Bedside Neurolysis for Palliative Care of Critically Ill Patients With Pancreatic Cancer

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In Switzerland, every year, 15.7 of 100,000 men and 15.9 of 100,000 women have a diagnosis of pancreatic carcinoma, with only few benefitting from therapy with curative intentions.[1,2] Successful surgery results in a gain of time but is not a cure. The 5-year survival rate is only 15%.[3] Most patients present with advanced disease at their first checkup.[4] Patients with pancreatic carcinoma frequently have severe uncontrollable pain, a result of tumor infiltration into the nearby celiac plexus, which poses the biggest challenge for their physicians.[5] Adequate symptom control in the form of pain management as well as preservation of the quality of life are the two most important aspects of palliative care.[6] It is at this juncture that the World Health Organization (WHO) pain ladder[7] (Figure 1), the reference standard for treatment of (pancreatic) cancer pain, meets its limitations because of frequent pain exacerbations. Neurolysis provides a more specific pain relief method (Figure 2; modified WHO pain ladder).

There are different approaches to how neurolysis can be performed. In this commentary, we introduce two methods for how the percutaneous approach may be conducted, which is either by computed tomography or ultrasound (US) guidance.

The percutaneous approach can be performed either antecrurally or retrocrurally. The antecrural (or transcrural) approach targets the celiac plexus,[8] whereas the retrocrural approach seeks to numb the splanchnic nerves next to the crura of the diaphragm (it is still referred to as a celiac plexus block, although numbing the splanchnic nerves).[8] The splanchnic nerves are, in addition to the celiac plexus, responsible for pain perception of the viscera.[8] The antecrural approach is preferred, as the celiac plexus may be reached directly, and the retrocrural approach holds more risks (pneumothorax is most common and, very rarely, transient paraplegia).[5,8,9] Kamdar et al[8] described a novel approach called the "single-needle retroaortic technique," which is a modified version of the retrocrural approach and a viable alternative to the percutaneous celiac plexus block, if the antecrural or retrocrural approach

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Abbreviations
US, ultrasound; WHO, World Health Organization

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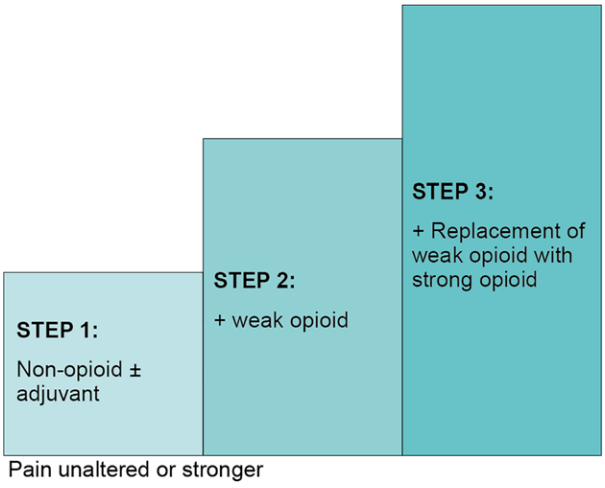
Figure 1. Therapy for malignant pain according to WHO.[7]



cannot be performed because of anatomic abnormalities or a tumor mass. Usually, this technique is controlled by computed tomography,[8,10] as are the other percutaneous techniques.

There is the possibility of percutaneous US-guided neurolysis, for which a new approach has been described by Bhatnagar et al.[11,12] Doppler US is then used to prevent any injection of the neurolytic agent into blood vessels.[11,12] Bedside US-guided celiac plexus neurolysis could be used in an inpatient or outpatient palliative care unit or hospice, as it can be done with a portable US device.[11]

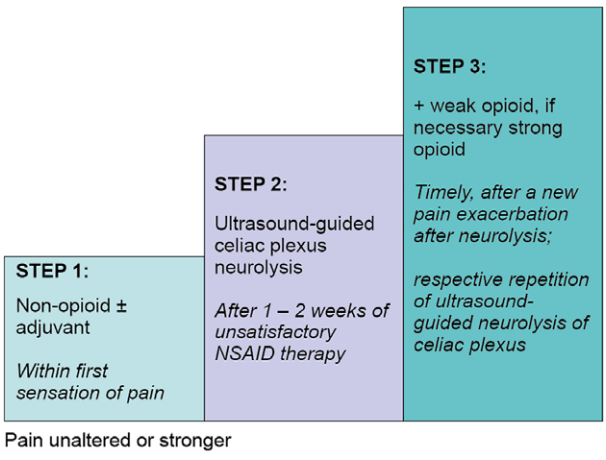
A local anesthetic is injected before administering the more permanent neurolytic drug to ensure the absence of pain when the latter is injected.[10] Bedside US-guided neurolysis decreases patients' discomfort compared to endoscopic US-guided celiac plexus neurolysis,[11] as it may be performed without having to move the patient and without the need for endoscopy or radiation, although discomfort in US-guided percutaneous neurolysis and endoscopic US-guided neurolysis has, to our knowledge, not been scientifically compared.

The demonstrable benefit of the percutaneous US-guided methods is the feasibility of their minimally invasive procedure.[11] They are safe and efficient methods to perform in an inpatient or outpatient setting and at bedside.[11,12] A patient receiving palliative care may be discharged after the intervention and subsequent brief monitoring of vital parameters without having to stay as an inpatient.

Ultrasound-guided neurolysis should be considered as a first-line alternative therapeutic option to minimize opioid dosages suggested in the "modified WHO pain relief ladder" (Figure 2). Research shows that neurolysis of the celiac plexus is effective and secure with a low complication rate.[13–15] However, any interventional therapy has known risks, which may lead to side effects.[13] These are rare[14] and transient, should they occur. As shown by Levy and Wiersema[14] and Levy and Chari,[15] the most common side effects of neurolysis are transient hypotension immediately after the procedure, transient diarrhea, and pain after using the endoscopic technique for neurolysis of the celiac plexus. These are also valid for any percutaneous technique.[16] Hypotension is treated with intravenous administration of a 0.9% potassium chloride infusion.[13] The elimination of the sympathetic nerves cause unantagonized parasympathetic nerves and explains the side effect of diarrhea.[17] If diarrhea persists and the symptoms are long lasting or severe, a peristalsis-inhibiting drug may be introduced. Wiechowska-Kozlowska et al[13] found no evidence that this procedure leads to chronic side effects.

A further important advantage of US-guided neurolysis is the decreased use of opioids after the procedure.[13,16,18] Laceration of vascular structures has become rare because of the use of Doppler US, which

Figure 2. Modified WHO pain ladder for pain management of pancreatic cancer in a palliative situation with respect to US-guided neurolysis of the celiac plexus. NSAID indicates nonsteroidal anti-inflammatory drugs.



shows arteries and veins.[15] Neurolysis is always a procedure that has to be performed near blood vessels.[15,19] The celiac plexus and the abdominal aorta anatomically lie in close proximity, and image-based neurolytic methods are safer.[11,13] If the neurolysis is performed via a percutaneous posterior approach,[20] the closeness to the radicular magna artery, an outflow of the aorta,[19,21] has to be additionally considered. Serious problems may occur if a blood vessel is lacerated. Very rare cases of a neurotoxic substance being injected into a vessel causing a spasm of the vessel, resulting in ischemia, have been documented, which may result in irreversible tissue damage.[22] However, should the neurolysis lead to any damaging of the radicular magna artery (Adamkiewitz), it may result in failure along the spinothalamic and pyramidal tracts.[9] The chances of this happening are insignificantly small.[9] A result of damage to the spinothalamic system would be loss of a pressure or tactile sensation and a temperature and pain sensation or the ability to register changes in these systems.[23] Partial destruction of the tractus pyramidalis would result in problems with fine motor skills.[23] However, Mercadante and Fulfaro[9] reported no evidence that alcohol or phenol in such small dosages may cause paralysis of any kind. Wiersema and Wiersema[20] described a risk of paraplegia of up to 1% of after the posterior percutaneous approach. After neurolysis, patients may temporarily have a burning sensation or pain at the site of injection.[17]

Neurolysis provides relief for a limited time because of either regeneration of nerves or metastatic disease causing pain in different parts of the body.[17] After a certain point in time, for example, when metastasis has already begun (liver or viscera), neurolysis may no longer be useful, as nociception now arises from a multifactorial etiology and is not only transmitted by the celiac plexus to the central nervous system.[17] Neurolysis is limited to patients whose celiac plexus has not been infiltrated by metastatic disease.[11]

Successful and timely administration of neurolysis alleviates pain and decreases the need for opioids, stabilizing the patient until death.[8,12,24,25] Also, it has been shown that neurolysis is still effective after 2, 4, 8, and 12 weeks.[18] Nagels et al[18] postulated that the effectiveness of percutaneous neurolysis will start to cease after 12 weeks, whereas neurolysis done by the endoscopic technique may be less effective but consistent after the same amount of time. Twelve weeks after neurolysis, the risk of a pain sensation may increase again, but the required opioid dosage, at least initially, would be less than without neurolysis, especially if nonsteroidal anti-inflammatory drugs or weak opioids are administered over an increasing number of weeks after the neurolytic procedure.[12,18] It is common for patients with pancreatic cancer to require increased dosages of opioids up until their death caused by progressive disease.[26] The question as to why neurolytic effects start to cease after a mean of 3 months is not fully understood. It is speculated that it is caused by reinnervation, or the residual plexus causes pain.[13,17,27] The consequence is that neurolysis will have to be performed multiple times, which should not be a problem, but it is often less effective than the first neurolysis.[28]

The time point for performing neurolysis is important. If the cancer is missed and has proceeded to grow, the procedure is often ineffective.[14,17] If metastatic disease exists—pancreatic carcinomas usually cause metastases early in the course of the disease—the perception of pain will be transferred to the central nervous system from various places. This implies that with progressive disease, pain management will be increasingly difficult. Neurolysis of the celiac plexus has to be taken into account early in the pain management of the disease, when metastases do not yet exist.[11,14] The earlier neurolysis is applied, the more effective it will be.[14] It may be appropriate to treat a patient with neurolysis even if he or she is under current treatment according to the WHO pain ladder[7]; if the pain cannot be controlled with the latter, then neurolysis should be suggested at the latest that the patient still has pain or most likely has side effects such as increased tiredness, respiratory depression, sedation, and constipation under maxed-out opioid administration.[29] If a patient had these kind of symptoms or cannot be treated adequately with nonopioids and opioids, as steps 1 and 2 in the WHO's ladder of pain relief recommend, then US-guided neurolysis should be considered as the primary method of pain management. Low-dosage opioids can be administered concomitantly if necessary.

In summary, US-guided neurolysis is a safe and efficient method with few side effects for treating pain in patients with pancreatic carcinoma adequately.[20,30]

In addition, US-guided neurolysis is feasible and less complicated than other techniques,[11] and patients are not exposed to radiation. Patients with a diagnosis of pancreatic cancer are most likely deemed palliative.[1] Bedside US-guided neurolysis may particularly be of help to those patients, as it is less time-consuming and, thus, less of a physical strain.[11] An innovative goal should be to extend bedside US-guided neurolysis not only to use it in an inpatient setting or a hospice, but also to be able to perform it at the patient's home via a mobile US device. An evaluation should take place for every patient if the potential risk of a neurolytic procedure is worth taking, compared to adverse effects that other pain management measures pose or that may arise from insufficient treatment of the pain. All patients with pancreatic carcinoma should be assessed for their own expectations for pain management.

Contrary to the current recommendation by the WHO's pain ladder, it makes sense to conduct US-guided neurolysis before the first administration of opioids in those patients. This is made clear in the modified version of the WHO's pain ladder (Figure 2). Exacerbation of pain may be reduced or avoided by the above-mentioned adjustment, and the first administration of opioids may be delayed, or, at least at the beginning of pain treatment, the dosage may be kept at a minimum. Thereby, adverse effects caused by opioids may be kept at bay, which results in a better quality of life in the palliative care of a patient with pancreatic carcinoma.[31]

Further controlled prospective research will be needed to postulate the positive or negative success of neurolysis in general and regarding the postneurolytic quality of life,[18] in contrast to the existing retrospective studies.[15] The existing literature is not conclusive and contradictive.[18] There are studies that promote neurolysis, some that do not recommend it, and others that have neutral findings.

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