical trial, of which we are aware, to compare EUS-CPN against pharmacotherapy and has provided evidence of superiority of EUS-CPN in terms of providing pain relief and some evidence of lower use of morphine. However, there are several limitations to this study: the trial excluded 484 out of 580 patients (83.4%) at diagnosis including those with metastatic disease, patients with estimated survival less than 3 months some of whom may potentially benefit from EUS-CPN. Therefore, the generalizability of the results in patients with pancreatic cancer was limited.

The complications of EUS-CPN, which are usually minor, were reported in the one clinical trial and several case series namely: diarrhoea, postural hypotension, alcohol inebriation and temporary exacerbation of pain. Diarrhoea is usually transient, lasts between 2 days to a week and responds well to loperamide. Typically, postural hypotension develops immediately after the procedure in the endoscopy recovery area when patients start mobilising and rapidly responds to intravenous fluids. Both diarrhoea and postural hypotension occur as the result of the unopposed parasympathetic activity after destruction of the sympathetic fibres in the coeliac ganglia. Spinal stroke distal to the T10 neurotome with permanent paraplegia is a severe complication of EUS-CPN, although this is exceptionally rare and has only been described in two case reports of one patient each (26), (27). In the current bibliography no lethal complications of EUS-CPN were reported and therefore the data suggests that EUS-CPN is safe.

Three meta-analyses of case series provided some evidence of the efficacy of EUS-CPN (29) (22) (30). The most recent and robust included 6 case series of 295 patients in total and reported a 4-5 points decrease in the pain visual analogue score (1-10 scale) at 1,2,4, 8 and 12 weeks after EUS-CPN ($p< 0.001$ for all the follow up times) (30). The other two meta-analyses reported similar results: Puli et al (N=283) reported pain relief in 80% (95% CI, 74.4- 85.2) and Kauffman et al reviewed 3 studies (2 of which were abstracts) (N=119), with pain relief in 72.5% (no CI or p-values displayed)]. The results of the largest clinical studies assessing EUS-CPN efficacy are summarised in table 3. Currently, there are no clinical trials assessing EUS-CPN in patients who develop pain later after diagnosis. Clinical trials of EUS-CPN are required in

broader patient groups to confirm if morphine requirements are less, and importantly to investigate if the administration of EUS-CPN at different time intervals post-diagnosis can improve the efficacy of the technique as pain can develop later in the natural history of the cancer. Such trials should also involve patients who may not have pain at diagnosis and those with metastatic disease.

Predictive factors for response to EUS-CPN

Between 20-28% of patients have a limited analgesic response to EUS-CPN (30), (29), (22). Several observational studies have assessed predictive factors for response or suggested variations of the procedure to achieve a higher efficacy (31), (32), (25), (24). Direct infiltration of the celiac plexus by the cancer as shown on CT and restricted spread of the injectate predicted a negative or limited response to the procedure. In an observational study, 47 patients with inoperable pancreatic cancer and a pain visual analogue score (VAS) ≥ 5 (0-10 scale) received EUS-CPN. Most had no benefit from opioid analgesics, although a small proportion had EUS-CPN without preceding narcotic use (number not stated) (31). The injectate contained radiological contrast and computerised tomography (CT) immediately after EUS-CPN illustrated the distribution of the injectate (31). Patients' VAS score was re-assessed 7 days post-EUS-CPN and patients were classified into either 'complete responders' (VAS= 0 or 1 or decrease by 3 points without increase in analgesics) or 'insufficient responders' (VAS score decreased < 3 points). The insufficient responders were firstly more likely to have direct celiac plexus infiltration from the cancer compared to the 'complete responders' (73.3% vs 28.1%, p= 0.005, odd ratio: 4.82, 95% CI=1.12-23.42) and secondly more likely to have a restricted injectate distribution, unilaterally to the celiac trunk (46.7% Vs 6.3%, p=0.0025, odd ratio=8.67, 95%CI= 1.51-71.48). Whether the clinical characteristics of pain in patients with direct plexus cancer infiltration differ from those without is unknown and also why this leads to poor pain outcomes after the procedure. One possibility could be that the malignant tissue prevents the injectate from spreading around the ganglia or the nociceptive signals are more potent and frequent, so that the standard neurolysis regime is insufficient. There were no associations between response and: ascites, metastasis and anatomical location of the tumour within the pancreas (31).

Direct visualisation of the celiac plexus at EUS is a positive predictive factor for a decrease in pain scores (32). In an observational study of 64 patients, 53 had EUS-CPN at the same time as the diagnostic EUS for suspected pancreatic cancer and were investigated for associations with 8 variables namely: direct visualisation of the celiac ganglia, VAS score at baseline ≥7, gender, age ≥ 65 years, tumour size≥ 25 mm, tumour anatomical location, histologically confirmed diagnosis and EUS-CPN at the same time as diagnostic EUS. Patients with direct ganglia visualisation were more likely to improve (decrease in pain score by 2 points on a 0-10 scale pain visual analogue score) (odd ratio: 15, p<0.001) (32). This indicates that a successful pain outcome is possibly linked with injection of the neurolytic agent as proximally as possible to the targeted ganglion. The other variables were not associated with response. Therefore, a successful response to EUS-CPN is more likely to occur in patients without tumour involvement of the coeliac plexus, where the neurolytic agent has a broader distribution and where the ganglia are directly visualised endoscopically.

Chemotherapy improves pain in pancreatic cancer

Chemotherapy in pancreatic cancer is prescribed to patients to improve survival but also has analgesic properties. In total, 16 clinical trials, published since 1997, investigated the efficacy of chemotherapeutics for inoperable pancreatic cancer and also reported changes in pain scores, either as an individual outcome or as one of the components of a quality of life assessment (33). These trials assessed pain either as a continuous score (0-100 or 0-10 scales) or as a proportion of participants who had ≥50% reduction in pain intensity or opioid consumption. The chemotherapies assessed were: gemcitabine, 5-fluorouracil, FOLFIRINOX, BAY12-9566 metalloproteinase, glufosphamide and combinations of gemcitabine with cicplatin, merimastat, permetexed, exatecan,capecitabine, axitinibe, bevacizumab, cetuximab, paclitaxel and combinations of 5-fluorouracil with mitomycin. Pain improved with every treatment regime apart from the BAY12-9566 and the best supportive care (33). Patients who received gemcitabine, the most widely used chemotherapeutic in pancreatic cancer, were more likely to report a reduction in pain compared to other monotherapies, whilst combinations of gemcitabine with other chemotherapeutics achieved better pain improvements compared to gemcitabine monotherapy (33). The reduction in pain scores varied from 8 to 25 points on a 0-100 scale (8 point reduction reported in patients who received gemcitabine either as monotherapy or as combination with capecitabine, and 25 in patients treated with FOLFIRINOX).The proportion of patients who reported ≥50% reduction in pain ranged between 5% (received 5-Fluouracile) to 67% (received gemcitabine).

Conclusion

Abdominal pain in pancreatic cancer is a common debilitating symptom which impacts negatively on patients' quality of life and leads to increased health care needs and costs, including frequent medical consultations, palliative and nursing care. Pain contributes to a decline in patients' performance status and therefore can adversely influence their eligibility for chemotherapy. Pain is frequently refractory even to strong opioid analgesics, whose side effects can further precipitate a decline in clinical status. Patients with pancreatic cancer pain have reduced survival times compared to those without and better analgesia may improve survival. Pain can be due to pancreatic ductal obstruction and/or pancreatic neuropathy. Standard practice for promoting analgesia is pharmacological therapy according to the WHO analgesic ladder. If pain is resistant to opioid therapy ketamine or EUS-CPN is indicated. The literature has reported pain improvement and reduction in morphine use in patients treated with EUS-CPN, although further clinical trials are required to refine its use, including the timing of administration and the precise technique. An in depth understanding of the pain mechanisms will enable individualised care, with particular analgesics antagonising the relevant pain pathways and inhibiting the neuropathic changes. Such developments will improve the quality of life of patients, and maybe enhance survival in patients with this aggressive cancer.

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