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Efficacy of Neurolytic Celiac Plexus Block in Varying Locations of Pancreatic Cancer

Influence on Pain Relief

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Background: **Neurolytic celiac plexus block (NCPB) is an effective way of treating severe pain in some patients with pancreatic malignancy. However, there are no studies to date that evaluate the effectiveness of NCPB related to the site of primary pancreas cancer. The aim of the study was to assess the effectiveness of NCPB in pancreatic cancer pain, depending on the location of the pancreatic tumor.**

Methods: **The prospective study was conducted in 50 consecutive patients diagnosed with pancreatic cancer. The patients were categorized into two different groups depending on tumor localization: group 1: patients with the cancer of the head of the pancreas and group 2: patients with the cancer of the body and tail of the pancreas. The qualitative and quantitative pain analyses were performed before and after NCPB. The patients underwent prognostic celiac plexus block with bupivacaine, followed by neurolysis during fluoroscopic control within the next 24 h.**

Results: **After NCPB, 37 patients (74%) had effective pain relief during the first 3 months or until death. Of the 37 patients who had effective pain relief, 33 (92%) were from group 1 and 4 (29%) were from group 2. In the remaining 13 patients (3 patients from group 1 and 10 patients from group 2), pain relief after NCPB was not satisfactory. Those patients were scheduled for repeated retrocrural neurolysis during computed tomography control. Computed tomography showed massive growth of the tumor around the celiac axis with metastases. After repeated neurolysis, pain relief clinically still was not satisfactory, necessitating additional opioid treatment.**

Conclusion: **In this study, unilateral transcrural celiac plexus neurolysis has been shown to provide effective pain relief in 74% of patients with pancreatic cancer pain. Neurolysis was more effective in cases with tumor involving the head of the pancreas. In the cases with advanced tumor proliferation, regardless of the technique used, the analgesic effects of NCPB were not satisfactory. (Key words: Neurolytic celiac plexus block, pain; pancreatic cancer; tumor localization.)**

THE number of patients with cancer of the pancreas is increasing steadily.[1,2] The symptoms of the disease frequently are vague and appear usually in advanced stages of the disease, after considerable tumor growth and metastatic spread. At this stage, efforts are concentrated mainly on palliative treatment and relief of pain.[3-6] A limited number of studies compare effectiveness of neurolytic celiac plexus block (NCPB) and drug therapy on pain relief in pancreatic cancer pain.[7,8] However, substantial data claim high effectiveness of NCPB in pancreatic cancer pain.[9-16] No studies to date have attempted to evaluate the effectiveness of NCPB–splanchnic block in pancreatic cancer pain related to the location of the primary pancreatic tumor and its spread.[17,18] Differentiation of the pancreatic tumor located in the head or in the tail and body of the gland usually is important because of variation in clinical picture of the symptoms, characteristic of pain, spread of the tumor, and even treatment strategy and prognosis.[4-6,19,20] Despite the claims of high effectiveness of NCPB[9,10,14,15] in advanced stages of the disease, effects of neurolysis can be limited.[21-25]

The aim of this prospective study was to evaluate the effectiveness of NCPB in pancreatic cancer pain, depending on the location of the pancreatic tumor (*i.e.*, the head or tail and body of the gland) using the posterior

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Table 1. Demographic Data of the Patients

	Group 1	Group 2
	Cancer of the Head of the Pancreas	Cancer of the Body and Tail of the Pancreas
Number	36	14
Age (yr)	63 ± 9[a*]	68 ± 9
Gender (male/female)	27/9	10/4
Weight (kg)	69 ± 3*	60 ± 10
Site of pain		
Epigastric/mezogastric	+++	++
Hypochondrial	+	+++
Back pain	+	+++
Accompanying symptoms	N, V, J, WL	N, WL
Time from the first symptoms to NCPB (days)	94 ± 10*	25 ± 4
Time from diagnosis to NCPB (days)	51 ± 9*	11 ± 4
Medication at the time of NCPB	Diclofenac 150–200 mg daily. Dextropropoxyfen 50 mg 3 or 4 times or *dextropropoxyfen/paracetamol* 65 mg or 650 mg 3 or 4 times daily	Diclofenac 150–200 mg daily. Morphine 20/40 mg two times daily or ketomebidone 10 mg three times daily

J = jaundice; N = nausea; NCPB = neurolytic celiac plexus block; V = vomiting; WL = weight loss.

* Results are expressed as the mean ± SD.

left unilateral, transcrural technique of the celiac plexus block.

Materials and Methods

After obtaining institutional approval from the Ludvika Hospital Ethics Committee and informed consent, 50 consecutive patients with adenocarcinoma of the pancreas and disabling pain were scheduled for NCPB to alleviate the pain.

At admission, we evaluated the following data: beginning of the early symptoms of disease (nausea, vomiting, weight loss, jaundice), beginning and evaluation of pain symptoms, pain characteristics, correlation between the early symptoms and the pain debut, subjective pain scoring according to a visual analog scale (VAS; 0–10), patient medication and analgesics dosage before neurolysis, and the time course from the pain debut and diagnosis at which neurolysis was performed (table 1). Patients were instructed to rate the intensity of their pain according to the VAS, with 0 to 10 points, marked within 10 mm (0.01 cm) to each point of the scale (0 = no pain, 10 = worst pain imaginable).

In quantitative pain evaluation, it was assumed that pain equal to 3 on the VAS scale was mild. In general, patients with pain scores up to this level did not require opioid medication. Patients with a VAS score equal to or greater than 4 were classified as having significant pain and required opioid medication. Pain assessment was performed before and after NCPB. The World Health Organization (WHO) guideline, nonsteroidal antiinflammatory drug (NSAID)-opioids sequence treatment was used for pain management.

The criteria for NCPB was pain intensity according to the VAS greater than 3, not responding to diclofenac, and demanding additional opioid medication (second and third step of World Health Organization guideline). Pain intensity for VAS equal to or less than 3 without additional opioid medication was also a criterion of effective pain relief after NCPB.

In all our patients, the diagnosis of pancreatic tumor was based on primary ultrasonography examination or (in cases with suspected diffuse metastatic spread) computed tomography (CT), with specific localization of the changes to the head or body and tail of the gland. The diagnosis of adenocarcinoma of the pancreas was confirmed after ultrasound-guided biopsy-cytology of the pancreas tumor. Staging of metastatic spread and tumor proliferation was based on interpretation of ultrasound-guided-CT examination according to the American Joint Committee for Cancer Classification, stages I–IV.[5,19,20] Patients with diagnosed adenocarcinoma of the pancreas were categorized into two different groups, depending on tumor localization.

Group 1

Cancer of the Head of the Pancreas. Thirty six patients of 50 (72%) had cancer localized to the head of

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Table 2. Effectiveness of NCPB in Patients with Pancreatic Cancer Depending on Tumor Localization

Group	Entry VAS	VAS after NCPB	Pain Relief from Baseline Value (%)	Effective VAS <3 (%)	Ineffective VAS >3 (%)	Duration of Pain Relief (Days)
1						
Head of the gland	5.40 ± 0.54*	1.8 ± 1.0	66.2	33 (92)	3 (8)	119†
2						
Corpus and tail of the gland	7.60 ± 0.88	5.5 ± 2.5	26.5	4 (29)	10 (71)	65
Total				37 (74)	13 (26)	

* results are expressed as mean ± SD

† results are expressed as mean

Pain relief = initial pain relief after NCPB. Duration of pain relief = effective pain relief without opioid medication.

NCPB = neurolytic celiac plexus block; VAS = visual analog scale.

the pancreas. Tumor proliferation in this group of patients (based on primary ultrasound-guided examination) was restricted to the head of the gland area, usually not larger than 2 cm in diameter and without distant metastases to the liver. Sixteen of 36 patients (46%) presented with local metastases to the surrounding lymph nodes and occasional invasion of pancreatic duct (metastatic-tumor spread; stage I or II).

These patients appeared with initial symptoms of nausea, vomiting, weight loss, anorexia, and jaundice. Patients complained of nonradiating, deep and constant, epigastric or mesogastric pain, occasionally radiating to the back. All patients in this group initially received diclofenac (150-200 mg daily) with moderate-good analgesic effect. In this group of patients, the time from diagnosis until performance of NCPB was 4-9 weeks (mean, 51 days) depending on the progress of pain symptoms.

Pain at the time of neurolysis was significant, with sleep disturbance and demand for extra pain medication with opioids (50 mg dextropropoxyfen, three to four times a day, or 65 mg dextropropoxyfen + 650 mg paracetamol, three times a day). The time from the first symptoms of nausea and vomiting until performance of neurolysis was 8 to 15 weeks (mean, 94 days). Pain at the time of neurolysis in this group of patients was according to VAS scale in the range of 4 to 6.5 scores (5.4 ± 0.54; table 2).

Group 2

Cancer of the Body and Tail of the Pancreas. Fourteen patients (28%) had cancer localized to the tail and body of the pancreas. Tumor proliferation was advanced, in most cases larger than 4 cm in diameter. Often, a palpable abdominal mass was present. Metastases to the liver and mesenteric and local lymph nodes were present in 95% of patients in this group (metastatic-tumor spread; stage III or IV).

These patients had initial symptoms of paroxysmal, deep mesogastric and periumbilical or hypochondrial pain radiating to the upper back or shoulder, along with weight loss and occasional nausea and vomiting. Jaundice was not present. This group of patients responded poorly to pain relief with diclofenac (150-200 mg daily) and required early supplementary pain medication with opioids (50 mg dextropropoxyfen, four times a day, followed by 10 mg ketobemidone, three times a day, or 20-40 mg morphine (morphine sustained-release) tablets, twice a day.

In this group of patients, the time from diagnosis to the decision to perform NCPB was 1 to 3 weeks (mean, 11 days), and time from onset of symptoms to time of neurolysis was 3 to 5 weeks (mean, 25 days). According to the VAS scale (table 2), pain in this group of patients at the time of neurolysis was between 6 and 9.5 (7.6 ± 0.88; rapid progress to severe, excruciating and disabling pain and total disturbance of night sleep). Based on entry values in pain assessment, it was assumed that effective pain relief after neurolytic block should be in the range of 3 or below on the 0-10 VAS scale. The technique of the neurolytic block was as follows: After informed consent, unilateral transcrural preaortal diagnostic celiac plexus block was performed with 40 ml bupivacaine, 0.5% (5 mg/ml with epinephrine 5 μg/ml), and was followed within 24 h by an NCPB. The block was performed according to the previously described unilateral technique,[26] in the right lateral position, under direct vision of image intensifier with C-arm fluoroscopy monitoring. All celiac block procedures were performed by the authors. At the time of primary neurolysis, authors performing the block were not aware of the extent of cancer proliferation. After verifying the correct position

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Table 3. Survival Time

	Number	3 Months	3–6 Months	6–9 Months	9–13 Months	Days of Survival (mean)
Group 1						
Head of the gland	36	1	19	14	2	203
Group 2						
Corpus and tail of the gland	14	14	0	0	0	85

Survival time from the time point of NCPB.

NCPB = neurolytic celiac plexus block.

of the needle by fluoroscopy, the contrast medium (5 ml Omnipac 300, with 5 ml lidocaine, 2%) was injected to assess the proper spread around the area of celiac plexus. Local infiltration with 1% lidocaine was used during introduction of the needle. Before the neurolytic block, patients were premedicated with pethidine (1 mg/kg). Patient blood pressure, heart rate, and oxygen saturation was monitored during the procedure, and intravenous infusion of 150 ml/h lactated Ringer's solution was started 3 h before the block was performed. For neurolytic block, 40 ml ethanol diluted with 2% lidocaine, to a final concentration of 60%, was used. All patients continued NSAID medication after NCPB. At the time of the first pain evaluation after neurolysis, personnel performing the assessment were unaware of the cancer location and extent and proliferation of the tumor or metastases. Further follow-up was made by telephone contact with the patient or family or by personal contact with the patient by a nurse. When necessary, an outpatient clinic appointment was arranged to ensure the accuracy of received data and to determine and assess the patient's condition, effectiveness of the therapy, or problems connected with the treatment. For subsequent CT-guided block in patients who did not obtain satisfactory pain relief after primary neurolysis, bilateral retrocrural (splanchnic) neurolysis, as described by Moore *et al.*,[15,22] was performed in with the patient in the prone position during CT control, with injection of 25 ml ethanol, 60%, in 2% lidocaine on each side. Before neurolytic injection, the spread of the contrast medium was shown retrocrurally, posterior to the aorta.

Results

No important differences were observed between the two groups with regard to age, gender, or weight. All patients experienced 6–10 h of effective pain relief after the prognostic celiac plexus block, with VAS pain scores less than 2, regardless of the time of pain debut, duration, severity, or character of pain, or pain medication. The effect of the neurolytic block was assessed 48 h after neurolysis. The assessment was performed by the acute pain service nurse, who was unaware of the location of the tumor or the aim of the study.

After neurolysis, 37 patients (74%) of 50 had effective immediate pain relief (VAS score 3 or less) during the first 3 months or until death.

Of the 37 patients who had effective pain relief, 33 of 36 were from group 1 (92% of patients with tumor of the head of the gland), and 4 of 14 were from group 2 (29% of patients with tumor of the body and tail of the pancreas). Of these 37 patients, 5 died within 3 months from the time of NCPB (4 were from group 2). They had effective pain relief, with VAS pain scores less than 3, without additional opioid medication (table 2). Survival time is presented in table 3.

In further follow-up (after 3 months), of the remaining patients[32] who had primarily a satisfactory response to NCPB, VAS pain scores gradually increased with survival time. Generally, recurrence of significant and severe pain (VAS score 4 or more) occurred gradually, mostly from the fourth month from the primary neurolysis (mean, 3.4 months or 119 days of effective pain relief without strong opioids). Among the patients who survived for 4 months and had recurrence of pain, seven underwent subsequent retrocrural neurolytic block with acceptable-moderate effect for the period of 3–6 weeks (VAS score between 3.5 and 4.5). All of these patients required strong opioid medication, with addition of adjuvant drugs because of recurrent pain within the last weeks of their life (survival time, 6.4 months or 203 days; table 3). Assessment of pain relief after NCPB is presented in table 2 and in figures 1 and 2. All patients who had effective pain relief up to 3 months were able to discontinue opioid medication and continue only with NSAIDs.

The patients in group 1 had much longer-lasting pain relief effect (mean, 3.4 months to 119 days) but also

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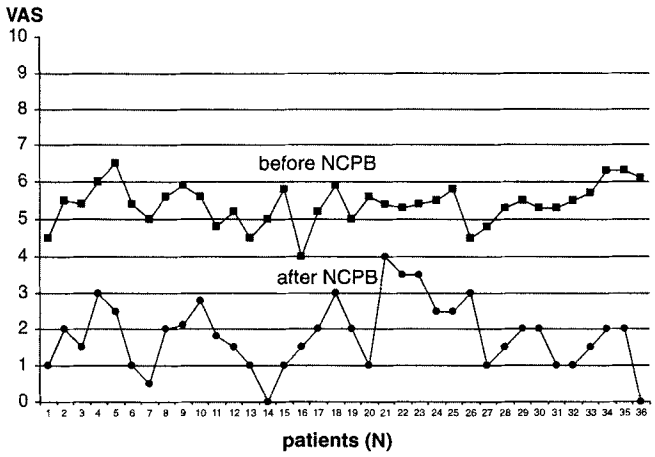

Fig. 1. Visual analog scale (VAS) scores in patients in group 1 (N = 36). VAS before neurolytic celiac plexus block (NCPB; base value 5.40 ± 0.54). VAS after NCPB (1.8 ± 1.0), with 66.2% of pain relief from baseline value NCPB.

longer survival time (mean, 6.3 months to 203 days) than the patients from group 2-(pain relief mean, 2.1 months to 65 days and survival mean, 2.3 months to 85 days).

Thirteen patients (26%) of 50 did not have satisfactory pain relief after NCPB, and the pain scores after NCPB remained within the preblock values (in group 1 mean VAS scores were 5.4 and 5.2 before and after NCPB, respectively. In group 2, mean VAS scores were 7.6 and 7.0 before and after NCPB, respectively, despite transient improvement in pain relief within the first 2-4 days after neurolysis.

Most of the patients who did not respond satisfactorily to primary NCPB were from group 2 (10 patients [71%]). Three patients (8%) were from group 1. Those 13 patients underwent subsequent neurolysis during CT control within 3-5 days after the first neurolytic block. In all these patients, CT scans showed massive growth of the tumor around the celiac axis that distorted the anatomy, with a shift of the aorta to the left and distortion of the position of the pancreas and the kidneys with distant metastatic spread. Anatomic changes considerably restricted access to the celiac area.

Before neurolytic injection, the spread of the contrast medium was shown retrocrurally, posterior to the aorta. The VAS scores assessed within 48 h after retrocrural CT-guided neurolysis did not change significantly and remained similar to the pain reports after the first NCPB. Pain relief still was not satisfactory, and patients continued with NSAID medication until death (150-200 mg diclofenac daily, 25 mg amitriptyline two times a day, and strong opioid-morphine sustained-release tablets in increasing doses of 30, 60, and 80 mg two times a day).

We encountered some adverse reactions and complications of minor importance after NCPB: 14 patients (28%) complained of back pain for 48-72 h, 9 patients (18%) had short-lasting (24 h) diarrhea that was corrected with intravenous rehydration, and 12 patients (24%) had transient urinary retention. Mild hematuria occurred in three patients without detectable hemoglobin changes or hematoma. The incidence of pronounced hypotension was low, (6 patients [12%]), probably because of routinely ordered infusion of fluids before the procedure. Two aortic punctures were noted without detectable hematoma.

Discussion

So far no studies, to the best of our knowledge, attempted to evaluate the correlation between the effectiveness of NCPB and pancreatic tumor location.[16,18] This study attempts to assess the effectiveness and duration of pain relief after NCPB, depending on specific cancer localization and different stages of cancer growth.

The cancer of the pancreas is localized to the pancreatic head in approximately two thirds of patients (65%) and to the body or tail in approximately 20% and occurred in a combination of sites in the remaining patients.[4-6,19,27] The early clinical picture of the disease usually is vague, but differentiation of pancreas cancer in the head or tail and body of the gland is connected with some differences in the picture of clinical symptoms and pain characteristics, different development of tumor pro-

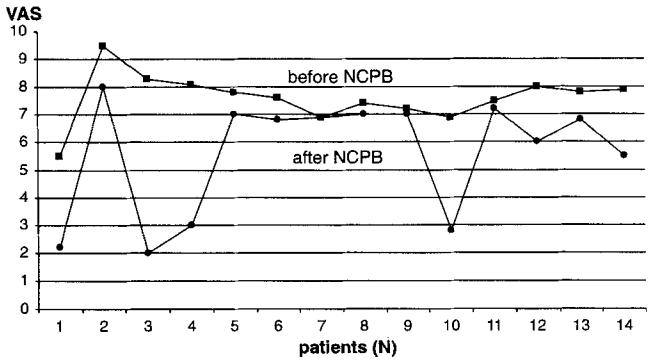

Fig. 2. Visual analog scale (VAS) scores in patients in group 2 (N = 14). VAS before neurolytic celiac plexus block (NCPB; base value 7.60 ± 0.88). VAS after NCPB (5.5 ± 2.5), with 26.5% of pain relief from baseline NCPB.

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liferation, and even different survival time.[4-6,19,20,25] Because the treatment strategy and prognosis may vary with different localization of pancreatic cancer, a specific diagnosis is desirable.[19,20]

We found considerable differences in the effectiveness of NCPB with respect to duration and degree of pain relief, but also in survival time, depending on pancreatic cancer location and advance of spread. In our study, patients with cancer of the head of the pancreas (group 1) had much more effective and long-lasting pain relief after NCPB (mean, 119 days), but also a longer survival time (mean, 203 days) compared with the patients with cancer of the body and tail of the pancreas (group 2), in whom pain relief post-NCPB was of a much shorter duration (mean, 65 days). Survival time in group 2 also was of shorter duration (mean, 85 days).

According to available data[4,5,19,20] and based on the observation in our study, it seems that there is a correlation between location of the tumor and advance of the disease in pancreatic cancer. We speculate that more advanced growth of the tumor at the time of diagnosis in patients in group 2, confirmed later by CT, restricted the spread of neurolytic solution and limited the pain relief after first precrural neurolytic block. However, this could not be confirmed by the differences in the spread of the dye during fluoroscopy control after needle placement during the first celiac neurolysis. Patients did not respond satisfactorily even after repeated, CT-guided retrocrural neurolysis. We could not find the proper explanation for block failure; however, these were the cases of cancer of the tail and body of the pancreas, with advanced progress of tumor infiltration and metastatic spread, in which pancreatic cancer pain became mostly multifactoral, and different pain mechanisms and pathways, other than visceral, must be considered.[4,24,28] Here the pain appears late, is usually more severe and paroxysmal, often disabling, with early tissue and nerve infiltration, involvement of peritoneal, retroperitoneal and somatic structures, and diffuse metastatic spread, in which celiac plexus block may have limited effects.[4-6,24,29,30]

However, some patients in this group responded with satisfactory pain relief after neurolysis, despite the advance of the disease (stage IV). A possible explanation was that metastatic spread and tumor proliferation in these patients was classified as stage IV, although tumor expansion was small enough to enable the effective spread of neurolytic solution. Less advanced cancer infiltration in these few cases was possibly also connected with pain, predominantly visceral, without a multifactoral component, which is more easily suppressed by celiac neurolytic block. Some patients in group 1 responded poorly to primary neurolysis, and these were shown (after CT examination) to have more advanced cancer proliferation then was classified originally. In the study by Ischia *et al.*,[24] shorter time of onset of pain to neurolytic block affected the duration of pain relief post-NCPB, giving a greater incidence of immediate and longer-lasting pain relief when a shorter-duration onset was noted from the first symptoms to NCPB. We could confirm these results only in connection with the patients in group 1; that is, in accordance with the clinical description of the symptoms of pancreas cancer in the head of the gland. In these cases, advance of the disease is less pronounced at the time of diagnosis, and pain symptoms appear earlier and are initially mostly of visceral origin and more easily suppressed by celiac plexus block.[4,5,19,24,29]

In our patients in group 2, onset of first symptoms and time from pain debut to neurolysis was of much shorter duration (25 days) than in group 1 (94 days). However, because of a much more advanced course of the disease in this group, neurolytic block had a limited effect.[4,22,24] In our study, patients from group 1, who had more effective and longer-lasting pain relief after neurolysis, also had primary good pain relief in response to NSAIDs, which is in correlation with the results from the study of Ischia *et al.*[24]

The patients in our study who had good pain relief after neurolysis were able to discontinue or decrease opioid medication, with improved alertness and quality of life. Reduction in opioid consumption in patients in group 1 and group 2 after NCPB is in agreement with observations from other studies.[4,7,24]

It is difficult to explain the good effect of diagnostic block with bupivacaine in all patients despite later failure of neurolytic block in patients in group 2; however, from clinical observations, effectiveness of diagnostic block with bupivacaine-lidocaine in visceral cancer pain seems to be more pronounced than are the effects of neurolysis.

Neurolytic celiac plexus block alone is capable of providing an effective, complete pain relief in pancreatic cancer pain until death only in a limited number of patients.[24] However, neurolysis effectively abolishes the visceral component of pancreatic cancer pain, which appears early in the course of the disease.[4,24] In visceral (celiac) pain, effectiveness of NCPB is approximately 70-80% for immediate pain relief and 60-75% for pain relief up to death.[24] Effectiveness of NCPB in complete

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pain relief in pancreatic cancer pain was evaluated and showed immediate pain relief in 40–52% of patients and pain relief until death only in 10–24% or patients.[24]

The duration of pain relief after NCPB usually is correlated with survival time as a function of time, in which longer survival is connected with higher incidence of recurrence of pain,[4,19,24] with highest effectiveness of NCPB within the first 3 or 4 months.[24] In our study, recurrence of significant and severe pain (VAS score 4 or more) occurred gradually, mostly from the fourth month after primary neurolysis (mean, 3.4 months or 119 days of effective pain relief without strong opioids). All patients with recurrent pain required strong opioid medication, with the addition of adjuvant drugs within the last weeks of life (survival time, 6.4 months or 203 days).

Average survival time in patients with pancreatic cancer pain is short and does not exceed 6 months. The delay of the effect of pharmacologic therapy, according to the World Health Organization guidelines,[31] may not leave much time for the effect of neurolysis. This might be especially important in patients with cancer in the tail and body of the pancreas who have rapid progression of the disease, late symptoms, more advanced tumor proliferation, and metastatic spread at the time of diagnosis and a very short survival time, as noted in our material. However, effectiveness of NCPB in these patients may be questioned. Patients in group 1, with pancreatic cancer in the head of the gland, in which NCPB was performed previously in the course of the disease, in a less advanced stage, had much more effective pain relief than patients with cancer of the tail and body of the gland, in whom progression of the disease was more advanced at the time of diagnosis and performance of the NCPB (group 2). These results, however, may need to be confirmed in a randomized study with a larger number of patients.

An individualized and integrated approach with different treatment strategies in the management of pancreatic cancer pain, depending on cancer location, is needed to achieve the optimal results Many data suggest that NCPB during a less advanced course of the disease has a more pronounced effect on pancreatic cancer pain.[14,21,22,24] The question arises whether World Health Organization policy guidelines[31] that recommend sequential pharmacologic (NSAID–opioids) treatment before NCPB are appropriate to achieve the optimal pain relief in all cases of pancreatic cancer.

In conclusion, this study shows that left unilateral transcrural NCPB provided an effective pain relief in 74% of patients with pancreatic cancer pain. The effectiveness of neurolysis was more pronounced in cases of cancer of the head of the pancreas. Effectiveness of neurolytic block was less pronounced in cases of cancer of the body and tail of the pancreas, in which CT confirmed massive local infiltration of periaortic space-celiac axis area and spread of metastases to the liver. In these cases, effects of neurolysis were limited, regardless of the technique used.

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